Special Article

Drug therapy of primary biliary diseases: classical and modern strategies

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1. Introduction

Definition: Primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) are both cholestatic liver diseases. A common feature of these disorders is the accumulation of bile acids in the liver and blood, presumably because of decreased biliary secretion and reduced bile flow.

Etiology: Etiology and pathogenesis of PBC and PSC are still unknown. PBC is considered to be an autoimmune disease [1]. Immunological mechanisms may also be involved in PSC since there is an association with ulcerative colitis [2] and autoantibodies can be detected [3]. Furthermore, genetic factors seem to play an important role in both diseases [3,4].

Therapy: Since the pathogenesis of both diseases is unclear, there is no definite causal treatment. However, ursodeoxycholic acid (UDCA) was shown to be highly effective. Other drugs which can be used alone or in combination with UDCA are promising and might further improve the outcome of the diseases.

2. Ursodeoxycholic acid

In 1981 the first observation that UDCA noticeably improves liver function tests was made in patients with chronic active hepatitis who underwent gall-

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stone dissolution with UDCA [5]. These data were confirmed in 1985 [6]. In the same year the first results were published on the treatment of six patients with PBC and 2 patients with PSC [7]. Since then, numerous clinical observations have been published that support the notion that UDCA is effective in cholestatic disorders and increasing experimental evidence supports the use of UDCA in these conditions [8].

UDCA is the 7β–epimer of chenodeoxycholic acid (CDCA) and represents a small fraction of the normal bile acid pool in humans [9]. During oral UDCA administration, endogenous bile acids are replaced from the bile acid pool and the proportion of UDCA increases up to 50% [10]. UDCA is efficiently taken up in the liver, conjugated primarily with glycine (and to a lesser extent to taurine) and secreted into bile with subsequent enterohepatic circulation [10].

2.1. Mechanisms of action

The exact mechanisms of action of UDCA in cholestatic liver diseases are unknown. The favorable effects can be classified into:
- reduced hydrophobic bile acid concentrations
- stimulation of choleresis
- influence on signal transduction and bile acid transporters
- hepatoprotective effects
- immunomodulatory effects

2.1.1. Replacement of toxic endogenous bile acids and stimulation of bile secretion. Influence on signal transduction and bile acid transporters

Under continuous oral treatment, UDCA becomes the predominant bile acid in serum, liver tissue and bile and replaces more hydrophobic (and therefore toxic) bile acids [11]. A further increase in hydrophilicity (*e.g.* caused by cholylsarcosine) is not superior to UDCA monotherapy [12]. Therefore, inhibition of absorption of toxic bile acids from the intestine and stimulation of excretion seem to be more important [9]. The enhancement of the biliary excretory capacity is caused by a stimulation of vesicular exocytosis, which is mediated by the activation of hepatocellular Ca^{2+}, α-proteinkinase C and mitogen-activated protein kinases [9,13]. A recently published paper suggests that activation of intracellular signal transduction is important for choleretic effects [14].

2.1.2. Cytoprotective effects on hepatocytes and bile duct epithelial cells

The cytoprotective effects of UDCA seem to be mediated through direct membrane stabilizing and anti-apoptotic effects [9,15]. Membrane stabilization is due to incorporation of UDCA into the more apolar domain of the membrane [16,17]. Another effect observed is reduction in mitochondrial membrane permeability [17].

2.1.3. Immunomodulatory effects

Several reports suggest that UDCA has some modulatory effects on immune functions. The expression of MHC class I molecules is increased in cholestasis which may activate cytotoxic T lymphocytes in PSC and PBC. This might be prevented by UDCA since it was demonstrated that UDCA down regulates the expression of abnormal MHC class I molecules in periportal hepatocytes and of MHC class II on cholangiocytes of PBC and PSC patients [9]. However, it is more likely that the effects on MHC class I expression are the result of improved cholestatic liver injury rather than a direct immunosuppressive effect of UDCA [8]. Furthermore, changes in the concentration of circulating IgM, of activated T lymphocytes and of IFN-γ were reported [18]. Taken together, the mode of action of UDCA seems to be multifactorial.

