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Clinical Hepatology Practice in 2016: From Science to Therapy

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Symposium 204
Clinical Hepatology Practice in 2016: From Science to Therapy

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A look at the liver: The latest developments in hepatology

Researchers and clinicians from across Europe and the USA met in Birmingham at the beginning of September 2016 for two days of discussion on the spectrum of diagnostics and treatment of chronic liver diseases, spanning from basic science to clinical practice.

Walking down Broad Street, turning down a side road and crossing one of the narrowboat canals, with screeching gulls sailing the skies above, it’s easy to imagine the crash of waves just out of sight. In reality Birmingham lies in the Midlands, in the heart of England; it’s the “city of a thousand trades” where the Industrial Revolution began, Britain’s second largest city, home to three universities, more than a million inhabitants and the International Convention Center (ICC). This was the venue for the 204th Symposium of the Falk Foundation, which brought together basic scientists, clinical researchers and gastroenterologists for discussions on current aspects of chronic liver diseases.

The ever-changing metropolis of Birmingham is a perfect symbol for the dynamic evolution of hepatology in recent years, an evolution which shows no signs of slowing down. And this is a necessary trend. There is a growing public understanding of the significance of liver diseases and related complications as causes of suffering and death, triggered not least by avoidable and lifestyle-related factors. Each year 2 million deaths from chronic liver disease are reported worldwide. The message that fatty liver disease is not normal, even though one in three Europeans suffers from steatosis, is gradually spreading. The relationship with metabolic syndrome is obvious. Is non-alcoholic fatty liver disease a disease or a syndrome? The symposium in Birmingham examined this question as well as current best practice in managing patients with non-alcoholic steatohepatitis.
One focal point of the symposium consisted in presentations and discussions on viral hepatitides, as hepatitis B and C form a large part of the burden of chronic liver disease worldwide. The enormous progress that has been made in the treatment of hepatitis C, making it possible to cure almost all patients with this form of viral hepatitis, must not distract attention from the fact that there remains a great deal of work to be done on hepatitis B. However, even for patients with chronic hepatitis B, research findings are leading to the development of new treatment approaches which require clinical evaluation. The symposium also saw intensive discussion of the question of the extent to which the rising number of hepatitis E diagnoses may indicate a problem which needs to be taken more seriously, as some of these infections very rapidly develop into cirrhosis. The pathogenesis of hepatitis E is crucial for the understanding of this issue.

The same is true of autoimmune liver diseases. Although primary biliary cholangitis (PBC), for example, is seen as a disease entity, every PBC patient is different. Instruments were presented which make it possible to better differentiate between these patients and stratify their treatment. It is expected that the currently limited treatment options will be expanded. The situation for primary sclerosing cholangitis (PSC) is very similar. Another important topic was cholestatic pruritus, which is often excruciating for the patient but extremely difficult to treat. It has a much more complicated pathophysiological background than has long been assumed. The good news is that it will be possible to develop differentiated treatment options as a result of this.

It is becoming increasingly clear how important immunological correlations are for the understanding and future treatment of chronic liver diseases. For example, immunotherapy solutions are indicated for hepatocellular carcinoma (HCC). However, HCC is also an example of the fact that regional treatment strategies remain very heterogeneous, in spite of consensus- and evidence-based recommendations by experts at an international level. It may be that the findings of scientists and clinical researchers on the diagnosis and treatment of chronic liver diseases need to be better communicated, when they are available. The Falk Foundation’s symposiums are an ideal platform for communication, as well as for scientific debates and networking.

Prof. G. Hirschfield
on behalf of the scientific organizing committee
What can be done to fight metabolic liver disease

In recent years, new scientific findings have significantly improved our understanding of non-alcoholic steatohepatitis (NASH), but there is still no NASH-specific treatment. Now it appears that some active ingredients which have already been approved or are in development do indeed have specific effects on the liver. At the same time, the need for lifestyle changes can’t be ignored.

The number of years of life lost due to complications of chronic liver diseases such as cirrhosis of the liver and liver cancer is constantly increasing. These cause more than 2 million deaths each year worldwide. As it is above all young people who are affected, the number of years of life lost is high. Cirrhosis comes in at fourth place in this regard, in comparison to other chronic, non-transmissible diseases, such as chronic obstructive pulmonary disease or diseases of the cardiovascular system, said I. Rowe, Leeds (Great Britain). Lifestyle is particularly significant here, specifically alcohol consumption, excess weight and a lack of physical activity. Metabolic liver diseases were one of the focuses of the 204th Symposium of the Falk Foundation in Birmingham.

Disease or syndrome?

C.P. Day, Newcastle-upon-Tyne (Great Britain), asked, for example, whether non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) are indeed diseases or should instead be referred to as syndromes.

A quarter of the global population has an NAFLD; in Europe this figure is believed to be as high as 33%. And this estimate may still be too low. “How can a disease be so widespread?” asked C.P. Day. NASH is the second most common reason for adults to be on the liver transplant list in the USA, after hepatitis C, and within a few years it is expected to rise to first place. Furthermore, in the Newcastle-upon-Tyne region, NAFLD is the most common cause of hepatocellular carcinoma (HCC). However, only a certain proportion of obese people develop NASH, liver fibrosis or other consequences. “For some patients NAFLD is absolutely a disease.” Patients with a poor prognosis should be identified early and rational treatment approaches should be developed for them, along with highly personalized therapies based on their individual pathophysiology, recommended C.P. Day. A key factor in prognosis, he said, is liver fibrosis, which is currently not adequately detected during diagnosis. Particular attention should be paid to this correlation.

