Innate Immunity in Gastrointestinal Disorders: Basic and Therapeutic Concepts

Carcinogenesis, Prevention and Treatment of Colorectal Cancer – State of the Art 2012
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Foreword

The Bavarian capital was the venue as international scientists convened in early 2012 at two symposia sponsored by the Falk Foundation e.V. to exchange the latest research findings in the fields of gastroenterology and hepatology, discuss points of controversy and together seek new ways to improve patient care.

Falk Symposium 181

Link between gastroenterology and hepatology: The innate immune system

Gastroenterology and hepatology continue drifting further apart as the result of the ever more detailed and far-reaching understanding of these two respective fields. An important link, however, is the innate immune system, whose involvement in the pathogenesis of gastroenterological and hepatological disease entities is equally strong. Thus, for H. Tilg (Hall/Tyrol, Austria), the role of innate immunity in gastrointestinal disorders seemed the ideal “hook” to draw together gastroenterologists, hepatologists and basic researchers and, together with R.S. Blumberg (Boston, USA), S. Endres (Munich, Germany), A. Kaser (Cambridge, UK) and M.P. Manns (Hannover, Germany), he assembled the scientific program of the Falk Symposium 181 in Munich as a forum for discussing these issues.

Falk Symposium 182

Colorectal carcinoma 2012: Looking for answers to unsolved questions

Colorectal carcinoma (CRC) claims 600,000 lives every year according to data of the WHO. And this number will only grow due to the constant increase in life expectancies. Over the past years, our understanding of the carcinogenesis of CRC has continued to grow and has resulted in enhanced diagnostic and therapeutic options. Still, emphasized H. Friess (Munich, Germany), “we need more advances!” Together with R.M. Schmid (Munich, Germany), M. Fried (Zurich, Switzerland) and C.J.H. van de Velde (Leiden, The Netherlands) he arranged a scientific program for the Falk Symposium 182 “Carcinogenesis, Prevention and Treatment of Colorectal Carcinoma – State of the Art 2012” that reflects the current state of research, diagnosis and therapy of this all-too-common malignancy.
The art of making the right choice

“Who needs what?”
This challenge is faced daily by countless clinicians when deciding upon a pharmacological therapy. Nor are the answers getting any easier as more and more new drugs crowd the market. The good news: The search for markers to guide management decisions is in full speed.

The range of treatment options in the management of inflammatory bowel diseases (IBD) continues to grow. In addition to the 5-aminosalicylates, steroids, antiand probiotics and immunomodulators, such as azathioprine, newer agents, such as the biologics, have become established elements of the management repertoire. Novel therapy concepts are waiting in the wings. Nutrition therapy is a further option for patients with Crohn’s disease. The challenge consists in selecting the right treatment for the right patient at the right time. The search is on for genetic and molecular markers that will provide guidance on the individual patient’s disease course, thus facilitating the choice of therapy. Predicting an individual patient’s future disease course remains one of the unsolved problems of IBD. “Patients’ disease course is variable and unpredictable,” observed J. Lee (Cambridge, UK), citing two case examples. Thus, deciding whether to immediately pursue an aggressive therapy or opting for a more moderate approach can be challenging. But there may be light at the end of the tunnel. The transcription signature for CD8+ T cells helps differentiate patients who require therapy escalation from those who do not. Here, there is a significant overlapping between Crohn’s disease and ulcerative colitis (figure 1).

Indeed, the signatures could be used interchangeably to recreate the same subgroups – termed IBD1 and IBD2


Figure 1 There are significant overlaps between Crohn’s disease and ulcerative colitis in terms of the transcription signature of CD8+ T cells.
Don’t forget mesalazine in Crohn’s disease

Until reliable markers have been identified and established, however, therapy decisions will need to be made the old fashioned way, based on the clinical picture. Still, recent studies have provided the impetus to rethink certain old strategies. For example, A. Dignass (Frankfurt/Main, Germany) presented a current study supporting the benefit of mesalazine in Crohn’s disease. This study compared the 5-aminosalicylate (n = 119) with budesonide (n = 134), in patients with mild to moderately active Crohn’s disease, an indication for which ECCO guidelines recommend the latter topically acting steroid. In this collective, mesalazine was not inferior to budesonide in terms of clinical remission rates (CDAI < 150) of 68.4% vs. 72.4% (figure 2).

Mesalazine, in the opinion of A. Dignass, thus has some value in the therapy of Crohn’s disease. Important here is correct patient selection and choice of the most suitable mesalazine formulation (figure 3).

Figure 2 Mesalazine is not inferior to the topically active steroid, budesonide, for inducing remission in mild to moderately active Crohn’s disease

Tromm et al. Gastroenterology 2011;140:425–434

Figure 3 The 5-aminosalicylates utilize a number of mechanisms to produce their therapeutic results. Many still remain poorly understood

E-health: The future of IBD treatment?

Adherence problems, which frequently impact long-term therapies, are not uncommon in patients with IBD. Modern technologies, however, may provide a new way of addressing these. A. Dignass presented data according to which the implementation of E-health in patients with ulcerative colitis resulted in improved adherence to a four-week therapy with 5-ASA in 31% of patients in a Danish collective and in 44% of Irish patients compared with controls. Recurrence rates, hospital admissions, surgery and side effects were comparable.

Steroids on trial

Harsh indictments against steroids were brought by T. Ochsenkühn (Munich, Germany). He recited the long list of serious side effects, such as Cushing’s syndrome, osteoporosis, skin changes (figure 4), hypertension, cataracts, glucose intolerance, psychiatric symptoms, adrenal insufficiency and, especially relevant in children, growth disturbances. This does not simply increase morbidity, T. Ochsenkühn warned, but also mortality. In fact, data from the TREAT register for Crohn’s disease show that prednisone is associated with a 2.1-fold increased mortality risk.

Too little attention has been paid to the steroid withdrawal syndrome which is often confused with extraintestinal manifestations of Crohn’s disease.

