Revisiting IBD Management: Dogmas to be Challenged

Question Dogmas
Seek New Paths
Keep What Works
Revisiting IBD Management: Dogmas to be Challenged
Brussels (Belgium), September 30 – October 1, 2011

Scientific Organization

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Cover
Localization of human α-defensin-5 and lysozyme in duodenal mucosa:
Lysozyme (green) in Brunner’s glands and Paneth cells,
human α-defensin-5 (red) only in Paneth cells

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Fig. 2: Kaser & Blumberg 2010
Fig. 3: Lees et al. 2011
Fig. 4: Leifeld et al. 2011
Fig. 5: Tromm et al. 2011
Fig. 6: Frøslie et al. 2010
Fig. 7: Colombel et al. 2010
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Foreword

National and international guidelines provide clear recommendations for the treatment of inflammatory bowel disease. However, progress continues to be made. New research findings require us to constantly re-assess established treatment strategies for Crohn's disease and ulcerative colitis, and, when necessary, discard them.

This was also the objective of the scientific organization committee of the Falk Symposium 179 “Revisiting IBD Management: Dogmas to be Challenged”, which took place in Brussels (Belgium). Inspired by the nine spheres of the Brussels' famous Atomium, G. D’Haens, Amsterdam (The Netherlands), A. Dignass, Frankfurt (Germany) and S. Vermeire, Leuven (Belgium) opened the discussion on eight central dogmas that have over recent years and decades formed our understanding of the pathophysiology and therapy of inflammatory bowel disease, reserving the ninth session for a preview of the future. The relevance of the intestinal microflora and the innate immune system in the pathophysiology of inflammatory bowel disease were as much a matter of discussion as were the role of steroids and TNF- inhibitors and the value of both well-established treatment regimens and innovative therapy concepts.

The strategy seems clear: The goal is a personalized therapy that will both improve response rates and reduce side effects. This goal has fueled the search for genetic and serological markers that will provide insight into an individual patient's prognosis and disease course, thus facilitating management decisions. Innovative drugs with new mechanisms of action accompany this development. The road to personalized medicine, as has also been followed in oncology, remains long and bumpy; the goal, however, is definitely realistic.

Already a reality is the increasingly targeted application of established therapies when well-known markers such as CRP, trough level or the TPMT genotype are included in management decisions. This development will continue: Not only will it make research in the field of inflammatory bowel disease more exciting but will also in the long term improve the prognosis even of severely ill Crohn's and ulcerative colitis patients.
Editors: Dear Professor D’Haens, you are one of the scientific organizers of the Falk Symposium “Revisiting IBD Management: Dogmas to be Challenged”. What did you have in mind when you arranged the program?

Professor D’Haens: When we prepared the program one and a half year ago, as soon as we were invited to have the meeting in Brussels, we tried to do something new. We did not want to arrange just a usual meeting with a basic and a clinical section, but something that perhaps could be more attractive for both scientists and clinicians. The “dogma idea” gave us the opportunity to break down the things on the different sessions we wanted to include. Then we decided to have the Atomium as the logo of the meeting, which has nine globes. And we were having nine sessions. All that fitted quite well together. That’s how the program was assembled.

Editors: What were the main topics of the meeting?

Professor D’Haens: D’Haens: We were still starting from the basic side, for example the role of autophagy which is believed to be a key component of the pathophysiology. But even that can be questioned. Then we went on to questioning other dogmas like the distinction between early and late Crohn’s disease. There might be a different immunological setting. But that can be questioned, too. When you put all the scientific data together, and that is what has been done in this meeting, you can question virtually everything we know. That was the goal and I think, that is what people are interested in.

Editors: One of the goals for the future is a more personalized therapy. Can this be reached within the next five to ten years?
Professor D’Haens:
Yes, this aim is realistic. We just started with it, but like the oncologists we are just at the beginning. At the moment we are looking for clinical features. The location and the severity of the disease and the endoscopic appearance are drivers for the type of treatment that the patient will have. At this point we don’t really have markers that help us to decide which treatment should be given. But there is extensive research ongoing. We are mainly looking for markers indicating rapidly aggressive disease. They would give us the opportunity to predict, which patients will have complications early in their disease. Those need more aggressive treatment early on. Potentially it would be successful to combine genetic or other markers. At the moment it is a bit early to speculate, but I’m sure that we will get there in the years to come.

Editors:
When you are looking at the pharmaceutical options, do you think there will be drugs with complete other mechanisms of action?

Professor D’Haens:
I am sure. Currently there are more than 20 drugs in development for the therapy of inflammatory bowel disease. We should not only focus on new drugs, but also look at new combinations. This is especially hard. Pharmaceutical companies don’t like combinations because of the toxicity assessments. But we should really work on this. Until now the SONIC study has been the only trial that looked at a combination, in that case the combination of azathioprine and infliximab. And this has been the best treatment ever reported in Crohn’s disease. Therefore, we will definitely need to look at combinations.
Focusing on the Pathophysiology of Autophagy Genes ATG16L1 and IRGM

Disturbances of inborn immunity are becoming more and more a focus of pathophysiological considerations of Crohn’s disease. In this context, the discovery of the two autophagy genes, ATG16L1 and IRGM, in hypothesis-free, genome-wide association studies (GWAS) has triggered a heightened degree of attention. ATG16L1 plays a key role in autophagy, while IRGM is crucial for initiating the process of autophagy, explained M. Parkes, Cambridge (Great Britain). IRGM variants result in reduced macrophage function. Thus, adherent-invasive E. coli strains, which are closely associated with Crohn’s disease, can no longer be eliminated. ATG16L1 mutations are associated with morphological changes of the Paneth cells in a mouse model. Similarly, NOD2 mutations block MDP-induced autophagy. Carriers of both mutations suffer a two-fold weakening of bacterial immunity.

Correlation: Intestinal Flora and Crohn’s Disease Phenotypes

E. Cario, Essen (Germany) observed that mutations of the NOD2 gene or of the autophagy genes cannot by themselves trigger intestinal inflammation: “Not every individual with one of these mutations actually develops an inflammatory bowel disease. The development is far more complex.” Other environmental factors are necessary to initiate the onset of the disease. She speculated that patients with IBD as a consequence of defective inborn immunity develop a colitogenic dysbiosis. Recent studies have shown that the dysbiosis in patients with IBD is characterized by a shift in the bacterial colonization of the bowel in favor of mucosal-adherent E. coli strains and a corresponding decrease in bacterial diversity. Here, specific changes in the composition of the intestinal flora appear to correlate with certain phenotypes. For example, a reduction in Faecalibacterium prausnitzii and an increase in adherent, invasive E. coli strains are typical for ileal Crohn’s disease.