Liver fibrosis is the decisive factor

It is not NASH in itself that determines liver-related morbidity and mortality, but the presence and the severity of liver fibrosis. There is a pressing need for non-invasive markers for both NASH and fibrosis of the liver.

It has already been shown that the Enhanced Liver Fibrosis (ELF) test, an algorithm of three fibrosis markers, makes it possible to predict the clinical prognosis of patients with chronic liver conditions. There are currently no specific treatment methods available for NASH patients.

Treatment is primarily based on lifestyle changes. Weight loss, supported by obesity specialists and nutritionists, is the most crucial factor, said P. Newsome, Birmingham (Great Britain), citing a prospective study involving almost 300 patients with histologically confirmed NASH. The authors were able to prove that the more weight was lost, the more the histological signs of NASH improved.
Liver fibrosis was observed to regress when weight reduction reached 10% or more. A meta-analysis of outcomes after bariatric surgery also shows improvements in steatohepatitis and fibrosis.

**Modern antidiabetics with antifibrotic effects**

For treatment of NASH, established medication treatment approaches for diabetes mellitus were tested. For example, in a recently published randomized and placebo-controlled double-blind study, the dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin led to a reduction in liver fat and liver fibrosis in NASH patients with prediabetes or newly diagnosed diabetes within 24 weeks. According to studies, the glucagon-like peptide-1 (GLP-1) agonist liraglutide reduces insulin resistance and lipotoxicity in NASH patients. Animal testing indicates beneficial metabolic effects produced by a combined treatment with GLP-1 and glucagon receptor agonists. The dual peroxisome proliferator-activated receptor (PPAR)α/δ agonist elafibranor reduced NASH inflammation in moderate to severe cases; the fibrosis did not develop any further. Furthermore, the sodium/glucose cotransporter 2 (SGLT2) inhibitor ipragliflozin improves hepatic steatosis, regardless of the patient’s weight loss.

**Multiple FXR ligands in clinical development**

In the randomized and controlled FLINT study (FXR Ligand Obeticholic Acid in NASH Treatment Trial), the farnesoid X receptor (FXR) ligand obeticholic acid, administered over 72 weeks, had beneficial histological effects in patients with non-cirrhotic NASH. The serum lipid values also improved. According to P. Newsome, the effects of various other steroidal and non-steroidal FXR ligands are also currently being investigated. In light of the visible successes of clinical trials, he spoke in favor of targeting certain patients for inclusion in trials. Treatment should primarily be provided to NASH patients with moderate to extensive fibrosis of the liver (F2, F3). In the future it is expected that NASH patients will be treated with combinations tailored to the individual. What is not yet known is how long this treatment will be necessary.
Clinical Hepatology Practice in 2016: From Science to Therapy

The spread and incidence of liver diseases are increasing, and in recent years hepatology has proven to be a dynamically evolving discipline. In Birmingham, convention attendees had the opportunity to catch up with the latest findings in the field. With the help of renowned experts, they were able to look to the future.

Data on disease burden

Liver diseases are a significant contributor to mortality worldwide. According to data gathered by the Bill & Melinda Gates Foundation, cirrhosis of the liver ranks fourth in terms of years of life lost to chronic, non-infectious diseases. I. Rowe, Leeds (Great Britain), presented current data which attribute 2 million deaths every year to complications from chronic liver diseases. Among these, hepatitis B is the predominant cause of mortality in Asia and sub-Saharan Africa; in Western Europe and in North and South America, it is hepatitis C. Half of all cirrhosis deaths worldwide are alcohol-related. There thus remains a need for preventative efforts in this field, too. One measure which seems to be effective here is managing alcohol prices.

While there have been significant achievements in the treatment and prevention of liver diseases in recent years, a better understanding of the natural course of some liver diseases is essential for further progress, for example the circumstances under which non-alcoholic fatty liver disease (NAFLD) leads to fibrosis or cirrhosis.

Reversing the process of liver fibrosis

Fibrosis, which is a gradual restructuring of the liver tissue as a result of constant inflammation, does not necessarily progress over time. It is a dynamic, potentially bidirectional process, emphasized J. Iredale, Bristol (Great Britain). Liver fibrosis and even cirrhosis are potentially reversible. If the driving stimulus is removed, liver remodeling takes place. Liver fibrosis must partly be understood as a failure of the matrix-degrading processes. It is therefore important to identify the mediators of matrix degradation and to gain an understanding of the underlying mechanisms. It may then be possible to develop serum markers for diagnostics on this basis. Macrophages seem to play a central role here as a source of metalloproteinases. The “pregnancy hormone” relaxin has proven to be a regulator in the balance of metalloproteinases and their inhibitors. Experimental data suggest that it may be significant as an antifibrotic therapy and as a means of lowering portal blood pressure.
New imaging techniques

Quantitative magnetic resonance imaging (MRI) methods create possibilities for examining the liver non-invasively and gathering disease-specific biomarkers. According to G.P. Aithal, Nottingham (Great Britain), it is thus possible to assess liver fat, iron accumulation and the extent of liver inflammation or tissue damage in the whole organ without the need for breath holds or the administration of contrast dyes. High-resolution MRI makes it possible to promptly and repeatedly evaluate the effects of therapeutic interventions, as well as the progression of portal hypertension. A scan can be used to determine multiple biomarkers at the same time. Studies have shown MR-based liver elastography to be at least as sensitive as transient elastography. For research purposes, use is made of 7-Tesla ultra-high field scanners, which are a highly sensitive tool for differentiating inflammatory changes from fibrotic ones and determining the percentage of different types of fats. And 13C MR spectroscopy enables new approaches to observing liver metabolism in vivo.