The use of corticosteroids should therefore be as limited as possible and carefully targeted. Their long-term use should be absolutely avoided. Steroids should also be avoided in patients with treatment-refractory Crohn’s disease or steroid-refractory ulcerative colitis, as well as in IBD patients who need maintenance therapy. And: The goal of therapy should always be mucosal healing.

Figure 4
Skin changes are common with steroids (Singleton et al. Gastroenterology 1979;77:887–897)
Announcement

Congress Reports Falk Symposia 181/182
with all presentations
(E 181/E 182)

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Falk Symposia Series
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Editors:
Prof. Tilg, in organizing the Falk Symposium 181, you targeted the role of the innate immune system in gastrointestinal disorders. What led you to this perspective?

Professor Tilg:
In recent years the innate immune system has been increasingly implicated in the pathophysiology of gastrointestinal diseases and has taken on an almost unbelievably central dimension. It is probable that the innate immune system is key to very many disorders in the fields of gastroenterology and hepatology. With this in mind, it seemed quite natural to formulate the topic so centrally. The other consideration was to build a bridge between gastroenterology and hepatology. The innate immune system is one of the very central and fundamental bridges for understanding both fields. These two disciplines have drifted apart significantly over the past two decades. Gastroenterologists no longer understand hepatologists and vice-versa. This, in my opinion, is an unfortunate development. A deeper understanding of the innate immune system shows us how closely the two fields are related and how they must be understood together.

Editors:
What does this mean for the pathophysiology of the inflammatory bowel diseases?

Professor Tilg:
Just looking at the genetics, it has become very evident that the inflammatory bowel diseases represent disorders of the innate immunity. We have discovered about 100 genetic factors to date of a postulated 300. When one delves into their nature, one sees that practically all are associated not simply with the field of immunology but in a majority of cases with the innate immunity. While these results of genetics research have not necessarily improved the diagnosis and therapy of these disorders, they have led us directly to the central problem of these disorders. The innate immune system appears to have two functions: First, to rapidly recognize enemies and, second, to interact in a physiologically construc-
Editors:
To date, the therapy of IBD has focused primarily on anti-inflammatory principles. Based on these new findings, should we not instead be attempting to influence the microbiota or the innate system at an early point in the course of the disease?

Professor Tilg:
This is completely correct. Right now we aren’t in the slightest approaching these disorders from a causal standpoint: Instead, we are treating the end stage of the disease, the immense, exaggerated inflammatory reaction which typically brings the patient to his doctor in the first place. The early stages of the disease are by then long past; the innate immune system has already been misdirected. Thus, many gastroenterologists are of the opinion that, while the currently available immunosuppressants and biologics are suitable for acute therapy and the first months of remission, in the long term we need completely different therapy concepts. Our current understanding of the complexity of these processes is, however, still inadequate to know exactly where we should begin. If, for example, we were to focus on the loss of tolerance to the physiological microflora, we would first need to understand which aspects of the microflora are affected and know how to alleviate this disturbance.

Editors:
One therapy concept under current development is immunotherapy with the ova of the helminth, Trichuris suis, the porcine whipworm. What is your opinion of this therapy concept?

Professor Tilg:
Behind this concept are a number of simple immunological observations. The first is the hygiene hypothesis, which postulates that the immune system has “forgotten” how to interact with physiological substrates, like worms. The other is the observation that the inflammation in Crohn’s disease is a Th1 mediated inflammatory response which can be corrected by the worms, thus adjusting the polarization of the immune response. In the meantime, however, the simple Th1 view is no longer tenable; hence, the worm concept may have outlived its usefulness. The concept, however, remains interesting and we will have to await the large phase-III studies.

Editors:
Genetic studies have shown that different genes are important for Crohn’s disease and ulcerative colitis. For example, genes that are relevant for the function of the epithelial barrier are more closely associated with ulcerative colitis. By contrast, autophagy genes are more specific for Crohn’s disease. Does not this suggest that we need to differentiate more in terms of our thinking, including with respect to the treatment of these disorders?

Professor Tilg:
The tendency to “treat alike” in the management of these quite different disorders reflects nothing more than a lack of understanding of the underlying mechanisms of these disorders. We basically ignore the fact that Crohn’s disease and ulcerative colitis are completely different and also show that we have failed to understand the very long period of the “early disease” process. In their intermediate and end stages, both major types of IBD are quite similar and respond to the same pharmacologic agents.

Nonetheless, we are on the right path. As we continue to pursue a better understanding of the disease course from a genetic standpoint, we discover molecules that play surprising roles in this process. We have no more than lifted the lid of the microbiota box. Taken as a whole, our microbiota contain 10 to 100 times more genetic information than do humans. We are still at the very beginning of this journey but we believe that the microbiota represent a key of central importance to the understanding of these diseases.

Editors:
Where along the disease course do novel biologics fit in?

Professor Tilg:
All therapies under current consideration, including those innovative concepts, focus on the late phase of the disorders. This is adequate when dealing with manifest disease. In fact, 80% of patients in the acute phase can be effectively treated using an anti-TNF-α antibody. We need to change our strategy, however, after three to six months.

Real progress is expected from the anti-migration therapies but new, attractive target molecules for the inflammatory reaction are scarce. I also expect the arrival of signal transduction inhibitors, which are already widely used in oncology.

Editors:
Characteristic for IBD is the disturbance of the mucosal barrier. Lecithin has been discussed for stabilizing the colonic mucosa. How promising is this in your view?

Professor Tilg:
Lecithin as a stabilizer of the mucous membrane may prove important in remission maintenance. Mucus and its preservation are important factors especially in ulcerative colitis. It may well be that, if we get good initial control over the inflammation, remission maintenance will not require such complicated strategies after all.

Professor Tilg, thank you for the interview.
Autoimmune hepatitis (AIH) is typically a disease of younger women. Still, it may occasionally manifest itself after the age of 50 years, said C.P. Strassburg (Hannover, Germany). Crucial for patients’ prognosis is early diagnosis and adequate immunosuppressive therapy. This is indicated in patients with confirmed AIH, elevated serum transaminase and IgG levels and histologically evident interface hepatitis or necroinflammatory activity.

