XXIII International Bile Acid Meeting: Bile Acids as Signal Integrators and Metabolic Modulators

The Challenge of Drug-Induced Liver Injury (DILI)

Challenges and Management of Liver Cirrhosis
Cover

The picture shows isolated, cultured biliary epithelial cells (cholangiocytes) from mouse tissue. The cell membranes have been stained with phalloidin-FITC in green while the nuclei have been made visible using a blue dye. The primary cilium (shown in pink) acts as a sensory cellular antenna, which in vivo reaches from the apical plasma membrane into the bile duct and is able to measure the flow and composition of bile. The bile salt receptor TGR5 (stained in red) can be detected in these cilia.


Portrait photos and photos of poster prize winners on pages 13 and 31

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VII Falk Gastro-Conference

XXIII International Bile Acid Meeting: Bile Acids as Signal Integrators and Metabolic Modulators
The Challenge of Drug-Induced Liver Injury (DILI)
Challenges and Management of Liver Cirrhosis

Foreword

How can bile acids be used to treat illness? How high is the risk posed by drug-induced liver injury and what can be done to prevent serious complications in liver cirrhosis? These are just some of the questions that were discussed at the VII Falk Gastro-Conference 2014 in Freiburg.

As clearly demonstrated by the fundamental research conducted in recent years, bile acids are not only needed for the digestion and absorption of fats, they also act as signalling molecules and enterohepatic hormones. It may, therefore, be possible to use bile acids and their derivatives as a treatment in many, previously unthought of, indications. Since this knowledge came to light, bile acid research has become far more fascinating, as proven by the papers presented at Falk Symposium 194, the XXIII International Bile Acid Meeting entitled “Bile Acids as Signal Integrators and Metabolic Modulators”. Scientists are pinning high hopes on norursodeoxycholic acid as an effective treatment for primary sclerosing cholangitis, the black box of hepatology for which neither satisfactory treatment nor comprehensive knowledge of the pathogenesis exist to date. Its direct anti-inflammatory and antiproliferative properties also make its use in indications beyond cholestatic liver diseases, such as NASH, conceivable. FXR agonists such as obeticholic acid, whose clinical use in primary biliary cirrhosis and NASH is the subject of current research, and TGR5 agonists, for which research is still largely in its infancy, are of similar interest.

Drug-induced liver injuries are often underestimated. At the same time they are of major importance for patients, doctors, the pharmaceutical industry and drug authorisation bodies alike. The Falk Workshop entitled “The Challenge of Drug-Induced Liver Injury (DILI)” looked at this subject in detail, and the problems quickly became clear. Amongst other things, DILIs are difficult to diagnose, and doctors then need to distinguish between dose-dependent and idiosyncractic DILIs and react to them accordingly. Since the damage caused by liver cirrhosis cannot be reversed, the onset of liver fibrosis should be prevented if at all possible by effectively treating the underlying disease. If the cirrhotic process has already begun and complications occur, such as portal hypertension, hepatic encephalopathy, hepatorenal syndrome, spontaneous bacterial peritonitis or hepatocellular carcinoma, treatment must be swift. There are a host of ongoing studies investigating how these problems arise and which measures benefit patients most, many of which were presented and discussed at Falk Symposium 195, “Challenges and Management of Liver Cirrhosis”.

Scientific Organizers of Falk Symposium 194
Prof. M. Trauner, PD Dr. V. Keitel, Prof. D. Häussinger, Prof. U. Beuers (from left to right)

Scientific Organizers of Falk Symposium 195
Prof. J. Bosch, Prof. F. Wong, Prof. M. Pinzani, Prof. A.L. Gerbes (from left to right)
Reducing bile acids to mere agents of fat absorption and digestion is shortsighted. This is because they also act as hormones and signal integrators, the effects of which can be utilised for therapeutic purposes. Promising newcomers to the field include norursodeoxycholic acid and obeticholic acid, though they bear a heavy burden of expectation.

For a long time, bile acids generated little excitement in medicine. Only in recent years has awareness gradually grown of the therapeutic potential lying untapped here, and of the fact that targeted research into these substances may hold the key to yet unsolved problems of hepatology. Much of this is still in its infancy, that is to say in the depths of basic (animal-based) experimental research. Nonetheless, some active ingredients have managed to make the transition from the lab to clinical research, and one or two substances are already well along the road to authorisation.
**UDCA: new competition for an ‘old friend’**

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid that has been used with great success in treating primary biliary cirrhosis (PBC), is an old friend in bile acid research. Despite this, the latest studies have given us a more precise understanding of one of its mechanisms of action: UDCA is able to stabilise the protective biliary HCO$_3^-$-umbrella – which is defective in PBC owing to insufficient expression of the bicarbonate transporter AE2 – and thus protect the bile duct cells from failure.

Current investigations conducted by U. Beuers, Amsterdam (The Netherlands), have now shown that this bicarbonate umbrella is stabilised by a glyocalyx, which ensures that constant pH conditions are maintained. If the umbrella is defective, the cholangiocytes become more susceptible to bile acid-induced apoptosis (Fig. 1).

**Fighting fatty liver disease and atherosclerosis**

Yet as successful as UDCA is in treating PBC, the results in primary sclerosing cholangitis (PSC) are extremely disappointing. According to M. Trauner, Vienna (Austria), the clinical characteristics of the latter disease still remain something of a black box in hepatology. However, success may now be achieved using a small chemical trick, namely shortening the side chain of UDCA by just one methyl group.

This norursodeoxycholic acid induces particularly effective bicarbonate-rich hypercholeresis. As a result of both this and other favourable effects, such as a direct anti-inflammatory, anti-proliferative and anti-fibrotic action, it is becoming a beacon of hope for PSC. A phase II study is about to be completed, and M. Trauner also presented exciting results from animal experiments showing the positive impact of norUDCA on fatty liver disease and atherosclerosis (Fig. 2).

![norUDCA: mechanism of action in the Mdr2 (Abcb4)$^{-/-}$-model for sclerosing cholangitis](image)
If apolipoprotein E-deficient mice are fed a western – i.e. high fat – diet, they develop fatty liver disease and atherosclerotic lesions (Fig. 3), but these developments can be prevented with norUDCA. A multicentre phase II study with norUDCA in non-alcoholic fatty liver disease (NAFLD) is scheduled to begin in the near future.

**Underestimated and often misdiagnosed: icteric nephrosis**

A further indication for norUDCA currently under discussion is icteric nephrosis, which in the opinion of P. Fickert, Graz (Austria), “receives far too little attention and is often misdiagnosed”. In extreme situations, certain bile acids can directly trigger icteric nephrosis, also known as cholemic nephropathy (Fig. 4). They can also be a cofactor in hepatorenal syndrome. In liver diseases, bile acids are increasingly excreted via urine, putting strain on the renal tubules, said M. Trauner: “Since norUDCA is excreted in the urine, it is conceivable that it will accumulate there and potentially have a favourable effect.”

In animal experiments on a CBDL (common bile duct ligated) mouse model of cholemic nephropathy, it was possible to show that hydrophilic bile acids can at least prevent cholemic nephropathy and that they inhibit the formation of casts in the kidneys, which cause atrophy and destruction of the tubules (tubular atrophy). Renal inflammation is reduced and fibrosis prevented. The bile acid composition in the urine of the mice also undergoes beneficial changes when norUDCA is administered, and the proportion of aggressive bile acids falls. “Renally excreted bile acids are a major trigger of cholemic nephropathy, at least in CBDL mice,” concluded P. Fickert.

