Evolving Therapies in Clinical Practice in IBD

Symposium 202
Prague (Czech Republic), April 29–30, 2016
Symposium 202
Prague (Czech Republic), April 29–30, 2016

Symposium 202
Evolving Therapies in Clinical Practice in IBD

Scientific Organizers:

Dr. M. Bortlik
Prague
(Czech Republic)

Prof. W. Krüis
Cologne
(Germany)

Prof. M. Lukas
Prague
(Czech Republic)

Prof. E. F. Stange
Stuttgart
(Germany)

Text
Dr. Beate Fessler
Medical Journalist, Munich (Germany)

Photos (portraits, impressions and presentation of poster prizes)
© Kai-Uwe Wudtke, Freiburg (Germany)

Cover photo Prague: Fotolia
Imprint

Editorial
Welcome to Prague!

Overview
In search of new targets

In brief
An overview of the latest developments in the treatment of IBD

Poster prizes

Interview
“In Crohn’s disease it is the defensins that tend to be missing, but in colitis it is the mucins.”
(Prof. E.F. Stange)

Speakers, moderators and scientific organizers
A lot has changed in the treatment of inflammatory bowel disease since the first symposium on Crohn’s disease and ulcerative colitis was held in Prague in 2003. This alone was reason enough to meet on the bank of the Vltava to share and critically examine recent discoveries and to discuss contentious issues. Looking back, it is clear to see how the treatment of inflammatory bowel disease has changed, particularly as a result of the introduction of tumor necrosis factor α antibodies. Further developments include the combination of these biologics with azathioprine and the often controversial discussion on when is the best time to initiate treatment. Furthermore, therapeutic drug monitoring has begun to play an established role in clinical practice, not only in non-responders but also during routine follow-up. Meanwhile, the first biosimilars are available and their use has sparked renewed discussions. However, biologics are not the only treatment option that requires examination. Instead, it is also still important to discuss conventional, long-established treatments with a view to optimizing their effect.

Although it cannot be denied that numerous innovations have been developed in recent years, they must not detract from the fact that there are still many unmet needs. There is still no cure for inflammatory bowel disease and it is only possible to influence the course of the disease to a limited extent. This is why it is essential that we keep looking for new targets for drug therapy. Despite the admittedly considerable progress made to surgical procedures, improvements are still needed here as well.

In light of the above, Symposium 202 of the Falk Foundation presented new pathophysiology-based treatment approaches, promising experimental research results and potential methods of improving established treatment regimens. Clinical problems were discussed from a practical point of view by drawing on numerous complex case studies. The event also focused on clearly identifying the unmet needs and examining future requirements. Ultimately, our objective must be to offer personalized treatment that retards disease progression significantly and thereby benefits our patients.

Prof. E.F. Stange
On behalf of the scientific organizing committee
In search of new targets

More and more drugs are being made available to treat inflammatory bowel disease (IBD). Despite this, the medical community has still not succeeded in curing the disease, in definitively influencing its course or in significantly reducing the need to perform surgery. We must continue searching for new targets.

There is no doubt that the development of TNF-α antibodies for treating moderate to severe Crohn’s disease and ulcerative colitis represented a significant step forward in gastroenterology. These antibodies reduce inflammation quickly and effectively and became an established part of the treatment regimen rapidly. However, a certain sense of disillusionment has since emerged because, despite this breakthrough, around 80% of Crohn’s disease patients still need to be operated on in the long term. As reported by G. Rogler, Zurich (Switzerland), who made reference to a Danish population-based cohort study, the use of biologics has also resulted in hardly any change to the course of the disease in comparison with the “pre-biologics era.”

Furthermore, the number of patients with stricturing and/or penetrating Crohn’s disease is still as high as before. E.F. Stange, Stuttgart (Germany), is also rather skeptical. “We’re failing to cure the disease. This is why we need new medication,” he stressed (see interview). According to G. Rogler, the lack of resounding success achieved by the biologics currently available could be attributed to the fact that cytokines only play a role at a late stage in the disease’s progression. As a result, we need to continue looking for new targets and more effective means of intervention.

![Overview](image)

Fig. 1: In IBD, the intestinal barrier is no longer intact. Wehkamp J, et al. Dtsch Arztebl Int. 2016;113(5):72–82
New anti-cytokines follow in the wake of anti-TNF and anti-integrin treatments

Biologics are still one of the key areas of research in the treatment of IBD. However, numerous new anti-cytokine strategies that were once seen as offering a beacon of hope have already had to be abandoned. According to G. Rogler, focus has now shifted from TNF-α and integrin antibodies to anti-IL-23 strategies. The IL-12/23 inhibitor ustekinumab has already been found to be an effective and tolerable antibody for treating Crohn’s disease. G. Rogler also anticipates that MEDI2070, an antibody against IL-23-p19 that binds selectively to the p19 subunit specific to IL-23, will sooner or later be available for use in clinical practice. It is hoped that this treatment will have a better benefit/risk profile than the dual inhibition of IL-12/23. While promising remission rates can also be achieved with the interleukin-6 antibody tocilizumab, the risks associated with this treatment are high, particularly the possibility of intestinal perforation.

Keeping T-lymphocytes in check

Another principle being followed is that of leukocyte anti-trafficking strategies, experience of which has already been gained in connection with other forms of chronic inflammation. B.E. Sands, New York (USA), cited the oral immunomodulator ozanimod as an example. Like fingolimod, an active ingredient used to treat multiple sclerosis, ozanimod is a sphingosine 1-phosphate analog. By modulating the sphingosine signaling pathway, it stops T-lymphocytes from leaving the lymph nodes and from furthering intestinal inflammation. Alicaforsen, an antisense oligonucleotide that targets the ICAM-1 adhesion module, is also undergoing clinical testing.

How can we repair a defective intestinal barrier?