The combination of a steroid and azathioprine remains the treatment of choice and leads to remission in 80% of patients. If this treatment fails, the diagnosis – and the patient’s compliance – should be re-assessed and, when appropriate, the induction therapy should be repeated. Budesonide is a well-tolerated alternative to prednisolone: The International Budesonide Trial, a prospective randomized double-blind study, found it to be comparably effective but better tolerated than the conventional steroid. In contrast to AIH, immunosuppressive therapy is quite ineffective in the treatment of primary biliary cirrhosis (PBC). The standard pharmacological therapy of this cholestatic disorder remains ursodeoxycholic acid (UDCA).

The focus is on rituximab in AIH

The liver is an organ of the immune system, as U. Protzer (Munich, Germany) clearly demonstrated. As a way of reaching a better understanding of the pathophysiology of AIH, E. Jäckel (Hannover, Germany) developed two animal models that can, in addition, be used to research therapeutic alternatives for patients not responding to conventional treatments. Currently in the researchers’ crosshairs is rituximab, a CD20 antibody that leads to B cell depletion.

Using a model, M.E. Gershwin (Davis, USA) was able to show that rituximab reduces both AMA and alkaline phosphatase. “Rituximab is certainly not suitable for every PBC patient, but some may respond to it,” M.E. Gershwin concluded.
Primary sclerosing cholangitis (PSC) is a serious chronic inflammatory disease that over the long term leads to a destructive fibrosis of the bile ducts and frequently progresses to cirrhosis of the liver. Currently lacking are effective, established therapies that extend patients’ transplantation-free survival. T.H. Karlsen (Oslo, Norway) cited genome-wide association studies (GWAS) of PSC which identified susceptibility loci that overlapped with those of other chronic inflammatory diseases, such as multiple sclerosis (MS). This overlap, T.H. Karlsen said, could provide new keys to understanding of the pathogenesis of this disorder with the potential for new treatment options. The current standard therapy with UDCA does improve laboratory findings and prognostic surrogate parameters, but not survival.

Things may be different with nor-UDCA, a UDCA derivative that, in animal experiments on MDR2−/− mice at least, has led to remission and possesses anti-inflammatory, antiproliferative and antifibrotic properties, explained M. Trauner (Vienna, Austria). A current clinical study will test the efficacy of nor-UDCA in patients with PSC.

C. Trautwein (Aachen, Germany) emphasized the importance of cytokines in hepatitis and acute liver failure. Compared with both the healthy liver and also the chronically diseased liver, there is a dramatic increase in the expression of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), which accelerates the closely intertwined processes of necrosis and apoptosis. Both must be stopped. This might be possible using ARC (apoptosis repres- sor with caspase recruitment domain), which in preliminary studies has been shown to protect against Fas- and ConA-induced liver damage.

The importance of the innate immune defenses in the control of hepatitis C was discussed by H. Wedemeyer (Han-nover, Germany). It appears that the hepatitis C virus interacts directly with NK cells and inhibits their function.

Driving obesity: Intestinal microflora and ER stress

"The intestinal microflora is one of the environmental factors that contributes to the development of obesity," concluded F. Bäckhed (Göteborg, Sweden). He was able to show in several studies that overweight and normal-weight mice differ in terms of their intestinal microflora; bacteria-free mice do not develop obesity even when fed corresponding diets.

Also involved in the development of overweight and type-2 diabetes mellitus is endoplasmatic reticulum (ER) stress, said G. Hotamisligil (Boston, USA), citing his own investigations.

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Activation of the hedgehog signal pathway in NASH: A double-edged sword

The prognosis of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) can be quite variable. In their attempt to elucidate this observation, researchers discovered the so-called hedgehog signal pathway. As hepatocytes die in patients suffering from NASH, these structurally changed hepatocytes (“ballooning hepatocytes”) release hedgehog (Hh) ligands. These molecules belong to the family of damage-associated molecular signals (DAMS) and their release can ramp up the wound healing process. By contrast, NAFLD is characterized by a more favorable clinical course even in the absence of activation of the hedgehog signal pathway.

In in-vitro studies of human hepatocytes, excessive activation results in development of NASH cirrhosis. “Cirrhosis is an exaggerated hedgehog status,” explained A.M. Diehl, warning of the sequence of inflammation, fibrosis and cancer.

The innate immune system also plays a key role in the pathophysiology of alcoholic steatohepatitis (ASH). Here, the Toll-like receptors (TLR) appear to be of great significance.

According to G. Szabo (Worcester, USA), mice with defective TLR4 but also with defective IRF3 (interferon regulatory factor 3) are protected from ASH. This is not the case with an MyD88 defect. This would suggest that an MyD88-independent TLR4 signal transduction pathway is decisive.

With respect to vitamin E, however, C.P.Day (Newcastle-upon-Tyne, UK) urged caution. Evidence suggests that overall mortality is increased in subjects taking vitamin E doses over 400 IU/day. This also applies to the risk of hemorrhagic stroke and prostate carcinoma.

Toll-like receptors are also found on intestinal epithelial cells.

The liver biopsy is an important component of the work-up of suspected NAFLD, said E.M. Brunt (St. Louis, USA). It is the only method that can diagnose NAFLD in patients with other serologically diagnosable liver diseases, such as autoimmune hepatitis (AIH).

Because this disorder is closely associated with overweight, insulin resistance and dyslipidemia, these parameters of the metabolic syndrome are naturally a focus of therapeutic efforts. According to findings of the PIVENS (Pioglitazone vs Vitamin E vs Placebo for Treatment of Non-Diabetic Patients with Nonalcoholic Steatohepatitis) and TONIC (Treatment of NAFLD in Children) studies, vitamin E may have a direct, favorable effect on the liver.

Be careful when using vitamin E against NASH

Toll-like receptors (TLR) are a component of the innate immune system. As H. Wagner (Munich, Germany) explained, signal transduction generally follows two main “highways”; namely via NFkB with induction of TNF-α and IL-12 or via IRF with induction of IFN-α. H. Wagner emphasized that
TLRs are expressed not only on cells belonging to the innate immune system but also on epithelial cells of the intestinal mucosa, where they play an important role in distinguishing between “friendly” and “unfriendly” microflora.