Genes or environment – Which is more important?

There is no doubt that genetic factors play an important role in the development of various liver diseases; they influence the severity of the disease as well as the patient’s prognosis. Modern sequencing technology and genome-wide analyses now allow detailed insights. However, weighing the diversity of environmental factors in order to assess causal and associative correlations is a complex business. It is also necessary to consider a variety of interactions between the organs, such as between the liver and intestine, said T.H. Karlsen, Oslo (Norway). It is increasingly believed that environmental factors play a dominant role in the development of complex liver diseases. Yet it is often not possible to make a clear-cut distinction between genetic and environmental influences, as they both contribute to disease progression, and do so interdependently.

Hepatitis E – A new epidemic or increased awareness?

Hepatitis E has long been seen as a self-limiting disease associated with travel. However, more and more infections are now being observed. In Germany the number of cases reported each year has risen from less than 50 in the early 2000s to more than 1,200 in 2015. Worldwide there are believed to be 70,000 hepatitis E deaths every year, predominantly in Africa and Southeast Asia. Should this be seen as a new epidemic, or is it simply that awareness of the RNA virus, which was identified in 1983, has increased? The virus is found in many animals, including domestic pigs. Hepatitis E is therefore a zoonosis. However, it is not clear which meat products are the main sources. Of the five genotypes known, it is primarily genotype 3 which is widespread in Central Europe, reported H. Wedemeyer, Hannover (Germany). However, studies from France, for example, have shown that seroprevalence rates for the hepatitis E virus (HEV) differ very significantly between regions. People who have frequent contact with pigs show increased seroprevalence. In China, genotype 4 has also been found in cow’s milk; this is not the case in Germany. Transmission via blood products is possible, too.

Hepatitis E infections typically take a mild to moderate course and are self-limiting. Fulminant HEV infections are observed in patients already suffering from chronic liver disease, in immunocompromised patients and in pregnant women. 1–4% of organ transplant recipients in Europe go on to develop a chronic hepatitis E infection, which can lead to cirrhosis within just 1–2 years, warned H. Wedemeyer. But the liver is not the only organ targeted by the virus. The virus is also found with above-average frequency in patients with neurological conditions such as Guillain-Barré syndrome and in patients with pancreatitis, thyroiditis and hematologic diseases. Experiments have confirmed that HEV can replicate in a variety of extrahepatic cell lines.

Chronic infections are treated with ribavirin. However, there are many contraindications and the treatment exerts selective pressure, which favors HEV variants that replicate more efficiently. In China, there is already a vaccine against HEV. According to H. Wedemeyer, work in the coming years must focus on identifying potential reservoirs of the virus, better understanding the pathogenesis, identifying high-risk patients and developing alternative antiviral drugs. It must also be discussed whether all blood products should be tested for HEV RNA in the future. This is currently handled differently in different regions.
**Viral hepatitis**

**Lessons from HCV research**

The historical development of hepatitis C treatment is an example of how basic research findings have been successfully carried over into medical practice within just 25 years. In the opinion of J.A. McKeating, Birmingham (Great Britain), in vitro replication models are essential for the development of direct-acting antivirals (DAAs) and for the identification of virus escape mutations. Although DAAs are now available for hepatitis C, there is a need for vaccines against the disease. For effectiveness tests there are currently only a small number of animal models available. Another problem is the high level of genetic diversity of the viruses. It remains unclear whether successful treatment of an HCV infection reduces the risk of liver cancer. It cannot be ruled out that the infection leaves epigenetic footprints which represent a pre-cancerous risk factor. There thus remains a significant need for new treatments, for patients with both virus-related and non-virus-related HCC.

**Why anti-HCV treatment is so efficient**

There are various reasons why it is possible to eliminate HCV so effectively, explained R. Bartenschlager, Heidelberg (Germany). The RNA virus does not integrate into the host cell genome and cannot form a reservoir – a clear difference from the hepatitis B virus or human immunodeficiency virus (HIV). HCV must replicate permanently in order to remain in the infected host. Furthermore, the virus particle has an extremely short half-life of just 45 minutes. Effective inhibitors of the dynamic replication process thus lead to a high elimination rate. This occurs as a result of the inhibition of enzymes that are crucial for replication, or of other proteins, such as NS3/4A, the RNA-dependent RNA polymerase NS5B or the non-structural protein NS5A. The high plasticity of the virus and its frequent mutations can cause resistances and cross-resistances to develop, which can be avoided through a combined attack on multiple molecular targets.

