Development of Medicinal Products for PSC

I was honoured to be asked by PSC Patients Europe to represent PSC patients at the December 2018 ‘European Medicines Agency stakeholder interaction on the development of medicinal products for chronic non-infectious liver diseases (PBC, PSC, NASH)’ to share what is important when developing treatments for PSC.

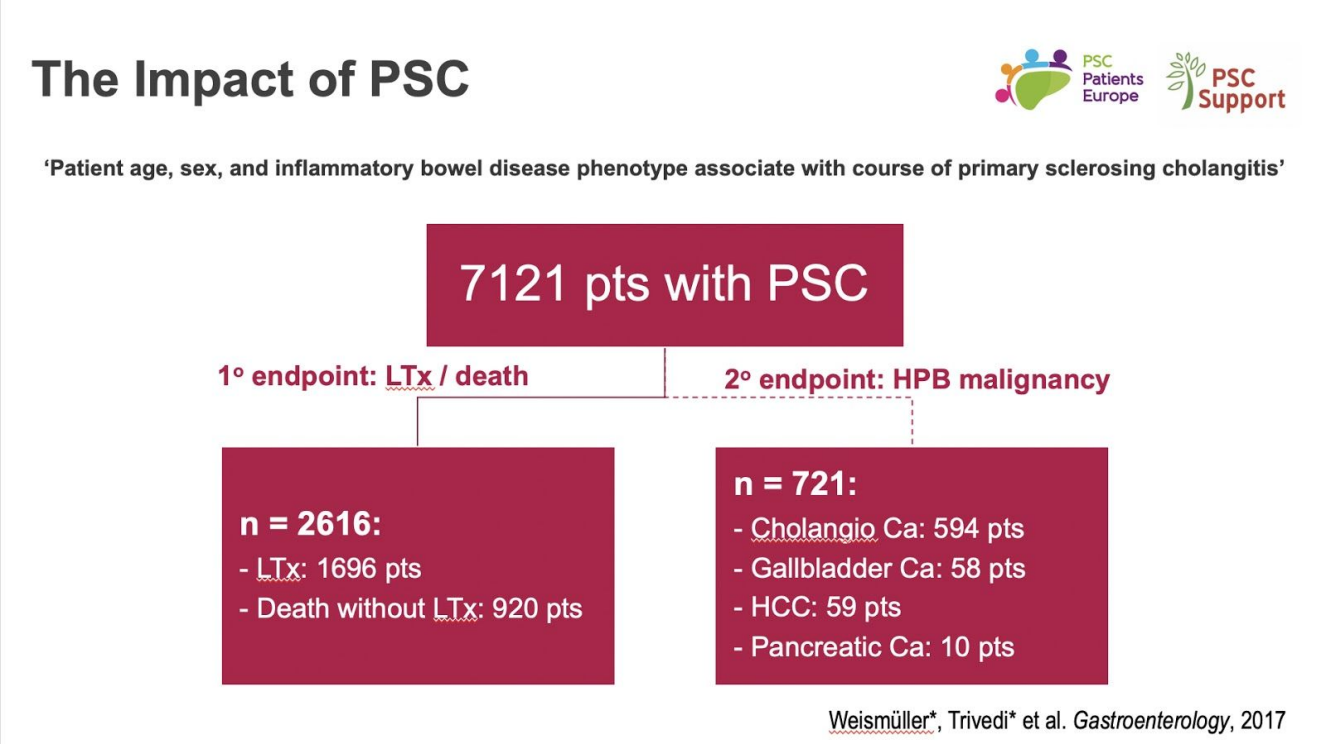
In this important meeting, I gave an overview of the impact of PSC on patients, based on information provided to us in our Research and Treatment surveys, and their implications on clinical trial design.

