

ANSWERING PIVOTAL QUESTIONS IN THE DIAGNOSIS AND TREATMENT OF PRIMARY BILIARY CIRRHOSIS AND NON-ALCOHOLIC STEATOHEPATITIS

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MEETING SUMMARY

Professor Trauner introduced the subject of liver disease and its burden within the European Union (EU) and across the globe. Professor Jones summarised the progress made in understanding the pathophysiology of primary biliary cirrhosis (PBC), current unmet needs in the ursodeoxycholic acid (UDCA) era, and novel therapeutic options for PBC treatment. Professor Ratziu discussed the emerging understanding of the complex multisystem pathophysiology of non-alcoholic steatohepatitis (NASH), summarised the available therapeutic targets, and detailed the trials of novel agents currently underway.

Opening Remarks From the Chair

Professor Michael Trauner

Professor Trauner welcomed the audience and thanked the sponsors, Intercept Pharmaceuticals, Inc., for allowing the opportunity to discuss PBC and NASH and answer some key questions in diagnosis and treatment. The audience were invited to engage in the discussion.

PBC and NASH: Serious Liver Diseases with Unmet Needs

Professor Michael Trauner

There is little need to remind an audience of specialists of the importance of liver disease; nevertheless, statistics on its impact on society make for stark reading. Liver disease is a major cause of morbidity and mortality in the EU,

affecting 6% of the population.¹ Chronic disease leads to cirrhosis, hepatocellular carcinoma, and liver transplantation. In the EU, liver cancer mortality stands at 47,000 deaths annually, and more than 5,500 liver transplants are carried out each year.² Overall, liver disease is the fifth-most common cause of mortality in the EU and is implicated in one in six deaths.¹

PBC and NASH stand out amongst the various aetiologies of liver disease, due in part to the recent major advances that have been made in understanding their pathobiology. Increased knowledge of the role played by bile acids in both conditions has helped to develop novel therapeutic targets and has led to improvements in the evaluation and assessment of patients. However, difficulties persist in patient management due to the lack of reliable biomarkers to assist in risk stratification and assessment of patient prognosis in these broad-spectrum diseases. Perhaps the most pressing challenge in the successful treatment of PBC and NASH is the failure of early diagnosis and concomitant lag in treatment, common in both conditions.

PBC Challenges: What is Treatment Success and What Will Emerging Therapies Offer?

Professor David E.J. Jones

There remains significant unmet need in the PBC patient population despite the existence of proven primary therapy in the form of UDCA, as illustrated by the deficit in transplant-free survival in UDCA non-responders compared with age and sex-matched community controls.³ There are a number of possible reasons for the impaired survival of patients treated for PBC: treatments may be used sub-optimally; the effectiveness of current treatments may be overestimated or may be

restricted to a subpopulation of patients, and the distribution of treatments to those in need may be sub-optimal.

In 2008 in the UK, 20% of PBC patients did not receive treatment with UDCA,⁴ and unpublished data indicate that many patients received doses now regarded as insufficient. UDCA also has issues with patient adherence, with barriers including weight gain, nausea, and hair loss. Addressing the above treatment-related issues, using a simple and consistent message underscoring UDCA's effectiveness and the need for all patients to at least receive it at the correct dose, is a logical first step in addressing unmet need.

To identify those UDCA-treated patients with unmet need, patients responding successfully must firstly be characterised. The two principal systems developed to identify treatment response are the Paris and Barcelona criteria (Table 1).^{5,6} These and related criteria (Toronto criteria) have been independently validated using the large UK-PBC cohort, confirming their ability to predict transplant-free survival and consequently the need for their incorporation into routine clinical use.⁷

Recent data from the Global-PBC Group indicate that baseline biomarkers are predictive of treatment outcome. Researchers showed that both elevated alkaline phosphatase (ALP) and bilirubin predict poor clinical outcome.⁸ Thus, both baseline characteristics and treatment response are important to predict event-free survival. This was confirmed by a univariate and multivariate analysis of the UK-PBC cohort, with baseline cirrhosis (as measured by albumin and platelets) and response to UDCA at 12 months (bilirubin, alanine aminotransferase [ALT], and ALP) predictive of transplant-free survival at 15 years. These data are further backed by a 50% treatment failure rate in younger patients in the UK-PBC cohort, despite apparently high overall response rates.⁹

Table 1: UDCA treatment-response criteria.