Scientists have already had the intestinal mucosa in mind as a new target for several years. This is because, as reported by E.F. Stange (Fig. 1), the intestinal barrier is no longer intact in IBD patients. This has far-reaching consequences. A permeable intestinal mucosa may lead to TNF-α antibodies being secreted into the intestinal lumen, where they are ineffective. Inversely, however, a greater impact is caused by the potential penetration of intestinal bacteria into the mucosa, which then leads to inflammatory defensive reactions. The ileum and colon of Crohn’s disease patients contain more adherent-invasive Escherichia coli than those of healthy people. E.F. Stange has also been able to show that in Crohn’s disease the function of natural peptide antibiotics called defensins which are produced by Paneth and other epithelial cells is impaired. This means that invasive bacteria can no longer be killed. “We are experiencing a paradigm shift in our understanding of inflammatory bowel disease, and are no longer regarding it as an autoimmune disease, but as a defect in the epithelial intestinal barrier,” he explained. As a result, scientists are working hard to find strategies for strengthening the intestinal barrier. One conceivable possibility would be an intervention that targets the defensins (see interview). Studies have found that during the treatment of ulcerative colitis the slow-release formulation of phosphatidylcholine has a favorable effect on the composition of mucus, thereby improving the intestinal barrier. In a randomized, placebo-controlled, multicenter study conducted over 12 weeks, a modified-release phosphatidylcholine was shown to considerably improve clinical remission, defined using the SCCAI (Simple Clinical Colitis Activity Index), in patients with mesalazine-refractory ulcerative colitis (Fig. 2).

Fig. 2: Significant improvement in disease activity in patients with ulcerative colitis under phosphatidylcholine (LT-02).
Karner M, et al. Am J Gastroenterol. 2014;109(7):1041–51, Fig. 2 (CC BY 3.0 DE)
An overview of the latest developments in the treatment of IBD

How can existing treatment strategies for Crohn’s disease and ulcerative colitis be applied as effectively as possible? What innovations are expected over the next few years and which areas still require research? Renowned experts answered these questions during the symposium.

Intestinal fibrosis is avoidable

Intestinal fibrosis is a serious clinical problem associated with inflammatory bowel disease (IBD). It is an extremely complex, dynamic process involving a wide range of cell types. The promoters discussed were a pro-fibrotic microbiota and the creeping fat characteristic of Crohn’s disease. According to F. Rieder, Cleveland (USA), it is a fact that inflammation and fibrosis are closely related to each other. The more active the inflammation, the greater the risk of fibrosis. The inflammatory milieu changes into a pro-fibrotic environment. This process also involves the release of certain cytokines, which act as fibroblast growth factors. “We must gain a better understanding of how fibrosis develops if we are to develop strategies to combat it,” advocated F. Rieder. He said that strictureplasty is a current safe and effective treatment associated with low relapse rates and a regression in intestinal wall thickness and inflammation. Although the development of antifibrotic drugs has begun, F. Rieder claimed that there is still “a long and difficult road ahead and we must find a way of making the fibrotic component into a therapeutic target.”

Magnetization transfer-weighted MRI for differentiation

Since fibrosis is associated with both fibrous structures and inflammatory components, it is often difficult to make a differential diagnosis,” claimed P.D.R. Higgins, Ann Arbor (USA). He added that even when the CT and MRI findings are negative, fibrosis cannot be ruled out. However, magnetization transfer-weighted MRI makes it possible to reliably distinguish acute inflammation from chronic fibrosis. Another approach is to search for serum biomarkers. The working group led by P.D.R. Higgins used glycoproteomics to search for such markers in patients who underwent surgery to treat fibrotic stenosis. The level of 14 serum markers was significantly lower after the surgery in comparison to the findings before the operation. Besides focusing on diagnostics, P.D.R. Higgins also ventured to take a look at possible future treatment options. Pirfenidone and nintedanib have already been approved for pulmonary fibrosis and further substances are in the pipeline. P.D.R. Higgins predicted that “antifibrotics will one day be in use.”
Laparoscopic surgery better than medication at treating ileocecal Crohn’s disease

Is surgery a better option for treating ileocecal Crohn’s disease than medication? The ECCO Guidelines (Statement 7A) give a clear recommendation on this and state that localized ileocecal Crohn’s disease with obstructive symptoms but no significant evidence of inflammation should be treated surgically. Generally speaking, the surgical intervention is moderate with a low morbidity rate. As explained by Y. Panis, Clichy (France), the procedure improves quality of life, but it is important that the patients are chosen carefully. He added that laparoscopic interventions are best performed in young, active patients. In such cases, hospitalization rates and the risk of postoperative complications are low and are “better than with open procedures.” Even during complex laparoscopies, the mortality rate is 0%.

Making the case for a multidisciplinary approach during the treatment of perianal Crohn’s disease

According to a Hungarian survey, 11% of patients with Crohn’s disease already had a perianal fistulizing disease at the time of their diagnosis. As reported by Z. Serclova, Prague (Czech Republic), the quality of life of these patients is significantly reduced and they suffer more frequently from depression or even suicidal thoughts. According to P.L. Lakatos, Budapest (Hungary), MRI “is superior to endoscopic ultrasound” when it comes to diagnosing the condition. Complex fistulas are an indication for biologics and around half of all patients respond to antibiotics. However, merely prescribing conservative treatment rarely leads to the desired results. The call made by P.L. Lakatos for a multidisciplinary approach was supported by Z. Serclova, who also advocated a combination of medication and surgical interventions. Conservative therapy was said to be purely symptomatic. A possible surgical technique is the advancement flap method, which has a success rate of 50–84% and a relapse rate of 33–88%. Risk factors for failure include stenoses, rectal inflammation, abscesses and vaginal fistulas. A new treatment concept is the ligation of the intersphincteric fistula tract (LIFT) procedure, which, during a recent evaluation of 26 studies, was found to achieve cure rates of 47–95% when used to treat non-Crohn’s fistulas.

