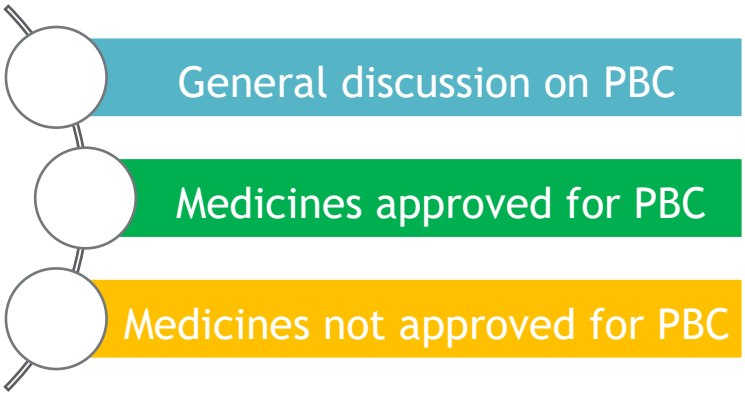
PBC Network EASL Newsletter

Welcome to the PBC Network 'EASL Newsletter'. In April, the *EASL International Liver Congress 2019* took place in Vienna. As one of the world's largest and most influential events dedicated to Hepatology, there are thousands of research studies presented at this four-day event covering a vast number of subjects. PBC, as a rare liver disease, is one of these subjects.

This newsletter gives an update on the most relevant findings on PBC presented at EASL 2019. Initially, you will see a key definitions sheet to guide you through this newsletter. 14 studies have been selected; summaries were divided in three sections.



A code has been added at the start of each research study summary (e.g. GS-02); which allows you to locate the original paper on the EASL website to find out more information.

We would also like to thank Achim Kautz, Ingo Van Thiel and colleagues at Leberhilfe Projekt gUG, as well as Prof. Christian Trautwein, director of the RWTH Aachen and international PBC expert, for managing the coordination, administration and dissemination of this newsletter.

For further information regarding the development of this newsletter please contact: Achim Kautz, kautz@leberhilfe-projekt.de

Key definitions

N = number of patients in the study

Medicines approved for PBC = Drugs which have been approved by phase III studies in terms of safety and effectiveness, they are recommended by official guidelines for use in PBC

Medicines not approved for PBC = These can be either

- experimental study drugs which are not yet available, or
- drugs which are approved for other indications than PBC; in the latter case, use of these drugs in PBC is "off-label"

Disease progression = Increased liver damage, worsening of symptoms

Measures of PBC disease progression = Alkaline phosphatase (AP), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT)

Not responding well to treatment = The drug did not improve the patient's condition or they experienced bad side effects

Well tolerated = Generally found to be safe in patients, no severe side effects or outcomes occurred

Effective = Improved liver functioning, progression of disease and/or disease symptoms

First line treatment = These drugs are given to patients when they are first diagnosed as they are the most widely used, or known to work well for most PBC patients, as recommended by guidelines

Second line treatment = These drugs are given if first line treatments are not effective for patients

Liver toxicity = When a medicine becomes toxic to the liver, this can lead to inflammation, scarring and, if untreated, liver failure and possibly death

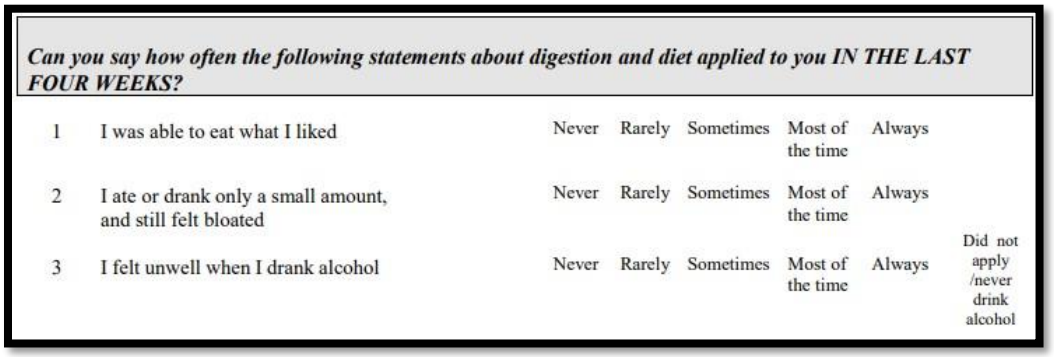
General discussion on PBC

FRI-001 The PBC-10: A validated short clinic symptom screening tool for primary biliary cholangitis

L. Alrubaiy, G. Mells, H. Bosomworth, S. Flack, H. Hutchings, J. Gordon, D. Jones. *St. Mark's Hospital. Multiple sites. UK*

Assessment of PBC symptoms is carried out using in-depth measures such as PBC-40 Quality of Life (QoL), which contains 40 questions about symptoms and different aspects of life. These measures are appropriate for research, but are too time consuming to be carried out in appointments with patients. There is a need for a short, clinically appropriate symptom screening tool in order to measure symptoms annually, as recommended by EASL guidelines. This study aimed to develop a short version of PBC-40 by analyzing a large dataset of PBC-40 responses then comparing these to responses from a new short version with 10 questions, the PBC-10.

Sample question from PBC-40 questionnaire



Can you say how often the following statements about digestion and diet applied to you IN THE LAST FOUR WEEKS?

