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Review

Pruritus, Fatigue, Osteoporosis and Dyslipoproteinemia in Pbc Patients: A Clinician's Perspective

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Abstract: In this review article, we summarize the most common clinical manifestations of Primary biliary cholangitis (PBC): pruritus, fatigue, osteoporosis, and dyslipoproteinemia and discuss their impact of the patients' quality of life. More than half of PBC patients suffer from pruritus or fatigue at the time of diagnosis. We discuss the pathophysiological aspects of the PBC clinical manifestations and treatment options. The pathophysiology of pruritus and fatigue is not adequately elucidated, but IL-31 is associated with the severity of pruritus and could be used to objectify the subjective reporting by questionnaires. Although PBC patients suffer from atherogenic dyslipidemia, they do not seem to have a higher cardiovascular risk; however, this observation needs to be clarified by further clinical studies. The second-line of PBC treatment affects pruritus severity: Obeticholic acid (OCA) worsens pruritus while fibrates improve it. Itching can be alleviated by both non-pharmacological and pharmacological approach, however the are multiple barriers to pharmacological treatment. There is no adequate treatment for fatigue today. Treatment of osteoporosis and dyslipidemia is similar for non-PBC patients; stage of liver disease should be considered in treatment. Further research to clarify the pathophysiology and to eventually discover an effective treatment to improve survival and quality of life (especially pruritus and fatigue) in PBC patients is needed.

Keywords: primary biliary cholangitis; pruritus; fatigue; osteoporosis; dyslipidemia; treatment

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1. Introduction

Primary biliary cholangitis was first described by Addison and Gull in 1851 in Mrs. Elizabeth, hospitalized at Guy's Hospital in London. The case report was published in the article "On a certain affection of the skin vitiligoidea—a plana, b tuberosa" in the now non-existent local medical magazine Guy's Hospital Reports [1]. PBC is a chronic autoimmune, non-suppurative inflammatory liver disease that leads to the destruction of small intrahepatic bile ducts and the development of liver fibrosis. In advanced stages, PBC can progress to liver cirrhosis. The etiology of the disease is not fully understood [2,3].

PBC meets the criteria to be classified as a rare disease [4]. The prevalence of PBC in Europe is 22.27 (95% CI 17.98–27.01) cases per 100,000 inhabitants, with an increasing trend. The incidence of PBC in Europe is 1.87 (95% CI 1.46–2.34). The disease occurs more often in women [5]. At least two of the three criteria below are required for a diagnosis of PBC:

- Increased ALP value above the upper limit of the norm lasting for at least 6 months
- AMA M2 positivity in a titer of at least 1:40; in case of AMA negativity, specific ANA positivity (anti-sp100 or anti-gp210)
- Histological findings consistent with PBC [2].

ANA positivity occurs in approximately 50% of patients with PBC; however, in patients with AMA negative PBC, ANA are positive in 85% of patients [6]. Multiple nuclear dot and rim-like/membranous antinuclear antibodies anti gp210, anti sp100 and anti sp 140 are used in the diagnosis of PBC [7–9]. AMA negative PBC patients have significantly worse prognosis than AMA positive PBC patients [10].

Overlap of PBC with AIH or PSC may occur in clinical practice. If transaminase activity is elevated in patients with PBC, PBC/AIH overlap syndrome should be considered. The patient needs to meet the diagnostic criteria of both diseases to confirm the diagnosis PBC/AIH overlap syndrome [11,12]. Patients with PBC/AIH overlap syndrome have worse prognosis and often progress to liver cirrhosis [13].

2. Clinical Manifestations of PBC

PBC can be asymptomatic, the diagnosis is usually established after an evaluation of laboratory findings. The most common clinical manifestations are pruritus, fatigue, osteoporosis, dyslipidemia, and jaundice, which occur in the advanced stages of the disease [14]. The clinical course of PBC was first described in detail by the famous English hepatologist Sheila Sherlock in 1959. Out of 42 patients, 20 had pruritus, and pruritus appeared in patients on average 11 years before the manifestation of jaundice. In 15 patients, all of whom had hypercholesterolemia, flat xanthelasma or tuberous xanthomas were present. Part of the patients had an asymptomatic course, the indication for a liver biopsy was hepatomegaly, and the diagnosis was confirmed by histological examination Osteomalacia and osteoporosis, not responding to vitamin D administration, were present in patients suffering from this disease. Some patients died of hepatic failure, but not earlier than after 4 years of follow-up. At the manifestation of liver failure, the serum cholesterol level decreased and the skin xanthomas disappeared [15].