3. Treatment of primary biliary cirrhosis

Up to now, several trials have been conducted evaluating drugs with different mechanisms of action, but without convincing evidence of benefit. In addition many drugs have an unacceptable profile of adverse effects.

3.1. Ursodeoxycholic acid in primary biliary cirrhosis

The first randomized controlled trial demonstrated in 1989 the therapeutic value of UDCA [19] which was confirmed by many other studies [20-23]. UDCA leads to an improvement in survival, slows down the

progression of the disease and reduces the need for liver transplantation [1]. A recent study demonstrated that patients receiving UDCA had a lower incidence of major complications and lower medical care costs compared to patients receiving placebo [24]. Based on these studies, UDCA has been established as the treatment of choice for PBC since it is safe and well tolerated in a dosage of 5-25 mg/kg/d [25]. The recommended dosage in PBC is 13-15 mg/kg/d [25]. The only significant side effect is diarrhea, which probably occurs in less than 5% of patients. According to biochemical data and the Mayo risk score, no further improvement is achieved when higher doses are administered [25,26]. Less than 10 mg/kg/day seem to be not effective [27].

3.1.1. Effect on laboratory values

In all trials it was shown that even short term treatment with UDCA leads to a marked improvement in the serum markers of chronic cholestasis [28]. However, only 30 % of UDCA treated patients have a complete normalization of their biochemical tests, whereas 70% are incomplete responders [29]. Recent evidence suggests that the effects of UDCA are not primarily related to the stage of the disease [30] but to the degree of cholestasis. Thus, a therapeutic approach with a more powerful choleretic compound might be more effective in those subjects and first results of a prospective controlled pilot study with sulindac support this hypothesis. Sulindac, a nonsteroidal antiinflammatory drug with choleretic properties [31], could further improve liver biochemistries in these patients, when given 100-300 mg per day, in combination with UDCA [32].

3.1.2. Effect on survival

UDCA leads to a significant increase in survival in most controlled trials [1]. This effect is especially visible in studies with advanced disease (bilirubin > 1,4 mg/dl, and /or histological stage III, IV)[33]. Patients with PBC on UDCA have been followed for a maximum of 12 years and the survival time of these patients exceeded those of historical controls [34]. In a recently published long term trial the ten years survival on UDCA in 225 patients was higher than that of untreated patients as predicted by the Mayo model [35]. This suggests that the real benefit from UDCA may be greater in early stages than in later stages of the disease.

The effects of UDCA in PBC were questioned in a recently published meta-analysis which missed to show a benefit in survival, number of transplantations or survival free of transplantation [36]. The authors evaluated 11 trials but, in 8 studies, data were not well defined (UDCA-dosage, stage of the disease, treatment time and definition in treatment failure). Therefore, it is not possible to draw any conclusions from this meta-analysis. In a second meta-analysis, using the same 11 studies, the authors demonstrated that the risk of death or need for orthotopic liver transplantation (OLT) in the UDCA group is statistically significantly lower than in untreated patients [37].

3.1.3. Effect on histology

The effect of UDCA on liver histology has been less conclusive and conflicting results have been published. In some trials a benefit on liver histology could not be observed [21,23,38,39]. Furthermore, improvement in histology, which was seen in other studies, was only related to inflammation without influence on liver fibrosis and bile duct alterations [39-42]. However, in a recently published trial, UDCA decreased the progression rate to extensive fibrosis [43]. This possible benefit of UDCA is supported by the observed antifibrotic effects in experimental trials [44].

3.1.4. Effect on symptoms and portal hypertension

A beneficial effect on pruritus and fatigue as observed by some groups [22,45-47] was not confirmed by others [21]. Improvement of liver enzymes is probably not correlated with the amelioration of pruritus [48]. Nevertheless pruritus improved in patients with a complete normalization of cholestasis [29]. Therapy with UDCA seems to reduce the onset and severity of portal hypertension [49] and to lower the risk of esophageal varices [50].

3.1.5. Summary and conclusions

Ursodeoxycholic acid has been extensively evaluated and shown to improve liver biochemistries and survival in patients with PBC. Although UDCA slows the progression, it does not cure the disease and as there are some patients who respond incompletely to UDCA monotherapy with respect to their

laboratory values, there is a need for new drugs or combination therapies (Table 1).