**UDCA derivatives for combating hepatitis B?**

Whilst appropriate treatment for hepatitis C infections appears to have been largely established, additional research is still needed when hepatitis B is concerned. To address this problem, Chinese researchers have now struck upon UDCA derivatives which may be able to prevent infection. To provide some background, the sodium/bile acid cotransporting polypeptide) is primarily expressed in the liver and acts as a bile acid transporter there. However, it also works as a functional receptor for hepatitis B and D viruses in order to reach the liver cells. Cells that express NTCP can therefore become infected with HBV and HDV.

“UDCA derivatives may be potential inhibitors that could prevent such infection from developing,” explained W. Li, Beijing (China). Initial data show that inhibiting the NTCP transporter does in fact lower the risk of HBV infection.

**FXR agonists en route to clinical application**

Obeticholic acid, a derivative of chenodeoxycholic acid which acts as an agonist of nuclear receptor FXR (farnesoid X receptor), has already made its way into clinical trials. A.J. Sanyal, Richmond (USA), presented data from a double-blind proof-of-concept study showing that patients with type 2 diabetes and fatty liver disease benefitted from the administration of obeticholic acid. In the study, GGT and triglyceride levels were lowered, and insulin sensitivity improved within the short observation period of just a few weeks. “Obeticholic acid is an insulin sensitizer,” explained A.J. Sanyal. Results are now also being eagerly awaited from FLINT, a prospective, randomised, double-blind trial, which was halted in January 2014 following a planned interim analysis (Neuschwander-Tetri BA, et al. Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial. Lancet. 2014. doi: 10.1016/S0140-6736(14)61933-4).
FXR agonists for combatting diarrhoea

FXR is also a good target for antidiarrhoeals, explained S.J. Keely, Dublin (Ireland). Similarly to physiological concentrations of bile acids, agonists of the nuclear receptor inhibit chloride secretion and thus prevent diarrhoea. This antisecretory effect is mediated by inhibiting CFTR expression. On the other hand, if a disruption of enterohepatic circulation leads to increased levels of bile acids being released in the colon, this can trigger bile acid-induced diarrhoea. “Bile acids are also enterocrine hormones that influence the function of the intestinal epithelium,” S.J. Keely said in summary.
Many different factors are involved in the aetiology of intrahepatic cholestasis of pregnancy (ICP) (Fig. 6), and sulphated progesterone metabolites appear to play a key role in its development. The condition is severe in 1 out of 1000 women, with serum bile acid levels > 40 μmol/L. Transaminase levels are also raised, and bilirubin increases in some women. The consequences are far reaching, with an increased risk of premature birth, foetal hypoxia and stillbirth. Although sulphated progesterone metabolite levels are always slightly raised during pregnancy, they increase much earlier and more markedly in ICP, “reaching three or four times those of a normal pregnancy,” explained C. Williamson, London (Great Britain). Experimental studies are now leading us to the conclusion that this impairs the function of FXR (farnesoid X receptor) and thus contributes to the pathogenesis of ICP.

TGR5 antagonists for combating cholangiocarcinoma and cholestatic itching

According to S. Härtels, Erlangen-Nuremberg (Germany), bile acid-induced itch could conceivably be a further indication for the use of TGR5 antagonists. This is because TGR5 is also expressed by primary afferent neurons in the skin together with TRPA1 (transient receptor potential channel, member A1). TGR5 ultimately activates TRPA1 in order to release pruritogenic neuropeptides in the spinal cord. When activated by bile acids, this leads to scratching reflexes and neuronal hyperexcitability in mice.

If the G protein-coupled bile acid receptor TGR5 is activated by bile acids or TGR5 agonists, this can lead to cholangiocyte proliferation, which in part happens via the transactivation of EGFR (epidermal growth factor receptor), explained V. Keitel, Düsseldorf (Germany). At the same time, TGR5 activation has an anti-apoptotic effect. Inhibiting EGFR blocks the cholangiocyte proliferation that is dependent on TGR5. TGR5 antagonists may therefore be a potential treatment option for cholangiocarcinoma, which is often characterised by the overexpression of TGR5.

K. Reue, Los Angeles (USA), presented DIET1 as a regulator of FGF15-dependent bile acid synthesis, which is involved in maintaining bile acid homeostasis.

Fig. 6 Aetiology of intrahepatic cholestasis of pregnancy (C. Williamson, London)
Session II

Bile acids and liver regeneration

TGR5 and hepatic stellate cells are crucial to liver regeneration

The liver's ability to regenerate is impressive – under physiological conditions. When, in animal experiments, two thirds of the liver are removed, complete regeneration is achieved within 7–10 days under the influence of cytokines, growth factors and hormones. However, bile acid overload occurs in the course of this process, and TGR5 then has a critical role to play: "In this case TGR5 has a protective effect," explained T. Tordjmann, Orsay (France). The absence of TGR5 leads to disastrous consequences, as he was able to show in TGR5-KO mice: following partial hepatectomy, excessive hepatic inflammation, periportal bile infarcts and altered bile composition occur. Above all, the bile acid pool becomes more hydrophobic, and thus becomes dangerous to the liver. The mechanisms of how TGR5 is involved in regulation are still unclear. T. Tordjmann has put forward the working hypothesis that TGR5 controls the cholecystohepatic shunt, which is also damaged in TGR5-KO mice.

Hepatic stellate cells are likewise heavily involved in liver regeneration, and should be viewed as mesenchymal stem cells, explained C. Kordes, Düsseldorf (Germany). He was able to show that the presence of tauroursodeoxycholic acid leads to differentiation from hepatic stellate cells to hepatocyte-like cells. FXR and TGR5 are also involved in this process. At the same time, protective mechanisms such as beta-catenin-dependent Wnt signalling pathways ensure that excessive stem cell differentiation caused by bile acids does not occur in normal tissue.

FGF15: on the trail of the enterocin regulatory system with SISCAPA

D.J. Mangelsdorf, Dallas (USA), has managed to track down FGF15, an enterocin regulator of hepatic bile acid metabolism, using a new, highly sensitive mass spectrometer (SISCAPA = Stable Isotope Standards and Capture by Anti-Peptide Antibodies). FGF15 is necessary for the FXR-dependent repression of bile acid synthesis. Amongst other things, D.J. Mangelsdorf was able to demonstrate that the expression of Klotho beta in the liver is needed for FGF15 to exert these effects on bile acid metabolism and on the maintenance of bile acid homeostasis.

Of mice and not men

Investigating progressive familial intrahepatic cholestasis (PFIC) in animal models is problematic. This is because, according to R.P.J. Oude Elferink, Amsterdam (The Netherlands), unlike humans, mice are capable of detoxifying hydrophobic bile salts. For this reason, he has developed a mouse model where the detoxification capacity is dramatically reduced, and therefore more closely resembles the human situation.
Microbiome shifted towards pathogenic organisms in liver cirrhosis

J.S. Bajaj, Richmond (USA), explained that dysbiosis, bile acids and cirrhosis are closely connected. Patients with liver cirrhosis exhibit dysbiosis with an overgrowth of bacteria and a shift towards pathogenic organisms. The functioning of the microbiota is altered. This is evident when the stools of patients with liver cirrhosis are compared to those of controls. ‘The microbiome is different’ said J.S. Bajaj, summarizing these studies. As the severity of the liver cirrhosis increases so the number of autochthonous bacteria falls (Fig. 7). The metabolism of primary bile acids to secondary bile acids then only occurs to a limited extent.

Overweight and HCC: disturbed intestinal flora as the link

The risk of hepatocellular carcinoma (HCC) increases. Lowering of the DCA level can protect against HCC. This could explain the connection between overweight and increased risk of HCC and leaves space for speculation about potential treatments.