1	I was able to eat what I liked	Never	Rarely	Sometimes	Most of the time	Always	
2	I ate or drank only a small amount, and still felt bloated	Never	Rarely	Sometimes	Most of the time	Always	
3	I felt unwell when I drank alcohol	Never	Rarely	Sometimes	Most of the time	Always	Did not apply /never drink alcohol

The researchers identified the 10 most important questions to form the short questionnaire. The statistical analysis found that the new short questionnaire represents experiences of PBC accurately and is reliably measuring PBC symptoms. This was also further supported by carrying out analyses with a second group of patients.

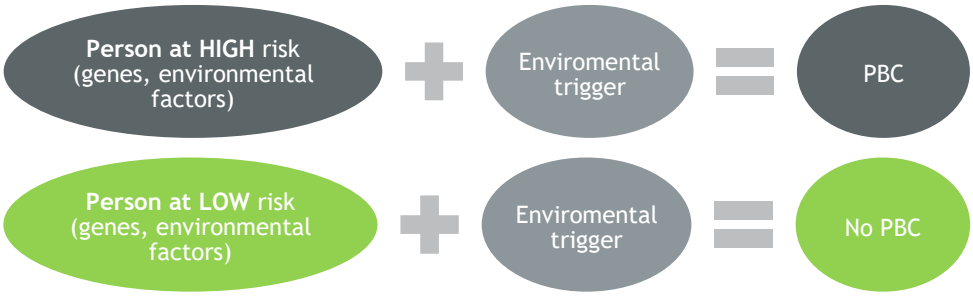
A further analysis revealed that PBC-10 accurately represents the six quality of life aspects of PBC (fatigue, psychological, cognitive, physical, skin and eating or drinking domains). Overall, this new 10 question version of PBC-40 QoL has the potential to be valuable in appointments with PBC patients to keep track of symptoms, disease progression and response to treatment.

FRI-015 Environmental triggering in primary biliary cholangitis: Disease risk relates to coal mining activity

J. Dyson, A. Blain, M. Hudson, S. Rushton, D. Jones. ***Newcastle University. Newcastle upon Tyne Hospitals NHS Foundation Trust. UK***

The causes that lead to the development of PBC are unknown but thought to involve both genetic and environmental factors. Research has suggested environmental factors may trigger PBC in patients who are already at risk, however the mechanism behind this is unknown.

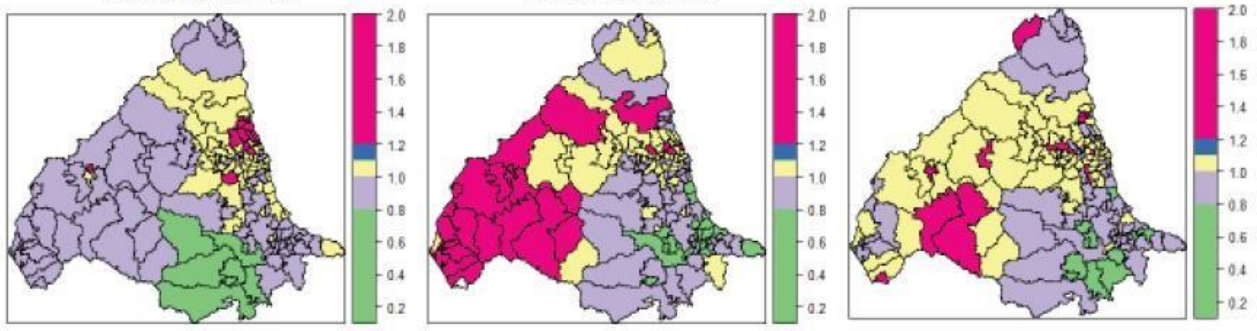
Graph demonstrating possible mechanism behind PBC development



This was investigated by comparing PBC patients with PSC (primary sclerosing cholangitis) patients and AIH (autoimmune hepatitis) patients within North-East England and North Cumbria. The researchers looked at whether local environmental factors were associated with the proportion of people with each disease across the different areas.

The risk of PBC across postcode districts compared to the other two diseases was calculated. This identified that different postcode districts have high and low rates for each disease, see the diagrams below. Pink indicates higher risk of having that disease.

Figure 1. Relative risk for each disease in the North East of England and North Cumbria



Specifically, coal mining areas seemed to be strongly associated with a higher rates of PBC. The authors suggest that this link to PBC development is via exposure to environmental changes due to coal-mining or specific substances which are released as a result of mining. Also, compared to PBC, PSC occurred more in rural and less socioeconomically deprived areas and no local pattern was found for autoimmune hepatitis. However, the authors offer no explanation for why this occurred or how it may link to other factors such as genetics.

In summary, this research suggests that living in areas with coal mining activity is a possible trigger of PBC in patients whose genetics put them at risk of PBC. However, the results were a matter of controversy and it was suggested that they might also be a matter of coincidence, rather than a real cause or trigger of PBC. The study still does not address why or how exactly people get PBC

and how the risk factors interact, but shows that the debate about the origins of PBC is still very active.