3.2. Immunosuppressants in primary biliary cirrhosis

Because PBC appears to be an autoimmune disease, several immunosuppressive drugs have been tested in randomized controlled trials [28]. However, so far none has been shown to be of great benefit and their use is limited due to their side effects.

3.2.1. Steroids in primary biliary cirrhosis

Although prednisolone was the first immunosuppressive therapy to be used in PBC, only one small controlled trial was published [51]. The results were rather disappointing and steroids as a monotherapy can not be recommended [52,53]. Recently, it has been shown that short-term administration of methylprednisolone increases cholic acid synthesis and turnover, as well as intestinal production of toxic deoxycholic acid [54]. This could limit the therapeutic value of steroids. Nevertheless the combination of corticosteroids with UDCA seems to be superior to UDCA monotherapy [55,56]. As long term or even life time treatment is necessary in patients with PBC, glucocorticoid-induced side effects like osteoporosis are a major problem.

Budesonide in primary biliary cirrhosis

Budesonide is a topical non-halogenated glucocorticoid with a high first pass effect of more than 90% resulting in fewer systemic side effects [57]. In a controlled, double blind trial a 2 year combination therapy with budesonide (2 x 3 mg/day) and UDCA improved laboratory values and histology in patients with early stages of the disease [58]. In another trial budesonide was less effective and had more side effects [59]. However, this was an uncontrolled one year study which included patients with late stage PBC and who were incomplete responders to UDCA monotherapy. Furthermore, it is possible that the advantage of the high first pass effect of budesonide is abolished in patients with liver cirrhosis and portosystemic shunts. Thus, it is too early to conclude whether budesonide is effective or not, especially when subjects with end stage liver disease are included.

3.2.2. Azathioprine in primary biliary cirrhosis

There are only a few trials with azathioprine as a monotherapy. No improvement on survival was observed [60-62]. However, in one trial azathioprine in combination with prednisolone and UDCA had a beneficial effect [63]. Furthermore, azathioprine may allow to reduce the glucocorticoid dosage to prevent side effects.

3.2.3. Methotrexate in primary biliary cirrhosis

There are contradictory studies concerning the treatment of PBC with methotrexate (MTX). With respect to liver histology the degree of inflammation and bile duct injury improved in some patients but the degree of liver fibrosis and the histological stage, which are the most important parameters, did not improve or even continued to progress [64]. Furthermore, the use of MTX is limited due to its toxic side effects. Patients with PBC receiving methotrexate 15 mg/wk are more susceptible to interstitial pneumonitis (up to 15%) than patients with psoriasis or rheumatoid arthritis [65]. With a low dose of MTX (7,5 mg/week) side effects were prevented but the treatment was ineffective [66]. The minimal effective dose for MTX in PBC seems to be 12,5 – 20 mg/week [67]. Methotrexate might be beneficial in patients with early stage disease [68,69]. However, these two studies were uncontrolled trials.

In most studies combination-therapy of UDCA with MTX did not show any additional benefit to that achieved by UDCA alone [70-72]. Only in one trial symptoms and laboratory values improved. Histology and the natural history were not investigated [73]. At present MTX should be avoided or very carefully recommended.

3.2.4. Cyclosporine A in primary biliary cirrhosis

Treatment with cyclosporine has been disappointing because of limited efficacy and a marked toxicity [74]. The modest improvement in liver function tests, histology and survival are counterbalanced by the development of hypertension in some and worsening renal function in most patients [75]. Cyclosporine A (CSA) may be helpful in selected cases.

