Liver Diseases in 2013: Advances in Pathogenesis and Treatment
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“Hepatitis C”: This diagnosis has long been synonymous with a life-long, incurable disease. The only available therapeutic option was to minimize the viral load as far as possible to reduce the risk of progression to fibrosis, cirrhosis and ultimately hepatocellular carcinoma.

This frustrating scenario is on the cusp of a dramatic change. With the development of DAAs (direct-acting antivirals), a cure appears to be within reach for a significant proportion of patients. This is also due to the shift from pegylated interferon as an indispensable component of therapy and towards interferon-free strategies.

In liver autoimmune diseases, early diagnosis and adequate therapy are of paramount importance for patient prognosis. This allows a majority of patients to be satisfactorily treated, with a prospect of an almost normal life expectancy, with steroids in combination with azathioprine for autoimmune hepatitis and ursodeoxycholic acid (UDCA) for primary biliary cirrhosis. But what can be done with non-responders? Primary sclerosing cholangitis continues to be a “black box”. Clinical data on nor-UDCA as well as bile acid receptor agonists is therefore eagerly awaited to allow these gaps to be bridged.

If the liver disease nevertheless progresses to hepatocellular carcinoma, surgery is the therapy of choice, although this continues to have a high rate of recidivism. For some patients therefore, liver transplantation will continue to be inevitable in the future. Of particular interest here is data showing that in at least some cases, immunosuppression may not be required in the long term.

There were intense and at times controversial discussions around these topics at the international Falk Symposium 191 “Liver Diseases in 2013: Advances in Pathogenesis and Treatment”. This exchange between basic research and clinical practice will also form the basis for even better care of patients in hepatology.
Liver Diseases in 2013: Advances in Pathogenesis and Treatment

Don’t just stand by and watch when viruses or steatosis threaten the liver

Hepatotropic viruses induce chronic hepatitis, fibrosis and cirrhosis as well as hepatocellular carcinoma. For hepatitis C, however, the future now looks bright: New, direct-acting antivirals promise a cure for a majority of patients. At the same time, the problem of non-alcoholic steatohepatitis continues to grow, although this could easily be prevented by weight control and exercise.
Curing hepatitis C is no longer wishful thinking

Viral hepatitis, first and foremost hepatitis C, is currently the main focus of hepatology. The reason is simple: the rapid development of active substances that promise a cure for the first time in the majority of cases. Given a worldwide population of 170 million HCV-infected patients, the current “hype” is entirely understandable, particularly as the number of deaths due to hepatitis C has now exceeded those due to HIV infections. The development of therapeutic strategies began in the mid-80's with the use of interferon (Fig. 1) and came to a temporary halt with the approval of the first protease inhibitors in 2011. Telaprevir and boceprevir in combination with pegylated interferon (PEG-IFN) and ribavirin substantially improve the success of treatment of genotype 1 HCV infections and allow a shorter treatment duration for two thirds of the patients. Yet they are not without their problems, as M.P. Manns, Hanover (Germany), made clear. Skin rashes can occur or anemia can force treatment to be discontinued. In addition, they are only effective for genotype 1 and there are differences in response for genotype 1a and 1b.

Interferon is not the only way

Treatment strategies with new DAAs (direct-acting antivirals) such as NS3/4A protease inhibitors, NS5A inhibitors as well as nucleoside and non-nucleoside NS5B polymerase inhibitors, some of which will soon be approved, promise a real breakthrough. In combination with PEG-IFN and ribavirin, they have achieved very high rates of recovery within 12-24 weeks in patients with genotype 1 infections, according to G.M. Dusheiko, London (Great Britain). Now, however, there is particular interest in interferon-free therapeutic regimes with or without ribavirin, with more than 90% of genotype 1 patients achieving sustained virological response (SVR).

With genotypes 2 and 3, patients without cirrhosis treated with sofosbuvir plus ribavirin achieved a SVR12 of 98% in genotype 2 and 61% in genotype 3. Genotype 2 patients with cirrhosis also responded well (SVR12: 92%), unlike cirrhotic genotype 3 patients that had not previously responded to therapy with PEG-IFN and ribavirin (SVR12: 34%) and remain the “problem children”. Even patients with treatment failure under telaprevir or boceprevir can benefit from the new DAAs. The combination of daclatasvir plus sofosbuvir with and without ribavirin achieved nearly 100% SVR rates in these patients.

Fig. 1 Chronic Hepatitis C: Diagnostics and Therapy “Hand in Hand” (M.P. Manns, Z Gastroenterol 2013;51:363–370)
Hepatitis D: nearly a third cured with PEG-IFN

Direct antiviral therapy is not possible for patients with hepatitis D. There are currently 30,000–50,000 patients infected in Germany (Fig. 2). The largest global trials for hepatitis D are HIDIT (Hep-Net International Delta Hepatitis Intervention Trial) 1 and 2, two multicenter, international trials sponsored by Hep-Net. The first trial demonstrated that out of a total of 90 patients with chronic HDV, 28% achieved complete recovery with pegylated interferon over a period of 48 weeks. Adding adefovir showed no additional benefit versus placebo. Monotherapy with adefovir did not achieve HDV RNA negativity. HIDIT 2 investigates the benefit of treatment with tenofovir versus placebo in addition to PEG-IFN-α2a in a total of 120 patients over 96 weeks. A 5-year follow-up is planned.

Chronic sleep apnea: bad for the liver

Although the majority of chronic hepatitis cases are caused by hepatotropic viruses, an inflammatory liver disease can also simply be caused by fatty deposits in the liver. This can lead to cirrhosis when not detected early enough. Non-alcoholic steatohepatitis (NASH) should always be considered according to V. Ratziu, Paris (Fig. 3). An existing NASH can be worsened by obstructive sleep apnea.

NASH: When should it be considered?