The representation of asymptomatic patients varies in various stages. In our experience, about a quarter of patients had no symptoms at the time of diagnosis. In a study led by Prince et al., up to 61% of patients had no symptoms when PBC was diagnosed [16,17]. It should be noted that some asymptomatic patients may develop clinical symptoms after some time. After 18 years, 76% of patients with PBC had pruritus or fatigue [18].

The pathophysiology of pruritus in PBC is not clear. In cholestatic diseases, chemical compounds from the bile enter the bloodstream to a greater extent, from where they can reach the skin, causing pruritus. Molecules that are directly causally related to the development of pruritus have not yet been identified. Bile acids could be a potential cause of pruritus. Patients with cholestatic pruritus have higher serum levels of bile acids, and the administration of bile acids worsens the pruritus [19]. Nasobiliary drainage significantly reduces the intensity of pruritus. However, bile acids are probably not the primary cause of pruritus in patients with PBC. The first symptom of PBC is often mild pruritus, but patients have normal bile acid levels at that time. Bilirubin metabolites could also play a role in the pathogenesis of pruritus [20]. In the past, opioids were thought to have primary role in the development of pruritus. This seems no to be true. Although patients with PBC have indeed elevated opioid levels, these correlate with the stage of the underlying disease but not with the intensity of pruritus [21]. Autotaxin hydrolyzes lipophosphatidyl acid to lipophosphatidylcholine. This pathway is activated in pruritus in patients with PBC [20]. The level of autotaxin correlates with the intensity of pruritus [22]. No significant changes in the intestinal microbiome have been observed as of yet in relation to pruritus [23].

In recent years, the role of IL-31 in the pathophysiology of pruritus has been described. IL-31 is a member of the IL-6 family of cytokines, which have a pro-inflammatory nature [24]. IL-31 is produced mainly by Th2 cells but also by other cells (mast cells, eosinophils, basophils, dendritic cells, and macrophages). IL-31 binds to IL-31 receptor in the epidermis and sensory nerves, where it causes skin dysfunction and inflammation, which can lead to pruritus (see Figure 1) [25]. In children with atopic dermatitis, IL-31 levels correlate with the intensity of pruritus [26]. In addition to atopic dermatitis, elevated levels of IL-31 have also been observed in other dermatological pruritogenic diseases: prurigo

nodularis, psoriasis, cutaneous T-cell lymphoma, bullous pemphigoid, chronic urticaria, allergic contact dermatitis and others [25]. Higher levels of IL-31 were also found in dialysis patients with pruritus [27]. IL-31 also plays a role in the pathophysiology of cholestatic liver diseases. Patients with intrahepatic cholestasis in pregnancy have higher IL-31 values than pregnant patients without this diagnosis [28]. IL-31 levels correlate with the intensity of pruritus in patients with PBC [29–31].