**Tracking down intestinal microbacteria**

Metagenomics makes it possible to establish the genome of the intestinal microflora in humans and establish correlations with clinical parameters. Using data from comprehensive investigations, J. Wang (Shenzhen, China) was able to show that 40% of the genes contained in the microbiome are shared by at least 50% of individuals. Even more exciting are the results of the Chinese Type-2 Diabetes Study according to which type-2 diabetics exhibit changes in microbiota. “There is a clear dysbiosis in type-2 diabetics,” J. Wang said. Nutrition can affect the intestinal metagenome.

**Autophagia genes: Specific for Crohn’s disease**

Inflammatory bowel diseases are polygenic disorders. Over the past few years, genome-wide association studies (GWAS) have identified a number of associated genes with overlap between Crohn’s disease and ulcerative colitis. There was a stronger association with ulcerative colitis for genes relevant for the epithelial barrier, such as ECM1, HNF4 or E-cadherin. By contrast, the autophagia genes ATG16L1 and IRGM are more closely associated with Crohn’s disease, said M. Parkes (Cambridge, UK).

**NLRP3 inflammasome: Friend or foe?**

Proinflammatory cytokines such as TNF-α, IL-1 and IL-18 play a central role in the pathogenesis of IBD. Less clear is the role played by the NLRP3 inflammasome (cytosolic protein complex), which is closely associated with IBD. When stimulated by microbial substances, this protein complex can activate caspase-1, thus ultimately also IL-1 and IL-18. Using an acute DSS colitis model, M. Schnurr (Munich, Germany) showed that mice with an NLRP3 or caspase-1 defect released smaller amounts of IL-1. NLRP3−/− mice also developed less severe colitis than did wild-type mice.

Still, “enterobacteria may lay the groundwork for the development of colitis in humans,” W. Garrett said.

Inflammasome is for the study of the interactions between intestinal microbiota and the host, said W. Garrett (Boston, USA). Using a colitis model, she was able to show that the enterobacteria Klebsiella pneumoniae and Proteus mirabilis have colitogenic properties. Intestinal inflammation, however, occurs only in the presence of an appropriate “microbial” environment. Introduced into otherwise bacteria-free mice, these microorganisms did not cause inflammation. In addition, not all Klebsiella and Proteus strains were equally colitogenic in this model.

Colitogenic: Enterobacteria

Inflammation, however, occurs only in the presence of an appropriate “microbial” environment. Introduced into otherwise bacteria-free mice, these microorganisms did not cause inflammation. In addition, not all Klebsiella and Proteus strains were equally colitogenic in this model.

NLRP3 inflammasome: Friend or foe?
That chronic intestinal inflammation promotes the development of colorectal carcinoma is beyond doubt, reported F.R. Greten (Munich, Germany).

Here, a key role is played by the transcription factors, STAT3 and NFkB. At the same time, F.R. Greten cited current study data according to which acetylsalicylic acid may protect against colon carcinoma.

A "new kid on the block" in the network of the intestinal innate immune system was introduced by J. Ruland (Munich, Germany): The C-type lectin receptor (CLR). It is, however, less specific than TLR. Essential for this signal transduction is the adaptor protein, CARD9. Genetic polymorphisms of CARD9 may be associated with inflammatory disorders in humans.

According to M.F. Neurath (Erlangen, Germany), necrosis (in addition to apoptosis) should be considered in the study of IBD.

5-Aminosalicylates are an established option in mild to moderate ulcerative colitis for both inducing and maintaining remission. Patients' adherence, however, is often poor in maintenance therapy. And it is especially here, according to A. Dignass (Frankfurt/Main, Germany), that adherence is crucial.

The risk of disease recurrence is significantly increased in non-adherent patients. This was underscored by a study of 99 patients observed over a period of nearly 30 months. About 90% of patients who continued mesalazine as prescribed remained in remission compared to only about 40% with poor compliance. This difference is highly significant.

Adherence is improved by once-a-day dosing, which is not associated with any reduction in efficacy. This was shown by a study comparing the once- and three-times-a-day administration of mesalazine pellets (Salofalk® Granules). For induction therapy in patients with distal ulcerative colitis, the pellets were shown superior to the Eudragit-coated tablets both in terms of clinical (78% vs. 55%) and endoscopic (67% vs. 43%) remission.

When deciding on therapy options, T. Ochsenkühn (Munich, Germany) argued for an approach that always keeps the objective of permanent mucosal healing firmly in view. In addition, steroids should be avoided whenever possible due to their many serious side effects.

Also unclear is how to identify those patients who, because of a foreseeable aggressive disease course, should be treated from the beginning using a "top-down" approach. The transcription signature of CD8+ T cells may provide the first evidence in this regard, said J. Lee (Cambridge, UK).

New IBD drugs are appearing on the horizon and are already drawing the expectant attention of researchers and clinicians. One focus of attention are substances that inhibit leukocyte migration, a factor that, as P. Rutgeerts (Leuven, Belgium) explained, "plays a key role in intestinal inflammation." Among the selective anti-migration strategies (SAM) is the anti-α4-integrin, natalizumab, which, however, carries with it the increased risk of progressive multifocal leukencephalopathy. Also promising, said P. Rutgeerts, are the anti-α4β7-integrin, vedolizumab, as well as etrolizumab, a rhuMAb β7. This latter agent not only prevents the migration of leukocytes into the intestinal wall but also returns to the circulation any leukocytes that may have already invaded the mucosa.
Genetics determine the intestinal microflora

The increasingly comprehensive understanding of the genetic basis of inflammatory bowel diseases has begun to make its entrance into clinical research, noted S. Schreiber (Kiel, Germany). The impact of genetic predisposition on the intestinal microflora was demonstrated in twin studies. For example, the composition of the microflora in monozygotic twins is similar, regardless of whether or not they are healthy. The degree of similarity is significantly higher than in dizygotic twins or in individuals who are not related. In addition, the degree of bacterial diversity is also genetically determinable, as is the loss of protective bacteria in ulcerative colitis.