Gene Defect at XBP1 Leads to ER Stress

Stress reactions of the endoplasmic reticulum (ER) have also been discussed as triggers of intestinal inflammation. ER stress has been shown in laboratory experiments to cause intestinal inflammation that is very similar to that seen in IBD in humans, said A. Kaser, Cambridge (Great Britain). The basis for this is a gene defect of the unfolded protein response (UPR) transcription factor, XBP1. Under normal circumstances, UPR offers protection against proteins that are incorrectly folded secondary to factors such as hypoxia, viral infections or oxygen radicals and which cause stress in the ER. Secretory cells, such as Paneth cells and goblet cells depend on properly functioning UPR. Disturbances of UPR function lead to ER stress. “An XBP1 deletion causes ER stress in both the small bowel and colon,” A. Kaser explained.

Defensins: The Body’s Own Antibiotics

The defensins represent the essential regulators of the intestinal microflora. “One could describe them as the body’s own antibiotics in the context of the innate immune system,” said J. Wehkamp, Stuttgart (Germany). The activation of defensins could therefore be a potential therapeutic approach in IBD. J. Wehkamp was able to show that E. coli Nissle 1917, but not other E. coli strains, induces the release of human α-defensin-2. His explanation: E. coli Nissle 1917 is a flagellate. “This results in flagellin-induced induction, a very frequently observed process in nature.”
**Dogma 2**

**No Bacteria – No Inflammatory Bowel Disease**

**Does Enteric Nutrition Affect the Intestinal Microflora?**

Complete rest for the bowel, enteric nutrition and a consequent elementary diet have a positive effect on intestinal inflammation. This, however, holds only for Crohn's disease, not for ulcerative colitis, emphasized J.M. Rhodes, Liverpool (Great Britain).

For example, elementary diet is comparable to prednisolone for remission induction in Crohn's disease. By contrast, patients with ulcerative colitis do not profit from bowel rest and intravenous nutrition, said J.M. Rhodes, citing a small study. Why does enteric nutrition work in Crohn's disease? The answer is unclear but "we might be affecting the intestinal microflora," J.M. Rhodes opined.

**Pouchitis: Use Antibiotics**

Bacteria play an important role in the development and persistence of pouchitis. Nearly all patients respond to antibiotics during the first inflammatory episodes. "Later in the disease course, however, response rate get lower and lower," explained B. Shen, Cleveland (USA). Specifically, he recommended metronidazole or ciprofloxacin for two weeks. Non-responders should be treated an additional two weeks. If this is unsuccessful, a combination of ciprofloxacin and metronidazole or rifaximin can be tried. If patients still do not respond anti-inflammatory treatment with 5-ASA, steroids, immunomodulators or biologicals is the next step. Patients with pouchitis, who initially respond to antibiotics but then relapse, can be re-started on antibiotics. In patients with frequent relapses, which B. Shen calls "antibiotic-dependent pouchitis," probiotics can be tried.

**Antibiotics are Effective, but the Study Data is Meager!**

J.-F. Colombel, Lille (France) is convinced of the benefits of antibiotics in IBD. It was first shown in interleukin-10-deficient mice that antibiotics could both prevent the development of colitis and exert a favorable effect on manifest colitis. This may also apply in humans, J.-F. Colombel noted, pointing to a systematic review of ten randomized, controlled studies of patients with Crohn's disease that documented a significant advantage for antibiotics in remission induction. Further, a meta-analysis of two randomized studies found a positive effect for antibiotics in the prevention of postoperative relapses. In addition, he was able to show that antibiotics can be successfully used not only in Crohn's disease but also in patients with ulcerative colitis. He did, however, admit that the quality of the studies was often poor and that concrete endpoints were lacking, and called for further studies. Here, he also recommended that the effects of antibiotic therapy on the intestinal microflora should be carefully monitored. One promising option is the use of combination therapies. For example, in one study a combination of budesonide with an antibiotic was shown superior to combination with placebo in patients with disease involving the colon.

**Tracking the Genome of Symbiotic Bacteria in Humans**

More comprehensive information on the genomes of the bacteria colonizing the human gastrointestinal tract will be provided by "metagenomics!" Only about one-third of these bacteria are common to all humans. The "Human Microbiome Project" has as one of its objectives to identify the factors, such as nutrition or diseases, that determine the composition of the intestinal flora and to better understand how this biosystem functions within our organism, said J. Raes, Brussels (Belgium). According to our current understanding, the normal, healthy intestinal flora can be broken down into three enterotypes based on the predominant microorganisms, Bacteroides, Prevotella and Ruminococcus and are independent of factors such as ethnic origin, age, sex or BMI. It is conceivable that enterotype-specific diagnostics and therapy could be developed for patients with IBD.
Inflammatory bowel diseases were once considered classic autoimmune diseases. Those times are gone. More and more evidence leads to the conclusion that these disorders pathophysiologically reflect disturbances of the intestinal barrier function, which are associated with dysbiosis and a weakened innate immune system. Pathogenetic studies, furthermore, have provided proof that Crohn’s disease and ulcerative colitis are not simply two sides of the same coin.

Dysregulation of the immune response to intestinal bacteria secondary to genetic susceptibility: This has become the current conception of the pathogenesis of inflammatory bowel disease (IBD), said M. Parkes, Cambridge (Great Britain). The decisive step in this direction was the discovery of gene mutations that are closely associated with Crohn’s disease and/or ulcerative colitis, most notably the NOD2 gene, an intracellular receptor for components of the bacterial wall. Thus, both commensal and pathogenic intestinal microbes, as well as the immune mechanisms that interact with this system, have increasingly become a focus of attention. Meanwhile, findings from animal experiments and studies on humans, including hypothesis-free genome-wide association studies (GWAS), increasingly suggest that IBD represents a disturbance of the intestinal barrier function. “In persons with the corresponding genetic predisposition, a weakened mucosal immunity may allow intestinal bacteria to induce inflammatory reactions in the mucosal membrane,” M. Parkes explained.

Dysbiosis Impacts a Weakened Innate Immune System

Figure 1  Process of intestinal inflammation in IBD

Breakdown of the Intestinal Barrier

A. Darfeuille-Michaud, Clermont-Ferrand (France) provided a succinct explanation of how this inflammatory reaction occurs: Patients with IBD experience a shift in the equilibrium between protective and harmful intestinal bacteria. The resulting dysbiosis allows migration of aggressive microorganisms into the intestinal mucosa. The intestinal barrier collapses. Due to genetic defects, the innate immune system does not react adequately. This opens the gates to the development of intestinal inflammation (Figure 1).

