Lisbon (Portugal), May 8–9, 2015

Falk Symposium report

Falk Symposium 197

Autoimmune liver diseases

Scientific organizers

Prof. Dr. U. Beuers,
Amsterdam
(The Netherlands)

Prof. Dr. H. Cortez-Pinto,
Lisbon
(Portugal)

Prof. Dr. P. Ginès,
Barcelona
(Spain)

Prof. Dr. A.W. Lohse,
Hamburg
(Germany)

Prof. Dr. A. Parés,
Barcelona
(Spain)
International Symposia and Workshops

Symposium 203
XXIV International Bile Acid Meeting: Bile Acids in Health and Disease
Düsseldorf, Germany
June 17 – 18, 2016

Symposium 204
Clinical Hepatology Practice in 2016: From Science to Therapy
Birmingham, Great Britain
September 2 – 3, 2016

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

Workshop
Communication and System Relevance in Liver Damage and Regeneration
Düsseldorf, Germany
January 21 – 22, 2016

Symposium 201
Gut-Liver Interactions: From IBD to NASH
Innsbruck, Austria
March 11 – 12, 2016

Symposium 202
Evolving Therapies in Clinical Practice in IBD
Prague, Czech Republic
April 29 – 30, 2016

FALK FOUNDATION e.V.
Leinenweberstr. 6
79108 Freiburg
Germany

Congress Department
Tel.: +49 (0)761/1514-125
Fax: +49 (0)761/1514-359
E-Mail: symposia@falk-foundation-symposia.org
www.falk-foundation-symposia.org
The significance of autoimmune liver diseases is often underestimated

Despite chronic liver diseases being some of the most common chronic conditions worldwide, their significance is often underestimated. This is particularly true for autoimmune diseases of the liver, such as autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC). The backgrounds of these conditions and the state-of-the-art in diagnostics and treatment formed the focus of scientific presentations and discussions at the international Falk Symposium 197 in Lisbon.

There is a much lower awareness in the public of liver disease compared to heart disease or cancer despite the fact that epidemiological studies show a worldwide, significant increase in chronic liver diseases such as cirrhosis of the liver and hepatocellular carcinoma. Cirrhosis of the liver is a prime example of this, says Prof. Dr. P. Ginés, Barcelona (Spain): “According to statistics, the disease was the 18th most frequent cause of death in 1990. By 2003, it had already moved up to 13th place.” Together, cirrhosis of the liver and liver cancer are the sixth most frequent cause of death worldwide. Despite this, there is little awareness of the conditions among the public.

Fig. 1: Autoimmune hepatitis occurs in all age groups.
(Groenbak L, Vilstrup H, Jepsen P, J Hepatol 2014; 60: 612)
**Increasing incidence of autoimmune liver diseases**

Although the exact causes are still unknown and such observations could be due to differences in diagnostic recording, there are strong indications to suggest an increasing incidence and prevalence of autoimmune liver diseases, such as AIH, PBC and PSC. This is especially the case in industrialized countries. "At least we are also seeing rising scientific interest in these conditions," says Prof. Ginès, referring to the huge surge in scientific publications on the topic. "Autoimmune diseases are currently being intensively researched," explains the hepatologist.

**Men and women across all age groups affected**

Nevertheless, misconceptions of the conditions still prevail in many areas, which often leads to delays in diagnosis. For example, it is wrong to assume that AIH is a disease that typically occurs in middle-aged women, explains Prof. Dr. A.W. Lohse, Hamburg (Germany). Although a significant proportion of women in their fifties and sixties develop the disease, AIH can affect individuals of all ages, including men (Fig. 1).

In Lisbon, similar findings were reported for PBC and PSC, with scientists emphasizing that the two conditions can occur in both men and women of all ages and that PSC and AIH sometimes even develop in children and adolescents.

**The importance of early diagnosis**

Prof. Dr. U. Beuers, Amsterdam (The Netherlands), underlined the importance of diagnosing these diseases as early as possible in order to give patients the best chance of receiving optimal treatment. The prospects for treatment are often better than most people assume, especially for AIH and PBC. Patients with elevated LFT values and unexplained fatigue should always be tested for AIH, while severe pruritus and elevated LFT values initially point towards a cholestatic liver disease such as PBC or PSC.