Milk fat: More delta-proteobacteria in the gut

E.B. Chang, Chicago (USA), also considered the development of inflammatory bowel disease in the context of intestinal flora, nutrition and bile acids, thus creating an additional link. He felt that altered dietary habits are partly responsible for the increase in Crohn’s disease and ulcerative colitis. He identified milk fats, a major component of the western diet, as the culprit. Unlike PUFA (polyunsaturated fatty acid) it increases the risk of experimental colitis.

Changes in the intestinal flora resulting from overweight can have severe consequences. Animal experiments have shown that an increase in gram-positive bacteria in the gut leads to increased development of hepatocellular carcinoma. E. Hara, Tokyo (Japan), explained how this could happen.

The increase in gram-positive bacteria leads to higher levels of deoxycholic acid (DCA), one of the secondary bile acids, which is formed by 7-alpha dehydroxylation. Enterohepatic circulation brings the toxic DCA into the liver where it can damage the DNA. This leads to the induction of inflammatory and tumour-promoting factors, primarily interleukin (IL)-6, PAI (plasminogen activator inhibitor)-1 and GM-CSF (granulocyte-macrophage colony-stimulating factor).

Fig.7  Autochthonous bacteria reduce with worsening cirrhosis and can predict negative outcomes  [Bajaj JS, et al. J Hepatol. 2014;60:940-947]
When the diet is rich in milk fats, detailed examination of the gut flora shows delta-proteobacteria to be present. These are able to induce mild distal colitis in IL-10 deficient mice. The connection with the bile acids also works because milk fats stimulate the conjugation of bile acids with taurine which in turn promotes the growth of dangerous bacteria.

In animal experiments the formation of these delta-proteobacteria and colitis in IL-10-KO mice can be inhibited with omega-3 fatty acids. Probiotics can also modulate the gut flora. As A. Moschetta, Bari (Italy), explained, this leads to increased deconjugation of ileal bile acids with faecal excretion of bile acids and causes downregulation of the gut-liver FXR-FGF15 axis which results in increased synthesis of new bile acids in the liver.

P.A. Dawson, Atlanta (USA), was able to show that the inhibition of the ileal apical bile acid transporter affects cholesterol metabolism and is able to reduce atherosclerosis in ApoE-deficient mice. That does not happen when transport via the basolateral cell membrane is inhibited. The critical factor for the atheroprotective effect is the suppression of ileal FGF15 expression.

M. Rudling, Stockholm (Sweden), focussed on the problems of using mouse models to investigate bile acids. The synthesis of bile acids is regulated by the end-products in a negative feedback mechanism.

However, bile acid metabolism in mice is also influenced by typical mouse-specific bile acids such as alpha and beta muricholic acid. This could help us to better understand the differences in bile acid regulation between humans and mice. It appears that bile acids are important for more than just liver and intestinal function.
Biliary atresia: what determines the prognosis?

41% of neonatal cholestasis cases are due to biliary atresia. By comparison, progressive familial intrahepatic cholestasis (PFIC) is only responsible for 10%. S.J. Karpen, Atlanta (USA), reported that some of the affected children require a liver transplant within 2 years after a Kasai procedure whereas others can live for years with their own liver. Studies are currently in progress to find out why this is.

The focus is on genetic mutations affecting either the immune system or the flow of bile and the tendency towards cholestasis. The NIDDK-ChiLD- ReN study is at present investigating the ABCB4 variants in 195 children with biliary atresia. Half of the children received a transplant before their second year of life and half were over four years old when they underwent transplantation.

Farnesoid-X Receptor (FXR): The Master Regulator

F. Lammert, Homburg (Germany), focussed on different variants of nuclear bile acid receptors in liver disease. FXR is thought to be the “Master Regulator”. It is a physiological sensor for bile acids and plays a major role in bile acid homeostasis. Among the findings for FXR variants were associations with gall stones, primary biliary cirrhosis (PBC) and intrahepatic cholestasis. Like NOD2 variants, certain FXR variants also appear to increase the risk of spontaneous bacterial peritonitis.

Lammert identified PPAR (peroxisomal proliferator-activated receptor) gamma as another nuclear receptor that is relevant in liver disease. Associations have been found between certain genotypes and increased levels of adiponectin; one meta-analysis found them to be linked with an increased risk of fatty liver.

Adolf Windaus Prize

The Falk Foundation has been awarding the Adolf Windaus Prize for outstanding work in bile acid research since 1980. The prize, worth 15,000 euros, this year went to Prof. Dr. Steven Kliewer from Dallas for his research into nuclear bile acid receptors. The prize was presented to him by Prof. Dieter Häussinger, Düsseldorf.
Outstanding posters

Falk Symposium 194

Three poster prizes were awarded at Falk Symposium 194 “XXIII International Bile Acid Meeting: Bile Acids as Signal Integrators and Metabolic Modulators” in Freiburg for outstanding work in bile acid research. These prizes were endowed by the Falk Foundation and were presented to the prize winners by Prof. Dieter Häussinger from Düsseldorf, one of the symposium’s scientific organisers.

The first prize was awarded to D. Slijepcevic, Amsterdam (The Netherlands), for his work on “Impaired uptake of conjugated bile acids and hepatitis B virus preS1-binding in Na+-taurocholate cotransporting polypeptide knockout mice”.

A. Miethke, Cincinnati (USA), received second prize for his study “Pharmacological inhibition of intestinal bile acid re-uptake changes bile composition and blocks progression of liver disease in a murine model of progressive familial intrahepatic cholestasis (PFIC) type 3”.

Third prize went to Y. Li, Richmond (USA), for the study “Taurocholate activates YAP via sphingosine-1 phosphate receptor 2 in cholangiocytes”.

Editors: Professor Trauner, what do you feel are the unmet needs in hepatology?

Professor Trauner: Now that drugs with direct antiviral action have been developed and have made the treatment of viral hepatitis into more of a financial problem than a pharmacological or therapeutic one, primary sclerosing cholangitis (PSC) is certainly among the open questions in hepatology. PSC is a cholestatic liver disorder that is very appropriately referred to as hepatology’s last black box. Our understanding of this disorder is still poor. For that reason we still can’t treat it effectively. But we hope that new therapeutic approaches will take us a step further both in treatment and in our understanding of the pathophysiology. When you see what strategies are effective you can also draw conclusions about the disease itself. In terms of quantity, fatty liver and non-alcoholic steatohepatitis (NASH) will roll towards us like an avalanche in the next few years. We do not have any good biomarkers for diagnosis and prognosis of either PSC or NASH. Transaminase levels are of only moderate value. In many patients with NASH or viral hepatitis they are in the area that we have defined as high normal. Low normal levels can be achieved by giving antiviral treatment or by altering the diet and introducing exercise and weight reduction.

Editors: What can bile acid research contribute to help solve this problem?

Professor Trauner: Bile acids are good biomarkers. It is not only the level of bile acids that is important here but also their composition. In my view this is determined much too rarely, perhaps because the procedures used to be very time-consuming and complicated. Nowadays there are high-throughput procedures that deliver complete composition spectra. Bile acids are more sensitive than liver function test results as markers of treatment response in cholestatic liver disorders or of hepatotoxic side effects of drugs. At the end of the day, intrahepatic cholestasis of pregnancy can only be diagnosed with certainty by determining the bile acid profile. We even have data showing that, in the case of sepsis, the levels of the different bile acids on admission to the intensive care unit predict survival in the first 24 hours. However, interest in bile acids has increased primarily because of their role in mediating signal transmission. This makes them potential therapeutic agents. This was already evident in the case of ursodeoxycholic acid but has become even more obvious for norursodeoxycholic acid.

