Critical Evaluation of Current Concepts and Moving to New Horizons in the Management of IBD

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Falk Symposium 196

CRITICAL EVALUATION OF CURRENT CONCEPTS
AND MOVING TO NEW HORIZONS IN
THE MANAGEMENT OF IBD

Frankfurt, Germany
March 6 – 7, 2015

Scientific Organization:
A. Dignass, Frankfurt (Germany)
S. Danese, Rozzano (Italy)
G.J. Mantzaris, Athens (Greece)
B.E. Sands, New York (USA)
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* = Posters of Distinction
Session I

The “omics” era of research
Metabolomics in inflammatory bowel disease

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Crohn’s disease and ulcerative colitis represent the two major phenotypes of inflammatory bowel disease (IBD) which are characterized by chronic inflammation of all or parts of the gastrointestinal tract. The pathogenesis of both diseases is influenced by genetic predispositions as well as microbial and environmental factors. Currently, there is an emerging consensus hypothesis that a microbial dysbiosis is involved in initiating the disease or maintaining it. These compositional alterations may be reflected in altered metabolic activities of the gut microbiota and has led to the use of ‘omic’ profiling techniques to improve the understanding of the pathophysiology of IBD. Omics-technologies such as genomics, transcriptomics and proteomics provide information regarding the genotype, whereas metabolomics represents a direct readout of the phenotype. Metabolomics involves the high throughput identification, characterization and quantification of small molecule metabolites by different analytical techniques and has already been performed in different biofluids. In the past few years, metabolomics has increasingly been applied in a number of studies of experimental and human IBD. Most of these studies focused on exploring disease-related metabolites to gain more insight in different metabolic pathways. So far, the application of different metabolite profiling techniques in IBD has revealed different metabolites that allow to discriminate IBD patients from healthy controls. In addition, separate IBD subtypes could be differentiated. Some of these metabolic changes were directly associated to alterations of specific gut microbial populations, implying a perturbation in the gut microbiome in the development or maintenance of IBD. The present lecture will cover the emerging contribution of metabolomics for the discovery of an IBD signature and the possibility to identify biomarkers linked with a metabolic imbalance.
Translation of genes into mechanistic advances – Potential to control intestinal inflammation?

Arthur Kaser
Division of Gastroenterology and Hepatology, Department of Medicine, Addenbrooke’s Hospital, University of Cambridge, Cambridge, UK

Human genetics has laid bare the genetic underpinning of inflammatory bowel disease, hence populating one part of the equation in this disease that is thought to emerge from complex environment – gene interaction. While long lists of susceptibility loci are shared between Crohn’s disease and ulcerative colitis, and indeed amongst multiple immune-related diseases, Crohn’s disease is unique in that two of the three susceptibility genes that account for a very large fraction of overall heritability are indeed specific for only this disease. Modeling genetically affected pathways provides a unique opportunity to create a ‘window’ to raise and test hypothesis on environmental triggers of the disease.

How such modeling can advance insight into the disease is discussed in the context of hypomorphic autophagy. Hypomorphic autophagy has emerged as one of the disease-defining genetically affected pathways in Crohn’s disease, based on the discovery of the ATG16L1-T300A genetic risk variant and further risk genes involved in this pathway. We recently demonstrated that an important function of autophagy is to restrain endoplasmic reticulum stress in the intestinal epithelium and in particular Paneth cells. In case the capacity is lost due to hypomorphic autophagy function in the epithelium in the context of unresolved ER stress, spontaneous discontinuous, transmural ileitis emerges that phenocopies ileal Crohn’s disease. This insight may not only open up novel therapeutic targets, but also provide an opportunity for patient stratification, and also for informing the search for environmental factors triggering the disease.
The human gut contains $10^{14}$ bacteria and many other microorganisms such as Archaea, viruses and fungi. This gut microbiota has co-evolved with host determinants through symbiotic and co-dependent relationships. Bacteria, which represent 10 times the number of human cells, form the most depicted part of this black box owing new tools. Re-evaluating the gut microbiota showed how this entity participates to gut physiology and beyond this to human health. Studying and handling this real ‘hidden organ’ remains a challenge for clinicians. In this review, we aimed to bring information about gut microbiota, its structure, its roles and the way to capture and measure it. After bacterial colonization in infant, intestinal microbial composition is unique for each individual although more than 95% can be assigned to four major phyla. Besides its biodiversity, gut microbiota major characteristics are stability over time and resilience after perturbation. In pathological situations, dysbiosis (i.e. imbalance in gut microbiota composition) is observed with a loss in overall diversity. IBD associated dysbiosis was specified with the reduction in biodiversity, the decreased representation of different taxa in the Firmicutes phylum and an increase in gammaproteobacteria. Beyond depicting gut microbial composition, metagenomics allows the description of the combined genomes of the microorganisms present in the gut, giving access to their potential functions. In fact, for each individual overall microbial metagenome outnumbers by a factor of 150 the size of human genome. Besides a functional core in which there is redundancy for mandatory functions assuring the robustness of the ecosystem, human gut contains an important diversity and high number of non-redundant bacterial genes. Clinical data, treatment, and all the factors able to influence microbiome should enter integrated big data sets to put in light pathways of interplay within the supra organism composed of gut microbiome and host. A better understanding of dynamics within human gut microbiota and microbes-host interaction will allow new insight into gut pathophysiology especially regarding resilience mechanisms and dysbiosis onset and maintenance. This will lead to description of biomarkers of diseases, development of new probiotics/prebiotics and new therapies.
High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in IBD and heterozygous advantage in ulcerative colitis

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Genome-wide association studies of the related chronic inflammatory bowel diseases (IBD) known as Crohn’s disease and ulcerative colitis have shown strong evidence of association to the major histocompatibility complex (MHC). This region encodes a large number of immunological candidates, including the antigen-presenting classical human leukocyte antigen (HLA) molecules. Studies in IBD have indicated that multiple independent associations exist at HLA and non-HLA genes, but they have lacked the statistical power to define the architecture of association and causal alleles. To address this, we performed high-density SNP typing of the MHC in > 32,000 individuals with IBD, implicating multiple HLA alleles, with a primary role for HLA-DRB1*01:03 in both Crohn’s disease and ulcerative colitis. Noteworthy differences were observed between these diseases, including a predominant role for class II HLA variants and heterozygous advantage observed in ulcerative colitis, suggesting an important role of the adaptive immune response in the colonic environment in the pathogenesis of IBD.
Session II

Imaging in IBD
Role of bowel ultrasonography in diagnosis of IBD

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Ultrasonography has become an important diagnostic tool patients with IBD in recent years. It has been shown to be of particular value in primary diagnosis as well as in follow up of patients. A variety of trials have shown that ultrasound of the large and small bowel in patients with Crohn’s disease has at least the same diagnostic significance as other imaging tools such as MRI. The advantage of bowel ultrasonography is the evaluation of bowel wall stratification, the evaluation of vascularization and the evaluation of motility. Bowel ultrasonography is quick and inexpensive and it assesses real time movement of the bowel. Bowel ultrasonography has recently been implemented into the ECCO imaging guidelines as an important diagnostic tool during initial diagnosis as well as during disease monitoring in patients with Crohn’s disease and ulcerative colitis. However, up to now there are only very few European countries where ultrasound is practiced by gastroenterologists themselves.

Different bowel wall parameters have been implemented in bowel ultrasonography including wall thickness, overall echotexture, rigidity, prestenotic dilatation, lymph nodes, mesenterium, ascites, vascularization (color duplex, contrast enhanced ultrasound) and complications such as fistulæ, abscess, ileus/subileus.

Indication of ultrasound in IBD include primary diagnosis and staging as well as monitoring of therapeutic success. It could also be used to determine recurrence of CD or UC. In particular in Crohn’s disease it has been proven to be of value in detection of complications such as fistulæ, abscesses, stenosis or extraintestinal abdominal complications.

Bowel ultrasound is an easy and cheap method that is highly sensitive and reproducible and represents a suitable method to evaluate and to monitor disease activity in IBD patients.

A new field of interest is the use of contrast enhanced ultrasonography (CEUS) in patients with CD. CEUS is particular helpful in determining inflammatory masses in CD and to characterize abscesses.

Perianal ultrasound is an easy method to determine inflammatory activity in patients with perianal Crohn’s disease including perianal fistulæ and abscesses.
Diagnostic imaging approaches play an important role in the diagnosis and management of patients with inflammatory bowel diseases (IBD). The diagnostic approach should be guided by considerations of diagnostic accuracy, concerns about patient exposure to ionizing radiation and tolerance of the endoscopic and/or imaging technique. There is no significant difference with regard to the clinical diagnostic value (sensitivity, specificity and accuracy) between ultrasound, CT and MRI for the evaluation of the extent of inflammation, stricturing or penetrating disease or extraluminal complications such as abscesses. Because of the lack of radiation MR-imaging of the intestine is recommended as the first line imaging modality in patients with suspected or established IBD. Standardized protocols for the grading of inflammation e.g. before and after therapeutic intervention of the small and large bowel such as the MaRIA score or the Lemann score are available but not yet widely used in clinical practice. New experimental MR-imaging approaches try to evaluate the degree of intestinal fibrosis/inflammation in stricturing Crohn’s disease.

References:


Molecular endoscopy: Where are we going?

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Molecular imaging during endoscopy has recently opened new avenues for clinical diagnosis and therapy. The introduction of novel molecular imaging modalities that can not only define disease states based on structural changes and morphology, but instead allow *in vivo* visualization and characterization of molecular and biochemical alterations on a cellular level add a new dimension to our current diagnostic possibilities. The advents of innovative endoscopic devices coupled with the introduction of novel targeting ligands contribute to the recent advances made in the field of molecular imaging.

Recent progress concerning molecular imaging studies in animals and human patients as well implicate that this approach can be used to improve detection of mucosal lesions in wide field imaging and for *in vivo* characterization of the mucosa with the ultimate goal of assessing the likelihood of response to targeted therapy with biological agents. In particular, molecular endomicroscopy for assessment of mucosal immune responses ("immunoendoscopy") emerges as novel approach for optimized endoscopic diagnosis and individualized therapy. This concept has been recently used for the prediction of clinical responsiveness in the field of anti-TNF therapy. These findings indicated that molecular imaging with labelled antibodies may be used during endoscopy to predict response to subsequent anti-TNF therapy with adalimumab. Further studies are needed before this concept may enter clinical routine, however. Future studies may also address the usefulness of this approach with other antibodies used for IBD therapy in the clinic.

Reference:

What will be the future? Integrating imaging into clinical practice

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Recent developments in the treatment strategies for IBD recommend frequent evaluation of mucosal healing. This cannot always be done by endoscopy as suggested in a recent manuscript by key opinion leaders.

New imaging techniques are required to allow a rapid assessment of mucosal inflammation. Ultrasound (US) is one of the options for this purpose in the future. Unfortunately US is not in the hands of gastroenterologists in many countries. But why take this as given and unchangeable fact? New ultrasound techniques such as elastography and shear wave analysis will better allow differentiation of tissue fibrosis and inflammation in the future. They have the potential to become a routine technique that will allow a better tailoring of therapy to the individual needs. Those techniques will avoid to use expensive therapies in patients that cannot benefit e.g. because the already have a fibrotic stricture as we have done in the past.

New MRI techniques (such as magnetization transfer and others) also will be better suitable to discriminate between fibrosis and inflammation. They will not only be important for future clinical practice. They also will provide quantifiable clinical endpoints for clinical trials in fibrosis disease. Our lack of such quantifiable endpoints for anti-fibrosis treatments in IBD is the reason for a complete lack of the respective developments so far.

With the equipment present at many centers US and MRI can easily be upgraded to those new techniques making it possible to introduce them relatively rapidly into clinical practice.

The latter will be more difficult with molecular endoscopy. However, at dedicated centers the technique may become suitable to tailor treatment decisions and predict treatment responses in IBD. The “try and error approach” we still have to pursue with our immunosuppressant and biological drugs is frustrating both for the clinician and surely more for the patient.

Thus it is obvious that the integration of the new imaging techniques into clinical practice will benefit the IBD patients and be an important step forward in an individualized medicine approach in the field of IBD.
Session III

Management of the challenging IBD patient – A multidisciplinary approach
Cell-based therapies in IBD

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Crohn’s disease (CD) is characterized by chronic inflammation in segments of the digestive tract and tissue damages. A significant progress has been made over the two last decades in the management of CD. However, a fraction of CD patients experiences severe disease, refractory to all available therapies. Different cell-based therapies are under investigation in IBD, based on usage of stem cells of hematopoietic or mesenchymal origin, or on expansion of regulatory T cells. Evidence for the feasibility and efficacy of hematopoietic stem cell transplantation (HSCT) has been reported in several types of severe treatment-resistant immune mediated inflammatory diseases. Analyses of the EBMT database provided evidence for the feasibility and the toxicity of the HSCT procedures in immune mediated diseases. Despite long-term benefits, it is associated with a high morbidity and a 2–10% mortality rate, making it an acceptable option for only highly refractory patients. The effect of HSCT on the disease is probably associated with a resetting of specific immune responses. Beyond short series, autologous HSCT as primary treatment for CD has been investigated in prospective studies. Prolonged drug-free remission is observed in a high proportion of patients. The ASTIC trial, an international investigator-initiated randomized study, evaluates the early and late effects of autologous unselected HSCT on CD over 5 years in accredited transplant centers from six European countries. Forty-eight patients underwent mobilization of stem cells, and 45 patients were randomized to transplantation at one month (n = 23) or one year after (control arm, n = 22). One patient died following HSCT. Results at one year have been recently presented in international congresses. Accordingly to the EBMT guidelines, HSCT should be proposed only in patients with active CD refractory to immunosuppressants and biologics, and after consideration of all therapeutic options including surgery. Future research should focus on selection of patients and reduction of risks related to HSCT.

Mesenchymal stem cells (MSCs) represent another option for the treatment of refractory diseases. Preclinical studies suggest the potential efficacy of MSCs in models of autoimmunity, inflammation, and tissue damage. Phase 1/2 clinical trials using MSCs have been initiated in CD. Locally administered MSCs showed results in the treatment of perianal fistulae. MSCs (autologous or allogeneic bone marrow-derived), which have immunosuppressive properties, have also been tested though IV infusions in luminal disease. The safety and efficacy of a single injection of escalating doses of autologous ovalbumin-specific regulatory T cells in patients with active CD refractory to conventional therapy has been investigated in a phase 1/2a clinical trial. This therapy was well tolerated and demonstrated dose-related efficacy. A phase 2b trial recently started.
Tandem talk

CD patient with intra-abdominal infection (abscess): The place and timing of biologics (and when) and surgery

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Despite the progress of medical therapies in the treatment of Crohn’s disease, surgery remains an integral part of the management. Patients with uncomplicated inflammatory disease, medical therapy is preferred, but complications such as strictures and perforations usually require surgical care. An intra-abdominal abscess or phlegmon is almost invariably linked to a perforated bowel. The perforation can be overt or concealed. The first line treatment will be antibiotics with or without drainage. The development of adequate percutaneous drainage procedures introduced a shift towards a more conservative approach. However most patients will require elective surgical resection especially in the presence of concomitant stenosis or fistulae. Patients with an intra-abdominal abscess should be approached by a multidisciplinary surgical-medical team.

Surgery may be scheduled at a later time point in case of: 1. A large abscess or phlegmon, 2. Severe malnourishment, 3. Long term systemic steroid use. All these factors will increase surgical morbidity or complicate a laparoscopic procedures.

Large abscesses should be drained radiologically or laparoscopically to improve the general condition of the patient. If sepsis persists urgent surgery with resection and stoma formation may be required. Adequate drainage significantly reduces the risk for subsequent operative complications and increases the chance for primary anastomosis. Whether every patients requires delayed surgery after an adequately drained abscess is of debate. Recurrent abscesses or enterocutaneous fistualae and/or symptoms of obstruction will indicate surgery.

A retrospective cohort of patients with an intra-abdominal abscess who were radiologically drained and treated with antibiotics followed by anti TNF therapy has been published out of the Mayo clinic. The conservative approach resulted in an equal number of new abscesses than the surgical approach. We, however have not adopted this practice at our institution since the cohort may have been subject to selection bias and we deem surgery to be a necessary step for most of those patients anyway. In addition, anti TNFs may increase morbidity in case intra-abdominal sepsis recurs.

For severely malnourished patients parenteral nutrition is indicated to improve the general condition. Serum albumin and clinical nutrition assessments should guide decision making in those patients. If patients are on long term (> 14 days) systemic steroids, steroids should be tapered to a dose of less than 20 mg prednisone equivalent
Carcinogenesis and the dysplasia-carcinoma sequence differ for IBD-associated and sporadic adenocarcinomas. Early loss of \( P53 \), \( vHL \), 9p tumour suppressor gene and \( c-KRAS \), and late loss of \( APC \) are seen in IBD cancers, the reverse of the usual sequence in sporadic colorectal carcinoma.

As known, the likely risk of adenocarcinoma is increased in UC but based on the location and appearance of the change. It is important to distinguish between flat dysplasia which has a significant risk of progression (particularly for high grade dysplasia) and polypoid dysplasia. The latter can be subdivided into sporadic adenoma (proximal to the colitic zone), adenoma-like dysplastic lesions (occurring in the colitic zone), and atypical dysplasia-associated lesion/mass (DALM). If HGD is found in flat lesions, up to 42% of patients will harbour an adenocarcinoma and colectomy should be recommended. If LGD is found in flat dysplasia, complete polypectomy is possible and if there is no associated adenocarcinoma and if careful biopsy assessment of the surrounding colonic mucosa fails to detect the presence of flat dysplasia. However, if flat dysplasia is detected in biopsies from the adjacent mucosa, if adenocarcinoma is present, or if complete polypectomy with clear margins cannot be achieved the lesion is regarded as an ominous DALM and colectomy is indicated.

Adenoma-like lesions (ALL), regardless their localization, can be endoscopically removed, if complete polypectomy is possible and if there is no associated adenocarcinoma and if careful biopsy assessment of the surrounding colonic mucosa fails to detect the presence of flat dysplasia. If, however again, flat dysplasia is detected in biopsies from the adjacent mucosa, if adenocarcinoma is present, or if complete polypectomy with clear margins cannot be achieved the lesion is regarded as an ominous DALM and colectomy is indicated.

The situation is different in dysplasia detected in Crohn’s colitis. The risks are similar but because of the segmental nature of the inflammation a segmental surgical resection of dysplastic areas can be considered. The benefits of this must be set against a significant risk of metachronous tumours in the retained segment of colon.

In summary, DALMs are a heterogenous population of tumors in which cancer risk is not equal among these various subtypes. Hereby, adenoma-like DALMs have a low risk of malignancies and can be endosopically removed but non-adenoma like DALMs have a high risk of malignancies and are usually indication for colectomy.
Patients with inflammatory bowel disease and a history of cancer: The risk of cancer following exposure to immunosuppression

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Immunomodulators and biologic agents (hereafter referred to jointly as ‘immunosuppression’) are effective in treating IBD and recent evidence supports their introduction earlier in the disease course. An important concern to both patients and physicians considering immunosuppression for the treatment of IBD is the potential associated cancer risk.

Several important clinical questions deserve attention with respect to IBD therapy and cancer. First, does medical therapy for IBD predispose to developing cancer? Second, in an IBD patient with a history of cancer, does IBD therapy impact cancer recurrence? Third, once cancer develops in an IBD patient, is the cancer outcome different? Finally, in an IBD patient with current cancer, does the cancer therapy affect IBD outcomes?

In a recent multicentric study, patients from 7 medical centers were identified based on a diagnosis of IBD and cancer with subsequent exposure to anti-TNFα (“anti-TNFα arm”), thiopurines or methotrexate (“antimetabolite arm”), or without subsequent immunosuppression exposure (“control arm”). 255 patients met inclusion criteria. Prior cancers included 121 solid, 62 gastrointestinal, 55 dermatologic, and 17 hematologic malignancies. During the follow-up period, 75 (29.4%) patients developed incident cancer: 36 (14.1%) a new cancer, 33 (12.9%) a recurrent cancer, and 6 (2.4%) a new and recurrent cancer. Incident cancer rate per 100 person-years for patients exposed to anti-TNFα, anti-metabolites, and controls was 2.6 with 795 person-years of follow up, 14.8 with 122 person-years of follow up, and 8.52 with 422 person-years of follow up, respectively. There was a significant difference in time to subsequent cancer between groups, with patients exposed to anti-TNFα being less likely to develop a new or recurrent cancer compared to controls (p = 0.0110). In this series of IBD patients with a history of cancer, exposure to immunosuppression following a cancer diagnosis was not associated with an increased risk of incident cancer compared to patients who did not receive these agents. Prospective data is needed to confirm these findings.

References:


Axelrad J et al. ECCO 2015.
Management of IBD patients with current immunosuppressive therapy and concurrent infections

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In an era of increasing use of immunomodulator therapy and biologics, opportunistic infections have emerged as a pivotal safety issue in patients with inflammatory bowel disease (IBD). Clinical studies, registries and case reports warn for the increased risk for infections, particularly opportunistic infections. Today’s challenge to the physician is not only to manage IBD, but also to recognize, prevent and treat common and uncommon infections. The 2014 European Crohn’s and Colitis Organisation (ECCO) guidelines on the management and prevention of opportunistic infections in patients with IBD provide clinicians with guidance on the prevention, detection and management of opportunistic infections. Proposals may appear radical, potentially changing current practice, but we believe that the recommendations will help optimize patient outcomes by reducing morbidity and mortality related to opportunistic infections. In this ongoing process, prevention is by far the first and most important step. Prevention of opportunistic infections relies on recognition of risk factors for infection, the use of primary or secondary chemoprophylaxis, careful monitoring (clinical and laboratory work-up) before and during the use of immunomodulators, vaccination and education of the patient. Special recommendations should also be given to patients before and after travel.
Session IV

Immune suppression in IBD: End of an era, or tried and true?
Safety of thiopurines: New data, new concerns?

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Thiopurine-induced liver nodular regenerative hyperplasia (NRH) is attributed to a dose-dependent toxic effect on endothelial cells lining the sinusoids and the terminal hepatic venules. NRH was initially reported in patients treated with 6-thioguanine, but may also complicate treatment with azathioprine. NRH may lead to irreversible portal hypertension, with a possible fatal outcome. Alerts signals are progressive drop in platelet count (below 150,000/mm³), splenomegaly, any element of biological cholestasis and any sign of unexplained portal hypertension. When NRH is suspected, non-invasive tests should be performed: magnetic resonance techniques may demonstrate abnormalities suggestive of NRH or signs of portal hypertension and transient elastography may show abnormal vessel stiffness. Diagnosis can be confirmed by liver biopsy. In cases of highly suspected or proven NRH, or unexplained portal hypertension, thiopurines should be definitely withdrawn.

Thiopurines promote clinical manifestations of chronic viral infections, such as skin, anal and genital warts, shingles and herpes flares. They also promote severe forms of varicella and hemophagocytic lymphohistiocytosis (HLH) that can kill. HLH is mainly related to primary infections (more often than reactivations) with EBV or CMV.

Current use of thiopurines for inflammatory bowel disease is associated with a 1.3 to 1.7 overall relative risk of cancer in adequately powered cohorts after adjustment for confounders. This excess risk is reversible after thiopurine withdrawal. An excess risk of lymphoma is associated with current exposure to thiopurines. Most of the thiopurine-promoted lymphomas are post-transplant-like EBV-associated B-cell lymphomas. These lymphomas may occur in patients seropositive for EBV and are attributed to the cytotoxicity of thiopurines on EBV-specific immune cells that prevent the proliferation of EBV-infected B-lymphocytes. Young (<35-year-old) men seronegative for EBV may also develop fatal early post-mononucleosis lymphomas mimicking those encountered in X-linked lymphoproliferative disease. Finally, non-EBV-related hepatosplenic T-cell lymphomas may occur in patients exposed to thiopurines, alone or in combination with TNFα antagonists. These rare lymphomas are mainly seen in young men after two years of therapy with thiopurines and TNFα antagonists. Thiopurines may promote also, in the long-term, acute myeloid leukemia and severe myelodysplastic syndromes because of proliferation of defective DNA mismatch repair blood cells that escape the cytotoxic effect of drugs. Non-melanoma skin cancers are more frequent than all other cancers and are usually not life-threatening. Current exposure to thiopurines is associated with an increased risk of non-melanoma skin cancers. Whether the excess risk persists in former users of thiopurines is debated. Finally, current exposure to thiopurines is associated with a frank excess risk of urinary tract cancers (renal and bladder cancer) in IBD patients older than 65 years, especially in men.
Efficacy of thiopurines: Can we reconcile new data with clinical experience?

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The efficacy of thiopurines in IBD has been demonstrated over several decades through case series, randomised controlled trials, withdrawal studies and meta-analyses. Whilst their onset of action is slow, making them inappropriate as induction agents in patients with active disease, in people who can tolerate them and in whom they are effective, they often maintain remission very effectively and with low rates of loss of response. However, their role in IBD has been challenged recently for a number of reasons. First, the availability of other effective drugs such as anti-TNF agents and, more recently, vedolizumab, has offered patients and physicians alternative therapeutic options. Second, the safety profile of thiopurines has been scrutinised and new, previously unidentified, risks have emerged. Finally, two recent trials in early Crohn’s disease have called their efficacy into question.

It is important to keep these new data in context. Several issues regarding the trials of thiopurines in early Crohn's disease require that we interpret the results within the limitations of the trials; the findings are not necessarily translatable to all patients. In addition, it is important to note that in nearly all trials of thiopurines, no attempt was made to optimise thiopurine therapy. Clinical practice, case series, meta-analyses and sub-analysis of randomised controlled trials suggest that optimised thiopurine therapy may well be significantly more effective than non-optimised therapy, although it is important to remember that safety data on thiopurine use is also largely derived from non-optimised therapy. Nevertheless, whilst some recent new risks have been identified, the absolute risk of thiopurine use remains very low.

Ultimately, the role of thiopurines in IBD depends on a balance of cost, efficacy and safety. Data supporting their ability to prevent disease complication and progression exists but is largely of a lower quality than that for the biological drugs. In an era in which IBD healthcare expenditure is increasingly driven by drug costs, a better understanding of the pharmacoeconomics of thiopurines is required.
Best practice for the use of immune suppression in IBD: Thiopurines, methotrexate, cyclosporine, tacrolimus

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Thiopurines like azathioprine or 6 mercaptopurine still form the backbone of maintenance therapy in Crohn’s disease and, less so, in ulcerative colitis. Due to their delayed onset of action (3–6 months latency) they should not be used for acute relapse but are of proven efficacy in maintaining remission and avoiding steroid dependency. A more novel indication is the suppression of antibody formation during infliximab treatment and combination treatment to enhance the efficacy of infliximab in both diseases (whereas the combination of thiopurines with adalimumab has not been shown to be superior to monotherapy).

Classical side effects are nausea, vomiting, rarely pancreatitis (about 2%), elevated liver enzymes, very rarely lymphoma and more often leukopenia. The latter cannot be reliably avoided by excluding patients with low activity of thiopurine-methyltransferase (TPMT) and both efficacy and toxicity exhibit only a loose correlation with drug levels. Best practice is to use these drugs if properly indicated, closely monitor the patients for side effects and stop the drugs if no longer required.

Currently, due to many alternatives, methotrexate is rarely indicated in IBD. We sometimes use it in patients with an indication but intolerance for thiopurines. Some practitioners for historical reasons see an indication preferably in those with joint problems but clear evidence is lacking. Efficacy and side effects are probably comparable to thiopurines with the additional problems of hepatic and pulmonary fibrosis as well as an absolute contraindication during pregnancy. Hepatic toxicity is cumulative usually requiring cessation after some years of continuous treatment, particularly following evidence of fibrosis in a liver biopsy.

With the exception of questionable evidence in Crohn’s fistulae both cyclosporine and tacrolimus are probably effective only in ulcerative colitis. Here, cyclosporine has been shown to be as effective as infliximab in acute disease. Some, like us, prefer oral tacrolimus to i.v. cyclosporine but this is just eminence based. It seems rational to prefer it as first line to an anti-TNF because of its short half-life, whereas starting with the anti-TNF precludes calcineurin inhibitors for many weeks because both should not be combined for toxicity reasons. Best practice requires continuous drug level monitoring of both substances and, in particular, screening for renal toxicity even if this is usually reversible. The long term efficacy in maintaining remission is questionable and a matter of debate, it is usually wise to combine it upon achieving remission with a thiopurine and stop it if possible after some months. A novel but sometimes very effective indication is refractory proctitis which responds quite well to local (suppository) tacrolimus.
The forces that are reshaping the delivery of health care through much of the developed world are especially acute within academic centers which carry the responsibility for delivering that care while advancing medical knowledge and ensuring well trained physicians.

Gastroenterology will not be spared any of those forces, and in some ways represents the leading edge of their impact. Though the dynamics vary within the context of the healthcare delivery and scientific enterprise of individual countries, common elements are demands for greater accountability and transparency in how academic medical centers demonstrate their value while assuring broad access to their expertise. In the United States, underlying many forms of change in the payment scheme are the common elements that will increasingly place the risk for the cost of care on providers rather than the payers, be they government or private as has historically been true. At the same time, academic medical centers, with gastroenterology responsible for addressing the burden of digestive diseases, must remain the stem cells for health care integrating all of their missions and providing the foundation of medical advances which will ultimately improve human welfare. What will academic gastroenterology units look like if they are able to effectively respond to these forces? GI divisions and faculty will own new roles including responsibility for system success in caring for patients. They will evolve their training programs to provide the next generation with skills needed to succeed including the discipline of system improvement, team leadership, and others. And there will be new models that will drive the organization of research that are not as conventionally self-contained within the gastroenterology units, but fostering research teams that have hubs and spokes. The vitality of GI divisions will depend on the willingness to seize ownership of the new value proposition of disease management ensuring each patient achieve the best outcome with the most effective use of resources and endeavor within their systems to capture some of that value to invest in their training and research missions. In the course of that evolution, gastroenterology will be well served by rebalancing dependence on existing modalities. If procedural gastroenterology becomes the sole value proposition that will lead to an increasingly narrow view of the field.
Session V

Biologics and pharmacokinetics:
What clinicians need to know
Pharmacokinetics of biologics: A primer

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Monoclonal antibodies (MAbs) against tumor necrosis factor (TNF) exhibit complex pharmacokinetics (PK) and pharmacodynamics (PD, response). Many factors impact anti-TNF-MAb PK, altering MAb clearance and therefore the half-life: albumin, weight (particularly obesity), disease (severity, stage, co-morbidities), and concomitant administration of immunosuppressants (e.g. methotrexate). These factors can alter MAb exposure, impacting on the likelihood of clinical response.

The formation of antidrug antibodies (ADA) is another potential factor that can affect MAb PK. Factors impacting the likelihood of developing ADA are classified as patient-related (concomitant immunosuppressants, prior ADA against other anti-TNF-MAbs) or product-related (structure, manufacturing process, aggregate formation, route of administration, dosing regimen). Repeated episodic exposure can induce ADAs, shortening the effective treatment interval. Avoiding intervals where anti-TNF-MAbs are non-measurable is important for efficacy and may delay onset of ADAs. Thus patients whose factors predispose them to having faster clearance (or short half-life) such as severe disease, low albumin or high body weight may need shorter dose intervals to reduce the likelihood of intermittent exposure.