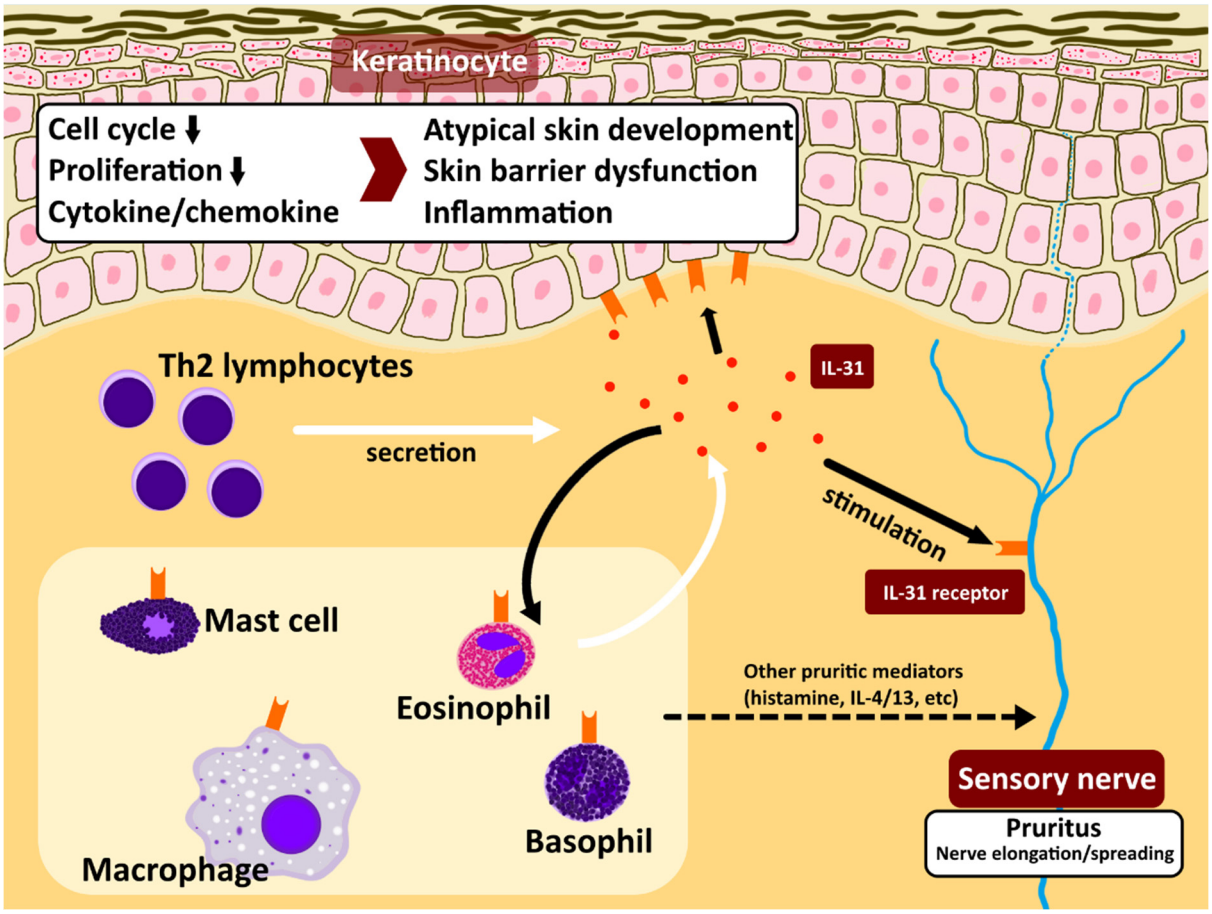

Figure 1. IL-31 in the pathogenesis of pruritus (modified from [25]). Hypothesis of the role of IL-31 in the pathogenesis of pruritus. IL-31 is primarily produced by Th2 cells, although some innate immune cells can also produce IL-31. The IL-31 receptor is expressed by various cells, including peripheral sensory nerves, epidermal keratinocytes, and immune cells. IL-31 binding to its receptor on sensory neurons stimulates the nerve, causing pruritus. IL-31 also plays an important role in skin barrier dysfunction and inflammation.

However, these correlations do not mean causation and further experimental and clinical observations will be needed to clarify the cause of pruritus in this group of patients. In patients with PBC, pruritus appears mainly in the evening and at night, the predilection places being the upper limbs, back and chest. In a small number of patients, despite treatment, pruritus significantly reduces the quality of life (intractable pruritus), which can lead to suicide attempts [32]. These patients can be prioritized on the waiting list for liver transplantation.

We can assess the severity of pruritus with several questionnaires. The PBC-40 questionnaire includes three questions related to pruritus: (a) Itching disturbed my sleep; (b) I scratched so much I made my skin raw; (c) I felt embarrassed because of the itching [33]. When evaluating the intensity of pruritus, we can also use specific questionnaires, for example, the 12-Item Pruritus Severity Scale [34].