Interleukin-1β blockade in autoinflammatory disorders

The cytokine interleukin-1β plays a central role in “autoinflammatory disorders,” said C.A. Dinarello (Aurora, USA). In addition to rare diseases such as familial Mediterranean fever (FMF), these include extremely common entities such as diabetes mellitus, gout and, according to recent studies, cardiac insufficiency. Studies of IL-1β inhibitors are already in progress.
“A goal of basic research: Blood tests to recognize adenomas”

Interview
with Professor Dr. Helmut Friess (Munich, Germany)

International experts gathered for the Falk Symposium 182 joined together for a workshop addressing the question of basic research in the field of colorectal carcinoma. Under discussion were new strategies for solving problems that impact diagnosis and treatment. In this interview, Prof. Dr. Helmut Friess, director of the surgical clinic of the Klinikum rechts der Isar in Munich, Germany, provided an overview of current thinking on this very important topic.

Editors:
Despite advances in currently available therapies, both the incidence and the mortality of colorectal carcinoma have been steadily increasing. What findings of basic research may help us reach a turning point in this development?

Professor Friess:
Most important of all is diagnosing colorectal carcinoma as early as possible. Colonoscopy remains the current gold standard in diagnosing this malignancy. Although it very precisely diagnoses these tumors at any early stage, preventive colonoscopy, however, still enjoys only limited acceptance in the general population. Despite personal invitations, it is at most 20% of the target population group that actually take advantage of this offer.

Besides the further development of virtual colonoscopy, an important challenge for basic research is to identify and establish new screening tests that would prove more acceptable to a broader segment of
the population. The main focus would be blood tests, which already can detect serum markers for adenomas. This process, however, will still take some time. The currently available blood tests simply lack the adequate sensitivity and specificity.

**Editors:**
Also problematic is our ability to formulate a prognosis: Many aspects of therapeutic decision making hinge on this.

**Professor Friess:**
This is very true. For example, we find tumors that are absolutely comparable in terms of their histopathology or tumor stage to be quite distinct in terms of their biology: This has a profound impact on their prognosis. Today, tumors are assessed according to the TNM classification. Patients with no evidence of lymph node metastases are typically spared chemotherapy. Many patients have good outcomes with this practice. Others don’t – these are the ones we need to identify.

We are therefore actively seeking gene signatures that would facilitate risk stratification. This approach will also become more clinically significant as more and more novel – and expensive – drugs become available. The emphasis will be on carefully targeting their use. This will depend on our being able to reliably identify those patients who will benefit from these expensive treatments.

**Editors:**
Genomics and proteomics have taken off in medical research. Have there been any breakthroughs here?

**Professor Friess:**
Whereas we had, in the past, worked extensively with single genes, it is now possible, using microarrays, to analyze nearly all genes at once. This provides a veritable flood of information, which, however, we are not yet able to fully interpret. Our job now is to sift through this multitude and identify the genes that are of real prognostic relevance. Plenty of basic research will be needed in this area.

**Editors:**
The observation that cetuximab is effective only in Kras wild type individuals was the first step toward personalized medicine in colorectal carcinoma. Have there been any further advances in this area?

**Professor Friess:**
Testing for a Kras mutation has become a standard part of the work-up of colorectal carcinoma. Beyond this, however, no other markers have become firmly established in the area of personalized medicine to date. Markers that indicate changes in microsatellite instability will probably have some consequences. Still, the age of personalized therapy has begun. The development will necessarily parallel the development of new drugs, which will be effective in some, but not all, patients.

It is crucial to identify biomarkers in the tumors that provide a valid indication not only of a given patient’s expected response to treatment but also of that patient’s potential risk for side effects. We are still taking baby steps in this area, however.

**Editors:**
The observation that cetuximab is effective only in Kras wild type individuals was the first step toward personalized medicine in colorectal carcinoma. Have there been any further advances in this area?

**Professor Friess:**
Yes. It has been shown that DCCs do occur with colorectal carcinoma. And, there is evidence that they are relevant with respect to metastases. Beyond that, very little has been confirmed. Imagine also that, of 1000 DCCs that enter the bloodstream, only three are of any importance. Possibly, we are dealing with a kind of selection of tumor cells against which the medication successfully employed against the primary tumor is no longer effective. These disseminated cancer cells can then proliferate and form a new tumor.

**Professor Friess, thank you for the interview.**
The treatment of colorectal carcinoma must be stage-appropriate: Ideally, following an R0 resection. That sounds easy – putting it into practice often raises many questions.

You have diagnosed “non-metastatic colorectal carcinoma”. Treatment of choice is surgery with the objective of an R0 resection. Truly helpful studies of the surgical approach in patients with colorectal carcinoma (CRC), however, are sparse, observed E. Tiret (Paris, France). There is, however, fairly solid evidence that, in cases of colon carcinoma, at least, a laparoscopic approach is comparatively as effective as conventional open surgery.

Whether this observation can be applied to rectal tumors remains an open question. Conversely, it is unclear whether total mesorectal excision (TME), which has become the established method for resection of rectal carcinomas, will play any significant role when applied to the treatment of colon cancers (mesocolic resection, figure 5).

Figure 5 Compared with conventional open surgery, TME reduces local recurrence rates and improves overall survival in patients with rectal carcinoma.
This question will need some thought: Chemo-therapy in UICC stage II

Following resection, the question of adjuvant chemotherapy must be answered. According to W. Schmiegel (Bochum, Germany), however, this “can only enhance the success of a technically successful operation.” Chemotherapy should begin about four weeks following curative R0 resection of the primary tumor and locoregional lymph nodes. According to findings of the MOSAIC Study, patients with stage III CRC benefit from a combined chemotherapy with oxaliplatin and 5-FU/folinic acid. This approach improved overall survival by 4.4% compared to 5-FU/folinic acid alone. By comparison, there was no advantage for combined chemotherapy for patients with stage II CRC (survival advantage with chemotherapy only 0.1%; figure 6).