“An Orchestra of Intestinal Inflammation”

Primary factors in this “orchestra of intestinal inflammation”, as A. Kaser, Cambridge (Great Britain) put it, are genetic defects (Figure 2).

According to M. Parkes, nearly 100 susceptibility loci for IBD have been found in GWAS. In only 28 of these there was overlap between Crohn’s disease and ulcerative colitis (Figure 3).

Specific for Crohn’s disease are, for example, genes associated with the cellular innate immune system, such as NOD2 or the two mutually independently acting autophagy genes, ATG16L1 and IRGM. By comparison, genes such as ECM1 or HNF4α, which control the epithelial barrier function, are associated with ulcerative colitis. Also important, A. Kaser said, are genes that affect the extent of stress in the endoplasmic reticulum (ER), such as XBP1 or ORMDL3. Also under discussion are secondary factors that may trigger the inflammatory process, including environmental factors such as nutrition, toxins or tobacco. In addition, persistent infections, neurogenic stress or ischemia may drive intestinal inflammation.

Questionable: The Value of Antibiotic Therapy

The relevance of pathogenic bacteria in the pathophysiology of Crohn’s disease and ulcerative colitis has also inflamed the discussion regarding the value of antibiotic therapy. Meta-analyses indicate a favorable effect but there is a broad consensus that the quality of the available studies remains inadequate for the purpose of formulating concrete recommendations. There is still plenty of work to be done. At the same time, new understanding of the pathophysiology of IBD may provide the basis for development of innovative treatment principles.
Editors:
In the last decade researchers in IBD found a lot of genes involved in the disease and collected a lot of information about the intestinal microbiota. But there was no progress for the patient. What is the problem?

Professor Vermeire:
I don’t think there is necessarily a problem. The translation to the clinic takes time of course. You should not forget that the progress in genetics has been extremely fast. Only two years ago we had only 30 genes, in the last year we’ve had 100. You can’t expect that everything is translated immediately to the clinic. And also these genetic findings have shown very surprising pathways. It takes time for us – both for scientists and clinicians – to understand what these new pathways are doing and how they could be connected to Crohn’s disease or to ulcerative colitis. At the moment it’s a huge amount of data and we are only starting to analyze and fully understand them with new techniques. I think it’s normal that you need months to digest the findings and to see what we can do with it. And I don’t want to be a pessimist – I am a real optimist – but IBD is quite heterogenic and complex. Nobody of us is expecting that one gene will have a direct link to the clinic. The same is with one bug. It would not be that easy to explain the disease. We have to understand the interaction between the genes and between the genes and the microbiota, what pathways will be activated or suppressed. There is still a lot to be done.

Editors:
Would a more individualized therapy be possible this way?

Professor Vermeire:
Absolutely. I think we could do this in five years. We will have to work together with the scientists and come up with
a small set of genes, maybe also bugs or other molecular markers which could predict specific outcomes. You cannot work with 300 genes. We need to identify the top five or the top ten, which really make a clinical difference. This is a point of research in the coming years and I know that everybody is waiting for this. It will become crucial to identify for instance those patients that are better candidates for anti-TNF-strategies and others, who need another kind of medication. Same for the prediction of progressive disease. We all have to see that the budgets in the countries are getting tighter, so we will have to use existing tools better and to predict the best therapy and follow up for a given candidate.

Editors:
How important are the defensins from your point of view?

Professor Vermeire:
It’s a very interesting target. And it’s fascinating to think that we can boost the innate immunity in patients with defensin-deficiency. But it won’t be so easy. First, I think it is not going to be successful in patients with already very active ongoing disease. It’s more for the prevention or in a very early state of the disease. But we should pursue that route, because at the end of the day we do not only want to help patients with existing disease, and even more, protect them from disease progression but also prevent the disease in risk patients. Maybe we should put defensins in yoghurt and individuals at risk should take some defensins? Who knows! This is a very simplified way of putting things, but this is what we can potentially do with the information from the bench.

Editors:
The use of antibiotics was discussed controversially. What is your opinion about that?

Professor Vermeire:
We use antibiotics and we most often use them for those patients with complications of their Crohn’s disease, for example with abscesses, perianal complications or patients with acute severe colitis. The conclusion from that session should be that more studies are absolutely needed. The quality of the existing studies is relatively poor in terms of study design or sample size. Also, we cannot make one conclusion out of one metaanalysis because there is too much heterogenity with regard to doses and types of antibiotics. What we need are antibiotics, which target also the “sticky” mucosa-associated bacteria. Otherwise you can give antibiotics as much as you want without any success.

Professor Vermeire, thank you for the interview.
“Mixed Lymphocyte Reaction” to Anti-TNF-α Antibodies

Severe cases of IBD can be successfully managed with the anti-TNF-α antibodies, infliximab or adalimumab. There are, however, anti-TNF strategies such as the soluble TNF-α receptor, etanercept, or the TNF-α antibody, CDP571, that have no impact on intestinal inflammation. Based on numerous studies, G.R. van den Brink, Amsterdam (The Netherlands) may have found a possible reason: Effective TNF-α antibodies, but not etanercept, bind to TNF-α on stimulated T cells and simultaneously activate the Fc receptor of monocytes. Conversely, CDP571 binds only weakly to this receptor. “This is evidence for the importance of the Fc receptor for the efficacy of anti-TNF strategies,” G.R. van den Brink emphasized.

Exploring the Causes for Secondary Failure

About 40% of patients initially responsive to a TNF-α blocker later develop secondary treatment failure or cannot continue the therapy because of side effects. Loss of efficacy most commonly occurs within the first six months. In such cases, said J. Satsangi, Edinburgh (Great Britain), it is important to determine whether patients’ complaints are actually due to a re-ignited intestinal inflammation or have a completely different etiology, such as a stricture or bile acid malabsorption. A useful response, in his opinion, is measurement of fecal calprotectin, a highly sensitive, non-invasive marker for active inflammation.

Crohn’s Disease and Ulcerative Colitis: Comparable Response to Biologicals

Crohn’s disease and ulcerative colitis are distinct entities in terms of their histology, clinical presentation and endoscopic features. TNF-α, however, plays a central role in both disorders. In ulcerative colitis, production of the inflammatory mediator is increased in the intestinal mucosa while, in Crohn’s disease, it is also elevated in the submucosa. Thus, both diseases respond similarly to anti-TNF strategies, explained H. Tilg, Hall/Tyrol (Austria), both in the induction and maintenance of remission.