Should severe ulcerative colitis be treated using rescue therapy or surgery?

Regardless of whether ulcerative colitis manifests in children or the over sixties, the diagnostic procedure, indications for surgery and the effectiveness of the medication are all similar. However, as stressed by A.E. Dorofeyev, Kiev (Ukraine), the risk of severe side effects is greater among older patients, while differential diagnoses are more frequent and require clarification. The intravenous administration of systemic steroids is the standard method of treating acute severe ulcerative colitis. If treatment fails, however, cyclosporine and TNF-α antibodies are available as rescue therapies. There is no difference between the response rate and colectomy rate in both the short and long term. M. Martí Gallostra, Barcelona (Spain), explained that the side effects, postoperative complications and mortality rate are also comparable. Surgery may also show very good long-term results. A multicenter, randomized study is required to look into the different indications for surgery as opposed to a rescue therapy. According to M. Martí Gallostra, our objective must be to “save lives rather than colons.” Emergency surgery is always indicated in cases of acute severe ulcerative colitis, toxic megacolon, perforation, hemorrhage and severe sepsis. The mortality rate is 5–8%, while the morbidity rate is 25–50%.
How can IBD be treated in patients with a history of cancer?

Immunosuppressive therapies, like those frequently indicated for severe IBD, increase the risk of certain malignant tumors. For example, thiopurines are associated with an increase in lymphomas, non-melanoma skin cancers and – in rare cases – carcinomas of the genitourinary tract. According to J. Cosnes, Paris (France), TNF-α antibodies are “largely safe except for malignant melanomas.” As demonstrated by G. Novacek, Vienna (Austria), who presented a patient who developed both prostate cancer and a melanoma while under combined immunosuppression, the risk is particularly high for patients prescribed an immunosuppressive combination therapy. What are the options for treating severe IBD in patients with a history of cancer? Retrospective observational studies of patients who have previously suffered from cancer do not demonstrate that immunosuppressive therapy significantly increases the risk of new or recurrent cancer. However, J. Cosnes believes that these investigations are frequently “underpowered” or biased. They therefore “do not give a green light” to the use of these drugs. He recommended waiting for two to five years before prescribing an immunosuppressive therapy to patients with a moderate to high risk of relapse. Furthermore, latent cancer should be ruled out before starting treatment. He added that budesonide, low-dose steroids or a limited resection can be used to bridge the gap.

“Surgery does not cure the disease”

Around 80% of patients with Crohn’s disease have to undergo surgery as the disease progresses and 70% of these patients relapse and subsequently require a second, third or even fourth operation. “Surgery does not cure the disease,” emphasized A. Dignass, Frankfurt (Germany). This is why, in order to control the disease, it is essential that postoperative relapses are prevented. The risk of relapse is particularly high in smokers and in patients with a high pre-operative disease activity, a penetrating disease, an endoscopic inflammation at the anastomosis and an extensive case of the disease. The younger the patient at the time of the operation, the more likely they are to require another procedure. The one-year relapse rates show that prevention is most successful using an anti-TNF-α treatment.

What are the benefits of combination therapies?

While much hope has been pinned on combination therapies providing a more effective treatment method for IBD, W. Kruis, Cologne (Germany), criticized the lack of data collected for these drugs. He commented that although they are an attractive option for improving the effect of currently available single agents, they require an “experienced hand.” When treating ulcerative colitis with a 5-aminosalicylic acid such as mesalazine, it makes sense to combine both oral and rectal preparations. Patients with relapsing ulcerative colitis remain in remission for a significantly longer period of time when receiving this combination therapy. It is also worth considering combining oral and rectal administration during induction therapy in patients with markedly active ulcerative colitis. The combination of azathioprine with allopurinol may also prove beneficial. The 6-thioguanine nucleotide (6-TGN) levels increase, improving the effect of the immunosuppressant. In a study of 110 IBD patients, 76% of first-line patients and 60% of primary non-responders were able to achieve clinical remission when taking a combination of azathioprine 1.9 mg/kg of body weight with allopurinol 100 mg/day.

How should non-responders or patients with an insufficient exposure to active substances be treated?

Should active substance levels and anti-drug antibodies (ADA) be monitored when treating patients with biologics? According to A. Gils, Leuven (Belgium), therapeutic drug monitoring is recommended within a treatment algorithm to distinguish primary non-responders from patients with insufficient exposure to active substances. It is also advisable for patients with secondary loss of response and for patients in clinical remission. This is because there is a direct association between serum concentration and the effect of a biologic. If, for example, serum concentration in patients in clinical remission is lower than the threshold concentration, the ADA levels should be tested. If the results are negative, the patient’s compliance should be checked and the therapy intensified. The dose should also be increased in the event of low ADA levels. If the ADA levels are high, treatment should be stopped and, in the event of a relapse, patients should be treated with an in-class or out-of-class active ingredient.
**SPECIAL LECTURE**

**Epidemiological studies show CRC is less and less common in patients with ulcerative colitis**

Epidemiological studies often reveal exciting results, such as the finding that the risk of colorectal carcinoma (CRC) is declining in patients with ulcerative colitis. Data from a national Danish cohort study, which observed IBD patients between 1979 and 2008, showed a 1.34-fold increased risk between 1979 and 1988 and a 1.09-fold increased risk between 1989 and 1998. As explained by D. Duricova, Prague (Czech Republic), the relative risk stood at 0.57 between 1999 and 2008. While 17.82 cases of CRC were expected, only 8 were actually observed. Other publications on this matter seem to confirm this trend. While the incidence rate stood at 4.3 per 1,000 patient years in the 1950s, this had dropped to 1.21 between 2000 and 2013. Certain risk factors must, however, always be taken into account when evaluating an individual patient’s risk. In patients with ulcerative colitis, these risks mainly include the comorbidity between primary sclerosing cholangitis and IBD, which increases the likelihood 9-fold, as well as the duration and extent of the disease.