Paris Criteria	Barcelona Criteria
Bilirubin ≤ 1 mg/dl + AST $\leq 2 \times$ ULN + ALP $\leq 3 \times$ ULN after 1 year of UDCA at 13–15 mg/kg/day	ALP decreased by 40% or normalised after 1 year of UDCA at 13–15 mg/kg/day

UDCA: ursodeoxycholic acid; AST: aspartate aminotransferase; ULN: upper limit of normal; ALP: alkaline phosphatase.

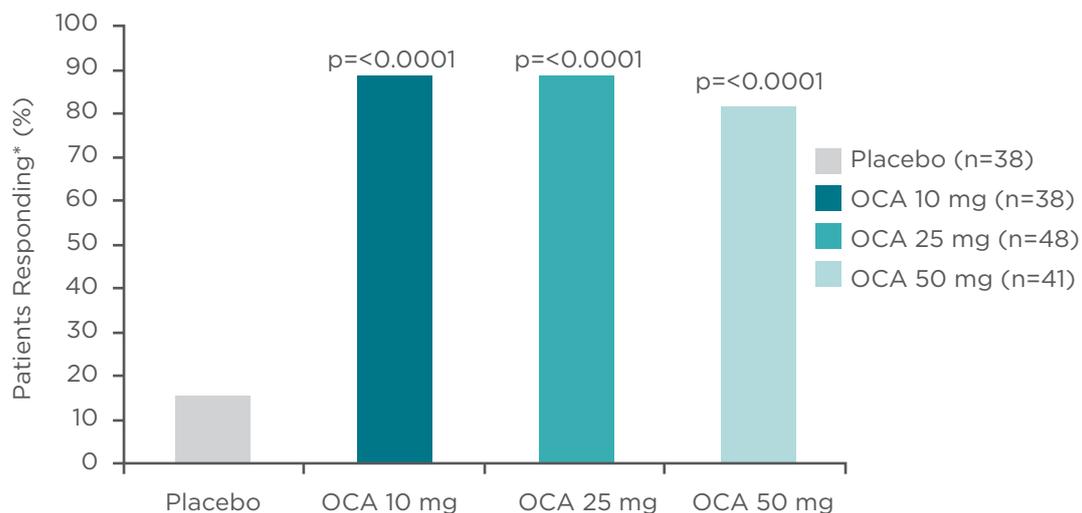


Figure 1: Efficacy of OCA in PBC patients on stable UDCA treatment.

*Primary efficacy endpoint was percentage change in plasma alkaline phosphatase (ALP) from baseline; patients with a placebo-subtracted ALP reduction of $\geq 10\%$ were defined as responders.

OCA: obeticholic acid; PBC: primary biliary cirrhosis; UDCA: ursodeoxycholic acid.

Adapted from Hirschfield GM et al.¹⁴

These younger patients represent a high-risk group in which novel therapies may be most useful.

The above described unmet clinical need necessitates new therapies. There are four elements of the PBC disease process that may offer novel therapeutic targets. The autoimmune response may be addressed through targeted immunosuppression. The secondary cholestatic phase may be amenable to 'second-line' bile acid therapies or manipulation of the microbiota. Biliary epithelial protectant agents may offer a novel route to preserve bile ducts. Finally, those patients who already have fibrosis/cirrhosis may be targeted using antifibrotics. Research into novel therapeutics is complicated by the incomplete picture in terms of biomarkers, difficulties in identifying early stage patients who may respond to immunosuppressant therapies, a lack of clarity regarding therapy-specific response criteria, and the inherent difficulties of trial design caused by a lack of hard endpoints and validated histological measures.

Despite these challenges, it is currently an exciting time for novel PBC therapeutics. Drugs targeting peroxisome proliferator-activated receptor (PPAR)- α (fibrates) and Farnesoid X receptor (FXR) (obeticholic acid [OCA]) systems are joined by norUDCA, which may protect via the creation of a bicarbonate 'umbrella' and has anti-inflammatory and anti-fibrotic effects, and rituximab (RTX),

which targets B cell depletion. A number of other new therapies are also in the early stages of development, including the ileal bile acid absorption blockers A4250 and LUM001, and the immunological agents NI-0801 and ustekinumab.

The fibrates act via PPAR- α agonism, which has been linked to the regulation of bile acid synthesis and detoxification and the modulation of phospholipid secretion, which helps to protect the bile duct epithelium through the formation of micelles.¹⁰ Currently, there is an inadequate number of well-designed trials examining fibrates in PBC. The trials that exist, and associated meta-analyses, have failed to demonstrate clinical efficacy despite biochemical improvements, and have also shown possible safety concerns.¹¹⁻¹³ As a result, despite a logical mechanistic basis, fibrates lack a solid evidence base for efficacy and are associated with possible adverse outcomes in the long term.