Editors: In chemical terms ursodeoxycholic acid and norursodeoxycholic acid differ only minimally. There are nevertheless still clear differences in efficacy.
Professor Trauner: Chemically the difference really is trivial. In norursodeoxycholic acid the side chain is just one methyl group shorter. But that is exactly the point on the molecule at which the conjugation of ursodeoxycholic acid takes place, specifically amide formation with the amino acid glycine. With UDCA and other bile acids, this conjugation causes them to be kept in the enterohepatic circulation. However, norUDCA is not conjugated because it lacks the methyl group. This means that it is subject to cholehepatic shunting and induces bicarbonate-rich hypercholeresis. Cholehepatic shunting also allows more specific targeting of the bile duct epithelium. This can also be shown in animal experiments. If bile acids are infused and the conjugation capacity of the liver is exceeded, the flow of bile generally increases more than would be expected. In the case of norursodeoxycholic acid this effect could be said to be built in because it is not conjugated in the first place. The induction of bicarbonate-rich hypercholeresis promotes the formation of the biliary bicarbonate umbrella over the bile duct cells. This has a protective effect.

Editors: Did you aim to develop norursodeoxycholic acid specifically?

Professor Trauner: I suppose we did, because we knew where the conjugation occurs on the molecule. But it really was essential to remove only one methyl group. If you shorten the side chain any more the efficacy is reduced or disappears completely.

Editors: You said that PSC is a black box in hepatology. Norursodeoxycholic acid could make it possible to move towards a more effective treatment regime.

Professor Trauner: We are confident. In animal experiments we have been able to show that cholehepatic shunting of the substance does not just activate the biliary bicarbonate umbrella. It is also present where disease processes take place and exerts anti-inflammatory effects, not only because the bile is less toxic but also because norUDCA possesses direct anti-inflammatory properties. That makes this bile acid interesting for non-cholestatic diseases as well. It has also been shown to be effective in schistosomiasis, which is the most frequent cause of liver fibrosis worldwide and is especially important in African and South American countries.

NorUDCA is currently being tested in a Phase II study that will be completed very soon. We hope it will be possible to present the first results in spring next year.

Editors: Ursodeoxycholic acid is used successfully in primary biliary cirrhosis and has become established as its standard treatment. Can we assume that norUDCA would be even more effective in PBC?

Professor Trauner: Yes, it looks that way, especially because the bicarbonate umbrella is damaged in PBC and norUDCA is particularly good at restoring it. In the area of cholestatic diseases, PBC is certainly the next indication.

Editors: Does that mean it’s the end of the line for ursodeoxycholic acid?

Professor Trauner: At the moment I’d say that norursodeoxycholic acid is only an option for those who do not respond to UDCA. Because of the long experience I’d stay with UDCA and only switch in the case of non-responders. There is no reason to change from something that has proved its worth – something that one has found to be helpful.

Editors: Can you envisage other indications for norursodeoxycholic acid?

Professor Trauner: Among the cholestatic liver disorders, the genetically caused syndromes of childhood are also worth considering. Cystic fibrosis is another possible indication. In my view NASH is also a potential candidate. Ursodeoxycholic acid has not demonstrated a convincing effect in this case. The direct anti-inflammatory effect of norursodeoxycholic acid is independent of cholestasis and also has a favourable effect on the blood vessels. These patients actually tend to die of vascular disease rather than liver disease.

Editors: For a long time now research has been looking at the different bile acid agonists and antagonists that act on FXR or TGR5. What can clinicians really hope for?

Professor Trauner: The most comprehensive data available so far are those for obeticholic acid, a chemically modified chenodeoxycholic acid and an agonist of the nuclear farnesoid X receptors (FXR). One Phase III study of PBC has been completed. In the case of NASH data are available from a pilot study. But a long-term study lasting one and a half years and sponsored by NIH is more interesting. It was terminated early because of positive results and has recently been published in the Lancet. There are also Phase II studies on the use of FXR ligands in portal hypertension. A great deal of data on TGR5 ligands is available from fundamental research. But none of the substances has so far made it into clinical studies.

Professor Trauner, thank you very much for the interview.

Editors: What can clinicians really hope for?
Hepatotoxicity of drugs: a problem for patients, doctors and pharmaceutical research

Liver toxicity is a problem not only for doctors and patients but also for pharmaceutical research and drug authorisation bodies. It is still one of the leading causes of acute liver failure.

Right up until the end of the 20th century, DILI (drug induced liver injury, Fig. 8) was the primary reason to refuse to authorise a drug or to withdraw it from the market again months or years later. Hepatotoxicity still is a major issue, as L.B. Seeff, Bethesda (USA), explained. More than 600 drugs are under suspicion (Fig. 9).

Idiosyncratic DILI is a particular problem, as the meeting heard from H.W. Jaeschke, Kansas City (USA). It is independent of dose, unpredictable and almost impossible to reproduce. Idiosyncratic hepatotoxicity even causes problems at the animal model stage as F. Ballett, Paris (France), made clear: “Most of the substances that are known for idiosyncratic DILI are negative in conventional animal experiments.” He explained that, because it occurs so rarely, the risk can only be detected in very long clinical studies or post-marketing.
The MetaHeps® technology is an innovative way of confirming the suspicion in patients with suspected DILI. It generates a personalized cell model from the patient’s own blood cells. “This model reflects the clinical situation (the individual hepatotoxicity) and makes it possible to predict the liver toxicity of drugs,” explained A. Benesic, Munich (Germany).

**DILI or not – a difficult question**

Diagnosing DILI with certainty is at least as difficult. There is no objective gold standard. It is much more a case of making a diagnosis of exclusion in which all the other causes of liver damage have to be ruled out. One instrument for investigating causality of liver damage when drugs are being used is RUCAM (Roussel Uclaf Causality Assessment Method). The RUCAM score takes account of temporal relationships, risk factors and other possible causes (Fig. 10).

However, P.B. Watkins, Research Triangle Park (USA), felt that this is not a reliable option. The same holds true for evaluation of the causality by experts. If both methods are used they by no means always lead to the same result. It seems to be the case that the frequency of DILIs tends to be underestimated and cases are not reported often enough. G.P. Aithal, Nottingham (Great Britain), felt that under-reporting is a problem for pharmacovigilance. He referred to a study which found the incidence to be 16 times higher than the incidence estimated from spontaneous reports. However, spontaneous reports are still the most common cause of changes in the conditions for authorisation. He called for the development of algorithms to enable a diagnosis to be made on the basis of drug, patient and environmental conditions.

**Pharmacogenetics decide pharmacokinetics**

Various different factors decide whether a patient develops idiosyncratic DILI. External influences such as alcohol consumption play a part but so do sex, age and other factors. The patient’s own genetic background also affects the pharmacokinetics of a drug. As J. Maas, Frankfurt (Germany), explained, this means that pharmacogenetics plays a major role in the pathogenesis of DILI.

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</tr>
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<td>0.0%</td>
<td>0.0%</td>
<td>18.9%</td>
<td>39.6%</td>
<td>41.4%</td>
</tr>
</tbody>
</table>

**Kappa = 0.31**

Fig. 10 Agreement between expert opinions and the 5 point RUCAM score in 40 cases of DILI [Rochon J, et al. Hepatology. 2008;48(4):1175-1183]

Whether patients are among the “slow” or “rapid” metabolisers is thus critical because it affects their exposure to the active agent.