Table 1 Drugs for monotherapy and combination-therapy in primary biliary cirrhosis

Treatment of choice: monotherapy	ursodeoxycholic acid (UDCA)	• 13-15 mg/kg/day • 3x daily or in one single dose • lifelong therapy
Treatment of patients who are incomplete responders to UDCA monotherapy	UDCA + + prednisone/prednisolone	13-15 mg/kg/day + 10-15 mg/day
	+ budesonide	+ 3x3 mg/day
	+ azathioprine	+ 50-100 mg/day
	+ methotrexate	+ 7.5 mg/week

3.3. Other therapies in primary biliary cirrhosis

3.3.1 Colchicine

An alternative approach to therapy of PBC is the prevention of fibrosis using agents that inhibit collagen formation [76-78]. Colchicine is a safe and inexpensive drug with a long term effect on the biochemical parameters of disease activity. However, complications of cirrhosis, deaths and transplantations were not reduced [78,79]. The combination of UDCA and colchicine lead to further improvement in laboratory values [80,81]. This was not confirmed by others [48,82] and the influence on the effect on liver histology was not convincing [48,83]. A triple therapy with colchicine, MTX and UDCA may be beneficial for patients who incompletely respond to UDCA [84]. Colchicine in addition to UDCA was less effective than treatment with MTX and UDCA [85].

3.3.2. Bezafibrate

In a preliminary study the combination with UDCA and bezafibrate was superior to UDCA alone with respect to alkaline phosphatase (AP) and IgM [86]. Side effects were not observed. In another trial monotherapy with bezafibrate showed a significant reduction in laboratory values which was similar to that seen with the combination of UDCA and bezafibrate [87]. It is believed that bezafibrate stimulates phospholipid excretion into bile.

3.3.3. D-Penicillamine and chlorambucil

D-Penicillamine is not recommended in PBC as efficacy was lacking and major side effects were observed [88,89]. In a randomized trial with chlorambucil a benefit on laboratory values, especially on serum bilirubin was observed [90]. Although the patients were treated with a suboptimal dose, all of them developed bone marrow suppression. Therefore the drug cannot be recommended.

3.3.4. Summary

In summary all patients with PBC should be treated with UDCA at a dosage of 13-15 mg/kg/d. Patients incompletely responding after 6-12 months should be treated with a combination therapy (Table 1).

4. Treatment of primary sclerosing cholangitis

4.1. Treatment with ursodeoxycholic acid

Because treatment with UDCA in PBC was effective and well tolerated several studies were conducted in PSC [91]. Similar to PBC all studies resulted in a marked reduction of cholestasis [92-96], and even bilirubin, which is a strong prognostic marker, improved. Thus, UDCA is the treatment of choice in all stages of PSC. Patients should be treated as early as possible, and prolonged or permanent therapy must be recommended, as no major side effects have been observed [91]. The recommended dosage of UDCA is 15-20 mg/kg. Dosages less than 10 mg/kg seem to be without effect [96,97].

There are only limited data on histological changes during UDCA therapy. Most studies showed the cellular infiltration of the portal triads improved

whereas all other changes were not significantly influenced [92,94]. Improvement was more pronounced with higher dosages of UDCA [96]. There was no influence of UDCA on the histologic progression when patients with an histological advanced disease were treated [93,98]. Up to now no study had sufficient power to assess the effects of UDCA on survival. Treatment of pruritus, osteoporosis and vitamin deficiencies due to steatorrhea should follow the general guidelines [99] (see below). Improvement of symptoms was observed in some individuals on UDCA therapy but not in all subjects [93,95].

4.2 Other medical therapies

Attempts have been made to treat patients with immunosuppressive, antiinflammatory and antifibrotic agents. None of these drugs could stop the natural course of the disease. On the other hand, treatment may even be harmful because of the high frequency of bacterial cholangitis.

4.2.1. Steroids in primary sclerosing cholangitis

Patients with ulcerative colitis (UC) who are on steroids can develop PSC, or experience progression of the disease. Thus, monotherapy with corticosteroids is not effective [91]. No benefit was seen in a one year uncontrolled study, where patients with late stage PSC were treated with budesonide. Serum AP and aspartate amino transferase levels improved, while serum bilirubin concentrations increased. In addition a significant improvement in portal inflammation was noted, whereas the degree of fibrosis and the stage of the disease were not significantly affected [100]. Minor effects were observed with prednisone in combination with UDCA when compared with the combination of budesonide and UDCA [101]. Positive results were also obtained with the triple therapy of UDCA, prednisolone and azathioprine (decrease in liver enzymes) [102]. However, the benefit of such a combination therapy has to be confirmed in a long term trial with a larger group and a more detailed description of the histological status.