**Antiviral treatment in patients with renal insufficiency**

DAAs have also revolutionized the treatment of patients with HCV infections and renal insufficiency, said M.-C. Londoño, Barcelona (Spain). Renal function must be taken into account during treatment with medication for 10–16% of all HCV patients due to cryoglobulinemia, diabetes mellitus or HCV-associated glomerulonephritis. HCV patients on hemodialysis have a relatively high mortality rate. Recently, in the RUBY-I study, a combination therapy based on ombitasvir was able to achieve a response rate (SVR12) of 90%, lasting over 12 weeks, in patients with renal insufficiency who were infected with genotype 1. A similar outcome was achieved over 12 weeks in the C-SURFER study using the combination of grazoprevir and elbasvir. The treatments proved to be generally well-tolerated.
New approaches to treating chronic hepatitis B

Until now it has not been possible to cure chronic hepatitis B, because transcriptionally active virus DNA remains present in the nuclei of the host organism’s cells. Chronic HBV infections cause around 1 million deaths from cirrhosis and liver cancer worldwide every year. F. Zoulim, Lyon (France), is convinced that improved treatments with the potential to provide a cure will be available within the next 10 years. For example, entry inhibitors which block the penetration of HBV into hepatocytes are in clinical development. Other efforts are focused on cccDNA (covalently closed circular DNA), an annular DNA structure that acts as a virus reservoir. The aim is to inhibit factors in the creation of cccDNA to prevent this from forming. Further strategies include attacking the virus capsid or using siRNA (small interfering RNA) in attempts to exploit the mechanism of RNA interference for the targeted switching-off of viral genes. It appears useful to combine DAAs with immunotherapy.

Reactivating HBV during immunosuppressive therapy

The natural course of a chronic HBV infection is fundamentally determined by the interaction with the immune system – most patients’ immune systems manage to suppress virus replication. During immunosuppressive therapy, hepatitis B may be reactivated. This can be prevented through treatment, but close attention is required on the part of doctors who use immunosuppressants, particularly oncologists and rheumatologists, emphasized J.J. Feld, Toronto (Canada). There is a lack of consensus on which screening strategies are optimal, particularly with regard to patients who are HBsAg-negative but anti-HBc-positive. Even though the risk of becoming HBsAg-positive again is low (reverse seroconversion), the consequences can be serious, especially as B-cell-depleting treatments such as with rituximab become more common. J.J. Feld spoke in favor of treating and closely monitoring high-risk patients who are positive for anti-HBc.

The immunology of viral hepatitis

The body’s immune response influences the course of viral hepatitis. Whether hepatitis viruses can be eliminated also depends on non-specific and acquired immune responses. A central role is played by CD8-positive T cells, said R. Thimme, Freiburg (Germany). CD8-positive T cells are capable of destroying virus-infected cells. They also prevent the virus from replicating by releasing cytokines which have an antiviral effect. However, without the support of CD4 cells, these killer cells are quickly used up. This phenomenon seems to be an important reason why HBV and HCV can persist in the body. CD8-positive T cells are thus a promising objective for immunotherapeutic approaches to HBV infection, for example via a PD-1 blockade, and for the prevention of HCV infections. The goal of these therapeutic approaches is to stimulate the body’s own antiviral immunity by overcoming the depletion of certain T cell populations.

Experiences before and after liver transplantation

Positive results have also been achieved with interferon-free treatments in HCV-infected patients before or after liver transplantation (LTx). In post-LTx patients, various combinations of DAAs have achieved over 95% effectiveness against genotype 1, reported D. Mutimer, Birmingham (Great Britain), and over 80% in patients infected with genotype 4. For some patients on the transplant list, the anti-HCV treatments are continued up until the transplant takes place. DAA treatment improves the MELD (Model for End-stage Liver Disease) score used for classifying disease severity; some patients were able to be removed from the transplant list. Relapses after transplants appear to be rare, if the polymerase chain reaction (PCR) findings were negative for at least the 4 weeks immediately before the transplantation. But even when HCV does recur after a transplant, most patients have a good chance of recovery.

In brief

Experiences before and after liver transplantation

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Autoimmune liver diseases

Primary biliary cholangitis: What comes after UDCA?

For patients with primary biliary cholangitis (PBC), ursodeoxycholic acid (UDCA) is the first-line treatment. 60–70% of patients respond well to UDCA. In around a third of patients, the effect weakens over the course of the disease or they are non-responders. The biochemical response of every patient should thus also be checked in the long term, recommended D.E.J. Jones, Newcastle-upon-Tyne (Great Britain). This could be done using either the Barcelona criteria, or the Paris-I or Paris-II criteria. The farnesoid X receptor (FXR) agonist obeticholic acid (OCA) has been approved in the USA and recently also in Europe for patients with insufficient UDCA response. In two randomized studies, OCA proved to be effective for non-responders in doses of 10–50 mg/day; in some cases UDCA and OCA were combined. Further FXR agonists are currently in development. There is still a need for suitable treatment options for pruritus and fatigue in particular.