On the other hand, one must not forget that the inflammatory process in IBD may be sustained by mechanisms of inflammation that are independent of TNF-α, such as the NKG2D pathway, explained M. Allez, Paris (France). They do not respond to TNF-α blockade but do present the possibility of developing other treatment strategies. Frequently, renewed response may be achieved simply by optimizing the biological regimen based on the trough level. Low infliximab trough levels are associated with a shortened period of response in Crohn’s disease together with reduced mucosal healing; in patients with ulcerative colitis, there is an increased colectomy rate, M. Allez explained.
**Dogma 4**

**Steroids are Beneficial in the Treatment of Inflammatory Bowel Disease**

**Steroids: No Induction of Apoptosis**

Steroids' anti-inflammatory effects are due to several causes. For one, they inhibit the release of pro-inflammatory cytokines from immune cells, including TNF-α, interleukin-2 and interleukin-17, as well as inhibiting blastic transformation. Unlike TNF-α inhibitors, however, they do not, at clinically relevant doses, induce apoptosis. "This may be one reason for the different respective efficacies of steroids and TNF-α inhibitors," explained Y. Chowers, Tel Hashomer (Israel). Also problematic is the development of steroid resistance, which is associated with increased glucocorticoid receptor (GR)-β concentrations. Non-steroidal GR agonists are under current study as an alternative. Their effects on the release of individual cytokines is quite variable. In addition, they do not induce GR down regulation and could therefore overcome the problem of steroid resistance.

**Can Steroids Reduce the ATI Risk?**

Steroids have a favorable effect on the development of antibodies to infliximab (ATI): Within 16 weeks, 42% of patients receiving placebo but only 26% of those taking prednisolone developed ATI, explained B.G. Feagan, London, Ontario (Canada), citing study data. At the same time, he reviewed the grave risks of long-term therapy with steroids. Safety data from the TREAT register clearly show that long-term therapy with steroids doubles the risk of serious infections. With infliximab, there was a 1.4-fold increased risk. Data for mortality risk are comparable (HR: 2.0 vs. 1.1). In contrast, azathioprine is not associated with any increased risk, either in terms of infection or of mortality. Current research has focused on identifying new steroids and new formulations that preserve steroid efficacy while reducing the risks.

"Yes, I’ve ordered steroids," admits G. van Assche, Leuven (Belgium). Steroids are considered useful for inducing remission but not for maintenance of remission. About one-half of patients showing initial response become steroid-dependent within a year or require surgery. In fact, the risk of postoperative complications shows a dose-dependent increase in patients treated with steroids, this in contrast to treatment with an immunomodulator, such as azathioprine, G. van Assche emphasized. He cited in this regard findings of a study using prednisolone (20 mg/day) that shows a 3.7-fold increase in the overall rate of complications and even a 5.5-fold increase in the probability of infection. By contrast, azathioprine or 6-mercaptopurine (6-MP) had no unfavorable effect on postoperative complications.

S. Danese, Rozzano (Italy) cited budesonide as a steroid with low systemic bioavailability that is practically as effective as prednisolone for inducing remission but has a better safety profile. "It is, however, also not suitable for maintenance of remission," S. Danese warned. Also under study is oral beclomethasone. It showed comparable efficacy to prednisolone in mild to moderately active ulcerative colitis with response rates of 64% versus 66%. Data on its safety profile, however, remain limited.
Late Crohn’s disease is characterized by the development of strictures and penetrating complications, all of which contributes to the overarching necessity of surgical intervention. At the same time, there is an evolution in immunobiological conditions. This change, said E. Louis, Liège (Belgium), leads to a shift in response to therapeutic measures: “Because of these biological differences, anti-TNF strategies are more effective in early Crohn’s disease than in late Crohn’s disease.” He was able to show that the proportion of interleukin-17 (IL-17)-producing CD4+ cells first begins to increase in a late disease stage (illness duration greater than two years). With a duration of less than four months, the proportion of IL-17-producing CD4+ cells was low and comparable to that of healthy controls. According to S. Kugathasan, Atlanta (USA), all definitions of “early” versus “late” Crohn’s disease are arbitrary and “don’t solve the problem.” No less challenging is the search for suitable makers to differentiate between these two entities. Meta-analyses have failed to identify a genetic pattern that might facilitate the differentiation with respect to disease onset in younger versus older patients with Crohn’s disease or ulcerative colitis. This might also be evidence of the close pathogenetic relationship between IBD with first onset during childhood and disease first manifesting in adulthood, S. Kugathasan said. Nor have any clear patterns been identified with respect to potential serological markers that would facilitate differentiation. The overall prevalence of serological markers, however, tends to be lower in younger patients.

M. Sans Cuffi, Barcelona (Spain) explained the complex process of fibrinogenesis in the gut. Key molecules for the fibrotic process include angiotensin II, TGF-β1 and interleukin-13 (IL-13). They offer targets for therapeutic interventions, which have shown positive results in early preclinical studies.

Treat Promptly – Treat Individually

We’re always too late with treatment, emphasized S. Schreiber, Kiel (Germany), noting that “we simply don’t have good markers that indicate severe disease.” Unlike cardiovascular disorders in which intensive preventive care is obligatory, an aggressive therapeutic approach is often unnecessarily postponed in patients with IBD, “not least because of the fear of side effects.”
Innovative Therapies Improve the Management of Patients with IBD

Be Careful with anti-TNF-α Strategies in Patients with Multiple Sclerosis

There is an association between IBD and multiple sclerosis (MS). In fact, the risk of developing MS is increased 1.4-fold in patients with IBD. The pathophysiological concepts in IBD and MS are also similar. For example, TNF-α is involved in the inflammatory process in both disorders. Still, “the effects of therapeutic interventions are different,” emphasized S. Ghosh, Calgary (Canada). Therapy with TNF-α blockers in patients with IBD may lead to an exacerbation of MS or to demyelination. S. Ghosh explained that activation of TNFR1 causes demyelination, while activation of TNFR2 leads to remyelination. It would, therefore, be necessary to develop much more selective anti-TNF strategies for these to be beneficial in MS.

A Last Resort: Transplantation of Autologous Hematopoietic Stem Cells

In some cases, despite exhaustion of all available pharmacological and surgical options, treatment results may remain unsatisfactory. In these patients, autologous hematopoietic stem cell transplantation (HSCT) may represent a last resort. In a phase-I study of 24 patients with active Crohn’s disease, who did not respond to conventional therapy, remission was achieved in all patients with HSCT. Within the first year, 91% required no medication; after four years, this was the case with 39%. No patient died during treatment.

Budesonide and Mesalazine are of Equivalent Efficacy in Mild to Moderate Crohn’s Disease

Despite the many innovations, the 5-aminosalicylates, such as mesalazine, have retained their importance as a central component of national and international recommendations for the treatment of IBD, emphasized A. Dignass, Frankfurt (Germany). Mesalazine remains the drug of choice for inducing and maintaining remission in mild to moderately active ulcerative colitis.