Approved medicines

FRI-038 Good performance of the biochemical response criteria after three months of ursodeoxycholic acid treatment in patients with primary biliary cholangitis

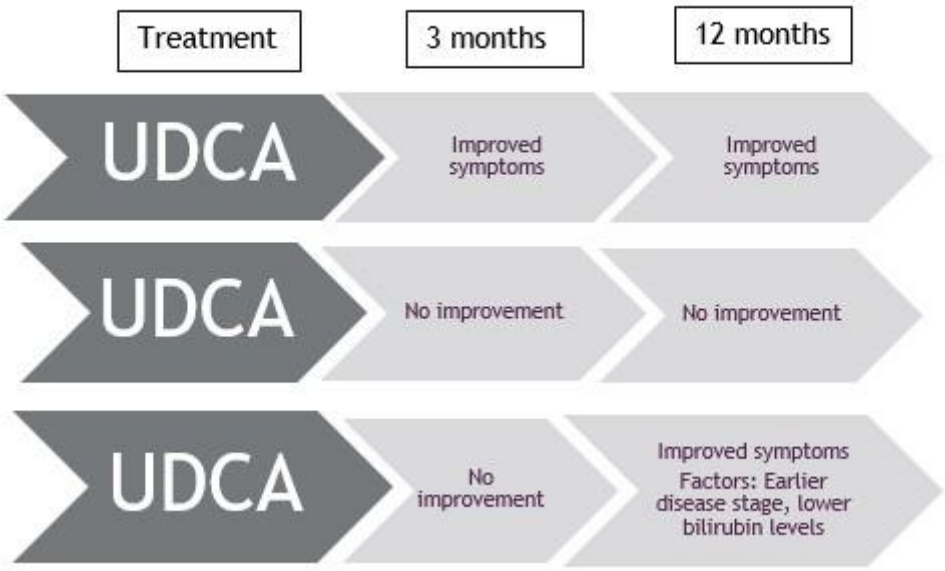
L. LLovet, A. Reig, O. Ortiz, M. Londondo, A. Pares. ***Single site. Spain***

The effect of treatment on PBC patients, is typically measured by looking at their liver function one year and two years into treatment. This means if a treatment doesn't work for a patient, it may not be identified until a year into taking it. It is important to know if common treatments for PBC such as ursodeoxycholic acid (UDCA) are ineffective for patients earlier than one year into treatment, as this enables patients to switch to a treatment plan that improves liver functioning, protecting it from damage, sooner.

The researchers compared patients' response to UDCA at 3 and 12 months. They found that most patients who did not benefit from the treatment at 3 months were also unlikely to benefit at 12 months. These findings indicate that measuring PBC symptoms earlier in the patients' treatment journey is most likely a sensible approach as this allows those who don't benefit to switch onto another treatment sooner.

That said, a small proportion of patients whose liver functioning did not improve at 3 months into taking UDCA did improve at 12 months. This outcome was found to be associated with being at an earlier disease stage and having lower bilirubin levels. See the graph below showing the three different outcomes for patients within this study.

Graph of outcomes following UDCA treatment and associated factors



Overall, the study indicates the need to measure change in liver function earlier into treatment. It is interesting as it could enable patients to have improved symptoms and quality of life sooner, by switching or taking additional medicines sooner. However, as the study was only carried out in one centre, larger studies are needed to confirm these findings.

GS-18 Preventive administration of ursodeoxycholic acid after liver transplantation for primary biliary cholangitis prevents disease recurrence and prolongs graft survival

C. Corpechot, O. Chazouillères, A. Montano-Loza, et al. ***Multiple sites. Europe, Canada***

Previous research indicates that for PBC patients following a liver transplant (LT), PBC does not recur for around 80%, although typical autoantibodies remain in the blood (e.g. AMA-M2). However, for the remaining 20% there is a potential for PBC to recur. These patients are usually given UDCA following re-diagnosis to prevent damage to the new liver. But, there is a potential argument for UDCA to be used as a preventive measure to reduce the chances of PBC recurrence. The *EASL PBC guidelines of 2017* state the following:

> ***"Treatment with UDCA lowers liver enzymes and may lower the incidence of recurrent PBC [259], but there is insufficient evidence to make an absolute recommendation for its use post-transplant. In practice, UDCA is considered in patients with suspected recurrent PBC, and frequently prescribed."***

To investigate this potential, a large international group of PBC LT patients who were given UDCA as a preventive measure were analysed. It was found that taking UDCA as a preventative measure did lead to a lower rate of PBC recurrence and improved liver function for a longer time period.

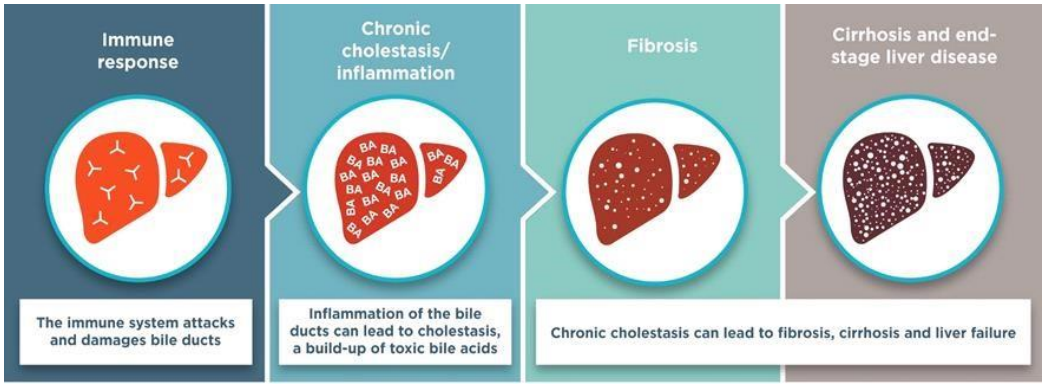
Certain factors such as younger age at LT or type of immunosuppressive therapy and use of protocol vs clinically driven biopsies were also found to increase likelihood of PBC recurrence. A specific type of immunosuppressive therapy (cyclosporine) following LT was found to be associated with longer functioning of the transplanted liver.

In summary, this shows that continuing to take UDCA following LT may be beneficial, as it lowers PBC recurrence and prolongs transplanted liver function. Despite only 20% of PBC LT patients being at risk of PBC recurrence, the benefit of treating all patients with UDCA as a preventive measure may outweigh the risk.