Just how best to proceed in UICC stage II is a matter of current discussion. There is a consensus that high-risk patients, such as those with T4 tumors or tumor perforation, should undergo adjuvant chemotherapy with 5-FU/folinic acid. Opinions do differ on whether patients without additional risk factors should receive chemotherapy.
Neoadjuvant radiochemotherapy under attack

Patients undergoing resection of rectal carcinoma have usually already completed some form of radio(chemo)therapy. Two regimens are currently in use:

• Short-term therapy with radiation (5 x 5 Gy) followed immediately by surgery (this is an option for all tumors);

• Long-term therapy with a 5-FU based radiochemotherapy followed after 6–8 weeks by surgery (suitable for cT3-4- or N+ tumors).

Studies have confirmed that both approaches reduce local recurrence rates, although there is no significant impact on overall survival.

Based on these data, C. Rödel (Frankfurt/Main, Germany) called the currently applied therapies into question. He also pointed to studies currently in progress that are investigating novel neoadjuvant regimens. These may in the long term open the way from a “one-size-fits-all” approach to an individualized response- and risk-adapted therapy.

Primary tumor or liver metastases: Where to operate first?

Liver metastases are detected in nearly one in four patients with CRC at the time of first diagnosis. If operable, the classic approach has been to first remove the primary tumor.

The opposite approach, however, is also an option, said B. Nordlinger (Boulogne-Billancourt, France), noting that liver metastases may have a greater impact on survival. A third option is a simultaneous combined operation at which both the primary tumor and the liver metastases are resected. This spares the patient a second operation and the removal of the liver metastases is not delayed.

A comparison of these three strategies in 156 consecutive CRC patients resulted in no significant difference in terms of five-year survival rates. B. Nordlinger recommended the simultaneous approach following brief chemotherapy in patients in whom liver metastases have not spread significantly. A “reverse” approach is, in his opinion, advisable in patients with advanced liver metastases requiring a “major resection” (Figure 8).

Overall survival
2470 patients


Figure 8 Overall survival in patients with colorectal carcinoma that has metastasized to the liver has significantly improved over the past 15 years
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The histopathologist: A crucial member of the multidisciplinary team

Even in this age of genomics, proteomics and transcriptomics, the histopathologist stands with the surgeon, radiologist, gastroenterologist and oncologist as an integral part of the multidisciplinary treatment team. Among his basic functions, said P. Quirke (Leeds, UK), is to assess the quality of the operation and assure the adequacy of resection margins. P. Quirke also made recommendations about biopsies. These should contain as much tissue as possible. Small lesions should be divided and, with larger lesions, tissue should be sampled separately from the central portion. Finally, the tissue should be obtained and preserved in a manner that makes it suitable for raf/ras studies.

Prognostic parameters: miR-21 Expression, IRS and hMLH1

MicroRNAs are small, non-coding RNA molecules that regulate the expression of genes. Specific microRNAs are overexpressed in carcinomas and can serve as markers for diagnosis, prognosis and therapeutic outcome. As C.C. Harris (Bethesda, USA) explained, high miR-21 expression in colon carcinoma (as well as in other carcinomas) is associated with a poorer survival. In the Hong Kong Validation Cohort, the therapeutic success rate of adjuvant chemotherapy with 5-fluorouracil (5-FU) in patients with stage II/III colon carcinoma was lower in patients with high miR-21 levels than in those with lower levels. Another valuable prognostic parameter in colon carcinoma is the inflammatory risk score (IRS).

Colon carcinomas with microsatellite instability (MSI) are associated with a reduced risk of distant metastases. T. Kirchner (Munich, Germany) presented an immunohistochemical algorithm for estimating the risk of distant metastases in patients with carcinoma of the right half of the colon. Based on data from a case-control study, he was able to show that the risk of distant metastases in patients with loss of the mismatch repair protein hMLH1 stands at only 5%. hMLH1-positive patients were further stratified using CD133 and β-catenin. Patients at highest risk for distant metastases (94%) were hMLH1-positive individuals with high CD133 and β-catenin levels. By comparison, in patients with low CD133 and β-catenin levels, the risk was only 47%.

The combination of IRS and miR-21 expression provides a more reliable prognosis than do the individual parameters separately.
**DCC: More questions than answers**

Another focus of intense research is the elucidation of mechanisms that underlie metastatic dissemination. Here, however, there are still more questions than answers, said **C.A. Klein** (Regensburg, Germany). Comparison of cells from primary tumors with disseminated cancer cells (DCC) reveals a significant genetic disparity. Thus, the characteristics of the primary tumor by themselves represent an inadequate biomarker for determining the prognosis and planning adjuvant therapy.

**FIT – not gFOBT!**

What good are stool and blood tests in screening for colorectal carcinoma? **T.F. Imperiale** (Indianapolis, USA) provided some answers to this question. Based on his interpretation of current research, the conventional guaiac-based fecal occult blood test (gFOBT) should be retired in favor of the fecal immunohistochemical test (FIT). He discussed an intraindividual comparison of 1821 persons undergoing colonoscopy. In this study, the sensitivity of FIT for detecting colorectal carcinomas and advanced adenomas was significantly higher than that of gFOBT (87% vs. 74%; 35% vs. 18%). Blood tests for DNA or RNA are still no substitute for stool tests: Their specificity and sensitivity are too low.

**Colorectal carcinoma**: A disease with many faces

The many advances in understanding the pathogenesis of colorectal carcinoma (CRC) should not give us a false sense of security, said **S. Tejpar** (Leuven, Belgium). Our grasp of tumor biology is still fraught with gaps and many question marks remain. Also, as S. Tejpar noted, not every “colon carcinoma” is the same: It is a disease with many faces and with differences in pathogenesis and distinct prognoses. Thus, right-sided colon carcinomas respond less favorably to therapy, regardless of type, than do those on the left, with a median survival of 28.4 vs. 16.2 months, respectively.

