Podcast Episode 2: Primary Biliary Cholangitis Highlights from EASL 2023

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Robert Mitchell-Thain
Hello. Welcome and thank you very much for joining us today to discuss the PBC highlights from EASL 2023. My name is Robert Mitchell-Thain, I'm the CEO of the PBC Foundation.

Kath Houghton
Hi. Thanks, Robert. And I'm Kath Houghton. I work as a nurse specialist with PBC patients in Newcastle and also do some research as well. And I think we're here to just go over a couple of abstracts that we chose to highlight. So if we move to our next section. This is an abstract from the GLIMMER trial looking at a new drug linerixibat, which is to treat itch in people.

To test the itch on people they used a tool, as we call them, tools, which is a questionnaire called the EQ-5-D and they wanted to try and understand the relationship between severe itch and poor quality of life, leading to depression often in people. And we know how devastating pruritus can be, or itch for people with PBC. So they wanted to just sort of have a look at why this affects people so badly.

So talking about the method, I think they used past questionnaires, the EQ-5-D measures, just to try to understand this relationship through a study called GLIMMER, which was placebo controlled and using mostly female patients, about 150, aged averagely around 55 who were on this new drug.

Now the scores at baseline show that over 60% of the patients had severe itch and they also showed severe sleep disturbance. And about a third of these patients showing higher incidence of severe itch also suffered with depression, unsurprisingly. And even patients with mild to moderate itch, they also had depression in over 80% of patients reporting that mild to moderate itch.

Robert Mitchell-Thain
Thanks Kath, I think you've hit the key parts of this right here in this poster in terms of itch being more than itch, it has implications for health-related quality of life in terms of severe sleep interference and depression. And again, this highlights not only the patient experience, it highlights the acknowledgment by researchers and health care clinicians of patients' quality of life and the consequences of that. And again, it also highlights the work that's going on in the background to address this for patients.

Kath Houghton
Yeah, I agree. I think more importantly, they're suggesting that physicians treating patients with itch need to be a lot more vigilant and appreciate the effects of itch on people's lives. So, you know, maybe treat a bit more aggressively and understand how they can suffer otherwise with it as well.

Robert Mitchell-Thain
Those are important points so thank you for raising those. And I think if we move on to the second poster that we want to highlight and again, there are three parts to PBC, there are the liver tests themselves, there is the symptom burden on a daily basis and then there is the histological changes and damage that goes on. And I think this second poster raises some really, really important points in terms of the correlation between the symptom burden and people living with primary biliary cholangitis and the fact that that does not associate with transient elastography measures.

This poster was from the Wednesday, so it was Wednesday number 310 and the lead author was Houri.

Kath Houghton
Essentially what they're saying is, like Robert said, symptoms and biomarkers and worsening PBC, biological PBC do not correlate. So they've done this by using elastography. So that is a measure of liver stiffness. So liver stiffness is a measure of scarring in the liver and with increasing scarring, the liver stiffness increases which shows increasing liver damage.

So they've done this looking at over a two-year period using PBC-40 to sort of highlight people who are symptomatic and then looking at their liver stiffness reports and essentially it shows that there is no correlation between the two. So people's blood tests and symptoms don't correlate. It doesn't mean that their PBC is worse because of it.

And people often worry about this symptomatic and especially if they're quite new and they think, does this mean my disease is worse and I'm progressing? And obviously this is a nice abstract to show just to reassure people that it doesn't.

Robert Mitchell-Thain
You're absolutely right. I think this abstract has two main focus points in terms of the power of the data. And again, this is over 200 patients that are involved. And so the first one is reinforcement to clinicians that actually both aspects of PBC need to be explored and treated, but also reassurance to patients themselves who may experience a decrease in their quality of life because maybe the symptoms have got worse for a particular period of

time and they're concerned that their disease is progressing. And this paper again is just one of the tools we can use to reassure patients at that point of their journey.

Kath Houghton
Yeah, I agree. The only caveat was that it did look like patients who suffered with itch did have a higher elastography score. So there is some correlation there. But we do know, or we think, that people who suffer with itch quite badly have more damage to their bile ducts and, you know, are more difficult patients to treat. So there is that small association.

Robert Mitchell-Thain
If you're happy to move on to our next poster again. So this was from the Thursday now, so ID THURSDAY-324. And this was evaluating pruritus and fatigue in patients with treatment refractory primary biliary cholangitis. Again, another really important piece because this is looking again at patient quality of life overall and not just where we are in terms of liver biochemistry.

Kath Houghton
Yeah, I think this is a really important study because it's looking at the tools, or the questionnaires that we use to assess people's itch, quality of life, fatigue scores, etc. And just wanted to validate them to say they give us a true reflection.

So they're using the NRS [numerical rating scale] itch score, the PROMIS [P*atient-Reported Outcomes Measurement Information System*] fatigue score. And the objective was to gather evidence, like I say, regarding the content validity of these tools and whether it captured the perspectives of patients with PBC clearly and was of use, so they were able to measure and report these experiences correctly, really.