Metabolic risk factors
- BMI > 25 kg/m²
- Hip circumference approx. 94/80 or 102/88
- Arterial hypertension 135/85 mmHg
- Glycemia > 6.1 mmol/l
- TG > 1.7 mmol/l
- HDLc < 1/1.3 mmol/l
- Ferritin 350 µg/ml
- Atheromatosis
- First-degree relative family history

Changes in liver values
- Steatosis on ultrasound
- Diagnosis of cirrhosis

Fig. 2 Worldwide prevalence of hepatitis D (Delta) (www.hepatitis-delta.org)

Fig. 3 When should NASH be considered? (V. Ratziu, Paris)
The more pronounced the chronic intermittent hypoxia is, the more pronounced the development of fibrosis. Procollagen 3-N terminal peptide (P3NP) has recently been identified as a non-invasive marker of NASH and fibrosis. Treating NASH initially involves improving metabolic risk factors. Resounding successes have been achieved with bariatric surgery, said C.P. Day, Newcastle-Upon-Tyne (Great Britain). Steatosis improved in 91% and steatohepatitis improved in 81%, potentially also improving fibrosis. Nevertheless: Bariatric surgery is not considered as the treatment of choice for NASH, said C.P. Day, though nor is NASH a contraindication if obesity surgery should be considered for other reasons.

**Vitamin E? Beware of prostate cancer!**

Successful drug strategies for NASH that directly target the liver are in rather short supply. Pentoxifylline showed questionable histologic benefit, resveratrool reduced fat in the liver and caspase inhibitors improved ALT levels. Positive study results exist for vitamin E, said C.P. Day, that show it could be effective in some patients. He advised caution, however, because it was shown that the risk of hemorrhagic stroke and prostate cancer is increased by vitamin E supplementation, and daily intake of more than 400 IU also leads to an increase in overall mortality.

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**Outstanding posters**

Three poster prizes were awarded for outstanding work in the field of hepatology at the Falk Symposium 191 “Liver Diseases in 2013: Advances in Pathogenesis and Treatment” in London. The award, sponsored by the Falk Foundation e.V., was presented to the winners by Dr. R.W. Chapman, Oxford, one of the symposium’s scientific organizers.

1st Prize: **Prof. Dr. Amal Kumar Santra**, Center for Liver Research, Kolkata (India)

2nd Prize: **Dr. Andrew King**, University of Birmingham (Great Britain)

3rd Prize: **Dr. Esther Raskopf**, University Hospital Bonn (Germany)
Liver-associated mortality is on the increase, whilst treatment options remain limited, said P. Newsome, Birmingham (Great Britain): “There is still no cure for cirrhosis of the liver.” Researchers have concentrated their search for therapeutic options on hematopoietic stem cells, mesenchymal stromal cells, human embryonic stem cells and a few other cell types, with positive results in animal studies. A randomized controlled trial was conducted to compare autologous bone marrow mononuclear cell transplantation (BMMCT) combined with G-CSF (granulocyte colony-stimulating factor) in 58 patients with decompensated alcoholic liver disease and cirrhosis. Improvement in MELD score was comparable and BMMCT exhibited a similar safety profile. A comparable concept is currently being studied in the REALISTIC (Repeted Autologous Infusions of Stem Cells in Cirrhosis) trial. Patients with a MELD score between 12 and 15 and decompensated hepatic cirrhosis are treated either with G-CSF alone or in combination with bone marrow stem cells and are compared with a control group. The primary endpoint is the change in MELD after 3 months. P. Newsome also pointed out that the most appropriate procedure must be selected each time for (stem) cell treatment as well (Fig. 4).

An interesting therapeutic approach for autoimmune liver disease was presented by A.W. Lohse, Hamburg (Germany), using cellular therapy to modulate immunity. This is based on the idea that there is a regulatory dysfunction in the immune system, with the balance shifting against the regulatory T cells. Equilibrium could potentially be restored by the transfer of regulatory T cells.

**Inhibiting the inflammasome-dependent inflammatory mechanism**

The inflammasome is a cytosolic protein complex found in macrophages and neutrophilic granulocytes. Two activation steps stimulate caspase 1, which ultimately converts the pro-inflammatory cytokine interleukin-1β into its ac-
tive form, explained W.Z. Mehal, New Haven (USA). This causes inflammation (Fig. 5). Caspase-1 deficient mice thus have reduced inflammation and fibrosis.

The inflammasome-dependent inflammatory mechanism plays a crucial role in inflammatory liver disease and is thus a target for treatment. For example, interleukin-1 receptor antagonist ameliorates inflammasome-dependent alcoholic steatohepatitis in mice. TLR (Toll-like receptors) antagonists or antagonists for the ATP receptor P2x7 may also be of relevance.

Fig. 5
Not always lifelong: immunosuppression after LTx

Does a liver transplant equate to lifelong immunosuppression? Not necessarily, according to A. Sanchez-Fueyo, London (Great Britain).

He indicated that a not inconsiderable proportion of transplant recipients develop spontaneous tolerance during follow-up and are able to discontinue immunosuppressive medication. In a current study immunosuppressive drugs were discontinued in 42% of 102 patients. Spontaneous rejection occurred in just over half. Time since transplantation was a crucial factor for patient response: if transplantation had occurred in the last 6 years, just 13% of attempts to discontinue medication were successful, versus 80% of patients where more than 11 years had elapsed (Fig. 6).

Serious consequences of CD39 deficiency

A search is now underway for markers that could provide information to identify patients for whom an attempt should be made. It appears worthwhile to check the serum ferritin level. This is higher in patient who developed a tolerance. The molecular profiling of liver tissue from tolerant and non-tolerant patients showed differences in genes that are involved in iron metabolism. Iron metabolism could also be significant in controlling rejection.

ASA against HCC

Hepatic recruitment of HBV-specific pathogenic CD8+ effector cells does not require selectins or integrins. Instead, platelets are involved. They express CD44 and therefore can interact with hyaluronic acid in the hepatic sinusoids. “Platelets play a key role in this process” emphasized L.G. Guidotti, Milan (Italy).

Consistent intake of platelet-aggregation inhibitors such as ASA or clopidogrel reduce hepatic homing of HBV-specific effector CD8+ cells. In chronic hepatitis, this can prevent hepatocellular carcinoma (HCC) or delay its onset and extend survival. The principle, according to L.G. Guidotti, only functions in immune-mediated liver pathology, not with pure fibrosis.
**Session II**

**Viral hepatitis I**

**Reconstitution of T-cell response with HBV infection**

The T-cell response in patients with chronic HBV is weak or almost undetectable (Fig. 7). Optimizing antiviral therapy offers the opportunity to reconstitute the antiviral T-cell control. This allows transient low CD8+ T-cells to reconstitute. In addition, there are indications, according to M. Maini, London (Great Britain), that long-term treatment with nucleos(t)ide analogues normalizes T-cell function, above all in patients that will achieve an HBsAg seroconversion. PEG-IFN therapy did not result in a regeneration of HBV-specific T-cells. The expansion of NK (natural killer cells) with antiviral potential is activated however. A look at complementary effects on the immune system forms the rationale for combining nucleoside analogs and PEG-IFNs in M. Maini’s view. The antiviral T-cell response can also be improved by boosting the existing T-cells.