4.2.2. Additional drugs

Uncontrolled and controlled trials and case reports were published with azathioprine [103], cyclosporine A [104], methotrexate [105,106], tacrolimus [107],

colchicine [108,109] and pentoxifylline [110]. Recently a combination therapy with UDCA and sulphasalazine has been performed in three patients with PSC. In this report the combination therapy seems to be superior to UDCA monotherapy [111]. A study with nicotine was not effective. In this pilot trial 75 % of patients suffered from severe side effects which led to the discontinuation of the study [112]. Thus, at present none of these drugs can be recommended as a monotherapy. It is very likely, that with a better understanding of the underlying pathophysiology, additional new molecules with different modes of action will be introduced.

4.3. Endoscopic and surgical treatment

Dominant stenoses of the bile ducts are common in PSC. In a 12 year prospective trial on the effect of UDCA, 28/96 patients developed a progressive stenosis of major bile ducts [113]. UDCA monotherapy was unable to improve the transplant free survival over 2 years [93], but UDCA plus endoscopic dilatation of duct stenoses did [114]. This is to be expected since stenoses are not likely to improve on medical treatment. Therefore, frequent endoscopic approaches are necessary to manage this complication [114]. Beside repeated dilatations, intermittent stenting or nasobiliary catheter perfusion are additional options in the treatment of biliary stenosis. Thus, endoscopic retrograde cholangiography (ERC) is not only the gold standard for diagnosing PSC but also an important tool in the management of the disease.

Dominant strictures may also be managed surgically by dilatation or choledochojejunostomy. However, the procedure is reserved for patients with an early histological stage and symptomatic extrahepatic or perihilar strictures. There is no benefit for patients with a more advanced disease [115]. Surgical intervention may complicate future liver transplantation [116].

4.4. Cholangiocarcinoma

Patients with PSC have a significantly increased risk to develop cholangiocarcinoma (CC) [114]. The mean 10-year mortality rates for CC is 25% [117]. In a large multicenter study from Sweden

bile duct carcinoma was observed in 8 % of patients with PSC, followed for 63 months [118]. Furthermore, CC can be detected in up to 20 % of explanted livers [119]. Alcohol consumption is an additional risk factor for developing CC in PSC. There is no correlation between the course of PSC and the development of CC [120]. The incidence of cholangiocarcinoma was higher in patients with PSC and inflammatory bowel disease than in patients with PSC only [117]. At present it is unclear whether treatment with UDCA will influence the development of bile duct carcinoma [114].

4.4.1. Diagnosis and therapy of cholangiocarcinoma

The diagnosis of cholangiocarcinoma in PSC is difficult because endoscopic brush cytology, biopsies and imaging are not reliable. The serum levels of carbohydrate antigen (gastrointestinal cancer antigen, CA 19-9) can rise temporarily in association with a biochemical relapse of PSC, resulting in insufficient sensitivity and specificity [120-122]. As CA 19-9 and carcinoembryonic antigen (CEA) are not helpful in identifying patients with premalignant changes who would benefit from surgery [123], their prognostic value is limited. The detection of K-ras mutations and p53 dysfunction seems to be promising [124,125].

With advances in surgical techniques, the number of curative resections for hilar cholangiocarcinoma has increased. However, the recurrence rate after curative resection is high. There is no established adjuvant therapy. CC is a highly resistant tumor and unresponsive to driamycin, mitomycin C and cisplatin [126]. The benefit of liver transplantation for patients with clinically apparent cholangiocarcinoma is extremely poor. However, in patients with a microscopic tumour detected in the explanted liver, survival is similar to those transplanted with PSC without cholangiocarcinoma [127]. Because of the high recurrence rate and lack of positive prognostic variables, transplantation should be used reluctantly as a treatment for cholangiocarcinoma [128]. Transplantation in combination with preoperative irradiation and chemotherapy seems to be associated with prolonged disease-free intervals and an improved overall survival in highly selected patients with early-stage cholangiocarcinoma [129].