Primary sclerosing cholangitis – Improving description of phenotypes

The very high co-morbidity of primary sclerosing cholangitis (PSC) and inflammatory bowel diseases (IBD) could indicate that intestinal involvement suggests a genetically different disease entity from classic IBD, according to G. Hirschfield, Birmingham (Great Britain). Other autoimmune diseases such as Sjögren’s syndrome or Hashimoto’s thyroiditis also appear concomitantly. The clinical appearance of PSC varies greatly – it may be asymptomatic, or slowly or rapidly progressive. There are also contributing genetic, epigenetic and environmental factors. The clinical phenotypes of the disease and the individual risks must be better described than is currently the case, in order to enable more targeted therapeutic approaches. At the same time, prospective studies are increasingly being initiated which enable science-driven pharmaceutical development and target different pathomechanisms of the disease.

Findings on the development of pruritus

Pruritus often manifests in patients with cholestatic diseases in particular, and is detrimental to their quality of life, sometimes dramatically so. A part is played in this by mechano-insensitive nociceptors whose signals are transported via the posterior horn of the spinal cord to the thalamus and eventually reach the primary sensory cortex and further regions of the brain. Pain has an inhibitory effect on pruritus which is transmitted via the spinal cord. Lyosphosphatidic acid (LPA) has been identified as an important mediator of cholestatic pruritus, said U. Beuers, Amsterdam (The Netherlands). There are also other pruritus-specific neurotransmitters and receptors. Furthermore, there are molecules such as bile acids or endogenous opioids which have more modulating effects. The enzyme autotaxin (ATX) is a catalyst for LPA production; increased ATX activity is specific to cholestatic pruritus. ATX inhibitors and LPA receptor blockers are thus possible alternatives to current therapy recommendations, but are not yet available for clinical trials. The results of the FITCH study on bezafibrate are expected in a year’s time. Also being investigated are the effects of ASBT (apical sodium-dependent bile acid transporter) inhibitors and PPAR (peroxisome proliferator-activated receptor) agonists.

Developing more rational treatments for AIH

The current treatment of patients with autoimmune hepatitis (AIH) is rather non-specific. Understanding the pathomechanisms offers the possibility of developing rational and specific treatment approaches and in particular of inhibiting fibrosis. Antigen-specific CD4-positive T cells seem to be a key factor in AIH, which could be used to generate an antigen-specific tolerance, said A.W. Lohse, Hamburg (Germany). On the other hand, there have long been monoclonal antibodies on the market that target a number of the cytokines involved. Tumor necrosis factor (TNF)-α is overexpressed in AIH patients in particular in intrahepatic T cells, and infliximab has already proven to be a valuable third-line treatment for these patients. The TNF-α inhibitor should thus be tested as a potential first-line treatment for this indication.
Hepatocellular carcinoma

Clinical practice guidelines are often not followed in HCC cases

Hepatocellular carcinoma (HCC) is the third most common cause of death among all cancers worldwide. The patient’s prognosis deteriorates dramatically from the BCLC (Barcelona Clinic Liver Cancer) stage B. The global BRIDGE study using data from more than 18,000 patients confirmed that treatment approaches differ regionally despite the existence of international clinical practice guidelines. For example, in stage C, the tyrosine kinase inhibitor sorafenib is used relatively infrequently. There is a tendency to use transarterial chemoembolization (TACE) too frequently, observed P.R. Galle, Mainz (Germany).

Many attempts at treatment with medication have failed in clinical trials. One exception is the international RESORCE study, which achieved a median overall survival time of 10.6 months using regorafenib (placebo: 7.8 months). Also encouraging are immunotherapy approaches, which are assessed predominantly in combination with standard treatments. Clinical trials supported by biomarkers should make it possible to define particular subgroups of HCC patients who will benefit from specific therapies.

The biology of liver cancer evolution

In HCC, cells with stem cell properties can be found, known as cancer stem cells (CSCs). CSCs are seen as being responsible for the initiation and spread of the tumor and for cancer relapses. The working group under S.S. Thorgeirsson, Bethesda (USA), proved that every cell within a hepatic cell line can in principle be transformed to become malignant and reprogrammed to become a CSC. Hepatic progenitor cells are more easily transformed than hepatoblasts and mature hepatocytes. Once they have become malignant, the cells develop into aggressive liver tumors. Their histopathology does not make it possible to draw any conclusions about the original cell; every transformed cell can generate a broad spectrum of tumor subtypes. However, similarities can be observed between the subtypes in terms of gene expression. In the future, this will provide oncologists with a tool enabling them to classify morphologically different primary tumors according to phenotype.

Immunological approaches to HCC

At present immunotherapy solutions for HCC patients are being evaluated. This is based on the finding that the body’s immune responses influence the prognosis. It was possible to identify spontaneous tumor-induced immune responses that target cancer growth. Ablative treatments change the number, phenotype and function of various immunological cell populations; this in turn correlates with the probability of survival, according to T.F. Greten, Bethesda (USA). When intrahepatic CD4-positive T cells die as a result of oxidative stress, this accelerates tumor growth. On the other hand, vital CD4- and CD8-positive T cells disrupt tumor growth. Attempts are being made to exploit these correlations. Initial clinical trials have achieved encouraging results in HCC patients using immune checkpoint inhibitors. Other experiments include adoptive immune cell transfer and vaccine strategies.