Budesonide is the preferred pharmacological treatment for patients with mild ileocecal Crohn’s disease. There is, however, only limited data comparing the efficacy of budesonide and mesalazine. A current study has now shown the equivalence of these two therapeutic regimens. This study of 309 patients compared budesonide, given as enteric-coated (Eudragit-L) gastric acid-resistant tablets at doses of 9 mg once daily or 3 mg three times a day, with mesalazine 1.5 grams three times a day. Remission rates (CDAI ≤ 150) for budesonide, regardless of dosage regimen, stood at 69.5% compared to 62.1% for mesalazine.

antisense oligonucleotides inhibit SMAD7 protein and re-establish TGF-signaling, explained T.T. MacDonald, London (Great Britain).
Personalized therapy: This is the long-term goal for patients with inflammatory bowel disease. With the wide variety of treatment options, it should be possible, so the researchers believe, to tailor an individualized regimen for each patient. This, however, is still pie in the sky. Thus, the discussions at the Falk Symposium 179 in Brussels alternated between scientists’ visions of the future and ways of further optimizing established therapeutic approaches.

Primarily, the pharmacological therapy of Crohn’s disease and ulcerative colitis is still based on the use of 5-aminosalicylates (5-ASA), steroids, immunomodulators and biologicals. These should be administered in a sophisticated manner and as individualized as possible. In reality, however, things look somewhat different: A. Dignass, Frankfurt (Germany) explained that 64% of patients receive an inadequate dose of 5-ASA and 75% are not treated topically. Furthermore, 77% receive steroids for periods in excess of three months and nearly two-thirds of patients with an indication for an immunosuppressant are not given this option; those, who are treated with immunosuppressants frequently receive an inadequate dose. Here, there is certainly room for improvement.

Figure 4 Mesalazine granules are superior to Eudragit-L enteric-coated mesalazine tablets for induction of remission in distal ulcerative colitis

Mesalazine: Give an Adequately High Dose

Mesalazine administered in the acute therapy of mild to moderate ulcerative colitis should be given at a daily dose of at least 3 grams for remission induction, A. Dignass explained. “For maintenance of remission, between 1.2 and 2 grams daily are indicated, depending on the preparation.” The form of application also has bearing on the therapeutic success. Thus, a recently published study found that mesalazine granules (Salofalk® Granules) were more likely to produce endoscopic remission in distal ulcerative colitis than were Eudragit-L enteric-coated tablets (Salofalk® Tablets) (figure 4).

Achieving therapeutic success is often hampered by inadequate adherence to the pharmacological regimen. This can be improved, A. Dignass said, by prescribing medications that are taken once a day. “It has been demonstrated for a number of new mesalazine preparations that once-a-day dosing is at least as effective as regimens according to which medication is taken two, three or even four times a day,” he said, citing, among others, a study showing comparable efficacy for the once and three times daily administration of mesalazine granules (Salofalk® Granules). Mesalazine plays a subordinate role in the therapy of Crohn’s disease. Only recently, however, has one study shown the non-inferiority of mesalazine compared to budesonide in the treatment of mild to moderately active Crohn’s disease. Thus, mesalazine may be worth a try in selected patients with Crohn’s disease (figure 5).

Mucosal Healing is the Number-one Therapeutic Goal

Crohn’s disease progresses in the majority of patients, observed S. Schreiber, Kiel (Germany), developing a chronic inflammatory course that in the long-term causes irreversible damage to the intestinal mucosa. According to P. Rutgeerts, Leuven (Belgium), 19–36% of patients already exhibit strictures, fistulae and abscesses at the time of first diagnosis. Both clinicians emphasized the importance of mucosal healing as a central therapeutic goal. Patients in whom persisting mucosal healing can be achieved show significantly lower resection rates, S. Schreiber explained: “Mucosal healing is a good marker for the success of an intervention.”
**Key to Success:**

**Early Combination Therapy**

In many cases, however, this important therapeutic objective can only be reached by the early addition of biologicals in the sense of a top-down therapy. G. D’Haens, Amsterdam (The Netherlands) provided evidence that ulcerations heal more rapidly and completely, and relapse is more effectively prevented using a top-down therapy than a conventional step-up therapy. The SONIC study found that steroid-free remission and mucosal healing was achieved significantly more often with a combination of azathioprine with a biological than with either substance as monotherapy.

More recently, it has been shown that patients with moderate to severe ulcerative colitis also profit from combined therapy. S. Schreiber cited findings of the EXTEND study, which document that the earlier the disease is aggressively treated, the better the mucosal healing. Conversely, the later in the disease course a biological is started, the poorer the changes for mucosal healing (figure 7).

**Individualized Therapy:**

**Start Now!**

Conventionally, the decision to treat aggressively at an early stage is tied to clinical parameters, including patient-, disease- and treatment-associated data such as age, weight loss or TPMT genotype, the extent and localization of the disease, the occurrence of complications such as fistulae and strictures, and also the need for steroids or previous failure of therapeutic regimens.

The objective of current research efforts is the identification of biomarkers that allow more accurate prediction of patients’ future therapeutic course and response to different therapies. Of particular interest are biomarkers that could provide an early indication of whether an aggressive clinical course is to be anticipated – one that requires a correspondingly early and aggressive intervention. Individualized therapy, however, is already possible, declared P. Rutgeerts, when available tools such as CRP, trough levels and endoscopic findings are used to guide therapeutic decision making. In addition, each treatment step should be given adequate time to achieve efficacy. Drugs that produce no results should be discontinued. Besides the discovery of new prognostic markers, researchers look forward to new biologicals with different mechanisms of action as well as agents, which get at the root cause of IBD, namely the changes in microflora and disturbances of innate immunity.

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**Figure 7** Combination therapy in Crohn's disease results in improved mucosal healing and corticosteroid-free clinical remission compared to monotherapy

**SONIC study**

Week 26

<table>
<thead>
<tr>
<th>Treatment</th>
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<th>Corticosteroid-free clinical remission</th>
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Announcement

Congress Report Falk Symposium 179
with all presentations
(E 179)

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Revisiting
IBD Management:
Dogmas to be Challenged

Editors
G. D’Haens
A. Dignass
S. Vermeire
Crohn’s Disease: Clinical Predictors for Very Severe Disease

While the localization of disease involvement in Crohn’s disease tends to remain unchanged over the course of the disease, the same cannot be said of disease severity. Predictors for a very severe disease course include patient age less than 40 years, stricturing or penetrating disease, fever, weight loss in excess of 5 kg, and elevated platelet counts, said J. Panés, Barcelona (Spain), who identified the following characteristics of “very severe disease”: resection length greater than 70 cm, more than two resections, colectomy, stoma placement or complex perianal disease involvement. “Within five years, 18% of Crohn’s disease patients are affected,” J. Panés said.