Pruritus may occur in all PBC stages; its impact on the prognosis of PBC has not been studied in detail [35]. However, there are indicators that the presence of pruritus may worsen the prognosis of PBC patients. PBC patients with pruritus have biochemically and histologically more advanced disease at the time of diagnosis compared to asymptomatic PBC patients. During follow-up, the prevalence of pruritus increased in untreated patients, where histological progression of PBC can be assumed [36]. Higher AST, ALP, bilirubin levels, higher Mayo risk score and lower albumin in univariate analysis, and higher ALP level and higher Mayo risk score in multivariate analysis were clinical predictors of baseline pruritus in another study. Patients with pruritus had biochemically more advanced PBC compared to patients without pruritus [37]. Pruritus severity did not correlate with PBC stage, but severe pruritus is more common in the ductopenic variant of PBC, which has a worse prognosis [38]. On the other hand, pruritus may decrease in intensity or even disappear completely in advanced stages of PBC, including cirrhosis [39].

Fatigue is a common clinical manifestation of PBC; its cause is not clear. Central and peripheral mechanisms may play a role in the pathophysiology of fatigue in PBC. Central causes include depression, sleep disturbance, autonomic dysfunction, and organic changes in brain structure that have been documented on MRI. Peripheral causes are: changes from aerobic to anaerobic metabolism with accumulation of lactate; abnormal levels of some amino acids: reduced values of valine, leucine, isoleucine and tryptophan and increased levels of phenylalanine [40,41]. To assess fatigue, the PBC-40 questionnaire is completely sufficient. It includes eight questions that assess fatigue in PBC patients [33]. Fatigue is poor prognostic factor in PBC. Fatigue patients have reduced 9-year transplant-free survival compared with non-fatigue patients. Fatigue PBC group had reduced transplant-free survival in both UDCA responders and UDCA untreated patients compared with non-fatigue PBC group. However, UDCA responders with low fatigue had similar transplant-free survival compared to UDCA responders without fatigue [42].

The prevalence of osteoporosis is approximately 30%, or 44% in those waiting for a transplant. The prevalence of fractures in patients with PBC is 10–20% overall, and 22% in patients on the waiting list for liver transplantation. Low levels of insulin growth factor and osteoblastic trophic factor have been observed in PBC patients with osteoporosis [43].

Since cholesterol is formed in the liver, when the bile ducts are obstructed, cholesterol is absorbed to a greater extent into the bloodstream. On the other hand, reduced secretion of the bile acids leads to the reduced absorption of cholesterol in the intestine [44]. This imbalance leads to the hyperlipidemia and dyslipidemia in PBC patients. Most patients have higher total cholesterol and LDL-C values. Elevated serum triglycerides are also common in PBC [44,45]. The level of LDL-C does not decrease even with the progression of the disease, when there is a decrease in cholesterol synthesis, because the expression of LDL-C receptors for LDL-C on the liver cells is decreased. On the other hand, in the initial stages of PBC, HDL-C values are elevated, but in the stage of liver cirrhosis, HDL-C values fall below the lower limit of the norm [46]. The increased levels of HDL-C in the initial stages of PBC are probably due to the reduced level of hepatic lipase rather than to the disruption of its production by liver cells [47]. Apolipoprotein A1, which is the main protein forming HDL-C, has two classes: lipoprotein A1 and lipoproteinA1:A2. Lipoprotein A1 has anti-atherogenic properties, and its concentration compared to lipoprotein A1:A2 is higher in patients with PBC than in patients without PBC [44]. However, in patients with PBC, there is a reduced level of lecithin-cholesterol acyl transferase, which leads to an increase in the level of lipoprotein X, which reduces the oxidation of LDL-C, protects the endothelial cells in the vessels, and slows down atherogenesis [48]. The traditional parameters of lipoprotein metabolism inaccurately determine the cardiovascular risk of patients with PBC. Therefore it is advisable to investigate apolipoprotein B-100, which is associated with large LDL-C particles and accelerates atherosclerosis [44,49]. Compared to patients without PBC, patients with PBC do not have higher insulin values or a higher HOMA index. Patients with PBC have lower visceral and subcutaneous fat accumulation than patients without PBC. Metabolic syndrome was found in 31% of patients with PBC