**Reducing the risk of interval carcinomas**

Colonoscopy remains the screening method of choice for detecting colorectal carcinoma (CRC). Yet, even when patients undergo regular screening colonoscopies, the occurrence of interval carcinomas cannot be excluded. Thus, as many as 2–9% of CRC develop within 6 to 36 months of previous colonoscopy and, in 0.3–0.9% occur within 3 to 5 years of endoscopic polypectomy. One reason for these observations is the development of new, rapidly growing adenomas. However, new cancers may also develop as a result of the incomplete removal of an existing lesion or even its oversight, said **D.A. Lieberman** (Portland, USA), noting that “more than 15% of polyps larger than 1 cm in diameter are missed.” This risk can, in his opinion, be reduced by improvements in the quality of colonoscopy, beginning with a meticulous bowel preparation and extending through efforts to assure that the colonoscopy is as complete as possible. Finally, a high adenoma detection rate of over 20% reduces the probability of an interval carcinoma.

**Aspirin against cancer in Lynch syndrome**

Patients with Lynch syndrome (hereditary non-polyposis colorectal carcinoma, HNPCC) who take 600 mg of acetylsalicylic acid (ASA) daily for at least two years can reduce their risk of cancer after five years by about 60%. ASA is, therefore, just as safe and effective as colonoscopy. Based on this result from the CAPP2 Study, **J. Burn** (Newcastle-upon-Tyne, UK) recommended that patients with potentially hereditary colorectal carcinoma should take ASA regularly beginning with 100 mg per day. The CAPP3 Study, in which the efficacy of different ASA doses is tested in patients with Lynch syndrome, should provide data for establishing an optimum dose.
The data remains unclear in ulcerative colitis

Less clear is the chemoprotective efficacy of 5-aminosalicylates in patients with ulcerative colitis, said H. Herfarth (Chapel Hill, USA). There is no doubt, however, that these agents are an effective and safe option for remission maintenance in patients with ulcerative colitis.

CT colonography: High sensitivity with larger lesions

Computed tomography (CT) based virtual colonography offers an alternative to colonoscopy. The method has already been investigated in several studies, but the findings have been divergent. D.C. Rockey (Dallas, USA) pointed to data from the largest study to date, a multicenter study with 2600 participants, which found a sensitivity of 90% for CT colonography in detecting polyps greater than 10 mm in diameter. This is similar to colonoscopy, whose sensitivity is generally reported at 95%. D.C. Rockey emphasized that the sensitivity of CT colonography is clearly dependent on the size of the lesions. For example, the probability of detecting 5-mm lesions is only 31%, with a 75% probability of detecting lesions 9 mm in diameter. His conclusion: The sensitivity of CT colonography in detecting lesions larger than 6 mm is comparable to that of colonoscopy.

Flat adenomas represent a challenge

Polyps may be overlooked even with colonoscopy. As many as 26% of polyps 1 to 5 mm in diameter may be missed. A special problem, regardless of their size, are the flat or sessile adenomas, of which 42% are overlooked, explained M. Anders (Hamburg, Germany). Lack of experience on the part of the endoscopist is one reason. In addition, factors such as inadequate preparation or distention of the bowel, a rushed endoscopy or only a fleeting look into the flexures and folds may result in adenomas being missed.

Improvements in technique can be advantageous. For example, pooled data of 4422 patients from five studies showed an advantage for HD-white light endoscopy compared to standard methods with a significantly higher rate of detecting adenomas.

Polypectomy: Avoid “piecemeal” resection

Removing a polyp in one piece is the goal of endoscopic polypectomy, explained M. Jung (Mainz, Germany). A “piecemeal” resection should be avoided whenever possible. Submucosal saline injection lifts flat adenomas and facilitates excision. At the same time, a positive “lift-off” phenomenon is considered evidence for low malignancy. By contrast, a negative lift-off phenomenon is associated with an already advanced adenoma.

T1 carcinoma: A case for combined endoscopic-laparoscopic resection

Can a T1 carcinoma of the colon or rectum be safely removed endoscopically or is conventional open surgery required? The former option is less invasive; the latter allows for complete lymph node resection. A. Meining (Munich, Germany) could not provide a simple “yes” or “no” answer to this question, because there are practically no follow-up data available for exclusive endoscopic resection. Some conclu-
sessions can be drawn from data collected between 1972 and 2002 in the polyp register of the Neuperlach Clinic in Munich, Germany, which includes follow up for periods of two years or more for a total of 249 patients with endoscopically resected T1 tumors. In the low-risk group (n = 188) only 2.7% of patients developed local recurrence, lymph node metastases, distant metastases or died as a result of their cancer. In the high-risk group, this number was 18.4%. Still, A. Meining warned, the reliability of the risk parameters is not particularly high; hence, the decision must be made on an individual basis.

D. Hahnloser (Lausanne, Switzerland) had a different answer to the question of "endoscopy or surgical resection", proposing a combined endoscopic and laparoscopic technique. This allows the endoscopist a more aggressive approach, thus increasing the likelihood of complete excision. In addition, there is always the option of conversion to a laparoscopic operation should it prove impossible to remove the polyp or in cases of perforation or when the excised tissue is found on frozen section to actually represent an invasive carcinoma.

Rectal carcinoma: TME as method of choice

The introduction of total mesorectal excision (TME) as a new method in the surgical therapy of rectal carcinoma has significantly reduced the risk of local recurrence and improved overall survival. Whether this technique can be carried over to colon carcinoma, however, remains unclear and no randomized studies have yet been published, noted E. Tiret (Paris, France). For the adjuvant therapy of colorectal carcinoma, a variety of therapeutic regimens have become established depending on disease stage. The recommendations for UICC stage II colon carcinoma are unclear. Patients experiencing intestinal obstruction as a result of a tumor may receive some relief from "bridging" using self-expanding metallic stents (SEMS).

Preserving the sphincter: Important but not at any price

When contemplating the treatment of rectal carcinoma, the patient has one overriding wish: Retaining control over bowel movements. Preservation of the sphincter, however, is not the best option in every case, explained A. D’Hoore (Leuven, Belgium), who noted that a balance must be drawn between oncological security and maximum preservation of functions. Preserved functioning and quality of life are important endpoints.