**Anyone who wants to find out more …**

DILI is not just a problem for hospitals. About half of all cases occur in primary care. Anyone who wants to know more about the hepatotoxicity of drugs should visit www.livertox.nih.gov. This site gives comprehensive information on individual active agents.
Editors:
Professor Gerbes, the Falk Workshop on The Challenge of Drug-Induced Liver Injury (DILI) has been held at your initiative. What motivated you?

Professor Gerbes:
The problem of drug-induced liver injury is often underestimated but is highly relevant. That is apparent just from the fact that over half of all cases of acute liver failure are caused by drugs and that drugs are also responsible in 5% of the patients who present to hospital with jaundice.

That has consequences for the industry, authorisation bodies and patients. DILI is a frequent reason for withdrawing drugs from the market and for terminating development in late clinical phases.

Editors:
The real problem seems to be idiosyncratic liver damage.

Professor Gerbes:
We have to keep two things separate here that we are often not so conscious of.

In the case of dose-dependent hepatotoxicity the rule is the greater the quantity the greater the damage. A typical example is paracetamol. At high doses it can provoke severe liver damage. This risk can be avoided by keeping to the recommended dosage.

Idiosyncratic liver damage is much harder to nail. It occurs independent of dose, depending instead on how the individual patient reacts to a drug. You can prescribe a drug to 10,000 patients. 9999 will be fine and one patient will develop liver failure.

Editors:
It is still relevant though, especially with drugs that are prescribed very frequently. When must the doctor consider DILI?

Professor Gerbes:
If liver damage occurs and there is another clear cause, such as an acute hepatitis B infection, there is no need to search further. But in patients on medication DILI must always be considered as a possible differential diagnosis if the pathogenesis is not immediately clear.
The problem is that, at present, DILI is a diagnosis of exclusion. Basically, all the other causes of liver damage that could be responsible have to be excluded. Not least because these are often treatable – like viral hepatitis, for instance.

Editors: Are patients with damaged livers at particular risk from potentially hepatotoxic drugs?

Professor Gerbes: That’s a good question and a difficult one to answer. At the moment there is no really good evidence showing that a damaged liver is more often threatened by drugs than a healthy liver, even though the idea seems reasonable. However, the damage can be more severe in these patients.

Editors: Does jaundice always have to be present in DILI?

Professor Gerbes: No, because each drug has a different pattern of damage. Often there is “only” a rise in transaminases. Some patients have primary icterus, others have both. The values need to be clearly elevated though – to about three times the normal level. Then we have to assume that there is relevant liver damage.

Editors: If the doctor suspects DILI what should he or she do then, in practical terms?

Professor Gerbes: If the LFT values are abnormal the doctor should try to exclude any other potential causes by taking a detailed history. Perhaps the patient picked up hepatitis during a stay overseas or drinks alcohol excessively. If DILI is still suspected the problem is often that the patient takes not just one but several different medications. And, not infrequently, two may have been started at the same time.

Editors: Can we assume that the drug that was started most recently is always the one that triggered the acute liver damage?

Professor Gerbes: That’s another problem. The interval between taking the drug and the appearance of damage can vary considerably. It is usually weeks but can be months. It is even possible for the damage to become apparent only after the patient has stopped taking the drug. The search for the drug responsible for DILI can be frustrating in cases like this.

Editors: How fast do we need to act?

Professor Gerbes: The patient should stop taking the drug under suspicion as soon as possible. It is difficult to make a prognosis, though. If the initial damage is already considerable and continues to increase over the next few days, we move into a realm where the damage can be measured on a scale used for acute liver failure, like the King’s College criteria.

Editors: And finally, could you comment on the hepatotoxic risk of paracetamol, which only last year was again the subject of intense discussion?

Professor Gerbes: The good thing about paracetamol is that we have a lot of data about the relationship between dose and efficacy. This means we are able to define doses that just about anyone can take without significant risk of liver damage. If acute liver failure is seen while on paracetamol, the dose that has been taken is usually much higher.

But it becomes a problem when larger quantities of alcohol, for example, were consumed before taking the painkiller. This activates enzymes that degrade paracetamol to produce toxic metabolites and at the same time reduces the endogenous antioxidant “rescue system”. In this situation doses in the upper normal range can be enough to cause liver damage.

Professor Gerbes: thank you very much for the interview.
Liver cirrhosis brings numerous problems extending well beyond the liver. They include variceal bleeding, life-threatening hepatorenal syndrome, spontaneous bacterial peritonitis and – last but not least – hepatocellular carcinoma. When these problems occur, appropriate measures have to be taken fast.

The numbers are considerable. In Europe 29 million people suffer from liver disease caused by alcohol, hepatitis B or C viruses or by metabolic syndrome, which can itself be associated with non-alcoholic fatty liver. Every year 170,000 people die of the consequences of cirrhosis and 47,000 die of hepatocellular carcinoma. As J. Bosch, Barcelona (Spain), pointed out, “that exceeds the numbers dying of breast cancer”. In addition there are 5,500 liver transplants per year because of cirrhosis. Unlike liver fibrosis, where it is possible to turn the clock back and reverse the damage, liver cirrhosis cannot be cured. It is also associated with a multitude of complications including portal hypertension, hepatic encephalopathy, kidney problems, bacterial infections and, moreover, hepatocellular carcinoma (Fig. 11).

Acute variceal bleeding becomes less frightening

Liver cirrhosis is the most frequent cause of portal hypertension, the consequences of which are severe. Raised mechanical/dynamic flow resistance and elevated blood flow resulting from...
Splanchnic vasodilation increase the portal pressure. There is also an increase in the risks of spontaneous bacterial peritonitis (SBP) and portosystemic encephalopathy. Beta-blockers have become established in the treatment of portal hypertension. But they are not without problems, as J.G. Abraldes, Edmonton (Canada), stressed. There are absolute or relative contraindications in 15% of patients. Similar numbers of patients discontinue treatment because of side effects. The increase in mortality risk is particularly great in patients with refractory ascites. The discussion about beta-blockers was set in motion by a study showing that, in patients with refractory ascites, propranolol was associated with a higher incidence of postparacentesis circulatory dysfunction. The association was highly significant. However, the results of a recently published study disagree. This study looked at the mortality of 322 patients with liver cirrhosis and ascites (117 of them refractory) on the waiting list for liver transplants. The study found that non-selective beta-blockers were associated with improved survival in patients with ascites awaiting liver transplantation. According to J.G. Abraldes, acute variceal bleeding has lost some of its horror in recent decades. Prophylactic antibiotic treatment can considerably reduce the infection rate and the mortality. Overall, the mortality has declined considerably. Variceal bleeding is less important than bacterial infections, kidney failure or liver failure.

**Type 1 HRS:** terlipressin plus albumin as treatment of choice

Terlipressin combined with albumin is considered to be the first-line treatment for type 1 hepatorenal syndrome (HRS). Norepinephrine could become an alternative to terlipressin but, according to P. Angeli, Padua (Italy), sufficiently comprehensive data are not yet available. A comparison of cumulative survival rates with noradrenaline and terlipressin found survival to be about the same with both substances ($p = 0.591$) (Fig. 12). In contrast, as P. Angeli noted, the combination of midodrine and octreotide combined with albumin was much less effective than terlipressin combined with albumin. At the same time he emphasised that liver transplantation was an “excellent option” for selected patients. These patients should also be given terlipressin and albumin before the operation because this combination improves survival without a transplantation and reduces the risk of acute kidney damage or chronic kidney disease after transplantation. However, that gives rise to a different problem. This medication reduces the MELD score which pushes the patient back down the waiting list and delays transplantation. P. Angeli felt that this “negative” effect should be considered when drawing up the list of priorities.