**Endogenous cell factors as target**

Hepatitis C viruses demonstrate high variability and a high rate of replication. Primary targets for antiviral therapy are the viral enzymes. Would it also not be possible to include patient factors as a target in the considerations, asks T. Pietschmann, Hanover (Germany). The focus here is on endogenous factors required by the virus for replication. Genotypes do not play a role here and the risk of resistance is eliminated.

**Future sequencing technology**

In molecular diagnostics of HCV infection, real-time PCR is “excellent” according to M.R. Thursz, London (Great Britain), and has demonstrated fully comparable bDNA detection.

![Fig. 7 Therapeutic options for restoring antiviral T-cell control (M. Maini, London)](image-url)
The detection of HCV core antigen offers an alternative to HCV RNA to monitor viral replication. It loses sensitivity at LLOD 500–3000 IU/ml, however. The future lies in new revolutionary sequencing technologies such as NGS (next generation sequencing) or “deep sequencing”, which allows transcripts to be detected reliably even at very low copy numbers.

**Careful consideration required:**

**HCV eradication before LTx**

If there were any evidence of serum HCV-RNA in patients infected with hepatitis C virus (HCV) prior to liver transplantation (LTx), recurrence of HCV post transplantation is preprogrammed. Eradication of HCV by effective antiviral therapy prior to liver transplantation is an effective strategy for preventing reinfection, according to X. Forns, Barcelona (Spain).

“Triple therapy prior to liver transplant should only be indicated in patients with compensated cirrhosis of the liver, e.g. when HCC is the indication for the liver transplant, and there is no clinically significant portal hypertension”, said X. Forns. He proposed an individualized procedure based on the data which uses an algorithm (Fig. 8) that is essentially based on the genotype and previous response to antiviral therapy.

![Fig. 8](image-url)

**Individualized procedure for liver transplantation – as of October 2013**

(X. Forns, Barcelona)

**Patients awaiting LTx (HCV)**

- **Child-Pugh < 8 (MELD < 18)**
  - **Genotype 2,3 or 4**
    - **Naïve**
      - **PEG-IFN + RBV***
    - **Relapser**
      - **PEG-IFN + RBV***
    - **Non-responder**
      - **No treatment***
- **Child-Pugh ≥ 8 (MELD ≥ 18)**
  - **No treatment**
  - **Null-responder**
  - **Consider clinical trial IFN-free (DAAs)**
  - **Consider clinical trial IFN-free (DAAs)**
  - **VL > 1 log<sub>10</sub> after lead-in**
  - **VL < 1 log<sub>10</sub> after lead-in**
  - **PEG-IFN + RBV + TPV/BOC**

* Consider clinical trial

**TPV = Telaprevir**
**BOC = Boceprevir**
**RBV = Ribavirin**
**VL = Viral load**

**Do not add protease inhibitors if portal hypertension and albumin < 35 g/l**
Session III

Viral hepatitis II

Predictive value of quantifying HBsAg

M. Cornberg, Hanover (Germany), called for HBsAg clearance to be improved. This could be achieved in the coming years by the combination of IFN and nucleos(t)ide analogs (NUC). Toll-like receptor agonists and therapeutic vaccines are a long-term option. This requires biomarkers that indicate the immune control of HBV and can be used as predictors for the loss of HBsAg.

The HBV DNA assay is not suitable for this because the reduction of HBV-DNA under nucleos(t)ide analogues is not accompanied by an improvement in intrahepatic cccDNA. Quantification of HBsAg is a better marker for immune control. The advantage has been shown in various experiments. For example, low HBsAg levels (< 1000 IU/ml) in combination with low levels of HBV-DNA (< 200–2000 IU/ml) constitute a high positive predictive value for inactive carrier state versus reactivation. A combination of HBsAg < 1000 IU/ml and HBV-DNA < 2000 IU/ml is associated with low incidence for HCC and HBsAg levels < 100 IU/ml have a high predictive value for spontaneous HBsAg clearance. Data on co-infection are scarce.

M. Cornberg showed that in patients with HBV/HIV coinfection HBsAg levels tend to be higher than in HBV monoinfection.

“Towards eradication”

The protease inhibitors telaprevir and boceprevir are approved for the treatment of HCV infection as a triple therapy in combination with interferon (IFN) and only in genotype 1. Therefore, DAAs that function without IFN promise a long-lasting virological response and are active against more genotypes are highly anticipated. These include asunaprevir, daclatasvir, sofosbuvir or faldaprevir and others.

The combination of these DAAs (direct-acting antivirals) with and without ribavirin was investigated in different therapeutic regimes in treatment-naive and pre-treated patients as well as with different genotypes.

With the most promising results: perhaps an SVR (sustained virological response) that is up to 100% depending on regimen and genotype.

Even patients who do not respond to telaprevir or boceprevir may benefit. Genotype 3 still appears to be problematic. Although sofosbuvir plus ribavirin did at least achieve an SVR of 93% within 12 weeks in genotype 2, this was only 61% in genotype 3. The combination of genotype 3 and cirrhosis above all was problematic, with an SVR of only 21%. Nevertheless G.M. Dusheiko, London (Great Britain), painted a rosy future for IFN-free HCV therapy: simpler, shorter, safer, more effective, better tolerated but unfortunately not more affordable. “We are moving towards eradication.”
Hepatotropic viruses and obesity increase the HCC risk

The most frequent complication in HCV infection is hepatocellular carcinoma (HCC), which itself is in most cases a secondary complication of advanced cirrhosis of the liver. Out of 214 patients with compensated cirrhosis of the liver, 68 developed an HCC following HCV infection, leading to death in 44%.

The best form of prevention is eradication of the virus, as shown in a Danish study. Patients with positive HCV RNA developed HCC more frequently than patients with negative HCV RNA. The inverse is true if alcohol abuse or diabetes accompanies HCV infection (Fig. 10).