**Low-cost biosimilars boost the use of biologics**

Infliximab, the first biologic approved for the treatment of IBD, was made available in 2000. The first biosimilar was approved at the end of February 2014. Since then, the comparability between biosimilars and original preparations has become one of the most discussed topics concerning the immunosuppressive treatment of Crohn’s disease and ulcerative colitis. Norway was the first country in which a biosimilar infliximab was approved. In the experience of B. Moum, Oslo (Norway), to date, it is able to achieve comparably good remission and response rates. According to B. Moum, the availability of cheaper biosimilars has already had tangible clinical consequences in Norway. For example, more patients are being prescribed TNF-α antibodies, even if they only have a moderate form of the disease. These drugs are being prescribed at an earlier stage and treatment is not being stopped for financial reasons.

**Nor-Switch study investigates whether it is possible to successfully switch patients to a biosimilar**

Discussions now focus less heavily on initiating treatment with a biosimilar than on switching patients from an original preparation to its “imitation.” According to data collected by J. Jahnsen, Nordbyhagen (Norway), this latter practice does not seem to present any problems either. In addition to initiating treatment with a biosimilar, he ventured to switch 37 Crohn’s disease patients and 19 ulcerative colitis patients to a biosimilar. As the study progressed, no relevant differences were noticed in terms of the Harvey Bradshaw index (HBI), CRP and infliximab trough levels. Only the calprotectin level worsened slightly after the switch. J. Jahnsen therefore believes that the greatest hurdle is convincing patients to switch to the cheaper drug. More data will be provided by the Nor-Switch study, which is the only blind study to address the issue to date. It is currently examining the effects of switching from the original infliximab product to the biosimilar infliximab.

**One-year data on the switch from the Czech Republic**

M. Lukas, Prague (Czech Republic), presented data for the one-year period following the switch to the biosimilar infliximab. 74 patients, 56 of whom had Crohn’s disease and 18 ulcerative colitis, were observed (average age: 34 years). The average disease duration was 10 years. A third of the patients suffered from perianal disease. 69% were in clinical remission at the time of the switch, while in 22% the disease activity was assessed as mild to moderate. After 56 weeks, CRP and fecal calprotectin were the same as at the baseline. By the end of the observation period, treatment had been intensified in 23.5% of the patients with Crohn’s disease and in 37.5% of the patients with ulcerative colitis. Clinical response, which was calculated using the SCCAI and HBI, was comparable. There were no noticeable findings in relation to safety. M. Lukas also stressed that the immunogenicity of the biosimilar was comparable to that of the original preparation.
It is even possible to switch children – who, according to P.L. Lakatos, Budapest (Hungary), are the “most sensitive group of patients” – from an original infliximab preparation to a biosimilar without any clinical or biochemical changes. This was concluded by a study conducted in Poland in which 32 children from three hospitals were observed following the switch. Interesting results were also collected by a prospective, non-controlled observational study undertaken in Hungary that included both TNF-α-naive patients and patients who had to be prescribed a biologic again following a drug holiday of at least 12 months. According to P.L. Lakatos, the results achieved by the biosimilar were “as to be expected.” This also applies to the trough level.

Toxicity is a limiting factor in stem cell transplantation in IBD

The ASTIC Trial (Autologous Stem Cell Transplantation International Crohn’s Disease Trial) is currently investigating the impact of hematopoietic stem cell transplantations (HSCT) in patients with Crohn’s disease when performed as an early or delayed intervention. C.J. Hawkey, Nottingham (Great Britain), presented the study’s two-year data. The study included patients with treatment-resistant Crohn’s disease with a moderate to severe disease activity who had failed to respond to at least three immunosuppressants and for whom a surgical procedure was not an option. To date, the study has found that although the disease is only cured in extremely rare cases, the intervention improves a number of disease parameters. For example, there is a significant improvement in the SES-CD score as well as in the endoscopic findings. 26% of the patients experienced complete regression, while 82% saw partial healing of the ulcerative lesions one year after the HSCT. However, problems are caused by the high toxicity, particularly during the peritransplant stage, meaning that the procedure is viewed critically when used to treat Crohn’s disease: “Toxicity is the limiting factor,” said C.J. Hawkey.

Treatment with mesenchymal stromal cells is still only a pipe dream

Mesenchymal stromal cells (MSCs) are currently moving into the spotlight as a possible somatic cell therapy. They are able to modulate the immune system by acting on regulatory T-cells. This means they are also potential candidates for treating Crohn’s disease. Unlike in the case of HSCT, cytotoxic therapy does not need to be administered before beginning treatment with MSCs. Although limited evidence is available, initial data collected about intravenously administered allogeneic MSC therapy shows that the treatment is effective in cases of luminal disease. 12 out of 15 patients achieved a clinical response, while 8 of 15 achieved a clinical remission. Although allogeneic or autologous MSCs improve fistulizing disease when injected into the fistulas, the method is still in its infancy. Besides an increased risk of infusion reactions, infections and malignancies, the MSCs that are actually suitable for clinical therapy still need to be precisely defined. For the time being at least, G.M. Forbes, Perth (Australia), does not recommend MSC therapy.