Microbiome: Distinguishing between hype and hope

The human microbiome is described as a kind of extracorporeal organ which is roughly as complex as the liver. In fact, it is probably many times more complex than this. The intestinal microbiome is connected to the liver physiologically and pathophysiologically in a number of ways, explained M. Pallen, Coventry (Great Britain). Bile acids produced in the liver influence the intestinal bacteria; microbial products reach the liver quickly via the portal vein. The barrier function of the intestine, energy homeostasis and the control and induction of inflammations result from this communication. The intestinal microbiome is thus involved in liver diseases in a number of different ways. In NAFLD patients, intestinal bacteria are involved in obtaining as much energy as possible from the food consumed. In the case of chronic alcohol abuse, microbial metabolic products increasingly reach the liver via the disrupted intestinal barrier and the portal vein, and once there, trigger immunological responses. Attempts are being made to influence these processes through treatment with antibiotics, pre- and probiotics and fecal microbiota transplants. It has however proven difficult to generate reproducible results from studies and to gain a consistent image of this “astronomically complex” situation. Correlation is not causation, warned M. Pallen; not everything that is published should be believed, and research requires a healthy dose of skepticism.
Liver disease complications

Reducing the danger of variceal bleeding
According to F. Nevens, Leuven (Belgium), there are indications that a daily dose of 12.5 mg of the beta-blocker carvedilol, which also inhibits α-adrenergic receptors, provides better protection from varicose vessel ruptures in cirrhosis patients with high portal blood pressure than other non-selective beta-blockers. In a current meta-analysis, carvedilol achieved a more significant reduction in venous pressure than propranolol or nebivolol. In addition, it slows the progression of small to large esophageal varices. In patients with recurrent ascites, beta-blockers should be used with caution, as this can lead to hemodynamic and other complications. New experimental treatment strategies include antifibrotics such as obeticholic acid or simvastatin, which also affects liver fibrosis. With regard to the prevention of portal vein thrombosis, the medication enoxaparin has proven to improve prognosis. In acute, recurrent cases of variceal bleeding, self-expanding, covered esophageal stents seem to be superior to the balloon tamponade.

Recognizing acute-on-chronic liver failure
Acute-on-chronic liver failure (ACLF) refers to acute hepatic decompensation in patients with pre-existing liver disease, accompanied by organ failure and a high mortality rate. ACLF should be distinguished from acute decompensations without further clinical issues. The CLIF (chronic liver failure) ACLF score can be used to make the diagnosis, determine the severity of the disease and assess the prognosis, explained R. Jalan, London (Great Britain). The CLIF-C OF score should make it comparatively easier to detect organ failure and improve applicability in everyday practice. It encompasses biomarkers such as bilirubin, creatinine, clotting (INR), mean hemodynamic pressure and assessment of respiration. Moreover, the CLIF-C AD score can identify patients with acute decompensation who do not (yet) have ACLF but are likely to develop it.

Ascites management in cirrhosis patients
Half of all patients with compensated cirrhosis of the liver develop ascites within 10 years, said A. Cardenas, Barcelona (Spain). The usual treatment fails for approximately one in ten patients with ascites. The treatment of choice is then large-volume paracentesis for intra-abdominal relief. Volume replacement with albumin is also necessary; this not only improves the colloid osmotic pressure but also has a number of other benefits such as antioxidant, hemostatic, endothelium-stabilizing and immunomodulating effects. Some patients benefit from the insertion of a transjugular intrahepatic portosystemic shunt (TIPS). However, obstructions and a high incidence of encephalopathy must be taken into account. In a pilot study, midodrine led to improvements in systemic hemodynamics in patients with therapy-refractory or recurrent ascites, which also led to increased survival rates compared to standard treatment. The ALFA pump, which transports ascites fluid to the bladder, is not yet supported by sufficient experience and there are concerns about its safety.

Nutrition and liver health
The liver is vital for the body’s ability to process food and convert it into energy that the organism can use. In the opinion of A.A. Jackson, Southampton (Great Britain), it should be explained to overweight patients that even moderate weight loss has many beneficial effects: Fat metabolism is improved, insulin sensitivity is increased, the risk of thrombosis is reduced, inflammatory markers decrease and vascular endothelial function improves. In stressful situations such as during infections or traumatic events, specific deficiency symptoms may occur which can sometimes be accompanied by cell damage and dysfunctions. For the treatment of malnutrition there are clinical practice guidelines and recommendations, such as the International Malnutrition Task Force (IMTF). The main goals are to regain control of the metabolism with an adequate supply of macronutrients and micronutrients and to remove the causes underlying the malnutrition. This must take place in the correct sequence with the organ systems being considered in their entirety, in order to avoid further damage. One problem here is that there are no good quality criteria for this and it is currently unclear exactly how deficiencies and corresponding interventions affect cellular functions.
Perspectives in hepatology

Conserving donor livers

Transplant livers can be stored and transported for several hours in cooled preservative solutions safely and at low cost. Disadvantages are metabolic depletion, the inability to predict organ function in the recipient, and ischemic reperfusion damage. There are various approaches for improving liver preservation before transplantation, said P. Dutkowski, Zurich (Switzerland). This includes working with different temperatures and degrees of oxygenation. Attempts are being made to simulate in vivo conditions using devices for normothermic perfusion, which makes it possible to improve the potential usability of the donor organ. A recently published British pilot study gives grounds for optimism that in the future, normothermic perfusion will allow more transplants to be made available. Attempts are also focusing on being able to preserve donor organs outside of the body for longer than three days and on making even at-risk organs suitable for transplantation. In part this involves combining different organ preservation methods.