ADAs can have no effect, or can impact efficacy through MAb binding, inhibiting its function or potentially causing hypersensitivity reactions (PD). ADA can also increase MAb clearance (PK). Because of their impact on MAb clearance, ADAs have been linked to lower serum drug concentrations, potentially negatively impacting clinical response. ADAs have been reported for biologics in most therapeutic areas. ADAs are well documented in clinical studies due to FDA and EMA recommendations regarding testing and impact of immunogenicity.

Lastly, the dose metrics (e.g. mg vs. mg/kg) can cause issues as well. MAbs such as infliximab are dosed on a mg/kg basis, which commonly results in low concentrations in patients with low body weight. Conversely MAbs such as adalimumab are administered as a flat (mg) dose, which can result in low concentrations in high weight patients.

In this presentation the impacts of these factors on MAb concentrations (PK) and potential dose considerations for dose adjustment will be reviewed.
References:


Is there a therapeutic range for anti-TNF antibodies?

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There is a wide variation of serum concentrations of adalimumab (ADM) and trough levels (TL) for infliximab (IFX) early after induction. For ADM it has been reported, in moderate to severe Crohn’s disease and ulcerative colitis, that only < 5% of the variations in serum ADM concentrations can be explained by classic pharmacokinetic (PK) factors such as body weight, BMI and albumin. Taking into account PK factors specific for monoclonal antibodies (mab) like age, sex, CRP, disease activity and concomitant IMM this figure rises to < 12% of the variations being explained. It seems therefore crucial to elucidate other factors determining the variations in serum concentrations early after induction to improve mab therapy. Several potential factors (except for anti-drug antibody (ADA) formation) that have been reported to potentially impact on serum concentration. (see Figure) These include not only the mab itself but also concomitant medications, factors inherent to the patient and factors relating to the underlying disease or disease activity. We postulate that many of these factors interact with each other including with ADA formation. Furthermore there is increasing evidence that early low concentrations of both IFX and ADL drive immunogenicity (i.e. anti drug antibody (ADA) formation). All PK studies with anti-TNF mab have shown that a high early concentration of the mab predicts long term remission and or mucosal healing (except for minority of cases experiencing a primary non response). This is in contrast to patients with early low concentrations of the mab that are clearly at risk for loss of response. One of the factors accounting for low concentrations is clearly the formation of neutralizing ADA. ADA bind the mab hereby neutralizing its effect and leading to enhanced clearance through immune complex formation.

Figure: Factors potentially influencing serum concentration of the mab. Several factors including factors inherent to the patient, the underlying disease, concomitant medications and the mab itself interact to influence serum concentrations (*) Factors where PK impact has been shown in the literature are depicted in bold.
Target serum concentrations

Because of the clear relationship between serum concentrations and long term clinical response most clinicians call for precise cutoffs or target serum concentrations. This is unfortunately an over-simplification. Indeed the receiver operator curves for TL/serum concentration and response are suboptimal. Therefore proposing an ideal cutoff has only modest positive predictive value. It seems that the most important events determining long term disease control occur very early on. We speculate, although this remains to be demonstrated prospectively, that not in all patients, low concentrations can be overcome by dose optimizations. Some investigators even argue that a high serum concentration may be more the consequence of disease control than something that should be targeted. Nevertheless in general in clinical practice we consider an IFX TL between 3–7 µg/ml and an ADM serum concentration between 5–8 µg/ml adequate.

Recommendations for clinical practice

It is important always to have PK factors and immunogenicity in the back of your mind when starting an anti-TNF mab. By incorporating these concepts many problems down the road, including loss of response, infusion reactions, need for steroids and lack of therapeutic options, can be avoided. In addition, we hereby summarize guidelines for anti-TNF mab use in IBD. These incorporate PK and ADA determinations, for different situations during anti-TNF mab treatment. (See Table)

<table>
<thead>
<tr>
<th>Event in the course of mab treatment (*)</th>
<th>Measure Timing</th>
<th>Suggested Action</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary non response?</td>
<td>TL after induction</td>
<td>TL ↑ stop TL ↓ ? escalate</td>
<td>Primary non response confirmed ($) Mostly for ADM in UC</td>
</tr>
<tr>
<td>Early TL monitoring</td>
<td>TL w4–w10</td>
<td>TL ↑ continue TL ↓ use combo</td>
<td>Long term response likely Follow closely (consider early escalation)</td>
</tr>
<tr>
<td>Before stepping down to monotherapy</td>
<td>TL 6m – 1y</td>
<td>TL ↑ step down TL ↓ continue</td>
<td>Only consider stepping down when in 'deep remission'</td>
</tr>
<tr>
<td>Late monitoring (asymptomatic patient)</td>
<td>TL/ADA</td>
<td>TL ↑ continue (or consider increasing dosing interval) TL ↓ continue (do not step down to monotherapy) TL 0 ADA ↓ dose optimize (**) and recheck ADA ADA high (or persistent ADA + after dose optimization) discontinue + switch to 2nd line within class (upon flare)</td>
<td></td>
</tr>
<tr>
<td>Loss of (complete) response: ($)</td>
<td>TL /(ADA)</td>
<td>TL ↑ : switch to other class TL ↓ or 0 ADA 0 : dose optimize(****) ADA + : switch to 2nd line within class</td>
<td></td>
</tr>
<tr>
<td>Dose optimization(****)</td>
<td>TL before + 4–8w after</td>
<td>If TL not higher after: failed dose escalation</td>
<td>Post intervention TL high(er) is informative for success of dose escalation</td>
</tr>
<tr>
<td>Suspected infusion reaction (IR) or delayed hypersensitivity</td>
<td>TL/ADA</td>
<td>TL ↑ TL 0 ADA 0/+ TL 0 ADA high</td>
<td>IR due to ADA unlikely seek other cause Use combo proceed cautious Switch to other agent</td>
</tr>
<tr>
<td>Retreatment (after long drug holiday)</td>
<td>TL/(ADA) w2–w6 after restarting</td>
<td>TL ↑ TL ↓ ADA 0/TL 0 ADA high</td>
<td>Start using combination therapy Long term response likely Keep combo, watch closely Discontinue</td>
</tr>
</tbody>
</table>
Biosimilars: Doppelgänger or imposter?

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Biologics have been used in IBD from 1999, and now are key in the protocols of treatment of ulcerative colitis (UC) and Crohn’s disease (CD). To date several monoclonal antibodies are the only one type of biologics used in inflammatory bowel disease (IBD), the patent protection of the first one, infliximab (REMICADE®), expiring in most European countries in 2014–2015. One biosimilar of infliximab under two different trade names (Inflectra®, Remsima®) was approved recently by EMA and is reaching market in different countries by now. This adds new complexity to clinician’s decision making. Recently, a poll done by ECCO has demonstrated considerable heterogeneity in the knowledge of European gastroenterologists about biosimilars. EMA has considered that “high similarity” in preclinical studies together with clinical data from two trials in ankylosing spondylitis and rheumatoid arthritis, warrants the “extrapolation” for all approved indications for original infliximab (Remicade®), specifically CD and UC. In spite of EMA clearance, a number of issues such of extrapolation, interchangeability, and substitution remain controversial for many clinicians. Some have expressed doubts even regarding the quality of the new products, but EMA regulations are very strict and quality is fully warranted. Biosimilars are not designed to be better drugs, but can be cheaper, and may facilitate access to new treatments in many populations. Market issues at the national level will most likely determine the way biosimilars change the field of IBD treatment.

CONFLICTS OF INTEREST

Session VI

New treatment strategies
Post-surgical prophylaxis in Crohn’s disease: Which patients, which agents?

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Crohn's disease (CD) evolution is characterized by increasing proportions of patients developing complications such as strictures, abscesses and fistulas that require surgical management. Over 70% of patients will require bowel resection surgery during the course of their disease, and half of these patients will require a second surgery. After resection of an diseased intestinal segment, CD recurrence concerns up to 60% of patients already within a year post surgery. The mucosa just above the site of the intestinal anastomosis is at particularly high risk of relapse. Prophylactic medical therapy to prevent recurrence has been shown effective with a variety of medications, but the recurrence rate remains high, demanding that a better risk stratification of patients is achieved. Recognized risk factors for postsurgical CD recurrence include young age at diagnosis and at surgery, smoking, need for repeated surgeries, and penetrating disease. These patients require full dose immunosuppressive or anti-TNF therapy, which should be initiated already in the immediate post-operative period, to prevent the onset of an inflammatory activity in the bowel. Systematic follow-up by endoscopy to monitor treatment benefit should also be part of the management, as endoscopic recurrence heralds clinical relapse in these patients. The role of noninvasive markers of mucosal inflammation such as stool calprotectine levels show promise to complete this monitoring. Although the efficacy of mesalazine and imidazole antibiotics has been long been recognized, more aggressive approaches such as thiopurines and anti-TNF antibodies have shown higher efficacies in direct comparison trials. The potential place of anti-homing agents is not yet defined, but these agents should in principle be of interest for this prophylactic indication, due to their mode of action and interesting side effect profile. The current recommendations are based on a step-up approach that includes first immunosuppressors and/or imidazole antibiotics, followed by an anti-TNF agent, such as infliximab and adalimumab, both already tested in randomized trials in this indication. When endoscopic recurrence is identified during follow-up, upscaling to anti-TNF or dose escalation is advocated. Recently the use of trough levels for the optimalization of anti-TNF therapy has also been shown helpful in this setting.
Treat to target: Which targets, and why does it matter?

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We have seen remarkable advancement in the treatment of ulcerative colitis and Crohn’s disease over the past several decades as our therapeutic armamentarium has evolved to include immune modulating agents, non-systemic steroids and biologics. However, despite these advances that include short-term improvements in hospitalization and surgery rates, the current positioning of therapies and end-points based on clinical outcomes have not influenced the long-term natural history of IBD.

To date, therapeutic end-points have been based, primarily, on symptoms (e.g. Mayo score for UC, CDAI or HBI for Crohn’s disease) yet it is now well-clarified that there is a poor correlation between patient-reported outcomes and biological evidence of disease determined by endoscopy, histology or biomarkers (e.g. CRP or calprotectin).

In the setting of other chronic disorders such as diabetes, hypertension and rheumatoid arthritis; defined treatment targets (i.e. HgbA1c, diastolic blood pressure < 90, and ‘remission’) have been demonstrated to impact on long-term outcomes and disease-related complications.

More recent clinical trials that have incorporated biological parameters such as confirmation of endoscopic disease and utilized endoscopy as an end-point have demonstrated both a reduction in placebo responses, but also evidence of reduced hospitalizations and surgeries (over 12 months). In addition, improved therapies and surveillance colonoscopies for ulcerative colitis have begun to reduce the risk of colon cancer.

As IBD remain chronic diseases, treating to target is an iterative process through induction and maintenance therapy. To optimize outcomes and change the natural course of disease it will be necessary to achieve resolution (or improvement) in the inflammatory indicators of disease and to continually re-assess evidence of endoscopic (and eventually histologic) healing and adjust therapies accordingly to maintain healing. At present, endoscopy may be the gold-standard although efforts are underway to identify less invasive biomarkers as surrogates for endoscopic/histologic disease activity.
Intervening in early IBD: Missed opportunity or over-treatment?

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Crohn’s disease is a chronic, progressive and disabling condition. New therapeutic goals have emerged in Crohn’s disease such as the need to look beyond symptoms by achieving mucosal healing that is known to be associated with better outcomes. Anti-TNF (Tumor Necrosis Factor) therapy is the most potent drug class to induce and maintain mucosal healing in Crohn’s disease. Recent evidence indicates that the efficacy profile of thiopurines has been overestimated while the increased risk of malignancies (lymphoma, non-melanoma skin cancers, myeloid disorders) has been underestimated. Methotrexate is well-tolerated, but its potential for disease modification is unknown. Achieving mucosal healing in patients with early Crohn’s disease might be the best way to change disease course and patients' life. In 2015, anti-TNF treatment should be the first-line therapy in patients with Crohn’s disease who suffer from severe and/or complicated disease and in those with poor prognostic factors. In the remaining patients, a rapid step-up approach based on a tight monitoring is recommended. In ulcerative colitis, disease duration does not influence the efficacy of biologics and a rapid-step up approach is recommended for all patients.
Are we ready to withdraw therapies in IBD: Which patients, which agents?

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The global benefit-risk ratio of long term immunosuppressant or anti-TNF treatments appears favourable. Nevertheless reasons exist to contemplate treatment cessation: patients’ preference and side-effects, infection in high risk patients, risk of cancers, pregnancy and cost.

For immunosuppressants, particularly purine analogues, the main risk over long term seems to be cancers, including lymphomas, non melanoma skin cancers and urinary tract cancers. Those become significant after 50–60 years of age. The long term safety profile of methotrexate is probably better. Recent long term data with anti-TNF appear reassuring apart from the persisting risk of severe and opportunistic infections, particularly in older people and the risk of melanoma. The risk of relapse after withdrawal of immunosuppressant (when used as monotherapy) is around 50% over 3–5 years both in Crohn and ulcerative colitis. The risk of relapse after anti-TNF withdrawal, usually assessed while an immunosuppressant co-treatment was continued, was around 50% over 1–2 years. In Crohn’s disease a state of deep remission characterized not only by clinical remission but also tissue healing and normalisation of biomarkers was associated with a lower risk of relapse both after immunosuppressant and anti-TNF withdrawal. In Ulcerative colitis, no predictor could be found. Furthermore a substantial proportion of the relapsers (20%) had to undergo colectomy. Retreatment with the same drug was usually effective and well tolerated. Biomarkers could also predict short term relapse risk and could thus be used to resume therapy before the occurrence of the relapse. In conclusion, stopping therapy in ulcerative colitis, due to the risk of severe flare and colectomy is probably risky, while in Crohn’s disease, the existence of predictors of the risk of relapse, the ability to monitor the patients and the good tolerance and efficacy of retreatment should encourage us to explore further the concept of cycles of treatment.
Special Lecture

Tailoring treatment to the individual patient – Will IBD medicine be personalized?

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The complexity of IBD pathogenesis and the heterogeneity of patients’ clinical manifestations, response to therapy and outcome are well recognized. These features imply that each IBD patient may have a unique set of conditioning factors causing Crohn’s disease (CD) or ulcerative colitis (UC), including particular environmental exposures, a distinct genetic make up, a unique gut microbiota and specific inflammatory pathways. If so, when these factors come together to trigger and sustain IBD the underlying mechanisms are likely to be highly individualized. Therefore, it should come as no surprise the common clinical observation that responses to anti-inflammatory therapies such as immunosuppressive drugs, anti-cytokines or anti-adhesion molecules, only benefit a portion of patients rather than all those suffering with CD or UC. To improve this situation it is obvious that there is need for a better classification of patients not simply at the clinical level, which is intrinsically flawed, but at a far more comprehensive level. To do so it will be necessary to refine the four major components of IBD pathogenesis in each subject carrying a diagnosis of CD or UC. The environmental factors to which the patient has been exposed from conception/birth to the time of diagnosis must be listed and the associated epigenetic modifications identified. The genetic variants carried by the patient must be detected by whole genome and/or whole exome sequencing to identify individual arrays of variations linked to specific biological pathways. The gut microbiota must be analyzed not only at the 16S level, but also at the more relevant metatranscriptomic, metagenomic and metaproteomic levels to gain an understanding not only of the composition but mainly the function of intestinal microbes. Complete “omics” analysis of each patient should also be performed, including tissue and blood transcriptomics, metabolomics and proteomics to gain an overview of the body composition, function and response to stress. Finally, the dominant pro-inflammatory and immunoregulatory mediators and pathways responsible for inflammatory damage must be characterized to pinpoint the specific molecules that are actually mediating tissue injury. Once all this massive amount of information is collected – ideally in a prospective sequential fashion – high throughput bioinformatic analyses must be carried out to functionally integrate the results and identify the key “hubs” (nodes or controllers) of the inflammatory network that will then become focused targets for therapeutic intervention. Adopting this approach drugs and lifestyle modifications that can modulate those targets can be adopted while avoiding those do not affect these pathogenic components. This way a tailored treatment of IBD can be offered to each patient with the expectation of a complete or nearly complete blockade of the disease cause and mechanisms, and perhaps even a change in the natural history of the disease. This is the essence of “personalized medicine”, which is increasingly recognized as the ideal approach to achieve a complete cure and avoid recurrences not only in IBD, but many other chronic
complex disorders. This scenario is out of reach at the moment for logistic and financial reasons, but it is fully realistic and will become a certainty within a decade or two once comprehensive biobanking will be routinely used, and the cost of high throughput technologies will be low enough for daily clinical applications.
Session VII

Novel therapies for IBD
Management of mild to moderate UC

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Managing mild to moderate UC on the first view appears to be a simple task. However real life often proofs the opposite and creates a challenging situation. In theory mild to moderate disease should be sufficiently treated by mesalamine or alternatively by a probiotic. Insufficient treatment comprises the danger of leading to a flare and hence and exacerbation of the entire disease with risk of progressing to severe disease. What are considerations with regard to patient management in this situation? Certainly, disease distribution is the critical information, since it is allowing for planning the optimal route of administration, namely local versus systemic treatment. Novel pharmacological strategies might allow for reaching high local concentration even at the left side of the colon or alternatively administer locally active budesonide throughout the entire colon frame, thus avoiding systemic side effects. Therapy planning has to involve the patient to identify how this can be included in daily life. Including the patient implies that depending on the condition, disease activity and even life quality the individual therapy requires timely adaption. A recent study by Pedersen an colleagues provides evidence that this strategy can be followed and leads to an overall better outcome. A last thought, besides the patient not taking the appropriate dose or lacking adherence to therapy, should consider that a worsening of disease could be due to infectious complications including Clostridium difficile or CMV colitis. If all considerations fail within a reasonable time frame, therapy should be escalated. Patients in this situation often hesitate in accepting the need of immunosuppression. Future options, potentially including phosphatidylcholin, might bridge the gap in between mesalamine, probiotics and immunosuppressive strategies.
Targeting leukocyte trafficking in IBD: What is the clinical evidence?

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An emerging approach to the treatment of inflammatory diseases is inhibition of leukocytes migration into inflamed tissue by blocking cellular adhesion molecules. Integrins are heterodimeric proteins that regulate cellular movement. The $\alpha_4\beta_7$ integrin, that is primarily involved in the recruitment leukocytes to the gut is present on the surface of a small population of circulating T-lymphocytes. The major ligand for $\alpha_4\beta_7$, MAdCAM is selectively expressed on the endothelium of the intestinal vasculature and is present in increased concentration in inflamed tissue. In addition lymphocytes also express Alpha 4 beta 1 receptors that interact with vascular cellular adhesion molecule 1 [VCAM-1]). This latter molecule is widely expressed on vascular endothelium in most tissues. Therefore interference with this interaction theoretically could result in relatively non specific interference with lymphocyte trafficking.

Several drugs that exploit these mechanisms have shown efficacy in randomized controlled trials. In Crohn’s disease, natalizumab, a CDR-grafted humanized antibody directed towards the Alpha monomer has been shown to be effective for both induction and maintenance of remission.

Two recent controlled trials evaluated natalizumab as induction and maintenance therapy in patients with active Crohn’s disease. In ENACT I, 905 patients were randomly assigned to receive 300 mg of natalizumab or placebo at weeks 0, 4, and 8. The primary outcome was response, defined by a decrease in the Crohn’s Disease Activity Index (CDAI) score of at least 70 points, at week 10. In ENACT II, 339 patients who had responded to natalizumab in the first trial received 300 mg of natalizumab or placebo every four weeks through week 56.

In ENACT 1, the natalizumab and placebo groups had similar rates of response (56 percent and 49 percent, respectively; $p = 0.05$) and remission (37 percent and 30 percent, respectively; $p = 0.12$) at 10 weeks. In ENACT II continued treatment with natalizumab resulted in response rates of (61 percent vs. 28 percent, $p < 0.001$) and remission rates (44 percent vs. 26 percent, $p = 0.003$) through week 36 than did switching to placebo.

In ulcerative colitis, a Phase II clinical trial evaluated two doses of a humanized antibody, MLN-02 directed to the $\alpha_4\beta_7$ integrin against placebo. 181 patients with active ulcerative colitis who had failed 5-ASA or no treatment were evaluated. Six weeks after the administration of two infusions of drug or placebo, approximately one-third of patients who received the antibody were in remission as compared to 14 percent of those who receive placebo ($p = 0.03$). Parallel improvements in endoscopy, histopathology and health-related quality of life were also demonstrated. Therapy was well-tolerated and there was no evidence of opportunistic infection.

Two randomized controlled trials have also evaluated the use of anti-sense to VCAM-1 in patients with ulcerative colitis with favourable results.
Recently the risk of progressive multifocal leukoencephalopathy (PML) has been an important limitation to the use of natalizumab. This uncommon, progressive neurological disorder is frequently seen in patients who are severely immune-compromised (HIV, malignancy). The disease is related to reactivation of a Papova virus (JCV) that is latent in approximately 60% of the population. This disturbing occurrence has resulted in very limited use of natalizumab for the treatment of Crohn’s disease.

Notwithstanding the seriousness of PML, it is highly likely that current toxicity concerns can be dealt with through additional research and that more selective adhesion molecule inhibitors will ultimately become valuable agents for the treatment of IBD. However, existing data from both human and animal studies indicate that the development of PML following treatment with the more selective agents is unlikely. In support of this notion data from recent Phase III trials of vedolizumab in ulcerative colitis and Crohn’s disease have confirmed this to be an effective molecule that selectively reduces gut inflammation. Multiple other agents that exploit the concept of selective inhibition of cell trafficking that are currently under development will also be discussed.

References:


Targeting the microbiome in IBD with antibiotics, probiotics and fecal microbiota therapy: State of the art in 2015

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Patients with IBD exhibit an abnormal composition of their fecal and mucosa-associated microbiota (dysbiosis) and often polymorphisms in genes involved in the host perception and response to microorganisms in the intestine (genetic susceptibility). Dysbiotic changes consist in differences in the proportions of microorganisms (especially lower counts of firmicutes), higher concentrations of microorganisms (microbial load), higher instability and lower microbial gene richness, and sometimes the presence of pathobionts such as some *Escherichia coli*, mycobacteria, *Fusobacterium avium*. It is thus important to determine whether therapeutic interventions targeting the microbiota may alter the course of IBD. Those include antibiotics, probiotics and fecal transfer. Overall, the evidence for their efficacy is limited so that those approaches are not included in guidelines however some data judged as preliminary and the rational are strong enough to invest in research and expect clinically relevant discoveries. In this presentation we will update knowledge in this field and discuss the research strategy in this field.
The IL-12/23/STAT axis as a therapeutic target in IBD: Mechanisms and evidence in man

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Interleukin (IL)-12 and IL-23, two heterodimeric cytokines sharing the common subunit p40, are over-produced by antigen-presenting cells infiltrating the inflamed gut of patients with Inflammatory Bowel Disease (IBD) and supposed to play a major role in promoting and/or sustaining the pro-inflammatory cytokine response in these disorders. In particular, circumstantial evidence indicates that IL-12 targets mostly T cells and innate lymphoid cells and through activation of Stat4 promotes T helper (Th)1 cell polarization as well as IFN-γ and IL-21 production, while IL-23 triggers Stat3 in both immune and non-immune cells thus amplifying Th17 cell programs. Genome wide association studies have shown that variants in the IL-23 receptor gene confer genetic risk for the development of IBD. These observations and the demonstration that IL-12 and IL-23 drive detrimental immune responses in animal models of colitis have paved the way for the development of drugs inhibiting these cytokines. Two monoclonal antibodies (ustekinumab and briakinumab) targeting p40 have already been used for the treatment of patients with active Crohn’s disease and shown to be effective in patients resistant or intolerant to TNF blockers. Moreover, blockade of IL-12/IL-23 appears to be effective in treating psoriasis-like lesions developing in IBD patients following treatment with anti-TNF. Although, it remains unclear whether the therapeutic effect of these drugs is due to neutralization of either IL-12 or IL-23 and the reason why such a treatment is more effective in patients who were previously treated with anti-TNF, these studies show that blockade of IL-12/IL-23 is safe as no drug-related serious adverse event was documented. Phase III clinical trials are currently ongoing to further evaluate the efficacy and safety of ustekinumab in CD patients, while the effectiveness of such antibodies in UC remains to be ascertained.

In conclusion, data emerging from human studies support the pathogenic role of IL-12/IL-23 in IBD and suggest that inhibitors of IL-12/IL-23 may enter into the therapeutic armamentarium of these diseases.
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An usual presentation of Crohn’s disease in a patient with familial Mediterranean fever (FMF)

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Introduction: Chronic abdominal pain sometimes constitute a particularly challenging clinical problem, if the patient has two diseases in which abdominal pain is the dominant feature in both them [1]. At this point, not only is the diagnosis of another chronic abdominal pain a frequently daunting task, but also the treatment of both diseases is always a big concern. Although familial Mediterranean fever (FMF) disease is more frequent in Turkey than other countries, the association of FMF and Crohn’s disease (CD) is very rare and may lead a challenge for diagnosis of abdominal pain and treatment [1, 2, 3, 4]. Herein, we report a young man with FMF disease presented with severe and intolerable abdominal pain relieved only by narcotic analgesics and eventually diagnosed with CD that has been successfully treated with anti-TNF (tumor necrosis factor) due to steroid refractory. Also we discuss the tools of our diagnosis, and the therapeutic of difficulties in our management.

Case: A 16-year-old young man with previous history of FMF presented with severe abdominal pain, vomiting, diarrhea, fever, anemia over a period of three weeks. The patient had been diagnosed with FMF since his adolescence, and prescribed with regularly the colchicine therapy. Genetic verification turn out that he was homozygous for M680I mutation. Laboratory tests showed predominantly a significantly higher C-reactive protein (CRP) level: 265 ng/dl (normal range [NR]: 0–8 ng/dl), hypoalbuminemia (albumin: 2.3 g/dl, NR: 3.5–6 mg/dl) and anemia (hb: 10.5 g/dl, NR: 12–15 g/dl). Severe and intolerable abdominal pain was the most important problem for him and did not respond any painkillers. He rated to his abdominal pain at 10 on a scale of 0 to 10 (with 10 indicating the most severe pain). At first, colonoscopy was performed for etiology of prolonged diarrhea and abdominal pain. Colonoscopy showed multiple linear and aphthous ulcers in terminal ileum, thought not specific, but was first suggested to CD. Pathological examination of biopsy specimens had no characteristic features of CD or any diseases. A computed tomography of the abdomen revealed asymmetric wall thickness in almost all of the small bowel especially in the proximal part of duodenum and jejunum, and showed a special finding as “comb sign” that refers to the hypervascular appearance of dilated vasa recta in mesenteric border of an acute inflamed bowel (Figure 1). To us and literature, this “comb sign” was strongly suggestive clue for CD. Upper endoscopic examination demonstrated the multiple deep ulcers (more than 25 ulcers observed) shaped as geographic type and located longitudinally into the mesenteric side of 2nd and 3rd part of duodenum (Figure 2 a,b). Duodenum biopsy specimen showed no specific findings. Consequently, we diagnosed the CD with clinical, laboratory, endoscopic and supporting radiological findings. Initially, corticosteroid (methylprednisolone 60 mg/day) therapy was started by the intravenous route, but no clinical and laboratory benefit was observed in 10 days period. Then abdominal pain worsened, and transdermal fentanyl 50–100 mg/48 h was initialized at last. Fentanyl was continued for pain relief until the resolution of disease.
Avoid from risk of bowel perforation related deep ulcers, anti-TNF treatment (infliximab 5 mg/kg IV 0, 2, 6 weeks) was started after the quick tuberculosis screening with tuberculin purified protein derivative-PPD (4 mm) and QuantiFERON test (negative). Then, abdominal pain was getting better within the following days, and elevated CRP level dropped to normal range at 12th day. After the second infusion of Infliximab, upper endoscopic examination demonstrated the significant improvement in deep ulcers. At 31th day of hospitalization, he was discharged without complaint.

**Discussion:** FMF is an autosomal recessive autoinflammatory disorder characterised by episodic abdominal pain, febrile attacks and serositis. Colchicine is the most effective treatment for prophylaxis of FMF attacks and related complications as well. Abdominal pain is the major component of FMF disease, but severe and intolerable pain requiring narcotic analgesics and extending up to 3 weeks is usually not related exactly to FMF [4, 5]. In this situation, physicians should be aware of the another disease or reason may coexistence with FMF. But many disorders (organic or functional) can cause chronic abdominal pain and show similar clinical picture causing a challenge with FMF. Therefore, it is necessary a careful consideration, clinical interrogation and appropriate diagnostic tests supported by advanced radiological and endoscopic methods for accurate diagnosis [6, 7]. In this context, CD and FMF share similar symptoms and signs such as abdominal pain, bowel ulceration, so the diagnosis of CD in patient with FMF is not easy if there is no CD related specific feature [7]. Moreover, non steroidal anti-inflammatory drugs commonly use excessively for pain relief, thus multiple ulcers may be observed in the all intestinal lumens [8]. Tuberculosis and amyloidosis can also present with the same ulcers and clinic picture mimicking CD [8, 9, 10]. Although it is claimed that the association of CD or inflammatory bowel disease and FMF is common and onset late age, there are only few published case reports in contrast to this claim [3, 11, 12]. In our case, another organic pathology was considered due to severe abdominal pain requiring narcotic analgesic, anemia, prolonged diarrhea, and serious high CRP level. So the diagnosis of CD was made with supporting clinical, endoscopic signs and radiological methods as “multiple deep linear ulces”, “comb sign”, “wall thickening with asymmetric distribution” and with exclusion of diseases such as tuberculosis with QuantiFERON test [6]. Abdominal pain in the course of CD could not be expected to be severe and intolerable requiring narcotic analgesics unless obstruction or perforation [13]. We think that the cause of severe and prolonged abdominal pain in our patient is probably related multiple deep ulcer located especially in proximal part of duodenum having intense nerve roots provided by celiac plexus and excessive inflammation presenting with serious elevated CRP level [13]. CD with duodenal ulcers is considered a very rare entity, and only five case have been reported, and all of them have been treated with anti-TNF due to refractory to all immunosuppressive drugs [13]. We had to use fentanyl, because the abdominal pain did not respond any painkillers available in Turkey. Fentanyl is a narcotic analgesic and commonly use for cancer-related and postoperative pain, but there is limited data on the use of fentanyl as painkiller for CD related abdominal pain [14]. To our knowledge, we say this case the first report the use of fentanyl for relief in Crohn’s disease related abdominal pain. Fentanyl is useful and safe drug for intolerable abdominal pain, if the diagnostic process extend unwillingly for a long time.
In this patient, intestinal tuberculosis was the most important issue that should be considered in the differential diagnosis of severe abdominal pain and multiple ulcers, because tuberculosis commonly seen in Turkey and immunosuppressive drugs could deteriorate the clinic condition if the patient had tuberculosis [9]. A physician should not be consider to use immunosuppressive drugs for CD until tuberculosis rules out exactly in regions where tuberculosis is endemic or semi-endemic like Turkey [10]. When there is no specific histopathological or clinical findings for CD or tuberculosis, making the differential diagnosis with sophisticated radiological methods is more appropriate for clinician [6]. Although many signs have been shown for differential diagnosis in magnetic resonance imaging and computed tomography, we use “comb sign” due to highly suggestive and related early and active CD [15]. While this sign is not specific for CD, the presence of comb sign help in differentiating CD from tuberculosis and neoplasms such as lymphoma or metastases in case of no powerful evidence supporting these diseases [16]. It is reported that “comb sign” is useful marker in both diagnosis and treatment and as well as in predicting CD activity [17].