FRI-026 Long-term assessment of the effects of obeticholic acid in patients with primary biliary cholangitis on immune and inflammatory markers

G. Hirschfield, F. Nevens, M. Shiffman, et al. ***Multiple sites. US, Canada, Europe***

Obeticholic Acid (OCA) is a newer approved medicine for PBC, which is given as a second line treatment for patients who do not respond well to UDCA. It works by improving bile flow and reducing inflammation. This is now the only second line PBC treatment which has been studied in terms of its long-term effects.



Ref: Intercept Pharmaceuticals

The researchers carried out a trial giving patients 5-10mg of OCA per day or a placebo drug, whilst continuing UDCA treatment. This was part of a larger study called POISE. The patients enrolled had experienced inadequate symptom improvement or bad side-effects whilst taking UDCA for 12 months.

The researchers found that most measures of PBC symptoms, including liver damage and inflammation were reduced due to OCA treatment at 36 and 48 months into combined treatment. Also, biological signs of cell death and inflammation were reduced in those taking OCA + UDCA compared to patients taking the placebo + UDCA.

In conclusion, this research suggests that combined treatment of OCA and UDCA can improve liver condition and may protect it from further damage. However, as the measures in this study were taken from the blood rather than the liver directly, direct evidence is needed to support these findings. Currently, observational data looking at this is being gathered.

Prof. Christian Trautwein from Aachen, Germany commented on these results: "This is a first hint that OCA is helpful in these patients, but more studies are needed."

FRI-037 Change in lipids: Characteristics and response to obeticholic acid in TARGET-PBC, a diverse, large United States real-world cohort

C. Levy, M. Mayo, E. Carey, et al. *Multiple sites. US*

PBC can affect the levels of lipids in a patient's blood, and may lead to 'hyperlipidemia', which is an abnormally increased level of any or all lipids in the blood. However, PBC has not been found to increase the risk of heart disease.

Treatments for PBC such as OCA have been found to reduce total cholesterol (TC), primarily due to lowering high-density lipoproteins (HDL), and a small increase in low-density lipoproteins (LDL) may also occur. A high level of HDL is associated with decreased risk of heart disease whereas a high level LDL is associated with an increased risk of heart disease.

The researchers carried out a long-term study at 35 US sites using PBC patients who have been taking OCA for at least 3 months. Data from medical records was analysed. After around 15.5 months of OCA treatment, the researchers identified a decrease in TC and HDL, see the chart below.

Median decreases in lipids in PBC patients at 15.5 months into OCA treatment

Following OCA treatment, there was no prominent decrease in LDL for PBC patients overall. However, for PBC patients, without cirrhosis, LDL levels increased slightly whereas for patients with cirrhosis LDL levels decreased. The LDL decrease in cirrhotics may be due to the progression of liver disease, rather than the treatment.

This research shows that OCA treatment may not have as clear an impact on lipid levels in PBC patients as earlier studies suggested. More research is needed to investigate the influence of OCA and different factors on lipid levels in PBC patients, especially as this study contradicts earlier research where OCA was found to increase LDL.

Prof. Trautwein considered these findings "interesting because maybe OCA may not have a negative impact on cholesterol levels, meaning OCA could be safer than previously thought regarding this aspect."

*Not significant: meaning the difference identified was not large enough to accurately and reliably say LDL did decrease

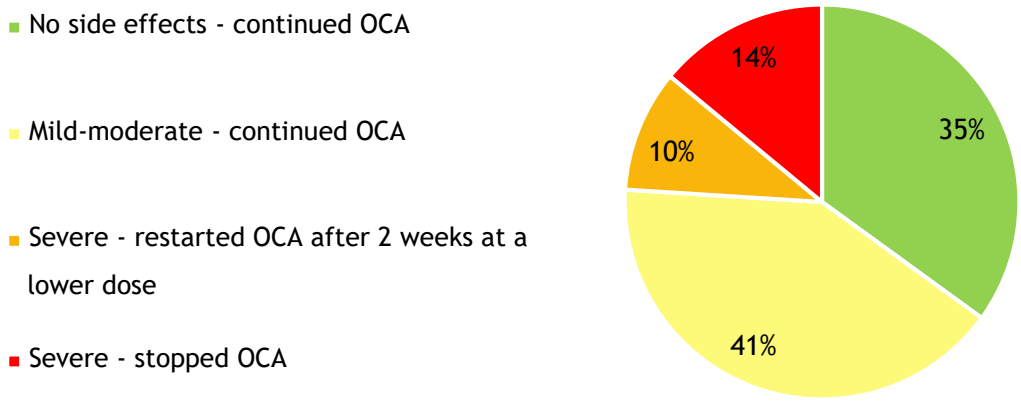
FRI-049 Real world experience of obeticholic acid for the treatment of primary biliary cholangitis in the secondary care setting

A. Pratt, L. Turner, J. Hutchinson, L. Maher, D. Orange, C. Millson. ***York Teaching Hospital NHS Foundation Trust. UK***

Obeticholic acid (OCA) has been found to mainly reduce two laboratory markers, which at high levels, indicate worsening of PBC by the POISE study group. These two markers are alkaline phosphatase (AP) and bilirubin, which are found in the blood. For some patients, OCA causes bad side effects (SE) such as itching, which can lead them to stop treatment. Half a year ago, one clinic in California found that almost a third of patients stopped OCA treatment due to SE; these observations were published at the AASLD Liver Meeting in San Francisco (Nov 2018)[1].