Donors must be checked diligently before conducting fecal microbiota transplants

Fecal microbiota transplantation (FMT) has become increasingly popular in recent years. Despite this, when used to treat IBD, the method has failed to achieve the same impressive effect in terms of preventing a relapse as it has when treating a Clostridium difficile infection. The procedure does, however, seem to have a favorable effect on remission induction in ulcerative colitis. Researchers have conducted a study in which 38 patients with active ulcerative colitis were given 50 ml of a fecal microbiota transplant by enema and 37 patients were given a watery enema once a week for a period of 6 weeks. After 7 weeks, 24% of the first patient group were in remission compared with 5% of the second patient group. However, the effect is still disputed. It’s a case of the chicken or the egg? In other words, is the dysbiosis observed in IBD patients the cause or the effect of the intestinal inflammation? So far, there is no long-term evidence on the topic. According to W. Reinisch, Hamilton (Canada), we need more information about the intestinal microbiome and about how best to use it. FMT should currently only be carried out during clinical studies because there are still a number of problems that need to be resolved, including screening donors for infections, autoimmune diseases and cancer.
Small bowel transplantation generally performed when TPN fails

11–14% of all small bowel transplants are performed as a result of short bowel syndrome caused by Crohn’s disease. This makes Crohn’s disease the second leading indication for this type of transplantation. Reasons for performing the procedure include extensive inflammation of the small bowel or repeated resections. The treatment of choice for short bowel syndrome is total parenteral nutrition (TPN). This method is very effective at treating Crohn’s disease and has five-year survival rates of between 87 and 92%. As alluded to by P. Drastich, Prague (Czech Republic) this level of survival is much higher than, for example, with systemic sclerosis (33%) or radiation enteritis (53%). Criteria for a place on the transplant list range from a loss of intravenous access to multiple septic infections or liver failure caused by TPN. The survival rate of Crohn’s disease patients following the transplantation is similar to that of patients with other indications. This is also the case for the survival of the transplant itself. In a five-year follow-up study conducted in the USA observing 134 patients with Crohn’s disease and 935 patients with another indication for a transplant, the five-year survival rate was 62%. 42% of the patients suffered an acute rejection and almost 20% lost the transplant.

Can Crohn’s disease develop after pouch surgery?

Around 30% of patients with relapsing, extensive ulcerative colitis require surgery within five years. The most common form of surgery is a proctocolectomy with ileal pouch-anal anastomosis. T. Molnár, Szeged (Hungary), explained that doctors should not wait too long before performing this surgery because preoperative clinical deterioration is associated with an unfavorable outcome. The indications he named for performing pouch surgery ranged from acute therapy-refractory ulcerative colitis, acute complications such as perforations or a megacolon, continuous chronic disease activity with steroid dependency or intolerable side effects. The feared complications include pouchitis. T. Molnár is skeptical as to whether pouch surgery can really lead to the development of Crohn’s disease, as was indicated in two case reports presented by M. Bortlik, Prague (Czech Republic). One possible explanation is that Crohn’s disease is not diagnosed until the surgical procedure is actually being performed. In general, Crohn’s disease is a relative contraindication for an ileal pouch-anal anastomosis (IPAA) due to the high rate of complications and pouch failure.

Acute severe ulcerative colitis during pregnancy requires quick recognition and effective treatment

During pregnancy, adherence to treatment often falls, increasing the risk of an acute flare-up of ulcerative colitis. At the same time, the active inflammation has a detrimental effect on the course of the pregnancy. M. Protić, Belgrade (Serbia), explained how she decided to treat a pregnant patient suffering from steroid-refractory acute severe ulcerative colitis with infliximab as a rescue therapy in the second trimester between the 17th and 23rd weeks of pregnancy. A healthy child was born in the 36th week of pregnancy. Generally speaking, Z. Zelinkova, Bratislava (Slovakia), recommended identifying flare-ups in pregnant patients with severe ulcerative colitis as quickly as possible and ruling out possible differential diagnoses, such as pregnancy-related diarrhea. Treatment should be initiated immediately and must be as effective as possible. Z. Zelinkova stressed that the long-term use of prednisone < 15 mg/day does not lower the infant’s birth weight. If steroid treatment does not work, medical teams should consider using infliximab or cyclosporine. At the same time, low-molecular heparin must be administered to protect against thrombosis. The treatment method applied also depends significantly on the stage of the pregnancy. Gastroenterologists and gynecologists should work together closely when determining which approach to adopt.
Should terminal ileitis be treated using accelerated step-up therapy or surgery?

M. Diculescu, Bucharest (Romania), explained how he treated monozygotic twins with Crohn’s disease limited to the terminal ileum with an induction therapy of budesonide 9 mg/day followed by a maintenance therapy of azathioprine. The treatment proved successful at first. However, the patients had to stop taking azathioprine due to high lipase levels. Instead, they were switched to adalimumab and budesonide was slowly tapered. Surgery could be considered as an alternative to accelerated step-up therapy. According to J. Örhalmi, Hradec Králové (Czech Republic), the correct timing for performing surgery is still a matter of contention. He named both sound arguments for performing surgery at an early stage as well as for waiting until a later stage of the disease. Benefits of early surgical intervention include the immediate elimination of symptoms and fast remission, while the disadvantages include postoperative complications and a postoperative relapse. Arguments against the use of medication range from the need to take it in the long term and side effects to higher costs and the risk of a subsequent extensive resection. However, the choice of treatment ultimately comes down to whether the patient is willing to undergo surgery.

