New Treatment Targets in Gut and Liver Diseases

Symposium 205
Lucerne (Switzerland), October 21–22, 2016
Symposium 205
New Treatment Targets in Gut and Liver Diseases

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www.falk-foundation-symposia.org

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1st edition 2017

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Photos (cover picture, portraits, impressions and awarding of poster prizes)
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Image page 13 © Shutterstock
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Focus on the liver and the intestines

For a long time, there was almost no progress in the treatment of inflammatory bowel disease (IBD) and cholestatic liver disease – but now, things are gathering speed. New innovations are emerging, but it is not yet clear what the latest developments will mean for everyday clinical practice. Potential changes to treatment regimens were just one of the topics that were discussed at length at the 205th Symposium of the Falk Foundation in Lucerne.

In recent years, the progress made in the treatment of chronic hepatitis C in particular has dominated the headlines. In light of the spectacular cures we have seen with this condition, the progress that has been made in other areas of hepatology and gastroenterology has received rather less public attention and been the subject of less discussion. However, even with Crohn’s disease and ulcerative colitis, major advances have been made, and new treatment options have either become available, or their development has progressed further. In terms of everyday clinical practice, this will probably lead to the establishment of new treatment regimens with more complex treatment algorithms.

The situation is similar when it comes to the cholestatic liver diseases primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). PBC is a relatively treatable condition because the majority of patients respond well to standard treatment with ursodeoxycholic acid (UDCA). In practical terms, these patients no longer need to fear developing cirrhosis of the liver. Patients who respond well to UDCA have a normal life expectancy.

However, the situation is quite different for PBC patients who are non-responders. Far more progress is needed in terms of treatment development for these patients. This could be achieved with the approval of the farnesoid X receptor (FXR) agonist obeticholic acid as a co-treatment to be used with UDCA.

One very promising product for PSC patients is the UDCA derivative nor-ursodeoxycholic acid (norUDCA), which is still in clinical development. The initial clinical data is very promising.

Alongside the emerging advances in the treatment of IBD and cholestatic liver disease, the increasingly differentiated understanding of these complex conditions was a much discussed topic in Lucerne. The spotlight here was on new findings regarding environmental factors that trigger the development of an acute flare-up of disease, or disease progression in general. In future, these findings could facilitate more targeted prevention of disease pathogenesis and acute complications.

Prof. G. Rogler
on behalf of the scientific organizing committee
Establishing therapeutic advancements as treatments is often a great medical challenge. According to G. Rogler, Zurich (Switzerland), this is indeed the case for inflammatory bowel disease (IBD) and cholestatic liver disease at the moment. Once new active ingredients have been approved or are just about to be approved in both areas, the next step is integrating the new treatment options into everyday clinical practice.

New treatment options for inflammatory bowel disease

The new treatment options that have become available for IBD are the integrin inhibitor vedolizumab and the IL-12/IL-23 antibody ustekinumab. The new biologics represent a light at the end of the tunnel in the efforts to make IBD treatment more effective and possibly even to obtain cures. According to C. Fiocchi, Cleveland (USA), the innovations are the fruit of years, and even decades, of very intensive research. Until this point, treatment of IBD was largely based on anti-inflammatory strategies. Initially sulfasalazine was used, but now mesalazine is the first-line treatment. Today, it remains the established standard treatment for ulcerative colitis and is a proven treatment option for the mild form of ileocecal Crohn’s disease.

Topical steroids instead of systemic steroids

However, mesalazine cannot sufficiently control the disease in all patients, so immunosuppressants must often be prescribed as well. For decades, corticosteroids have been used in this scenario, bringing with them all of the drawbacks of this particular group of active ingredients in terms of potential side effects. According to G. Rogler, one alternative is the topical steroid budesonide, which stands out because of its significantly lower risk of side effects due to its local activity.

The search for new treatment targets

According to C. Fiocchi, other immunosuppressants, such as azathioprine and methotrexate, and for some years now also substances which interfere with pathogenesis, such as TNF inhibitors, are considered standard treatment. However, even with these active ingredients, it is not always possible to achieve satisfactory control of the disease, meaning that the search is still on for new targets and therapeutic approaches. This situation is not likely to change even with the establishment of new, even more specifically targeted biologics such as vedolizumab and ustekinumab.