and in 43% of patients without PBC [50]. However, in another study, Italian authors found significantly higher values of adiponectin, resistin, and leptin in PBC patients than in healthy controls and in patients with non-alcoholic steatohepatitis [51]. In a Chinese retrospective cohort study, patients with PBC had significantly more frequently arterial hypertension compared with patients without PBC [52]. The question remains: what is the real cardiovascular risk for patients with PBC? A higher cardiovascular risk was found in PBC patients compared to the healthy population only in a retrospective cohort study from Sweden that analyzed patients treated between 1964 and 2008; during most of this period, neither adequate PBC nor adequate cardiovascular treatment was available [53]. Neither other studies nor the meta-analysis of published studies found a greater cardiovascular risk in patients with PBC compared to patients without PBC [54].

PBC is frequently associated with other autoimmune diseases. Sicca syndrome occurs in a significant proportion of PBC patients [55]. Patients suffer from mucosal dryness, mainly xerostomia, dry eyes and vaginal dryness. Histological confirmation of the diagnosis or a typical clinical presentation with the presence of anti SSA/Ro ad/or anti SSB/La antibodies are required for evidence of sicca syndrome [56]. Approximately 20% of PBC patients suffer from one of these diagnoses: thyroid disease, arthralgia, Raynaud's syndrome, sclerodactyly or fibrosis alveolitis. Other autoimmune diseases are seen in less than 5% of PBC patients [14]. Associated autoimmune diseases impair quality of life of PBC patients.

3. Effect of PBC Treatment on PBC Complications

UDCA is the gold standard for the treatment of PBC. It changes the proportions of bile acids in the bile, which is associated with the adjustment of biochemical parameters [57]. UDCA is a drug that patients tolerate very well. Pruritus occurs in a very small proportion of patients, especially when starting UDCA treatment [58]. Combination therapy with UDCA + corticosteroids/azathioprime is more effective than UDCA monotherapy or immunosuppressive corticosteroids/azathioprime therapy in patients with PBC/AIH overlap syndrome [59]. In long-term treatment, UDCA does not affect the frequency or intensity of pruritus [14].

For non-responders to UDCA, a second-line of PBC treatment is indicated [60]:

- OCA [61]
- bezafibrate, possibly other fibrates [62]
- budesonide [63].

OCA is a synthetic derivative of chenodeoxycholic acid; it acts as an FXR agonist [64]. In the POISE registry study, approximately half of the patients achieved response after one year of UDCA + OCA treatment. The most serious side effect of OCA treatment was pruritus, which was described in 56% of patients in the OCA 5–10 mg group, in 68% of patients in the OCA 10 mg group, and in 38% of patients in the placebo group [61]. In the long-term treatment of OCA, the most serious adverse effects of treatment are pruritus (77% of treated patients) and fatigue (33% of treated patients) [65]. The number of patients suffering from pruritus increased from 59% to 77% after 3 years of combined treatment with UDCA and OCA [61,65]. Over 8% of PBC patients had to discontinue OCA treatment due to pruritus in real clinical practice [66]. Long term OCA treatment leads to improvement of interface hepatitis and lobular hepatitis, it does not, however, improve liver fibrosis [67]. OCA treatment led to a decrease in cholesterol and HDL-C values but did not affect LDL-C or triglyceride values [68].

Fibrates act through nuclear PPARs. Fibrates in the second-line treatment of PBC not only lead to a therapeutic response but also significantly reduce the intensity of pruritus, which was confirmed in a meta-analysis that evaluated the therapeutic effect of fibrates in the treatment of patients with PBC [69]. Yet it is still an "off-label" treatment for PBC.

Budesonide treatment does not affect pruritus. During treatment with budesonide, osteopenia is found more often than in the placebo group [63].