But age is also relevant, said A. Vogel, Hanover (Germany). Therefore the risk is highest for HCV patients more than 65 years old in which a lasting virological response has not been achieved. Along with hepatotropic viral infection, obesity should not be underestimated as a risk factor for HCC. A prospective study of over 900,000 adults including 57,000 cases of cancer showed that the risk of liver cancer was 4.5 times higher in subjects with a BMI $\geq 35$ kg/m².

In Great Britain, non-alcoholic steatohepatitis has since become the most common cause of HCC, according to A. Vogel. The pathogenetic mechanism is still not yet completely understood. Excess fat appears to influence the interaction between adipocytes, hepatocytes and immune cells. Metformin reduces the risk of HCC by about 50%. As insulin and IGF-1 levels come down, tyrosine kinase signaling is reduced and thereby blocks the mTOR pathway.

And the winner is sorafenib!

Resection is the best treatment option for patients with HCC in non-cirrhotic liver. It is indicated in the early stages with at most three foci, said J. Bruix, Barcelona (Spain). Portal pressure and bilirubin levels are also crucial when deciding on treatment and both should be within normal range. 50–70% of patients experience a relapse within 5 years of resection. At that stage chemoembolization and chemotherapy, internal radiotherapy (brachytherapy) or liver transplantation should be considered. There is no evidence supporting chemotherapy in advanced hepatocellular carcinoma. “According to Prof. Bruix it is the oral multikinase inhibitor sorafenib that is “making the running” here, as convincingly demonstrated in the SHARP study. It significantly improved the median survival by 2.8 months compared to placebo (10.7 months vs. 7.9 months).
**Undervalued:**
**Oxysterols in biliary carcinomas**

Cholangiocarcinomas are closely linked to hepatobiliary inflammation, said G.J. Gores, Rochester (USA). He confirms Virchow’s hypothesis from 1863 in the process: “Lymphoreticular infiltration of cancer reflected the origin of cancer at sites of inflammation”. All too often, in his view, insufficient attention is paid to the significance of changes in the composition of bile in the pathogenesis of biliary carcinoma. Oxysterols, which are oxidated metabolites of cholesterol and are abundant in bile, are endogenous ligands for the hedgehog signaling pathway. Inhibition of this signaling pathway, by vismodegib for example, can at least reduce the occurrence of tumors in rats.

**Palliative stents in cholangiocarcinoma: metal preferable to plastic**

Prognosis is poor in cholangiocarcinoma, with 5–10% 5-year survival rates. Surgery represents the only chance of cure. Most patients however have non-resectable tumors and the risk of recidivism is high. Stents are used as a palliative approach, with plastic and metal stents available.

A current randomized trial comparing SEMS (self-expanding metallic stents) to plastic stents in a total of 91 patients with unresectable complex hilar cholangiocarcinoma shows the superiority of SEMS. Draining success rates were higher (82% vs. 54%) and early complications were less common (24% vs. 41%), explained S.P. Pereira, London (Great Britain).

The UK photostent 02 trial with 240 patients showed that the combination with a photodynamic therapy (PDT) had no additional benefit: overall survival did not differ significantly with 9.2 months after stent therapy alone and 6.1 months after combination therapy.

![Figure 10](image.png)

**Figure 10** Cofactors such as diabetes increase HCC risk in patients with HCV (B.J. Veldt, et al., Hepatology 2008;47:1856–1862)
Editor:
Professor Manns, a number of hepato-
logical problems were discussed at the
International Falk Symposium 191. Which
topic is currently of most concern to
hepatologists worldwide?

Professor Manns:
The focus is undoubtedly on treating
chronic hepatitis C as we now have a re-
alistic chance of actually curing this in-
fec tious disease in the form of the new
direct acting antivirals which come on
line from 2014. This is highly relevant.
There are currently 170 million people
around the world infected with the hepa-
titis C virus (HCV) and the incidence of
deaths is higher than in HIV-infected pa-
tients. HCV infection is the number 1
cause of liver transplants. Moreover, un-
like HBV infection, there is no vaccination.
And there will be none.

Editor:
What were the decisive advances?

Professor Manns:
The development of the two protease in-
hibitors boceprevir and telaprevir was
already a step in the right direction as
they act directly on viral structures.
However, they are only effective in com-
bination with PEG interferon (PEG-IFN)
and ribavirin, and only in genotype 1.
The breakthrough finally occurred with
substances that act on crucial structures
of the virus: NS3/4A protease inhibitors,
NS5A inhibitors and nucleoside and
non-nucleoside NS5B polymerase inhib-
itors. Combinations of these agents al-
low long-term virologic responses, in
some cases in 90% of patients, to be
achieved without interferon and in some
cases without ribavirin, largely regard-
less of genotype. The aim is to achieve
recovery within 8–12 weeks with a fixed-
dose combination of substances such as
a polymerase inhibitor and an NS5A in-
hibitor. Recovery is demonstrated to re-
duce not only liver-related mortality but
also overall mortality rates. There is
therefore death beyond the liver.

Editor:
The therapeutic goal for HBV has also be-
come more ambitious: HBsAg loss. Is this
realistic?
Although the options available to date, pegylated interferons and nucleos(t)ide analogs, do reduce HBV DNA considerably, HBsAg loss is only partially achieved. One successful approach might be long-term suppression of virus replication followed by stimulation of the immune system. The main candidates here are TLR (Toll-like receptor) agonists, which stimulate the innate immune system or therapeutic vaccination which activates the acquired immune system. Until we actually achieve HBsAg loss in the majority of patients through time-limited treatment, however, it is important to suppress viral infection as best we can.

Current long-term data from 2011 and 2013 have shown that treating liver cirrhosis patients with entecavir or tenofovir not only prevents progression of cirrhosis but even reverses the cirrhosis.

Editor: Is research into other forms of viral hepatitis neglected?

Professor Manns: No, not at all. The results of the HIDIT-2 trial (Hep-Net-International Delta-Hepatitis Intervention Trial) were presented at the AASLD 2013 meeting. This compares PEG IFN in combination with tenofovir or placebo for the treatment of patients with Hepatitis D. 2 years ago it was shown that treatment with PEG IFN leads to HDV RNA negativity in 28% of patients. No benefit was shown for the combination with adefovir. The chronic form of hepatitis E (HEV) is mainly found in patients with chronic immunosuppression. They are treated effectively with ribavirin.