According to C. Fiocchi, the key to developing new active ingredients to treat IBD is improving our understanding of the disease. It is clear that various endogenous and exogenous aspects of pathophysiology come into play here. C. Fiocchi mentions the genome, the exposome, the microbiome, and the immunosome of the intestines in this context (Fig. 1). In his view, if we were able to better understand the interactions between these four aspects, we would be able to identify new approaches to the development of new treatment options for IBD. However, researching the relationships between these aspects is not easy, because epigenetic effects also have to be taken into account, and according to C. Fiocchi, these can even have an effect during development in the womb.
The latest in cholestatic liver disease

According to U. Beuers, Amsterdam (The Netherlands), therapeutic advances have not been limited to IBD – significant progress has also been made in treating cholestatic liver diseases. As an example, he mentioned the farnesoid X receptor (FXR) agonist obeticholic acid, which has meanwhile been approved as a co-treatment to be used with ursodeoxycholic acid (UDCA) for primary biliary cholangitis (PBC). UDCA is an established standard treatment for PBC. If the bile acid is administered early, the development of cirrhosis of the liver can be avoided in more than 60% of patients. “Without this treatment, patients exhibit cirrhosis of the liver after 7 to 15 years on average, along with the resulting complications such as the need for a liver transplant, or even the death of the patient due to liver decompensation,” says U. Beuers. However, thanks to UDCA, nowadays, two thirds of PBC patients have a normal life expectancy. “Nevertheless, the treatment is often not carried out in a sufficiently systematic manner, and the bile acid is often not given at a high enough dose,” warned the hepatologist.

Modified bile acid – hope for progress in the treatment of PSC

The need for therapeutic advances is particularly acute in the case of PSC, for which there is no effective treatment option available to date. According to R.W. Chapman, Oxford (Great Britain), the condition may be associated with other diseases such as IBD, but it can also be associated with tumors, or other autoimmune diseases. This suggests that there may be a common genetic background (Fig. 2).

PSC: Associated disorders

- Points to the possibility that different genetic constitutions play a role in different individuals with PSC
- Suggests that there are shared genes between PSC and other diseases
According to U. Beuers, the modified bile acid norUDCA is currently developing into a very promising option for the treatment of PSC. Because norUDCA is barely conjugated, it strongly stimulates bicarbonate secretion, which means that it has a high level of choleretic efficacy (Fig. 3). “NorUDCA has a clear anticholestatic effect. In a phase 2 study, it was shown that alkaline phosphatase in serum was reduced by about 30%,” says U. Beuers. Looking to the future, he believes we can expect a combination therapy made up of UDCA and norUDCA that will greatly improve treatment.

Still much research to be done

Quite apart from the need for new therapeutic approaches to the treatment of cholestatic liver diseases, P. Fickert, Graz (Austria) suggests that much research still needs to be done on the conditions themselves. This is because the etiology of PBC and PSC remains as opaque as ever. In both of these conditions, loss of bile duct functionality causes restructuring processes, which in turn cause liver fibrosis to develop. As the disease progresses, this may develop into cirrhosis of the liver. Thanks to the constantly improving understanding of the complex regulation of choleretic and through this, the improvements in the understanding of the underlying pathogenetic processes, further advances in the development of new treatment options for PBC and PSC can be expected in the future according to P. Fickert.

From the New and Complex Concepts to the Real Patient: Science and Clinic in IBD

March 31 – April 1, 2017
Madrid, Spain

Congress Venue
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Calle del Capitán Haya, 43
28020 Madrid
Spain

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The latest on diseases of the liver and the intestines

What is the latest news regarding the understanding of these diseases and what new treatment concepts are emerging for IBD and chronic liver disease? What environmental factors trigger pathogenesis, and what factors could encourage the development of acute flare-ups? What do we need to be careful of when making decisions, and what should the treatment aims be? The experts at the 205th Symposium of the Falk Foundation in Lucerne gave answers to these and other topical questions.

Treatment of hepatitis C – a success story

As a result of infection with the hepatitis C virus (HCV), both the innate and the acquired immune system are activated in the fight against the viruses. However, the immune responses are often unsuccessful, and immune response failure and chronification occur in about 70% of patients with an HCV infection. About 20–30% of patients with chronic HCV infection subsequently develop liver fibrosis which progresses into cirrhosis.