“We Treat in Order to Heal the Mucosa”

“Personalized therapy must also be evidence-based,” P. Rutgeerts, Leuven (Belgium) emphasized, opening his presentation on the importance of IBD treatment tailored to patients’ individual situation. Individual therapy decisions should, in his view, be driven by the therapeutic goal, namely, mucosal healing. “We treat in order to heal the mucosa.” Personalized therapy, however, requires reliable biomarkers – these remain to be established. In addition there is no evidence that an individualized therapy is superior to treatment following an established algorithm.

IL23R Variants: Predictor for Response to TNF-α Blockade

Whether patients respond early to an anti-TNF-α antibody depends on many factors, including the IL23R gene variants, said D. McGovern, Los Angeles (USA). In a study of 90 patients with ulcerative colitis, 61% achieved clinical response within 14 weeks (three infusions of infliximab), with 52% in remission. Multivariate regression analysis identified high pre-treatment CAI and negative ANCA status as independent positive predictors of response. Also relevant for response to TNF-α antibody therapy were IL23R gene variants. Carriers of IL23R variants associated with an increased risk of IBD responded better than did carriers of IL23R variants associated with a reduced IBD risk (34.6% vs. 74.5%).

The importance of mucosal healing was also emphasized by S.B. Hanauer, Chicago (USA), who cited numerous studies that document the positive effect of mucosal healing on the long-term course of the disease. Periods of remission are longer and there is less need for hospitalization and surgery.
Immunosuppressants: More Dangerous in the “Combipack”

A variety of immunosuppressants including azathioprine, methotrexate, calcineurin antagonists and TNF-α antibodies are used in the treatment of exacerbations and chronic inflammatory disease in patients with IBD. Within the first five years after diagnosis, over 80% of IBD patients receive steroids. During the same period, nearly 60% of Crohn’s patients and nearly 70% of ulcerative colitis patients are prescribed azathioprine, while a TNF-α blocker is ordered for 25.6% and 11.1% of Crohn’s and ulcerative colitis patients, respectively. This according to data from the Oberpfalz cohort presented by J. Schölmerich, Frankfurt (Germany). Despite their different mechanisms of action, they have one thing common: They increase the risk of opportunistic infections, malignancies and lymphomas. And the risk is especially high when immunosuppressants are combined. J. Schölmerich pointed to data according to which the combination of two or three immunosuppressants is associated with a 14.5-fold increased risk of opportunistic infections compared with only 3.4-fold for monotherapy with azathioprine and 11.1-fold for monotherapy with infliximab. “It is very probable that the combination of immunosuppressants is riskier than the respective monotherapies,” J. Schölmerich concluded from the available data, adding, however, that “this has not been unequivocally proven.”

Prevent Opportunistic Infections

The prevention, diagnosis and therapy of opportunistic infections have become one of the important challenges of clinicians treating IBD patients, observed J.-F. Rahier, Yvoir (Belgium). In addition, the new guidelines of the European Crohn’s and Colitis Organisation (ECCO) contain concrete recommendations that, according to J.-F. Rahier, “may seem radical, but are necessary to reduce the morbidity and mortality associated with opportunistic infections.” The most important step, J.-F. Rahier said, is effective prevention. This requires knowledge of the risk factors, such as age over 60 years, comorbidities and malnutrition, as well as contact with pathogens. He recommended appropriate monitoring and prophylaxis for patients before and during treatment with an immunosuppressant. This includes the recommended vaccinations, including – and especially – when they travel.

Do Not Miss EBV-associated Lymphoproliferations

Should, for example, patients undergoing immunosuppressive therapy develop fever, lymphadenopathy or hemophagocytosis, systemic EBV infection should be ruled out, said L. Beaugerie, Paris (France), this in order to promptly identify EBV-associated lymphoproliferation. In fact, the majority of lymphomas occurring in IBD patients treated with immunosuppressants result from a loss of immunological control of EBV infections. Also increased is the risk of HPV-associated cervical cancers, making the yearly preventive screening in female patients especially important. Immunosuppressants may, however, also protect against malignant transformation. The CESAME cohort study showed that azathioprine reduced the risk of advanced colorectal neoplasias by nearly 80% in patients with extensive colitis.

Discontinue Immunosuppressants in Patients with Acute HBV Infections

What, if a patient with IBD has, however, already developed an infection or cancer? Answers to these questions were provided by A. Kohn, Rome (Italy). She recommended, for example, that immunosuppressants should be discontinued in IBD patients with acute severe colitis and Clostridium difficile infection. The same holds for patients with acute HBV infection, when possible. If the immunosuppressant therapy is required, patients can undergo treatment with antiviral medications with subsequent shift to immunosuppressant therapy. By contrast, interruption of therapy is not required in acute HCV infection nor is chronic HCV infection in IBD patients a contraindication for immunosuppressants or anti-TNF-α antibodies.
Predicting Disease Course with Genetic Cluster Analyses

Both Crohn’s disease and ulcerative colitis can have very divergent courses following first diagnosis. For example, data from the IBSEN study that followed IBD patients over 10 years show that 43% of Crohn’s patients experience a long-term reduction in disease severity after the first flare, while 32% develop a chronic, relapsing disease course. It would be of importance in planning patients’ therapeutic management to be able at the time of first diagnosis to predict the future course of the disease using genetic or molecular markers, observed S. Vermeire, Leuven (Belgium): “It would then be possible to identify patients, who will require an aggressive therapeutic approach early on in the their disease.” The first steps toward this kind of personalized therapy have already been taken. For example, genetic cluster analyses based on the transcription signatures of analogous CD8+ T cells allow for grouping of IBD patients according to the severity of patients’ subsequent disease.

Already Established: CRP and Fecal Calprotectin

CRP is a marker for inflammatory activity and a predictor of early recurrence, while fecal calprotectin serves as a marker for mucosal lesions as well as for achievement of deep remission, explained M. de Vos, Gent (Belgium). The role of antimicrobial antibodies such as ASCA and p-ANCA, together with Omp-C antibody and antiglycan is under current investigation. This holds also for a variety of other inflammatory markers, in particular fractionated exhaled NO (FeNO). Antimicrobial antibodies such as ASCA and p-ANCA assist in differentiating between Crohn’s disease and ulcerative colitis; their value for predicting therapy response, however, appears rather slight.

Preliminary data indicate an association between FeNO and Crohn’s disease: Studies have found a good correlation between FeNO and CDAI, as well as an adequate correlation with fecal calprotectin.