Martine Walmsley, PSC Support 31 December 2018

The Impact of PSC

Survival

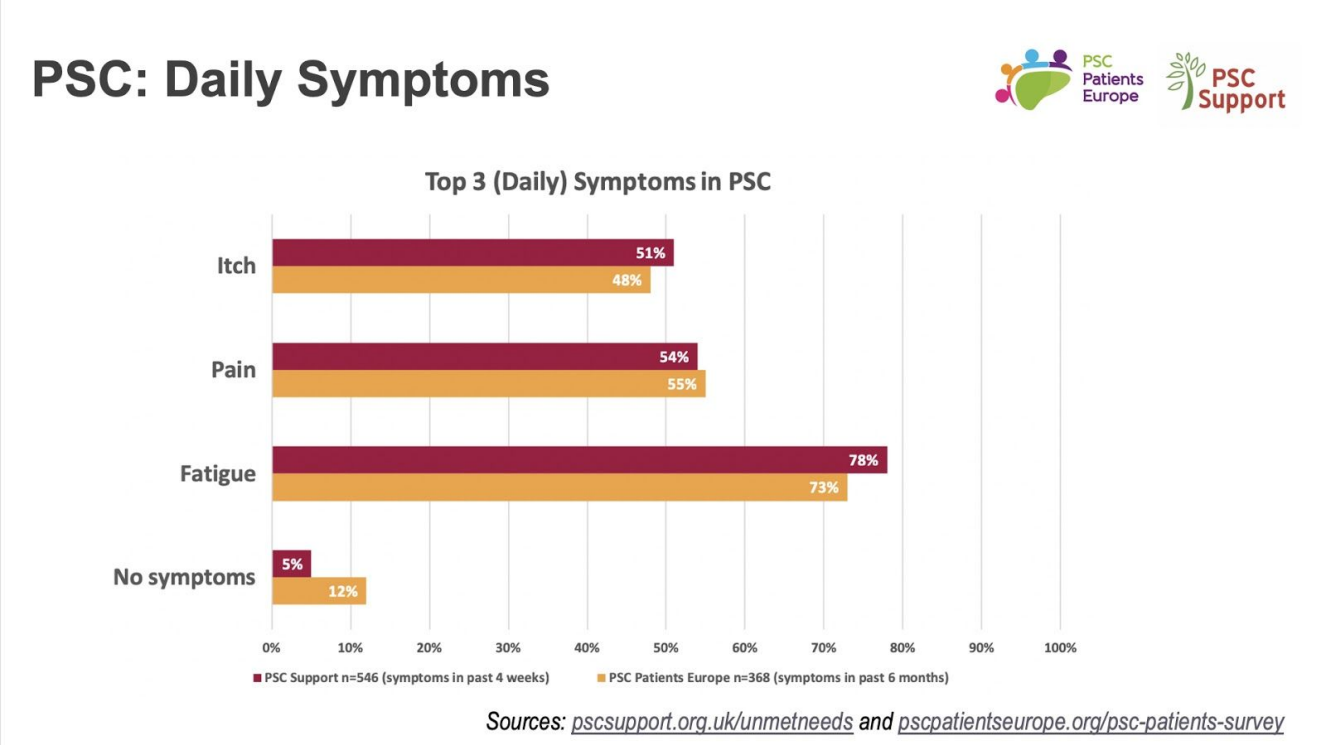
It’s critical to remember that there is currently no medicine available to treat PSC, that is, to halt of slow progression of the disease or its complications, and patients are dying early. I presented data from the landmark Weißmüller, Trivedi et al study from 2017 to illustrate this [1]. I chose this study because it looked at health records from over 7,000 PSC patients over a 30 year period in 17 different countries. This is represents a huge amount of data, with a significant proportion of UK data, thanks to participants in the UK-PSC registry. The data is sobering, showing that nearly 40% of the PSC patients observed needed a liver transplant or died, with just over 10% developing a cancer in the liver or biliary system, and most common being bile duct cancer.