According to C. Neumann-Haefelin, Freiburg (Germany), these patients have an increased risk of liver cancer, and the rate of tumor formation is approx. 1–6% per year. However, thanks to the huge progress that has been made in treatment, about 90% of patients with a chronic HCV infection can be cured. Unfortunately, the treatment costs are very high, and prophylactic strategies are still very much needed: “We are still trying to develop a vaccine against the HCV virus,” says C. Neumann-Haefelin.

Despite the high cure rates, the problems are by no means over, even in the case of HCV infection. According to estimates, about 60–180 million people worldwide suffer from a chronic HCV infection, which according to B. Müllhaupt, Zurich (Switzerland), is a huge burden on healthcare systems: “Worldwide, hepatitis C remains the most common cause of the development of hepatocellular carcinoma, and the most common reason for liver transplantation being required.” Another problem is the high number of unreported infections.

The situation with hepatitis B virus infection (HBV) is different from that of HCV infection. A vaccination is available for this disease, but if a chronic infection occurs, the cure rate is much lower than with HCV. Therefore, there is still a real need for effective treatment options for HBV infection, as P. Lampertico, Milan (Italy), explained. According to his estimations, about one million people globally die from the consequences of this disease each year.
Hepatitis E – more than just a liver disease

According to H.R. Dalton, Cornwall (Great Britain), the significance of the hepatitis E virus (HEV) infection is still widely underestimated. The risk is particularly high for pregnant women, in whom the reported mortality rate is about 25%. The incidence of HEV infections is constantly increasing, although the infection goes unnoticed in most patients. The symptoms that occur are also often misconstrued. The common symptoms mentioned by H.R. Dalton are jaundice, lethargy, abdominal symptoms, pain, nausea, fever, and myalgia. Less frequently reported symptoms include pruritus, weight loss, headache, and joint pain. Extrahepatic manifestations are a particularly important factor in this context. Here, the HEV infection can affect various organ systems. These effects may range from neurological symptoms to Guillain-Barré syndrome, encephalitis and myelitis as well as autoimmune thyroiditis or myocarditis. The infection can also manifest as pancreatitis and cause renal complications. Thrombocytopenia may also occur, as well as monoclonal gammopathy.

The latest on the pathogenesis of cholestasis

One of the main topics discussed at the symposium was cholestatic liver disease. Not only was the hope of progress in treatment discussed, but new data on pathogenesis was also presented. According to B. Stieger, Zurich (Switzerland), the formation of bile is based on the interaction of transport proteins in a complex system. If this interaction is disrupted, there is a risk of cholestasis and of the accumulation of bile salts in the hepatocytes. This can cause cell damage and may lead to cholestatic liver disease. A distinction should be made between congenital cholestasis that is caused by mutations in the transport protein genes, and the acquired form of the disease. The latter is caused by environmental factors such as medicinal products and their metabolites, or lesions in the area of the bile ducts, causing inhibition of transport proteins. Immune reactions also play a central role here and according to B. Stieger, both primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) should be considered immune-related diseases. Both conditions develop when there is a background of pronounced and complex genetic predisposition.

PSC – hepatology’s black box

According to R.W. Chapman, Oxford (Great Britain), one of the biggest problems in hepatology is PSC, which is a chronic, progressive disease of the bile ducts with fibrosis and the formation of strictures which can lead to cirrhosis of the liver and liver failure. The condition is still not completely understood, but according to R.W. Chapman, it is “hepatology’s black box”. The disease is more common in men than in women (2:1), and it is disproportionately more common in non-smokers and those who do not drink coffee. It is also closely associated with other diseases. Thus, 70–80% of PSC patients also have inflammatory bowel disease (IBD). Conversely, about 5% of patients with IBD develop PSC. There is also an association with autoimmune diseases such as psoriasis, vitiligo and thyroid disease. Furthermore, PSC is regarded as a premalignant disease, because there is a significantly increased risk of cancer. According to R.W. Chapman, 10% of patients develop cholangiocarcinoma, and there is also an increased risk of colon cancer and hepatocellular carcinoma. Approximately 10% of patients with PSC have a particular form of disease in which the IgG4 levels are elevated. The course of the disease is worse in these patients compared to patients with normal IgG4 levels. As yet, there is no effective treatment for PSC, but there are new therapeutic approaches that are in the clinical trial stage. For now, however, a liver transplant is the only chance for patients with advanced-stage disease.