Other medications are undergoing clinical trials for PBC treatment, including PPAR agonists seladelpar and elafibranor. Seladelpar 5/10 mg improves pruritus, sleep, and fatigue in patients with PBC [70]. A decrease in the intensity of pruritus is associated with a decrease in the levels of bile acids and IL-31 [29]. Seladelpar at 10 mg daily was superior to placebo in achieving a biochemical response after one year of treatment in a phase III clinical trial; normalisation of ALP was observed in 25% of patients in the seladelpar group but in none in the placebo group. The reduction of pruritus was greater in patients treated with seladelpar compared to placebo [71]. More than half of patients achieved a therapeutic response and 15% of patients normalized ALP at week 52 when treated with elafibranor at a dose of 80 mg [72]. Treatment with elafibranor also led to a reduction in the intensity of pruritus [73]. Greater pruritus reduction was seen in elafibranor group compared to placebo according to the itch domain of PBC-40 quality of life questionnaire and 5-D Itch total score [72]. The non-steroidal FXR agonists cilofexor and tropifexor led to improvements in cholestasis. The limiting factor for their use is pruritus [74]. Setanaxib is a NOX1/4 inhibitor; in addition to improving cholestasis, it also improves fatigue in patients with PBC [74,75].

We can conclude that PPAR agonists alleviate pruritus and FXR agonists, on the contrary, worsen pruritus. This fact may be important to consider before starting a second-line treatment for PBC in non-responders to UDCA with pruritus. In these patients, pharmacologic relief of pruritus should be considered before starting OCA. The effect of first- and second-line PBC treatments on pruritus is shown in Table 1.

Table 1. Effect of first- and second-line PBC treatment on pruritus.

Medicament	Effect on Pruritus
Ursodeoxycholic acid	-
Obeticholic acid	↑
Fibrates	↓
Budesonide	-

4. Management of Pruritus, Fatigue, Osteoporosis and Dyslipoproteinemia in Patients with PBC

Pruritus is a serious clinical manifestation of PBC that impairs the quality of life [76]. Intractable pruritus can even be an indication for a liver transplantation [77,78].

There are some general precautions to follow when managing pruritus. The patient should not wear too tight clothes; woolen clothes are not suitable as well. Aromatic detergents or fabric softeners should not be used when washing clothes. It is necessary to minimize skin contact with irritating substances. The application of dry heat (sauna) or hot baths, as well as the application of cold to the skin, is not advised. Patient should not bathe or shower for more than 20 min. The patient should not consume hot or spicy foods; the use of alcohol is strictly inappropriate. Stress can also increase the intensity of itching. When bathing or showering, the patient should not rub his skin intensively. It is advisable to use non-alkaline soaps or shower gels; the use of slightly warm water is suitable. Local moisturizing preparations or local preparations with cooling or anesthetic effects (based on menthol or polidocanol) are suitable. It is necessary to prefer loose cotton clothes. The patient should have his nails trimmed so that he does not injure himself when scratching [35].

The first effective treatment of pruritus in patients with PBC ever described was cholestyramine [79]. The bile sequestrant and anion resin exchanger cholestyramine at a dose of 4–16 g daily is the only drug registered for the treatment of pruritus in cholestasis and is considered a first-line drug in the management of pruritus in patients with PBC. Cholestyramine can bind several amphiphilic substances with potential pruritogenic effect in the intestine. It reduces the intensity of pruritus after about 2 weeks of treatment. The initial dose of cholestyramine should be 4 g per day, with a possible increase to a maximum dose of 16 g per day according to drug tolerance. Possible adverse events like

serious gastrointestinal problems should be kept in mind. The drug is not very effective for moderately intense and intense pruritus [35]. Even colesevelam, an anionic resin exchanger with 7 times greater binding capacity for bile acids than cholestyramine, is not effective in the treatment of cholestatic pruritus of moderate and severe intensity [80].

Rifampicin is a pregnane X receptor agonist and induces some hepatic transporters, such as cytochrome P4503A4 or MRP2, leading to the biotransformation and excretion of potential pruritogens. The initial dose of rifampicin is 150 mg per day; the dose can be increased to 600 mg per day if the drug is tolerated. A meta-analysis showed that rifampicin is more effective than placebo in the management of PBC pruritus [81]. Although in a meta-analysis, patients treated with rifampicin had similar frequency and type of adverse effects than patients treated with placebo, adverse effects of the treatment, especially an increase of serum transaminases, swelling of the lower limbs and gastrointestinal complaints, can limit the use of the drug [35,81,82]. Liver tests should be carefully monitored during treatment with rifampicin [35]. Phenobarbital is also an inducer of cytochrome P4503A4, but this drug has a lower antipruritic effect than rifampicin [83]. In countries where cholestyramine is not registered or available, rifampicin may be the first choice for the treatment of pruritus in PBC.