4.5. Primary sclerosing cholangitis and colorectal cancer

80% of patients with PSC suffer from ulcerative colitis (UC) which is often mild or even asymptomatic [114]. Interestingly the severity of UC increases within the first years after liver transplantation [127,130], and proctocolectomy does not affect the progression of PSC [131]. PSC seems to be an independent risk factor for the development of colonic dysplasia and of colon carcinoma in patients with UC [132]. This risk is further increased in subjects with PSC and UC after liver transplantation. Therefore, repeated colonoscopies are strongly recommended in these patients [133]. Results of a recently published trial showed that UDCA therapy was associated with a decreased prevalence of colonic dysplasia in patients with PSC [134]. Further trials are needed to confirm these results.

5. Extrahepatic manifestations of cholestatic liver diseases

5.1. Pruritus

Patients with chronic cholestatic liver diseases frequently suffer from pruritus. Pruritus reduces life quality considerably and in severe cases even liver transplantation can be indicated. Because the pathogenesis of pruritus is unknown, treatment is not based on scientific evidence but on empirical knowledge [135] (Table 2). Considering the literature accumulation of toxic bile acids and an increase of pruritogenic substances seem less important. More recent findings suggest that an increase in neurotransmission, mediated by endogenous opioid agonists, may be responsible for the development of pruritus [135].

5.1.1. Treatment

Although bile acids seem to be less important in the pathogenesis of pruritus, cholestyramine, a non-absorbable bile acids binding anion exchange resin, is effective in more than 90% [136]. In cases where patients do not tolerate the side effects like bad taste, bloating, diarrhea and constipation, colestipol can be used. Patients in whom cholestyramine is not

Table 2   Recommendation for the treatment of pruritus

first line	ursodeoxycholic acid	12-15 mg/day
	cholestyramine	4-16 g/day in increasing dosage
	colestipol	5-30 g/day
second line	naloxone	2-3x0.4 mg/day
	naltrexone	50 mg/day orally
	ondansetron	3x4-3x8 mg/day orally
third line	rifampicin	300-500 mg/day up to 10 mg/kg/day
	metronidazole	3x250 mg/day for one week
	2,6-di-isopropylphenole	up to 15 mg/day
fourth line	plasmapheresis	3x/week, after that once every two weeks
	liver transplantation	in cases which are refractory to treatment

effective, treatment with enzyme-inductors such as rifampicin [137] phenobarbital [138] and s-adeno-syl-methionine (SAMe) [139] may be helpful. The weak effects of antihistamines are likely to be due to their sedation [140].

As mentioned above, disturbances in the neuro-transmission/neuromodulation of the central nervous system seem to be involved in the pathogenesis of pruritus. Potent opiate antagonists, such as nalmefene [141], naltrexone [142], and naloxone [143], are effective in 50 – 60 % of the patients [135]. Other neurotransmitter-systems, such as serotonin, might also be involved in the pathogenesis of pruritus. Some authors suggest that the 5HT3 serotonin antagonist ondansetron may ameliorate pruritus [135,144]. However, further investigations are needed to determine whether specific serotonin receptor subtype ligands have a place in the treatment of pruritus.

5.2. Fatigue

Fatigue affects up to two-thirds of PBC patients, but its etiology remains obscure [145]. Like pruritus it may be centrally mediated [135] since increased serotonergic neurotransmission in the central nervous system contributes to fatigue [146,147]. There are no convincing data about the efficacy of UDCA [1,22,93] or other drugs. A benefit due to antioxidant therapy has to be further investigated [148].

5.3. Osteoporosis

Osteoporosis is a frequent complication in cholestatic liver diseases and is present in almost all patients with end stage liver disease [149]. Its pathogenesis is not well understood. Osteoporosis is more frequently seen in PBC than in PSC [150], although factors specifically related to PBC have not been defined [151]. Dual-energy X-ray absorptiometry is the method of choice for evaluating and monitoring osteoporosis [152].

Risk factors for the development of osteoporosis in biliary liver diseases are not well defined. The role of disease severity [153], vitamin D receptor genotypes in PBC, cholestasis itself and Sjögren syndrome are currently discussed [154]. Inflammatory bowel disease in combination with PSC may or may not be an additional risk factor [150].