In brief

PSC patients 70–80%

IBD patients 5%
**IgG4-associated cholangitis**

A distinction should be made between PSC with elevated IgG4 values and IgG4-associated cholangitis (IAC). The two diseases are entirely different entities. With IAC, additional organs (especially the pancreas) are often affected; however, the disease is not associated with IBD. In the cholangiography, it is difficult to distinguish biliary changes from PSC. The distinction is, however, important because unlike PSC, IAC responds very well to steroid treatment (up to an including regression of bile duct strictures).

**NASH – still a big therapeutic challenge**

For non-alcoholic steatohepatitis (NASH) too, there is still a lack of effective treatment options, as M. Heikenwälder, Heidelberg (Germany) demonstrated. As the condition is closely associated with obesity, it can be assumed that there will be a further increase in its incidence and prevalence worldwide. This is because obesity is currently becoming increasingly common, especially in developing and newly industrialized countries. NASH is also associated with type 2 diabetes, hypertension, and dyslipidemia, and here in particular with elevated triglycerides and a high total cholesterol level. The disease is by no means harmless – it is associated with a significantly increased risk of developing cirrhosis of the liver and hepatocellular carcinoma. According to A.J. Sanyal, Richmond (USA), this is why NASH has long been one of the leading causes of liver-associated morbidity and mortality.

**Alcoholic hepatitis: Often, the only remaining option is best supportive care**

Additional common causes of liver-related mortality listed by F. Stickel, Zurich (Switzerland) include alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). The progression of both conditions follows the same pattern, transitioning into hepatitis, cirrhosis of the liver, and hepatocellular carcinoma. Neither ALD nor NAFLD should be underestimated as diseases, even if a relatively small percentage of patients actually exhibit disease progression leading to fatal liver disease. Thus, only 10–35% of patients with ALD develop alcoholic steatohepatitis and of those only 8–20% develop cirrhosis of the liver. According to N. Lanthier, Brussels (Belgium), the parallels in the progression should also be reflected in the terminology. The alcoholic form of the disease should therefore be known as alcoholic hepatitis (AH). From a histological point of view, it is based on alcoholic steatohepatitis (ASH). This physician recommended steroid treatment as one of the most effective therapeutic measures, alongside abstinence from alcohol. For this treatment, a reduction in acute mortality was documented, but no reduction in long-term mortality, as is the case for other therapeutic measures. The only other treatment options are the “best supportive care” options, with administration of N-acetylcysteine, vitamin B1, management of infections, and nutritional therapy to combat malnutrition, which is usually present.
Dysbiosis as a cause of disease?

Alongside genetic predisposition, environmental factors may also promote the manifestation of Crohn’s disease and ulcerative colitis, and trigger acute flare-ups. Thus, according to C.N. Bernstein, Winnipeg (Canada), there is a connection between Crohn’s disease and a NOD-2 mutation, although there are certainly also Crohn’s disease patients who do not have such a mutation. The composition of the intestinal flora is also significant in pathogenesis – it is likely that the changes to the microbiome are the most important factor here. To date, no one has been able to document a link to a specific infection. However, there have been observations that the use of antibiotics can promote the manifestation of the disease, even if the antibiotics were taken some time previously. According to A. Macpherson, Bern (Switzerland), the microbiome is made up of many different bacteria. This is an extremely complex system that is also very variable. When it comes to inflammatory bowel disease, it is hard to say what came first, the chicken or the egg: “It is possible that the microbiome causes an intestinal inflammation, but it is equally possible that the inflammatory processes are attributable to changes in the intestinal flora,” said the physician.

Environmental factors trigger IBD

For A.N. Ananthakrishnan, Boston (USA), there can be no doubt that environmental factors are extremely significant in the pathogenesis of IBD. Therefore, quite different stimuli could trigger immunological dysregulation, which can certainly lead to the manifestation of Crohn’s disease or ulcerative colitis. Thus, many studies have shown an inverse relationship between breastfeeding and the occurrence of IBD in later life. This could be mediated through a direct influence that the mother’s milk may have on the child’s microbiome, or through an indirect influence on the frequency of infections in childhood. The clear increase in the incidence of IBD in newly industrialized countries also highlights the impact of industrialization and the associated environmental pollution. In addition, frequent intake of non-steroidal anti-inflammatory drugs seems to increase the risk of IBD.

