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REVIEW

Primary biliary cholangitis review – new management strategies emerge

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Introduction

Primary biliary cholangitis (PBC) is an autoimmune, cholestatic liver disease that disproportionately affects middle- to older-aged women. It is progressive and, left untreated, results in biliary cirrhosis and portal hypertension, with ensuing complications of ascites, variceal bleeds, hepatic encephalopathy, and, ultimately, death.[1] Since 1997, ursodeoxycholic acid (UDCA) has been approved for managing PBC, significantly influencing the rate of progression and, in turn, adverse outcomes.[2-4] Up to 40% of patients will suboptimally respond to first-line treatment with UDCA, requiring add-on therapy.[5] Despite this, PBC as an indication for transplant has declined significantly over the past decades, highlighting the impact of improved management and therapeutic options.[2]

PBC is characterised by immune-mediated targeting of the biliary epithelial cells of the intrahepatic bile ductules. It disproportionately affects women in a ratio of 9:1.[6] It may be diagnosed incidentally in an asymptomatic patient or following first presentation with end-stage liver disease and decompensation. The most frequent initial symptoms are fatigue and pruritus, affecting up to 80% of patients. A diagnosis is made if two of the following three criteria are met:[3,6]

1. Chronically elevated alkaline phosphatase (ALP) of unclear cause;
2. Positive anti-mitochondrial antibody (AMA) or PBC-specific anti-nuclear antibodies (e.g. anti-glycoprotein 210 [anti-gp210] and anti-SP100); or
3. Histology typical of PBC, including non-suppurative, destructive cholangitis.

It is noteworthy that 90–95% of patients with PBC are AMA positive, and liver biopsy is rarely needed unless there is concern about overlapping diseases, such as autoimmune hepatitis (AIH). One may also find a patient who is AMA positive with normal liver function tests (LFT) who is asymptomatic. These patients need annual monitoring with LFTs to decide on the development of PBC and the need for treatment, as a positive AMA alone does not diagnose PBC. Up to 16% of these patients develop PBC in the ensuing five years.[1]

PBC is associated with other autoimmune diseases, which should be screened for. These include hypothyroidism, Sjögren syndrome, Raynaud's phenomenon, rheumatoid arthritis, scleroderma, and coeliac disease. Fatigue and pruritus are found in up to 80% of patients, and up to 30% report sicca symptoms. Prompt treatment initiation is key to slowing disease progression to end-stage liver disease.

Ursodeoxycholic acid

UDCA remains the first-line treatment and standard of care in treating PBC at 13–15 mg/kg/day in divided doses.[2,3] It is generally well tolerated with minimal adverse effects. It is a synthetic bile acid that promotes bile excretion and reduces the severity of cell injury. It is also noted to have an independent anti-inflammatory effect by modulating the immune system.[7] Its efficacy has been well established in multiple trials, and it continues to be the backbone of therapy since registration with the Food and Drug Administration (FDA) in 1997.

UDCA is recommended in all patients, regardless of disease stage, but it appears to be most effective when started early.[7] It is imperative that once UDCA is initiated, an assessment of treatment response is gauged and documented to guide prognosis and the need for additional therapies. According to a large retrospective cohort study of 3 902 participants by the Global PBC Group, the five-year liver transplant-free survival was 95.3% in complete responders, 91.2% in incomplete responders, and 84.7% in those who did not receive UCDA treatment.[8]

Multiple scoring systems, such as the Barcelona score, may be used to assess biochemical responses to UDCA. This is measured 12 months after starting UDCA and is a 40% reduction in ALP from baseline or ALP normalisation, or the modified Toronto score: ALP 1.67 × ULN (upper limit of normal).[6,7] While many patients have at least a partial response to UDCA, up to 40% may exhibit an inadequate response, highlighting the need for additional therapies.[9]

Obeticholic acid

Obeticholic acid (OCA) is a potent farnesoid X receptor agonist that modulates bile acid synthesis. It is an approved second-line therapy for those with partial- or non-response to UDCA or as monotherapy in patients intolerant of UDCA. It gained approval through the phase III POISE study, where it met its primary endpoint defined as ALP < 1.67 × ULN with > 15% decrease from baseline and a normal bilirubin (POISE criteria).[10] Subsequently, OCA has shown beneficial outcomes in multiple real-world studies, including improved cholestatic liver enzymes, aspartate

aminotransferase-to-platelet ratio index score, and transplant-free survival.[1,6]