Editor: There are often no way to avoid transplantation in several liver diseases. Post-transplantation success rates are falling. Why?

Professor Manns: Since the introduction of the MELD score system for organ donation donors are increasingly older, organ recipients are increasingly severely ill. This has a negative impact on outcomes. Although fewer patients die whilst on the waiting lists, 1-year survival after transplantation has fallen from 84% to 52% after introduction of the MELD score system. What we really need is a national register and increased willingness on the part of donors. Or we manage to cure HCV infection in the majority of cirrhosis patients. Then we would need 25% fewer liver transplants and the problem would be at least partially solved.

Editor: After liver transplantation, patients must be immune-suppressed for their entire lives. At the Symposium, data were just presented that show at least a portion of patients tolerate the new organ without immune suppression. This would substantially improve quality of life. Do you have experience with this?

Professor Manns: This is a topic that we find very interesting and we want to do a study on it soon. Organ tolerance without medication – this is the dream of every immunologist. A pioneer of this approach is Professor Sanchez-Fueyo from London. He observed that a portion of patients who independently discontinued their immunosuppressants were able to tolerate their donated organs. This is similar to the situation, by which patients with autoimmune hepatitis discontinue their medication. At least 20% do not relapse.

Additional studies are now needed to show for which patients and how long after transplantation withdrawal of immunosuppression can be attempted.

Professor Manns, thank you for the interview.
When detected early and treated adequately, the majority of patients with an autoimmune liver disease have good chances of an almost normal life expectancy. Primary sclerosing cholangitis remains the “problem child”. Still, recent research outcomes are also encouraging here.

Autoimmune diseases of the liver

Autoimmune diseases of the liver are characterized by inflammatory damage of hepatocytes or bile duct epithelium, which when untreated leads to fibrosis of the liver and ultimately cirrhosis or hepatocellular carcinoma. They are rather rare, but frequently already occur early in life and reduce life expectancy considerably when first detected in advanced stages.

“If cirrhosis is there, the race is over” said M.P. Manns, Hanover (Germany). The reasons for the lack of treatment, according to G. Hirschfield, Birmingham (Great Britain), include the fact that the pathogenetic mechanisms leading to the loss of tolerance are not always completely understood. The entire range of risk factors was discussed (Fig. 11).

Activation of autoreactive T-cells is of significance for the pathophysiology of autoimmune hepatitis (AIH). As yet unpublished data show that regulatory T-cells occur in increased numbers intrahepatically with AIH. Under steroids, they decline significantly. If a flare occurs, they start to increase again.

Autoimmune hepatitis (AIH) also in older women

It is well-known that autoimmune hepatitis occurs in up to 90% of women, but not only in younger ages, as long assumed. “It occurs equally at all stages of life” emphasized U. Beuers, Amsterdam (The Netherlands). In other words: This diagnosis must be taken into consideration in older women as well. Game-changing diagnostics are hypergammaglobulinemia and the typical autoantibodies ANA, LKM-1 and SMA. Genetically, HLA-DR3 and 4 are present. Ultimately, histology is crucial, and last but not least the good response to immunosuppression, either through steroids alone or in combination with azathioprine.

In patients with AIH, but without cirrhosis, the more tolerable budesonide can be used as an alternative to prednisone. It has similar effectiveness, but fewer steroid-specific side effects when combined with azathioprine (European AIH-BUC 38; M. Manns, et al., Gastroenterology 2010;139:1198–1206).
**Budesonide during adolescence**

This also applies to adolescents, as shown by a pediatric sub-analysis currently published (European AIH-BUC Pediatric Sub-analysis; M. Woynarowski, et al., J Pediatr 2013;163:1347–1353). In youths between 9 and 17 years of age (n = 46), budesonide was equally successful in achieving and maintaining biochemical remission as prednisone, each in combination with azathioprine. Steroid-specific side effects were more infrequent, and in particular there was no weight gain as occurred in patients treated with prednisone: The young people gained 5.1 kg within the first 6 months under prednisone, and in contrast to only 1.2 kg gained under budesonide. If azathioprine is not tolerated, mycophenolate mofetil (MMF) can be tried. If azathioprine is not adequately effective, the next step is administration of tacrolimus. In a few selected patients infliximab was also tried, however, it can also trigger an AIH. The anti-CD20 antibody was also successfully used in some individual cases. “Especially when using infliximab and rituximab, a careful risk-benefit analysis must be performed in individual cases”, said M.P. Manns. In older patients with mild progression of AIH, treatment is not mandatory in his view.

**UDCA* for PSC:**

**no cholangiocarcinoma in responders**

The current outlook for primary sclerosing cholangitis (PSC) is also exciting, but in contrast to primary biliary cirrhosis (PBC), treatment with ursodeoxycholic acid (UDCA) is controversial. A current study (S. Al-Mamari, et al., J Hepatol 2013;58:329–334) based on data from the Oxford PSC Register evaluated 139 patients and showed that the extent to which alkaline phosphatase improved in serum (SAP) under UDCA was decisive for treatment success. If the SAP level was below 1.5 times the normal level after 2 years, the patients had a significantly better prognosis than patients with higher levels. In particular, no patient developed a cholangiocarcinoma during treatment with UDCA compared to 13 patients who did not respond to UDCA. SAP levels below 1.5 times the normal level were achieved under UDCA in 40% of the patients.

**Block VAP-1 for PSC**

An innovative approach for PSC is based on the relationship between PSC and colitis ulcerosa, which are frequently associated but do not always occur together at the same time. In the search for the “link”, it was shown that gut-derived mucosal lymphocytes are recruited to the liver via portal circulation and can trigger an inflammation, according to D.H. Adams, Birmingham (Great Britain). Long-lived memory cells can recirculate over many years. The endothelial adhesion molecule VAP (vascular adhesion protein)-1, is significantly involved in the recruitment of these lymphocytes, which act by inducing MAdCAM1 and are especially up-regulated in PSC (*Fig. 12*).

Blocking VAP-1 therefore is an applicable therapeutic strategy for PSC that should be investigated.