At this EASL congress, a study from UK also looked at the use of OCA in a real-life setting. It included patients who previously did not respond well to UDCA. In the study, they took OCA, either instead of UDCA (38%) or as an additional medicine alongside UDCA (62%). As in the US study, severe itching (pruritus) was the most common side effect of OCA. See the chart below for a breakdown of the proportion of patients who experienced pruritus in the study and whether this led to them stopping treatment.

Outcomes of OCA treatment: pruritus and discontinuation



In summary, 31% of patients discontinued OCA following SE (including pruritus and other side effects). This is a higher number than identified by the POISE study group (which led to approval of OCA in PBC). However, at 6 months, average AP levels were reduced, suggesting OCA improved liver function. The difference between this study and the POISE study is that study this was carried out in a natural clinic setting whereas the POISE study was a controlled research study. This may mean the results in this study are more similar to what would occur in real life. Nonetheless, longerterm research needs to be carried out for longer to assess how side-effects may change over time and how this relates to discontinuation of treatment.

Managing side effects may help more patients to stay on treatment. A small study from Canada with 40 PBC patients (Abstract FRI-056) showed much lower drop-out rates; although itching increased in more than half of participants, only two patients discontinued OCA because of pruritus and a third because of worsening liver disease. Notably, patients in the Canadian study had been included in a patient management programme at the beginning of their OCA treatment.

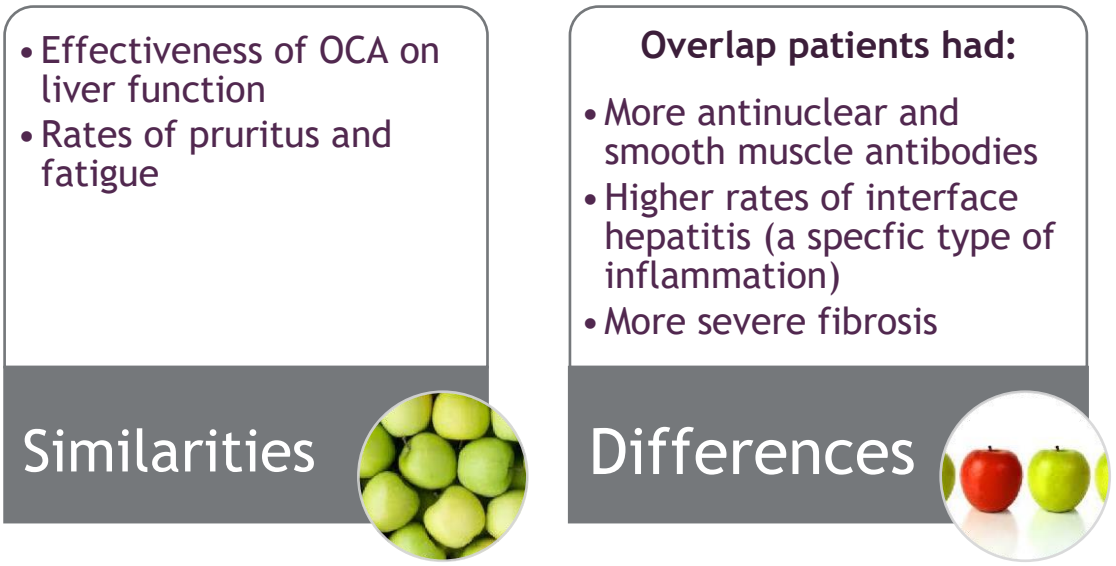
1. *Therapy in Patients with Primary Biliary Cholangitis (PBC) Treated in a Tertiary Care Liver Center. AASLD 2018. Abstract 1923.]*

FRI-043 Primary biliary cholangitis-autoimmune hepatitis overlap syndrome: Characteristics and response to obeticholic acid in TARGET-PBC, a diverse, large United States real-world cohort

M. Mayo, C. Bowlus, E. Carey, et al. *Multiple sites. US*

In rare cases, patients have symptoms that are categorised under two different immune disorders of the liver. This means they cannot be diagnosed with one or the other, they are diagnosed with having an ‘overlap syndrome’. One example of this is primary biliary cholangitis-autoimmune hepatitis overlap syndrome. These patients are at a higher risk of liver damage and often receive treatments for both PBC and AIH.

This study compared patients (N= 485) across 35 US sites, with this overlap syndrome (14.6%) and with PBC only (85.4%), looking at how they differ in their characteristics and response to OCA. However, by the last time patients were evaluated, most were taking both OCA + UDCA. Overlap patients and PBC-only patients differed in some characteristics but were similar in regard to treatment effects, see below.



Overall, this study found that patients with overlap syndromes differ in some ways to those with PBC only. However, this is unlikely to influence the effectiveness and safety of OCA treatment or OCA + UDCA combined treatment. One thing that complicates the interpretation of this research is the ongoing debate around whether overlap syndrome patients have two separate diseases, whether one disease is more dominant or if the combination of the two results in a different disease entirely. More research is needed in this area to clarify.

Prof. Trautwein commented on the study: "The definition of overlap syndrome is not always the same. It will be a challenge for hepatologists to better define this and ensure definitions are consistent."

Non- approved medicines

FRI-052 Long-term bezafibrate therapy does not prevent the progression of primary biliary cholangitis in patients with advanced disease

A. Reig, L. Llovet, P. Sese, M. Carlota, A. Pares. ***University of Barcelona. Spain***

A common approach when treating PBC is to combine UDCA treatment with other drugs, if UDCA alone is not effective enough. A lot of PBC research aims to identify new drugs for this purpose. Fibrates have been approved for hyperlipidemia for many years. While not currently approved for PBC, they are being investigated as possible PBC add-on treatment. Past research showed that adding fibrates to UDCA may improve liver chemistry and pruritus, and possibly reduce PBC related liver damage.