**AIH: Long-term steroid treatment in sufficient doses**

Steroids are the first-line treatment for AIH, says Prof. D.C. Gleeson, MD, PhD, Sheffield (Great Britain), but must be administered in sufficiently high doses and continued in the long term. To reduce the risk of side effects, prednisone doses may be reduced after remission has been achieved if the patient undergoes concomitant treatment with azathioprine, an immunosuppressant. Laboratory values return to normal within six to 12 months in up to 90% of patients following this treatment, with between 60% and 70% achieving histological remission.

Budesonide treatment should always be considered as an alternative to prednisone for non-cirrhotic patients, as this will reduce side effects. According to the largest study conducted on AIH, budesonide is at least as effective as prednisone and has the advantage of considerably reducing the risk of steroid-associated side effects (Fig. 2). All patients in the study received additional treatment with azathioprine.
**PBC: Two thirds of patients respond well to ursodeoxycholic acid**

PBC is routinely treated with ursodeoxycholic acid (UDCA), with two thirds of patients responding well to the bile acid, says Prof. Dr. A. Parés, Barcelona (Spain). “The prognosis for responders is extremely good – their life expectancy does not differ from that of the general population” (Fig. 4). He emphasizes that further advances in treatment are required for non-responders, however. Scientists are currently working on developing various strategies.

**Promising treatment norUDCA undergoes clinical trials**

One such drug undergoing development is norursodeoxycholic acid, explains Prof. Dr. M. Trauner, Vienna (Austria), which is a modification of UDCA. NorUDCA accumulates as a result of cholehepatic shunting in the liver and bile and produces a clear “cholangioprotective” effect. “This justifies hopes that norUDCA will achieve higher clinical efficacy than UDCA,” explains Prof. Trauner. Hepatologists are hopeful that the modified UDCA will represent a breakthrough in PSC treatment in particular. Following initial positive experimental data and promising study results, the active ingredient is now undergoing testing for PSC as part of a European multicenter study.
Clear regional differences

The incidence of autoimmune liver diseases is 1–2/100,000 people per year. Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) have approximately the same incidence on a global scale, reports Dr. P. Jepsen, Aarhus (Denmark). There are significant regional differences, however. Most PBC studies have concluded a steadily rising incidence of 1–2/100,000. “However, morbidity is considerably reduced in the Netherlands and New Zealand, and higher in North East England,” says Dr. Jepsen. These findings could be a result of differences in the incidence of risk factors for autoimmune liver diseases, or may be attributed to methodical differences in study designs.

Genetic correspondence between autoimmune diseases

According to Dr. T.H. Karløen, Oslo (Norway), genome-wide association studies (GWAS) in particular have made it possible to identify various genes associated with autoimmune diseases of the liver: “In the last few decades, modern genome analysis techniques have afforded us new insights into these diseases.” In many cases, this has increased our understanding of how genes and environmental factors interact in pathogenesis. Studies have also shown clear genetic similarities between autoimmune diseases. “There appears to be a uniform pattern in these diseases that we have yet to fully understand,” explains Dr. Karløen.

Extraintestinal manifestations

When diagnosing autoimmune diseases of the liver, it should be considered that patients may also present with extraintestinal manifestations, warns M.A. Heneghan, MD, London (Great Britain): “Around one in two patients complains of joint pain at the time of first presentation. Skin changes are another common symptom.” Complaints are often misdiagnosed, which can considerably delay a correct diagnosis. According to Heneghan, MD, joint pain is usually transient and improves with steroid or immunosuppressant treatment. Furthermore, the high comorbidity with other autoimmune diseases must also be taken into account.