In a few published cases, it is reported that the CD clinic course and treatment in patients with FMF has more aggressive and do not respond to intensive medical therapy including intravenous corticosteroid, azathioprine and cyclosporine [11, 13]. Similarly, the clinic of FMF in patient with CD is shown more severe like frequent disease attacks, secondary amyloidosis and subsequent renal failure [1]. Postulated mechanism is speculated that FMF and CD share common genetic and inflammatory pathway, so the one disease triggers the other and the more severe clinic is observed. The reasons for failure of that medical treatment are not fully understood [11]. For solving the treatment problem, anti-TNF drugs commonly use and become frequently successful. The use of anti-TNF agent is commonly needed due to failure of all immunosuppressive drugs including corticosteroids in all published cases [11, 13]. Similarly in our patient, the corticosteroid failed, so the success of treatment was achieved with the anti-TNF treatment with a quick decision and using literature knowledge. The age of onset of CD was reported significantly higher in FMF patients than in patients of Crohn’s disease-only. Most of patient were over the three decades age except patients with 8-month and 11 years [12]. Our case was different in terms of the presence of a very young age unlike the previous reports.

In conclusion, a physician should be aware of the coexistence disease with FMF in case of abnormal findings suspecting another organic disease like CD. This should be keep in mind that the treatment of two disease is more difficult than one, as is diagnosis. For the association of FMF and CD is very rare, the assistance should be taken from published literature in management of differential diagnosis and treatment.

The authors declare that they have no conflict of interest.
References:


Figure 1: Abdominal CT image demonstrated multiple linear hypervascularity of the distal arterial arcades (vasa recta) that characteristic for “Comb sign” (green arrow) and asymmetric wall thickening (blue arrow) in duodenum and other part of small bowel suggesting intense inflammatory activity supporting Crohn's disease

Figure 2 a–b: Endoscopic view of second (a) and third (b) part of duodenum. Prominent and multiple (more than 25 ulcers observed) deep ulcers is shown in mesenteric side of duodenum lumen
Incidence of serious infections and tuberculosis among patients with inflammatory bowel disease receiving anti-tumor necrosis factor: A Tunisian monocenter experience

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Introduction: Anti-TNF medications have shown their efficacy in the management of IBD. However, these agents have increased risk of active tuberculosis (TB) and other serious infections.

Aims: To evaluate the incidence of serious infections and tuberculosis in IBD patients receiving anti-TNF therapy from 2006 to 2013.

Methods: Serious infections (defined as life threatening infections, requiring hospitalization and/or intravenous antibiotics or leading to significant disability and/or incapacity) and TB cases in patients receiving or within 3 months following anti-TNF therapy were retrospectively analysed. Patients demographics, IBD medications, duration of anti-TNF therapy and infection details were collected.

Results: A total of 75 patients treated with infliximab (n = 65) or adalimumab (n = 10) were enrolled. Of these, 62 (82.7%) had Crohn’s disease and 13 (17.3%) had ulcerative colitis. 54 patients (72%) were taking additionnal immunosuppressive medications.

Before anti-TNF therapy, all patients had a TB screening with chest X-ray, TST and IGRA (Interferon-Y release assay: Quantiferon® in our center). No patients had active TB and 2 patients had latent tuberculosis diagnosed by a positive TST and so received an anti-TB chemoprophilaxis regimen. However, 21 other patients received anti-TB chemoprophylaxis regimen because of denutrition.

13 cases (17%) of serious infections occurred of whom 10 were under combotherapy. The most common site of serious infection was the intra-abdominal collections (n = 4). 8 occurred in patients receiving anti-TNF therapy for less than 6 months, including, 3 cases of intra-abdominal collection, 2 cases of tuberculosis of whom one patient already received chemoprophylaxis, 1 case of E. coli bacteremia, one case of scrotal abscess and one case of zona (reactivation of VZV). The other five infections occurred after 6 months (mean 18.6 months ± 12 months) and included 1 case of CMV colitis, 1 case of upper urinary tract infection, 1 case of abdominal collection, 1 case of Staphylococcus aureus bacteremia and 1 lower tract respiratory infection. All these infections resolved with treatment.

Conclusion: This study shows that serious infections are common in patients with anti-TNF therapy. The most frequent site was intra-abdomen. TB reactivation is the second most frequent complication that was seen even after chemoprophylaxis. These data provide a need for vigilance in patients on multiple immunosuppressive medications.
Frequency and clinicopathological features of loss of response to infliximab in Crohn’s disease

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Introduction: Although Infliximab (IFX) has proven to be an effective medication for patients with Crohn’s disease (CD), loss of response (LOR) to the 5 mg/kg dose is a common occurrence. LOR to IFX decrease quality of life of a patient undergoing treatment.

Methods: This study investigated clinicopathological features associated with the LOR to IFX. Seventy-five CD patients achieved remission after the induction therapy and received regular maintenance therapy consecutively in our institute. None of the patients had received previous biological therapy. Our study protocol was designed to include patients who maintained response to IFX (G-I), and patients who had lost response to IFX (G-II). We evaluated clinical outcome and long term outcome of LOR to IFX in comparison with patients maintained response to IFX.

Results: Loss of response occurred in 15 of the 75 patients (20%). We enrolled 60 patients in G-I, 15 patients of LOR in G-II. Median disease duration until first IFX was 5.3 years in G-I, 10.2 years in G-II (p < 0.05), average age was 32.1 years in G-I, 29.2 years in G-II, the ratio of males to females was 35:25 in G-I, 9:6 in G-II (n.s.). In disease location, colonic type: ileo-colonic type: ileal type was 15:23:22 in G-I, 1:4:10 in G-II (p < 0.05). In concomitant therapy, azathioprine was administered in 22% in G-I, 68% in G-II (p < 0.05). In previous therapy, surgery had been performed in 27% in G-I, 38% in G-II (p < 0.05). Median duration until LOR is 230.9 days in G-II. After drug response is lost, we escalated the dose of Infliximab to 10 mg/kg in 8 patients, reduced the interval of administration in 3 patients, switched to adalimumab in 4 patients. After we escalated the dose or reduced interval, mean level of C reactive protein decreased 2.6 mg/dl to 1.6 mg/dl in G-II. Recent level of C reactive protein was 0.22 mg/dl in G-I, 0.54 mg/dl in G-II.

Discussion/Conclusion: During the observation period, LOR increase risk of surgery. In Tunisia, we are not able to measure serum trough levels of IFX and ATIs in common. Our results showed that remission after induction, short disease duration until the introduction of IFX and colonic type CD was protective against loss of response.
Insulin-like growth factor mRNA binding protein 3 and CD163-positive macrophages – Markers of development in ulcerative colitis and colorectal cancer pathology

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Introduction: Ulcerative colitis (UC) is a prevalent inflammatory bowel disease of the colon and is related with other lesions as a colorectal cancer (CRC). Many molecular and cell markers play a major role in development of these diseases. Different precanceroses and some tumors have been investigated for insulin-like growth factor II mRNA binding protein 3 (IMP3) expression, which was exclusively found in cells and correlated with disease aggressiveness and progression.

Methods: The immunohistochemical expression of IMP3 in lesions cells and density of CD163-positive macrophages was evaluated in 26 patients (4 UCs, 10 CRCs and 8 with non-specific colitis). The results were compared with clinical and pathological parameters of investigated patients.

Results: The patients with UC showed irregular expression of IMP3, but this expression was stronger in CRC specimens and not found in non-specific colitis patient specimens (NSC) ($\chi^2 = 6.88, p = 0.002$). After analysis, we found that the number of CD163+macrophages in UC patients were more as compared CRC and NSC ($\chi^2 = 10.1, p = 0.04$). Finally, we found that the more intense expression of IMP3 in CRC specimens correlated with low number of CD163+ macrophages in tumor ($\chi^2 = 12.2, p = 0.032$) and in tumor border in these patients.

Discussion/Conclusion: The expression IMP3 and low density of CD163-positive macrophages support a role for these two markers as a diagnostic and/or prognostic biomarker in ulcerative colitis and colorectal cancer.
Pre-treatment evaluation for infectious disease in IBD patients – Who’s to vaccinate?

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Introduction: The most recent ECCO guidelines have emphasized the need for a more accurate screening in IBD patients. The aim of this study was to investigate the prevalence of hepatitis B and C, latent tuberculosis, and the immunization status for mononucleosis, varicella and cytomegalovirus in a cohort of IBD outpatients.

Methods: Data on hepatitis B (HBsAg, anti-HBs, anti-HBc) and C (anti-HCV), tuberculosis (TBC; Mantoux skin test or Quantiferon Gold), mononucleosis (anti-VCA IgG), varicella (anti-VZV IgG), and cytomegalovirus (anti-CMV IgG) were registered together with the following data: age, gender, disease, duration of disease. Vaccinated patients against hepatitis B were excluded from analysis.

Results: Data from 270 patients were analysed (ulcerative colitis [UC] 119, Crohn’s disease [CD] 151; mean age 41 years ± 15, males 152); data on screening positivity are given in table 1 by dividing patients in 2 age groups, less than or equal to 35 years and older than 35 years.

<table>
<thead>
<tr>
<th></th>
<th>Latent TBC (n = 171)</th>
<th>anti-HBs (n = 227)</th>
<th>HBsAg (n = 228)</th>
<th>anti-HBc (n = 207)</th>
<th>anti-HCV (n = 225)</th>
<th>anti-VZV (n = 83)</th>
<th>anti-VCA (n = 120)</th>
<th>anti-CMV (n = 113)</th>
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<tr>
<td>age ≤ 35 yrs % +ve</td>
<td>0.0%</td>
<td>2.0%</td>
<td>2.1%</td>
<td>2.3%</td>
<td>0%</td>
<td>81.1%</td>
<td>83.6%</td>
<td>38.8%</td>
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<tr>
<td>age &gt; 35 yrs % +ve</td>
<td>7.5%</td>
<td>4.0%</td>
<td>1.5%</td>
<td>5.9%</td>
<td>3.9%</td>
<td>91.3%</td>
<td>93.9%</td>
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There was no difference between UC and CD patients; a significant positive correlation was found between age and anti-HCV positivity (p < 0.005), anti-HBc (p < 0.03), latent TBC (p < 0.004), and anti-CMV positivity (p < 0.003).

Discussion/Conclusion: An age over 35 years significantly increases the probability to test positive for TBC, hepatitis C, and anti CMV; although not significant, an important percentage of younger patients was negative for Epstein-Barr virus (16%) and for varicella (19%). The latter data may be important for vaccination issues.
The role of clinical index (PCDAI) and video-capsule index (CECDAI) in pediatric Crohn's disease

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Introduction: The clinical index of severity in pediatric Crohn's disease (PCDAI) has been well established for determining the severity of the disease at the time of diagnosis as well as during the treatment. It's been known that mucosal inflammation does not correlate well with patients' symptoms. The aim of our study was to evaluate whether Capsule Endoscopy Crohn's Disease Activity Index (CECDAI), a tool to assess mucosal disease, can correlate with the clinical index (PCDAI).

Methods: We prospectively analyzed children with Crohn's disease (CD) admitted to the Department of Pediatrics in Clinical Hospital Centre Rijeka in the period 2010–2014. Besides laboratory and endoscopic studies, all the children underwent video capsule endoscopy with CECDAI calculated by the investigator. PCDAI was made at the time of admission.

Results: In our study there were 33 patients; 24 (72.7%) with newly diagnosed CD, and 9 (27.3%) on control examination. There were 24 (72.7%) boys and 9 (27.3%) girls with mean age 14.06 years, range 10–17. According to PCDAI, 11 patients (33.3%) had inactive and 15 (45.5%) mild disease, while 3 (9%) and 4 (12.2%) had moderate and severe disease, respectively. The results with CECDAI were: 7 (21.2%) patients had inactive disease, 15 (45.5%) had mild, 3 (9.1%) moderate and 8 (24.4%) severe disease. When comparing these scores using Pearson's correlation, we found moderate, but statistically significant correlation between PCDAI and CECDAI, R = 0.517 (p = 0.0018, p < 0.05). When we analyze only newly diagnosed patients, PCDAI was as follows: 5 patients (20.8%) had inactive disease, 12 (50%) mild disease, 3 (12.5%) moderate and 4 (16.7%) severe disease, while CECDAI was: 3 patients (12.5%) had inactive disease, 12 (50%) mild, 2 (8.3%) moderate and 7 (29.2%) patients severe disease. The correlation was moderate, but statistically significant, R = 0.616 (p = 0.0013, p < 0.05). Among patients on control examination, in 6 patients (66%) PCDAI showed inactive disease, and in 3 (34%) mild disease, while CECDAI showed in 4 patients (44.4%) inactive disease, in 3 (33.4%) mild, 1 (11.1%) moderate and in 1 (11.1%) patient severe disease. The Pearson correlation was statistically insignificant, R = -0.268 (p = 0.485, p < 0.05), probably due to inadequately small group of patients.

Discussion/Conclusion: PCDAI is commonly used tool in assessing disease severity, but with the lack of reflecting the activity of mucosal inflammation. The video capsule endoscopy is a relatively new diagnostic method in pediatric patients, but with an irreplaceable place in determining intestinal mucosa. We found that CECDAI significantly correlates with clinical index, PCDAI, and can both be used in everyday clinical practice.
Adjuvant imunoglukan P4H in the biological therapy of Crohn’s disease decreases secondary morbidity in patients in remission – Preliminary report

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Introduction: Secondary intercurrent infectious or allergic diseases in patients with inflammatory bowel diseases (IBD) represent a very important problem in daily clinical practice because of their significant contribution to quality of life and work ability. Beta-glucans are known to act as non-specific immunoimodulators that exhibit an anti-inflammatory effect, as evident in animal and human studies in patients suffering from IBD. Imunoglukan P4H capsules are nutritional supplements containing 100 mg of beta-(1,3-1,6)-D-glucan as a natural polysacharid complex isolated from oyster mushroom Pleurotus ostreatus and 100 mg of vitamin C. The aims of study were to evaluate the clinical effect and safety of Imunoglukan P4H additional therapy in Crohn’s disease (CD) patients treated with biological therapy during maintenance of remission during 12 months.

Methods: A double-blinded, placebo-controlled, randomised bicentric study was carried out which included 53 CD patients randomly divided into two groups treated with Imunoglukan P4H 1 capsule daily (23 patients) and placebo (30 patients) respectively. All patients also continued their biological maintenance therapy. Before inclusion the patients were required to: consented (written), completed a SBDQ, CDAI was evaluated, blood picture was performed, standard biochemical tests (bilirubine, AST, ALT, ALP, GMT, AMS, Na, K, CRP) and fecal calprotectin were also determined. These tests and questionnaires were repeated at 2-months intervals, at which time the patients reported intercurrent diseases and their lengths. All data was recorded in patient’s protocol and statistical signification was tested by matching of two ratios with Yates correction and by Mann-Whitney test.

Results: From 53 included CD patients 39 reached the end of trial, 14 patients interrupted the study prematurely. Imunoglukan P4H was administered to 10 patients and placebo to 29 patients. 0/10 patients in Imunoglukan P4H group (IG) and 1/29 patients in placebo group (PG) interrupted prematurely preparate consumption for intolerance and 1/10 patients in IG and 2/29 patients in PG for relapsing of CD. This differences were not statisticaly significant (p = 0.5519 and 0.7508 resp.). In 6/10 of IG patients and in 25/29 of PG patients at least one intercurrent infectious or allergic disease occurred (95% CI, p = 0.0384). In 4/10 resp. 11/29 of patients one intercurrent disease, in 2/10 resp. 7/29 of patients two, in 0/10 resp. 5/29 of patients three and in 0/10 resp. 2/29 of patients four diseases were reported. Imunoglukan P4H also significantly decreased number of intercurrent diseases compared to placebo in this study (95% CI, p = 0.0196). The treatment did not influence SBDQ, CDAI, blood count and biochemical parameters tested.
Conclusion: Preliminary results of this pilot study are very promising. Imunoglukan P4H added to biological therapy of CD patients in remission significantly reduced the secondary morbidity in comparison to placebo. This preparate was well tolerated, no adverse or undesirable effects were observed and the course of CD remission remained unchanged.
Monitoring vital signs during infliximab infusion – Is it really useful?

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Introduction: Monitoring vital signs is a part of the surveillance protocol during Infliximab infusions in most IBD reference centers. Despite being innocuous, it is a time consuming task, representing another burden to already strained healthcare professionals. In this era of increasing medical care costs, and with the growing number of IBD patients treated with biological agents, it becomes essential to analyze if this practice is able to predict or identify adverse reactions to infliximab. The aim of this study is to evaluate the usefulness of monitoring vital signs during Infliximab infusions.

Methods: It was a monocentric retrospective study colliging patients receiving infliximab treatment with a complete medical records. For each patient receiving infliximab infusion, pulse (HR), systolic blood pressure (SBP) and temperature (Temp) were registered during infliximab infusions. Acute adverse reactions were also recorded.

Results: A total of 332 infliximab infusions were administered to 50 patients (average of 6.5 infusions per patient; median age: 32 years old; 58% females; Crohn’s disease – 40, ulcerative colitis – 10). The overall incidence of acute infusion reaction was 1.8% (6 of 332 infusions), affecting 5 patients (10%). None of them was serious. Comparing baseline vital signs between groups with and without acute reactions, no relevant differences were noted (HR: 78 vs. 81/min, p = 0.23; SBP: 106 vs. 109 mmHg, p = 0.12; Temp: 35.9 vs. 36.1ºC, p = 0.68).
Vital signs measured immediately before and during acute reactions were also compared. No significant change was noted in all cases, except during the two reactions, maintaining stable heart rate, blood pressure and temperature.

Discussion/Conclusion: Scheduled monitoring of vital signs during infliximab infusions was unable to predict acute reactions or to identify patients with increased risk of such reactions, though it can help to assess its severity. Such conclusions do not suggest a more distant surveillance, but emphasize that clinical symptoms should be the main focus.
Dietary habits in Tunisian patients with Crohn’s disease

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Introduction: Patients with Crohn’s disease (CD) may suffer a wide range of nutritional deficiencies explained in part by their dietary habits. The aim of this study is to investigate the dietary behaviors in a cohort of patients with CD and to assess their impact on the social life of patients.

Methods: We assessed several dietary behaviors, through a simple pre-established questionnaire in a single Tunisian referral centre. During the outpatient clinic of gastroenterology, 180 patients followed for CD diagnosed at least 3 months before the start of the study, were requested to participate.

Results: A total of 174 patients completed the questionnaire. The mean age of patients was 33.21 years (14–71 years) with a sex ratio M/F 0.87. The mean follow-up is estimated at 29.9 months (3–240 months).

Among our patients, 29.3% (n = 51) believed that food could trigger the disease, while 66.6% (n = 116) thought that it could also play a role in triggering a flare. In total, 89% of patients (n = 155) had received advice on their diet for after the diagnosis of their disease. The pleasure of eating was altered in 18.3% of patients (n = 32). Seventy-three percent of patients (n = 127) believed that their eating behavior could cause nutritional deficiencies.

To prevent disease flare, our patients mainly avoid: spicy foods (93.1%; n = 162), fruits and vegetables in general (43.1%; n = 75), especially tomatoes, citrus fruits, cruciferous vegetables and legumes and dairy products (31%; n = 54). One hundred and five patients (60.3%) reported refusing to eat out for fear of triggering a flare and 12% (n = 21) did not share the same menu as the other members of their family.

When their disease is active, only 6.3% of patients (n = 11) followed a normal diet, while 93.6% (n = 163 adopting a low residue diet (52.8%; n = 92) and/or avoid dairy products (26.4%; n = 46).

Discussion/Conclusion: In this cohort, most patients with CD adopt restrictive diets having a detrimental effect on both their nutritional status and their social life.
Perioperative and long-term morbi-mortality associated with surgery for ileocecal Crohn's disease

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Introduction: Surgery in Crohn's disease (CD) is an effective method to induce remission and avoids potential drug-related complications. However, the decision to operate on ileocecal Crohn's disease is usually tempered by concern for early recurrence and the potential for multiple small bowel resections leading to short bowel syndrome.

The aim of this study was to report the long-term clinical outcome of patients undergoing ileocecal resection for Crohn's disease

Methods: From 1995 to 2014, data from patients with ileocecal CD that underwent ileocecal resection were retrospectively analyzed. We performed a descriptive and analytical study to determine the demographic, clinical, biological features of the patients and looking for independent prognostic factors. Disease recurrence was defined as symptoms in addition to endoscopic or radiological evidence of disease activity.

Results: Two hundred twenty-four patients underwent ileocecal resection for Crohn's disease during the study period, with a median follow-up of 69.3 months. The mean age at the first resection was 32.5 [14–68] years, and the sex-ratio was M/F 132/92.

The indications for the initial resection were mainly stenosis (61.6%; n = 138) and intra-abdominal abscess (25.9%; n = 58). Postoperative complications included prolonged ileus in 8 (3.5%), wound infection in 19 (8.4%), urinary tract infection in 9 (4.0%), intra-abdominal abscess in 6 (2.6%), and wound dehiscence in 3 (1.3%). There was only one operative death.

During follow-up, 18 (8%) patients developed a recurrence requiring further surgery, with a mean time frame between initial ileocecal resection and operation for recurrence being 68.3 months [7–156]. A second recurrence developed in only 6 patients (2.6%) with a mean time interval of 48 months leading to a second resection in five patients. We performed a permanent ileostomy for the last patient.

The most frequent sites of first surgical recurrence were the anastomotic ileum in 15 patients (6.7%). Three (1.3%) patients had experiences recurrences in other ileal sites. Within five years after surgery, the cumulative probability of clinical recurrence was 26.9% and of surgical recurrence 2.12%.

At multivariate analysis, the only independent variable associated with an increased risk of clinical recurrence was active smoking (HR = 3.18; 95% CI; p = 0.002)
Discussion/Conclusion: In our population the results of surgery for ileoceleal CD are good with approximately 73% of patients remain symptom-free and only 2% of patients requiring a second surgery after 5 years. Therefore, surgical resection of ileoceleal Crohn's disease should not be unduly delayed for fear of risking short bowel syndrome. This approach should minimize overall disease-related patient morbidity by avoiding long periods of chronic illness.
Education of Tunisian patients with Crohn's disease on the risks of smoking remains challenging

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Introduction: The detrimental effect of smoking on development and progression of Crohn's disease (CD) is generally accepted. Although health care professionals undoubtedly spend a lot of time in education of patients, the actual awareness of smoking risks in CD patients is unclear.

Methods: We assessed several smoking behavior parameters and patients' awareness on different consequences of smoking, through a simple questionnaire in a single Tunisian referral center. During the outpatient clinic of gastroenterology, 106 patients with inflammatory bowel disease and 142 patients without an inflammatory bowel disease (non-IBD controls, NC) matched by sex and age were requested to participate. Questionnaires included questions on former and actual smoking behavior, cessation attempts, nicotine dependence (Fagerström score), and willingness to quit smoking. Patients were questioned on their awareness of smoking-related risks on several aspects of health, including detrimental effects on CD.

Results: Fifty-nine patients with Crohn's disease (CD) (49% male, 32 years, 54% never smoked), 47 with ulcerative colitis (UC) (54% male, 35 years, 57% never smoked) and 149 NC (52% male, 42 years, 55% never smoked) were enrolled. At diagnosis, CD patients were more active smokers compared to UC patients (32% vs. 17%, p < 0.005). Previous attempts to stop smoking and nicotine dependence were similar in all groups. Remarkably, smoking cessation rates after diagnosis were not higher in CD compared to UC (56%, vs. 53% p = 0.18). In the 3 groups, the majority of patients recognized dangers of smoking on general health (99%), lung cancer (95%), myocardial infarction (89%), and stroke (78%). Although CD patients more frequently acknowledged risks of smoking on their disease, only 18% were aware of the link with CD development, 28% of increased surgical rates, and 29% of increased postoperative recurrence rates. Of note, within the CD population, awareness was unrelated to actual smoking behavior. Increased surgery rates were acknowledged by 26% of active, 25% of former and 28% of non-smokers (p = 0.36). Active smokers not willing to quit smoking, most often denied a potential bad influence of smoking on their disease. Previous surgery, level of education and employment did not influence awareness. UC patients were more frequently aware of an inverse relationship between smoking and UC development (29% UC, 9% CD, 0.07% NC, p < 0.001).

Discussion/Conclusion: Although CD patients were better informed on the detrimental effects of smoking, the awareness rate still low. These data may also suggest more denial for the adverse consequences of smoking in active smokers. More efforts are needed to be done on informing and educating patients regarding the risks of smoking.
Vitamin B12 deficiency in patients with ileal resection for Crohn's disease: Frequency and predictive factors

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Introduction: Vitamin B12 deficiency is involved in a broad range of hematological, neurological and mucocutaneous disorders. Absorption occurs at the terminal ileum. Patients with Crohn's disease (CD) in whom the terminal ileum (RTI) was removed may suffer from a deficiency in this vitamin. The aim of the study was to determine the frequency of vitamin B12 deficiency and associated factors in patients followed for CD with RTI.

Methods: We collected prospectively sera from patients followed for CD in clinical remission with RTI from January to September 2014. Patients in which the metabolism of vitamin B12 is disturbed (total gastrectomy, pernicious anemia or chronic intake of proton pump inhibitors) were excluded. We performed a descriptive and analytical study to determine the demographic, clinical, biological features of the study population and looking for independent predictive factors of vitamin B12 deficiency.

Results: A total of 51 patients were included. The average age of patients at baseline was 35.56 years [16–77] with a sex ratio M/F = 1.04. Forty-three percent of patients were active smokers at the time of inclusion. The average time frame between RTI and diagnosis of CD was 58.5 months [1–264] while that between RTI and inclusion was 69.5 months [5–300]. The mean extent of RTI was 39.48 cm [7–110], the mean remaining healthy small intestine was 356.6 cm.

The mean serum vitamin B12, hemoglobin and mean corpuscular volume were respectively 297.86 ng/l [34–501]; 12.4 g/dl [7.5–16.5] and 86.4 fl [61–105.2]. Vitamin B12 deficiency was seen in 9 patients (17.6%).

Univariate analysis shows that vitamin B12 deficiency was associated with an age over 40 years at baseline (p = 0.015), a folate deficiency (p = 0.028), resection of more than 30 cm of the ileum (p < 0.030) and a healthy remaining small intestine less than 3 m (p = 0.041). In multivariate analysis, only ileal resection upper 30 cm (p = 0.046) was found as an independent risk factor for vitamin B12 deficiency.

The mean serum vitamin B12 was significantly higher (312.6 ng/l) in the subgroup of patients who was included within 5 years from RTI [G1] compared with the subgroup of patients [G2] included more than 5 years after RTI (263.5 ng/l); p = 0.046.

The threshold limit for the appearance of a vitamin deficiency was 60.5 months. Vitamin B12 deficiency was not correlated neither with endoscopic (p = 0.606) nor with clinical recurrence (p = 0.490).

Discussion/Conclusion: Our work demonstrated that vitamin B12 deficiency in patients followed for CD with RTI was seen in 17% of patients. It is correlated with extent of ileal resection (> 30 cm) and delay after resection (beyond 5 years) probably related to the depletion of liver stocks. These patients should be screened for replacement therapy.
Anemia and Crohn behavior: What relationship?

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Introduction: Anemia is a common complication in Crohn’s disease (CD). Iron deficiency and inflammation are the most common mechanisms. It is often assumed that control the activity of the disease is sufficient to correct anemia well tolerated but some anemia persists even after controlling inflammation. Thus the need to identify the prognostic aspects of this condition. The aim of this study is to evaluate the relationship between anemia and the features of CD.

Methods: From January 2011 to December 2013, data from patients with ileocecal CD were retrospectively analyzed. We performed a descriptive and analytical study to look for an association between anemia and Crohn’s disease behavior. We defined anemia as a hemoglobin (Hb) < 12 g/dl for women, and a Hb < 13 for men.

Results: We included 227 patients with CD. There were 104 women and 113 men, with a sex ratio M/F 1.08. The mean age was 34.34 years, ranging from 14 to 71 years. The topography of the intestinal lesions at diagnosis was 22.9% in small bowel (n = 52) patients, colic in 30% (n = 68) and ileocecal in 47.1% (n = 107). Eighty-six percent of our patients (n = 195) had anemia whose mechanism was essentially inflammatory 48% of patients (n = 109). Iron deficiency anemia was present in 37% (n = 84) by vitamin B12 deficiency in 3.9% (n = 9) and mixed in 5.7% (n = 13). An alleged drug-induced anemia (thiopurine) were present in 5.2% (n = 12).

We observed a statistically significant association between the stenosing and penetrating CD behavior (22%; n = 50) and anemia (p = 0.039). Ileocolonic location (L3) was significantly associated with anemia (p = 0.029) however ileal location was associated with normal Hb levels (p = 0.002).

Discussion/Conclusion: Anemia is a frequent condition in CD patients and is associated with penetrating behavior and ileocolic location. These patients should be screened for close follow up and treatment.
Poor recognition and management of iron deficiency anemia in Crohn's disease: A missed opportunity

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**Introduction:** Iron deficiency anemia (IDA) is a common complication of Crohn’s disease (CD) that has an impact on the patient's quality of life. IDA is caused by inadequate dietary intake, malabsorption of iron and iron loss through intestinal bleeding. Current guidelines recommend that all patients with IBD should be assessed for IDA and that iron supplementation should be given as indicated. The aim of this study was to ascertain the prevalence of IDA in our IBD cohort, to look at whether iron replacement therapy (and in what form) was given and to assess treatment response.

**Methods:** We performed a retrospective study in patients with CD followed-up between 2008 and 2013 in our department. 287 proved CD patients underwent the analysis according to age, signs, clinical course and activity of the disease. Complications and treatment options were recorded. The routine blood tests, including screening parameters for IDA: hemoglobin (Hb), mean cell volume, ferritin, C-reactive protein (CRP) were tested for each patient at first visit. The WHO definitions of anemia were used. Iron deficiency was diagnosed if ferritin < 30 ug/l in quiescent IBD or < 100 ug/l in active IBD (CRP elevated).

**Results:** 287 patients with CD were identified. 5 patients were excluded because of insufficient data. 224/282 (79.4%) were checked for IDA using the screening parameters. 182/224 (81.2%) of this group were found to be anemic. 130/146 (71.4%) had evidence of iron deficiency. 78/130 (60%) were treated using oral and/or intravenous (IV) iron preparations or blood transfusions. Most of our patients (64/78) received oral iron while 10 patients had IV iron (2 had failed oral therapy) and 4 had blood transfusions. The recurrence rate of IDA was 27/64 with oral iron, 4/10 with IV iron and 3/4 with transfusions. We also noted that there were 42/224 patients (18.7%) with iron deficiency in the absence of anemia. Only 3 of these patients were treated for iron deficiency.