Daily symptoms

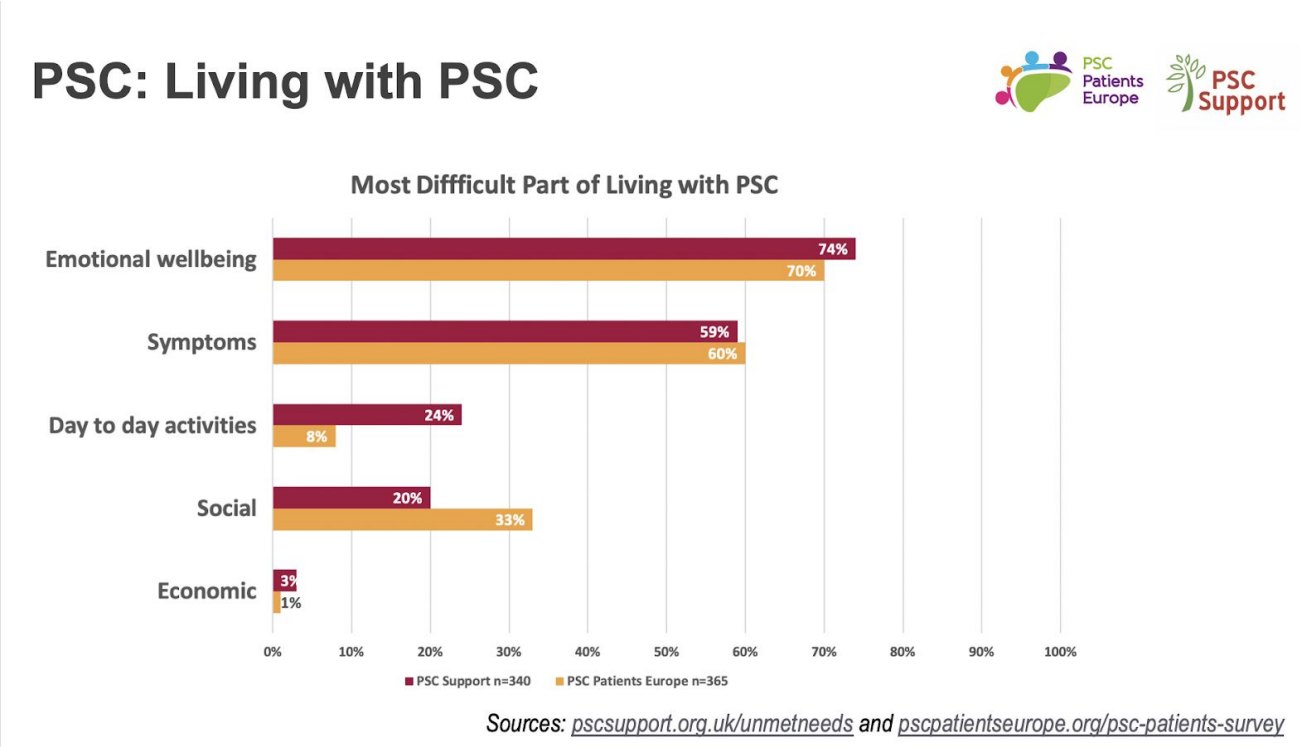
I also wanted to convey to the EMA that people with PSC suffer with debilitating daily symptoms, regardless of the stage of their disease. These symptoms are not always recognised in scientific literature on PSC and are therefore can be overlooked in research studies (as well as clinical care*). The two patient organisations, PSC Support [2] and PSC Patients Europe [3], conducted two separate surveys to gauge the patient perspective of having PSC, and found that only 5-12% of patients reported having **no symptoms** in the previous 4 weeks (PSC Support) and 6 months (PSC Patients Europe). We found the most common symptoms reported were fatigue (about three-quarters of respondents in both surveys reported fatigue), and pain and itch (again, around half in both surveys). I highlighted pain as an important and significant symptom for patients as it is often overlooked despite being a major problem when not well-controlled.

** addressing clinical care was beyond the scope of my presentation on this occasion but something I consistently address at other times.*



Uncertainty

To add to the struggle for patients, we don't know what symptoms or complications will strike, or when - making PSC full of uncertainties. I recounted my own experience. When I was diagnosed with PSC, my daughter was less than a year old, and I didn't think I would live to see her go to school, let alone grow up. She's thirteen years old now and I'm still here but so are those uncertainties.



This is typical. Another question in our surveys asked patients to describe the most difficult part of living with PSC. Nearly three-quarters of respondents said that the **emotional impact** was one of the most difficult aspects, and nearly two-thirds of those emotional difficulties were around **uncertainty about the future.**

Two thirds said that **symptoms** were the most difficult part to live with and these impact on every part of daily life: on work/education and social lives, and on our thoughts and feelings [2].