Autoimmune diseases of the liver in children

Autoimmune diseases of the liver occur differently in children and adolescents, explains R. Liberal, MD, London (Great Britain). Children usually suffer from one of two forms of the illness – the “classic” autoimmune hepatitis (AIH) as well as an overlap syndrome with sclerosing cholangitis, often shortened to ASC. In most cases, the conditions initially manifest themselves as unspecific symptoms and are easy to mistake for other liver diseases. The possibility of an autoimmune disease of the liver should be suspected if the family history for this is positive, which is the case in around 40% of affected children. The disease usually responds to immunosuppressants, which inhibit progression, induce remission and increase long-term survival rates.
The importance of considering the possibility of AIH with every acute or chronic liver disease

If findings match the criteria for the disease, the possibility of AIH should be considered in practically all age groups. “AIH is by no means a disease that only affects young women,” emphasizes Prof. Dr. A.W. Lohse, Hamburg (Germany). “The possibility of AIH should therefore be considered in all patients with acute or chronic liver disease.” Quick diagnosis and treatment play an important role in the patient’s prognosis. “The mortality rate of AIH is very high if the disease is left untreated,” continues Prof. Lohse. Around a third of adults and half of children with AIH already present with cirrhosis of the liver at the time of first diagnosis. The disease is primarily diagnosed clinically, in particular following detection of autoantibodies, hypergammaglobulinemia and, according to D.G. Tiniakos, MD, Newcastle upon Tyne (Great Britain), characteristic histology. The most important antibodies are ANA (anti-nuclear antibody), SMA (smooth muscle antibody) and LKM-1 (liver kidney microsomal antibody), says Dr. L. Muratori, Bologna (Italy).

Budesonide – an effective alternative to prednisone

According to Prof. D.C. Gleeson, MD, PhD, Sheffield (Great Britain), AIH is primarily treated with steroids, which may be combined with azathioprine. Laboratory values return to normal within six to 12 months in nine out of ten patients taking the medication, with 60% to 70% achieving histological remission. Remission can usually only be maintained with a sufficiently high dose of steroids, the side effects of which should be taken into account. According to the medical expert, locally effective budesonide is an effective alternative to prednisone in non-cirrhotic AIH patients, as it shows a good clinical efficacy in patients with AIH and considerably lowers steroid-associated side effects. In addition to azathioprine and 6-mercaptopurine (6-MP), mycophenolate mofetil (MMF), cyclosporine A, tacrolimus and TNF-α inhibitors may be considered for difficult-to-treat patients, says Prof. Dr. C. Schramm, Hamburg (Germany). Scientists are also working on the development of new treatment strategies, such as MBP (myelin basic protein) – charged nanoparticles which have been used by PD Dr. J. Herkel, Hamburg (Germany), in a mouse model to induce regulatory T-cells (Tregs) and effectively treat autoimmune reactions. According to Dr. G. Bouma, Amsterdam (The Netherlands), there is a lack of prospective studies on the question of how long AIH should be treated for. What is clear, however, is that treatment must be continued for a number of years after LFT values have returned to normal, and is “in many cases a lifelong therapy.”

PBC: Development of prevalence remains unclear

According to Dr. P. Invernizzi, Rozzano (Italy), findings on primary biliary cirrhosis (PBC) also suggest a rising prevalence. These data could be misleading, however, as this increase could be a result of differences in study designs. Rising life expectancy, especially in Europe, improved diagnostics and the fact that patients are living much longer thanks to ursodeoxycholic acid (UDCA) treatment, may also suggest a supposedly higher prevalence. Similarly to AIH, PBC is not limited to one age group or gender, but can occur in men and women of all ages, explains G. Hirschfield, MD, Birmingham (Great Britain).

Ursodeoxycholic acid as first-line treatment for PBC

UDCA is the standard treatment for PBC and should not be withheld from patients, says Prof. Dr. A. Parés, Barcelona (Spain). Despite this, only two thirds of patients respond well to the bile acid. “Those that do respond, however, will achieve a similar life expectancy to the general population,” emphasizes the medical expert. There is still a lack of satisfactory treatment options for non-responders, however. According to Prof. Parés, there is still huge demand for research, but he believes that advances are possible in various areas. Combining UDCA with budesonide is one possible way of optimizing treatment, he explains, as cholestasis appears to improve when UDCA is combined with fibrates.