**Discussion/Conclusion:** Prevalence of IDA in our CD group exceeded 60%. Current practice in our trust does not comply with guidelines as only 60% of IDA patients were treated. Iron replacement therapy was mostly administered in the oral form. Recurrence of IDA was similar (about 40%) with both oral and IV iron therapy. There is little guidance on management of iron deficiency in the absence of anemia and supplementation was not widespread in this group.
Poly(ADP-ribose)polymerase activation in pediatric patients suffering from Crohn's disease

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Introduction: The pathomechanism of Crohn’s disease (CD) is not fully understood, however several data suggest the role of inflammatory factors, oxidative-nitrative stress and the consequent activation of poly(ADP-ribose)polymerase (PARP). PARP enzymes are essential in numerous physiological mechanisms, including DNA-repair, expression of inflammatory genes or activation of NF-kB signaling pathway. However its role in CD is not known, therefore our aim was to examine the colonic PARP activation in pediatric patients suffering from CD.

Methods: Colonic biopsies of CD patients with macroscopically intact (CDintact: n = 7) and inflamed (CDinflamed: n = 10) mucosa, and control biopsies (C: n = 12) were analyzed. PARP-1 mRNA expression was measured by real-time PCR from fresh-frozen biopsy samples. Paraffin embedded sections of biopsies were immunostained with anti-PAR (end product of PARP) antibody to estimate the localization of active PARP. The degree of PAR positivity was determined by a blinded experimenter (scoring: 1–10).

Results: PARP-1 expression was significantly elevated in the inflamed mucosa of CD compared to the control and CDintact biopsies (CDinflamed vs. C or CDintact, p ≤ 0.05). The amount of PAR was significantly higher in the colon mucosa of CD patients compared to the controls (CDintact vs. C, p ≤ 0.05; CDinflamed vs. C, p ≤ 0.001). The observed increment correlated with the elevated Pediatric Crohn’s Disease Activity Index, the neutrophil, lymphocyte counts and serum C-reactive protein levels.

Discussion/Conclusion: Activation of PARP can be observed in the colon mucosa of children with CD. PARP activity associated with the intestinal inflammation and clinical activity of the disease. These data suggest that PARP plays an important role in the pathomechanism of CD. Further studies are required to explore the exact regulatory pathways of the PARP activation and its consequences.
Factors associated with moderate and strenuous physical activity in IBD patients

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Introduction: There are few data available on physical activity and the factors associated with strenuous or moderate exercise in inflammatory bowel disease (IBD) patients. Our aim was to determine physical activity and factors associated with strenuous and moderate exercise in a large group of German and Irish IBD patients.

Patients and methods: The study included 526 IBD patients (median age 38 years [range 16–89]; 272 males) attending one of two clinics in Dublin, Ireland and Frankfurt, Germany. Patients completed a structured questionnaire, the Godin Leisure-Time Exercise Questionnaire, assessing usual leisure time exercise habits. The questionnaire also assessed education, smoking status, previous surgery, current medical therapy, disease activity (Short Mayo Score and Short HBI) and quality of life.

Results: Three hundred and eighty five patients (73%) undertook moderate or strenuous physical exercise at least one a week. Binary logistic regression analysis showed that moderate or strenuous exercise was significantly and independently related to younger age (RR = 0.97 [95% CI: 0.96–0.99]; p = 0.001), low disease activity (0.56 [0.03–0.82]; p = 0.01), higher education (1.72 [1.12–2.66]; p = 0.14) and longer disease duration (1.03 [1.01–1.06]; p = 0.02). In contrast, moderate and strenuous exercise was unrelated to country of origin, disease type, current steroid, immune modulator or biologic use, previous surgery or smoking status. Physical activity was closely related to quality of life with those taking some strenuous or moderate exercise having significantly better disease related quality of life (p < 0.001).

Conclusion: A large proportion of European IBD patients take at least some moderate or strenuous physical exercise on a weekly basis. This can be predicted on the basis of demographic and clinical features, allowing us to target specific groups for special consideration.
Three-year steroid-free remission and safety of azathioprine treatment in inflammatory bowel disease patients

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Introduction and aim: Azathioprine (AZA) is widely used for induction and maintenance of remission in steroid dependent patients with inflammatory bowel disease (IBD). We investigated its efficacy and safety in maintaining steroid-free remission in steroid dependent IBD patients three year after the institution of treatment.

Methods: Data from consecutive IBD outpatients referred in our Institution, between 1985–2012, were reviewed and all patients treated with AZA were included. AZA was administered at the recommended dose of 2–2.5 mg/kg.

Results: Out of 2472 consecutive IBD outpatients visited in the index period, AZA was prescribed to 360 patients, 189 (52.5%) were affected by Crohn's disease (CD), 171 (47.5%) by ulcerative colitis (UC). Seventy-eight patients with a follow-up < 36 months were excluded from the study. Two hundred and eighty-two patients were evaluated, 152 (53.9%) with CD and 130 (46.1%) with UC. One hundred and fifty-four (54.6%) were male and 128 (45.4%) female (average age of 33.75 ± 13.82 SD years, range 14–76 years). Three year after the institution of treatment, 170 (60.3%) patients still were in steroid-free remission (101 CD vs. 69 UC, 66.4% and 53.1%, respectively, p = 0.0279), 62 (22%) had a relapse requiring retreatment with steroids (38 UC vs. 24 CD, 29.2% and 15.8%, respectively, p = 0.0091), 50 (17.7%) discontinued the treatment due to side effects (27 CD vs. 23 UC, 17.8% and 17.7%, respectively). Loss of response from 1st to 3rd year of follow-up was low, about 12%.

Conclusion: Three year after the onset of treatment 60% of patients did not require further steroid courses. After the first year loss of response was low in two subsequent years. In the present series the maintenance of steroid-free remission was significantly higher in CD than in UC patients. The occurrence of side effects leading to the withdrawal of AZA treatment has been low.
Clinical features of active tuberculosis developed during anti-tumor necrosis factor-α therapy in patients with inflammatory bowel disease

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Introduction: Inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and Crohn's disease (CD) are chronic disorders that cause inflammation in the gastrointestinal tract. Anti-tumor necrosis factor-α (TNFα) antibodies are widely used for the treatments of active UC and CD. However, anti-TNFα therapy is associated with increased risks of infections, moreover, in Korea, there is a specific concern about reactivation of tuberculosis (TB) because the prevalence of latent and active TB is still high. We aimed to analyze the clinical features of Korean patients with IBD in whom active TB was developed during anti-TNF therapy.

Methods: Twenty-four cases of active TB developed in patients treated with infliximab (n = 21) or adalimumab (n = 2) or both (n = 1) for active UC (n = 3) or CD (n = 21) were reviewed retrospectively. We evaluated the patient characteristics, the interval between the initiation of anti-TNF therapy and the onset of the disease, the screening tests for latent TB infection, the concomitant immunosuppressive drug uses, and details of diagnosis and treatments of TB.

Results: Median age at diagnosis of UC or CD was 27 years (range 12–52) and female was 25% (n = 6). Median time to the development of active TB after the initiation of anti-TNF therapy was 5 months (range 2–45). Two patients had past histories of treatments for the previous TB infections. Tests for latent TB infection were performed in 20 patients using tuberculosis skin test (TST, n = 16), or interferon gamma releasing assay (IGRA, n = 12) or both tests (n = 8) and the positive findings of at least one of the two tests were observed in 2 patients. TB scars on the chest X-ray were found in 2 patients. The 2 patients with latent TB infection and 1 of the 2 patients with TB scars on their chest X-ray received anti-TB prophylaxis with isoniazid for 9 months. The most common site of active TB development was lung (n = 20), followed by mediastinal lymph nodes (n = 2), intraabdominal lymph nodes (n = 1), and peritoneum (n = 1). Sixteen patients (66.7%) have received one or more other immunosuppressive medications, including corticosteroids (n = 6), and azathioprine (n = 13). Eighteen patients (75%) were using mesalamine before TB developed. The TB infections were cured in 23 patients, but 1 patient was died for the disease progression.

Discussion/Conclusion: Most of the patients with active TB had negative results in one of the latent TB tests. Active TB was developed even in patients who had received anti-TB prophylaxis for the latent TB infection and anti-TB treatments for the previous TB infections. Therefore, physicians should thoroughly review patient histories, TST and IGRA results, and chest X-ray findings before starting anti-TNF-α therapy for IBD and pay attention to the risk of TB development during anti-TNF therapy, especially in countries with high prevalence of TB.
Risk factor analysis for therapy-related adverse events and infections in elderly patients with inflammatory bowel disease (IBD); an IG-IBD study


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Elderly patients with IBD present problems related to concomitant pathologies and, in case of infections, a worse outcome compared to younger patients. This study is based on a retrospective data collection on the first 3-years period following diagnosis in different age groups.

Methods: The database includes 1723 patients with 433 diagnosed over age 65 years (group 1: UC 280, CD 153, males 231), 450 patients between 40 and 65 years (group 2: UC 289, CD 161, males 271), and 840 patients diagnosed before age 40 years (UC 523, CD 317, males 438); data on therapy, adverse events (AEs) and their outcome (no, mild, moderate, or severe permanent damage), IBD-related and -unrelated hospitalizations and on infections were extracted together with the Charlson comorbidity score (CCS), and concomitant therapies (proton pump inhibitors, PPI, antithrombotics, AT, antihypertensives, and antidiabetics).

Results: the numbers of AEs analyzed for the different therapies were similar in the 3 groups (tab. 1), as well as AEs requiring hospitalizations. Mild (p < 0.045) or moderate (p < 0.003) permanent damage from AEs was more frequently observed in group 1 and 2. IBD-related hospitalizations in the first 3 years following diagnosis were
similar in the 3 groups, but the hospital stays were significantly longer in group 1. On univariate analysis as significant risk factors for infections we identified CCS (OR = 1.418; 95% CI: 1.053–1.909; p < 0.021), the use of 2 (OR = 1.738; 95% CI: 1.185–2.550; p < 0.005) or 3 (OR = 3.065; 95% CI: 1.665–5.645, p < 0.000) immunosuppressors (IMM), PPI use (OR = 1.727; 95% CI: 1.005–2.967, p < 0.048), and AT use (OR = 2.143; 95% CI: 1.272–3.611; p < 0.004). Risk factors for AEs were the use of 2 (OR = 3.880; 95% CI: 2.857–5.270; p < 0.000) or 3 (OR = 4.231; 95% CI: 2.556–7.004, p < 0.000) IMM.

**Conclusions:** Elderly IBD patients have longer hospital stays due to their disease and more frequently permanent damage from AEs. Risk factors for infections were comorbidities, the association of 2 or more IMM, as well as concomitant medications, PPI and AT.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 n = 433</th>
<th>Group 2 n = 450</th>
<th>Group 3 n = 840</th>
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<tr>
<td><strong>INFECTIONS</strong></td>
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<td>Infections total, %</td>
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<td>Hospitalization due to infections, %</td>
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<td><strong>HOSPITALIZATIONS</strong></td>
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<td>IBD-related, %</td>
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<td>Length of stay; days mean ± SE</td>
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<td>12.1 ± 0.6</td>
<td>12.2 ± 0.4</td>
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<td>5.1%</td>
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<td><strong>AE</strong></td>
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<td>from 5-ASA, %</td>
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<td>from IMM, %</td>
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<td>from BIO, %</td>
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<td>Hosp. for AE, %</td>
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<td><strong>Permanent damage from AE</strong></td>
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<td>mild, %</td>
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<td>moderate, %</td>
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</table>

Tab 1: infections, hospitalizations, and adverse events in different age groups
What do healthcare practitioners know about fatigue in patients with IBD and how do they manage it?

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Introduction: Fatigue is one of the top complaints in inflammatory bowel disease (IBD) with 41% of patients in remission and 86% in active condition reporting fatigue. However patients report that their complaints of fatigue are often not addressed in clinical consultations. To date there are no studies exploring this topic from the clinician’s perspective. This study aimed to gain an understanding of healthcare practitioners’ (HCPs) perception of IBD fatigue as experienced by people with IBD.

Methods: Descriptive phenomenology was carried out. Purposive sampling was used to identify a range of professionals (gastroenterologists, IBD nurses, general practitioners, dietitians, psychologists and pharmacists). In-depth semi-structured interviews were conducted with 20 HCPs who work with people with IBD between June and December 2012. Colazzi’s framework was used to analyse the data. The study was approved by the local university ethics committee.

Results: Three main themes and several sub-themes were identified. The main themes were: the phenomenon of fatigue as perceived by HCPs; the impact of fatigue on patients’ lives; and the methods used by HCPs to deal with fatigue. Fatigue was identified as an important, but difficult and often frustrating, symptom to understand. HCPs reported that fatigue impacts on the emotional, private and public aspects of patients’ functioning; however they suggested very few methods on how to assess and manage fatigue. Many expressed a desire for better education. There was consensus that managing fatigue should be a multi-disciplinary effort, but with little idea of clearly defined roles.

Discussion/Conclusion: Despite fatigue being one of the symptoms frequently reported by IBD patients, it remains poorly understood by HCPs. There is a need for a systematic and structured assessment and management of this distressing symptom and HCPs should communicate with each other about care for each individual patient.
Experience of living with fatigue as reported by people diagnosed with inflammatory bowel disease – A phenomenological study

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Introduction: Fatigue is one of the main symptoms of inflammatory bowel disease (IBD), however, little is known about specific areas of life affected by fatigue, its pattern over time or how people with IBD manage it. This study aimed to address this shortfall in evidence.

Methods: Descriptive phenomenology with face-to-face in-depth interviews. Twenty participants diagnosed with IBD and reporting fatigue were purposively selected. Interviews were audio-recorded, transcribed verbatim and analysed using Moustakas’ method, which involves seven steps and analyses data at two levels: i) textural level – which generates a description of the phenomenon, ii) structural level – which describes underpinning factors and their relationships with fatigue.

Results: Participants found fatigue difficult to describe and used different terms, metaphors and similes to describe their experience. The terms fatigue, tiredness and exhaustion were used interchangeably. Fatigue was described as ‘heaviness of the body and fuzziness of the brain’ with a constantly fluctuating pattern and severity. The invisible and fluctuating nature of fatigue makes it difficult for patients to describe to others.

Fatigue was perceived to impact on all aspects of daily functioning. Participants spoke of being trapped in an unreliable body, which made them feel angry, frustrated, isolated and depressed, and lead to loss of self-confidence and identity.

Physical, psychological, cognitive and situational factors were perceived to contribute to fatigue. Different methods to manage fatigue were attempted by participants (e.g. sleep and rest, pacing, energy preservation, exercise, stress reduction, help seeking), but few were used systematically, possibly resulting in their apparent limited effectiveness.

Discussion/Conclusion: Fatigue is a complex symptom (both multi-causal and multidimensional) and reduces quality of patients’ lives. Patients need to be informed that fatigue is part of IBD, and they need advice on how to manage it, encouragement to report it and to seek help when needed.
Development and psychometric testing of an inflammatory bowel disease fatigue (IBD-F) patient self-assessment scale

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Introduction: Fatigue is one of the main symptoms of inflammatory bowel disease (IBD) and is frequently reported by people in active and quiescent disease. Different fatigue assessment scales have been used to measure fatigue, but none has been developed or sufficiently tested in IBD. This study aimed to develop a new fatigue scale specific to the needs and experiences of people with IBD.

Methods: A sequential mixed methods design was used: a qualitative phase (Phase 1) to assess patients’ experience of fatigue and four mixed qualitative-quantitative phases (Phase 2–5) to refine the scale and to assess its psychometric properties. The study was undertaken July 2010–July 2013. Phase 1–4 participants were purposively selected from a group of volunteers self-reporting fatigue, and participants for Phase 5 were randomly selected from the Crohn’s and Colitis UK membership database.

Results: 567 people participated in the study. The resulting IBD-F questionnaire has 3 sections: Section 1 – fatigue assessment; Section 2 – fatigue impact on daily activities; Section 3 – additional comments about fatigue. Initial validation suggests that the questionnaire has good face and content validity and acceptable to excellent test-retest stability (ICC 0.74 for Section 1 and 0.83 for Section 2) and a high degree of internal consistency with Cronbach’s alpha value of over 0.9.

Discussion/Conclusion: The participants in the study confirmed that fatigue in IBD is burdensome. Items generated and refined by people with IBD-fatigue reflect their experience and form the basis of this new IBD-fatigue scale, which is psychometrically robust and its reliability falls within statistically acceptable ranges. The fatigue scores obtained by this disease specific IBD-F self-assessment scale strongly correlated with the existing fatigue scales (MFI and MAF) developed with other diseases. The scale can be used by patients and practitioners to assess severity and impact of fatigue in people with IBD.
Assessing fatigue in inflammatory bowel disease comparison and validation of three fatigue scales: IBD-F, MFI and MAF scales

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Introduction: Patients with inflammatory bowel disease (IBD) report fatigue in both quiescent (41%) and active disease (86%); however, due to its subjective nature it is difficult to assess. Many different fatigue scales exist, although most have not been tested with IBD populations. Only one scale has been developed specifically for people with IBD. We aimed to assess validity and reliability of three fatigue assessment scales in an IBD adult population and to determine factors correlated with fatigue.

Methods: A cross-sectional study. Participants (n = 605) were randomly selected and completed questionnaires assessing fatigue, anxiety, depression, quality of life and IBD activity. A sub-group of responders (n = 70) were sent the same mailing 6 weeks later for test-retest. The fatigue scales used were: the Inflammatory Bowel Disease Fatigue (IBD-F), the Multidimensional Fatigue Inventory (MFI) and the Multidimensional Assessment Fatigue (MAF). Internal consistency was measured by Cronbach’s alpha and test-retest reliability by the intra-class correlation coefficient (ICC).

Results: 465 (77%) questionnaires were completed for the test and 69% for retest. All three scales are highly correlated (p < 0.001). Test-retest suggests good agreement for all scales’ total scores with ICC values of 0.74 and 0.83 (IBD-F Section 1 and 2), 0.74 (MAF) and 0.65–0.84 (MFI). Age, gender, bowel condition, anxiety, depression and IBDQ scores were significantly associated with level of fatigue (p < 0.001) for all three fatigue scales. Older patients had lower fatigue scores, females had higher scores than males, colitis patients had significantly lower scores than Crohn’s patients, patients with a higher level of anxiety and depression had higher fatigue scores and better IBDQ was associated with lower fatigue scores.

Discussion/Conclusion: All three tested fatigue scales were found to be valid and reliable measures of IBD fatigue. Factors such as age, gender, bowel condition, quality of life, anxiety and depression are significantly associated with fatigue and should all be taken into account in the process of care delivery to people with IBD and fatigue.
Cerebral vein thrombosis: A rare complication of Crohn’s disease

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Introduction: Dural venous thrombosis is rare. Since the basal ganglia have a rich venous drainage, venous infarcts are hardly encountered in this region. Inflammatory bowel disease may cause thrombotic complications in arterial and venous systems. Cerebral vein thrombosis is an infrequently seen complication of these diseases with a highly fatal course. Herein, we report a case of dural vein thrombosis associated with Crohn’s disease.

Case report: A 25-year-old young male patient was admitted to our clinic with complaints of abdominal pain and diarrhea. Detailed history revealed that he suffered from Crohn’s disease for 3 years and received various therapies. In physical examination, he had a blood pressure of 120/80 mmHg, a heart rate of 94/minute, temperature of 38.6°C. Laboratory tests revealed WBC: 13.500, Hb: 10.2 g/dl, Plt: 554.000/mm³, BUN: 13 mg/dl, creatinine: 0.85 mg/dl, SGOT: 34 IU/l, SGPT: 35 IU/l, Sedimentation: 80 mm/h, C-reactive protein: 84 mg/l. The patient receiving mesalazin was started steroid medication for disease activation. In the second week of treatment, he was admitted to the emergency department with complaints of headache, nausea and vomiting, fever, fecal and urinary incontinence, and clouding of consciousness. Neurological examination and neuroimaging with magnetic resonance imaging revealed a thrombus filling the left transvers sinus, sigmoid sinus and sinus rectus. The patient was started anticoagulant medication in the neurology department and hospitalized until his general condition was normalized.

Discussion: Thromboembolism is a rare complication of inflammatory bowel disease. Thrombocytosis may be together with focal intravascular thrombosis, however, it has yet to be defined if the thrombocytosis itself causes the thrombus. It is thought that thrombocytosis in the active phase of Crohn’s disease may aggravate the thrombus. Neurological signs and symptoms as in our patient during the course of Crohn’s disease may be suggestive of cerebral vein thrombosis.
Interstitial lung disease in a patient with Crohn's disease using mesalamine

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Introduction: Either primary involvement of the lungs or the drugs used in treatment (i.e. sulfasalazine) may cause pulmonary complications associated with inflammatory bowel diseases. Sulfasalazine may cause various pulmonary syndromes including hypersensitivity pneumonia, pulmonary eosinophilia, and fibrosing alveolitis. Association of mesalamine (5-ASA) use and pulmonary involvement is very rare. Herein, we report a case with interstitial fibrosis due to mesalamine use.

Case report: A 26-year-old young male patient who underwent colonoscopy 1 year ago with complaints of abdominal pain and aphthous stomatitis had a diagnosis of Crohn's disease. Steroid medication and mesalamine was started for treatment. Disease remission was achieved, but he was admitted to our clinic with complaints of fever, cough, dyspnea and hemoptysis during follow-up. Thoracentesis was performed for pleural effusion detected on chest radiogram and antibiotic therapy was started. However, the patient had no symptomatic improvement. Pathological and microbiologic analysis of sputum cytology and thoracentesis was non-specific. Bronchoscopic biopsy, broncho-alveolar lavage and bronchial brush cytology revealed negative results for malignancy and tuberculosis. Pulmonary function tests showed a restrictive pattern. Interstitial lung disease was detected on High Resolution Computed Tomography. Considering that the pulmonary changes might be associated with mesalamine use, administration of mesalamine was stopped and prednisolone 40 mg/day, and azothiopurine 50 mg/BID was started. The patient had resolution of pulmonary symptoms in a few days, and pleural effusion resolved.

Conclusion: Pulmonary symptoms in patients suffering from inflammatory bowel disease may be associated with mesalamine or sulfasalazine use. Stopping these medications and using steroid and other alternative medications may be considered for these patients.
Azathioprine in the elderly – Is it tolerated and is it safe?

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Introduction: Azathioprine (AZA) for maintenance of remission in inflammatory bowel disease (IBD) is standard practice. Side effects are common. Of 353 consecutive patients commencing AZA in our organisation, 36% were not taking it at one year. With an ageing population, IBD is increasingly relevant in those over 75 years old.

Methods: All patients commenced on AZA between June 2005 and October 2012 over the age of 75 was identified. TPMT was checked and AZA was prescribed at 2–2.5 mg/kg, with 50% dose reduction in those with low TPMT. Full blood count and LFTs were monitored weekly for 8 weeks.

Results: 25 patients were identified, (7 CD, 18 UC). The mean age at which AZA was started was 78 (range 75–86), 16 were male (64%). All patients were followed up for at least one year. 12 (48%) were intolerant of AZA. Reasons for stopping AZA were; hepatitis, 2 (8%); vomiting, 5 (10%); pancreatitis, 1 (4%); myelosupression (1); joint pain (1); infection (1); and general malaise (1). The mean duration of AZA use in these patients was 34 days (range 3–89). 13 (52%) tolerated the drug well with one of this group having the drug actively withdrawn at 701 days in complete remission. There were four deaths (16%). Two died in the group intolerant of AZA (84 year old died of stroke 888 days after 13 days of AZA; 82 year old died in the community 140 days after 5 days of AZA). Two people died in the AZA treated group (83 year old died in the community on day 1476 of AZA; 79 year old died following cardiac arrest on day 212 of AZA).

Discussion/Conclusion: Our data demonstrate that AZA is effective treatment in the elderly. It appears to be less well tolerated than in the general population with 48% intolerant of the drug within 3 months. The increased incidence of drug intolerance in this population group may suggest that low-dose azathioprine and allopurinol co-therapy should be considered first-line therapy in this group.
Diagnostic benefit of MRE following CT

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To establish the additional diagnostic yield of MRE in patients previously investigated with CTAP and ileo-colonoscopy

Introduction: In patients presenting with symptoms suggestive of IBD (abdominal pain and/or diarrhoea) as ECCO guidelines, colonoscopy is the first line test at our institution. A magnetic resonance enterography (MRE) is then performed in patients where there is a continuing clinical suspicion of small bowel Crohn’s disease. However in patients who present to non-IBD physicians, computed tomography of the abdomen and pelvis with contrast (CTAP) is often the first line investigation. In this situation MRE is commonly performed to exclude small bowel disease following review in the gastroenterology clinic. We want to evaluate the additional diagnostic yield of MRE in this clinical scenario.

Methods: Our radiology department maintain a prospective electronic database. We searched for all patients who underwent CTAP followed by MRE within the same 12 month period between February 2005 and February 2013. Electronic medical records were then reviewed.

Results: 80 patients were identified. The mean age at time of MRE was 49 (range 17–87), indication for investigation: assessment of known Crohn’s disease; 18 (23%), abdominal pain; 34 (43%). Mean time between CTAP and MRE; 127 days (range 3–352) Final diagnosis was Crohn’s disease; 37 (45%), coeliac disease; 4 (5%), irritable bowel syndrome 4 (5%). In 11 (14%) MRE added further information or changed management for the patient. Of this group in 3 patients MRE identified terminal ileal (TI) inflammation that was not identified at CTAP. In two of these cases ileal-colonoscopy collaborated TI inflammation and in the third case capsule enteroscopy confirmed TI inflammation. In all three the final diagnosis was Crohn’s disease. Overall MRE identified one (1.25%) patient with possible CD that was missed at CTAP and ileo-colonoscopy.

Discussion/Conclusion: The diagnostic yield of MRE in patients previously investigated with ileo-colonoscopy and CTAP was low. Suggesting that MRE has a limited diagnostic role in this situation and should be reserved for patients where clinical suspicion remains high despite negative CTAP and ileo-colonoscopy or to further define complex disease.
Novel insights into IBD carcinogenesis: DNA damage response

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Introduction: The risk of developing colorectal cancer (CRC) in inflammatory bowel disease (IBD) is positively related to the extent, duration and severity of chronic inflammation. Adenocarcinoma arises diffusely in chronically inflamed epithelium via low- and high-grade dysplasia. Surveillance colonoscopic biopsies, taken randomly, identify the presence of dysplasia as the best marker for future cancer development and prophylactic colectomy (to reduce the risk of cancer). Colectomy is not always necessary as the different degrees of dysplasia have variable rates of malignant progression and regression and can be difficult to distinguish from epithelial regeneration. The clinical utility of dysplasia is limited by the poorly defined pathogenesis and it is difficult to predict which patients with dysplasia will develop cancer. The crucial stage in understanding the biology is to characterise the early changes that occur in IBD associated CRC. For example the DNA damage response (DDR) protects against the development of cancer by activating cell cycle arrest, apoptosis, DNA repair and cellular senescence.

Methods: Surveillance colonoscopies were analysed (2007–2014) and confirm low-grade dysplasia is not a robust marker of malignant potential. A tissue microarray was created with a series of IBD associated colorectal cancers and interrogated with proteins involved in the DDR.

Results: The DDR is active in dysplasia, but deregulated in IBD cancer, indicating that DDR inactivation is a key step in transition to malignancy.

Discussion/Conclusion: Inactivation of the DDR can occur due to mutations either affecting several proteins including checkpoint kinase 2 or p53 resulting in abrogation of cell cycle arrest, defective apoptosis and survival of cells with mutations that replace cells lost through inflammation. Sequencing of human IBD associated CRC will permit the identification of novel mutated genes involved in the DDR.
Body composition in Crohn’s disease patients but not in ulcerative colitis patients is different compared to healthy controls

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Introduction: Chronic illness, various intestinal and extraintestinal disease manifestations, and malnutrition affect the health status of inflammatory bowel disease patients. An impaired health status can be accompanied by changes of the body composition. The bioelectrical impedance analysis (BIA) is a widely used method to examine body composition in patients suffering from chronic diseases. In this study we compared the body composition/phase angle of Crohn’s disease (CD) and ulcerative colitis (UC) patients with pair-matched controls.

Methods: We evaluated the body composition of 38 CD patients (19 male and 19 female) and 35 UC patients (16 male and 19 female). The four groups were compared to 72 pair-matched healthy individuals. Matching criteria were body mass index (± 2 kg/m²), age (± 5 years), and gender. Body composition was assessed by BIA (Nutriguard-M, according to manufacturer's protocol). Additionally, we measured biochemical markers of inflammation and nutrition (hemoglobin, leucocytes, CRP, albumin, iron, ferritin, folic acid, vitamin B₁₂) as well as clinical activity indices.

Results: The phase angle in female CD patients was 5.51° and significantly lower than in healthy controls (5.98°, p = 0.037) (Fig. 1). Comparing male CD patients with healthy controls we also found a significant difference (6.25° vs. 6.83°, p = 0.015) (Fig. 2). Interestingly, no significant difference of body composition/phase angle was observed when comparing UC patients with matched healthy controls. We observed no general correlation of any of the disease activity markers with the phase angle as a parameter of body composition.

Discussion/Conclusion: Our observations demonstrate a significant difference of the phase angle as a global parameter of body composition between CD patients and healthy controls. No significant differences were found when comparing UC patients and healthy controls. These observations may reflect the different nature of both diseases (course of disease, affected parts of the gastrointestinal tract, medications, etc.). Generally, BIA seems to be an appropriate method to assess the health status in IBD patients.
Low dose AZA and allopurinol co-therapy: Is it safe to use without metabolite monitoring?

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To establish whether LDAA therapy is safe without TML measurement.

Introduction: Low dose azathioprine (AZA)/mercaptourine (MP) and allopurinol co-therapy (LDAA) is a proven therapeutic option in inflammatory bowel disease (IBD) patients who develop side effects or hepatotoxicity to standard dose AZA/MP. It has been suggested that this combination is not safe to be used without measurement of thiopurine metabolite levels (TML).

Methods: LDAA therapy was introduced in our unit in 2010. Standard dose AZA is given at a dose of 2 mg/kg in TPMT wild-type. LDAA therapy is given at 25% of the standard AZA/MP dose. After commencing LDAA we monitor full blood count (FBC) and liver function test (LFT) weekly for 8 weeks and 3 monthly thereafter. 6-Thioguanine (TGN) and 6-methyl-MP nucleotide (MMPN) levels checked at 4–16 weeks.

Results: 76 patients started LDAA. Indications; drug side effects to standard dose AZA/MP, 42; hepatotoxicity, 19; Hypermethylation (MMPN:TGN ratio > 11), 9; gout, 4; high TPMT, 2; TML were available in 64 (84%). 11 (14%) stopped LDAA due to: intolerance; 9 (12%), leucopenia; 1 (1%), 1 (1%) non-compliant. Median TGN was 375.5 pmol/10^8 red blood cells (RBC) (range: 86–1083) with 6TGN (> 250) in 50 (78%). 6MMPN < 100 in 23 (30%). The remaining 41 (54%) median 6MMPN level was 170 (range 103–1205). Of the 64 (84%) patients remaining on LDAA at 6 weeks total white cell count < 3.5 10^9/l in 3 patients. TGN levels were 275, 483 and 686 pmol/10^8 RBC. Dose adjustment was made in a further 11 patients following TML; LDAA dose was increased in 9 due to low TGN; median 177 pmol/10^8 RBC (range 97–321) and reduced in 2 due to high TGN (1033 and 790). 2 of 19 patients on LDAA for hepatotoxicity had abnormal LFTs on starting LDAA; 1, autoimmune hepatitis/PSC and 1 under investigation. Neither stopped or reduced LDAA.