The FXR agonist OCA is the most extensively evaluated of the second-line therapies. OCA represents the logical extension of bile acid therapy beyond UDCA, sharing a number of properties (choleretic, anti-apoptotic, and antioxidant effects) as well as a number of additional direct and indirect, FGF19-mediated effects on bile acids. In a recently published Phase II trial (n=165) involving UDCA non-responders, OCA achieved an approximate 90% response rate at all doses tested (Figure 1).

Discontinuation due to pruritus (itch) was an issue in this study,¹⁴ but has been addressed by a dose reduction at Phase III.

Quality of life (QoL) is often the key outcome from the perspective of patients and does not appear to be modified by current treatments. Currently, 35% of PBC patients perceive their QoL as impaired, and almost half feel that their health is worse than it was a year earlier.⁴ B cell depleting agents such as RTX may have a role in reducing fatigue. In summary, the actions needed to improve QoL for PBC patients begin with improving community, patient, and first-physician awareness of the disease and its presentations. Improved physician awareness of the need for therapy with UDCA ($\geq 95\%$) and identification of non-responders must be matched with a systematic approach to management. Built-in triage for high-risk/non-responding patients should migrate these individuals into clinical trials and onto second-line therapies as they become available. In parallel, continued evaluation of second-line therapies and their integration into stratified management pathways is required. Finally, improvement of awareness, assessment, and treatment of symptoms in PBC using systematic approaches and a focus on patients' QoL in addition to the above measures has the potential to dramatically improve the lives of PBC patients.

NASH: Diagnostic Challenges, Therapeutic Targets, and New Paths to Treatment Success

Professor Vlad Ratziu

Recent strides in the understanding of non-alcoholic fatty liver disease (NAFLD) and NASH should soon begin to translate into improved therapeutic options. However, diagnostic challenges still exist, both in terms of disease recognition and risk stratification. Many patients are still underdiagnosed and undermanaged, as in the 61% of patients in retrospectively confirmed cases from a recent database analysis who received no NAFLD care.¹⁵ Beyond recognition of the disease itself, the nature of NAFLD as part of a multi-organ metabolic syndrome must also be recognised. NAFLD is a multi-system disease, and extra-hepatic comorbidities such as Type 2 diabetes (T2D), sleep apnoea, and arterial dyslipidaemia must be addressed. Direct effects of

these comorbidities have been demonstrated, for example, sleep apnoea-related hypoxia modifies the progression of liver fibrosis in NASH. In terms of the liver condition itself, assessment of cofactors of fibrosis in conjunction with disease severity (steatosis/NAFLD or steatohepatitis/NASH), disease stage, and an estimate of prognosis are essential first steps for adequate management.

Identification of patients at risk of progression is a further diagnostic challenge. Recent evidence from serial biopsies suggests that the presence of inflammation and steatosis alone, and not necessarily the full necroinflammatory histology characteristic of NASH, are enough to put patients at risk of progression.¹⁶ Features associated with risk of rapid progression to fibrosis in NAFLD patients include diabetes, metabolic syndrome, magnitude of ALT elevation, and extent of insulin resistance.¹⁷ In NASH patients, risk of progression to severe fibrosis is associated with older age (>45 – 50 years) and T2D.^{18,19} There is a small genetic component, with predisposing polymorphisms in *PNPLA3* and *TM6SF2*,^{20,21} as well as associations with obesity, arterial hypertension, hypertriglyceridaemia, insulin resistance, and elevated ALT/aspartate aminotransferase.^{18,19,22} Despite the progress this information represents, further work is needed to identify biomarkers and particularly to create a non-invasive methodology for assessing risk of progression in NAFLD and NASH.

Improvements in the understanding of NASH pathophysiology have led to the identification of new therapeutic targets. NASH pathophysiology appears to derive from metabolic abnormalities, with insulin resistance — particularly in adipose tissue — likely to be the major predisposing disorder. Free fatty acids, chemokines, and insulin drive further metabolic dysregulation as well as directly causing inflammation and cell death, leading ultimately to fibrogenesis and progression towards cirrhosis. This complex and interconnected pathophysiology results in numerous drug targets but also a need to target multiple pathways to reduce fibrogenesis in the long term.