Estimating prognosis

Surrogate markers that promote optimal response to UDCA treatment and long transplant-free survival may, according to Dr. H.R. van Buuren, Rotterdam (The Netherlands), be a newly developed score comprising the age of the patient, bilirubin, alkaline phosphatase and platelet count after one year of UDCA treatment. Prof. Dr. R. Poupon, Paris (France), ex-
ppects that advances in vibration-controlled transient elastography (VCTE) will help us determine how the disease will progress in individual cases and whether progressive fibrosis is likely. What’s more, the procedure is non-invasive and therefore expected to have high acceptance among patients, unlike biopsies.

**Still no effective treatment for fatigue**

According to **Prof. D.E.J. Jones**, MD, PhD, Newcastle upon Tyne (Great Britain), fatigue continues to represent an unresolved problem, with one in two PBC patients suffering from it. 20% of patients are so severely affected that they are unable to go about their everyday life. “Fatigue puts an extreme strain on those affected,” says Prof. Jones. Patients are generally advised to engage in regular physical activity. However, there are currently no effective medication strategies to counteract fatigue.

**PSC: High comorbidity with inflammatory bowel disease**

Primary sclerosing cholangitis (PSC) is not always easy to diagnose, explains **Dr. C.Y. Ponsioen**, Amsterdam (The Netherlands), as a differential diagnosis must be conducted to rule out a range of other conditions. According to **Prof. Dr. U. Beuers**, Amsterdam (The Netherlands), this is the case in particular for IgG4-associated cholangitis, which can be deceptively similar to PSC. Further examples of conditions that may need to be ruled out by differential diagnosis are sporadic cholangiocarcinoma, choledochothiasis, surgical bile duct trauma and, rarely, ischemic or eosinophilic cholangitis, says Dr. Ponsioen. PSC is also frequently associated with other diseases, in particular inflammatory bowel disease (IBD), with around 50% of patients presenting with ulcerative colitis or Crohn’s disease at the time of first diagnosis. “This increases to a staggering 80% ten years after diagnosis,” as pointed out by Dr. Ponsioen. On the other hand, only 3% of patients with IBD develop PSC.

The possibility of an overlap syndrome should also always be considered, says **Prof. Dr. O. Chazoullières**, Paris (France). This concerns AIH in particular, which can appear as PSC-AIH as well as PBC-AIH.

**Considering high risk of cancer in PSC patients**

PSC also seems to be a predisposition for tumor development. The cumulative risk of developing a bile duct carcinoma is 20% after 30 years and 13% for a colorectal carcinoma after the same amount of time, says Dr. Ponsioen. Tumors, especially cholangiocarcinomas (CCA), may be difficult to diagnose early, explains **Dr. L. Fabris**, Padua (Italy). This applies in particular if a CCA develops in an area of dominant stenosis. Regular, usually annual, colonoscopies are essential for ensuring early diagnosis of a colon carcinoma in patients.

**The role of high genetic susceptibility**

According to **Prof. Dr. A. Franke**, Kiel (Germany), PSC primarily develops as a result of genetic susceptibility. He states genetic constellation in the HLA system as the main risk factor. “We do not know what triggers PSC and leads to manifestation and exacerbation of the disease, however,” emphasizes Prof. Franke. Certain variants of HLA-associated genes appear to cause a type of ‘point of no return’ in the effects of environmental factors. The exact backgrounds are still unknown, however. **P. Trivedi**, MD, Birmingham (Great Britain) believes that the high comorbidity with IBD suggests a general association with autoimmune disease-released genetic constellations.

**Irksome symptom: Pruritus**

Pruritus, which is often severe, puts a large strain on patients. According to **Dr. A.E. Kremer**, Erlangen (Germany), this symptom is usually particularly severe in the evenings and the early hours of the morning. In women, it also tends to increase in severity prior to menstruation, during hormone replacement therapy and in the late stages of pregnancy. Symptoms may be alleviated by cholestyramine and, as a second-line treatment, by rifampicin. Naltrexone and sertraline were also described as having therapeutically effective.