Increased risk of IBD due to staying at high altitudes

S. Vavricka, Zurich (Switzerland), has made the interesting observation that staying at high altitudes evidently increases the risk of IBD. This applies to both mountain tours and long-haul flights. “It appears that hypoxia may promote inflammatory processes,” explains the scientist. He was able to confirm this hypothesis using experiments in the pressure chamber. An increase in the HIF (hypoxia induced factor) was demonstrated there. “Under hypoxic conditions, the signaling pathways may change,” said S. Vavricka. At an altitude of 3,400 meters above sea level, the incidence of inflammatory mediators such as interleukin-6 (IL-6) and C-reactive protein (CRP) increases. At an altitude of 4,500 meters, the oxygen saturation of hemoglobin also drops to 80%. The results are in line with the data from patients with IBD that shows that long-haul flights or climbing tours in the mountains often precede an acute flare-up. According to D. Iliopoulos, Los Angeles (USA), the molecular background of the observed effects is still unclear.
Anti-integrins as a new option for IBD

The treatment of inflammatory bowel disease is largely based on mesalazine, which plays a particularly central role in the treatment of ulcerative colitis. If treatment with mesalazine does not achieve complete success, according to S. Schreiber, Kiel (Germany), additional glucocorticoids and/or oral immunosuppressants, and possibly also biologics are indicated. If this is also unsuccessful, surgery should be considered. It is important to ensure effective therapy right from the start: “This can delay progression,” says S. Schreiber. In his experience, the later the treatment begins, the more difficult it is to have a corrective influence on disease progression. The treatment options here are now expanding to include the integrin inhibitor vedolizumab and the IL-12/IL-23 antibody ustekinumab, which increases the chances of an effective, tailor-made therapy in IBD patients. According to S. Ghosh, Birmingham (Great Britain), this also implements the concept of targeted therapy in IBD, which is all about intervening to correct the dysregulated signaling pathways caused by the disease. These expanded treatment options are a further step towards tailor-made therapy. According to S. Ghosh, it is now extremely important to stratify patients and define subgroups that qualify as candidates for the treatment option in question. According to M.D. Long, Chapel Hill (USA), the safety of the new active ingredients needs to be monitored carefully. This is because there is evidence that they can provoke the onset of autoimmune diseases such as psoriasis or vasculitis by way of a “paradoxical inflammation”.

Mesalazine – established as a standard treatment for decades

Even in light of the new treatment options, the proven concepts should by no means be pushed into the background, says W. Kruis, Cologne (Germany). The standard treatment still plays a central role in the treatment of IBD. This applies particularly to mesalazine, which exhibits a topical action in the intestines, says W. Kruis. The active ingredient can be administered via various routes of administration, and it has been established as a standard treatment for IBD for decades. According to W. Kruis, mesalazine is usually administered orally, in the form of tablets, or granules. The active ingredient is protected during its passage through the stomach and the small intestine, and is released mainly in the large intestine, with a partial delayed release. In the case of active distal disease in particular, an additional rectal administration is indicated in order to achieve the maximum possible treatment success. These treatment options are often neglected, however. For rectal administration, mesalazine is available in various pharmaceutical forms, including enemas, foams, or suppositories. “In order to ensure compliance, it is important to ask the patients which route of administration they prefer,” says W. Kruis. The combination of oral plus rectal administration makes it possible to reach almost the entire large intestine. In his experience, the later the treatment begins, the more difficult it is to have a corrective influence on disease progression. Here it is particularly important that rectal administration achieves high active substance levels in the distal colon, as the distal areas are primarily responsible for the symptoms. No systemic side effects have been reported for rectal administration of mesalazine. If mesalazine is not sufficient to achieve complete treatment success, the active ingredient can be combined with rectally administered budesonide.
Relying on proven strategies

According to H. Herfarth, Chapel Hill (USA), in addition to mesalazine and steroids, methotrexate also has an important role to play. This immunosuppressant is mainly used as maintenance treatment for ulcerative colitis. Apart from this, as J. Cosnes, Paris (France) notes, azathioprine also continues to play an important role as an immunosuppressant for the treatment of inflammatory bowel disease. According to P. Michetti, Lausanne (Switzerland), TNF inhibitors will likely become increasingly important in the treatment of IBD because the active ingredient infliximab is now also available as a biosimilar. It should be noted here that the biosimilar active ingredient has not been tested in IBD, only in rheumatoid arthritis. The data that was obtained was extrapolated to other indications such as IBD, so special attention should be paid to pharmacovigilance.