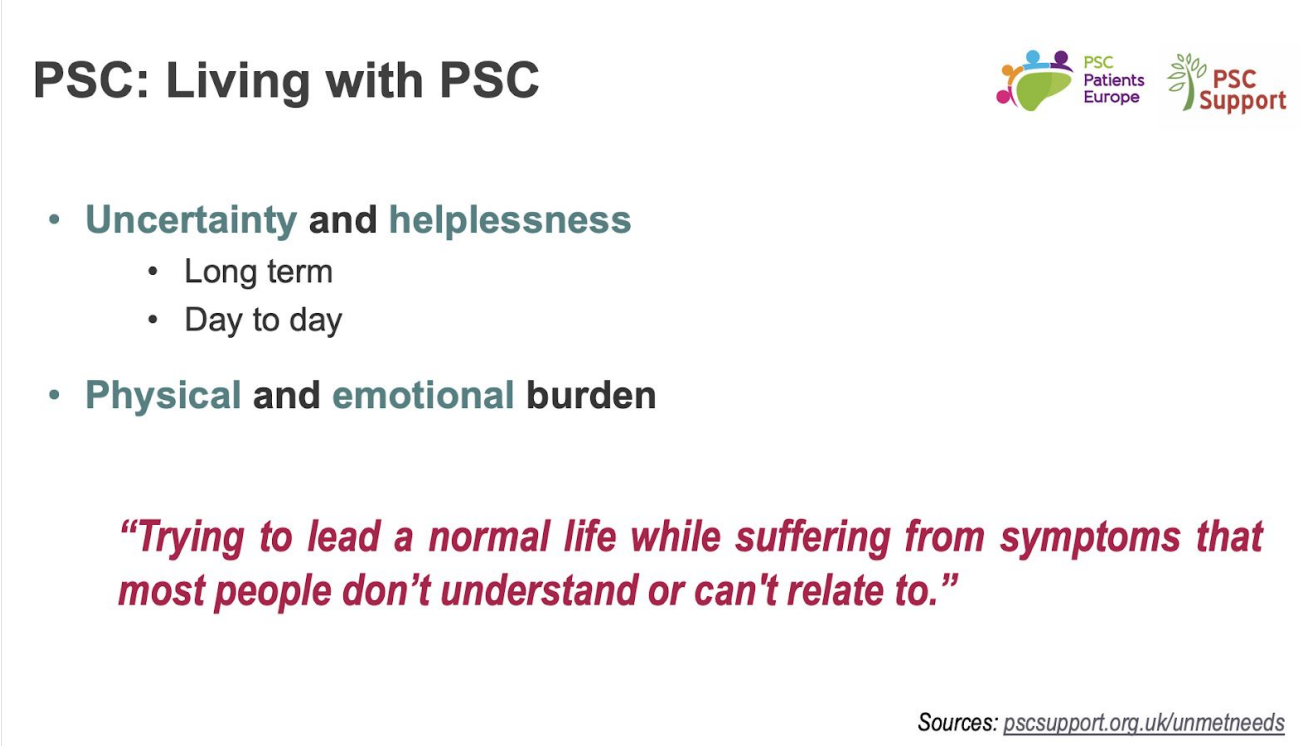
In the long term, patients worry most about early death, disease progression, needing a transplant, becoming too ill for transplant, PSC returning after transplant, cancer, and repeated bile duct infections [2].

Day to day, patients and families never know what symptoms will strike, making it difficult to plan ahead. It makes us socially unreliable, which in turn can lead to social isolation and other psychological issues [2].

Helplessness

PSC brings a huge sense of helplessness. While we don't have treatments, patients have a disease no one can treat, or predict. Families feel frustrated and helpless, unable to help.

There is a huge physical and emotional burden associated with having PSC. One patient said the most difficult thing was, *"Trying to lead a normal life while suffering from symptoms that most people don't understand or can't relate to."* [2] And that's what I wanted to emphasise, that all anyone wants to do is lead a normal life, just like everyone else.