Discussion/Conclusion: Decisions regarding stopping LDAA were made based on FBC rather than TML monitoring. TML monitoring was used to ensure adequate dosing. These data therefore suggest that LDAA therapy dosed by weight and TPMT status with weekly FBC monitoring is safe without TML monitoring.
Optimizing anti-TNF-α therapy in IBD: Monitoring of trough levels and anti-drug antibodies

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Introduction: Primary or secondary failure of anti-TNF-α therapy in Crohn’s disease (CD) or Ulcerative Colitis (UC) are frequently observed in clinical practice and the relevance of adequate dose levels and anti-drug antibodies is still not well-defined and is attracting more interest.

Methods: A retrospective chart analysis of infliximab (IFX) or adalimumab (ADA) trough-levels and anti-drug antibodies in patients, being treated for CD or UC in our department. Evaluation was especially focused on consequences of laboratory testing for patients (therapy continued unchanged, therapy ceased, dose escalation effective/ineffective).

The aim was to investigate, whether laboratory testing for trough levels and anti-drug antibodies has relevant implications for further medical treatment.

Results: In 40 patients with primary or secondary loss of response to anti-TNF treatment (22 CD, 18 UC) we performed 45 laboratory tests (31 for IFX, 14 for ADA), resulting in 43 trough levels and 45 tests for anti-drug antibodies. 18 patients suffered from UC (9 women), 22 patients were treated for CD (14 women). According to Montreal classification course and behavior were severe in most cases (UC: 13/18 with E3; CD: 12/22 with B3, 7 of these with B3p). 31 measurements in IFX patients (15 CD, 16 UC) revealed 7 neutralizing antibodies, mean trough level was 8.17 µg/ml. 14 measurements in ADA patients (9 CD, 3 UC) indicated one neutralizing antibody, mean trough level was 10.36 µg/ml.

In patients treated with IFX, laboratory testing had relevant implications (discontinuation of treatment, successful improvement of therapy) in 22/31 (68%). For patients under ADA laboratory testing resulted in therapeutic modifications in 6/14 (43%).

Discussion/Conclusion: In patients with primary or secondary loss to anti-TNF-α therapy measuring trough levels and anti-drug antibodies seems to be relevant in a significant number of patients, as it may have impact on further therapy. Especially patients treated with IFX seem to benefit from laboratory testing (relevant therapeutic modifications in 68% vs. 43% ADA).
Ionizing radiation exposure in patients with inflammatory bowel disease: Are we overexposing our patients?

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Introduction: Crohn’s disease (CD) is a lifelong condition. Multiple imaging investigations are often performed during follow-up. This could cause overexposure to radiation. The aim of our study was to determine mean radiation dose in patients with at least a 5-year course of CD and to determine possible risk factors associated with exposure to high doses of radiation.

Material and methods: We conducted a retrospective study including patients who’s CD. Epidemiologic features of patients, characteristics of the disease, and types of imaging investigations that were performed during follow-up and cumulative radiation effective dose were determined. Risk factors associated with exposure to high doses of radiation were then, determined.

Results: One hundred sixty-seven patients were included. There were 92 males (55.1%) and 75 females (44.9%) with mean age at diagnosis of 31.4 years (11–75 years). Global radiation dose was 18.81 mSv (0.02–120.02). Twenty seven patients (16.2%) were exposed to more than 35 mSv and 4 patients (2.4%) had an exposure of more than 75 mSv. Use of Infliximab, age at disease onset ≤ 24 years old and number of flares ≥ 8 were independent risk factors of radiation exposure more than 35 mSv with odds ratios (OR) 2.543; 1.631 and 3.158, respectively. Similarly, use of Infliximab and number of flares ≥ 8 were independent risk factors of radiation exposure more than 75 mSv with OR 4.256 and 7.012 respectively.

Conclusion: Radiation risk seems to be increased with severe course of CD. Both referring physicians and radiologists have the responsibility to minimize radiation exposure. Entero-magnetic resonance imaging (Entero-MRI) may reduce this risk.
Effect of azathioprine on peripheral blood lymphocytes subsets in Crohn's disease patients

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Introduction: Azathioprine (AZT) is an immunosuppressive drug that is used in chronic inflammatory diseases such as Crohn's disease. It has been suggested that its molecular mechanism of action consisted in inducing apoptosis of T cells. Our goal was to determine whether azathioprine (AZT) modulates peripheral blood lymphocyte subsets (PBLS) in Crohn's disease patients.

Patients and methods: We conducted a prospective study including Crohn's disease outpatients during a 6-month period. We excluded patients who were put on immunosuppressive drugs other than azathioprine. We assessed absolute CD3(+), CD3(+) CD4(+), CD3(+) CD8(+) PBLS counts and CD4/CD8 ratios for patients who were put on AZT (AZT+) and those who did not take AZT (AZT-). Both groups (AZT+) and (AZT-) were compared to assess the effect of AZT on PBLS. Statistical analysis was performed using SPSS version 21.0.

Results: We included 62 patients. There were 21 males and 41 females of a mean age of 32.3 years old (8–61 years old). AZT was administered by 42 patients. Both groups (AZT+) and (AZT-) were comparable with regard to age and sex. Comparison of both groups showed a significant decrease in absolute total lymphocyte count (1368/mm³ vs. 1769/mm³, p = 0.014) and in PBLS counts in (AZT+) groups versus (AZT-) group: CD3(+) (762/mm³ vs. 1060/mm³, p = 0.006), CD3(+) CD4(+) (430/mm³ vs. 555/mm³, p = 0.036), CD3(+) CD8(+) (296/mm³ vs. 412/mm³, p = 0.04). However, CD4/CD8 ratio was roughly the same in both groups (1.6 vs. 1.5, p = 0.63) in (AZT+) and (AZT-) respectively.

Conclusion: Our findings suggest that azathioprine reduces peripheral blood lymphocyte subset (PBLS) counts in Crohn's disease patients. However, the balance between CD3(+) CD4(+) and CD3(+) CD8(+) is maintained. Larger studies are needed to confirm these results.
Clinical outcome of perianal fistulae in Crohn’s disease and impact of treatment strategies over the time

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Introduction: Perianal fistulae in Crohn’s disease (pfCD) is associated with complications leading to recurrent surgery and tissue damage. Immunosuppressive drugs (IS) including anti-TNF have changed the management of pfCD. Our aim was to describe the management and the natural history of a cohort of patients with active pfCD.

Methods: A retrospective study of pfCD patient’s registered between 2000 and 2014 in our department. The data collected were age, gender, personal and family history and the characteristics of the disease. Fistulae lesions included simple and complex fistulae. pfCD treatments included antibiotics and surgical drainage (with or without seton). Medical treatments including IS and anti-TNF were recorded at pfCD diagnosis and over follow-up. The effectiveness of treatment was assess.

Results: Seven hundred and ninety-nine records were reviewed. Eighty-six had perianal fistulaes. There were 44 men and 40 women with a mean age of 30.64 years. The mean delay of onset of perianal fistulas from the date of diagnosis of CD was 4.32 years. The perianal lesions were isolated in 8.1% of cases, associated with ileal involvement in 16.8% of cases, a colonic involvement in 26.7% of cases and ileocolonic involvement in 48.8% of cases. The CD was non-stricturing, non-penetrating, stricturing, and penetrating in 51.8%, 14, 2%, 26% of cases respectively. The clinical symptoms of perianal fistulae was represented by perianal purulent discharge in 81.4% of cases and the gas or stool emissions through the vagina in 8.1% of cases. The proctology exam allowed to individualize more fistulaes, anal fissures in 28% of patients and anal stenosis in 3% of patients. Pelvic MRI was performed in order to classify and search fistulas pelvic collections in 2/3 of cases this review showed complex fistulas in 59% of patients. Antibiotic therapy based Metronidazole or ciprofloxacin was prescribed in all patients. It was associated with a seton drainage in 51% of cases. Infliximab therapy was administered in 43% of patients. This treatment was associated with azathioprine in 30% of cases. The evolution of lesions was satisfactory (complete or partial response) in 82% of cases. The mean follow-up was 3.87 years with a recurrence of fistulas in 12% of cases.

Conclusion: In our study the prevalence of perianal fistulae in Crohn was 11%. The management of these lesions remains complex and follows a strategy integrating various therapeutic methods available.
Colectomy and ileorectal anastomosis during ulcerative colitis and Crohn’s disease: Results during follow-up

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Background: The aim of this study was to determine the follow up of the rectum state, functional results and quality of life after colectomy and ileorectal anastomosis (IRA) in inflammatory bowel disease (IBD).

Methods: Patients with ulcerative colitis (UC) and Crohn’s disease (CD) who underwent IRA from 2001 to 2014 were evaluated retrospectively.

Results: A total of 39 patients (female 49%) with a median age of 33 years (14–80) were included. CD (n = 28) and UC (n = 15). Median follow-up was 5.76 years (range 1 month–27 years). Mortality and morbidity rates were 2% and 11%. 8 surgical complications occurred, including 3 infectious complications (13.9%); 2 (7.7%) cases of anastomotic leakage and 1 case of pulmonary embolism. After a median follow-up of 5.76 years (range 1 month–27 years), 37 patients still had a functioning anastomosis; 1 patient had died and 1 had a proctectomy. The mean rates of 24 h and nocturnal defecation were 5.12 and 1.72. A disturbance of fecal or flatus continence occurred in 3 patients. There was no case of fecal incontinence to solid stool. Five patients complained of fecal precipitancy. Fourteen patients were taking some form of anti-diarrheal treatment. These drugs were taken regularly, often in large amounts, by 4 patients. Fifteen patients had developed symptomatic proctitis, 3 with severe endoscopic lesions. 9 patients required immunosuppressive treatment and 3 patients required biotherapy. Strictures of the rectum occurred in 2 patients, but one was minor. Three patients developed a rectal fistula. We didn’t note any case of rectal dysplasia.

Conclusion: Colectomy with ileo rectal anastomosis during CD or UC is safe with low postoperative morbidity and mortality.
Role of miRNA26b in inflammatory bowel disease

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Introduction: Crohn’s disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders of the gastrointestinal tract. Tumor necrosis factor alpha (TNF-\(\alpha\)) is one of the central cytokines in the underlying pathogenesis of mucosal inflammation in inflammatory bowel disease (IBD) and has been the primary target of biologic therapies. Previous studies on genome-wide expression profile of miRNAs revealed a significant up-regulation of miRNA26b after TNF treatment of HCT116 colorectal tumor cells. The aim of this study was to determine whether the miRNA26b could be a biomarker of inflammation and response to anti-TNF treatment in IBD patients.

Methods: Total RNA of all biopsy samples and serum was extracted. We examined 12 patients with CD and 10 patients with UC before anti-TNF treatment, 6 CD and 6 UC patients complete responders to anti-TNF treatment, 5 CD and 4 UC non-responders to anti-TNF treatment and 15 healthy controls. MiRNA26b expression profile was assessed using quantitative reverse-transcription polymerase chain reaction (qRT-PCR). U6 (an ubiquitous small nuclear RNA) was used as an endogenous control to normalize the expression level of target miRNA.

Results: The miRNA26b relative expression levels did not differ significantly between biopsies and serum samples in all cases. In both cases of active CD and UC before anti-TNF treatment miRNA26b expression was significantly overexpressed compared to healthy controls (\(p < 0.001\)). After TNF treatment miRNA26b was significantly upregulated only in CD cases and no in UC (relative expression levels in CD cases before treatment 28.99 ± 1.93, relative expression levels in CD cases after-TNF treatment 47.61 ± 3.008). It is interesting to notice that complete responders CD patients had increased miRNA26b levels (47.61 ± 3.008) compared to primary non-responder CD patients (37.76 ± 0.72), (\(p < 0.001\)).

Conclusion: Our data suggest that miRNA26b has the potential to be a specific biomarker in patients with CD, who are treated by anit-TNF agents.
Therapeutic options in the treatment of the moderate ulcerative colitis in patients with HBV or HCV infection

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Introduction: We assessed the efficacy and safety of mesalazine-budesonide combined therapy versus azathioprine in inducing remission in moderate UC in patients who associated UC with HBV or HCV infection.

Methods: This comparative analysis was performed on 37 patients with UC: A group composed of 12 patients who associated UC with viral B or C infection and B group consist of 25 patients without viral infection. In A group 5 patients were treated with oral mesalazine (Salofalk®, 2–3 g/day) and oral budesonide (3 mg x 3 times/day), for 6–8 weeks and 7 patients (with contraindicated corticoids therapy) were treated with azathioprine (1–1.5 mg/kg/day). In B group 15 patients were treated with oral mesalazine and budesonide and 10 patients were treated with azathioprine. We evaluated the Powell-Tuck index and endoscopic classification at baseline, after 1, 3, 6 and 12 months. Also, we monitored the liver function tests.

Results: In A group most of the patients (7 cases) presented left-sided UC, 4 patients had proctitis and only one extensive colitis. In B group the localization was: left-sided UC in 11 cases and proctitis in 14 cases. The distinctive features in patients with viral infection consists in the high incidences of: rectal bleeding (66.66%), diarrhea or paradoxical constipation (83.33%) and extraintestinal manifestation (58.33%). Also, they have a lower incidence of abdominal pain (33.33%) or weight loss (8.33%). Rapid response to associated treatment was observed in most patients without viral infection (60.0%) and only in one case (20.0%) in A group. At 3 months, the rate of clinical and colonoscopically confirmed remission after mesalazine-budesonide therapy was: 60.00% in A group and 53.34% in B group. Comparatively, the remission rate after azathioprine monotherapy was: 28.58% in A group and 50.0% in B group. Three patients with HBV or HCV infection discontinued azathioprine treatment due to leuco-trombocytopenia (one case) and increased aminotransferases levels (3 cases). We observed increases of the levels of HCV-RNA (one case) and HBV-DNA (3 cases). The diminution of the mean Powell-Tuck score at 3 and 6 months suggest a more slowly response in patients with viral infection.

Discussion/Conclusion: Mesalazine associated with budesonide achieved high remission rate in short term treatment in moderate UC and remains the first-line therapy in patients who associate UC with HBV or HCV infection.
**Comparative assessment of the risk to develop of the colorectal carcinoma in the usual therapeutic strategies for ulcerative colitis**

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**Introduction:** The aim of our retrospective study was to evaluate the incidence of colorectal cancer (CRC) in patients with UC. All patients were endoscopic and double contrast enemas examined and histological confirmed.

**Methods:** We monitored 67 patients with moderate to severe UC (for a period of 12 years) which were structured in two groups: A group composed of 40 patients who treated with oral mesalazine (Salofalk®, 2–3 g/day and oral budesonide, 3 mg x 3 times/day) in period of induction of remission and B group consist of 27 patients were treated with azathioprine (1–1.5 mg/kg/day).

**Results:** The incidence of CRC after 12 years was 13.44% (9 cases). The most of them had extensive severe colitis (6 patients) and a long duration of UC (8 cases). The type of adenocarcinoma was: papillary (2 cases), tubular (3 cases), mucinous (one case), villous (one case) and undifferentiated (2 cases). Most of those patients had Duke’s B stage (4 cases) or C stage (3 cases). The incidence of CRC was significantly high in B group (18.52% comparative with 10.00% in A group). The localization of carcinoma was: right colon (one case), transverse colon (one case), left colon (3 cases), sigmoid (one case) and rectum (3 cases). We established a strong correlation between the risk of development CRC and UC duration, but we identified a lower level of relationship between risk of CRC and frequency of recurrences. Development of CRC was not correlated with values of C reactive protein, baseline hemoglobin rates and albumin levels. We not determined a relationship between therapy for remission of UC and the incidence of CRC.

**Discussion/Conclusion:** The risk of development CRC was associated with duration of UC and extension of colitis. The risk of CRC was similar in mains usual therapy for inducing remission UC.
Red cell distribution width – RDW – as a marker of activity in inflammatory bowel diseases

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Introduction: Recent studies have shown a strong association between RDW and conditions of oxidative stress and inflammation. However, its utility as a marker of inflammation in IBD has not been studied extensively.

Methods: A total of 79 patients, 39 men and 40 women were studied with a mean age of 41.5 years. The study included 39 patients with CD, 19 with terminal ileitis and 20 with Crohn colitis, plus 40 patients with UC, 21 with left-sided colitis and 19 with pancolitis. The following parameters were calculated in the IBD group: CRP, ESR, WBCs, Hb, RDW, CDAI and 9-Partial Mayo score. The study included 20 healthy volunteers as a control group adapted according to age and sex, to whom the RDW, WBCs and Hb were estimated.

Results: An increased RDW, was observed in the group of CD (15.89 ± 3.56 vs. 13.32 ± 0.9, p = 0.002) and in patients with UC (14.95 ± 1.58 vs. 13.32 ± 0.9, p = 0.075), compared with the control group. A positive correlation was found in all patients between RDW and ESR (r = 0.124, p = 0.349). Positive correlation resulted in the group of CD between RDW and CRP (r = 0.261, p = 0.163), RDW and WBCs (r = 0.273, p = 0.145) and RDW and CDAI (r = 0.280, p = 0.141). In the group of UC a statistically significant association was found between RDW and ESR (r = 0.598, p = 0.001), RDW and CRP (r = 0.594, p = 0.001) and a positive correlation between RDW and Mayo score (r = 0.296, p = 0.218).

Discussion/Conclusion: RDW seems to be a convenient and reliable index of activity in IBD, though it requires more detailed study in the future.
A case of breast cancer following infliximab for treatment-refractory Crohn's disease

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Introduction: Crohn’s disease is an inflammatory condition characterized by transmural involvement of the whole gastrointestinal system. Some drugs are used for its treatment but the treatment is not always simple. Generally, 5-ASA, corticosteroids and immunosuppressive agents are used and anti-TNF antagonists (infliximab, adalimumab) are utilized when treatment with former agents proves unsatisfactory. Several side effects develop from the use of infliximab and even malignant conditions including hepatosplenic T-cell lymphoma and skin carcinoma may sometimes develop. A case with Crohn’s disease refractory to 5-ASA, corticosteroid and azathioprine treatments who developed breast carcinoma following infliximab treatment is being presented in this report.

Case: S.E, aged 44 years, presented to our polyclinic with weight loss, abdominal pain and flatulence. The patient was under follow-up and treatment for 7 years for Crohn’s disease, with no response to conventional therapy. Upon identifying inflammatory stricture with abdominal MR, the medicines the patient has been using was discontinued and anti-TNF-alpha (infliximab) treatment was initiated after receiving the consent of the patient. Quantiferon TB gold test performed prior to infliximab treatment was negative, so was PPD. The patient described that there were no masses or abnormalities in either of the breasts before treatment and anti-TNF was given according to the standard protocol. At month 3 of treatment, the patient detected a small mass at the left breast. Mammography was performed and demonstrated a 15 x 9.5 mm hypoechoic lesion containing millimetric components and a number of lymph nodules at the axillary region the largest of which was 14 mm. A lesion of BI-RADS4 appearance was identified with double-breast two-way mammography. Invasive ductal carcinoma + ductal carcinoma in situ (high grade) was detected in the biopsy from this lesion (picture 1, 2). In the report, ER (-) in the invasive tumor; in in situ areas, ER 60% (+), PR (-), Cerb B2 80% (+++), p53 1% (+) and Ki67 5%. Mastectomy was therefore performed and axillary lymph nodes were resected. No pathology was identified in the lymph nodes. The patient was then admitted to the general surgery clinic and intestinal resection covering an area of 40 cm including the stricture zone was performed for Crohn’s disease.

Because breast cancer was detected following infliximab treatment in this case, we believe that a breast examination (physical examination, mammary USG) must be performed in female patients prior to infliximab therapy.
New treatment modalities for IBD with flavonoids

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Introduction: Flavonoids are phytochemicals of plant origin with potent anti-inflammatory activities. They are mainly derived from fruits, vegetables and teas. There are some in vitro investigations on their mode of action in inflammatory models showing their antiinflammatory effectivities. IBD patients express high levels of cytokines and chemokines in the inflamed mucosa and their suppression could lead to mucosa healing. Flavonoids induce anti-inflammatory effects comparable to the effect of Mesalazine.

Methods: Therefore we used two models of experimental colitis in mice to examine the anti-inflammatory activity of a flavonoid combo which has previously been used as a nutritional supplement for prevention of colorectal carcinomas and adenomas in patients (Hoensch et al. World J Gastroenterol. 2008). Mice undergo experimental colitis models (TNBS- and oxazolone-colitis) and were treated with a flavonoid combo consisting of epigallocatechin gallate and apigenin. The mice received a daily oral application of the tea flavonoids for 7 days and were compared to mice with corn starch application.

Results: Under the flavonoid therapy regimen the severity of the Th1- and Th2-mediated colitis models was significantly reduced as shown by a miniendoscopy based colitis score. Others have reported that in experimental mice models with Crohn-like lesions treatment with flavonoids can induce remission of inflammatory lesions (Hur et al. Nutr Res. 2012).

Discussion/Conclusion: We suggest as future therapy approach to treat patients with IBD with a flavonoid combo to induce and maintain a stable remission of their chronic inflammatory bowel disease. For that a controlled, randomized clinical study should be initiated.
Low dose azathioprine and allopurinol in azathioprine intolerant patients: Is it tolerated and is it effective in IBD?

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To report the safety, tolerability and therapeutic outcome at 12 months, for LDAA in patients who have failed standard dose azathioprine.

Introduction: Despite the advancement and introduction of new biological therapies, thiopurines remain effective treatment options for the maintenance of remission for IBD. Once tolerated and therapeutic, thiopurines have many advantages over biologics for long-term maintenance therapy. However intolerance and adverse events are common. We have previously published our 36 month follow-up data reporting that 56.5% of our patients stop thiopurines due to side effects, abnormal liver function tests (LFTs) or therapeutic failure. Low dose azathioprine and allopurinol (LDAA) co-therapy is a well proven treatment option and has been used at our institution since 2010.

Methods: We maintain a prospective IBD data-base. After starting LDAA we monitor full blood count and LFTs weekly for 8 weeks. 6-Thioguanine (6-TGN) and 6-Methylmercaptopurine (6 MMPN) nucleotide levels are checked at 4–6 weeks. We searched our database for patients who started LDAA and had a minimum of 12 months follow-up. We recorded the indications for therapy, metabolite levels, and blood monitoring and clinical outcomes.

Results: 62 patients were started on LDAA. 25 (40%) were male. Mean age was 47 (range 16–77). Disease type UC, 21; CD,35; IBD(U), 6. Reasons intolerant to standard dose azathioprine were: drug side effects (nausea and arthralgia) 24; hepatitis (ALT 2x upper limit normal) 20; Hypermethylation (TGN: MMPN ratio > 11), 12. Gout 4; High TPMT 2.
At 12 months 44 (70%) remained on LDAA and were in clinical remission (HBI < 1 for CD), (stool frequency < 4 and no bleeding for UC) with therapeutic 6TGN levels on LDAA, of these 7 (11%) required additional treatment with biologic therapy.

Discussion/Conclusion: LDAA is well tolerated and effective in patients who failed standard dose azathioprine due to drug side effects and hepatotoxicity. This therapy results in resolution of hepatotoxicity and will allow more IBD patients to achieve clinical remission.
Clinical significance of liver injury secondary to tumor necrosis factor-alpha antagonist therapy in patients with inflammatory bowel disease

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Introduction: In patients with inflammatory bowel diseases (IBD), biologic therapy in order to inhibit tumor necrosis factor-alpha (TNF-alpha) has become a safe and efficient treatment modality. However, although safe, anti-TNF-alpha agents are potential causes of drug-induced liver injury. It has been suggested that anti-TNF-alpha agents lead to autoimmune hepatitis by triggering development of autoantibodies. In this study, our aim was to report our experience in 16 IBD patients with elevated serum alanine aminotransferase (ALT) levels due to anti-TNF-alpha therapy.

Methods: In this retrospective study, we evaluated 172 patients who received anti-TNF-alpha therapy due to IBD. A total of 16 (9.3%) out of 172 patients (12 women, mean age: 39.6) were identified as having elevated ALT levels indicating liver injury at any time after starting anti-TNF-alpha therapy.

Results: Of these 16 patients, 11 had Crohn’s disease and 5 had ulcerative colitis, 10 patients received infliximab and 6 patients received adalimumab. Mean ALT level was 72 U/l (reference value: < 45 U/l) and the mean time period from first drug injection to the identification of ALT elevation was 243 days. While 6 patients recovered spontaneously, 3 patients had undergone liver biopsy indicating steatohepatitis in all and 7 patients were followed-up on therapy due to mild elevation of ALT. All of the patients had negative serologic test results for autoimmune liver diseases.

Discussion/Conclusion: Liver injury caused by anti-TNF-alpha agents is usually mild and be apparent during the first 8 months of the therapy and usually it is not necessary to withdraw the drug in mild cases. Although most common clinical presentation of liver injury caused by anti-TNF-alpha agents carries autoimmune features, steatohepatitis could be another causative condition.
Terminal ileitis in adult patients with Crohn's disease: Is there still a place for surgery as first-line therapy?

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Introduction: Although uncomplicated terminal ileitis is usually managed medically, limited resection could represent a relevant alternative. It was demonstrated in a pediatric population that early surgery was associated with a reduced need of immunosuppressors (IS) and biologics. The aim of this case-control retrospective study was to compare the course of the disease according to the carried treatment (medical or surgical) in adult patients.

Methods: Each patient with an uncomplicated and limited terminal ileitis treated by intestinal resection was matched with two controls treated medically. Matching was performed according to three major criteria i.e. length of ileitis, disease duration, history of intestinal resection and three minor criteria (smoking status, sex and age). The need for IS, biologics, steroids, hospitalization, surgery and the rate of relapses or recurrences were assessed and compared during a two years follow-up.

Results: Fifty-one patients were identified (18 cases and 36 controls). The clinical, demographic and radiological characteristics were similar between cases and controls except for the B3 phenotype more frequent in the cases (p = 0.01). During the follow-up, the patients treated surgically received less corticosteroids, IS and biologics as compared to the controls (p = 0.01, p = 0.05 and p = 0.02 respectively). Thirty eight percent of the patients initially treated medically needed a surgery during the two years of follow-up. The number of hospitalization days and the rate of recurrences were similar in the two groups (p = 0.1, p = 0.4).

Discussion/Conclusion: In selected patients, surgery appears to be an attractive alternative to the medical management leading to a diminished use of steroids, IS and biologics but prospective studies are needed to define more precisely the best candidates to this strategy.
OCT4B1, a spliced variant of OCT4, is expressed in inflammatory bowel disease

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Introduction: OCT4, a POU-domain transcription factor is considered to be a key factor in maintaining the pluripotency of stem cells. Several OCT4 isoforms are differentially expressed in human pluripotent and non-pluripotent cells. Aim of our study was to identify the presence of developmentally early cells in both peripheral blood and intestinal tissue from patients with Crohn's disease (CD) and ulcerative colitis (UC).

Materials and methods: Both blood and tissue samples were collected from 17 patients with active CD and 13 UC, as well as form 4 healthy individuals. Total RNA was extracted and cDNA was prepared. OCT4 expression and isoform determination were documented by reverse transcription-PCR and real-time PCR. SOX-2 expression levels were also examined by real-time PCR. The isoforms expressed in the studied cases were confirmed by sequencing.

Results: In all samples, OCT4B1 isoform was expressed. OCT4B1 expression levels were higher in blood samples from CD and UC. More specifically, in blood samples OCT4B1 was expressed 6.87 ± 1.94-fold greater in CD and 3.37 ± 0.53-fold greater in UC compared with healthy controls. Similar results were obtained in tissues samples, also. On the other hand, the mRNA levels of SOX2 were found slightly increased compared to healthy controls, in both blood and tissue samples of CD patients only.

Conclusion: Our results are in agreement with previous studies, showing that OCT4 is expressed in peripheral blood in patients with CD. Developmentally early cells, such as hematopoietic stem progenitor cells (HSPCs), mesenchymal stem cells (MSCs), endothelial progenitor cells (EPCs), and very small embryonic-like stem cells (VSELs), are mobilized into peripheral blood in response to tissue/organ injury, suggesting a role of these cells in repair of damaged intestinal tract.
Visceral adipose tissue adipokine expression is differentially regulated in TLR9\(^{wt/wt}\) versus TLR9\(^{-/-}\) mice in a model of chronic inflammatory bowel disease

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**Introduction**: Adipokine secretion of visceral adipose tissue has been implicated in the human inflammatory bowel disease process. Adipocytes have been demonstrated to express functional TLR9 molecules. Of note, both TLR9-deficient and leptin-deficient ob/ob mice show a more moderate course of chronic DSS-induced colitis (DSS-CC) as compared to wild-type animals.

**Methods**: We characterized mRNA expression levels of various adipokines in visceral adipose tissue during DSS-CC as compared to baseline levels in TLR9\(^{wt/wt}\) versus TLR9\(^{-/-}\) mice. Additionally, the effect of inhibiting TLR9 signaling via TLR9 blocking peptide on adipokine secretion was evaluated in 3T3-L1 adipocytes in vitro.

**Results**: TLR9\(^{wt/wt}\) mice demonstrated significantly increased leptin mRNA expression levels during DSS-CC, while leptin mRNA expression was reduced in colitic TLR9\(^{-/-}\) animals as compared to baseline. Visfatin expression was increased in colitic TLR9\(^{-/-}\) mice, whereas it remained unchanged in TLR9\(^{wt/wt}\) animals. CTRP-3 expression was found to be reduced in colitic TLR9\(^{-/-}\) mice, while it remained unchanged in DSS-CC in TLR9\(^{wt/wt}\) animals. In vitro, TLR9 blocking peptide inhibited leptin protein accumulation in cell culture supernatants of 3T3-L1 adipocytes, while visfatin protein accumulation was increased.

**Discussion/Conclusion**: Pro- and anti-inflammatory adipokine expression levels in visceral adipose tissue during DSS-CC are differentially regulated in TLR9\(^{wt/wt}\) versus TLR9\(^{-/-}\) mice. Since visceral adipose tissue adipokine secretion has been implicated in the inflammatory bowel disease process in humans, our results warrant further studies dissecting a potential interplay between the TLR9- and leptin-signaling pathways in visceral adipose tissue during inflammatory bowel diseases.
Metastatic Crohn’s disease following rectal resection: A case report

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We report a case of a 24-year-old female patient with Crohn’s disease diagnosed in 2009 (with small bowel involvement, erythema nodosum, arthralgia, iron deficiency anemia and hypokalemia). We initiated azathioprine treatment and then added infliximab, switched to azathioprine plus steroids, then adalimumab and finally cyclophosphamide, all of which eventually had no effect.

In 2010 the patient was admitted presenting abdominal pain, significant diarrhea (5–6/day), burning pain and secretions peranally. The diagnosis was intersphincteric fistula at 6–9 o’clock with an anorectal abscess, with partial destruction of the sphincter due to Crohn’s disease. An incompetent sphincter between 3 and 9 o’clock was demonstrated, with severe proctitis. The abscess was drained and ciprofloxacin/metronidazole orally was initiated. She was discharged symptom free for further outpatient infliximab therapy and daily wound cleansing. However, she soon complained of persisting wound infections and perianal fistulation. Therefore, the patient underwent a subtotal proctocolectomy in 2012, leaving a rectum remnant with permanent ileostomy. In 2013 the situation required a laparoscopically assisted abdomino-perineal excision of the rectum remnant. This procedure left a large perineal wound cavity which did not heal for 1½ years. Subsequently, she also developed a vaginal fistula and surgical repair was attempted with a gracilis interposition but this approach also failed and the large open wound persisted.