Targeted therapy – a new era in the treatment of IBD

In the treatment of diseases such as Crohn’s disease and ulcerative colitis, the treatment aims are currently changing, as F.M. Dias, Porto (Portugal), has demonstrated. This amounts to a new era for treatment, because it is no longer just about relieving the patient’s symptoms. Rather, the aim of treatment is to heal the inflammatory lesions. The success of the treatment must therefore be monitored using imaging techniques and/or colonoscopy. Again and again, the same questions arise: How long should treatment, for example, with a biologic such as an anti-TNF antibody continue, and is it possible to discontinue treatment once the lesions have healed? “We know, however, that every second patient then has a relapse within twelve months,” explains S. Ben-Horin, Tel Aviv (Israel). Nevertheless, according to his reports, around 35% of patients remain in remission long-term. Depth of remission can be used as a criterion to determine whether discontinuation of therapy makes sense. This is because patients in whom no deep remission is achieved, i.e. who still have signs of inflammation in the endoscopy, have a high risk of relapse. If biologics are discontinued, the patient should also continue to be treated consistently using the standard treatment – i.e. according to the same regimen as patients who have just had surgery for IBD. According to J.D. Lewis, Philadelphia (USA), it is also essential to ensure that patients are well-informed regarding the risks of treatment, especially when they are being treated with immunosuppressants and biologics. The risk of infection must be addressed, along with the possible increased risk of tumors. “It should be noted, however, that such secondary diseases are not necessarily due to the medication – there may be an increased risk caused directly by the disease itself,” the US scientist suggested.

Could stem cell therapy be used in Crohn’s disease?

Stem cell therapy was also introduced as a potential new treatment option for patients with severe Crohn’s disease. According to M. Allez, Paris (France), both autologous hematopoietic stem cell transplantation (HSCT), allogeneic stem cell transplantation, and transplantation of mesenchymal stem cells are conceivable here. HSCT is currently being investigated for immune-mediated diseases in particular. The procedure offers the chance of a significant improvement in the clinical situation in the case of severe and otherwise therapy-refractory Crohn’s disease. However, it is also associated with a high risk of complications and a significant mortality rate.
Gut 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

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As is the tradition at the Falk Foundation symposia, young scientists were honored for their outstanding research at the 205th Symposium in Lucerne. Poster prizes were awarded to (in alphabetical order):

**Natalia K. Lajczak** from the Royal College of Surgeons in Ireland, Dublin, for her research on the regulation of epithelial defensin secretion in the colon through bile acids.

**Dr. Alicja Sznarkowska**, University of Gdańsk, Poland, for her poster on the association of IL-10 polymorphism in immune response in the context of chronic hepatitis B infection.

**Apor Veres-Szekely**, Semmelweis University Budapest, Hungary, for his research on the role of interleukin-24 in the pathogenic mechanism of IBD-associated tissue remodeling.
“Relevant therapeutic progress is currently being made in hepatology and gastroenterology”

Prof. Dr. Dr. G. Rogler, Zurich (Switzerland), scientific organizer of the 205th Symposium of the Falk Foundation gave his view of the progress that has been made in the treatment of inflammatory bowel disease and cholestatic liver disease, and the consequences of this for everyday practice.

Editor: Professor Rogler, to what extent have there been new developments in the treatment of inflammatory bowel disease and chronic liver diseases such as cholestatic liver disease?

Prof. Rogler: There are new treatment options in both areas, some of which have already been approved and some of which are still in development and are likely to be approved soon. In light of this, we are currently seeing some very positive developments for both inflammatory bowel disease and cholestatic liver disease, which could well have an impact on everyday practice.

What impacts do you expect?

We expect that in future, we will be able to treat patients more effectively; especially those patients for whom we have hitherto had no satisfactory treatment options. However, the importance of the new treatment options is still not entirely clear. There is still uncertainty about how and when the active ingredients should be used and to what extent they can be combined with the current standard therapeutics. We are currently working to clarify these issues. However, it is already clear that the treatment algorithms will become more complex due to the new treatment options. We therefore need to ensure that we also develop and adapt the guidelines in such a way that new knowledge and opportunities are quickly put into practice so that they can benefit patients.

What proportion of patients will benefit from the new developments?