Unfortunately, pruritus is a notable side effect of OCA treatment, an already troubling and difficult-to-manage symptom in PBC. It did not, however, lead to treatment discontinuation in most patients. More recently, there has been concern regarding hepatic decompensation with the use of OCA in more advanced liver disease. Consequently, it is no longer recommended for use in patients with decompensated cirrhosis, any previous episodes of decompensation, or compensated cirrhosis with evidence of portal hypertension.[1]

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptor (PPAR) agonists are a diverse group of drugs that offer significant promise as effective PBC treatment. The PPAR nuclear receptor exists in distinct isoforms, namely α (alpha), β (beta), γ (gamma), and δ (delta). PPAR agonists have affinities for different isoforms or combinations thereof and can modulate diverse metabolic processes, including lipid and bile metabolism and inflammation.[1,5,9]

Bezafibrate is a pan PPAR agonist (α, β, and δ) used as a second-line PBC treatment. In 2018, a phase III placebo-controlled trial (BEZURSO study) evaluated the use of bezafibrate 400 mg plus standard dose UDCA versus UDCA plus placebo in patients with PBC and inadequate response to UDCA therapy alone. After 24 months, 67% of those in the bezafibrate group had complete normalisation of their ALP, with some improvement in pruritus also noted. Up to 20% of patients reported myalgia, and there was an associated 5% increase in serum creatinine in the treatment group.[7,11]

Similarly, a large retrospective cohort of almost 4 000 patients in Japan showed a statistically significant reduction in all-cause and liver-related mortality or liver transplant with a combination of UDCA plus bezafibrate as opposed to UCDA treatment alone.[1,12] There has been concern about decompensating events in those with advanced disease, and bezafibrate is not recommended in those with decompensated cirrhosis.[1,3]

New therapies recently approved by the FDA include elafibranor and seladelpar. They are more selective PPAR agonists and have demonstrated good outcomes in PBC treatment. Both agents were evaluated in randomised controlled trials (RCT), where the primary endpoint was the POISE composite of ALP $< 1.67 \times$ ULN, $\geq$ 15% decrease from baseline, or bilirubin $\leq$ ULN, at 52 weeks.[1]

A phase III RCT of elafibranor (ELATIVE study), a dual PPAR-α/δ agonist, was positive. Patients with an incomplete response to UDCA were assigned to receive elafibranor 80 mg or a placebo while continuing their UDCA. The endpoint was met in 50.9% of the 108 patients in the elafibranor group and two of the 53 patients (3.8%) in the placebo group without significant concerns of serious adverse events (SAE).[13]

Seladelpar, a selective PPAR-δ agonist, showed equal promise in the RESPONSE study, a phase III RCT that included 128 patients in the active arm and 65 in the placebo arm. The primary endpoint was met in 61.7% of patients (79) receiving seladelpar 10 mg daily and 20% (13) in the placebo arm at 52 weeks.[14] A two-year open-label extension study noted an increase to 79% at 24 months in patients meeting the primary endpoint. There were no SAEs, and, notably, there was an improvement in pruritus scores.

Saroglitazar, a dual PPAR-α/γ agonist, is currently undergoing a phase III RCT (EPICS-III study).[1]

Other

Despite PBC being an autoimmune disease, immune-suppressive agents have shown little effect on disease progression, except in PBC-AIH overlap syndromes.[7] Finally, it is worth noting that itch remains a significant source of morbidity for many patients. Thus far, only seladelpar 10 mg has shown significant improvement in pruritus, while OCA may worsen it.[1] As a result, there is interest in various inhibitors of the ileal bile acid transporter (IBAT) as a means to treat pruritus. The mechanism of action is decreasing the ileal absorption of enteric bile acids, thus decreasing serum levels of circulating bile acids. Unfortunately, diarrhoea is almost an inevitable side effect, but trials for various IBAT inhibitors are ongoing. These include linerixibat, volixibat, and maralixibat.[1]

Conclusion

Almost 30 years after the approval of the first treatment for PBC in the form of UDCA, we are moving into an era where multiple options for treatment exist, and the opportunity for dual or triple therapy may provide significant benefits. Treating patients with decompensated cirrhosis remains a significant challenge. It is imperative to aim for early diagnosis and treatment and to consider the criteria that may help clinicians to better risk stratify their patients to identify those who may benefit from early combination therapies.[9] Unfortunately, there is a lack of data directly comparing the various second-line therapies. Decisions on which to use will need to be personalised according to disease stage, comorbidities, and accompanying symptoms.

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