Table 3 Recommendation for the treatment of osteoporosis

• well balanced nutrition, physical activity, muscle building		
• vitamin D3	500-5000 IE/day orally or 100,000 IE/mo. i.m.	
additionally calcium	1000-1500 mg/day	
• calcitonin monotherapy		only in low calcium diet
• estrogens	0.6 mg/day	side effect: cholestasis
• biphosphonates alendronate etidronate followed by calcium	10 mg/day 1 x 400 mg for two weeks 500 mg for 76 days	

5.3.1. Treatment

No therapy has shown to be satisfactory for metabolic bone disease associated with cholestatic liver disease (Table 3). In an early stage physical exercise and maintaining adequate serum vitamin D levels and calcium intake may be sufficient. Monitoring of dietary intake of calcium and vitamin D is reasonable and the threshold for initiating supplementation should be low [155]. The results on treatment with calcitonin monotherapy are controversial. Whereas some authors could show a benefit [156], the majority was unable to find an significant improvement [157]. Probably a combination with vitamin D (1,25-dihydroxyvitamin D) and calcium is effective [158]. UDCA does not seem to have an influence on osteoporosis [150,159].

In subjects in menopause and with low bone mineral density, estrogens are the standard treatment to prevent osteoporosis [160]. Unfortunately there are little data on estrogen therapy and PBC, but it seems to be safe and effective [161]. Today in postmenopausal patients biphosphonates (alendronate) are the first choice of treatment [160], but with respect to PBC, results are controversial [162]. In a recently published trial, cyclical etidronate alternated with calcium could not improve bone density [163]. However, PBC patients treated with prednisolone seemed to benefit [164].

5.4. Steatorrhea

In cholestatic liver diseases steatorrhea can occur for three reasons: when bile acid concentration in the duodenum is below the critical micellar concentration, micelle formation and fat absorption are reduced. In patients with PBC, sicca syndrome is accompanied by a decreased secretion of pancreatic enzymes and in some patients celiac disease develops [165,166]. For treatment, fat intake should not exceed 20% of the total energy intake. In severe cases middle chain triglycerides can be effective. Deficiencies in fat soluble vitamins A, D, E and K are seldom but have to be expected in manifest steatorrhea and should be supplemented by intramuscular injections. Furthermore, pancreatic enzymes can be administered in high dosage (Table 4).

6. New immunosuppressants

During the past 50 years, many immunosuppressive drugs have been described. Eventually, the mechanisms of action were found to fall into five groups: (i) regulators of gene expression; (ii) alkylating agents; (iii) inhibitors of *de novo* purine synthesis; (iv) inhibitors of *de novo* pyrimidine synthesis; and (v) inhibitors of kinases and phosphatases. Most of the new immunosuppressive drugs have been developed for organ transplantation and more recently for autoimmune diseases [167]. Two of these drugs which might be interesting candidates for the treatment of PBC and PSC are tacrolimus (FK 506) and mycophenolate mofetil (MMF). However, their therapeutic use is often limited, due to their toxic side effects like bone marrow suppression, which can be observed in many patients.

Tacrolimus (FK506), a metabolite of an actinomycete *Streptomyces tsukubaensis*, was shown to be immunologically effective. Adverse side effects

Table 4 Treatment of steatorrhea and vitamin deficiencies

steatorrhea	• reduction of fat intake to 40-50-(30) g/day	
	• middle chain triglycerides (MCT)	
	• lowering cholestyramine dosage	
	• glutenfree diet	
	• pancreatic enzymes	
vitamin deficiencies	vitamin A	25000-50000 IE i.m., 3x/week or 3x25000 IE/week
	vitamin K	10 mg/mo. i.m.
	vitamin E	100-400 mg α-tocopherol/mo. i.m. or 10-20 mg/day
	vitamin D$_3$	500-5000 IE/day oral or 100000 IE/mo. i.m.
	calcium	100-1500 mg/day
zinc deficiencies	substitution sometimes necessary	

of the drug include neurotoxicity and nephrotoxicity [168]. Extensive efforts in identifying compounds with an improved therapeutic utility may lead to the design of safer FK506-related immunosuppressants [169]. Sirolimus is structurally related to the immunosuppressive agent tacrolimus, and retains a pharmacokinetic and drug interaction profile similar to cyclosporine and tacrolimus [170]. It is the latest pharmaceutical agent to complete phase III trials, acts to inhibit IL-2 driven lymphocyte proliferation and reduces the risk of acute rejection to below 20% [171]. However, the molecule causes severe hyperlipidemia, and the long-term consequences both on the pathogenesis of cardiovascular disease and on lipid-associated renal injury have yet to be determined [172].