Modulators of the endogenous opioid system can also be used in the treatment of cholestatic pruritus. Naltrexone is an μ-opioid antagonist with an antipruritic effect at a dose of 25–50 mg per day; in individual cases, its dose can be titrated up to 150 mg per day [35]. In a meta-analysis, naltrexone had a greater antipruritic effect than placebo, but compared to rifampicin, the antipruritic effect was lower [81]. Among the most serious side effects of the drug are restlessness and insomnia. Treatment with naltrexone must be discontinued gradually. Sudden withdrawal of the drug may be accompanied by withdrawal symptoms. The κ-opioid agonists nalfurafine and difalikefalin may also be indicated in the treatment of cholestatic pruritus [35]. Since difelikefalin is very effective in the treatment of pruritus in dialysis patients, it is necessary to initiate studies with this drug for pruritus in PBC. The limitation of the drug is intravenous administration [84].

Sertraline is an antidepressant and a selective serotonin reuptake inhibitor. In cholestatic liver diseases, it has a comparable effect to rifampicin but is less hepatotoxic [85]. The calcium channel blocker gabapentin can also be used in the treatment of cholestatic pruritus [35,86].

A newer approach in the treatment of cholestatic pruritus is the use of IBATs, which prevent the reabsorption of bile acids from the intestine to the enterohepatic circulation and lead to increased elimination of bile acids via the stool. In the recently published phase II GLIMMER study, linerixibat reduced the intensity of pruritus in a dose-dependent manner, although no significant benefit over placebo was demonstrated. Surprising result was probably determined by the low dose of the drug and the small number of patients analyzed [87]. The efficacy of linerixibat in the Japanese subcohort is comparable to that of other patients [88]. Another IBAT, maralixibat, was also not more effective in treating PBC pruritus compared to placebo [89].

Phototherapy with ultraviolet B rays, albumin dialysis, plasmapheresis, and biliary drainage are among the non-pharmacological methods of treating pruritus, especially with high intensity [35,90].

In the treatment of skin itching in PBC, it is advisable to start treatment with cholestyramine. In cases of ineffectiveness or intolerance of the treatment, it is necessary to replace cholestyramine with rifampicin. In the event of the ineffectiveness or adverse effects patient should be treated with naltrexone. If none of these treatments are effective or tolerated sertraline or gabapentin can be tried, or the patient can be enrolled in one of the clinical trials. In addition to UDCA, patients with pruritus should be treated with fibrates, especially bezafibrate. If pharmacological treatment is not effective, elimination therapy or biliary drainage should be considered. With the exception of cholestyramine, the other drugs for treatment are not registered and their prescriptions are tied to specialists other than a hepatologist or a gastroenterologist. These facts contribute to the undertreatment of pruritus in patients with PBC [91].

Psychohygiene is particularly important in the management of fatigue in patients with PBC. No drug is currently registered for the treatment of fatigue in PBC patients. The results of clinical trials in patients with PBC fatigue do not encourage optimism. Only a clinical trial with modafinil demonstrated fatigue relief in PBC patients [92]. Rituximab, fluoxetine, ondansetron, and fluvoxamine did not affect fatigue in patients with PBC [93–96]. Some hope for the treatment of PBC patients was shown by a recently published study with setanaxib, which was better than placebo in treating fatigue [75].

Osteoporosis is a common finding in PBC patients, especially in the advanced stages of the disease. Treatment of osteoporosis is similar to that of patients without PBC. In patients with PBC, supplementation with fat-soluble vitamins and oral administration of calcium are necessary for osteoporosis [2]. Bisphosphonates should be used in the first-line of treatment, although their use has not been proven to reduce the number of fractures in this group of patients [43].

Patients with PBC often have hyperlipoproteinemia and dyslipidemia, but they do not have a greater cardiovascular risk compared to patients without PBC [54]. UDCA, OCA, and fibrates can improve the parameters of lipoprotein metabolism in PBC patients [62,68,97]. It is therefore questionable whether another hypolipidemic treatment should be indicated for PBC patients. Statins lower total cholesterol and LDL-C levels; in patients with PBC and their administration is safe [98,99]. In the case of the ineffectiveness of statin treatment for hyperlipoproteinemia, PCSK9 inhibitors can be added to the treatment [44].