Patients whose AP levels were not at the target level (indicating poor liver functioning) after taking UDCA for at least a year, were given 400mg of bezafibrate, a type of fibrate, daily alongside UDCA.

After around six years, patients who were given UDCA and bezafibrate showed increased bile flow in the liver, which is usually decreased in PBC. However, this did not prevent further progression of the liver disease or complications, see the table below for more details.

	Number of patients
Normalised ALP levels	28
Fibrosis scores higher than desired	16
Globe score which predicts poor disease outcomes	17
Progressed to advanced disease and had a liver transplant or other conditions	6
Progressed to advanced disease and died	2

● = Improvement in disease ● = Poor disease progression ● = Severe disease progression

The data above demonstrates that long-term treatment of UDCA and bezafibrate had a positive impact on about half of patients (52%) in the study for a short period of time, as shown by improved ALP levels. However, the treatment did not prevent or slow progression of PBC in patients with advanced disease.

According to the package information, bezafibrate should not be used in patients with cirrhosis; this study suggests that the use of bezafibrate in cirrhotic patients may not exist, and that it is more likely to have beneficial effects in PBC patients with earlier stages of liver disease.

Prof. Trautwein commented on these findings: "It is important to remember that in some countries, advanced disease with cirrhosis prevents the ability to use bezafibrate at all. This study gives an important message, showing that, in some patients, bezafibrate can be dangerous and worsen liver disease."

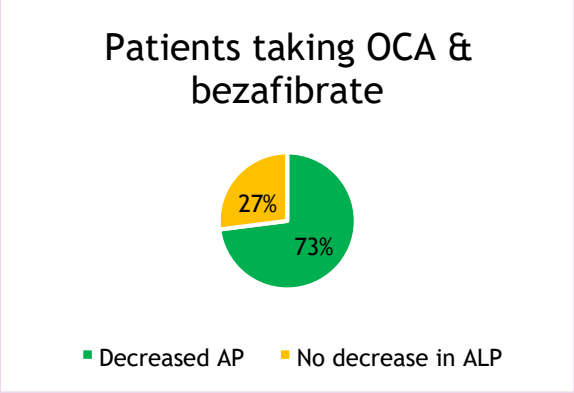
LBO-05 Bezafibrate improves the effect of obeticholic acid on cholestasis in patients with primary biliary cholangitis

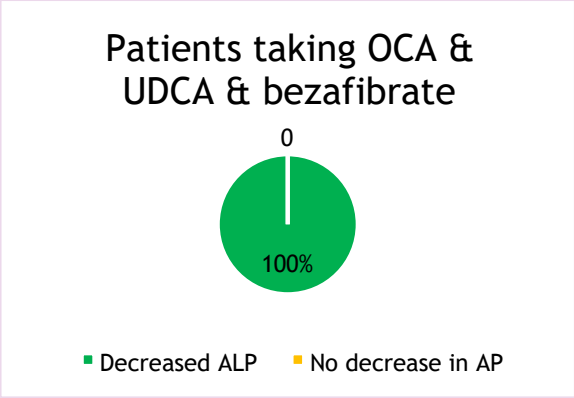
L. Smets, S. Liliane, K. Hannelie, V. D. M. Schalk, N. Frederik. *2UZ Leuven. Belgium*

Bezafibrate has the potential to improve the effectiveness of OCA in PBC patients. Bezafibrate is not yet approved for PBC but has been found to decrease levels of chemicals in the blood associated with worsening PBC symptoms e.g. ALP levels. For patients, who do not respond well to UDCA and OCA combined treatment, taking bezafilbrate too may be a solution.

This study included patients who had been taking OCA and UCDA for four to five years. They were given bezafibrate as an additional drug to OCA + UCDA. After 6 months, most patients taking all three drugs had reduced AP levels, indicating improved liver function and a lower risk of disease progression. See the proportion of patients whose AP levels were reduced below, per treatment option in the chart below.

Outcomes at 6 months





Further indicators of liver disease progression were reduced: biliribin, itching and pruritus. However these reductions were not large enough to be able to assume bezafibrate can reduce these in real life. This study also used a very small sample, therefore larger research studies are needed to support these findings. With a larger sample size, we can be more certain that the findings are accurate to real life.

A further perspective on bezafibrate is that it could become an alternative to OCA in the future. It is much cheaper and has been found by some studies to be much less likely to cause itching, a common side effect of OCA. However, this study looks at the effectiveness of OCA, UDCA and bezafibrate as a triple treatment and it appears this could be very effective, from observing the reduction in AP levels. A positive impact upon clinical measures of PBC would strengthen this argument. There is still ongoing debate about what treatments and combination of treatments are best and more research is needed for non-approved medicines such as bezafibrate to ensure safety and efficacy.

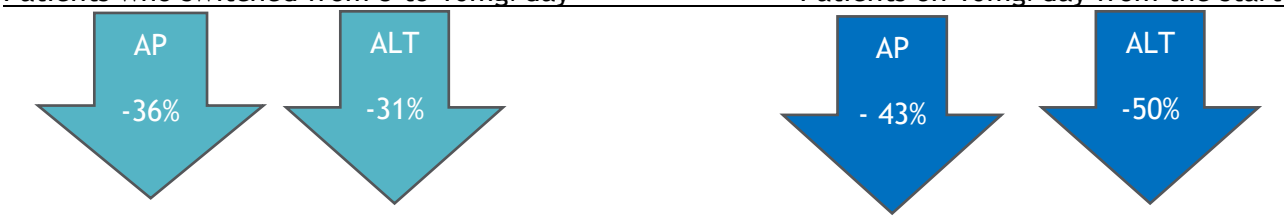
PS-122 Seladelpar for the treatment of primary biliary cholangitis: Experience with 26 cirrhotic patients

M. J. Mayo, C. Bowlus, G. Michael, et al. *Multiple sites. US*

Seladelpar is a new treatment for PBC which is not yet approved. It could be a promising add-on option for patients in whom UDCA is not effective. This study investigated the safety and efficacy of taking seladelpar in patients who have not responded well to UDCA, and some of whom have early cirrhosis.