MMF was initially derived from cultures of *Penicillium spp.* It is an immunosuppressive drug which appears to be free of side effects and longer treatment could probably be justified. The drug is currently the leading candidate for replacement of azathioprine [173]. Based on the experience in clinical trials the recommended dosage is 2 g/day. Two patients with PBC were treated with a combination of MMF 2 g and UDCA 1 g daily for 12

months. Both were incomplete responders to UDCA monotherapy. A decrease in elevated serum alkaline phosphatase levels to values close to the upper limit of normal, and an almost complete disappearance of the chronic inflammatory cell infiltrate, was observed without significant adverse events [174].

There are many other drugs which are potentially effective in primary biliary liver diseases. These include new regulators of gene expression, alkylating agents, inhibitors of *de novo* purine or pyrimidine synthesis and inhibitors of kinase and phosphatases. However, there is no or very limited experience with these drugs [28].

There are no data on the treatment of primary biliary liver diseases with cyclophosphamide. However, in subjects with autoimmune hepatitis, one study succeeded to induce and to maintain remission, using a combination of a tapering dose of corticosteroids and 1-1.5 mg/kg body-weight cyclophosphamide [175]. The dosage used in this 12 year trial was much lower than that used in other diseases and only minor side effects were observed. Therefore, cyclophosphamide might be an alternative in patients with PBC or PSC.

The results of the only trial with chlorambucil for the treatment of PBC were not convincing [90]. Fludarabine is an effective treatment for subjects with chronic lymphocytic leukemia which do not respond to initial treatment with chlorambucil. Pranlukast is a leukotriene antagonist known to suppress eosinophil infiltration in atopic dermatitis or bronchial asthma. This drug was tried in PBC which is also characterized by eosinophil infiltrates in the portal tract. Treatment with 450 mg/day resulted in a significant improvement of laboratory values [176]. Cladribine is a nucleoside analog with specific antilymphocytic activity that has been used in patients with autoimmune diseases. In four patients with PSC (stages I and II) the drug was well-tolerated. Cladribine decreased the hepatic lymphocytic inflammation in early-stage PSC without any symptomatic, biochemical, or radiologic improvements. Further studies with long-term follow-up are needed to assess if this anti-inflammatory effect can modify the progression of disease [177].

The novel synthetic immunosuppressive compound FTY 720 has a different mode of action as compared to other immunosuppressive drugs. It reduces peripheral lymphocytes. This mechanism potentiates the immunosuppressive effect when combined with other immunosuppressants like tacrolimus [178]. Further studies are being carried out to determine its effect after organ transplantation or treatment of autoimmune liver diseases.

Monoclonal antibody therapy is an exciting new development. Anti-interleukin-2 receptor antibodies might constitute a safe and efficient addition to the immunosuppressive induction regimen following OLT [173,179]. Anti-CD3 antibodies are also under current investigation. However, the benefit of these drugs has to be proven in further trials. Gene transfer and epithelial cell transplantation as well as hepatocyte transplantation technologies play an important role in the development of new therapeutic concepts for liver diseases. Most of these procedures and techniques are still experimental or have been applied to a small number of patients only.

The treatment of the overlap syndromes between primary biliary liver diseases and autoimmune hepatitis is still experimental and currently there is no accepted therapy [180,181].

In summary, the development of new drugs offer the opportunity to use combinations that block different pathways of immune activation. In addition drugs with different toxicity profiles can be selected in order to reduce the dosage of each drug. Until now, OLT remains the final solution in the treatment of primary cholestatic liver diseases and new immunosuppressive regiments are likely to further improve survival rates after transplantation.

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