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*Ursodeoxycholic acid is not approved for the treatment of PSC.*
With PBC, the search for active substances for the third of patients that do not adequately respond to standard treatment with UDCA is the priority. The more potent nor-UDCA is promising and is currently being investigated in approximately 30 centers in 11 European countries. Likewise the two cellular bile acid receptors TGR5 and FXR are the focus of research as a target. Agonists improve bile acid homeostasis but, similar to UDCA, also appear to have beneficial effects on the bicarbonate umbrella that protects the biliary epithelium (see Beuers interview).

A phase II trial is under way. Other agonists for nuclear receptors found are only at the preclinical stage: the PPARγ receptor agonist curcumin or also vitamin D2 as a vitamin D receptor agonist that could inhibit inflammation and fibrosis.

**Strive for normalization of liver values in autoimmune hepatitis**

If AIH is treated early, patients have a normal life expectancy. Whereas the previous therapeutic goal was only transaminase levels under 2x the upper limit of normal (ULN), normalization of transaminases is the new goal since the new AASLD American Guidelines in 2010. Only this will actually stop the progression.

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[Fig. 12] Histology of the liver in PSC (A.J. Grant, et al., Hepatology 2001; 33:1065–1072)

Stained MAdCAM-1 in the inflamed PSC liver (small portal vein on left, large on the right)
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Liver Diseases in 2013: Advances in Pathogenesis and Treatment

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C.P. Day
M.P. Manns
Non-alcoholic fatty liver disease (NAFLD) is common. It is present not only in up to a third of adults but also in 17% of 15–19-year-olds, with the risk of progression to NASH (non-alcoholic steatohepatitis) and further progression to cirrhosis (Fig. 13).

The pathogenesis of NAFLD is based on a complex interaction between environmental factors, genetic predisposition and intestinal microbiota. This leads to an overload of hepatocytes with fat that paves the way for progressive disease. The influence of free fatty acids that induce lipotoxicity is crucial, explained A.E. Feldstein, La Jolla (USA).

At the same time, the fat-laden hepatocytes release proangiogenic signals that, according to the hypothesis, lead to a pathological angiogenesis (Fig. 14).

In-vitro and animal studies have shown that microparticles from hepatocytes induce angiogenesis. Vanin 1, which is expressed by microparticles, ensures their uptake in endothelial cells. Blocking of vanin 1 inhibits angiogenesis and therefore the development of fibrosis.

Secondary onset fatty liver disease is rare. However, possible causes to be excluded diagnostically include not just alcohol misuse but also drugs, Wilson disease, beta-lipoproteinemia or chronic HCV infection. Conversely, NASH must be considered for each patient with cirrhosis, emphasized V. Ratziu, Paris (France).

He warned against over-diagnosing alcoholic fatty liver. “30–50 g of alcohol per day is not sufficient to develop liver disease.” A primary NASH is likely if metabolic and hepatic risk factors such as excess weight, hypertension, hyperlipidemia and a positive family history interact along with an elevated ferritin level, altered liver function values and steatosis verified by ultrasound.
**Pay attention to fibrosis progression**

If NAFLD develops into a NASH the situation becomes critical. According to a long-term trial of 280 patients over 150 months, the mortality risk of liver disease is over 6 times higher for NASH versus NAFLD. Patients with concomitant diabetes are particularly at risk. The strongest risk factor is stage ≥ 2 fibrosis, with a 20-fold increase in probability. **S.H. Caldwell**, Charlottesville (USA), made it crystal clear: “We must pay attention to fibrosis progression”. The NFS (NAFLD fibrosis score) was identified as a meaningful non-invasive fibrotic marker predictive of death or transplantation in a multicenter cohort study over 9 years. It takes into account age, glucose, BMI, platelets, albumin and AST/ALT. The APRI (AST/Platelet Ratio Index) and BARD (BMI, AST:ALT Ratio, Diabetes) perform significantly worse.

**Think before prescribing vitamin E**

For patients with NASH, improving metabolic risk factors is the treatment priority. Metformin, which has been shown to provide a benefit, is also an established treatment. In addition, it is worth looking at therapeutic options that focus directly on the liver. In a placebo-controlled comparison of pioglitazone and the antioxidants vitamin E in NASH, the PIVENS trial, both active substances improved steatosis and inflammation scores, but only vitamin E also reduced ballooning.

A direct correlation with overall mortality was recently shown for the NFS in a 12 year follow-up.

In contrast fibrosis was not influenced. In the TONIC trial of patients with fatty liver disease, vitamin E was superior not only to placebo, but also to metformin for NASH.

The conclusion by **C.P. Day**, Newcastle-Upon-Tyne (Great Britain), was: “Vitamin E can be effective in some patients with NASH.” At the same time, however, he warned against using it without careful consideration, citing increased overall mortality in patients given daily doses > 400 IU as well as an increased risk of prostate cancer. The combination of vitamin E with ursodeoxycholic acid (UDCA) has shown promising results in a pilot study.
IgG4-associated cholangitis: fatal if missed

Diagnosis of IgG4-associated cholangitis (IAC), next to IgG4-associated pancreatitis one of the most frequent manifestations of IgG4-associated diseases, (Fig. 15), is problematic. IgG4 levels over 4 times normal, according to U. Beuers, Amsterdam (The Netherlands), are highly specific. If they are lower, it could indicate another disease and in up to 20% of patients the IgG4 level is not elevated. Key clinical signs are jaundice (77%) and weight loss (51%). The disease may also involve abdominal complaints and, less commonly, steatorrhea or new onset diabetes.

Radiologic studies show diffuse swelling of the affected organ. It is particularly problematic that these patients are frequently misdiagnosed with cholangiocarcinoma or pancreatic carcinoma, since IgG4-associated diseases, once detected, respond well to treatment with corticosteroids (see Beuers interview). The pathogenesis of IgG4-associated disease is still unclear. There are indications, however, that the IAC is triggered by a specific immune reaction driven by B-cells against as yet unknown antigens.
**T-cell vaccine against HCV**

It is never too late for a vaccine against HCV, even despite the new DAAs, said E. Barnes, Oxford (Great Britain). She reported on the development of candidates for a T cell vaccine against hepatitis C using adenoviruses boosted with MVA (Modified Vaccinia Ankara). With these, it was possible to generate a large number of polyfunctional CD4 and CD8+ HCV-specific T-cells in healthy subjects. To inhibit the destruction of the adenoviruses by the body’s defense system, serotypes were used that only infect chimpanzees.