“Still Plenty of Room for Improvement”

We are still a long way from personalized therapy. That was clear from the presentation of G. D’Haens, Amsterdam (The Netherlands). While emphasizing the necessity of reliable biomarkers for predicting aggressive disease, he noted that, in certain areas, personalized treatment has already become a reality. Still, there remains “plenty of room for improvement.” An example is the individualized azathioprine therapy, which is based on thiopurine methyltransferase (TPMT) and 6-thioguanine (6-TG) levels. TPMT metabolizes 6-MP to pharmacologically inactive 6-methylmercaptopurine (6-MMP). The 6-TG and TPMT concentrations determine clinical response, G. D’Haens explained. In one study, 43% of patients with 6-TG activity over 35 pmol/hour/mg Hb showed response, compared with 81% of those with a lower activity (Ansari et al. 2008).

Whether it will ever be possible to cure IBD remains open, said C. Fiocchi, Cleveland (USA), noting the highly complex pathogenesis of these disorders, which is impacted by genetic predisposition, the composition of the intestinal microflora, and the functioning of the immune system, together with factors as nutrition, body weight, tobacco use, ethnic origin, stress and social
Future perspectives in the therapy of inflammatory bowel disease were a focus of discussion at the Falk Symposium “Revisiting IBD Management: Dogmas to be Challenged.” How it is possible even today to optimize treatment with currently available drugs was the topic of an interview with Professor Axel Dignass, chief of the Clinic for Gastroenterology, Hepatology, Oncology and Infectious Disease of Agaplesion Markus-Krankenhaus, Frankfurt (Germany).

Editors:
5-aminosalicylates remain drugs of choice for both inducing and maintaining remission in patients with ulcerative colitis. In many cases, however, they are not used, and, when they are, administration may be inadequate. How do you explain this?

Professor Dignass:
The potential causes can be sought equally in both patients and their doctors. First, many patients may neglect adherence, especially for maintenance of remission, since symptoms may be absent or very mild. Others may fear side effects and do not take their medication at all or not at the prescribed dosage. On the other hand, a sizeable number of physicians fail to prescribe doses recommended by the guidelines.

Editors:
The combination of oral and rectal application is superior to exclusive oral or rectal treatment for remission induction in ulcerative colitis. Which patients would you consider for this “double-barreled” approach?
**Professor Dignass:**
As a rule, every patient can be considered for this approach over a period of four weeks: The combination works significantly faster and more effectively. The time to remission, determined by the disappearance of blood in the stool and resolution of the imperative urgency of bowel movements secondary to inflammation can be cut in half by the addition of enemas or rectal foams. Exceptions include those patients with severe colitis characterized by massively increased stool frequencies. Rectal medication is often not feasible in these cases.

**Editors:**
The data are less clear for the benefit of mesalazine in Crohn's disease. When, in your opinion, would it be worth a try?

**Professor Dignass:**
There is an evidence-based indication for the topically acting steroid, budesonide, in the treatment of mild to moderately active Crohn's disease of the ileocecal region. Recent data show, however, that mesalazine preparations in which acrylic-based resin coatings delay release of the active substance are comparable to budesonide in terms of efficacy when dosed at 4.5 grams per day. For this reason, I use mesalazine in patients with mild to moderate Crohn's disease, who are reluctant to take steroids or in whom there is no rush for therapeutic improvement. Rapid symptomatic relief is more easily achieved using a systemic steroid.

**Editors:**
What criteria do you apply when deciding on using immunosuppressants or biologicals?

**Professor Dignass:**
First considerations are the age of the patient and the disease severity. A younger patient with extensive disease involvement, fistula formation and high inflammatory activity represents an ideal candidate for a TNF-α inhibitor. Chronic disease with lower inflammatory activity can often be satisfactorily treated with azathioprine.

Another criterion is the time window. When treating patients, who require rapid healing, I tend toward a TNF-α inhibitor. In cases with moderate disease activity in which the time to clinical improvement is of subordinate importance, I often prefer an immunosuppressant. In recent years, the situation with severe ulcerative colitis has become comparable. Here, infliximab has already been approved for quite some time and is integrated into the current DGVS and ECCO guidelines. Approval of adalimumab for the treatment of ulcerative colitis is expected in the near future.

**Editors:**
Combination therapies were also discussed during the symposium – for example an immunosuppressant plus TNF-α antibodies or, perhaps, a steroid. How do you see the role of such combinations?

**Professor Dignass:**
Combinations of azathioprine plus the TNF-α blocker, infliximab, produce better response rates than do the individual monotherapies. This has been clearly shown in controlled studies of Crohn's disease and ulcerative colitis. This combination is therefore considered very suitable for severely ill patients. It has also been shown that the production of antibodies to TNF-α blockers can be reduced by the simultaneous administration of azathioprine.

For these reasons, the combination treatment is, in general, rather well suited to the initial treatment phase. Should the patient, due to the severity of his disease, no longer require a combination, azathioprine would be discontinued after six months as the increased immunosuppression under this combination is associated with an elevated risk of severe opportunistic infections and potentially malignancies, such as hepatosplenic T cell lymphomas. Steroids can also suppress the formation of antibodies to TNF-α blockers. Because our goal is steroid-free remission, we use steroids with TNF-α blockers only when severe allergic reactions are expected or there has been a long interval since the last TNF-α antibody treatment.

**Editors:**
Over the next few years, numerous new biologicals will hit the market. What are your expectations in this regard?

**Professor Dignass:**
The therapy of Crohn's disease with high inflammatory activity is soberingly poor. Even the TNF-α blockers work in only 30–60% of these patients. We urgently need new drugs with different mechanisms of action for those patients, who do not profit from currently available therapies. In addition, we know that therapy with a TNF-α blocker often loses some of its efficacy. A significant proportion of patients no longer respond adequately after three to four years of treatment. We need new drugs for this patient group, too, in order to assure a sequential therapy.

Also lacking are drugs with fewer side effects for maintenance of remission in Crohn's disease. Because the new biologicals possess different mechanisms of action, it would be conceivable that they might be effective in these patients in whom currently available standard therapies fail. The studies conducted to date show that these agents are also effective in patients in whom treatment with a TNF-α blocker has failed.
Editors: Do these new mechanisms of action broaden the chances for individualized therapy?

Professor Dignass: This would require reliable markers. Many centers have focused their research efforts on identifying clinical, immunological or genetic factors that would facilitate personalized therapy — to date, without any spectacular success for the clinical routine. Only by obtaining a panel of multiple markers, such as ANCA, ASCA or patient’s NOD2 status allows for a bold prognosis of which patient is suitable for which therapy.