If the levels of alkaline phosphatase were not sufficiently lowered at 12 weeks, the dose of seladelpar was doubled from 5mg to 10mg. See below the median change in measures of PBC disease progression for the two groups of patients at 12 months into seladelpar + UDCA treatment.

Outcomes at 12 months



Overall, decreased AP levels indicate improved liver function and decreased ALT levels suggest an anti-inflammatory effect on cirrhosis due to seladelpar use. Regarding safety, three patients with cirrhosis experienced a severe adverse event. However, this was unrelated to seladelpar use and no liver decomposition/failure occurred. This suggests that seladelpar at 5mg and 10mg is safe for patients with early cirrhosis.

Earlier studies identified that higher doses seladelpar can be toxic to the liver, additionally, these did not include patients with cirrhosis. Cirrhosis may affect the metabolism of the liver and therefore risk of toxicity when taking certain drugs. This could mean that those with cirrhosis may be at a higher risk of liver toxicity when taking seladelpar, especially in more advanced stages of cirrhosis with decreased liver function.

In conclusion, this study offers promising results for seladelpar improving the condition of the liver safely, but more research is needed with larger groups of patients to confirm this.

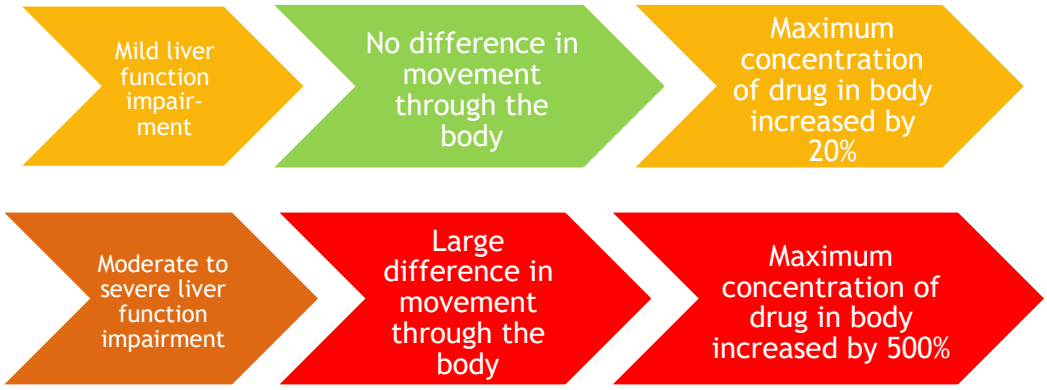
FRI-041 Pharmacokinetics, safety, and tolerability of seladelpar in subjects with hepatic impairment

L. Mao, R. Martin, A. Steinberg, P. Rohane, J. Nguyen, M. Standen, P. Boudes. *CymaBay Therapeutics. US*

Seladelpar is a potential treatment option for PBC patients whose condition does not improve following UDCA treatment. It has been shown to have anti-cholestatic and anti-inflammatory effects by decreasing production of bile acids and reaching different parts of the biliary system. It may prevent patients from going on to develop cirrhosis.

This study aimed to evaluate the safety of a single 10mg dose of seladelpar and how it moves through the body (pharmacokinetics) and whether disease stage has an influence on this. The study included patients with different stages of cirrhosis and reduced liver function, and compared them to people without PBC. See the chart below for a breakdown of the effect of seladelpar on the body depending on the severity of liver disease.

Pharmacokinetics of Seladelpar



Despite the difference in the maximum concentration reached by seladelpar in the body between those with mild vs moderate/severe liver disease, a single dose of the study drug was well tolerated overall. Also, all adverse events were mild apart from one severe adverse event for one patient (variceal bleeding). However, this was unlikely to be related to study treatment as the patient already had a history of bleeding episodes before taking seladelpar.

Overall, the study found that a single 10mg dose of seladelpar may be safe for patients at all stages of liver disease. But, as the maximum concentration of seladelpar identified in moderate to severe liver disease patients was so high, being 5x higher than in healthy patients, doses may have to be adjusted for longer term treatment.

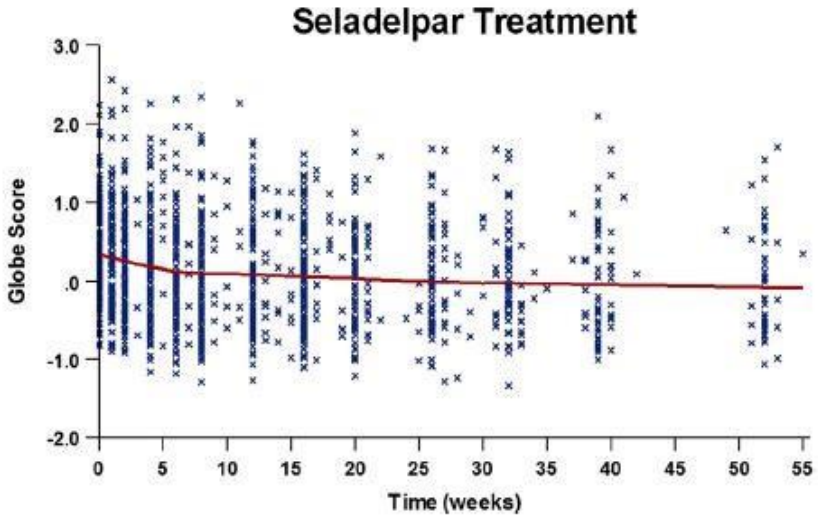
This suggests that lowering the dose of seladelpar and regular monitoring of the drug concentration may be necessary in patients with advanced liver disease, if use of seladelpar for PBC is approved, to ensure safety and prevent liver damage.