![Fig. 12 Cirrhosis: cumulative probability of survival on noradrenaline and terlipressin](Singh V, et al., J Hepatol. 2012;56:1293–1298)
Spontaneous bacterial peritonitis: targeted antibiotic treatment – and fast

Spontaneous bacterial peritonitis (SBP), which results from bacterial translocation, is among the feared complications of liver cirrhosis (Fig. 13). The more severe the liver disorder, the greater the risk. F. Salerno, Milan (Italy), also stressed that the risk of relapse – 43% within 6 months and 69% within one year – is very high.

Patients who have already had SBP are therefore at high risk of getting it again. Variceal bleeding and total bilirubin > 2.5 mg/dl are seen as additional risk factors. If a patient develops SBP, defined as a PMN score > 250/mm³ in ascites, antibiotic treatment should be started “as soon as possible”.

F. Salerno also recommended combining it with human albumin. He referred to a study investigating 126 patients with liver cirrhosis and SBP. Survival in hospital and 3-month survival were both higher with a combination of intravenous cefotaxime and albumin than with cefotaxime alone.

A meta-analysis by F. Salerno, in which 4 randomised studies were considered, also confirmed the usefulness of giving albumin. He discussed the increasing resistance shown by the pathogens, which is a particularly important aspect, noting that between 30 and 40% of those causing SBP have already been found to be resistant to quinolone (Fig. 14).

It is important to use the “right” antibiotic, and to limit antibiotic treatment to those patients who actually benefit from it, to avoid encouraging the development of multi-drug resistance (MDR).

Hepatocellular carcinoma: classification using BCLC staging

What should be done with hepatocellular carcinoma (HCC)? One answer is offered by the current BCLC (Barcelona Clinic Liver Cancer) classification (Reig et al. Semin Liver Dis. 2014) (Fig. 15), which considers the extent of the tumour, the degree of cirrhosis (the Child-Pugh score) and the clinical state of the patient (Performance Status, PS).

According to BCLC, curative procedures such as ablation, resection and transplantation should be considered in very early stages (1 nodule ≤ 2 cm, Child-Pugh A, PS 0) and early stages (1–3 nodules ≤ 3 cm, Child-Pugh A–B, PS 0). At present, as J. Bruix, Barcelona (Spain), explained, sorafenib is the only option for systemic treatment of advanced HCC (portal invasion, extrahepatic metastases, Child-Pugh A–B, PS 1–2). J. Bruix made reference to data from the SHARP and Asia-Pacific studies, both of which showed that overall survival (OS) was better on sorafenib.

“This improvement is nevertheless not associated with a significant objective response of the tumour” noted J. Bruix.

A prospective study has recently shown that patients who develop dermatological side effects at an early stage of treatment derive particular benefit from this multikinase inhibitor (OS: 18.2 months with sorafenib and 10.1 months without).

Fig. 13  Bacterial translocation leads to spontaneous bacterial peritonitis (F. Salerno, Milan)
<table>
<thead>
<tr>
<th>Variables</th>
<th>Quino</th>
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<th>Carbap</th>
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</table>

Fig. 14 Increasing resistance of pathogens to antibiotics [Cazzaniga et al., DLD 2010]

Fig. 15 Current BCLC staging system [Reig M, et al. Semin Liver Dis. 2014;34(4):444–455]

**Barcelona Clinic Liver Cancer (BCLC)-Staging and Treatment Strategy, 2014**

**HCC**
- **Very early stage (0)**
  - Single ≤ 2 cm
  - Child-Pugh A, PS 0

- **Early stage (A)**
  - Single or 3 nodules ≤ 3 cm
  - Child-Pugh A–B, PS 0

- **Intermediate stage (B)**
  - Multinodular
  - Child-Pugh A–B*, PS 0

- **Advanced stage (C)**
  - Portal invasion
  - Extrahepatic spread
  - Child-Pugh A–B*, PS 1–2

- **Terminal stage (D)**
  - Child-Pugh C**
  - PS 3–4

**Prognosis**
- Potential candidate for liver transplantation
- Portal pressure, bilirubin
- Associated diseases

**Treatment**
- Ablation
- Resection
- Transplant
- Ablation
- TACE
- Sorafenib
- BSC (best supportive care)

**Curative treatment**

**Palliative treatment**

*Note that Child-Pugh classification is not sensitive to accurately identify those patients with advanced liver failure that would deserve liver transplant consideration.*

**Patients with end stage cirrhosis due to heavily impaired liver function (Child-Pugh C or earlier stages with predictors of poor prognosis, high MELD score) should be considered for liver transplantation. In the, HCC may become a contraindication if exceeding the enlistment criteria.*
Liver fibrosis: no two cases are alike

As M. Pinzani, London (Great Britain), told the audience, liver fibrosis can be caused by a large number of noxious substances "when they exert an influence every day over a long period of time". Age and sex are also relevant as are genetic and epigenetic influences. Nonetheless, not all cases of liver fibrosis are the same. Different forms can be distinguished that depend on the pathomechanism induced by the harmful agent. Viral hepatitis and autoimmune hepatitis lead to post-necrotic fibrosis by causing chronic activation of wound-healing processes. In primary biliary cirrhosis and primary sclerosing cholangitis, disturbance of the epithelial-mesenchymal interaction leads to peribiliary fibrosis with formation of reactive cholangiocytes and influence of toxic bile salts. The main feature in non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) is the tissue damage caused by oxidative stress and visibly expressed as pericellular fibrosis. In M. Pinzani’s view this means it is unlikely that a single antifibrotic agent will ever be found to treat all the different forms of fibrosis. Specific antifibrotic treatments are not yet available. Investigation is currently in progress into a monoclonal antibody to LOXL2 (lysyl oxidase homolog 2), an enzyme responsible for the cross-linking of collagen in tissue.

Liver biopsy is a suitable method for evaluating liver fibrosis. But, as L. Castera, Clichy (France), pointed out, it also has its drawbacks. Above all, it is invasive and therefore opposes the trend towards non-invasive procedures. Two non-invasive methods are currently available to diagnose the extent of fibrosis: determination of serum levels of biomarkers and using transient elastography to measure the stiffness of the liver. Biomarker tests have been validated primarily for viral hepatitis and are more meaningful for evaluating cirrhosis than fibrosis (Fig. 16). Measurement of liver stiffness fails in 3.1% of patients and is not reliable in 15.8%. As L. Castera noted, “Transient elastography provides no usable results in 20% [of cases].” One factor is particularly important for obtaining reliable results in transient elastography: the patients must not eat or drink before the examination.

Non-invasive diagnosis of liver fibrosis increasingly popular

“Direct” markers
- Hyaluronate
- PIIINP
- Laminin
- Type IV Collagen
- MMP
- TIMP-1
- TGF-beta
- YKL-40

“Indirect” markers
- Prothrombine time
- Platelet count
- AST/ALT Ratio
Portal hypertension (PH) is a common complication of liver cirrhosis. There is a threat of gastrointestinal varices, variceal bleeding and ascites. The increased resistance to flow can be reduced with a transjugular intrahepatic portosystemic shunt (TIPS). The drugs currently in use – beta-blockers, terlipressin and somatostatin – are intended to lower the increased blood flow.

Researchers looking for new treatment approaches came upon statins. These agents attack transcription factor KLF2 and thus exert a positive effect on vasorelaxation and liver fibrosis in isolated liver. As J. Bosch, Barcelona (Spain), reported, clinical studies have now also shown that this principle could work. He mentioned the BLEPS (BLEeding Prevention with Simvastatin) study investigating simvastatin as an add-on to the standard treatment with beta-blockers and endoscopic band ligation following variceal bleeding. The study found that survival improved though without any effect on recurrent bleeding.