Clinical Trial Design

In the second part of the presentation, I wanted to be clear about what the patient perspective means for overall clinical trial design and endpoints. It means that we need to take care in what we measure to show a drug improves PSC, and this is a complex problem. Before we get onto that, I'll give a bit of background into the extent of this problem.

Surrogate markers of improvement

What makes a drug effective in PSC? This is the six million dollar question, because proving that a drug helps someone with PSC live longer, or not need a liver transplant, would require a very long trial, possibly more than 20 years. This length of study is not feasible for pharmaceutical companies. So how can we confidently say a PSC drug is effective? We must be able to quantify 'something' that is reasonably likely to predict an outcome, such as death, cancer or needing a transplant (disease progression). And so if the use of a new drug demonstrates a reduction in that 'something', then we can be reasonably confident that people taking the drug will be less likely to die early or need a transplant. That's easy then, shouldn't we simply use a surrogate marker in PSC trials? It's not that

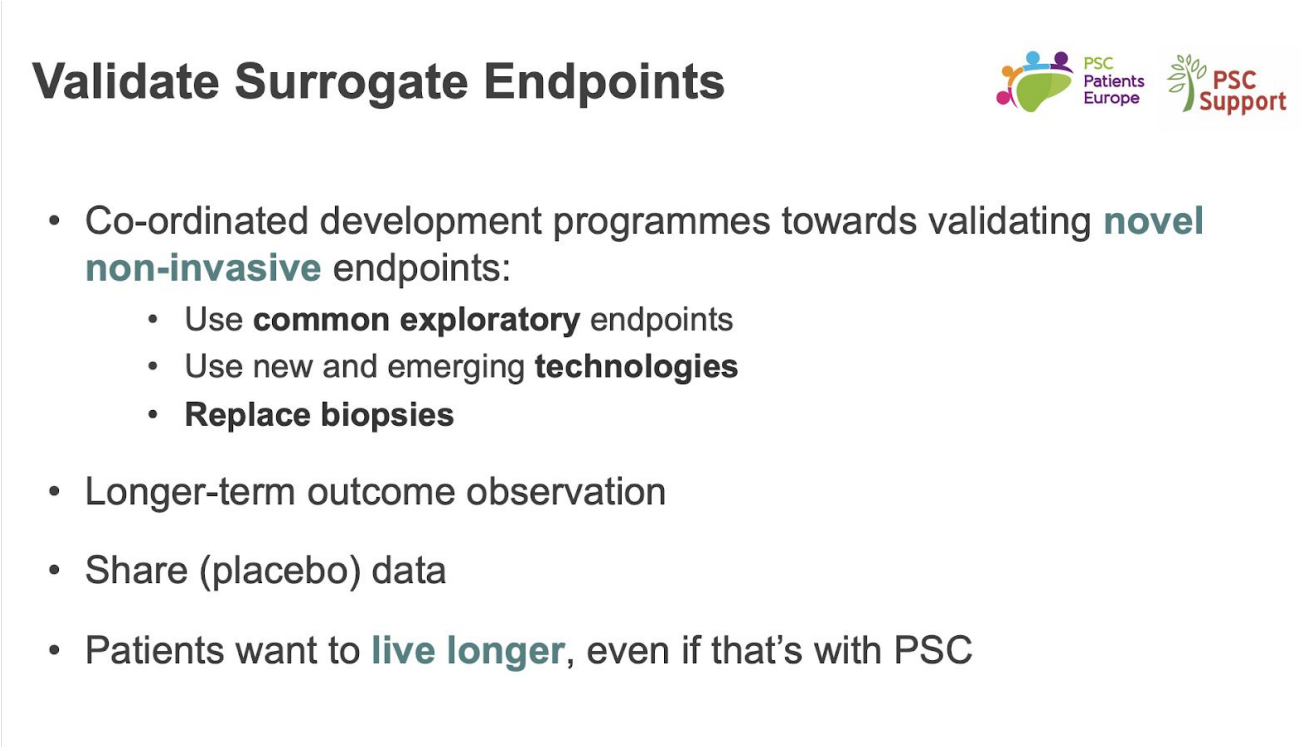
simple. We don't yet have a single surrogate marker that truly gives us confidence that it can predict disease progression in PSC, despite excellent research progress in recent years.