Foremost amongst the novel therapies targeting NASH are FXR agonists, such as OCA. The SCD1 inhibitor aramchol and the PPAR agonist GFT505 work by reducing liver fat, while the dual CCR2 and CCR5 antagonist cenicriviroc targets inflammation and may also have antifibrotic effects.

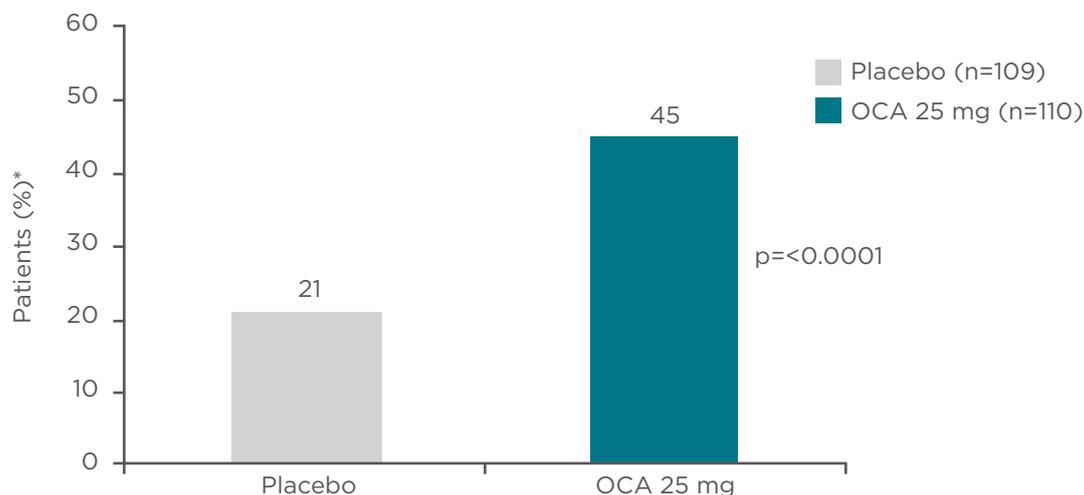


Figure 2: Patients treated with OCA achieving primary outcome measure.

* ≥ 2 -point improvement in NAS score without worsening of fibrosis.

OCA: obeticholic acid; NAS: NASH activity score.

Adapted from Neuschwander-Tetri et al.³¹

Other drugs target fibrogenesis by blocking collagen cross-linking (anti-lysyl oxidase-like 2 [LOXL2] monoclonal antibody, simtuzumab [SIM]) or by inhibiting the fibrosis-related protein galectin-3. The urgent need for effective therapies for NASH is recognised by the FDA, as illustrated by the granting of breakthrough status to OCA and fast-track status of the majority of the other novel compounds mentioned.²³⁻²⁷

The main mode of action of FXR-agonist therapies, such as OCA, in NASH is through direct cytochrome-modulated blockade of conversion of cholesterol in bile acids. However, as noted above, indirect effects via FGF19 are also present, which may act on metabolic pathways, improving glucose tolerance and insulin sensitivity and reducing lipogenesis and hepatic fat. Direct antifibrotic properties derived from blocking activation of quiescent hepatic stellate cells may also play a role.²⁸⁻³⁰ Data are available from a Phase IIb 72-week randomised, double-blind, placebo-controlled trial of OCA 25 mg/day (n=110) versus placebo (n=109) with both clinical and histological endpoints.³¹ NASH patients with active disease were eligible. There was a striking difference in the number of patients achieving the primary histological outcome measure (improvement in NASH activity score [NAS] ≥ 2) between placebo and OCA-treated patients (Figure 2).

There were across-the-board significant improvements in every histological feature that defines NASH (lobular inflammation, steatosis,

hepatocellular ballooning, and fibrosis). This represents the first human demonstration of antifibrotic efficacy in NASH, particularly noteworthy given that the trial was not powered for this outcome.³¹ Adverse event data showed mild-to-moderate effects in general. As with the above PBC data, pruritis was an issue;³¹ however, the PBC data also suggest that it may be addressed via dose adjustment.

As mentioned, the conjugated bile acid-saturated fatty acid aramchol modulates the amount of fat in the liver. It acts via two pathways: inhibition of fatty acid metabolism via blockade of SCD1 enzyme activity, and activation of cholesterol efflux by stimulating the cholesterol pump ABCA1.³²⁻³⁴ Results from a small (n=57) Phase IIa trial indicate that aramchol dose-dependently reduces liver fat, as measured by non-invasive magnetic resonance spectroscopy. This result is currently being confirmed in a population of NASH patients with active disease and metabolic syndrome in the Phase IIb ARREST trial (n=240). In addition to steatosis, NASH resolution, reduced NAS score, and metabolic improvements will be assessed.