**Preventing PVT with cirrhosis**

Does chronic liver disease equate to hypocoagulation? That was yesterday, E. Villa, Modena (Italy), felt. Now, cirrhosis is considered instead to be an unstable hemostatic condition with increased risk of bleeding and thrombosis. The approach to treatment has changed accordingly.

The aim is no longer only to prevent bleeding but also thrombotic diseases such as portal vein thrombosis (PVT). That this risk should not be underestimated is shown by the prevalence data.

These show that a PVT was found in 15–25% of in patients prior to liver transplantation or placement of a portosystemic shunt, in 7% of those hospitalized for liver disease and in 8–40% on autopsy. Anticoagulation with enoxaparin is reliable in preventing an PVT in advanced cirrhosis, as E. Villa showed in an independent prospective, monocenter, randomized controlled trial. The study enrolled patients with hepatic cirrhosis Child-Pugh scores of B7–C10 without PVT or spleno-mesenteric thrombosis.

**Inherited α1-antitrypsin deficiency: hiPSC plus gene therapy**

Is the use of human-induced pluripotent stem cells (hiPSC) an alternative to liver transplantation in patients with hereditary α1-antitrypsin deficiency? Potentially, according to S.T. Rashid, Cambridge (Great Britain), at least the reprogramming of the dermal fibroblasts of patients with PiZ α1-antitrypsin deficiency into disease-specific human hepatocyte-like cells has been achieved. The genetic defect in the cells was able to be corrected in terms of “molecular surgery”.

Cells developed in this way have been shown to be functional in mice with liver damage. Until this can be implemented as a cell-based therapy in humans, there is still a long way to go – with an uncertain outcome.
primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), according to G. Hirschfield, Birmingham (Great Britain). From his perspective, it is clear: “It is more than just the genome, it is the epigenome that determines the pathogenesis of autoimmune liver diseases.” Environmental factors continue to play a crucial role.

**Budesonide: more tolerable alternative in AIH**

The activation of autoreactive T-cells characterizes autoimmune hepatitis (AIH) immunity. Regulatory T-cells are elevated intrahepatically in AIH, and decrease considerably under steroids. Already in 1980, AIH under steroid therapy could be shown to have a significantly improved survival. For non-cirrhotic patients budesonide is an alternative to prednisolone. With a first-pass effect of over 90%, budesonide has considerably fewer systemic adverse effects.

M.P. Manns, Hanover (Germany), demonstrated a benefit for budesonide in a prospective randomized, double-blind multicenter trial (European AIH-BUC 38): the primary endpoint of complete biochemical remission with no steroid-specific side effects after 6 months was met in 47% of patients treated with budesonide/azathioprine versus just 18.4% receiving prednisone/azathioprine (Fig. 16). A biochemical remission was found in the context of the last follow-up examination in 60% of patients compared to 38.8%.

**Fatigue with PBC: maintain social contacts**

Current data from the British PBC cohorts show that patients with PBC suffer increasingly from fatigue. 45% complained about this, compared to only 22% in the control group. Fatigue was associated with a loss of autonomy, sleep disorders and depressions. The autonomic dysfunction appears to be a consequence of organic changes in the brain that can be detected in patients with PBC. This could be the reason that fatigue itself does not improve after transplantation. UDCA also did not have a positive effect. In contrast, exercise appears to help. In the British cohort, fatigue was frequently accompanied with an impairment in quality of life, however, not in all patients, stressed D.E.J. Jones.

**Fig. 16** Budesonide vs. prednisone (both in combination with azathioprine) for AIH: Biochemical remission and steroid-specific side effects (M.P. Manns, et al., Gastroenterology 2010;139:1198–1206)
Newcastle-Upon-Tyne (Great Britain). He ascribes this primarily to good social contact. Maintaining this is therefore especially important.

**UDCA: optimal in two thirds of PBC patients**

Ursodeoxycholic acid (UDCA, 13–15 mg/kg/day) has been recommended since 2009 in American and European guidelines for long-term therapy for PBC, including in asymptomatic patients. Favorable long-term effects are observed in particular in patients in the early stages of the disease at start of treatment and good biochemical response, according to R. Poupon, Paris (France). This good biochemical response after 1 year is defined by EASL as serum bilirubin of < 1 mg/dl, AP of < 3 ULN and AST of < 2 ULN, according to the Paris criteria, or as normalization or 40% reduction of SAP according to the Barcelona criteria. About one third of patients respond only suboptimally to UDCA. For these patients, the combination with budesonide or fenofibrate, depending on the biochemical situation, is an option (Fig. 17).

**PSC and IBD: closely associated**

Clinically the relationship is clear: Up to 10% of patients with inflammatory bowel disease (IBD) develop a PSC. Conversely, 70% of patients with PSC suffer from IBD. Particularly interesting here, according to D.H. Adams, Birmingham (Great Britain), is that both clinical characteristics normally occur at different points in time. This means a PSC can also still manifest after a colectomy and colitis ulcerosa can result after a PSC-related liver transplant. “Liver disease progresses independent of the progression of IBD,” he said.

**Nor-UDCA and FXR agonist: PSC treatment of the future**

One interesting treatment option for fibrosing cholangiopathies, according to M. Trauner, Vienna (Austria), is nor-UDCA, which in contrast to UDCA has an antifibrotic effect at least in mouse models. It could be significant not only for PSC but also for PBC. The clinical benefit is currently being studied in a Europe-wide trial. Agonists of the nuclear bile acid receptor FXR (farnesoid X receptor) and the bile acid receptor TGR5 are also among promising candidates for future treatment options. In mouse models the best results have been achieved with a dual agonist with a reduction in alkaline phosphatase (AP) and the ALT. Analogous to what could already be shown for UDCA in PBC, FXR also acts by improving the “bicarbonate umbrella,” among other things.

**Pruritus in cholestasis?**

**Cholestyramine**

Cholestasis is often associated with pruritus, frequently at the extremities, with intensity highest in the evenings and at night. Female patients suffer especially premenstrually, in late stages of pregnancy or during hormone replacement therapy. It is also more frequent in intrahepatic than extrahepatic cholestasis. What ultimately triggers the pruritus is still unclear. Bile acids and endogenous opioids have been ruled out by A.E. Kremer, Erlangen (Germany). The recommended therapy is first line treatment with cholestyramine, followed by rifampicin, naltrexone and sertraline. Experimental studies are being conducted into albumin dialysis or cannabinoids among others. UDCA is only indicated for intrahepatic cholestasis of pregnancy.
Editor: Autoimmune hepatitis (AIH) has an excellent prognosis providing that it is detected and treated at an early stage. How can this be achieved?