In August 2014 the patient initiated therapy with adalimumab (40 mg sc eow) plus azathioprine (100 mg), because by then a biopsy from the wound margins had revealed granulomatous inflammation, i.e. metastatic Crohn’s disease. She was also on extensive analgesic therapy (oxycodone, Fentanyl TTS). Finally, the vaginal fistula closed and the large wound gradually healed as evident during the regular wounds dressing changes under propofol anesthesia. Currently, she is successfully mobilized and feeling well. There was no evidence of granulomas or malignancy in the current histology report.
Natural history of azathioprine therapy in Crohn’s disease patients: An Indian study

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Introduction: Aim of this study is to assess natural history of Azathioprine (AZA) therapy in Crohn’s disease patients, long term safety profile and adverse effects of thiopurines in the Indian patients.

Methods: We retrospectively reviewed 164 cases of Crohn’s disease patients on azathioprine.

Results: Total of 164 patients of Crohn’s disease on azathioprine were included. Of which 33.54% were females and 66.46% males. Median duration of disease before diagnosis of Crohn’s disease was made was 36 months (1–240 months). 27% (n = 45) were categorised as L1 according to Montreal classification, 15.24% (n = 25) as L2, 35.37% (n = 58) as L3 and isolated upper GI (L4) in 4.27% (n = 7) cases. 10.98% (n = 18) were L1+L4 modifier, 1.83% (n = 3) were L2+L4 modifier and 4.88% (n = 8) were L3+L4 modifier. 22% were having B1 (non-stricturing, non-penetrating) disease, 61.6% were having B2 (stricturing) disease and 15.9% were B3 (penetrating) disease. 17% (n = 28) were having perianal disease. In 3% steroid alone was used in induction regimen, in 37% steroids plus AZA, in 32% steroids plus 5-ASA and in 28% cases surgery was done for induction. 37% (n = 61) cases were steroid dependent cases. Median duration of AZA therapy was 42.5 months (3–192 months). 77% (n = 127) of patients were maintained on remission without a single relapse. Out of 37 patients who had relapse on AZA, 9 were non-compliant to therapy. Biologics were used in 5 patients who were having frequent relapses on AZA. Adverse effects were noticed in 32% (n = 53). Most common adverse effect being haematological (n = 47), GI symptoms (n = 2), hepatitis (n = 1), reactivation of pulmonary tuberculosis (n = 1) and itching (n = 1). 6.7% (n = 11) discontinued AZA therapy, out of which 5 due to adverse effects and 6 due to incomplete knowledge of disease.

Conclusion: Relapse free long term remission maintenance can be achieved by AZA (77%). Most common adverse effect being haematological, but only 3% of patients discontinued AZA due to adverse effects.
The clinical factors associated with adherence of the patients with inflammatory bowel diseases to the treatment

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Introduction: Adherence of the patients with inflammatory bowel diseases is important to maintain the remission. However, the patients do not always keep their appointments for treatment. The aim of this study was to investigate the clinical factors associated with adherence of patients in terms of appointment keeping.

Methods: A total of 73 subjects were retrospectively investigated from Sep 2005 to Jan 2012 at secondary care university hospital. We reviewed medical records including the age, sex, residence, medications, the disease activity, and the rate of keeping the date. A punctual visit was defined as outpatient visit on the scheduled date ± 7 days. Good patients for the visit were defined as their punctual visit rates exceed 90%.

Results: Male to female ratio was 2.4. Mean age was 41.5 ± 15.4 years (range, 20 to 78). Ulcerative colitis was 53 cases (72.6%) and Crohn’s disease was 20 cases (27.4%). Mean duration of disease was 42.0 ± 41.6 months (range, 4–226). Mean overall punctual visit rate was 86.7 ± 16.0%. Thirty-eight patients (52.1%) were good patients for the visit. Azathioprine/6-mercaptopurine treatment was associated with good patients for the visit (odds ratio = 3.19, 95% confidence interval: 1.12–9.09, p = 0.03). However, other clinical factors did not influence the punctual visit rates.

Discussion/Conclusion: Our study demonstrated that the use of azathioprine/6-mercaptopurine was associated with keeping the appointment for meeting the doctor. Further prospective study would be necessary.
TL1A/TNFSF15 expression is highly upregulated in human intestinal myofibroblasts stimulated with pro-inflammatory factors that are components of the mucosal milieu in Crohn’s disease

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Introduction: Intestinal myofibroblasts (ISMFs) play a key role in gut fibrosis. TL1A/TNFSF15 and its receptor DR3 (TNFRSF25) belong to the TNF/TNFR superfamilies of proteins and are highly upregulated and functionally involved in intestinal inflammation. Recent studies in TL1A transgenic mice implicated TL1A/DR3 signalling in inflammation-induced intestinal fibrosis. We examined whether the pro-inflammatory mucosal environment that exists in Crohn’s disease (CD) may provide stimulatory signals that result to upregulation of TL1A in ISMFs.

Methods: ISMFs were isolated from endoscopically-obtained colonic biopsies from healthy controls (HC) and patients with CD. Cultured IMFs were stimulated with recombinant human IL-1α and/or TNF-α, or supernatants from HT-29 epithelial cells cultures, that were cultured in the presence of rhIL-1α+rhTNF-α + rhIFN-γ or supernatants from 24hs cultures of colonic mucosal biopsies from HC and CD patients. Total RNA was extracted from cultured ISMF and HT-29 cells and the relative expression of mRNA for TL1A, DR3 and DcR3 was measured by real-time RT-PCR and protein expression by immunofluorescence.

Results: Pro-inflammatory factors were found to induce the expression of TL1A in ISMFs and of its functional receptor, DR3, in intestinal epithelial cells. Specifically, IMFs stimulated with IL-1α and/or TNF-α expressed a significant upregulation of TL1A mRNA (p < 0.01 vs. unstimulated) and TL1A protein expression. Supernatants from cultures of TNF-α-stimulated HT-29 cells also induced the expression of TL1A in ISMFs (p < 0.05 for any combination vs. unstimulated HT-29 cell supernatants). Supernatants from CD-derived colonic tissue cultures induced significantly higher upregulation of TL1A expression (> 3-fold increase over HC, p < 0.05). In addition, the expression of DR3 was significantly elevated in cultured HT-29 epithelial cells stimulated with the combination of pro-inflammatory cytokines IL-1α + TNF-α + IFN-γ.

Discussion/Conclusion: Pro-inflammatory factors-induced expression of TL1A by ISMFs and DR3 expression on epithelial cells might orchestrate an interplay that contribute to the pathogenesis of chronic intestinal inflammation and fibrosis.
Increased pulse wave velocity and relationship with inflammation, insulin and insulin resistance in inflammatory bowel disease

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Introduction: Both ulcerative colitis and Crohn’s disease are forms of inflammatory bowel disease (IBD), which is characterized by chronic, progressive inflammation of the gastrointestinal tract. Recent studies have shed new lights on the importance of inflammation to the pathogenesis of arterial stiffness. We aimed to evaluation of the relationship between pulse wave velocity (PWV) measurement and biochemical parameters in inactive and active IBD patients without cardiovascular risk factors and comparison with the control group.

Methods: We enrolled 102 IBD patients without cardiovascular risk factors, and 74 matched controls and evaluated each patient in active and inactive disease periods. All patients completed a standard questionnaire form and we assessed various laboratory parameters. We carried out vascular measurements with a Mobil-O-Graph 24 h Pulse Wave Analysis Monitor, an automatic oscillometric device.

Results: Although cardiovascular risk factors, such as total cholesterol and low-density lipoprotein cholesterol were significantly lower \((p < 0.05)\) in IBD patients than controls, 24 h, day and night PWV values, erythrocytes sedimentation rate (ESR), C-reactive protein (CRP), insulin, homeostasis model assessment of insulin resistance (HOMA-IR) and homocysteine (Hcy) were higher in patients with active and inactive IBD than controls \((p < 0.05)\). Multiple linear regression analysis showed that PWV was positively correlated with age and duration of IBD.

Discussion/Conclusion: This study revealed increased PWV, Hcy, ESR, CRP, insulin, and HOMA-IR in patients with active and in active IBD and provides evidence to the potential contribution of inflammation and inflammation-related factors to arterial stiffening independent from conventional cardiovascular risk factors.
Risk matrix for prediction of disease progression in a referral cohort of patients with Crohn’s disease

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Introduction: Early identification of patients with Crohn’s disease (CD) at risk for subsequent complications is essential for adapting treatment strategy. The aim of the present study was to develop a prediction model including clinical and serology markers for assessing the probability of developing advanced disease 3, 5 and 7 years after diagnosis in a prospective referral CD cohort.

Methods: 271 consecutive CD patients (42.4% males, median follow-up: 10.9 years) were included. ASCA IgA and IgG and anti-OMP Plus™ antibodies were determined by QUANTA Lite® ELISA (INOVA Diagnostics, San Diego, CA), cut-off 25 U/ml. Detailed clinical phenotypes were determined prospectively from diagnosis during the follow-up by reviewing the patients’ medical charts. The analysis was limited to patients with inflammatory disease behaviour at diagnosis. Total exposure to steroids, azathioprine or anti-TNFs were 88.2%, 73.8% and 41.7%, respectively. At diagnosis, 45% had ileocolonic disease and 79.7% had inflammatory behaviour, while 52% had complicated disease behaviour and 41.1% had at least one resective surgery at last follow-up. Two definitions were used for advanced disease: 1. having intestinal resection or progression in disease behaviour and 2. having intestinal resection, progression in disease behaviour, or need for thiopurines (IBSEN definition).

Results: ASCA (IgA and/or IgG) but not anti-OMP Plus™ status, disease location, and need for early azathioprine were included in the 5-year prediction matrix. The probabilities of advanced disease during this period varied from 6.2% to 55% depending on the combination of predictors.
B1 behavior at diagnosis | colon only | ileal |
---|---|---|
ASCA poz | early AZA YES | 50.0% | 55.0% |
| early AZA no | 30.8% | 29.0% |
ASCA neg | early AZA YES | 11.1% | 22.2% |
| early AZA no | 6.2% | 18.8% |

Table 1: Association between ASCA IgA and IgG positivity, disease location and need for early azathioprine (AZA) with the probability of developing advanced disease 5-years after the diagnosis in patients with initial inflammatory disease.

The 3- and 7-year ASCA-based model resulted in probabilities of advanced disease ranging from 0 to 45.5% and from 11.1% to 64.7%. In addition, the model including ASCA, disease location, and early need for steroids but not age at onset, was only predictive for the outcome at 5-years if the IBSEN definition was used. In contrast, the association was lost if the need for azathioprine was excluded from the advanced disease definition.

**Discussion/Conclusion:** Our prediction models identified substantial differences in the probability of developing advanced disease in the short and intermediate course of CD. Markers identified in this referral cohort were different from those previously published in the population-based cohort suggesting that different prediction models should be used in referral setting.
The industrial food additive microbial transglutaminase is immunogenic in celiac disease children

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Introduction: Microbial transglutaminase (mTg) is capable of cross-linking numerous molecules thereby revolutionizing industrial food product qualities. It is a family member of human tissue transglutaminase (tTg), the autoantigen in CD. Despite declarations of the safety of mTg, direct evidence for immunogenicity of the enzyme in celiac patients is lacking.

Methods: The serological activity of mTg, tTg, gliadin complexed mTg (mTg neo-epitope) and gliadin complexed tTg (tTg neo-epitope) were studied in: 95 pediatric celiac patients (CD) mean age 8, 99 normal children (NC) mean age 8.5 and 79 normal adults (NA) mean age 28.1. Sera were tested by ELISAs, detecting IgA, IgG or both IgA and IgG: AESKULISA® tTg (tTg), AESKULISA® tTg New Generation (tTg neo-epitope [tTg-neo]), microbial transglutaminase (mTg) and mTg neo-epitope (mTg-neo). The results were correlated to the degree of intestinal injury, using Marsh criteria.

Results: Comparing pediatric CD patients with the 2 normal groups: mTg-neo IgA, IgG and IgA+IgG antibody activities exceed the comparable mTg ones (p < 0.0001). All mTg-neo and tTg-neo levels were higher (p < 0.001). tTg IgA and IgG+IgA were higher than mTg IgA and IgA+IgG (p < 0.0001). The levels of tTg-neo IgA/IgG were higher than tTg IgA/IgG (p < 0.0001). The sequential antibody activities, reflecting best the increased intestinal damage, going from M0 to M3c were: tTg-neo IgG > mTg-neo IgG > tTg-neo IgA > tTg IgA > mTg-neo IgA. Taken together, mTg-neo IgG and tTg-neo IgG correlated best with intestinal pathology (r² = 0.989, r² = 0.989, p < 0.0001, p < 0.0001, respectively). mTg-neo IgG had higher sensitivity than tTg-neo IgG, with lower specificity.

Discussion/Conclusion: mTg is immunogenic in children with CD and by complexing to gliadin its immunogenicity is enhanced. Anti-neo-epitope mTg antibodies correlate with intestinal damage to the same degree as anti-tTg. In view of the pathogenic role allocated to tTg antibodies, further studies are needed to explore the pathogenic potential of anti-mTg antibodies in CD.
The break in intestinal tight junction (TJ) permeability by industrial food additives explains the rising incidence of autoimmune diseases

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Autoimmune disease (AD) incidence is increasing worldwide. Simultaneously, the food industry introduces ingredients that revolutionize food product qualities by constantly transforming our food composition through new food processing technologies. The intestinal epithelial barrier, with its intercellular tight junction (TJ), controls the equilibrium between tolerance and immunity to self-antigens. As a result, particular attention is being placed on the role of tight junction dysfunction in the pathogenesis of AD. Tight junction leakage is enhanced by many luminal components, commonly used, industrial food additives being some of them. The results are linked, transformed molecules and delivery systems, resulting in intestinal mucosal load with altered physicochemical and immunogenic properties. It is hypothesized that commonly used industrial food additives abrogate human epithelial barrier function, thus, increasing intestinal permeability through the TJ, resulting in entry of foreign immunogenic antigens and activation of the autoimmune cascade.

Glucose, salt, organic solvents, emulsifiers, gluten, microbial transglutaminase, and nanoparticles are being exponentially used by food industries to improve the qualities of the food, as claimed by the manufacturers. However, all those food additives increase intestinal permeability by opening TJ paracellular transfer by the following described mechanisms: Rearrangement, disturbance and destabilization of TJ protein (Zonulin-1, E-cadherine, catenin, actine, occludin, and claudin), contraction of the perijunctional actomyosin ring, decrease in the hydrophobicity of the mucus layer, dissociation of the PTP1B-E-cadherin-beta-catenin complex, induction of actin disbandment and structural separation of TJ. In fact, in multiple AD, a breach in TJ integrity and function was observed. Future research on food additive exposures on intestinal permeability and autoimmunity interplay will enhance our knowledge of the common environmental mechanisms associated with AD. As a corollary, individuals with non-modifiable risk factors (i.e., familial autoimmunity or carrying shared autoimmune genes) should consider decreased exposure to some food additives in order to avoid increasing AD risk.
Comparative results after colectomy and ileorectal anastomosis versus ileal pouch-anal anastomosis for inflammatory bowel disease

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Introduction: The aim of this study was to compare the fate of the rectum, functional results and quality of life after ileorectal anastomosis (IRA) or ileal pouch-anal anastomosis (IPAA) in inflammatory bowel disease (IBD).

Methods: Patients with ulcerative colitis (UC), Crohn’s disease (CD) and indeterminate colitis who underwent either IRA or IPAA from 2001 to 2013 were evaluated retrospectively. 17 patients with an IPAA were matched by age, sex and follow-up duration with 39 patients with IRA and compared for functional outcomes and quality of life.

Results: A total of 56 patients (female 53%) with a median age of 33 (14–80) years were matched in two groups. In Group 1 (G1), 39 patients underwent 40 IRA (in 1 patient the anastomosis was done twice) for CD (n = 28) and UC (n = 15). In Group 2 (G2), 17 patients underwent IPAA for UC (n = 16) and CD (n = 1). Median follow-up was 6 years (range 1 month–27 years). Mortality and morbidity rates in G1 were 2% and 11%. 8 surgical complications occurred, including 3 infectious complications (13.9%) and 2 (7.7%) cases of anastomotic leakage and 1 case of pulmonary embolism. In G2, morbidity rate was 40% and so significantly higher (p < 0.05), but no case of surgical complications occurred at the short term. After a median follow-up of 6 years (range 1 month–27 years), in G1, 37 patients still had a functioning anastomosis; 1 patient had died and 1 had a proctectomy. In G2, 14 patients still had functional anastomosis, 1 patient had pouch surgical reconfection and 2 had surgical dilatation.

The mean rates of 24 h and nocturnal defecation were 5.12 and 1.72 in G1 versus 4 and 2 in G2 (n.s.). A disturbance of faecal or flatus continence occurred in 3 patients in G1 versus 2 in G2 (p < 0.05). There was no case of faecal incontinence to solid stool in both groups. Five patients complained of faecal precipitancy in G1 versus 3 in G2 (n.s.). In G1, fourteen patients were taking some form of anti-diarrheal treatment versus 9 in G2 (p < 0.05). Fifteen patients in G1 had symptomatic proctitis, 3 with severe endoscopic lesions, nine patients required immunosuppressive treatment and 3 patients required biotherapy. In G2, three cases of pochitis were recorded. Three patients in G1 developed a rectal fistula versus 3 in G2 (p < 0.05).

In G1, late obstructive episodes occurred in 2 patients, only 1 required laparotomy for division of adhesions and relief of obstruction. In G2, it occurred in three patients (p < 0.05) requiring surgical dilatation in two cases and anastomosis reconfection in 1 case. We didn’t note any case of rectal dysplasia or cancer.

Discussion/Conclusion: Colectomy with IRA is safer than IPAA with lower postoperative morbidity.
Postoperative morbidity remains high in patients with Crohn’s disease who underwent an ileocecal resection with a temporary stoma

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Introduction: In situations with high risk of anastomotic leakage a temporary digestive bypass is recommended in patients with Crohn’s disease (CD) undergoing an ileocecal resection.

The aim of this study is to assess morbidity in patients with CD who underwent an ileocecal resection with temporary stoma.

Methods: We retrospectively reviewed charts of all patients with CD who underwent an ileocecal resection in our center between 1998 and 2013. They were divided in 2 groups:

Group 1: patients who had a temporary digestive bypass (double ileostomy and colostomy or ileostomy upstream of ileocolonic anastomosis).

Group 2: patients who didn’t have a stoma.

Results: Of the 186 patients who underwent ileocecal resection, 53 (28.4%) had a temporary stoma; divided into 30 men and 23 women (sex ratio M/F = 1.3). The prevalence of smoking was similar in the two groups (25.5% vs. 20.7%, respectively; p = 0.765).

Complications specific of the disease were significantly more frequent in G1: collections (9.4 vs. 3%, p = 0.032), directed fistulas (15 vs. 4.5%, p = 0.021), occlusions (7.5 vs. 1.5% p = 0.043) as well as emergency interventions (7.5 vs. 0%, p = 0.018), and laparotomy (39.6 vs. 23.3%, p = 0.037).

Overall morbidity in G1 was 24.5% (n = 13): deep abscesses (7.5%; n = 4 including a case of peritonitis), ileus (5.6%; n = 3) and medical complications (9.4%; n = 5). Two patients required reoperation.

Compared to G2 (12.7%; n = 17) in G1 overall morbidity was significantly higher (p = 0.038).

The average hospital stay was longer in G1 compared to G2: 11.1 days vs. 7.3 p = 0.014. Two deaths were noted in G1 and none in G2.

Discussion/Conclusion: A temporary digestive bypass in ileocecal resection for Crohn’s disease is conducted to prevent postoperative complications. In our experience, postoperative morbidity remains high compared to patients who did not have a stoma. Patients should be informed.
Impact of vaginal delivery on development of peri-anal disease in female patients with Crohn's disease

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Introduction: Crohn's disease (CD) often affects women during the reproductive years. Although several studies have examined the impact of pregnancy on luminal disease, limited literature exists in those with peri-anal CD. The optimal delivery method in patients with Crohn's disease is unknown, and there is no large-scale evidence on which to base decisions. Decision regarding mode of delivery is a unique challenge in such patients due to concerns regarding the effect of the pelvic floor trauma during delivery.

Methods: We performed a retrospective chart review of patients with CD with established Crohn's disease. We assessed the association between the history of vaginal delivery prior to the diagnosis of Crohn’s disease and the development of peri-anal disease during the follow up.

Results: We identified 202 female patients with CD, with the mean age of 34 years [19–70]. Sixty-nine (34%) had a history of vaginal delivery, 9 through C-section and 124 (61%) never been pregnant. During the follow up 48 patients developed peri-anal disease, 41 had a fistulating peri-anal disease. Peri-anal disease occurred more frequently in women with history of vaginal delivery than those with no history of vaginal delivery (45% vs. 20%; OR = 3.36, 95% CI: 1.77–637; p < 0.001). This difference remains significant if we consider only fistulating peri-anal disease (37% vs. 17%; OR = 2.87, 95% CI: 1.47–5.61; p < 0.01).

Discussion/Conclusion: We observed a statistically significant association between development of peri-anal Crohn’s disease and vaginal delivery prior to diagnosis in female patients with Crohn’s disease. This was a retrospective study, with its inherent limitations; prospective studies with a larger cohort are required.
Two-year efficacy and safety of azathioprine treatment in the maintenance of steroid-free remission in Crohn’s disease patients

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Introduction: Azathioprine (AZA) is widely used for maintenance of remission in patients steroid-resistant or dependent with Crohn’s disease (CD). The aim of this study has been to investigate its efficacy and safety in maintaining steroid-free remission in steroid dependent and steroid refractory CD patients two year after the institution of treatment.

Methods: Data from consecutive CD outpatients referred in our Institution, between 2008 and 2012, were reviewed and all patients treated with AZA were included in this retrospective study. AZA was administered at the recommended dose of 2–2.5 mg/kg. Blood sample was analysed before administration of the drug, every 10–15 days for the first 3 months and then every 3 months following the institution of treatment.

Results: Out of 236 consecutive CD outpatients visited in the index period, AZA was prescribed to 138 patients (58.4%). Fifteen patients with a follow-up < 24 months were excluded from the study. Among patients, 55.1% were male and 58.1% female (average age of 32.5 years, range 15–70 years). Two years after the institution of treatment, 95 (77.2%) patients still were in steroid-free remission, 21 (17.0%) had a relapse requiring retreatment with steroids, 7 (5.7%) discontinued the treatment due to side effects.

Discussion/Conclusion: The study confirms that AZA is an effective therapeutic tool for maintaining steroid-free remission in CD patients. Two years after the onset of treatment more than two/thirds of patients did not require further steroid courses. The occurrence of side effects leading to the withdrawal of AZA treatment was low.
Crohn's disease predictors after a first episode of acute ileitis: Role of persistently high CRP within one month

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Introduction: Acute ileitis is a common emergency. Although infectious causes predominate, an inaugural push of ileal Crohn's disease (CD) should be considered. The objective of this study is to identify predictive factors of CD in patients with a first acute ileitis.

Methods: This is a single-center follow-up study performed between January 2010 and December 2013. Patients hospitalized for radiologically confirmed acute ileitis were included. An initial clinical, biological and morphological assessment was performed and the patients were reviewed in consultation with a 1-month biological assessment. Depending on the clinical course additional endoscopic assessment was performed if necessary. Univariate and multivariate analysis in search of predictors of CD were performed.

Results: The data were analyzed in 31 patients, including 14 women and 17 men (sex ratio M/F = 1.21). The mean age was 29.4 years (range 17–48 years). Ten patients were smokers (32.2%), 4 had a family history of CD (12.9%) and 7 an appendectomy history (22.5%). One patient had an abdominal defense at the time of inclusion. The average leukocyte rate 13598/mm3 and the mean CRP level was 39.4 mg/ml. An intra-abdominal abscess was initially present in 9.6% of cases (n = 3). Main causes are pyogenic infectious ileitis in 67.7% of patients (n = 21), ileal CD in 7 patients (22.5%). Three patients had intra-abdominal collections and 3 others had ileocecal tuberculosis (9.6%).

The average time before making the diagnosis of CD was 7.3 weeks. After a follow-up year, five patients required surgical management (16.1%). In univariate analysis, the presence of an abscess at diagnosis (p = 0.02) and the persistence of elevated CRP in control consultation to 4 weeks after hospitalization (p = 0.012) were two factors predictive of MC. Only the high CRP levels was found in multivariate analysis (p = 0.381).

Discussion/Conclusion: This study shows that acute ileitis is often due to pyogenic infections and quickly resolutive. Achieving an ileocolonoscopy should not be systematic but is required if persistently high CRP after a month.
Infliximab and adalimumab in TNF-α naive Crohn’s disease patients: A Tunisian cohort study

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Introduction: Tumor necrosis factor-α inhibitors (TNFi), infliximab (IFX) and adalimumab (ADA) have far become a major treatment of Crohn’s disease (CD). However, despite their broad clinical use, studies comparing their efficacy in TNF-α naive patients with CD are missing.

Methods: Consecutive TNF-α naive patients with luminal CD were retrospectively analyzed for short- and long-term efficacy of IFX and ADA.

Results: In total 62 patients, 52 (83%) starting IFX and 10 (17%) ADA, were included. At baseline the median Harvey Bradshaw-Index score was 8 (6–30) and 8 (5–36), the mean CRP 2.7 ± 2.9 mg/dl and 2.6 ± 3.2 mg/dl for IFX and ADA, respectively. In total 34/62 (55%) subjects were on concomitant immunomodulators, 18/62 (29%) were on steroids at start of anti-TNF.

There was no difference regarding clinical remission as defined by HBI < 5 points (IFX 28/52; 54% vs. ADA 5/10; 50%, p = 0.32) and steroid-free remission (IFX 27/52; 52% vs. ADA 6/10; 60%, p = 0.54) at week 12. Duration of disease was identified as predictor of response at week 12, defined as HBI drop ≥ 3 points (OR = 1.05; 95% CI: 1.024–1.097).

After 12 months there were 23/52 (44.2%) patients treated with IFX and 4/10 (40%) with ADA in remission (p = 0.42). Baseline CRP ≥ 0.7 mg/dl (OR = 0.24; 95% CI: 0.07–0.77, p = 0.01) was the only predictor of remission at month 12 in patients without anti-TNF intensification. There was a trend in favour of ADA (OR = 2.96; 0.87–10.07, p = 0.08), and smoking (OR = 2.12; 95% CI: 0.89–5.04, p = 0.09).

Discussion/Conclusion: IFX and ADA appear comparable regarding short and long-term remission in TNF-α naive luminal CD patients. Shorter disease duration and CRP ≥ 0.7 mg/dl are associated with higher rate of short- and long-term remission, respectively.
Peri-anal disease as a predictive factor of disabling Crohn's disease

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Introduction: The successful treatment of Crohn’s disease is dependent of an adequate prediction of the course of the disease, in order to promptly institute a more aggressive treatment approach in those patients with a higher probability of a poorer outcome. Peri-anal disease is considered a predictive factor for disabling Crohn’s disease. However, its real impact in the global prognosis is not well known. The aim of our study was to analyze whether the presence of perianal disease is an indicator of a more severe abdominal Crohn’s disease.

Methods: We proceed to a retrospective analysis of the data of patients with Crohn’s disease followed in our outpatient clinic. Number of hospitalizations and surgeries and the need of immunosuppressant and biologics because of abdominal disease were analyzed, comparing the patients with and without perianal disease.

Results: Two hundred and eighty-seven patients were identified, 60.9% females, with mean age of 33.8 years. Mean age at diagnosis was 27 years, with a mean duration of the disease of 86 months. Forty-six percent had 35.5% ileal, 35.8% ileo-colic and 26.8% colic disease, with upper digestive tract involvement in 4.1%. Twenty-six percent had peri-anal disease.

No differences between patients with or without peri-anal disease were found regarding the need to use steroids (p = 0.275) or hospitalization (p = 0.312) at diagnosis, as regarding the mean number of intra-abdominal surgeries (0.45 vs. 0.51, p > 0.05), or time to anti-TNF therapy (53 vs. 49 months, p > 0.05). Peri-anal disease was not a risk factor for intra-abdominal surgery (RR = 1.117, CI 95%), and patients without peri-anal disease had the first abdominal surgery earlier (34 vs. 21 months, p < 0.05). In the other hand, patients with peri-anal disease needed more cycles of steroids (3.53 vs. 2.31, p < 0.05), more hospitalizations (4.29 vs. 2.13, p < 0.05) and earlier immunosuppression with azathioprine (46 vs. 31 months, p < 0.05).

Discussion/Conclusion: Patients with perianal disease needed more cycles of steroids and earlier prescription of azathioprine. However, we may conclude that, overall, they did not have a more disabling abdominal Crohn’s disease, since they did not need more hospitalizations, surgeries or biologics because of abdominal disease.
Outcome of early surgery versus aggressive medical therapy in patients with newly diagnosed limited inflammatory/obstructive (A2/3L1B1/2) terminal ileitis: A two-year, prospective, single-center, pilot study

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Background: Data are scarce regarding the outcome of ‘curative’ early surgery (ES) versus ‘aggressive medical therapy’ [AMT, azathioprine (AZA) and anti-TNF biologics] for limited mixed inflammatory-obstructive Crohn’s terminal ileitis (LMI/OTI). EST achieves removal of the affected segment and induces prolonged remission reserving immunosuppressives for patients at high-risk for post-operative recurrence. AMT can induce and maintain remission of CD but may be associated with serious adverse events and cannot guarantee long-term avoidance of surgery.

Aim: To assess prospectively in a single-center pilot study the 2-year outcome of EST vs AMT in consecutive patients with LMI/OTI (phenotype A2/3L1B1/2).

Methods: Eligible were patients with newly diagnosed active (CDAI > 180) LMI/OTI CD (despite treatment with 9 mg/day budesonide for 6–8 weeks) and at high-risk for post-operative recurrence. LMI/OTI was defined as the combination of: a) raised inflammatory indices (leukocytes, platelets, CRP), b) involvement of ≤ 25 cm terminal ileum, characterized by a narrow lumen, ulcerated but slightly distensible bowel wall with pre-stenotic dilatation although not purely stricturing disease at enteroclysis or MRI enterography, and c) inability to pass the colonoscope to the proximal unaffected ileum. After a thorough discussion, enrolled patients opted for AMT or EST (laparoscopic or open). EST patients received AZA (2.5 mg/kg) for post-operative prophylaxis starting 14 days after surgery. AMT patients received standard doses of AZA and anti-TNF agents. Patients were followed for 2 years by physical examination and laboratory tests at bimonthly visits. Endoscopy was performed at 6, 12, and 24 months. Primary end-points were endoscopic remission (Rutgeerts score ≤ 1) for EST and avoidance of surgery for AMT.