SPECIAL LECTURE
Facts and fiction surrounding the intestinal microbiome

In recent years, the intestinal microbiome has become one of the top talking points of gastroenterologists, not least because it is discussed as a target for the development of new treatment options for both IBD and other intestinal diseases. However, despite intensive research, there is still much to resolve. For example, as mentioned by H. Tlaskalová-Hogenová, Prague (Czech Republic), it is still frequently unclear whether there is a causal link between diseases and the microbiome or whether there is simply an association. We also need to gain a better understanding of how diet, medication and other environmental factors influence the microbiome. Besides long-term nutritional habits, researchers have now been able to identify a wide range of factors that influence the composition of an individual’s microbiome. These include how the patient was delivered during birth, diet during the first few months of life (breastfeeding!), genetic susceptibility and the use of antibiotics.
New Treatment Targets in Gut and Liver Diseases

October 21 – 22, 2016
Lucerne, Switzerland

Congress Venue
KKL Luzern
Europaplatz 1
6002 Lucerne
Switzerland

Scientific organization
M. Allez, Paris (France)
C. Fiocchi, Cleveland (USA)
H. Herfarth, Chapel Hill (USA)
G. Rogler, Zurich (Switzerland)
S. Vavricka, Zurich (Switzerland)
From the New and Complex Concepts to the Real Patient: Science and Clinic

March 31 – April 1, 2017
Madrid, Spain

Congress Venue
Meliá Castilla Hotel
Calle del Capitán Haya, 43
28020 Madrid
Spain

Scientific Organization
S. Danese, Milan (Italy)
A. Dignass, Frankfurt (Germany)
J.P. Gisbert, Madrid (Spain)
F. Gomollón, Zaragoza (Spain)
At the Falk Foundation symposiums, it is traditional for young scientists to be recognized for outstanding research work.

The prizewinners at Symposium 202 “Evolving Therapies in Clinical Practice in IBD” are:

**Dr. Alexander Galushkin**, Rostov-on-Don (Russia), for his work: “The role of the innate immune components in predicting the risk of early relapse of Crohn’s disease”.

**Dr. Lucy Lynch**, Larbert (Great Britain), for her work: “Ileal inflammation at the resection margin may be predictive for increased risk of postoperative Crohn’s disease recurrence over a 10 year follow-up”.

**Ms. Eva S. Rodansky**, Ann Arbor (USA), for her work: “LYC-53976, a ROCK2-selective inhibitor, attenuates the fibrogenic response of intestinal myofibroblasts to TGF-β and substrate stiffness”.

From left to right: Dr. R. Müller for the Falk Foundation, prizewinners, Prof. E.F. Stange
“In Crohn’s disease it is the defensins that tend to be missing, but in colitis it is the mucins.”

The symposium held in Prague not only discussed the limits and possibilities of current treatment options, but also looked to the future. We asked one of the event’s scientific organizers, Prof. E.F. Stange, Stuttgart (Germany), where he believes the treatment of inflammatory bowel disease is heading.

Editor: Despite biologics having been available for many years, the need for surgical interventions and the progression of Crohn’s disease is still largely the same. Are researchers heading in the wrong direction?

Prof. Stange: Instead of working towards curing the disease, current research efforts are focusing on improving its symptoms and reducing inflammatory reactions. The cause of the disease, which as far as we know is linked to a defective intestinal barrier as opposed to an excessive immune response, is not being addressed. Nevertheless, it is still worthwhile developing new biologics because the substances available to date are only suitable for a certain proportion of patients, the majority of whom later suffer from a subsequent relapse. The expected launch of ustekinumab to the market is a very welcome development because it will give us an additional treatment option. In the long term, biologics will be used sequentially, provided we are not able to make an a priori selection of the patients who respond to a particular biologic.

In recent years, it has become clear that the immune response seen in IBD is not an autoimmune response to the body’s own tissues, but rather a response to a very wide range of bacterial antigens. In both diseases, commensal intestinal bacteria penetrate the intestinal mucosa, reaching all the way into the submucosa, the muscularis mucosa and the lymph nodes. Some bacterial DNA is even found in the blood. The likely cause of this is barrier defects, the characteristics of which vary between Crohn’s disease and ulcerative colitis. In Crohn’s disease, not enough of the body’s own antibiotics are formed on the surface of the intestine. However, findings to date suggest that this is not the case in ulcerative colitis. Instead, the problem here relates to the composition of the mucus. Insufficient mucus is formed for creating an antibacterial barrier retaining defensins and for keeping the intestinal bacteria from entering the intestinal mucosa. Therefore, in Crohn’s disease it appears to be the defensins that tend to be missing, but in colitis it is the mucins.
You have been able to demonstrate how in Crohn’s disease the Paneth cells do not produce enough α-defensins and there is a lack of antimicrobial protection. Has this discovery improved treatment of the disease?

Not yet. However, we are currently researching ways of replacing the missing defensins. It is a long and difficult process that will take five to ten years. The substances must be patented and tested for toxicity. Above all, however, we must find a way of getting high concentrations of defensins – which are intact polypeptides – to where they are needed. Here, they should be able to accumulate in the mucus and return antibacterial activity to normal.

How is it possible to place defensins in the ileum?

The idea is similar to the targeted release of mesalazine. The galenic formulation of the defensins enables them to be released in the terminal ileum. If the mucus layer is normal here, we would expect the polypeptides, which are positively charged, to accumulate in the mucus layer, which is negatively charged. This has already worked successfully in animal experiments. However, circumstances vary from patient to patient. The majority of Crohn’s disease patients have ileocecal involvement with the described defensin defect. However, there are also some patients who have a continuously diffuse colonic involvement. Since these patients are not only missing α-defensins, but are probably also lacking an induction effect of β-defensins, they require a different approach.

Besides local substitution, are there any other ways of influencing the production of defensins?

Probiotics are able to successfully influence the production of defensins in the colon but not in the ileum. For this to work, the induction system must be intact. This is why this method has an effect in patients with ulcerative colitis but not in patients with Crohn’s disease, where the system is unable to correctly perform signaling functions. The use of the Wnt signaling pathway is also being considered. However, this method could be described as being “Janus-faced,” as while it improves our ability to differentiate Paneth cells, it may also induce tumors. It will be difficult to separate these two effects. Although the principle itself is promising, it would be disastrous to improve the symptoms of Crohn’s disease at the price of the patient developing a bowel tumor. At the moment, we still rely on administering defensins locally.