5. Pruritus, Fatigue, Osteoporosis and Dyslipoproteinemia in PBC Patients after Liver Transplantation

In patients with PBC, there is no correlation between MELD score and fatigue, thus these complications need to be addressed as MELD exceptions in the evaluation for liver transplantation. Post-transplant, fatigue improves compared to the pre-transplant period at 6, 12, and 24 months after liver transplantation in patients with low (<17) and also high ≥17 pre-transplant MELD score. Nevertheless, 2 years after liver transplantation, 44% of all patients and 47% of patients with a low pre-transplant MELD score have moderate or severe fatigue [100]. Liver transplantation leads to rapid improvement of pruritus; improvement occurs as early as 24 h after liver transplantation [101]. In PBC patients, bone density decreases by 8–18% in the first 3–6 months after liver transplantation, with development of osteopenia and osteoporosis. The incidence of fractures in the first year after liver transplantation is between 20 and 40% in PBC patients. Post-liver transplant management in PBC patients should include screening for osteoporosis with subsequent treatment similar to that for postmenopausal osteoporosis [102]. Liver transplant patients have a higher cardiovascular risk than the general population. In elderly PBC patients and PBC patients with potential cardiovascular risk, coronary angiography and revascularization should be considered before liver transplantation. After liver transplantation, patients should be carefully monitored, and cardiovascular risk factors managed [103].

6. Conclusions

Pruritus and fatigue are the most common symptoms of PBC. They may occur before the diagnosis of PBC, and their presence may guide the PBC diagnosis. Decreased bone density and impaired lipoprotein metabolism are also common in PBC patients. Pruritus, fatigue, and osteoporosis often reduce the quality of life of PBC patients. Although patients with PBC have atherogenic dyslipidemia, its significance remains unclear and further studies will be needed to clarify its clinical importance. Questionnaires can be used to monitor both pruritus and fatigue. IL-31-level testing is also promising to follow pruritus severity. Pruritus should be managed using both non-pharmacological and pharmacological treatment. The only registered antipruritogenic drug is cholestyramine. Several drugs not registered for pruritus therapy and many of them cannot be prescribed by hepatologists or gastroenterologists in several developed countries. The second-line treatment of PBC can modify pruritus: PPAR agonists relieve it, while FXR agonists worsen

it. This information should be taken into account when choosing the second-line of treatment. Before the start of OCA therapy in non-responders to UDCA, it is necessary to consider the treatment of pruritus. There are no registered drugs for the treatment of fatigue. Osteoporosis and dyslipidemia in PBC patients shoud be treated according to generally valid recommendations.

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List of Abbreviations

AIH	autoimmune hepatitis
ALP	alkaline phosphatase
AMA	antimitochondrial antibodies
ANA	antinuclear antibodies
anti gp210	anti glycoprotein-210 antibodies
anti SSA/Ro	antibodies to Sjögren syndrome A antigen
anti SSB/La	antibodies to Sjögren syndrome B antigen
anti sp100	anti-nuclear protein antigen 100 antibodies
anti sp140	anti-nuclear protein antigen 100 antibodies
FXR	farnesoid X receptor
HDL-C	high-density lipoprotein cholesterol
HOMA	homeostatic model assessment
IBAT	ileal bile acid transporter
IL	interleukin
IL-31RA	interleukin-31 receptor subunit α
LDL-C	low-density lipoprotein cholesterol
MELD	model for end-stage liver disease
MRI	magnetic resonance imaging
MRP2	multidrug resistance-associated protein 2
NOX	nicotinamide adenine dinucleotide phosphate oxidase
OCA	obeticholic acid
PBC	primary biliary cholangitis
PCSK9	proprotein convertase subtilisin/kexin type 9
PPAR	peroxisome proliferator-activated receptor
PSC	primary sclerosing cholangitis
Th2 cells	T helper 2 cells
UDCA	ursodeoxycholic acid

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