**Portal hypertension: alternatives to measuring HPVG**

Determining the hepatic venous pressure gradient (HVPG) is a standard procedure when measuring portal blood pressure. In compensated patients the risk of varices increases when the pressure exceeds a threshold value of 10 mm Hg. HVPG > 16 mm Hg is an independent predictor of clinical decompensation. As A. Berzigotti, Barcelona (Spain), explained, the measurement of HVPG is “very useful” but is also invasive, expensive and by no means available everywhere.

In her view, Doppler sonography is an alternative. This method has high specificity and moderate sensitivity. Above all, as she reported, it permits a satisfactory diagnosis when signs of PH are visible. However, a negative result does not allow any options to be excluded with certainty. Physical signs of PH such as splenomegaly, visible porto-collateral circulation or spider naevi may be highly specific but have low sensitivity.
Hepatorenal syndrome: when the kidney is affected as well

As P. Ginès, Barcelona (Spain), explained, renal dysfunction is a common complication in patients with advanced cirrhosis and is associated with a poor prognosis. He described the pathophysiological connections. As a reaction to the arterial hypovolaemia, vasoconstrictor systems are activated. These include the renin-angiotensin system and the sympathetic nervous system. In advanced stages there is hypersecretion of vasopressin. This keeps the arterial pressure high which is hard on the kidneys and brings a risk of hepatorenal syndrome. Studies of cirrhosis with hepatorenal syndrome have found a marked increase in plasma renin activity and an increase in plasma norepinephrine, whose values greatly exceeded those found in patients with cirrhosis and ascites but without hepatorenal syndrome.

Acute kidney injury in liver cirrhosis: the stage determines the outcome

The Acute Kidney Injury Network (AKIN) defines acute kidney injury (AKI) in terms of the RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End-stage kidney disease) criteria (Fig. 18).

Various studies have confirmed the reliability of this system in decompensated liver cirrhosis. The cumulative survival of patients with liver cirrhosis admitted to intensive care units depends on the RIFLE criteria.

“The AKI stage determines the outcome” said F. Wong, Toronto (Canada). A study of cirrhosis patients who were hospitalised with an infection or developed an infection while in hospital found that the 30-day mortality of patients who developed AKI was 10 times higher than that of patients without AKI.

However, there is one bone of contention. Should the AKI definition include a cut-off value for serum creatinine of 1.5 mg/dl? “The discussion on this is still in progress” said F. Wong.
Even minimal hepatic encephalopathy (MHE) can limit work capacity

D. Häussinger, Düsseldorf (Germany), defined hepatic encephalopathy as a neuropsychiatric syndrome of acute or chronic liver disease that is associated with motor and cognitive dysfunction.

In pathophysiological terms it begins with low-grade cerebral oedema. This can exacerbate under the influence of precipitating factors such as ammonia, inflammatory cytokines or hyponatraemia and cause astrocyte swelling which in turn leads to an oxidative/nitrosative stress response and yet more astrocyte swelling in a vicious circle. Autoamplification of astrocyte swelling and oxidative/nitrosative stress occurs. Reactive oxygen and nitrogen species lead by various mechanisms to disturbed synaptic plasticity and disturbed oscillatory networks which finally result in the symptoms of HE. It may be possible to improve symptoms by preventing ammonia-induced RNA oxidation and/or nitration of tyrosine residues of specific astrocyte proteins. Investigations with indomethacin point in this direction.

MHE: increased risk of falling and injury

What are the consequences of minimal hepatic encephalopathy (MHE)? This was the question posed by K. Weißenborn, Hannover (Germany). With reference to numerous studies she provided evidence that even MHE causes deficits in attention and motor function and limits work capacity. A study of 110 women found that only 56% (40% of blue-collar and 80% of white-collar employees) felt themselves to be capable of working.

The results of the question on fitness to drive were similar. Only about half the women felt fit to drive a car. The risk of falling also increases. In a survey 40% of the patients with cirrhosis and MHE (18/45) reported that they had already fallen whereas only 13% of those without MHE (11/85) and 11.6% of control patients (43) had experienced a fall. The falls were associated with bruises, injury and – in 2 cases – fractures. Such falls and cognitive dysfunction demonstrably reduce the health-associated quality of life of cirrhosis patients. But MHE is not an independent risk factor limiting quality of life and is not linked with increased mortality.

Cognitive dysfunction in liver cirrhosis

Definition:
Irreversible destruction of the architecture of the lobules and blood vessels with inflammatory fibrosis and formation of connective tissue septa and micro- or macronodular regenerative nodules.

Fig. 19 Liver cirrhosis (R. Thimme, Freiburg)
Infections worsen the prognosis of patients with liver cirrhosis. Mortality is four times higher than in patients with cirrhosis but no infection. Earlier studies had already suggested a link between bacterial infection and variceal bleeding. Using animal models C. Steib, Munich (Germany), was able to show that intraperitoneal administration of lipopolysaccharides activates the Kupffer cells. This leads to an increase in the production of vasoconstrictors such as thromboxane A2 and leukotriene C4. They exert an additive effect on the portal pressure. The effect is mediated by TLR (Toll-like receptors). For practical purposes this means that antibiotic treatment should be given immediately in the case of acute variceal bleeding.

Acute-on-chronic liver failure (ACLF) often leads to acute decompensation of the cirrhosis and is associated with high 28-day mortality. This value is 4.7% in patients without ACLF and 78.6% in patients with stage 3 ACLF. R. Moreau, Clichy (France), noted that bacterial infections are “significantly more common than in patients without ACLF (33% vs. 22%).”

Spontaneous bacterial peritonitis and pneumonia occur significantly more often in patients with ACLF than in patients without it. The ACLF accompanying a bacterial infection is the most frequent of the forms with identifiable triggering events, as R. Moreau said, “with high significance (p < 0.001).” Other triggering events for ACLF, though less important than bacterial infections, are alcohol consumption within the last 3 months and gastrointestinal haemorrhage.

Liver cirrhosis brings with it a risk of developing hepatocellular carcinoma (HCC). In patients with HCC the prognosis following resection can be determined with reference to a molecular 5-gene score. G.J. Gores, Rochester (USA), referred to a study establishing a connection between the expression of the 5 genes HN1, RAN, RAMP3, KRT19 and TAF9 and the survival of the patient. The 5-gene signature was associated with a higher relapse rate after hepatic resection and shorter survival after relapse.
Session VII

Practical recommendations – treating patients with cirrhosis

Autoimmune hepatitis: yes to budesonide but not in liver cirrhosis

In 80% of patients autoimmune hepatitis (AIH) can be successfully treated with a combination of corticosteroid and azathioprine. U. Beuers, Amsterdam (The Netherlands), favours the use of budesonide, especially in young women. This topically-acting corticosteroid, over 90% of which is metabolized in the liver, has an efficacy similar to that of prednisolone but with fewer side effects (Fig. 20). However, budesonide is not an option for patients with AIH who have already developed liver cirrhosis. U. Beuers explained that, in their case, there is only limited metabolism of the corticosteroid in the liver and the steroid levels become markedly elevated.

There is a risk of portal vein thrombosis. At the same time he pointed out that drug-related side effects occur more frequently in patients with AIH and liver cirrhosis anyway.