The International PSC Study Group (world leaders in PSC research) acknowledge [4,5] that there is no one surrogate that can do the job, and therefore propose composite use of a number of markers for use in clinical trials. So important is the holy grail of defining endpoints in trials for PSC that there is a Liver Forum (PSC) Endpoints Working Group addressing this, of which I am a member. It includes academic researchers, industry and FDA and EMA representation. A consensus on clinically meaningful endpoints in PSC clinical trials will accelerate our goal of getting treatments for PSC patients and is important.

Should we use surrogates in PSC trials?

Patients do not like or trust surrogates, nor do we think they are the best way to judge treatments. The use of surrogates in clinical trials is controversial. In the past, drugs (for other conditions) have been approved on the basis of surrogates that have poor correlations with overall survival [6,7]. Some clinical trial design experts argue against the their use, saying they don't definitively test the drugs, and that hard endpoints (taking many years to reach) are preferable.

However, people with PSC don't have the luxury of time. Their unmet needs must be resolved as a matter of urgency. Surrogates speed up trial duration, so we accept them cautiously.



Longer term observation

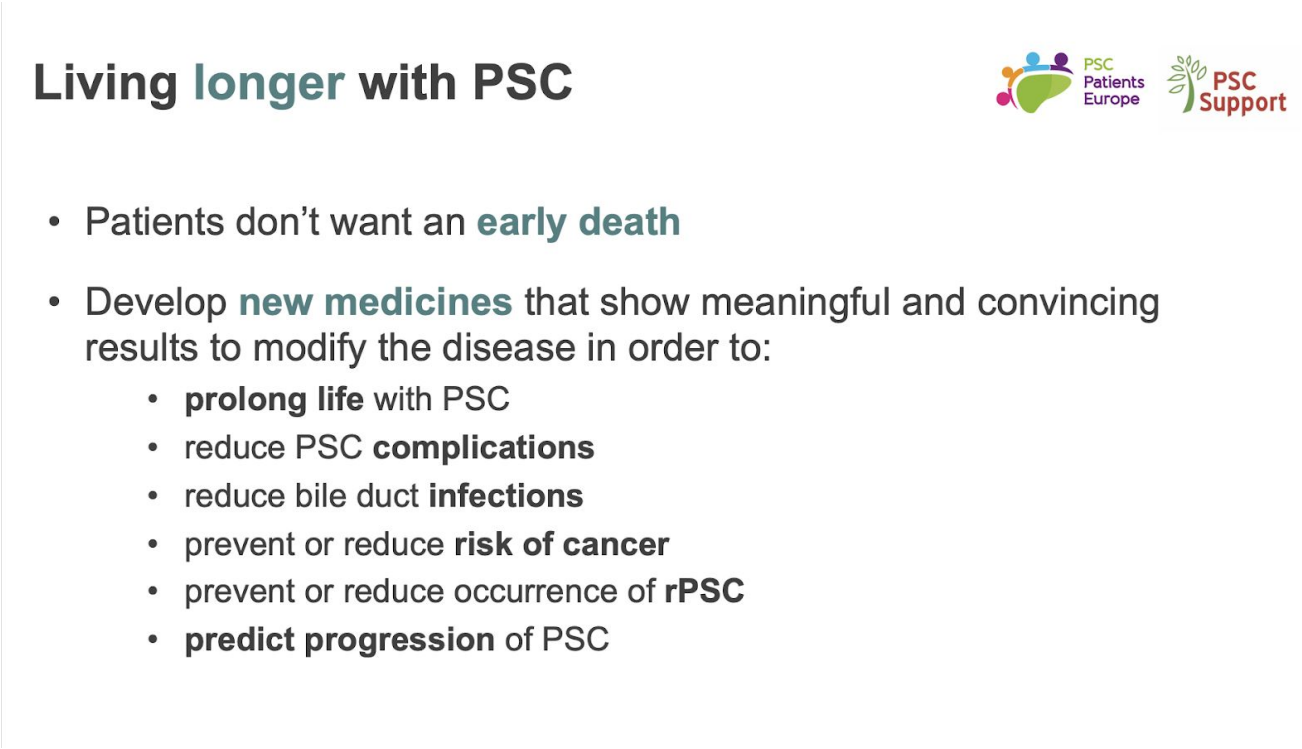
Investigators ought to consider longer term outcome observation when using surrogates and the enforcement of postmarketing studies is of critical importance so that we can be confident these drugs REALLY do demonstrate positive change.