Indications for transanal endoscopic microsurgery (TEM) include the resection of adenomas and carefully selected small T1 adenocarcinomas, said A. Kartheuser (Brussels, Belgium). Here, it is important not to ignore the risk of lymph node involvement, which, for pT1 tumors, stands between 10% and 34%.

Aggressive surgical strategies in advanced disease stages

This is the conclusion of P.B. Paty (New York, USA) based on a meta-analysis of four randomized controlled comparison studies of SEMS and emergency operations. The number of successful primary anastomoses was higher and the stoma rate lower overall. Still, the use of SEMS is associated with a higher rate of both clinically apparent and asymptomatic perforations, which increase the risk of dissemination of malignant cells.

Colorectal carcinoma has already reached a locally advanced stage of 10% of patients at the time of first diagnosis. Local recurrence affects 7–33% of patients. A review of the literature suggests that these patients benefit most from an aggressive surgical strategy with multivisceral resection, said P.R. O’Connell (Dublin, Ireland).
Microsatellite instability (MSI) can be therapeutically decisive, explained W. Schmiegel (Bochum, Germany), citing current studies. Thus, patients with stage II colon carcinoma and high MSI do not profit from an adjuvant therapy with 5-FU but have a generally very good prognosis.

The Colon Cancer Recurrence Score is a good prognostic indicator for recurrence risk

According to D. Church (Oxford, UK), the Colon Cancer Recurrence Score (RS), which is based on a multigene RT-PCR test technique, has been shown to be a good prognostic indicator of recurrence risk in patients with stage II colon carcinoma. In a multivariate analysis, the RS remained prognostically independent of factors such as mismatch repair (MMR), T stage, number of examined lymph nodes, grading or lymphovascular tumor invasion.

In general, there are two different approaches for the preoperative therapy of rectal carcinoma: A short-term regimen of radiation immediately prior to surgery that is suitable for all tumors and a long-term regimen with 5-FU based radiochemotherapy followed after six to eight weeks by surgery in patients with cT3-4- or N+ tumors. Both approaches result in reduced local recurrence rates but no improvement in overall survival.

C. Rödel (Frankfurt/Main, Germany) called this approach into question, citing a Polish and an Australian study that directly compared these two regimens. Among the patients studied, there was no significant difference in either sphincter preservation or, over a period of three to five years, in overall survival or local recurrence rates. He also pointed to studies currently in progress that are investigating novel regimens. These may in the long term open the way from a "one-size-fits-all" approach to an individualized response- and risk-adapted therapy.

M.W. Büchler (Heidelberg, Germany) argued for the view that too many patients undergo preoperative radiation. In support of his position, he cited a Dutch study according to which this approach does not improve overall survival but simply reduces local recurrence by 6%. These meager benefits are purchased dearly in terms of incontinence, impact of sexual functioning and, most importantly, induction of secondary malignancies.

In order to improve overall survival it is much more important to improve the quality of the surgical procedure. In this regard, C.J.H. van de Velde (Leiden, The Netherlands) emphasized the importance of the circumferential resection margin (CRM) for assuring the quality of the surgery.
Complete remission following neoadjuvant therapy – watch and wait?

If a patient shows complete response to neoadjuvant therapy, the next question is: Must surgery necessarily follow or can the patient safely be observed? S.D. Wexner (Weston, USA) presented studies according to which the watch-and-wait principle based on a strategy of close observation led to five-year survival rates that were comparable to those of resection. The side effects of the therapy were also avoided. There are, however, also risks associated with this approach that must be carefully discussed with the patient.

Primary tumor and liver metastases: Sequential or simultaneous surgery?

Liver metastases are detected in nearly 25% of patients with CRC at the time of first diagnosis. If operable, the classic approach has been to first remove the primary tumor. The opposite approach, however, is also an option, said B. Nordlinger (Boulogne-Billancourt, France), noting that liver metastases may have a greater impact on survival. A third option is a simultaneous combined operation at which both the primary tumor and the liver metastases are resected. The advantage: “The patient need not undergo a second operation and the removal of the liver metastases is not delayed.” A comparison of these three strategies in 156 consecutive CRC patients showed a five-year survival rate of 55% for the combined approach, 48% for the classical approach and 39% for the reverse approach. The differences were not statistically significant. In the majority of cases, liver metastases are not resectable at the time of first diagnosis. The primary goal of chemotherapy must therefore be to make non-resectable liver metastases resectable. High success rates with a resection rate of 70% were reported for the FOLFOXIRI regimen (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) in a phase II study. The regimen itself, however, is very toxic.

In addition, this damage to the hepatic parenchyma together with the patient’s weakened general condition following chemotherapy may significantly increase the relative surgical risk.

Hyperthermic intra-peritoneal chemotherapy in peritoneal carcinoma

Surgical resection of the intra-abdominal tumor mass in combination with hyperthermic intraperitoneal chemotherapy may be an option for CRC patients who develop peritoneal carcinoma. The current challenge is to determine which patients derive the greatest benefit, explained R. Salazar (Barcelona, Spain). He currently sees the clearest indication in patients in good general health and with a peritoneal carcinoma index (PCI) less than 21 in whom complete resection appears feasible.
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Other ingredients: Calcium stearate, basic butylated methacrylate copolymer (=Eudragit E), methacrylic acid methyl methacrylate copolymer (1:1) (=Eudragit L), glycine, silica colloidal anhydrous, hypromellose, macrogol 6000, cellulose microcrystalline, sodium carbonate anhydrous, povidone K25, t alc. Colouring agents: titanium dioxide (E171), iron oxide hydrate (E172), additionally Salofalk® 500mg tablets: cros carmellose 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, cet yl 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. Additionally Salofalk® 250mg suppositories: 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, cet yl 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 metabisulphite, 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® 250mg suppositories: prevention of recurrence of ulcerative colitis. 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, diarrhoea, flatulence, nausea, vomiting, impairment of renal function including acute and chronic interstitial nephritis and renal insufficiency. Hypersensitivity reactions such as allergic exanthema, drug fever, pancytopenia, 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 anaemia, agranulocytosis, pancytopenia, neutropenia, leucopenia, thrombocytopenia), 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
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