NASH: metabolic and hepatic aspects brought together for therapy

As M. Trauner, Vienna (Austria), told the audience, “10–20% of patients with non-alcoholic fatty liver develop liver cirrhosis which can progress to hepatocellular carcinoma” (Fig. 21). However, liver cirrhosis does not have to precede HCC. The carcinoma can also develop in pre-cirrhotic stages. A variant of the PNPLA3 gene coding for adiponutrin has recently been identified as a marker with prognostic relevance.

An investigation of 100 Europeans with HCC associated with NAFLD showed that the PNPLA3-rs738409 genotype roughly doubled the risk of HCC. Detection of this genetic variant could make it possible to identify patients at increased risk. According to M. Trauner, the combination with other risk factors such as age, sex, diabetes and cirrhosis is critical. In terms of treatment, attempts are being made to approach NASH from the metabolic and hepatic side. Metformin and statins could have favourable effects on complications of cirrhosis and the survival of cirrhosis patients.

Norursodeoxycholic acid and the FXR agonist obeticholic acid are also an option for the future and are currently being evaluated. However, the evidence for vitamin E in patients with cirrhosis is poor. It is recommended primarily for non-diabetic patients with NASH (without cirrhosis).

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Fig. 20 Efficacy and tolerability of budesonide combined with azathioprine compared to prednisone plus azathioprine in autoimmune hepatitis [Manns MP, et al. Gastroenterology. 2010;139:1198–1206].
HBV infection: nucleoside analogues are first-line treatment in decompensated liver cirrhosis

Antiviral therapy should be considered in the case of compensated cirrhosis with evidence of HBV DNA, even if transaminase levels are normal. R. Thimme, Freiburg (Germany), quoted the EASL recommendations. They specify that there should be no delay if the liver cirrhosis is already decompensated because the risk of HCC is even higher than in compensated cirrhosis and much higher than in patients infected with HBV who do not have liver cirrhosis. Antiviral therapy with entecavir or tenofovir (both nucleoside analogues) is indicated in patients with decompensated liver cirrhosis.

At the same time close observation is necessary so that HCC is not overlooked. Pegylated interferon is another option for patients with compensated cirrhosis associated with HBV.

Gustav Paumgartner Liver Research Fellowship

The Gustav Paumgartner Liver Research Fellowship is a new liver research post established by Leber Centrum München® (Munich Liver Centre) with support from Dr. Falk Pharma GmbH and CSL Behring. As the first scientist to be appointed to this fellowship, Dr. Christian Steib from Munich can look forward to successfully continuing his research into mechanisms and new treatment approaches in portal hypertension.
Treat HCV infection with DAAs as early as possible if cirrhosis is present

There has been a revolution in the treatment of hepatitis C. Innovative direct-acting antivirals (DAAs) such as sofosbuvir, daclatasvir and simeprevir, all of which were authorised in 2014, now make it possible to provide interferon-free treatment reaching high SVR12 rates. This also applies with cirrhosis. F. Zoulim, Lyon (France), recommended treating all patients with cirrhosis as soon as possible, giving preference to regimes without interferons. The choice of DAA depends on the genotype and the medical history. Simeprevir should not be used in patients who have not responded to a protease inhibitor. The problem patients still include those with a genotype 3 infection and liver cirrhosis and those with decompensated liver cirrhosis.

Outstanding posters

Falk Symposium 195

Three poster prizes were awarded at Falk Symposium 195 “Challenges and Management of Liver Cirrhosis” in Freiburg for outstanding work relating to liver cirrhosis. The prizes, endowed by the Falk Foundation, were presented to the winners by Foundation Chair Ursula Falk and the symposium’s scientific organisers Profs. Alexander L. Gerbes (Munich), Florence Wong (Toronto) and Massimo Pinzani (London).

The first prize was awarded to F. Reiter, Munich (Germany), for his poster “Calcitriol inhibits activation of hepatic stellate cells in vitro and ameliorates hepatic damage in vivo.”

Second prize went to C. Österreicher, Vienna (Austria), for “Hepatic stellate cells are the major source of collagen in murine models of liver fibrosis.”

J. Schewe, Munich (Germany), received third prize for her poster “Activation of Toll-like receptors (TLR) on isolated Kupffer cells (KC) and sinusoidal endothelial cells (SEC) of the liver: Opposing effects on the production of the vasoconstrictor thromboxane B2.”
Editors: Professor Thimme, liver cirrhosis can have many different causes – viral hepatitis, alcohol or non-alcoholic steatohepatitis. Are all these forms of liver cirrhosis comparable in terms of pathogenesis and prognosis, regardless of the cause?

Professor Thimme: At the moment the mechanisms leading from fibrosis to cirrhosis are being studied intensively and it looks as though the forms of cirrhosis should not be seen as entirely uniform. This is apparent simply from the fact that the risk of liver cirrhosis leading on to hepatocellular carcinoma is clearly different depending on the cause. It is relatively high for viral hepatitis and haemochromatosis but tends to be low for primary biliary cirrhosis. That means there are certainly different pathomechanisms at work on a molecular level. Up to now, though, these differences have not been clinically relevant. In clinical practice, liver cirrhosis is liver cirrhosis and the complications are treated in the same way. The monitoring is comparable too.

Editors: As yet, in spite of intensive research, there are no specific antifibrotic agents available for the treatment of liver fibrosis. Where is the problem?

Professor Thimme: The development of fibrosis is a multifactorial process that is currently being intensively studied. Different cell populations are involved as are cytokines and complex molecular processes which are still not understood down to the smallest detail. This means we cannot expect antifibrotic agents to come onto the market in the near future. But we do now know that fibrosis is generally reversible if the cause – where it’s known – is treated effectively. In concrete terms this means, for example, that I don’t need an antifibrotic to treat fibrosis developing from an HBV infection. Instead I have to treat the virus infection itself. Then the fibrosis disintegrates as well. This also applies if I induce weight reduction and improve the metabolic situation in the case of liver fibrosis due to NASH, or if I can achieve alcohol abstinence in case of ASH. You focus on the root cause to stop liver fibrosis from developing into liver cirrhosis.

Editors: What should be done if the development of liver cirrhosis cannot be stopped?

Professor Thimme: We should carry on treating the cause in that case too but we should look for possible complications at the same time. For example, an ultrasound examination is necessary, first and foremost to exclude hepatocellular carcinoma, and liver function tests should be carried out every 6 months. Gastroscopy should also be performed to spot varices at an early stage. The pros and cons of liver transplantation should be weighed up in every patient case.
with decompensated liver cirrhosis or liver cirrhosis with additional hepatocellular carcinoma. The MELD (Model for End-stage Liver Disease) score is used to evaluate the severity of liver disease. This takes into account the classic criteria such as Quick, bilirubin and creatinine values. After liver transplantation patients have a good prognosis. The fall-off in survival times observed in recent years is due to the fact that much sicker patients are now receiving transplants.

**Editors:**
The important thing is to recognise liver damage early on and to observe progress. How do you diagnose liver fibrosis?

**Professor Thimme:**
In certain constellations still by liver biopsy. Otherwise, we measure liver stiffness using transient elastography. A definite diagnosis is not possible with ultrasound.

**Editors:**
Would it be useful to screen for liver stiffness in high-risk patients?

**Professor Thimme:**
I don't think that general screening of liver stiffness would be useful. It would be more helpful to test liver function and to look in more detail in cases where the values are elevated. Raised liver function test values should always be taken seriously, even if these are often caused by a condition that is very easy to treat, like viral hepatitis, autoimmune hepatitis or haemochromatosis. It is not enough just to assume that NASH is the cause if the patient is overweight. It should always be remembered that NASH is a diagnosis of exclusion in which the other potential causes must be considered first.

**Professor Thimme,**
thank you very much for the interview.
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Falk Symposia 199-200

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