A good way to illustrate this would be to use the example of a patient with inflammatory bowel disease. In about two-thirds of these patients, the disease can be controlled well with the standard treatment that has been available to date. However, one third have recurring problems. Even the biologics and immunosuppressants that have been available to date often do not achieve satisfactory treatment success. Therefore, the search is still on for new treatment options for these patients in particular. The proportion of patients that will benefit from the advances in hepatology is likely to be higher still. Particularly in the treatment of chronic hepatitis C infection, there has been a kind of revolution in recent years, because we can now cure almost 100% of patients using the new treatment regimen. We are also on the cusp of major advances in cholestatic liver diseases such as primary biliary cholangitis, and particularly primary sclerosing cholangitis. With obeticholic acid and the promising study results for nor-ursodeoxycholic acid, two new treatment options are on the horizon, but here too, we need to learn how to make the best use of them. The question of how many patients could ultimately benefit from this has not yet been answered, especially since we will now have to determine through use in everyday clinical practice to what extent the new treatment options can be combined with the standard treatment.

To what extent should we expect to see previously unknown side effects?

It is in the nature of things that when we use new active ingredients, we are confronted with new side effects. In this area too we will have to learn how to respond to the new developments, and how to use our experience to
establish a sensible side effect management system. The exceptional level of participation among physicians and their keen interest in continuing medical education events and scientific symposia such as the Falk Foundation symposia reflects the fact that physicians are well aware of this situation.

Are there any new insights with regard to causes of disease?

One area that is flourishing at the moment in terms of new insights is that of triggers of acute flare-ups in inflammatory bowel disease. We now know that stays at high altitudes, for example, in the mountains, and evidently also long-haul flights are risk factors for the development of an acute flare-up. Other triggers may include heat exposure, intake of certain food ingredients, taking non-steroidal anti-inflammatory drugs, vitamin D deficiency, and a routine intake of iron supplements in early pregnancy. We are very interested in such observations. After all, prevention, and especially prevention of acute flare-ups, is at least as important as the development of new therapeutics. Environmental factors play a crucial role here. Moreover, very often they can be remedied using simple measures such as vitamin D substitution.

What are the consequences of this?

The better our understanding of the trigger factors and their effects, the more specifically we can advise patients with inflammatory bowel disease. Thus, we have already started recommending to women with IBD who want to have children that if they get pregnant, they should only take iron supplements if they have iron deficiency.

Furthermore, we advise all IBD patients to take vitamin D in order to avoid deficiency. In addition, it is of course essential that when we treat patients, we make the best possible use of the standard treatment. Thus far, this often has not happened consistently enough.

What exactly is going wrong in that respect?

For many patients with ulcerative colitis, in addition to the oral administration of mesalazine, rectal therapy with the active ingredient is also indicated. However, this is often not implemented. Instead, the patients often receive only the oral preparation, meaning that valuable treatment opportunities are missed. In concrete terms, only about 25% of patients for whom rectal treatment would make sense currently receive combined oral and rectal treatment. This means that simply by taking full advantage of the standard medication, the treatment of around three quarters of these patients could be improved. Making the most of conventional treatment also involves initially treating Crohn’s disease patients with a topical steroid therapy with active ingredients such as budesonide before administering systemic steroids. Systemic steroid treatment is only indicated if topical administration of steroids does not achieve sufficient success.

What is your perspective on future developments in the fields of IBD and cholestatic liver disease?

There has been a lot happening with both disease fields recently. The treatment regimens are a work in progress and there are currently no clear recommendations for best practices. Our challenge is to develop appropriate algorithms and incorporate them into the official guidelines. I personally believe that combination therapy will become more important in future for both IBD and cholestatic liver disease. It is very likely that in patients who do not respond adequately to conventional treatment, we will use the new therapeutic agents in addition to standard treatment in order to improve the chances of effective disease control.

Professor Rogler, thank you very much for talking to us.
IX Gastro-Conference

October 4 – 7, 2017
Berlin, Germany

Congress Venue
Maritim Hotel Berlin
Stauffenbergstr. 26
10785 Berlin
Germany

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

Scientific Organization
G.T. Furuta, Aurora (USA)
I. Hirano, Chicago (USA)
A. Schoepfer, Lausanne (Switzerland)
H.-U. Simon, Bern (Switzerland)
A. Straumann, Olten (Switzerland)

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

Scientific Organization
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I. Dotan, Tel Aviv (Israel)
H. Herfarth, Chapel Hill (USA)
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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 in IBD
Madrid, Spain
March 31 – April 1, 2017

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

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Berlin, Germany
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Eosinophilic Esophagitis – Medical and Dietary Treatment
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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

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Scientific Dialogue
in the Interest of
Therapeutic Progress