So they had 20 adult patients with PBC and pruritus and they were interviewed over the phone initially and consented. They've all been diagnosed at least five years and reported symptoms of itch. The majority of mild to moderate and some severe itch and obviously they were asked to evaluate the questionnaires.

So what they wanted to know was, were they easy to understand, were they easy to use and the appropriateness of the recall period. So, for instance, how is your itching been over the last four weeks or six weeks? Was that appropriate or would they want to ask over to longer period? And they also asked them to describe the amount of change in the current rating, how much change would be meaningful to the benefits? In other words, if their itch got worse or better, how many points up or down would need to go before it was very noticeable for the patients?

So for the tools, the NRS itch score, they were happy with it. Almost 60% thought at least a three-point change would show meaningful improvement, but only one or two-point change would show noticeable worsening which is quite interesting. And almost 80% of patients thought the recall was appropriate. So that was good. And the fatigue tool, PROMIS, almost 70% of patients said that only a one-point change would show both meaningful improvement and worsening. So that's slightly different. 100% said it was easy to use and around 80% said the recall was appropriate.

So it's important that these tools are validated and assessed because they are used a lot in research. And when you are doing a placebo controlled trial, you do want to be sure you're getting a true reflection of people's symptoms. Of course, we don't know whether they're on placebo or active ingredients. So we need to know that these tools will show us an improvement or not, depending on which drug they are. So it's completely unbiased. But I think it's really important that they're validated and it shows that they actually do work well.

Robert Mitchell-Thain
I think you're absolutely right. I think it's important that we have tools that are validated, but also tools that are patient centric, patient friendly, easy to understand and are not placing additional burden on the patients that are being asked to use them. So again, another really important piece of work that says that we have good tools that make a difference and are not adding to patient burden, which is fantastic.

Kath Houghton
So if you're happy to move on to the next one, I think we wanted to highlight this one just to show, PBC is seen as a sort of, a not very problematic disease and for the most part that's true. But for some patients they do have problems responding to treatment. Even without problems responding to treatment, they can end up getting into trouble.

So I think this next one talks about the risk of death, liver transplant and hepatic decompensation, even in people whose ALK-phos [alkaline phosphatase] and bili [bilirubin], which are the two main markers we look out for with people who are progressing, were within maybe just over the normal upper limit of normal, but not so far above the upper limit of normal that we would worry. And yet they seemed to go on to have problems.

Robert Mitchell-Thain
Thanks Kath, I think you've made really important points there. You know, historically, within the guidelines, we've looked at the 1.67 times the upper limit of normal, and anything below that is good news. Now let's bear in mind that the number of PBC patients who are leading to liver transplant or indeed death because of their PBC are becoming fewer and fewer.

So the interventions are working. The medicines are working. But what do we look at in terms of the ALK-phos and bilirubin? Historically it's been this 1.67 figure and this poster highlights that anything above normal is associated with higher risk. Now if you speak about higher risk as a clinician, that's an accepted part of medicine, if you will, we risk assess and then we make our decisions on that risk assessment. If you speak about higher risks to a patient, that becomes a lot more of a frightening proposition. So I think it's important to highlight in this poster that, whilst we are talking about higher risk, we are talking about relatively small numbers, but the risk is important enough that we as a community will hopefully look to action this as soon as is possible.

Kath Houghton
And they looked at over 3000 people, which I think is important and followed their results, ALK-phos, bili, ALT [alanine aminotransferase], AST [aspartate aminotransferase] and

albumin. And none of them had particularly high results and yet some did go on to need a liver transplant, which is quite surprising.

So in conclusion to this, it looks like there is an increased risk of decompensation and transplant and even death at lower threshold levels for serum liver biochemical tests and the risk of adverse liver outcomes is greater for patients who spend increasing amounts of time beyond the threshold for biometrics and composite scores. So in other words, those that are below the levels for us to treat according to guidelines, as they stand, with second-line therapies as they are licensed but are not quite within normal levels, it seems they are just at an increased risk for some of them as anybody who is above the level for treating them on second-line therapy.

Robert Mitchell-Thain
You're absolutely right again, I think this is a really important message to the community. We need to take this data and look at our practice and see how we can improve upon this in future.

Kath Houghton
Yeah, and I think that was the point they made, for effective monitoring. I think closer monitoring of these people and potentially trying to make second-line therapies available for these people to push that a little bit, to make them available sooner rather than let them get into trouble.

Robert Mitchell-Thain
Absolutely. Absolutely. So we've looked at Wednesday. We've looked at Thursday. Now Friday's session gave us some really interesting glimpses into the future of PBC and we thought we'd share a couple of highlights. Now I know that when we talk about Friday, so I'm going to talk about FRIDAY-331, which I know that caught your eye Kath. Do you want to share a couple of sentences why this looked so promising for you?

Kath Houghton
Yeah, we did this in Newcastle. Well, actually I say that, it was also Cambridge and maybe Birmingham. There were other sites that contributed. So this was looking at serum biomarkers from a cohort of patients that had given samples for research and for future research. So this was looked at and what came out of it was two markers. So the IL-6 marker was raised in all of the patients who suffered with fatigue, who reported high levels of fatigue, and they weren't in other patients. And also the IL-4. They looked at 20 biomarkers and compared them to symptoms and they also compared this to healthy volunteers.