**Does norUDCA represent a breakthrough in treatment?**

According to **Prof. Dr. M. Trauner**, Vienna (Austria), hopes for advances in PSC treatment are justified, and could become a reality in the near future. For example, scientists are currently working on developing obeticholic acid, an agonist of the nuclear farnesoid X receptor (FXR). Obeticholic acid is a modification of chenodeoxycholic acid, which has been shown to prevent cholestatic liver lesions in PSC and PBC in mouse models. Norursodeoxycholic acid (norUDCA), a modification of conventional UDCA, is a promising treatment for both types of cholestatic liver disease. NorUDCA accumulates as a result of cholehepatic shuntings in the liver and bile and produces clear “cholangioprotective” effects, says Prof. Trauner. Following promising initial studies, hepatologists are hopeful that the drug will represent a breakthrough for PSC treatment in particular. The clinical efficacy of the active ingredient is now being tested as part of a European multicenter Phase II study comprising approx. 160 patients with PSC.
Poster prize awards

Three poster prizes were awarded at Falk Symposium 197:

1st prize
The first prize was awarded to Malgorzata Milkiewicz, Szczecin (Poland), for her work on the correlation of the FGF19 expression with the severity of primary biliary cirrhosis.

2nd prize
The second prize went to Maren H. Harms, Rotterdam (The Netherlands), for an international follow-up study on the risk factors of hepatic decompensation in PBC.

3rd prize
Oana Beli, Timisoara (Romania), received the third prize for her work on autoimmune hepatitis in Romanian children with celiac disease.
Interview with Prof. Dr. Ulrich Beuers,
Tytgat Institute for Liver and Intestinal Research, Amsterdam (The Netherlands)

“The importance of striving for early diagnosis in autoimmune diseases of the liver”

The significance of chronic liver diseases still tends to be underestimated. We interviewed Professor Dr. Ulrich Beuers, one of the scientific organizers of Falk Symposium 197, about the importance of early diagnosis and having keen senses when it comes to autoimmune diseases of the liver.

Editor: Professor Beuers, why was an entire symposium dedicated solely to autoimmune diseases of the liver?

Professor Beuers: Autoimmune diseases of the liver include, in particular, autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis. Over the last few years, we have made considerable progress in the treatment for these diseases and developed a few very effective treatment strategies. Shedding light on these conditions is therefore very important, as early diagnosis and treatment are vital.

Editor: Which symptoms and results point to an autoimmune disease of the liver?

Professor Beuers: In particular, patients with unexplained fatigue coupled with significantly elevated LFT values should be tested. Patients that complain of pruritus and have elevated LFT values should be tested for cholestatic liver disease, i.e. primary biliary cirrhosis, which we will refer to as primary biliary cholangitis in future, as well as for primary sclerosing cholangitis and rare diseases. In such cases, further laboratory and imaging diagnostics should be performed.

Editor: Why is the name of primary biliary cirrhosis being changed?

Professor Beuers: This is in response to many international patient associations which expressed their wish for the name change during concerted action among experts in this area, which I had the great honor of coordinating. One of the reasons for this change is the fact that the diagnosis “cirrhosis” is unfortunately often associated with alcohol abuse, which is not the case for PBC. This makes many sufferers feel stigmatized, however, and prevents them from speaking about the disease. Another reason is that many PBC patients have stopped developing cirrhosis due to the very effective treatment of ursodeoxycholic acid, with two in three patients undergoing treatment with the bile acid enjoying a normal life expectancy. This was not the case 20 years ago before this treatment option had become established. During this time, practically all patients developed cirrhosis at some stage. As this no longer holds true, we believe that it is time that the disease’s name reflects this welcome development.

Editor: Are there any new findings for other autoimmune diseases of the liver?