Requirements and necessities

In the last 30 years new diseases such as NAFLD or hepatitis C, D, E have been defined and new treatments have been developed, from liver transplantation to direct-acting antivirals to TIPS. What is needed today, according to D.H. Adams, Birmingham (Great Britain), is above all antifibrotics and disease-modifying medications for patients with autoimmune diseases of the liver, methods for repairing and regenerating the organ and treatment options for treating liver carcinoma and for managing liver failure. But the options already available must also be implemented in practice, for example with a view to preventing hepatitis B, NAFLD and ALD or curing hepatitis C patients. There is still no adequate scientific understanding of various disease processes such as virus persistence in the body, autoimmunity and carcinogenesis. Progress is expected on the basis of innovative technologies and new discoveries. There is also a greater need than ever for good biostatisticians and bioinformaticians, in order to be able to handle large amounts of data and to implement clinical working processes which are improved through interdisciplinary collaboration. And research findings must be rapidly carried over into daily practice.
From the New and Complex Concepts to the Real Patient: Science and Clinic in IBD

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Spain

Scientific Organization
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A. Dignass, Frankfurt (Germany)
J.P. Gisbert, Madrid (Spain)
F. Gomollón, Zaragoza (Spain)
Poster prizes: Award for young scientists

It was not easy for the panel to decide who should receive the poster prize: “We saw a large number of posters which would have been worthy winners,” said Prof. R. Thimme, Freiburg (Germany), at the award ceremony. He thanked everyone who took part in the popular exhibit, which attracted a total of 63 independent contributions.

The prizes at the 204th Symposium “Clinical Hepatology Practice in 2016: From Science to Therapy” were awarded as follows:

Dr. Wafa Khamri, London (Great Britain), and colleagues were awarded 1st prize by the panel. This working group identified regulation errors in circulating CD4-positive T cells in patients with acute liver failure, which make it possible to understand why the adaptive immune responses of these patients fail. They propose plasmapheresis as a potentially immunomodulating treatment, in order to support immune responses in patients with acute liver failure.

Dr. Philipp Lutz, Bonn (Germany), and colleagues received 2nd prize for a method for differentiating between infective and non-infective forms of ascites in patients with cirrhosis of the liver. To achieve this, they determined and compared the number of polymorphonuclear (PMN) cells in ascites in 269 patients and prospectively monitored the participants for one year. They found differing values for patients with non-infective ascites, bacterial ascites and spontaneous bacterial peritonitis (SBP). This could help to identify patients without SBP who are at risk of developing bacterial ascites.

Dr. Hannah C. Jeffery, Birmingham (Great Britain), and colleagues received 3rd prize for explaining a mechanism that triggers the dysfunction of regulatory T cells ($T_{reg}$) in autoimmune liver diseases. According to their findings, an interleukin-2 supplement combined with $T_{reg}$ therapy may help to restore immune homeostasis in patients with inflammatory and autoimmune liver diseases.
“Liver disease can have many pathways to the same injury”

The reasons for liver disease range from congenital to acquired factors. We asked Prof. G. Hirschfield, Birmingham (Great Britain), one of the scientific organizers of the international symposium, what is more important: Genes or environment?

Editor: Professor Hirschfield, I would like to ask you to do a thought experiment: Take a representative cohort of the Birmingham population and beam it back to stone age, including yourself. You will be able to compare the epidemiology of liver disease to stone age men. What do you think you will find?

Prof. Hirschfield: A very clear difference will be that we now have a lot more lifestyle liver disease than we would have had in the past. There is a big difference in terms of obesity-related liver diseases; the hunter-gatherer way of life was of course much healthier in many ways, although with trauma and infection they presumably didn’t live as long as we do now. Thus, I presume they didn’t develop the liver diseases associated with the metabolic syndrome! On the other hand stone age men were much more prone to infectious liver diseases, some may have been acute and others I guess chronic. I don’t know if we would have seen autoimmune liver diseases: We certainly see them now with 5–10% of our patients having liver injury as a result of immune damage. We still don’t know the triggers of these diseases. Of note, something we have learned is that some of the genetic risk factors associated with disease today were actually present thousands of years ago as well.

What about genetic factors?

Genetic factors are risk factors for developing a disease. What we have learned during this conference is that the expression of genetic risk requires the presence of the relevant environmental factors. It is the fish-out-of-water context: Genes in the wrong context may have no impact at all. Those pathways would have existed and those risk factors were there, but it’s quite possible that they had no impact in stone age civilization, because lifestyle and environmental challenges were distinct.

There was some discussion at the conference about how to weigh the influences of genetic and environmental factors influencing hepatic diseases.

Without doubt the environment remains a key and most important factor. Our genes are only a reflection of us and how we live. That is really an example between stone age and now: We would have a lot lower cholesterol levels, we would eat a lot less and we would do a lot more of exercise. And so our bad genes may not have the opportunity to express themselves.
In oncology definitions of diseases are gradually changing in line with the growing knowledge about the pathophysiology, especially regarding genetic markers of cancer development. There is much more differentiation of disease entities. Would you expect something similar in hepatic diseases?