So the IL-6 with clinically significant fatigue. And interestingly, the IL-4-RA, receptor agonist, that was persistently raised in people with itch. So obviously there needs to be more research into this, but it is a potential new research trial to look at those levels and to see if we can identify more easily that biomarker and find a drug to target it.

I think they are using one of the mAbs [monoclonal antibody] in another area for people with raised IL-4. So whether it will be that I don't know, but it is an area that it looks like we

can do more research into to potentially find a drug to target this and maybe help people with fatigue in the future. So I thought that was quite exciting.

And then there's one more that also caught our eye, which is a study looking at a drug called golexanolone. Now that caught my eye because we are about to start a trial in this country targeting people with fatigue. So this is only being tested in the lab, in lab rats so far. And these rats had their liver bile ducts surgically ligated. So they were sort of cut, which gave them the effect of not working properly and so minimising the bile flow, which we suspect to cause fatigue, they essentially created PBC in the lab rats. And then could see that they were fatigued and they tested that using a treadmill and cognitive problems which they tested using, I think they call it a Y run, so they have to remember where they're going.

With fatigue and cognitive problems sort of brought on in a lab setting. They weren't able to do these things. They then introduced golexanolone, the drug, and it did improve both their fatigue and their cognition, which again is really exciting. So I look forward to seeing this working in practice.

Of course, it'll be placebo control, which it has to be, so it's unbiased and we can prove that it actually is working. But I just think it's another one to watch out for.

Robert Mitchell-Thain
Again, you're right, this is absolutely huge. We've been looking at disease progression for many years. We're now starting to look at other symptoms such as itch. And I think that the fatigue and the cognitive function that goes with that is the next big thing that we need to address now. So to see this science out there being shared, being talked about is absolutely vital and it gives us hope for the future. So, yes, thank you.

Kath Houghton
Yeah, I think so. I think so.

Robert Mitchell-Thain
So speaking of the future, where do we go from here? We thought long and hard about which posters to include, I mean, there were so many points of interest.
So given what we've shared today and what we weren't able to include, what would be your key take home message, really?

Kath Houghton
So what I was so pleased to see in EASL this year was so much talk about the symptom burden, so much more acknowledgment about the effects of the symptom burden on people who struggle. Fatigue has always been nearly impossible, but we are finding ways to try and improve that brain fog or the cognition as well and itch. And I was so pleased to see so many more people talking about this, acknowledging it's a huge problem and acknowledging that we need to help these people and trying to find ways to solve it. That was my big take home and it made me happy to see it.

Robert Mitchell-Thain
You're absolutely right. From the science to the disease progression treatments, the discussions around symptom burden. I think the key message for me is that normal is the new normal. This is where we're pushing, this is where we're going towards.

And I think it's absolutely vital for the clinicians and scientists to acknowledge that and to aspire to that. Obviously, you know, within the caveat of personalised medicine, and I think it's important for patients to know that this is a direction of travel and this is where all the hard work is pushing towards. And so I think that's the great message for me.

Kath Houghton
It is. It's great. And in the last even couple of years, we've learned so much more about PBC and it's changing. People's attitudes are changing. And I think the UK PBC Audit might have helped to wake people up a little bit as well. But you're right, normal is the new normal, not above normal and you're okay sitting there. We need them below, within the normal limits and we're learning that more and more so that it's really good to see.

Robert Mitchell-Thain
Kath, thank you so much. We were working at this all week at EASL. It is always a pleasure to work with you. Anyone who's been listening today, thank you so, so much for joining us. It's been an absolute pleasure.

Kath Houghton
Lovely. Thank you, Robert. Likewise, I enjoyed the meeting and thank you for anybody who might listen to this. I hope you might find it of use. Thank you. Bye bye.

Presentation list:

POSTER ID WED-297
The devastating impact of severe pruritus in primary biliary cholangitis
Poster: Philip Troke (Brentford, United Kingdom)

POSTER ID WED-310
Symptom burden in people living with primary biliary cholangitis does not associate with transient elastography measures
Poster: Inbal Houri (Toronto, Canada)

POSTER ID THU-324
Evaluating pruritus and fatigue in patients with treatment-refractory primary biliary cholangitis
Poster: Jörn Schattenberg (Mainz, Germany)

POSTER ID WED-268
Risk of death, liver transplant or hepatic decompensation in primary biliary cholangitis increases with increased duration and degree beyond established clinical thresholds for hepatic biomarkers and fibrosis scores
Poster: Kris Kowdley (Seattle, United States)

POSTER ID FRI-331
Identification of potential targets amenable to novel therapeutics to treat symptoms in primary biliary cholangitis
Poster: Aaron Wetten (Newcastle, United Kingdom)

POSTER ID FRI-359
Golexanolone, a GABA receptor-modulating steroid antagonist, improves peripheral inflammation, fatigue, locomotor gait, motor incoordination and short-term memory in rats with cholestasis and hepatic encephalopathy due to bile duct ligation
Poster: Paula Izquierdo-Altarejos (Valencia, Spain)