Cenicriviroc is a dual CCR2 and CCR5 antagonist that has shown potential for antifibrotic activity.³⁵ These two cytokines have overlapping proinflammatory and profibrotic properties, aiding the chemotaxis of inflammatory cells and activating profibrotic stellate cells.³⁶ The large international Phase II CENTAUR trial³⁷ (n=252) of cenicriviroc includes patients that have well-defined NASH

either with active disease or progression risk factors. The primary outcome is improvement of NAS score with no worsening of fibrosis, with the main secondary outcome being resolution of NASH with no worsening of fibrosis, which is likely to be important for approval as a NASH therapeutic.

As a selective dual PPAR- α and PPAR- δ agonist with no PPAR- γ activity, GFT505 combines liver-specific (PPAR- α) and multi-organ anti-inflammatory and fat-reducing activity (PPAR- δ).³⁸ Phase II trials have demonstrated improved lipid metabolism and insulin sensitivity in diabetic and pre-diabetic patients, and animal data suggest the presence of anti-inflammatory and antifibrotic properties in NASH.^{39,40} The 1-year Phase IIb GOLDEN trial⁴¹ (n=270) of GFT505 is highly anticipated, with preliminary results suggesting that the primary endpoint of NASH resolution with no worsening of fibrosis has been met.

SIM directly targets fibrosis through highly specific inhibition of LOXL2, the enzyme that promotes the cross-linking of collagen, which is key to the fibrotic process. LOXL2 levels may correlate with clinically relevant NASH endpoints, and blockade of collagen cross-linking has been demonstrated in other conditions.^{29,42} Two large 240-week Phase IIb trials are currently underway comparing two doses of SIM (75 mg and 125 mg) with placebo in either cirrhotic (n=259) or non-cirrhotic (n=222) patients. In the cirrhotic patients, the drug is administered intravenously every 2 weeks with a liver biopsy after 1 year, and endpoints are based on hepatic venous pressure gradient and event-free survival. In the non-cirrhotic trial, participants with NASH and bridging fibrosis receive a weekly subcutaneous injection; the primary endpoint is fibrosis and event-free survival (assessed as time-to-progression to cirrhosis).⁴³

Challenges remain in the NASH therapeutic pipeline. The multiple pathogenic mechanisms of NASH require therapies that target more than one pathway to achieve histological efficacy. Improved animal models and non-invasive outcomes for proof-of-principle trials are needed to speed up development. The lack of surrogates for hard outcomes, in particular non-histological outcomes, and response on therapy are also issues; however, an effective primary therapy will be required before this can be addressed. Nevertheless,

there has been tremendous progress in the field recently. Firstly, the medical need is now being recognised for NASH as a standalone condition related to, but not subsumed by, metabolic disorder. NASH is accepted as an indication for therapy and now has operational pathological definitions. Achievable surrogate endpoints have been set and the regulatory path for approving drugs in NASH is clear, with regulatory bodies behind the push for new therapies.

In conclusion, it is essential to assess liver injury in those with metabolic risk factors such as diabetes or obesity. NAFLD is a cause of liver cirrhosis and primary liver cancer, and prognosis is dependent on the fibrosis stage and also the presence of steatohepatitis (NASH), which ultimately drives fibrosis. There is a need to develop pharmacological agents that target NASH and a number of these are now being tested in large Phase IIb trials, with OCA soon moving into Phase III trials. Once we have demonstrated the efficacy of these drugs, tailoring of therapy to individuals and integrative approaches with diet and lifestyle will be the key concerns.

Concluding Remarks

Professor Michael Trauner

In summary, a significant proportion of patients with PBC have insufficient response to available treatment and require novel therapies. New strategies based around second-line bile acid therapies, particularly OCA, appear to be yielding results, while new immunological approaches targeting symptoms may help address key patient concerns such as fatigue. NASH remains an under-recognised liver disease in clinical practice. New non-invasive detection methods to track progression and measure therapeutic efficacy are needed, although some progress has been made in tracking fibrosis and the inflammatory component of the condition. Treatment of metabolic comorbidities may have a beneficial impact on liver disease but there is an urgent need for novel therapies beyond lifestyle modification. A number of new therapies are at Stage II of testing, including second-line bile acids and others targeting metabolic aspects of the disease alongside inflammation and fibrosis.

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