Still, this is the direction of the current development. For example, we already know that the IL-12/23p40 blocker, ustekinumab, has better chances of responses in patients with higher levels of soluble IL-2 receptor. In routine clinical practice, we continue to orient our management on the known clinical markers — age, pattern of disease involvement, extent of the inflammation and CRP. In addition, we can monitor for antibodies against TNF-α blockers, while trough-level determinations of TNF-α antibodies can predict whether a patient will (still) respond to treatment with a TNF-α antibody.

Editors: When all other pharmacological options have been exhausted, the transplantation of hematopoietic stem cells (HSCT) represents a “last resort”. Can this method already be offered to patients in good conscience?

Professor Dignass: HSCT is a highly effective method, which has response rates of over 90% in patients in whom all other therapies have failed. New register data show response rates of 60–70%. HSCT, however, is still not yet a standard method and should be performed – if at all – only in centers. Patients should be reported to the corresponding study registers. In addition, patients must be made aware of the fact that there is a mortality risk. Therefore, one must carefully weigh whether a disease such as Crohn’s disease, which has, on average, a normal life expectancy, should be treated with a method that has a risk of “death”. There are, however, patients for whom HSCT remains the only available option.

Professor Dignass, thank you very much for the interview.
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Salofalk®
Salofalk® Granules 500mg/1000mg/1.5g/3g; Salofalk® 250mg/500mg Gastro-resistant tablets, Salofalk® 2g/30ml and 4g/60ml Enemas; Salofalk® 1g Rectal Foam. Active ingredient: mesalazine (5-aminosalicylic acid). **Composition:**
1 sachet of Salofalk® granules 500mg/1000mg/1.5g/3g contains: active ingredient: 500 mg/1000 mg/1.5 g/3 g mesalazine. Other ingredients: aspartame (E951), carmellose sodium, citric acid, silica colloidal anhydrous, hypromellose, magnesium stearate, methacrylic acid-methyl methacrylate copolymer (1:1) (Eudragit L 100), methylcellulose, cellulose microcrystalline, polyacrylate dispersion 40% (Eudragit NE 40 D containing 2% Nonoxynol 100), povidone K25, simeticon, sorbic acid, t alc, titanium dioxide (E171), triethyl citrate, vanilla custard flavouring (containing propylene glycol). 1 tablet of Salofalk® 250mg/500mg contains: active ingredient: 250 mg/500 mg mesalazine. Other ingredients: Calcium stearate, basic butylated methacrylate copolymer (=Eudragit E), methacrylic acid methyl methacrylate copolymer (1:1) (=Eudragit L), glycine, silica colloidal anhydrous, hypromellose, macrogl 6000, cellulose microcrystalline, sodium carbonate anhydrous, povidone K25, talc. Colouring agents: titanium dioxide (E171), iron oxide hydrate (E172), additionally Salofalk® 500mg tablets: croscarmellose sodium. 1 Salofalk® 250mg/500mg/1g suppository contains: active ingredient: 250 mg/500 mg/1 g mesalazine. Other ingredients: hard fat; additionally Salofalk® 500mg suppositories: docusate sodium, cetyl alcohol. 1 enema of Salofalk® 2g/30ml or 4g/60ml contains: active ingredient: 2 g or 4 g mesalazine. Other ingredients: sodium benzoate (E211), potassium metabisulphite (E224), potassium acetate, carbomer 947P, sodium edetate, xanthan gum, purified water. Note: Salofalk® enemas contain sodium benzoate and potassium metabisulphite. See patient information leaflet. Salofalk® 1g Rectal Foam: 1 actuation contains: active ingredient: 1 g mesalazine. Other ingredients: sodium metabisulphite (E223), cetostearyl alcohol, polysorbate 60, sodium edetate, propylene glycol. Propellants: propane, n-butane, isobutane. Note: Salofalk® 1g Rectal Foam contains sodium metabisulfite (E223), propylene glycol and cetostearyl alcohol. See patient information leaflet. **Indications:**
Salofalk® granules 500mg/1000mg/1.5g/3g: acute treatment and prevention of recurrence of ulcerative colitis. Salofalk® 250mg/500mg tablets: acute treatment and prevention of recurrence of ulcerative colitis. Acute treatment of Crohn's disease. Salofalk® 250mg/500mg/1g suppositories: acute treatment of (1g: mild to moderate) ulcerative colitis confined to the rectum. Additionally Salofalk® 2g/30ml enemas: acute treatment of mild to moderate ulcerative colitis, localised in the rectum and sigmoid colon. Salofalk® 4g/60ml enemas: acute treatment of ulcerative colitis. Salofalk® 1g Rectal Foam: Treatment of active, mild ulcerative colitis of the sigmoid colon and rectum.
**Contraindications:** Known hypersensitivity to salicylates or any of the excipients, severe impairment of hepatic or renal function. Pregnancy and lactation: risk-benefit ratio. Additionally for Salofalk® Enemas and Rectal Foam: not to be used in case of sensitive patients (especially for known asthmatics or allergic anamnesis) due to the content of metabisulphite or sodium benzoate. **Side effects:**
Headaches, dizziness, peripheral neuropathy, abdominal pain, diarrhea, flatulence, nausea, vomiting, impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency. Hypersensitivity reactions such as allergic exanthema, drug fever, pancoitis, lupus erythematosus syndrome, allergic and fibrotic lung reactions (including dyspnoea, cough, bronchospasm, alveolitis, pulmonary eosinophilia, lung infiltration, pneumonitis), peri- and myocarditis, acute pancreatitis, myalgia, arthralgia, altered blood counts (aplastic anemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, trombocytopenia), changes in liver function parameters (increase in transaminases and parameters of cholestasis), hepatitis, cholestatic hepatitis, alopecia, oligospermia (reversible). Additionally for Salofalk® 1g Rectal Foam: abdominal distension, anal discomfort, application site irritation, painful rectal tenesmus. Salofalk® 1g Supp.: constipation. **Interactions and dosage:** see patient information leaflet. Available on prescription only. Date of information: 02/2012
October 3 – 6, 2012
Mainz, Germany

Congress Venue
Congress Center Mainz
Rheinstr. 66
55116 Mainz
Germany

October 3 – 4, 2012
Falk Symposium 185
Interfaces and Controversies in Gastroenterology
Scientific Organization
C. El, Wiesbaden (Germany)
P. R. Galle, Mainz (Germany)
J. Mössner, Leipzig (Germany)
C. Meyenberger, St. Gallen (Schweiz)
S. J. Spechler, Dallas (USA)
H. Yamamoto, Kawachi (Japan)

October 5 – 6, 2012
Falk Symposium 186
Challenges of Liver Cirrhosis and Tumors: Prevent it, Treat it, Manage Consequences
Scientific Organization
P.-A. Clavien, Zurich (Switzerland)
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