That is certainly what I hope, to be much more molecular and precise about how we diagnose and stage and stratify liver diseases. I don’t know whether it will be that easy to do as these are complex multifactorial diseases. Cancer I guess might be thought of a bit like an infectious disease, where the infection gets stronger as it becomes more resistant to attack by the body. Simplistically, cancer arises from a series of mutations that lead to the aberrant behavior of cells. Complex diseases like inflammatory liver disease can have many pathways to the same injury. We can look down a microscope at liver tissue and see patterns of injury like fatty change, interface hepatitis and fibrosis that can result from many insults and pathways. So it is harder to predict if we will be in as good a position to refine molecular signatures for liver diseases that allow us to get to so-called precision and personalized medicine. However, the field moves so fast and technology is so good that there won’t necessarily be one message that we are looking for. It is just going to be the composite of lots of messages. Basically, we need to measure as many facets of biology as possible, and use complex computer technology to teach us about new patterns.

Disease definitions still are very organ-related, but there is a lot of crosstalk between diseased organs. How will that change our understanding of liver diseases?

You are absolutely right. In liver diseases we have got a poverty of disease names, which is almost certainly wrong, in the sense that we are missing a lot. We are going to have to work to do that better. And it might be not just liver disease, it might be metabolic disease or an autoimmune disease affecting multiple organs. Because of how a disease presents itself and because of our historical thoughts we classify it narrowly into pigeon-holed liver diseases. The new technologies will allow us to breakdown those barriers.

It is often late when the doctor sees the liver patient for the first time and the organ already shows structural changes. Now we have learned that liver fibrosis and even cirrhosis can be reversible. What is your estimation of chances for these patients?

That is exactly what we are looking for and it is a challenge to implement. But the technology is improving to detect disease early. And we want all of our patients to be picked up before they have got significant fibrosis. Essentially, across liver disease having fibrosis is invariably associated with a bad outcome. We are talking about dynamic processes, and even cirrhosis is dynamic. That gives us the chance to shift the balance in the right direction and look to see reversal of fibrosis.

Is there a point of no return?

That is hard to define and very disease-specific. Without doubt there are patients who get to the point where their liver is not going to function without transplantation. And even if you take away the injury, the amount of damage is too much and it doesn’t get better. We have learned in hepatitis C, where we have brilliant therapies now, that it can still be too late for some patients, and additionally deleting hepatitis C won’t delete cancer risk. We hope that this will become less of a problem over time. Therefore one therapy for a disease is not enough.
You have mentioned autoimmune diseases. What do you think are the therapeutic strategies beyond ursodeoxycholic acid (UDCA) in primary biliary cholangitis (PBC)?

UDCA is a good therapy for lots of patients, particularly so when dosed correctly, and when given in ways that optimize patient compliance. There is now a new drug licensed by the U.S. Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) called obeticholic acid, for patients with PBC classified as UDCA treatment failures. For a group of patients, who don’t respond to therapy, this is excellent news. There is good biochemical evidence for improvement and we hope over time it will show that it slows down the disease. Obeticholic acid still tackles the bile acid pathway rather than tackling the underlying disease mechanisms which is a mixture of autoimmune injury and cholestasis. So beyond obeticholic acid, and even more exciting there may be other farnesoid X receptor (FXR) agonists and other drugs better in immunomodulation in the future years. So there is a lot of opportunity to further improve treatment in better targeting cholestases and the immune system.

What about combinations?

At the moment I would see obeticholic acid as an add-on therapy. The logic would be a better anticholestatic drug and a better immune drug all at the same time. But this takes a lot of effort, because we are talking about rare diseases which are slowly progressive.

The Global PBC Study Group has developed a scoring system to predict outcome, the GLOBE score. Is that a score doctors can use in daily practice?

I think it is. The message for doctors is: We want you to understand that every patient is different. One named disease is not equal to one disease or one disease cause. The GLOBE score is great, because it is very simple to calculate. It helps you to understand, where your PBC patient fits in that risk register and if UDCA is enough or if you need a different treatment. It is all about management of the disease. And it is very important for patients to understand where they are headed.

Another devastating hepatobiliary disease is primary sclerosing cholangitis (PSC). What is needed to progress with therapies for these patients?

PSC is a very difficult disease with a lot of confounding factors, characterized by strictures, inflammation and malignancy risk. There is a strong comorbidity between PSC and inflammatory bowel disease, but also concurrent autoimmune diseases, reduced bone density, pruritus and fatigue. It can range from asymptomatic and slowly progressive to rapidly evolving disease. It is now recognized that PSC is more common than once imagined. We are still unraveling the disease mechanisms and there remain lots of ideas. In terms of therapy we need a multifaceted approach. New drugs such as FGF19 analogs inhibit bile salt synthesis, inhibition of the apical sodium-dependent bile acid transporter (ASBT) may have a role in the future, and opportunities like norUDCA, which is a derivative of UDCA, seems to be quite promising. At the same time there are trials focused on an antifibrotic effort and there are lots of efforts around treating the colitis and lymphocyte tracking to the liver. So it is a hard but important nut to crack, but much more opportunity than we have ever had and much more novel choices of drugs, which again come back to cholestasis information and fibrosis.

Professor Hirschfield, thank you for this interview!
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