Results: Between 2007 and 2011, 17 patients [7M:10F, mean age 24 (18–67) years, 12 smokers] consented to undergo EST and 17 patients [8M:9F, age 26 (17–68) years, 13 smokers] received AMT. 2 years after EST, 3/17 (18%) patients had endoscopic recurrence and switched to biologics; 82% patients were in endoscopic remission. On AMT, 10/17 (59%) patients underwent surgery for complications (bowel obstruction and/or abscess, n = 5), lack of efficacy (n = 3) or adverse events to therapy (n = 2); seven patients were in clinical remission (3 in deep remission).
Conclusion: In this pilot study in consecutive CD patients selected by the A2/3L1B1/2 phenotype, EST appears to offer a better 2-year outcome than AMT. However, decisions should be taken on a case-to-case basis considering patient’s age, life expectations, disease activity, relative degree of obstruction vs inflammation, and treatment morbidity. Large prospective trials are needed to evaluate longer-term outcomes.
Comparison of the reliability of celiac disease serology to reflect intestinal damage

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Introduction: In view of the increasing importance of the serological biomarkers for the screening and diagnosis of celiac disease, their differential performance, and the lack of head to head comparison, we undertook the task to evaluate the reliability of those isolated or combined antibodies to reflect the intestinal damage in children with CD.

Methods: 95 pediatric CD patients (mean age 8.3 ± 4.4), 45 non-specific abdominal pain children (AP) (mean age 7.3 ± 5.1), 99 normal children (NC) (mean age 8.5 ± 4.2) and 79 normal adults (NA) (mean age 28 ± 5.1) were tested by the following ELISAs, detecting IgA, IgG or both, IgA and IgG: AESKULISA® Gliadin (AGA), AESKULISA® tTg (tTG; RUO), AESKULISA® DGP (DGP) and AESKULISA® tTg New Generation (Neo-epitope tTg complexed to gliadin = tTg-neo). The results were compared to the degree of intestinal injury, using revised Marsh criteria, where M0 is normal and M3c is maximally affected. Scatter diagrams and regression analysis comparing the 12 antibodies’ OD activities to the degree of the intestinal damage were correlated.

Results: In general, the comparison showed that most of the assays are able to differentiate patients with low and high degree of intestinal damage. Comparing the different correlations between CD associated IgA and IgG antibodies’ isotypes, the tTg neo IgA ($r^2 = 0.968$, $p < 0.0025$) and tTg-neo/DGP IgGs ($r^2 = 0.989$, $p < 0.0001$; $r^2 = 0.985$, $p < 0.0001$, respectively) stood out, significantly, as the best indicators of the intestinal damage in CD. The highest optical density (OD) values (medium OD 2.94 ± 1.2, $p < 0.0001$) were achieved by using the tTg-neo IgA ELISA in patients with Marsh 3c.

Discussion/Conclusion: Therefore, it is suggested that tTg-neo IgA/IgG antibodies should be preferably used to reflect intestinal damage during screening, diagnosing and monitoring compliance in childhood CD.
Methylation and expression of the genes that have a role in the Wnt signaling pathway in ulcerative colitis

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Introduction: Ulcerative colitis is a chronically inflammatory disease of colon. Wnt signaling regulates intestinal epithelial stem cell function. Secreted Frizzled-related protein (SFRP) and Dickkopf families inhibit Wnt signaling. A recent study has contributed to the accumulating evidence that the Wnt pathway also plays a distinct role in inflammation and immunity. Our aim is to investigate the methylation and expression status of WNT signaling pathway genes in ulcerative colitis.

Methods: Patient group composed of 20 people diagnosed with left sided ulcerative colitis and having surveillance colonoscopy, control group composed of 15 people having colon cancer screening, not having any complaints or endoscopic pathology. DNA and RNA are obtained from the biopsies inflamed and non-inflamed mucosa of the patient and control groups. SFRP2, SFRP4, SFRP5, APC1, APC2 and ACTB gene expressions are determined by Real-Time PCR and “Comparative CT (.Ct)” analysis. The methylation status of the genes are studied by using methylation specific PCR.

Results: For APC2 gene methylation; in patient group 8 people are methylated (40%) and 12 are un-methylated (60%) whereas in the control group 1 is methylated (6.7%), 14 are un-methylated (93.3%) (p = 0.018). In patient group, for SFRP5 gene, a significant relationship is observed between the methylation status and expressions (p = 0.015). Regarding the other genes, no significant statistical relationship is observed among the methylation, expression and inflammation status between the patient and control groups.

Discussion/Conclusion: In ulcerative colitis, it is suggested that the findings of the increase in the methylation of APC2, and the decrease in the expression due to the increase of SFRP5 methylation both have a relationship with inflammation. However, further studies are needed in order to suggest its relationship with ulcerative colitis.
Prospective anti-TNF withdrawal in quiescent Crohn's disease – 12 month clinical outcomes

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Introduction: Anti-Tumour Necrosis Factor (Anti-TNF) is an effective yet expensive intervention in Crohn's disease. The STORI trial outcomes suggest that withdrawal of Infliximab therapy may be safe.

Methods: Between April and July 2013 all those attending Paisley RAH and the Vale of Leven Hospitals with Crohn’s disease on anti TNF had their cases evaluated at 3 ‘virtual’ clinics. Assessment tool criteria for quiescent disease (absence of symptoms, no recent escalation, established 2nd line therapy and absence of active inflammation on endoscopy or radiology) were used to identify those in clinical remission. The 9 individuals were offered a withdrawal from anti TNF therapy with optimisation of 2nd line therapy as appropriate. 12 month clinical outcomes were prospectively recorded.

Results: Of 36 individuals identified, 8 patients were deemed to be in remission at the time of reassessment and were therefore withdrawn. 6 of those patients maintained a remission for the following twelve months. 1 patient relapsed within 1 month of withdrawal and another relapsed 11 months after withdrawal. Both achieved clinical remission on prompt retreatment.

Discussion/Conclusion: Withdrawing Anti-TNF therapy, in the context of quiescent Crohn's Disease, appears to be safe and effective, providing there are mechanisms in place for prompt assessment and reintroduction of therapy. The cost savings by using this strategy can be substantial. The estimated cost savings in our study for 1 year are 90,000 pounds.

References:

1. NICE Guidelines – CE technology appraisals [TA187] Published date: May 2010
   Infliximab (review) and Adalimumab for the treatment of Crohn's disease.

Selection of the optimal volume and method of surgery in non-specific ulcerative colitis

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Aim: To improve the results of treatment of the patients with severe form of non-specific ulcerative colitis.

Material and methods: Investigation was undertaken on 162 patients with heavy form of non-specific ulcerative colitis. In the process of study there was determined localization of the pathological process: distal – 20 (12.3%), left-side – 26 (16.1%), subtotal – 38 (23.5%), total – 78 (48.1%). Due to the presence of such complications as toxic dilatation and stricture of the colon the intraoperative colonofibroscopy has been performed. This study was induced by requirement of identification of the upper level of lesion.

Results: During comparison of the results of investigations before and after operation we observed contraindications in the pre- and intraoperational diagnosis. Thus, for example, in 2 patients who had diagnosis of distal form of disease during intraoperative colonofibroscopy there was found left-side localization of the process. In 4 patients with preoperative diagnosis of left-side localization of the ulcerative process the intraoperative colonofibroscopy revealed total lesion of the colon. Out of 14 patients with preoperative diagnosis the total form of necrotizing ulcerative colitis on the intraoperative colonofibroscopy was revealed subtotal form in 3 patients, and left-side form of necrotizing ulcerative colitis in 2 patients. Consequently we performed the following operations: abdominal-anal resection of the rectum in 18 (11.1%) patients, left-side hemicoloproctectomy in 24 (14.8%), subtotal coloproctectomy in 36 (22.2%), total coloproctectomy in 61 (37.7%), and total coloproctectomy with formation of pouch-anal anastomosis in 23 (14.2%) patients. Macropreparation was underwent histological investigation that confirmed justification of the selected operation volume. There were no recurrences in the long-term follow-up period.

Conclusion: Thus, in the majority of the cases the surgical intervention seems to be method of choice for treatment of non-specific ulcerative colitis and the volume of operative intervene has direct correlation with pre- and intraoperative investigations including intraoperative colonofibroscopy.
Preparation of a rectal stump for recovery surgery following total colectomy in ulcerative colitis

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Introduction: Probiotics produce a pronounced curative effect in IBD which is associated with changes in production of short chain fatty acids, a fall in secretion of anti-inflammatory cytokines, improvement in the Th1/Th2 ratio, the state of the intestinal barrier and elimination of pathogenic bacteria.

The goal of the present work is to improve results of recovery surgery in patients with IUDI by use of probiotics for normalization of the state of a rectal stump following total colectomy.

Materials and methods of the study: The study includes 115 patients with IBD. Total colectomy with formation of a rectal stump and application of ileostomy were performed in all the patients. The patients were distributed into 2 groups: the main group comprised 62 patients who received postoperatively a basic (sulfasalazine, Salofalk®, corticosteroids), systemic medication and probiotics, the control one consisted of 53 patients who received basic and systemic therapy only. Lactobacterium siccum and Bificoli siccum were used orally in 5 doses 3 times a day respectively. Bificoli siccum was used one time per rectum daily in the afternoon. The treatment efficacy was estimated according to clinical indicators, the amount of the rectal discharge, the period of epithelialization, occurrence of granulations, etc.

Results and discussion: Good results were achieved in 40 (64.50%) patients, satisfactory ones in 22 (35.4%). No unsatisfactory results were observed. The picture was quite different in the control group: good results were obtained in 21 (39.6%), satisfactory ones in 29 (54.7%), unsatisfactory ones in 3 (5.6%) patients.

Good results in patients of both groups in all cases were accompanied by normalization of the mucous structure (according to the data of endoscopy, a cytologic and histologic study), improvement in the general state, a decrease in discharges from the rectal stump. Following the recovery surgery, the postoperative period proceeded smoothly, without any complications. The patients of the main group continued receiving probiotics in the postoperative period and that was reflected in a reliable decrease of duration of the nearest postoperative period: 8 ± 0.7 days in the main group and 12 ± 1.2 in the control one (p < 0.05).

Conclusion: Thus, a continuous administration of probiotics in patients with IBD in the pre- and postoperative periods resulted in significant improvement of clinical and laboratory rates, which seems to be associated with their anti-inflammatory and adaptive properties and a role of dysbacteriosis in immune pathological processes. It is recommended to include continuous courses of probiotics into complex therapy of IBD as well as for preconditioning of a rectal stump for recovery surgery.
Protists fauna in patients with ulcerative colitis and colorectal cancer

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Introduction: Aetiology and pathogenesis of intestinal bowel diseases and colorectal cancer (CC) still remains unclear. Leading role of intestinal microbiota doesn't raise doubts, but intestinal protists fauna is only begun to study.

Methods: Intestinal Protozoa were detected in 62 patients with ulcerative colitis (UC) and 55 ones with CC and 200 healthy individuals. Triple coproscopy with evaluation of infection intensity was used.

Results: Blastocystis hominis (B.h.) were found in 83.8 ± 4.6% and 92.7 ± 3.5% of patients with UC and CC respectively and in 18.0 ± 2.3% of healthy individuals (p < 0.001). A high intensity of B.h. infection was observed only in patients with UC and CC (respectively in 26.9 ± 2.3% and 12.5 ± 2.3%) and was not found in healthy individuals. Prevalence of Chylomastix mesnili in patients with UC and CC and healthy individuals amounted to 16.1 ± 4.6%, 20.0 ± 5.3% and 3.0 ± 4.6% respectively (p < 0.05). Jodamoeba butschlii infectiousness in patients with UC and CC was correspondingly 4–2 times as high as in healthy individuals. Some changes in prevalence of other Protozoa were detected too.

Discussion/Conclusion: A high level of B. h. prevalence and intensity in patients with UC and CC is in agreement with data of Chandramathi et al. (2010–2012) on ability of antigen from B.h. to facilitate growth of human colorectal cancer cells. A high level of B.h. prevalence and intensity in patients with UC could indicate to the role of B.h. in inflammation induction. Thus study of protists fauna can complete our idea of UC and CC pathogenesis.
Efficacy and safety of endoscopic balloon dilatation of symptomatic intestinal Crohn’s disease strictures

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Introduction: Bowel strictures are a major cause of morbidity in patients with Crohn's disease (CD). Endoscopic balloon dilatation (EBD) is an alternative to surgical resection in selected patients. However, this technique has been evaluated only in some small and heterogeneous studies. This study aimed to evaluate the clinical efficacy and safety of hydrostatic EBD in a consecutive cohort of symptomatic intestinal CD strictures.

Methods: The records of all patients with CD in whom EBD was attempted over a 14-year period were examined retrospectively to determine the rate of technical success, complications and outcome. Clinical success rate was claimed if a patient remained asymptomatic and did not require surgery or further EBD, following technical success.

Results: Over the study period, 46 EBD were scheduled for 29 patients (13 female, 16 male, mean age 54.2 years) with CD symptomatic and radiographically confirmed ileo-colic stenosis. Disease duration was 10.3 (3–25) years. The mean follow-up period was 16.1 months (range, 6–60 months). EBD was mainly applied to anastomotic stenosis. Technical success was achieved in all patients. There was no major complication. As well, there was no procedure-related mortality. During the follow-up, 11 patients (37%) underwent an intervention, including 8 (27.6%) with repeat dilatation (median 2.7, range 2–5), and 3 (10.3%) with surgical resection. Median time from first dilatation to surgery was 9 (4–15) months and to repeat dilatation was 10 (6–19) months. Clinical success rate was 63%. Success rate after serial EBD was 89.7%. At univariate analysis, age < 60 years, disease duration < 5 years (p = 0.03), a greatest caliber of the balloon > 15 mm (p = 0.04) and active CD (p = 0.001) were associated to clinical success. There was no influence of all the following variables: gender, stricture localization, length and number, as well as postsurgical strictures when compared to naive lesions.

Discussion/Conclusion: EBD dilation is a safe and effective method that allows surgery to be avoided in approximately 90% of patients with CD-associated medically refractory short intestinal strictures. It should be considered as a real alternative to surgery. Dilatation may be repeated in recurrent intestinal obstructions and appears safe without morbidity.
Introduction: Survivin, a member of the inhibitors of apoptosis family. Survivin has been studied extensively in cancers but little is known about its role in IBD. Recently, it was found that the levels of survivin are increased in LPTs from CD patients. Promoter polymorphisms that affect survivin expression might be potential risk factors for the development of IBD. The aim of this study is to genotype the survivin promoter polymorphisms namely -31G/C, -241T/C, and -625G/C, in CD, UC patients and controls, and to identify a possible association between individual genetic variation and disease susceptibility.

Methods: The expression of survivin in tissues and blood of patients and controls was detected by semiquantitative RT-PCR. A total of 97 CD, 88 UC, and 152 healthy controls were evaluated for the three polymorphisms in survivin promoter. Polymorphisms were identified using the PCR-RFLP technique.

Results: No significant differences were found between mRNA levels of survivin between CD, UC patients and controls in both tissue and blood samples. The significant differences in both allele and genotype frequencies between CD, UC patients and controls were found in -31G/C polymorphism. For this SNP, the frequencies of the C alleles were 0.56 in CD, 0.63 in UC, and 0.48 in the controls, thus the -31C allele had a 1.46-fold increased risk of CD with statistical significance (95% CI: 1.02–2.10), and a 1.95-fold increased risk of UC with statistical significance (95% CI: 1.33–2.85). Our results indicate that the -625G/C and -241T/C polymorphisms were not associated with the development of CD or UC, however, these polymorphisms were found to be significantly over-represented in controls. The polymorphisms tested were not significantly associated with clinicopathological characteristics among CD and UC patients.

Discussion/Conclusion: Our finding suggested that survivin promoter polymorphisms -31C/G might influence the susceptibility to CD and UC in the Greek population.
Infliximab trough concentrations during the induction therapy predict short-term mucosal healing in patients with ulcerative colitis

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Introduction: Mucosal healing is an independent predictor of sustained clinical remission in patients with ulcerative colitis (UC) treated with infliximab (IFX). We investigated whether IFX trough concentrations (TC) during the induction phase can predict short-term mucosal healing (STMH) in UC patients.

Methods: Patients who underwent an endoscopy both at baseline and after induction therapy were eligible for this observational, retrospective, single-center study. STMH was defined as a Mayo endoscopic sub-score of 0 or 1, assessed after the induction phase, with a baseline sub-score of 2 or 3. Infliximab TC were evaluated in prospectively collected serum samples at weeks 0, 2, 6 and 14 after IFX initiation using an in-house developed and clinically validated ELISA.

Results: Patients with STMH (n = 55) had higher IFX TC (median [IQR]) compared to those without (n = 46) at week 2 (22.7 [15.9–31.6] μg/ml, p = 0.016, Mann-Whitney U test), week 6 (17.3 [9.6–25.3] μg/ml, p = 0.001) and week 14 (7.4 [3.4–11.2] μg/ml, p = 0.016). A ROC curve analysis identified a cut-off of 22.5 μg/ml at week 2 (AUC: 0.642, p = 0.016) and 12.8 μg/ml at week 6 (AUC: 0.691, p = 0.001), as predictive values for STMH. Univariate analysis identified IFX TC > 22.5 μg/ml at week 2 (p = 0.013, OR = 3.1 [95% CI: 1.3–7.3]), IFX TC > 12.8 μg/ml at week 6 (p = 0.002, OR = 3.9 [95% CI: 1.7–9.1]), female gender (p = 0.039, OR = 2.5 [95% CI: 1.1–5.9]) and azathioprine (AZA) at IFX initiation (p = 0.009, OR = 3 [95% CI: 1.3–6.9]), as parameters predicting STMH. Multiple logistic regression analysis retained IFX TC > 12.8 μg/ml at week 6 (p = 0.004, OR = 3.6 [95% CI: 1.5–8.6]) and AZA at IFX initiation (p = 0.024, OR = 2.7 [95% CI: 1.1–6.6]) as independent factors predicting STMH.

Discussion/Conclusion: This study indicates that early IFX TC may be important for guiding therapeutic decisions in UC patients treated with IFX, while concomitant immunomodulators may play a significant role towards STMH.
Presence of anti-GP2 IgG and IgA antibodies assessed by 2 different ELISA assays is associated with younger age at onset, stricturing disease behavior, need for surgery and ASCA/anti-OMP™ positivity

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Introduction: Recent studies have demonstrated that major pancreatic zymogen granule membrane glycoprotein 2 (GP2) is essential for host-microbial interaction and the initiation of bacteria-specific mucosal immune responses in the gut. Enhanced formation of antibodies against GP2 was identified in Crohn's disease (CD). The aim of the present study was to determine the predictive potential of the anti-GP2 antibodies in the determination of disease phenotype, therapeutic strategy and long term disease course in a prospective referral CD cohort. Association of anti-GP2 with conventional serologic markers were also assessed.

Methods: 271 consecutive CD patients (42.4% males, median follow-up: 131 months) were included. Anti-GP2 IgA and IgG were determined by 2 different ELISA methods (QUANTA Lite® anti-MZGP2 IgA and IgG ELISA, INOVA Diagnostics, San Diego, CA and the anti-GP2 IgA and IgG ELISA, Generic Assays, Dahlewitz/Berlin, Germany. Cut-off levels were 25 U/ml and 20 U/ml, respectively). Sera were assayed for ASCA and anti-OMP Plus™ as well. Detailed clinical phenotypes were determined prospectively during the follow-up by reviewing the patients’ medical charts.

Results: 10.2% and 12.2% of the CD patients were positive for anti-GP2 IgA/IgG and anti-MZGP2 IgA/IgG, respectively. The agreement between assays was good (kappa = 0.56). At diagnosis, 45% of the patients had ileocolonic disease and 79.7% had inflammatory behavior, while 52% had complicated disease behavior and 41.1% had at least one resective surgery at last follow-up. Exposure to steroids, azathioprine or anti-TNFs was 88.2%, 73.8% and 41.7%, respectively. Presence of anti-MZGP2 IgA/IgG was associated with pediatric onset (A1: 26.9%, A2: 11.6% and A3: 6.1%, p = 0.02), colonic or ileocolonic location (p = 0.035), stenosing disease behavior at diagnosis (B1: 10.8%, B2: 27.3%, B3: 4.5%, p = 0.015), penetrating disease behavior at last follow-up (p = 0.03), need for azathioprine (p = 0.025, OR = 3.74), need for surgery (p = 0.02, OR = 2.38), ASCA (p < 0.001) and OMP™ (p = 0.004) positivity.
Similarly, anti-GP2 IgA/IgG positivity was associated with pediatric onset ($p = 0.053$), complicated disease phenotype ($p = 0.005$) and lack of perianal disease ($p = 0.05$) at diagnosis, need for surgery ($p = 0.017$, OR $= 2.77$) and with ASCA ($p = 0.003$) and anti-OMP Plus™ ($p = 0.01$) positivity. None of the antibodies was associated with the time to initiation of steroids, azathioprine, anti-TNFs or behavior changes overall in patients with initial inflammatory disease in a Kaplan-Meier analysis. In contrast, both anti-MZGP2 and anti-GP2 IgA/IgG positivity was associated with the time to surgery ($p = 0.038$ and $p = 0.046$).

**Figure 1**: Association between the presence of anti-GP2 IgA or IgG antibodies and time to resective surgery

**Discussion/Conclusion**: Presence of anti-GP2 IgG and IgA antibodies was associated with disease phenotypes identifying patients at a younger age at onset, ileocolonic location, stricturing/complicated disease behavior, need for surgery and ASCA/anti-OMP Plus™ positivity in this prospective referral CD cohort. The agreement between the two anti-GP2 assays was good.
The role of colonic resistance: Changes of colonic microbiota participate in pathogenesis of IBD

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Introduction: The mechanisms explaining complex relationship between the commensal colonic microbiota and IBD have a common outcome, a violation of bacterial antigens exposure to effector T-cells and innate immune cells residing in the intestinal mucosa and/or alteration of the host immune response to bacteria. While the role of gut microbiota and respective immune changes has become more evident in recent years there is no sufficient database explaining the character of microbiota changes in IBD. The aim of this study is to find relation between changes of colonic microbiota and IBD.

Methods: Totally 104 individuals participate in the study. Among them 34 had proven IBD, (12 – CD, 22 – UC) others with at least three risk factors of IBD (family history, smoking, antibiotics, travel history, immune, etc). Colonic resistance studied in mucosal bioplates. Standard aerobic and anaerobic microbiology techniques with nosology identification and quantity composition of microbiota were used.

Results: Major autochthonic species (14 in total) were present in all samples: among them Lactobacteria, Bifidobacteria, E. coli, several other anaerobic species, were dominating. However, Lacto- and Bifidobacteria were found in significantly lower levels compared to healthy subjects (p = 0.02–0.0031). The general tendency for colonic resistance in IBD was decrease of autochthonic anaerobes (Bifido-, Lactobacteria, Bacteroides spp, Clostridia spp, Bacillae spp.) and significant growth of allochtonic aerobes and facultative anaerobes (E. coli Hly+, Pseudomonas, Serratia, Hafniae, P. mirabilis and other conditionally pathogenic Enterobacteriaceae). Enterococci were present in 60.0% of control and 7.14–20.69% of study group. Staphylococci were present only in study group (17.24–31.58%).

Discussion/Conclusion: Our data suggest that morbid changes of colonic mucosal microbiota, e.g. abnormal ratio of autochtonic and allochtonic species, may be considered as a strong characteristic feature of IBD. Meanwhile, there is no exact IBD "pathogen" found.
Results of the one-stage associated surgeries in ulcerative colitis

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Introduction: The problems of one-stage associated operative interventions in the abdominal surgery remain unresolved, are carried out from 1.5 up to 2% of the patients.

Methods of research: In the 132 patients underwent operative interventions due to inflammatory-ulcerative diseases of the colon. Of them 80 (60.6%) were men and 52 (39.4%) – women. With the purpose of diagnostics, besides standard investigations there were used: colonfibroscopy with biopsy, irrigography, virtual colonoscopy, computed tomography and others.

Results: As a result of research it was established, that in 57 (43.2%) patients there were diagnosed distal and left side lesions with non-specific ulcerative colitis. In 6 (4.5%) patients Crohn’s disease with a total damage of the colon was found. In 37 (28%) patients there was available functioning ileostoma after total colectomy due to non-specific ulcerative colitis.

Besides in 26 (19.7%) patients there were diagnosed accompanying surgical diseases of other organs of the abdominal cavity including chronic calculous cholecystitis – 16, ovarian cysts - in 6, anterior ventral hernia – in 4 patients.

Operations concerning the basic disease including abdominal-anal resection of the rectum and resection of the sigmoid intestine with formation of descendoanal anastomosis were performed in 32 patients, left-hand hemicolectomy, abdominal-anal resection of the rectum with formation of the transversoanal anastomosis were made in 25 patients. Of 32 patients with non-specific ulcerative colitis 6 ones were revealed Crohn’s disease with total damage of the colon. In 26 patients the total colectomy with formation of ileostoma was carried out and in 12 ones there was carried out colproctectomy with formation of ileoanal anastomosis with use of circular-suturing device. In 37 patients who had functional ileostoma applied after total colectomy due to non-specific ulcerative colitis there were performed anterior resections of the rectum and formation of the ileoanal anastomoses with use of circular-suturing devices. The associated surgeries included cholecystectomy – in 16 patients, removal of ovarian cysts – in 6 and herniotomy – in 4 patients.

In the postoperative period in 11 patients (8.3%) there were found the following complications: the partial necrosis of the descending intestine – in 2 patients, suppuration in the presacral area – in 2, partial failure of ileoanal anastomosis – in 4 patients. There were no lethal cases.

Conclusion: Thus, one-stage associated operations in inflammatory-ulcerative diseases of the colon do not contribute to the increase in rate of the postoperative complications and lethality. During formation of the interintestinal anastomoses the most results were obtained with use of circular-suturing devices.
To the problem of surgical rehabilitation of the patients after total coloproctectomy

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Background: Restoration of the continuity of the gastrointestinal tract after total coloproctectomy due to inflammatory-ulcerative lesions of the colon presents complex and difficult for recovery problem of the current colorectal surgery. This problem was connected with difficulties not only because of formation of iliac-anal anastomosis but also with restoration of reservoir function of the colon.

Aim: To evaluate efficacy of the methods of restorative operations after total coloproctectomy.

Patients and methods: This report presents experience of treatment of 31 patients who were made reconstructive operations after total coloproctectomy. The reasons of the coloproctectomy performance in these patients was total form of non-specific ulcerative colitis, Crohn's disease and diffusive polyposis of the colon. The first step was total coloproctectomy with formation of one-trunk ileostoma in 18 patients, the total colectomy with formation of the stump of the rectum and one-trunk ileostoma in 9 patients. In 4 patients the separation of the colon was performed by formation of two-trunk preventive ileostoma as palliative operation.

The following methods of reconstructive operations were performed: formation of S-shaped pouch from iliac intestine with ilio-anal anastomosis in 19 patients, J-shaped pouch-anal anastomosis in 8 patients, W-shaped pouch-anal anastomosis in 2 patients and ilioanal anastomosis in 2 patients.

Results: In the postoperative period the process of rehabilitation in the patients was more favourable in the patients with J- and S-pouch. Of them in the long-term period of observation the number of defeication in the day time was 1–2 times and more frequent stool was in the nocturnal time that was easily regulated with use of special diet. In the patients with W-shaped pouch and without ilioanal anastomosis there was loose stool with rate 8–10 time a day that was corrected with anti-diarrheal and infusive agents.

Conclusion: The formation of J- or S-shaped pouch-anal anastomosis seems to be effective methods of the reconstruction of continuity of the intestinal tube after total coloproctectomy that allows avoidance of patients from disability and improvement of the quality of life.
Results of the operative treatment of chronic colonic stasis (constipation)

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Background: The many authors offer different methods and volumes of the operations in the surgical treatment of the patients with chronic colostasis in the medical literature. In our clinic before 1990s due to colon stasis the following types of operation were performed more frequently: resection of the sigmoid intestine, left-side hemicolectomy right-side hemicolectomy. After performance of these operations there were occurred the recurrences of disease in the majority of cases.

Aim: To improve results of the surgical treatment of chronic colostasis.

Materials and methods: Investigation included 437 patients undergone operations due to chronic colostasis during the period from 1990 to present time. The clinical investigation and interviews from patients were performed for assessment of the results of surgical treatment. The patients were divided into two groups. Group 1 included 183 (41.9%) patients who had segmentary resections of the colon in the majority of cases: resection of the sigmoid intestine – 43 (23.5%), left-side hemicolecotmy – 133 (72.7%), right-side hemicolecotmy – 7 (3.8%) patients. Group 2 consisted of 254 (58.1%) patients who had predominantly subtotal colectomy – 96 (37.8%) and total colectomy – 158 (62.2%).

Results: The long-term results were evaluated with use of three ball scale. The good results were noted more frequently in Group 2 – 94.5% vs. 72.0%, and unsatisfactory results were more less 1.7% vs. 21.0%. The number of satisfactory results was 7.0% in group 1 and 3.8% in group 2.

Conclusion: Thus, such interventions as left-side hemicolecotomy, right-side hemicolecotomy and resection of the sigmoid intestine are not always justified. In the overwhelming cases there are revealed total lesion of the colon, for evaluation of which the complex diagnostic measures should be performed including the most current methods of investigations. We suggest that the total colectomy with iliorectal anastomosis is an operation of choice. The long-term results indicated about the most efficacy of this technique in relation to prevention of the disease recurrence and rehabilitation of the patients.
Pharmacological regulation of defensins in human colon mucosa in ulcerative colitis

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Introduction: the purpose of the work was the research of the human defensins (HBD) dynamics in colon mucosa in patients with ulcerative colitis (UC) who received the standard and a personalized therapy.

Methods: the clinical trial included 65 patients with extensive UC, mild and moderate activity (22–35 years old, female – 41, male – 24). The induction of UC remission assumed the acceptance of mesalazine (Salofalk®) 3–4 g/day p.o. and rectally 1–2 g/day; the maintenance of UC remission included the acceptance of Salofalk® 1.5 g/day p.o. or Salofalk® + Zacofalk NMX® 1.36 g 3 times a day, 40 minutes before meals for 3 years by patients with intolerant UC (n = 32; S+Z-therapy). Colon mucosa biopsy was performed endoscopically. Methods of the microbiota and proteome of colon mucosa research: culture-dependent methods, capillary gas-liquid chromatography, DNA-PCR analysis, 2DE/MALDI-TOF-TOF-MS. Control group – 20 healthy persons. "Statistica 12.0" was applied.

Results: It was noticed the reduction of all clinical symptoms in 65 patients. The decrease of HBD-2,3,4 expression in colon mucosa was revealed after 3 months in all UC patients; the greatest expressiveness of the dynamics of HBD-2,3,4 expression and the increase of HBD-1 expression were shown in S+Z-therapy. The reduction of the acetic, n-valeric, i-caproic acids concentrations and the increase of the n-butyrate concentration, the reduction of Escherichia coli, Proteus spp., Enterococcus spp., Staphylococcus spp., Streptococcus spp., Bacteroides spp., Clostridium spp. and the normalization of Bifidobacterium spp., Lactobacterium spp. in feces were noticed after 30 day in S+Z-therapy.