In which direction do you believe the treatment of IBD will move over the next five to ten years?

I expect the treatment of Crohn’s disease to start concentrating on the substitution of defensins, not, however, to treat flare-ups, but to prevent relapses. In terms of ulcerative colitis, attempts will be made to stimulate the goblet cells to produce mucus. This may also go hand in hand with the protective effect of smoking on ulcerative colitis. However, we still have very few specific ideas about how to stimulate mucus production at a regulated rate. I believe that one beacon of hope could be the use of slow-release phosphatidylcholine to replace the missing mucins. Ultimately, researchers will head down two different tracks. On the one hand, we will continue developing biologics that enable us to treat flare-ups effectively and, on the other hand, we will tackle the cause of the disease by strengthening antibacterial defenses in order to prevent relapses. This is important because biologics are unable to reliably prevent relapses in all patients.

Will fecal microbiota transplantation become an established treatment?

At first, I was extremely skeptical because there is conflicting evidence about fecal microbiota transplantation. However, we have since made some progress in our ability to define the specific bacteriological composition that could actually offer protection against the disease. By comparing a successful donor with other donors whose stools did not produce the desired effect, we can gain an insight into which bacteria are more protective.

Hematopoietic stem cell transplantation (HSCT) and mesenchymal stromal cell therapy received a lot of criticism. Do you also have concerns about these methods of treatment?

The use of mesenchymal stromal cells is completely experimental and scientists are completely justified in their concerns. HSCT has been able to achieve limited success in patients who are otherwise considered untreatable and who cannot receive either medication or surgery, for example in the case of severe esophageal disease. However, in the long term, patients relapse a few years after their immune system has been kick-started. If the barrier defect has not been repaired, the inflammatory process will start anew.

The majority of innovations discussed focus on the treatment of severely ill patients. However, the vast majority of people suffer from a mild to moderate form of the disease. Should scientists work on improving the outlook for these patients as well?

Yes, of course. Here, too, there is room for improvement. The only patients who are truly able to benefit from an excellent course of treatment are those with mild to moderate colitis, which can be treated effectively and without many side effects using mesalazine.

Professor Stange, thank you very much for talking to us!
Symposium 207

Mucosal Microbiome and Mucosal or Systemic Dysfunction: Mechanisms, Clinical Manifestations and Interventions

May 19 – 20, 2017
Brisbane, Australia

Congress Venue
Brisbane Convention & Exhibition Centre
Merivale St & Glenelg Street
South Brisbane, QLD 4101
Australia

Scientific Organization
W.D. Chey, Ann Arbor (USA)
P.R. Gibson, Melbourne (Australia)
G. Holtmann, Brisbane (Australia)
M. Simrén, Gothenburg (Sweden)
N. Talley, Newcastle (Australia)

FALK FOUNDATION e.V.
Lenenweberstr. 5
79108 Freiburg
Germany

Congress Department
Tel.: +49(0)761/1514-125
Fax: +49(0)761/1514-359
E-Mail: symposia@falk-foundation-symposia.org
www.falk-foundation-symposia.org
Dr. Martin Bortlik  
Clinical and Research Center for IBD  
Jankovcova 1569/2c  
170 04 Prague, Czech Republic  
mbortlik@hotmail.com

Prof. Dr. Jacques Cosnes  
Service de Gastroentérologie et Nutrition  
Hôpital Saint Antoine  
184, rue du Faubourg St.-Antoine  
75012 Paris, France  
jacques.cosnes@sat.aphp.fr

Dr. Mircea Diculescu  
Department of Gastroenterology and Hepatology  
Fundeni Clinical Hospital  
Sos. Fundeni 258  
022328 Bucharest, Romania  
mmdiculescu@yahoo.com

Prof. Dr. Axel Dignass  
Medizinische Klinik I  
AGAPLESION Markus Krankenhaus  
Wilhelm-Epstein-Str. 4  
60431 Frankfurt, Germany  
axel.dignass@fdk.info

Prof. Dr. Andrey E. Dorofeyev  
National Medical University  
n.a. A.A. Bogomoletz  
Chair of Internal Diseases  
17, Shevchenko Boulevard  
01030 Kiev, Ukraine  
dorofeyevand@gmail.com

Dr. Pavel Drastich  
Department of Hepatology and Gastroenterology  
Institute for Clinical and Experimental Medicine  
Videnska 1958/9  
140 21 Prague 4, Czech Republic  
drastich@hotmail.com

Dr. Dana Duricova  
Clinical and Research Center for IBD  
Jankovcova 1569/2c  
170 04 Prague, Czech Republic  
dana.duricova@seznam.cz

Dr. Marc Ferrante  
Gastro-entérologie  
University Hospital Leuven  
Herestraat 49  
3000 Leuven, Belgium  
marc.ferrante@uz.kuleuven.ac.be

Prof. Dr. Geoffrey M. Forbes  
Department of Gastroenterology and Hepatology  
Royal Perth Hospital  
GPO Box X2213  
Perth, WA 6847, Australia  
geoff.forbes@health.wa.gov.au

Prof. Dr. Ann Gils  
Therapeutic and Diagnostic Antibodies O&N II  
University Hospital Leuven  
Herestraat 49 - box 820  
3000 Leuven, Belgium  
ann.gils@pharm.kuleuven.be

Prof. Dr. Christopher J. Hawkey  
Nottingham Digestive Disease Centre  
University Hospital Queen’s Medical Centre  
Nottingham NG7 2UH, Great Britain  
cj.hawkey@nottingham.ac.uk

Peter D.R. Higgins, M.D.  
Associate Professor of Medicine  
Department of Gastroenterology  
University of Michigan  
Medical Science Research Bldg. I  
1150 W Medical Ctr Drive  
Ann Arbor, MI 48109-0682, USA  
phiggins@med.umich.edu