Professor Beuers: The first genome-wide association analysis of risk genes in autoimmune hepatitis has now been conducted by Dutch AIH working group. This is an important step towards increasing our understanding of the condition. We also know that almost all patients require lifelong treatment with immunosuppressants, as discontinuation of this medication induces relapses in up to 90% of cases. Discontinuation of immunosuppressant therapy should therefore only be considered after many years of treatment and completely normal LFT values. Patients that undergo this option must be closely monitored. We do still have concerns about primary sclerosing cholangitis, however, as there is still a lack of truly effective treatment options for this condition. While the condition is generally also treated with ursodeoxycholic acid, we do not have any valid study data to prove that this will increase life expectancy. What we can see, however, is that the bile acid significantly improves cholestasis in some patients. Scientists are currently working very intensively on developing various new PSC treatment approaches in extremely close cooperation with a network of centers.

Professor Beuers, thank you very much for the interview.
VIII Falk Gastro-Conference

October 14 – 17, 2015
Freiburg, Germany

Congress Venue
Konzerthaus Freiburg
Konrad-Adenauer-Platz 1
79098 Freiburg
Germany

October 14 – 15, 2015
Falk Symposium 199
Highlights from Hepatology 2015:
From Chronic Hepatitis to
Hepatocellular Carcinoma

Scientific Organization
O. Chazouillères, Paris (France)
J. M. Llovet, Barcelona (Spain)
D. Moradpour, Lausanne (Switzerland)
R. Thimme, Freiburg (Germany)

October 16 – 17, 2015
Falk Symposium 200
Therapeutic Strategies in Diseases
of the Digestive Tract – 2015 and Beyond

Scientific Organization
M. J. Bruno, Rotterdam (The Netherlands)
E. M. El-Omar, Aberdeen (Scotland)
P. Ginès, Barcelona (Spain)
D. K. Podolsky, Dallas (USA)
J. Schölmerich, Frankfurt (Germany)
Speakers, moderators and scientific organizers

**Prof. Dr. Ulrich Beuers**  
Department of Gastroenterology and Hepatology, G4-216  
Tytgat Institute for Liver and Intestinal Research  
University of Amsterdam  
Meibergdreef 9  
1105 AZ Amsterdam  
The Netherlands  
u.h.beuers@amc.uva.nl

**Dr. Gerd Bouma**  
Department of Gastroenterology  
Vrije Universiteit Medical Center  
De Boelelaan 1118  
1081 HV Amsterdam  
The Netherlands  
g.bouma@vumc.nl

**Prof. Dr. Olivier Chazouillères**  
Service d’Hépatologie  
Hôpital Saint Antoine  
184, rue du Faubourg St. Antoine  
75012 Paris  
France  
olivier.chazouilleres@sat.aphp.fr

**Prof. Dr. Helena Cortez-Pinto**  
Departamento de Gastroenterologia  
Hospital Santa Maria  
Av. Prof. Egas Moniz  
1649-001 Lissabon  
Portugal  
hlcortezpinto@netcabo.pt

**Dr. Luca Fabris**  
Department of Molecular Medicine  
University of Padua  
School of Medicine  
Via A. Gabeli, 63  
35121 Padua  
Italy  
luca.fabris@unipd.it

**Prof. Dr. Andre Franke**  
Klinische Molekularbiologie  
Christian-Albrechts-Universität  
Schittenhelmstr. 12  
24105 Kiel  
Germany  
a.franke@mucosa.de

**Prof. Dr. Pere Ginès**  
Liver Unit  
University of Barcelona  
Hospital Clinic  
c/ Villarroel no. 170  
08036 Barcelona  
Spain  
pinges@clinic.ub.es

**Prof. Dr. Dermot C. Gleeson**  
Liver Unit  
Sheffield Teaching Hospitals  
Sheffield  
Great Britain  
dermot.gleeson@sth.nhs.uk

**Dr. Michael A. Heneghan**  
Institute of Liver Studies  
NHS Foundation Trust  
King’s College Hospital  
Denmark Hill  
London SE5 9RS  
Great Britain  
michael.heneghan@nhs.net

**PD Dr. Johannes Herkel**  
Medizinische Klinik I  
Universitätsklinikum Eppendorf  
Martinistr. 52  
20251 Hamburg  
Germany  
jherkel@uke.uni-hamburg.de