FRI-045 Treatment of patients with primary biliary cholangitis with seladelpar for 52 weeks improves predicted transplant-free survival

C. Perez, P. Boudes, A. Steinberg, et al. ***Toronto General Hospital, University Health Network. Canada. Cymabay Therapeutics. US***

'Transplant free-survival' is defined as survival without liver transplantation and free from liverrelated death. This can be predicted by a tool called 'Globe score', which calculates risk from different measures in the blood and age. A lower Globe score means a better chance of transplantfree survival.

The researchers investigated the effect of seladelpar, a new drug for PBC not currently approved, on predicted transplant-free survival using Globe scores. The patients in the study had previously not responded well to UDCA and were started on 2mg, 5mg or 10mg of seladelpar daily in addition to UDCA. Overall, Globe scores decreased whilst taking seladelpar, meaning the likelihood of transplant free-survival increased, see the graph below.



At 52 weeks, the average decline in Globe scores across all patients in the study was 0.425. There were no significant differences between patients taking different doses of seladelpar but the largest average decrease was seen in the group of patients taking 5mg. Using Globe scores, the predicted rates of transplant-free survival were higher at 3, 5, 10 and 15 years when taking seladelpar + UDCA vs. UDCA alone.

In conclusion, seladelpar may have promising effects on transplant-free survival rates, however this is based on predictions. No real change in diseases progression, clinical events or overall liver function was measured. Therefore, from this study, it is too early to say if seladelpar reduces transplant free survival rates in real-life. Long-term data looking at the effect of seladelpar on actual liver function is currently being gathered and is needed to support these results.

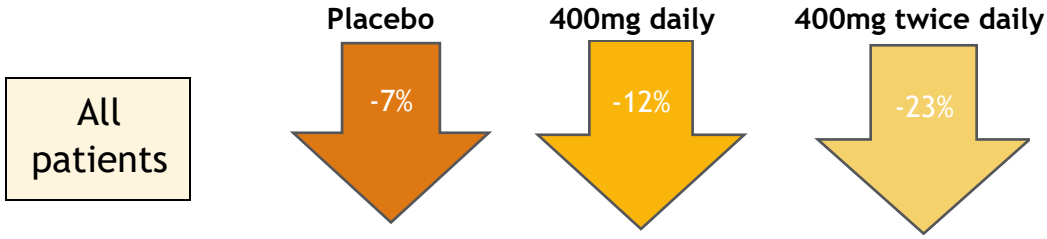
GS-02 Efficacy of GKT831 in patients with primary biliary cholangitis and inadequate response to ursodeoxycholic acid: Interim efficacy results of a phase 2 clinical trial

G. Dalekos, P. Invernizzi, F. Nevens, et al. ***Multiple sites. Europe***

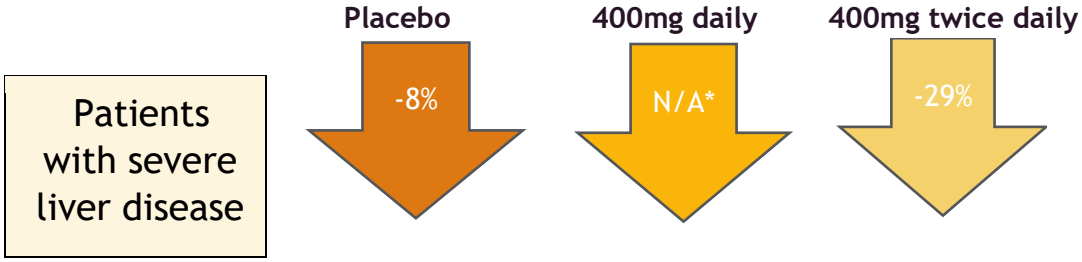
GKT831 is new drug for PBC, undergoing research. It works to stop NOX1/4 from working properly which usually triggers biological processes that cause inflammation and fibrosis. GKT831 has been shown to reduce inflammation and fibrosis in cells and animals.

This study aimed to evaluate the effectiveness and safety of the GKT831 in PBC patients for whom UCDA has been previously ineffective. They were given either i) 400mg a day, ii) 400mg twice daily, iii) placebo, all patients continued taking UDCA.

At six weeks into treatment, reductions in GGT (gamma glutamyl transpeptidase), a blood measure of liver and bile duct function were as below:



For patients with greater GGT at the start of the study, indicating more severe liver disease, the following reductions in GGT were observed:



Additionally, lower AP levels were also found in all groups, suggesting GKT831 led to better liver functioning through reducing oxidative stress in the liver. The largest decrease in AP levels was for patients taking 400mg of GKT831 twice daily, suggesting this may be more effective than one 400mg dose daily.

These results suggests GKT831 could have the potential to be highly effective, showing benefits for bile duct and overall liver functioning at six weeks into treatment. More research is needed looking at the longer term effects of GKT831, to see if it is safe and effective over time. The researchers are planning to assess quality of life and liver fibrosis at 24 weeks into GKT831 + UDCA treatment.

*result not published