Prof. Dr. Tibor Hlavaty  
Department of Internal Medicine  
Subdepartment of Gastroenterology  
University Hospital Bratislava  
Ruzinovska 6  
826 06 Bratislava, Slovakia  
thibor.hlavaty2@gmail.com

Dr. Jorgen Jahnsen  
Akershus Universitetssjukehus  
Postboks 75  
1474 Nordbyhagen, Norway  
jorgen.jahnsen@medisin.uio.no

Prof. Dr. Wolfgang Kruis  
Gastroenterologie und Pulmologie  
Evang. Krankenhaus Kalk  
Buchforstr. 2  
51103 Köln, Germany  
kruis@evkk.de

Prof. Dr. Peter L. Lakatos  
1st Department of Medicine  
Semmelweis University Medical School  
Koranyi u. 2/a  
1083 Budapest, Hungary  
lakatos.peter_laszlo@med.semmelweis-univ.hu

Prof. Dr. Milan Lukas  
Clinical and Research Center for IBD  
Jankovcova 1569/2c  
170 04 Prague, Czech Republic  
milan.lukas@email.cz

Dr. Marc Martí Gallostra  
Digestive and General Surgery  
Hospital General Vall d’Hebron  
Paseo Vall d’Hebron 119  
08035 Barcelona, Spain  
marcmartig@gmail.com

Dr. Tamás Molnár  
1st Department of Medicine  
Szeged University Medical School  
Koranyi Fasor 8  
6720 Szeged, Hungary  
molnar.tamas@med.u-szeged.hu

Prof. Dr. Bjorn Moum  
Division of Gastroenterology  
University Hospital Ullevaal  
& University of Oslo  
Kirkeveien 166  
0424 Oslo, Norway  
bjorn.moum@medisin.uio.no
Speakers, moderators and scientific organizers

Prof. Dr. Gottfried Novacek
Gastroenterologie/Hepatologie
Medizinische Universität Wien
Währinger Gürtel 18–20
1090 Wien, Austria
gottfried.novacek@meduniwien.ac.at

Dr. Julius Örhalmi
Department of Surgery
Charles University Hospital
Sokolská 581
500 05 Hradec Králové,
Czech Republic
orhalmi@volny.cz

Prof. Dr. Yves Panis
Service de Chirurgie Colorectale
Hôpital Beaujon
100, Bd. Général Leclerc
92118 Clichy, France
yves.panis@bjn.aphp.fr

Dr. Marijana Protic
Department of Gastroenterology and Hepatology
University Hospital Zvezdara
Dimitrija Tucovica 161
Belgrade, Serbia
marjana.protic@gmail.com

Prof. Dr. Walter Reinisch
Department of Medicine
Health Sciences Centre
McMaster University
1280 Main Street West
Hamilton ON L8S 4K1, Canada
reinisw@mcmaster.ca

Florian Rieder, M.D.
Department of Pathology, NC22
Lerner Research Institute
The Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195, USA
riederf@ccf.org

Prof. Dr. Dr. Gerhard Rogler
Klinik für Gastroenterologie & Hepatologie
Universitätsspital Zürich
Rämistr. 100
8091 Zürich, Switzerland
gerhard.rogler@usz.ch

Bruce E. Sands, M.D.
Professor of Medicine
Department of Gastroenterology
Mount Sinai School of Medicine
One Gustave L. Levy Place
New York, NY 10029, USA
bruce.sands@mssm.edu

Prof. Dr. Jürgen Schölmerich
Internist
Germanenstr. 8 b
65719 Hofheim, Germany
aed@kgu.de

Dr. Zuzanna Serclova
Surgical Department
University Hospital Bulovka
Budinova 2
180 81 Prague, Czech Republic
sercl@seznam.cz

Prof. Dr. Eduard F. Stange
Gastroenterologie/Hepatologie
Robert-Bosch-Krankenhaus
Auerbachstr. 110
70376 Stuttgart, Germany
eduard.stange@rbk.de

Prof. Dr. Dr. Helena Tlaskalová-Hogenová
Division of Immunology and Gnotobiology
Institute of Microbiology ASCR
Videnska 1083
142 20 Prague, Czech Republic
tlaskalo@biomed.cas.cz

Dr. Zuzana Zelinkova
5th Department of Internal Medicine
IBD Centrum
Tomasikova 50/C
831 04 Bratislava, Slovakia
zelinkova@assiduo.sk
International Symposia and Workshops

Workshop
Future Perspectives in Hepatology: From Basics to Clinics
Essen, Germany
January 19 – 20, 2017

Symposium 206
From the New and Complex Concepts to the Real Patient: Science and Clinic
Madrid, Spain
March 31 – April 1, 2017

Symposium 207
Mucosal Microbiome and Mucosal or Systemic Dysfunction: Mechanisms, Clinical Manifestations and Interventions
Brisbane, Australia
May 19 – 20, 2017

IX Gastro-Conference
Berlin, Germany
October 4 – 7, 2017

Symposium 208
Eosinophilic Esophagitis – Medical and Dietary Treatment
Berlin, Germany
October 4 – 5, 2017

Symposium 209
IBD 2017 – Therapeutic and Biological Barriers
Berlin, Germany
October 6 – 7, 2017

Workshop
Workshop on Oral, Gastrointestinal and Pulmonary GvHD
Regensburg, Germany
November 17 – 18, 2017

FALK FOUNDATION e.V.
Leinenweberstr. 5
79108 Freiburg
Germany

Congress Department
Tel.: +49 (0)761/1514-125
Fax: +49 (0)761/1514-359
E-Mail: symposia@falk-foundation-symposia.org
www.falk-foundation-symposia.org
Scientific Dialogue in the Interest of Therapeutic Progress