New and emerging technologies

I discussed the importance of novel endpoint development and urged researchers to develop markers that embrace new and emerging technologies with a view to replacing biopsies once and for all. There should be a coordinated effort from all stakeholders to include common exploratory endpoints in trials. Furthermore, coordinated data sharing, especially placebo data would speed up our search for effective PSC treatment.

What is improvement to a patient?

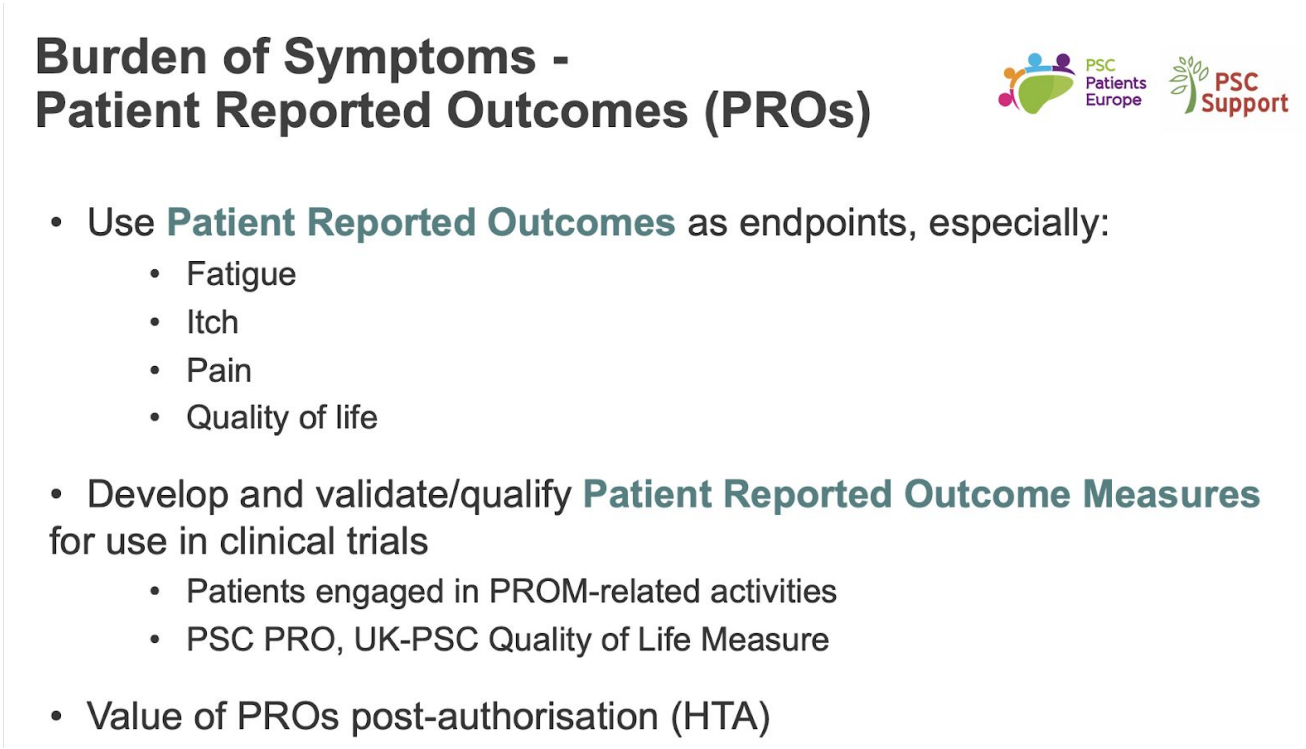
We are realists. We know it is not realistic to think that a new medicine for PSC will be a 'cure'. It's true that patients don't want to die early or need a liver transplant, or to get cancer. We want new drugs to help us live as long as possible even if that is with PSC. We want medicines to reduce our risk of complications and infection, rPSC, cancer and help us understand what will happen to us [2].