Discussion/Conclusion: S+Z-therapy was promoted to the restoration of HBD-1,2,3,4 in colon mucosa who were provided with mucosal defense against invasive bacteria, eliminated of dysbiotic relationship and showed anti-inflammatory effects in intestinal epithelial cells.
Development of a new immunoassay for the accurate determination of anti-infliximab antibodies in inflammatory bowel disease

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Introduction: The formation of antibodies to infliximab (ATIs) is closely associated with the loss of response to infliximab in patients with inflammatory bowel disease (IBD). Within the strategy of therapeutic drug monitoring, serum ATI levels have been mainly assessed by immunoassays based on the double-antigen format, in which ATIs were captured by immobilized infliximab or protein A on a carrier. However, in these assays, the presence of infliximab can interfere with the binding of labeled infliximab to the captured ATI leading to false-negative results. In the present study, we developed a novel immunoassay for ATIs which enables measurement in the presence of infliximab.

Methods: The new assay based on the dissoziation of immune complexes between infliximab and ATI at low pH-values and the use of biotinylated and peroxidase labeled infliximab preventing the re-formation of immune complexes. The presence of ATIs in the samples positive by the new method but negative by the conventional method was confirmed by Western blot analysis. ATI levels were measured using the novel immunoassay and the conventional method in 29 patients with Crohn’s disease (CD) under infliximab maintenance therapy. The serum infliximab trough levels were determined by enzyme-linked immunosorbent assay.

Results: ATIs were detected in 7 out of 29 patients (24.1%) by the new method, but the conventional method detected only 1 patients (3.4%) who had the two highest ATI titers assayed by the new method. In the new method, the addition of infliximab to the samples dose-dependently blocked the detection of ATIs. Patients positive for ATIs had significantly lower serum trough levels of infliximab (p < 0.01) and significantly higher clinical activity scores (p < 0.001) as compared with patients negative for ATI.

Conclusion: The new method makes it possible to measure serum ATI levels in the presence of infliximab and anti-adalimumab antibodies (data not shown). This method is useful for deciding the optimal management strategies for IBD patients with loss of response to TNFalpha-antibodies.

Reference(s):

Significance of fecal calprotectin measurement determining deep remission in ulcerative colitis

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**Introduction:** Deep remission is the desired end point of the treatment of ulcerative colitis (UC). Deep remission criteria involve invasive procedures (colonoscopy and biopsy) which are unpleasant for patients. For this reason, non-invasive markers which are correlated with endoscopic and histopathological remission are being identified. Fecal calprotectin (FC) is one of these markers. We aimed to study FC levels and its correlation with other inflammatory markers and colonoscopic-histopathological findings among our UC patients who are at clinical remission.

**Methods:** 43 patients with UC, who were at clinical remission for at least 6 months and none of them was using steroids, and 41 healthy volunteers (who were admitted to screen for colon malignancy and whose colonoscopy were normal) were included in this study. CRP, sedimentation rate (SR), fibrinogen and FC levels were measured. Colonoscopy was performed to all UC patients.

**Results:** Age and gender were similar between groups (UC: male 58%, female 42%, mean age 49, control: male 46%, female 53%, mean age 40). 70% of UC were distal and left-sided type, 25% of them was pancolitis. Mean FC (314.65 vs. 69.42 µg/g, p = 0.002) and fibrinogen levels (287.94 vs. 235.41 mg/dl, p < 0.001) were high at UC from controls, and this difference were statistically significant. CRP levels and SR were similar between the groups. CRP (1.10 vs. 4.20 mg/dl, p = 0.002) and FC levels (65.01 vs. 878.00) were low at UC who were at endoscopic remission from not at endoscopic remission; SR and fibrinogen levels didn’t show statistical difference. At histological remission, only FC (44.10 vs. 118.05, p = 0.009) was different between who were at histological remission and not.

**Discussion/Conclusion:** FC levels are helpful to distinguish active disease from inactive disease. FC levels are correlated with clinical, endoscopic and histopathological activity. FC was found more valuable than CRP, fibrinogen and SR to determine the disease activation.
Unfavorable course of chronic inflammatory bowel disease – Case presentation

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Introduction: The course of Crohn’s disease is characterized by acute exacerbations with abdominal pain, diarrhea, fever, anorexia, intestinal bleeding and weight loss. Most common bowel complications of the disease are strictures or stenosis, fistulas and abscesses. Among frequent extraintestinal manifestations are arthritis, ankylosing spondylitis, sacroileitis, episcleritis, uveitis and different skin lesions.

Case report: A 22-year-old female patient was transferred to our institution due to fever (39.5°C), diarrhea, arthralgias and disseminated erythematous plaques on the face, arms, trunk and legs. The skin changes were evolving over the last four days prior to admission to hospital. Urinary infection was confirmed and treatment with ciprofloxacin and metronidazole introduced. Six month previously, Crohn's disease of the ileum and sigmoid colon was diagnosed with colonoscopy and biopsies and treatment with mesalasine and budesonide was prescribed. In the diagnostic procedure at our ward, different viral and other infections were excluded and skin biopsy was performed. Histology confirmed a dense infiltration of neutrophilic polymorphonuclear leukocytes, establishing the diagnosis of Sweet's syndrome. Treatment with high doses of methylprednisolone (60 mg iv) resulted in a rapid improvement of both, gastrointestinal symptoms and skin lesions. In the following years, she gave birth to a healthy baby, during pregnancy she had no problems with her disease. After the birth, she had relapses of the disease, and therapy with infliximab was introduced, what is her current therapy.

Conclusions: Sweet's syndrome is a rare extraintestinal manifestation of chronic inflammatory bowel diseases, Crohn's disease and ulcerative colitis. The syndrome was originally described by RD Sweet in 1964 as an "acute febrile neutrophilic dermatosis" and is thought to be a hypersensitivity reaction and may be associated with different inflammatory, infectious or neoplastic diseases.
**Neutrophil-lymphocyte and platelet-lymphocyte ratios in treated inflammatory bowel disease patients**

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**Introduction:** Neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), have been described as prognostic markers in many chronic inflammatory and malignant diseases. The aim of this retrospective cohort study was to evaluate the effect of infliximab therapy on the NLR and PLR in pre-treated inflammatory bowel disease (IBD) patients with mesalazine ± azathioprine.

**Methods:** Medical records of adult IBD patients on infliximab treatment were retrospectively studied. The NLR and the PLR were calculated before the 1st dose of infliximab (T0) and at 2 weeks before the 2nd dose (T2). Wilcoxon-Signed Ranks test was used to determine the significance of the change of the NLR and the PLR between T0 and T2. Mann-Witney U test was used for the comparison of the change of the NLR and the PLR between patients pre-treated or not with sulfasalazine ± azathioprine. P < 0.01 was considered to be significant. SPSS v22 was used for the analyses.

**Results:** 35 adult IBD patients, 22 with CD, were included (17 women). 17 patients were pre-treated with mesalazine ± azathioprine. At T0 the median NLR was 2.84 (2.04–7.21) and the median PLR was 201.35 (128.59–263). At T2 the median NLR was 2.13 (1.26–2.56), p < 0.001 and the median PLR was 142.02 (90.43–186.66), p < 0.001. The decrease of the NLR and the PLR was the same between patients pre-treated or not with mesalazine ± azathioprine (p = 0.6).

**Discussion/Conclusion:** Infliximab therapy may lead to a significant reduction of both the NLR and PLR in IBD patients two weeks after the administration of its first dose. This effect appears to be independent of the pre-treatment with mesalazine ± azathioprine. However, large-scale relative studies are warranted to elucidate the effect of infliximab and mesalazine ± azathioprine on the aforementioned indices and to answer if they could serve as prognostic markers of response to IBD therapy.
Safety and efficacy of fumaric acid esters (FAEs) in steroid-dependent Crohn’s disease

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Background/Aim: Fumaric acid esters (FAEs) have been used successfully in the treatment of moderate to severe psoriasis vulgaris and several noninfectious granulomatous skin diseases (i.e. disseminated granuloma annulare, cheilitis granulomatosa, sarcoidosis). Here, we report the safety and efficacy of fumaric acid esters (FAEs) in steroid dependent Crohn’s Disease (CD).

Case presentations: Five patients (two male, three female) presented with Crohn’s Disease that have proved to be refractory to various therapies, including corticosteroids and TNFalpha-antibodies were treated with FAEs in tablet form (Fumaderm) according to the therapeutic schedule for psoriasis patients (240 mg td). After treatment with FAE (3–4 months), steroid free remission (CDAI < 150, fecal calprotectin < 200 µg/ml, CRP < 5 mg/l) was achieved in three patients. The side effects observed in this trial correspond to the well-known spectrum of adverse effects of FAE (minor gastrointestinal complaints: 1 pt, temporary lymphopenia: 2 pts, temporary flush: 3 pt).

Conclusions: On the basis of our findings FAE therapy seems to be a safe and effective regimen for patients with refractory and/or steroid dependent CD. However controlled trials are necessary to fully explore the efficacy, optimal dosage, and safety of FAE in the management of CD.
ACE gene's polymorphisms participate in IBD pathogenesis through changes of colonic microbiota and mesenteric vascularization

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Introduction: The role of gut microbiota has become more appreciated in recent years emphasizing the IBD etiology. However, exact mechanisms of interaction between immune system and microbiota remain to some extent unclear and furthermore, exact mechanisms that determine and provoke changes of colonic microbiota remain insufficiently discovered. Genetic predisposition to IBD is extensively discussed but it is still unknown if human genetic mechanisms may influence microbiota, not limiting to immune and inflammatory response. We hypothesized that angiotensin-converting enzyme (ACE) gene may induce morbid changes of colonic microbiota through changes of intestinal vascularization.

Methods: Totally 104 individuals participate in the study. Among them 34 had proven IBD, others with at least 3 risk factors of IBD (family history, smoking, antibiotics, travel history, immune, etc). Standard microbiology techniques and PCR for I/D ACE polymorphisms were used.

Results: DD genotype was found in 29 (27.9%), ID in 56 (53.8%) and II in 19 (18.3%) cases. Respectively, for DD, ID, and II groups following values of statistical parameters (%) in prediction of grades III–IV of dysbiosis were calculated: specificity – 80.0, 73.1, 46.1; sensitivity – 30.8, 62.8, 6.4; accuracy – 43.3, 65.4, 16.3; efficacy – 55.8, 67.9, 26.3; prognostic value – 82.8, 87.5, 26.4. For II genotype RR of extremely heavy disbiosis was 0.21–3.55, OR = 0.04–12.6 (95% CI). For ID genotype, RR = 0.82–1.40, OR = 0.29–7.53 (95% CI). For DD genotype, RR = 1.09–2.16, OR = 0.78–60.1 (95% CI, p = 0.031).

Discussion/Conclusion: Presence of D allele (ID, DD genotypes) increases chances for clinically significant dysbiosis 4.75 i 3.38 fold (OR = 12.7 and OR = 5.6, 95% CI OR = 1.06–62.6, p ≤ 0.031–0.0004). DD genotype carriers have highest risk of decompensated microbiota violations. While the exact role of microbiota changes in IBD remains unclear, it is defined that this changes play role in IBD pathogenesis. This study uncovers possible genetically determined mechanism of this changes.
Oral probiotic therapy with Propionibacterium Shermani potentiates efficacy of mesalazine in IBD

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Introduction: The IBD aetiology is still unclear, but the role of gut microbiota has become more appreciated in recent years. Following this idea, probiotics have been the subject of intensive research, mainly focusing on bifidobacteria and lactobacteria. However, existing reports of probiotic therapy of IBD are unclear giving no exact answers. The aim of this study was to introduce rarely used probiotic and understand whether oral probiotic therapy with P. Shermani has any therapeutic significance in IBD.

Methods: Specially designed strain of P. Shermani (T73) with high antagonistic potential was orally given to 12 IBD (4 CD and 8 UC) patients twice on a daily basis during 150–180 days in a form of suspension containing 1012–1014 bacteria. Another nine (3 CD and 6 UC) patients without probiotic treatment formed control. IBD of mild and moderate severity. Both groups' patients received mesalazine 1500–3000 mg daily as a basis therapy. Treatment efficacy evaluated according to World Gastroenterology Organization Global Guidelines and included CDAI, SF-36 and IBDQ scores as well as evaluation of disease course, severity, and complications.

Results: There were 2 (16.67%) and 2 (22.22%) recurrences requiring hospitalization during the study period. CDAI score at the end of study was 49.37 ± 3.14 points lower in study group (p < 0.05). SF-36 score difference between groups became 11.8 ± 0.84%. Abdominal pain, stool, and drug use for symptomatic therapies improved in study group, too. However, probiotic treatment did not influence anemia and other extra abdominal symptoms. Endoscopic picture and biopsies presented no specific differences between groups after treatment.

Discussion/Conclusion: We hypothesized that results of existing studies of probiotic use in IBD are confusing due to improper selection of probiotic agent. P. Shermani T73 is comparatively rare and understudied probiotic, showing its usefulness for use in IBD.
**The coherent polarimetric microscopy: A new diagnostic technology beyond the confocal microscopy of colon?**

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**Introduction:** Colonoscopy remains a major diagnostic technique for IBD. While confocal microscopy (CM) is being introduced into clinical practice, its use is still limited due to difficulties and subjectivity of results assessment. The fractal nature of the biological tissues stimulates creation and implementation of new optical methods in diagnostics and analysis of biological properties. In recent years, coherent polarimetric microscopy (CPM) became widely used in military and space innovations as a diagnostic tool. The object of this research is to combine CPM and CM for improving colonoscopy diagnostic value and accuracy in IBD.

**Methods:** Fluorescein sodium based endoscopic system was used for colonoscopy examination of 19 IBD patients. Obtained picture was real-time digitized by MathLab® software. In addition to visual assessment, following parameters were calculated: S-average polarization value, Mx-mathematic expectation, STD2-average squared variation, Dx-disperse, As-asymmetry, Ex-excess, MEDx-median. Stocks-polarimetry of obtained static visual images was the last step for data analysis. The data was compared with 26 control group healthy volunteers and histological findings in bioptates.

**Results:** Data obtained at the study showed that the pathological process involving inflamed colonic mucosal structures is usually accompanied by the sufficient enlargement and disorientation of anisotropic and amorphous optical components while inner layers remain less anisotropic. CPM variables obtained in control and study groups (respectively) were as follows: S = 0.3397492 vs. 0.4314872 (p < 0.05); Dx = 0.0087377 vs. 0.0112804 (p < 0.05); As = 77.3463338 vs. -2.0407966 (p < 0.000); Ex = 2591.8348943 vs. 1231.3691156 (p < 0.000); MEDx = 0.3529412 vs. 0.4196078 (p < 0.05). STD2 did not statistically differ in study group and control. Stocks-polarimetry showed 23.1–28.6% increase of Stocks vector maximal value in study group, and two-three fold evaluation of statistical distribution parameters.

**Discussion/Conclusion:** Endoscopic visualisation of intact and pathologically changed mucosa is a major diagnostic tool for IBD, though CM improves its value. CPM is a potent development of CM, possibly decreasing subjectivity of investigation due to 'human factor'.
Methods for evaluation of perianal fistulizing Crohn’s disease – Clinical case presentation

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Introduction: At least 20% of patients with Crohn’s disease will develop perianal fistulas during the disease’s course and about a third of those patients will have fistula recurrence after treatment. The available imaging techniques give the ability to correctly evaluate perianal fistulizing disease, potential complications (abscess formation), and the therapeutic answer to different treatment modalities, which facilitates clinical decision making and influences the prognosis of those patients.

Case report: We present twenty-one years old woman with Crohn’s disease (classified as A2L2B3p) with recurrence of perianal fistulas after cessation (at the patient’s own will) of treatment with adalimumab (with prior Infliximab therapy). Using endorectal ultrasound with intrafistular hydrogen peroxide application, transperineal ultrasound, endoscopy and pelvic MRI a rectovaginal fistula and a multiple tract perianorectal fistula with a perianal abscess cavity formation were identified. Contrast-enhanced perianal ultrasound provided the most accurate and detailed image of the fistulas topographic localization and the relation to the sphincter complex. A decision for surgical drainage followed by a subsequent therapy with adalimumab and antibiotic (ciprofloxacin) was made.

Discussion/Conclusion: Combination of diagnostic modalities (endoscopy with endorectal ultrasound and/or MRI) gives the highest accuracy and ensures the optimal therapeutic approach is selected.
Association of rs1568885, rs1813443 and rs4411591 polymorphisms with anti-TNF medication response in Greek patients with Crohn’s disease

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Introduction: The correlation between rs1568885, rs1813443 and rs4411591 polymorphisms and response to infliximab was investigated in a cohort of Greek patients with Crohn’s disease (CD).

Methods: One hundred and twenty-six patients diagnosed with CD were enrolled in this study. Infliximab at a dose of 5 mg/kg was administered intravenously at weeks 0, 2, 6 and then every 8 wk. Clinical and serological responses were assessed using the Harvey-Bradshaw Index. Serum C-reactive protein (CRP) levels and the endoscopic response were evaluated at baseline and after 12–20 weeks of therapy. The changes in endoscopic appearance compared to baseline were classified into four categories, and patients were classified as responders and non-responders. Genomic DNA from whole peripheral blood was extracted and genotyping was performed by allele-specific polymerase chain reactions. Chi squared test with Yate’s correction based on the S-Plus was used to compare the genotype frequencies.

Results: Eighty patients (63.49%) were classified as complete and 32 (25.39%) as partial responders to infliximab, while 14 (11.11%) were primary non-responders. No correlation was found between response to infliximab and patients’ characteristics such as age, gender and disease duration. There was consistency between Harvey-Bradshaw index scores and serum CRP levels. The TT genotype of the rs1568885 polymorphism was significantly related to partial response (p = 0.024) and resistance to infliximab (p = 0.007) while the AT genotype was more frequent in partial responders (p = 0.035) and in primary non-responders (p = 0.032). Regarding rs1813443, the CC genotype was found to be associated with partial response (p = 0.005) and primary resistance (p = 0.002) to infliximab while no association was found between the rs4411591 polymorphism and clinical response to infliximab.

Discussion/Conclusion: Based on our results, the rs1568885 and rs1813443 polymorphisms are associated with clinical and biochemical response to infliximab in Greek patients with Crohn’s disease.
Incidence and prevalence of the inflammatory bowel disease (IBD) in children of the Primorsko-goranska and Istrian county (Croatia) in the period of the 1995–2009

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Introduction: The main of this study was to determine the incidence and prevalence of the IBD in children of the Primorsko-goranska and Istrian county (Croatia) in the period of the 1995–2009. The assessment of clinical status was determined during the first hospitalization as well as the extent of disease activity, presence of complications, extraintestinal manifestations, presence of risk factors positive family history.

Methods: The subjects were children under the age of 18 years which have had their IBD diagnosed in period from January 1, 1995 to December 31, 2009. Diagnoses were set according to the ESPGHAN’s guidelines from 2005. Data were collected retrospectively from medical records and supplemented by personal contact. Epidemiological studies do not require of a control group. The collected data are stored in a database (Microsoft Excel 2007) and statistically analyzed.

Results: IBD was diagnosed in 144 children, with an average annual incidence of 8.64/100,000. The incidence of Crohn’s disease (CD) increased from 1.6/100,000 at the baseline to 6.0/100,000 in 2009. Ulcerative colitis (UC) has a weaker trend in incidence from 0.79 to 1.26, while indeterminate colitis (IC) has had a balanced growth with an average annual incidence of 2.16. Prevalence of IBD rose from 56.62/100,000 in 1994 to 127.1/100,000 in 2009. The median age when first IBD occurred was 11.9 years. The gender distribution has a slight advantage in male children compared to female children, but without statistical significance. A positive family history was present at 20% of patients with UC, 10.3% with CD and 13.9% with IC group. Intestinal complications were present in 7 patients with CD and 2 patients with UC. Extraintestinal manifestations were observed in 12.6% of patients.

Discussion/Conclusion: According to the examined data, the Primorsko-goranska and Istrian county can be classified into regions with high incidence of IBD, of which the incidence of CD has increased more than double than incidence of UC. Our research has noted the slow growth of the incidence of UC, our country belongs to countries with low incidence of UC.
Azathioprine discontinuation earlier than 6 months in Crohn’s disease patients started on anti-TNF therapy is associated with loss of response and the need for anti-TNF dose escalation

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Objectives: A substantial number of Crohn’s disease (CD) patients lose response to anti-TNF and therapy needs to be intensified. We aimed to prospectively determine predictors and frequency of anti-TNF loss of response and therefore the need for dose escalation and de-escalation in CD patients treated with infliximab or adalimumab.

Methods: All patients were anti-TNF naive, while concomitant azathioprine was administered for 6 months. In patients initially responding to anti-TNF and subsequently losing clinical response after the first 14 weeks of therapy, dose escalation was scheduled. During the follow up period and after 1 year of intensified administration, anti-TNF was de-escalated in patients in remission.

Results: 161 patients were started on infliximab (n = 96) or adalimumab (n = 65); however 29 (18.0%) did not respond to therapy and were excluded from further analysis. From the remaining 132 patients (infliximab = 77, adalimumab = 55), 31 (23.5%) needed a dose escalation for maintenance of remission, during a median 28 month follow up period. Factors associated with loss of response and therefore the need for anti-TNF dose escalation were azathioprine discontinuation earlier than 6 months and smoking. Most patients achieved clinical remission (n = 25, 80.6%) without other interventions and among them, 16 (64%) were successfully de-escalated to the standard maintenance infliximab or adalimumab dose schedule, after 1 year of intensified anti-TNF administration.

Conclusion: Azathioprine discontinuation earlier than 6 months and smoking in CD patients started on anti-TNF therapy is associated with loss of response and the need for anti-TNF dose escalation.
**Stool and plasma elafin and alpha defensins but not cathelicidin may be a useful clinical marker in differential diagnosis of inflammatory bowel diseases in children**

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**Introduction**: Recent findings suggest a central role of the bacterial microflora and the innate mucosal barrier interactions in the pathogenesis of inflammatory bowel diseases (IBD). Important factors providing mucosal barrier are antimicrobial peptides like elafin, alpha defensins and cathelicidin, which modify bacteria-host interactions. There is little known about their concentrations in children with IBD up to date. The objective of our study was to assess stool and plasma elafin, alpha defensins and cathelicidin concentrations in children with Crohn’s disease (CD) and ulcerative colitis (UC).

**Methods**: Thirty six children were enrolled to the study, including 15 children with newly diagnosed CD (8 boys, 7 girls, mean age: 13.8 yrs, range: 6.3–17.8 yrs), 21 with newly diagnosed UC (11 boys, 10 girls, mean age: 12.7 yrs, range: 6–17.5 yrs) and 18 healthy controls. Elafin, alpha defensins and cathelicidin concentrations were assessed in stool supernatants and plasma at the baseline, before the treatment and after 2 weeks of treatment using ELISA immunoassays (Hycult Biotech, the Netherlands). Statistical analysis was performed with Statistica 7.0 software (StatSoft, USA) using Mann-Whitney U test, Wilcoxon signed rank test and Spearman’s correlation rank test.

**Results**: We found increased stool and plasma elafin concentrations at the baseline in CD group as compared to UC group (p < 0.05) and controls (p < 0.05). Assessing stool and plasma alpha defensins concentrations at baseline, they were comparable to CD and UC group, but elevated when compared to controls (p < 0.05). During the treatment alpha 1–3 defensins concentrations in stool and plasma increased after 2 weeks in UC group (p < 0.05) and decreased in CD group (p < 0.05). Stool and plasma cathelicidin concentrations were comparable to CD and UC group at baseline and decreased during the treatment.

**Discussion/Conclusion**: Increased stool and plasma elafin concentrations in CD and alpha defensins concentrations in UC suggest different influence of bacterial microflora on mucosal barrier in pathogenesis of these diseases. Stool and plasma elafin and alpha defensins assessment may be a useful clinical marker in differential diagnosis between CD and UC in children.
Serum hepcidin levels predict intestinal iron absorption in IBD patients

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Background: Circulating hepcidin is proposed to regulate iron absorption by modulating iron export by ferroportin at the basolateral membrane of the duodenal mucosal cells and/or uptake into the cells at the apical membrane by DMT1. To date, no data have shown a relationship between plasma hepcidin concentrations and iron absorption in IBD patients. In the present study, we used stored samples from a human iron absorption study to further test the hypothesis that plasma hepcidin may explain interindividual variation in iron absorption in IBD patients.

Method: Serum ferritin (SF) and serum markers of inflammation [high-sensitivity C-reactive protein (hsCRP) and IL-6] were measured in stored samples from a human iron absorption study using commercially available immune-assays. Hepcidin-25 concentrations were determined in fasting samples from 71 adult subjects with IBD (31 UC, 40 CD) and 26 healthy controls. Hepcidin was measured by LC-MS.

Results: There was a positive correlation between hepcidin (mean: 2.3; range: 0.1–7.8 nmol/l) and hsCRP (p < 0.005), but not between hepcidin and serum ferritin (p > 0.05). Whereas iron absorption was negatively correlated with serum ferritin only in patients with inactive disease (hsCRP < 5 md/dl; p < 0.001), a negative correlation was observed with serum hepcidin in both active and inactive disease (p = 0.006), independent of IBD phenotype. Multiple linear regression models showed that serum hepcidin in isolation significantly predicted the interindividual variation in iron absorption.

Conclusions: Concentration of serum hepcidin, but not serum ferritin, was highly correlated with intestinal iron absorption in IBD patients.
Fig. 1: Correlation between serum hepcidin and intestinal iron absorption (n = 97; p = 0.006)
Diagnostic accuracy of zinc protoporphyrin/heme ratio for screening in iron deficiency anaemia in IBD patients

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**Background:** In the absence of a feasible, non-invasive gold standard, iron deficiency anaemia (IDA) is best measured by the use of multiple indicators. However, the choice of an appropriate single iron biomarker to replace the multiple-criteria model for screening for IDA at the population level continues to be debated. Zinc protoporphyrin (ZPP) has been shown to be a sensitive and specific screening marker for functional iron deficiency. This study evaluated for the first time the diagnostic value of ZPP in the diagnosis of IDA and differential diagnosis of IDA and anaemia of chronic disease.

**Methods:** The study population consisted of 116 patients with IBD (age, 36.40 ± 13.14 years, 59% female), who consecutively attended the Crohn Colitis Centre Frankfurt for routine evaluation between October 2009 and October 2012. Blood count, transferrin saturation (TSAT), serum ferritin (SF), C-reactive protein and ZPP were determined by routine assays. Anemia was defined, according to the World Health Organization criteria, as a hemoglobin concentration of < 13 g/dl for men and 12 g/dl for women. For the multiple-criteria model, ID was considered present if individuals had ≥ 2 abnormal values from SF (< 30 µg/l), TSAT (< 20%), and ZPP (< 40 µmol/mol Hb). Patients with anemia were classified as having iron deficiency anaemia (IDA), anaemia of chronic disease (ACD) or according to ².

**Results:** In contrast to SF, ZPP significantly correlated with hemoglobin. The receiver operating characteristic (ROC) curves for the various iron indicators used to diagnose IDA as defined by the multiple-criteria model indicated that the diagnostic accuracy of ZPP was superior to that of the other iron status indicators. As the most important finding of our study, ZPP has been shown to be elevated even in the case of ACD, indicating iron-deficient erythropoesis (fig. 1).

**Conclusion:** ZPP is not a simple parameter of iron deficiency, but rather a screening parameter of iron-deficient erythropoesis. These results clearly demonstrate the potential utility of ZPP in the detection of iron deficiency in IBD patients with inflammation and anaemia, even in the presence of ACD. Our findings indicate that ZPP can provide added value in diagnosing iron deficiency in anaemic IBD patients.

**References:**


Serum beta 2-microglobulin as a biomarker in inflammatory bowel disease

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Aim: To investigate the diagnostic utility of beta 2-microglobulin (B2-M) levels and analyze this correlation with the activity of inflammatory bowel disease (IBD).

Methods: We examined B2-M serum levels in 43 ulcerative colitis (UC) patients, 35 with Crohn’s disease (CD) and 30 control subjects, using an enzymatic method. Patients were divided into two groups according to two disease types: active and in remission. Subjects were also divided into two subgroups according to extent of the disease: left-side and pancolitis for UC and ileitis and ileocolitis for CD. All groups were compared for mean serum B2-M levels and also examined to see whether there was a correlation between serum B2-M levels and other inflammatory markers.

Results: The mean serum B2-M levels in the control group, UC and CD were 1.71, 2.41 and 2.24 respectively. B2-M values ≥ 1.96 mg/l had a 62% sensitivity, 76% specificity, a 79% positive predictive value, and a 58% negative predictive value for UC patients. B2-M values ≥ 1.70 mg/l had 80% sensitivity, 53% specificity, 66% positive predictive value, and 69% negative predictive value for CD patients. Mean B2-M values were significantly higher in ulcerative colitis and Crohn’s disease patients than in healthy controls (UC 2.41 ± 0.87 vs. 1.71 ± 0.44, p = 0.002; CD 2.24 ± 1.01 vs. 1.71 ± 0.44, p = 0.033). Also, mean B2-M values were significantly higher in active disease when compared to patients in remission (UC 2.66 ± 0.92 vs. 1.88 ± 0.41, p = 0.004; CD 2.50 ± 1.15 vs. 1.73 ± 0.31, p = 0.033). The difference between groups (UC and CD) in terms of serum B2-M levels was statistically insignificant (2.41 ± 0.87 vs. 2.24 ± 1.01, p > 0.05 respectively).

Conclusion: Serum B2-M levels may be used as an activity parameter in IBD.
Loss of response to anti-TNFα treatments in IBD: The importance of drug level monitoring

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Introduction: Treatment in inflammatory bowel diseases (IBD; Crohn’s disease [CD] and ulcerative colitis [UC]) has improved due to biologics. However, a problem is loss of response (LOR) maybe due to the formation of antibodies against these biologics. Our aim was to investigate antibody response against standard biologics infliximab (IFX) and adalimumab (ADA) in adult and paediatric patients with IBD.

Methods: We conducted a prospective, multi-center study assessing antibody levels in IBD patients with active disease by an enzyme-linked immunoassay (Immunodiagnostik AG, Bensheim, Germany) which is able to measure free and bound antibodies against IFX or ADA. We investigated a possible correlation between LOR during therapy and positive antibodies and furthermore linked clinics with antibody levels. LOR was defined as dose escalation, discontinuation of treatment or shortening of dosage interval.

Results: One-hundred-and-eighty-eight patients were included. 27/91 of CD patients (30%) and 12/45 (27%) of UC patients with IFX therapy showed positive antibody levels. In the ADA group in 3/46 (7%) with CD and 1/6 (17%) with UC antibodies were detected. 27% of antibody-positive CD patients and 100% of UC patients with IFX therapy had a LOR, whereas 67% of antibody-positive CD patients and 100% of UC patients had a LOR under ADA. LOR occurred in CD and UC patients in the IFX group at an average of 25 and 29 month, respectively, in the ADA group at 17 and 4 month, respectively. Correlation with clinics showed that most of the patients with positive antibodies showed low IFX or ADA levels with 63% and 43%, respectively.

Discussion/Conclusion: Our study suggests that occurrence of antidrug antibodies is a frequent event associated with LOR, and drug monitoring should be considered for the management of patients receiving biological therapies in IBD.
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Critical Evaluation of Current Concepts and Moving to New Horizons in the Management of IBD

March 6 – 7, 2015
Kap Europa
Frankfurt, Germany

Abstracts
Poster Abstracts