Professor Beuers: Autoimmune hepatitis (AIH) occurs across all ages, with a higher incidence in females than males. Acute-onset autoimmune hepatitis, with jaundice and very high transaminase levels, occurs in only one quarter of patients. In most cases initial symptoms are far less obvious. Clinically, the principal symptoms reported by patients are exhaustion or fatigue. Many suffer from joint pain, particularly in the small joints. Where young females present with pain in the small finger joints I would therefore always advise an ALT assay. The biochemical signs are clearer: high transaminases combined with more modestly elevated cholestasis markers rule out AIH as a differential diagnosis. A quite simple but more informative marker is IgG, which is elevated in many patients with AIH. If AIH is suspected, a liver biopsy must be performed and a histological analysis of the findings conducted. Today it often takes months, sometimes years until an AIH is properly diagnosed, because one finding is not followed up persistently enough. As a general principle, transaminases may not be elevated in young patients. This must always be clarified.

Editor: Primary biliary cirrhosis (PBC) is the most common autoimmune liver disease. One third of patients fail to respond adequately to ursodeoxycholic acid (UDCA). Are there predictors for this and if so what are the prospects for treatment?

Professor Beuers: Yes, biochemical predictors do exist. PBC patients with very high levels of alkaline phosphatase at the start of treatment have a poorer chance of achieving the target, say no more than 1.5 times normal values, after 1 year of treatment with UDCA. But we continue to treat these patients with UDCA as well. The data means we can no longer justify withholding this medication from PBC patients with elevated liver readings. Various options are currently being tested as add-on therapies in open-label trials. These include the FXR agonist obeticholic acid, the corticosteroid budesonide and the PPAR agonists bezafibrate or fenofibrate, for which small trials have shown an additional effect (in combination with UDCA) on laboratory markers and whose adverse event profile is well known. This combination will be increasingly common in my opinion, when the results of higher quality studies are available. The objective of individual treatment must be to improve the prognostic markers and with them, of course, the life expectancy and quality as much as possible. The exact procedure should be discussed with the patients in the individual cases.
**Editor:**
In sophisticated experimental investigations on the primary mechanism of action of UDCA in PBC, you came up with the idea of preserving the protective “bicarbonate umbrella” over the biliary duct cells. How should this be envisioned?

**Professor Beuers:**
Humans differ from many animals in that the bile has a high concentration of toxic (aggressive) bile acids. In the high millimolar concentration that is present in the bile, the biliary duct cells like many other cells would be destroyed, if these did not have any protection. We came to the conclusion based on our research work that bicarbonate forms a protective alkaline “umbrella” over the membrane of the biliary duct cells (the “biliary bicarbonate umbrella”), which prevents the attack of toxic bile acids. So long as an alkaline environment is maintained by bicarbonate, the bile acids are negatively charged (bile salts) and are not membrane-permeable.

In an acid environment, in contrast, they are protonated, therefore apolar and are able to pass through the biliary duct cell membrane. This leads to inflammation, premature cell aging, apoptosis and fibrosis. In patients with PBC, the bicarbonate transporter AE2 (anion exchanger 2) is inadequately expressed and holes form in the bicarbonate umbrella. UDCA appears to be able to protect the biliary duct cells by stabilizing the bicarbonate umbrella from toxic bile acids. I first speculated on the molecular intracellular mechanisms that could be responsible for the increase biliary secretion of bicarbonate through UDCA over 20 years ago in an article in the Journal of Clinical Investigation. This speculation has not been refuted to date.

**Professor Beuers:**
We conducted the world’s first randomized, placebo-controlled pilot study of UDCA in the treatment of PSC and were extremely favorably impressed by the data at the time. It resulted in a significant improvement in serum liver values that we have since recognized as prognostically relevant, such as bilirubin and alkaline phosphatase. Further studies led to different results. Currently, there are still no trials that meet the criteria to show convincingly that UDCA has, in particular, a favorable effect on survival rates of patients with PSC. The largest trial to date with an adequate dose of UDCA analyzed 198 patients, but it would have needed to include a minimum of 346 patients in the baseline calculations in order to assess the effect on survival rates during the trial and so in my view was considerably “underpowered.” Current data from Roger Chapman’s team in Oxford are interesting. It has shown that PSC patients given UDCA have an excellent prognosis if their alkaline phosphatase levels are below 1.5 times normal after two years of treatment. This is also my experience after 25 years of treating PSC patients.

**Editor:**
There are still no drug alternatives to UDCA, are there?

**Professor Beuers:**
That is correct. But we have to wait for the data on nor-UDCA. It follows essentially the same mechanism of action, the stabilization of the protective bicarbonate umbrella, but is more potent and could therefore have a better clinical effect.

**Editor:**
IgG4-associated cholangitis affects males over 60 in particular. If they have a suspected pancreatic or cholangiocarcinoma, the possibility of an IgG4-associated disease should therefore always be considered. The same applies in suspected cases of cancer affecting various organs. It was previously assumed that IgG4-associated cholangitis is a rarity. But as we look more closely into the disease, the greater the number of patients affected we find. And not infrequently what we actually find is that carcinoma or even PSC are misdiagnosed. This is particularly fatal since IgG4-associated disease can be treated very successfully with corticosteroids with response rates well over 90%. I would now advise against the treatment regimen we specified in the 2009 EASL Guidelines. It appears to be comparatively effective and better tolerated by patients to start with lower doses of corticosteroids and to administer them over a longer period. It’s likely that treatment will be similar to AIH – moderate to long-term low doses with corticosteroids in combination with azathioprine. Rituximab can be reserved for treating the extremely rare treatment-refractory patients and it appears to me to be unnecessary and too expensive based on the latest independent findings from Amsterdam that have characterized the IgG4-associated disease as an oligoclonal disease in which the IgG4 B-cell clones disappear from the blood after 4 weeks of prednisolone treatment. Liver transplantation in IgG4-associated cholangitis is normally excluded due to the higher ages of patients.

**Professor Beuers:**
Thank you for the interview.

* Ursodeoxycholic acid is not approved for the treatment of PSC.
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