For real people living with PSC, measuring improvement in our disease is not just about avoiding early death and complications: improvement isn't improvement without thinking about symptoms and quality of life. Patients want to liver longer and liver better with PSC.

Patient Reported Outcome Measures

As we've shown in our surveys [2] and vast experience of talking with patients at our meetings and online communities, the lived experience of PSC is a huge area of unmet need for patients. Therefore Patient Reported Outcomes (PROs) and how to measure them should also be incorporated in to every clinical trial.



Symptoms and Quality of Life

Remember, our most common symptoms are fatigue, itch AND pain and we would like to see all clinical trials collect data on these, not just those trials directly addressing symptoms. Instruments need to be developed focusing on PSC-specific quality of life [8].

There are currently two PSC-specific QoL measures under development, including the UK-PSC tool which has been driven and funded by patient organisations demonstrating the importance of PROs to PSC patients.

Equally, even if a medicine is proved to be effective, that's no guarantee that the drug will be licenced. I want us to be prepared to make a convincing case to the regulators so drugs become licenced quickly and so that patients can actually access effective drugs. There is real value in data from PROs for this purpose which is one of the reasons PSC Support initiated the QoL tool development. It is important that an effective medicine is made available and accessible to patients without delay, wherever they live, and we have been planning for that.

Real World PSC

Approval of Treatments for the Majority, not the Minority

Another layer of complexity is that there are many different phenotypes (presentations or 'types') of PSC, an issue which complicates the design of clinical trials. However we would like to see wider eligibility criteria to enable more people to take part in trials, obviously without compromising quality of trial design. An important group is children and young people with sclerosing cholangitis. We would like to see more trials like the recently reported NGM282 trial [9] which included broader eligibility criteria than previous studies, such as the inclusion of dominant structures, small duct PSC and compensated cirrhosis.

Eligibility Criteria

PSC Patients Europe PSC Support

- **Broader eligibility criteria**

Approve treatments for the majority, not the minority

We want treatments to be approved for the majority not the minority.

Cholangitis flares

Another group includes people who have had recent cholangitis attacks. We know in PSC, biochemistry fluctuates naturally as well as after cholangitis episodes. A cholangitis flare is a major episode for a PSC patient and as such this group is highly motivated to participate in trials. Wider screening windows and opportunities for re-screening for trial participation when it is clear a flare has subsided should be considered (where appropriate and without compromising trial design).

IBD measures

In particular, we would like to see appropriate IBD measures studied in trials, especially in children, as well as the impact of the intervention on other coexisting diseases. The EMA meeting discussion went so far as to suggest that PSC should be studied in all IBD trials. I wholeheartedly agree, and I hope we can convince IBD investigators.

Ursodeoxycholic acid (UDCA)

Some patients take UDCA . The EMA proposes that those on a stable dose of UDCA should be allowed in clinical trials (where they meet other eligibility criteria). However, there is a risk that taking UDCA could confound clinical trial results and therefore some investigators prefer to study participants who do not take UDCA. It's controversial. Stopping UDCA can be difficult mentally, and many patients don't want to come off it unless there is an effective alternative. Until that time, we support the EMA proposal but would urge all potential trial participants to consider carefully the benefits and risks of continuing to take UDCA during trials.

Conclusion

We know there are challenges ahead. We would like to see researchers, academics, patients and industry working together and collaborating to develop and validate endpoints for PSC and move forward clinical trial design.

The PSC patient community is ready and willing to work with all stakeholders in a positive collaborative way. We are well-organised, trained and have expertise within our networks to support and add value to research. People with PSC are suffering with the risk of early death and poor quality of life. There are no medical treatment options so time is of the essence. We urge investigators and sponsors to act now.

Our urgent goal should be to validate appropriate noninvasive endpoints, and let the focus not be solely on surrogates. It is critical always consider quality of life in clinical trials, and include Patient Reported Outcome Measures in endpoints.

Co-ordinated, pooled knowledge and true collaboration will accelerate PSC medicine development.

Ultimately, we want to live as well as possible with PSC, as long as possible.

Martine Walmsley, 31 December 2018

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