Treatment of autoimmune liver disease: current and future therapeutic options

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Abstract: Autoimmune liver disease spans three predominant processes, from the interface hepatitis of autoimmune hepatitis to the lymphocytic cholangitis of primary biliary cirrhosis, and finally the obstructive fibrosing sclerotic cholangiopathy of primary sclerosing cholangitis. Although all autoimmune in origin, they differ in their epidemiology, presentation and response to immunosuppressive therapy and bile acid based treatments. With an ongoing better appreciation of disease aetiology and pathogenesis, treatment is set ultimately to become more rational. We provide an overview of current and future therapies for patients with autoimmune liver disease, with an emphasis placed on some of the evidence that drives current practice.

Keywords: aetiology, autoimmune hepatitis, autoimmune liver disease, primary biliary cirrhosis, primary sclerosing cholangitis, pathogenesis, treatment

Introduction

Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) represent three relatively uncommon autoimmune diseases affecting the hepatobiliary system. These conditions have a broad clinical spectrum and a variable, usually slow, natural history, making prospective trial design for therapies challenging. However, having made a clear diagnosis of autoimmune liver disease and having interpreted the laboratory testing correctly to identify the predominant active liver injury, clinicians should seek to treat patients in a way that is most in keeping with the evidence, be it from randomized controlled trials or observational studies. Prior to therapy, patients should understand the goals of intervention and the limitations of any surrogates that might be used to evaluate treatment success. In this article, we present a critical overview of the currently available treatment options for the major autoimmune liver diseases, before providing insight into new potential therapeutic agents. A complete approach to the management of autoimmune liver diseases should also include adequate symptom control, early recognition of extra-hepatic manifestations and surveillance for complications (Figure 1), aspects which are covered more fully elsewhere [Decock *et al.* 2009].

Autoimmune hepatitis

The decision of which patients with AIH require therapy is founded on the results of prior placebo-controlled trials conducted over 30 years ago. These studies revealed that untreated, moderate–severe AIH [aspartate transaminase (AST) >5 × upper limit of normal (ULN), globulins >2 × ULN, liver biopsy showing confluent necrosis] has a very poor prognosis, with a 5- and 10-year survival of 50% and 10% respectively [Kirk *et al.* 1980; Murray-Lyon *et al.* 1973]. Such individuals should be offered treatment because of the clear survival benefit and patient outcome with appropriate immunosuppressive therapy is excellent, with 10-year survival rates exceeding 80% [Gleeson *et al.* 2011; Manns *et al.* 2010a; Hoeroldt *et al.* 2011].

Up to 30% of adults may have cirrhotic disease at diagnosis whereas *de novo* cirrhosis develops in around 12% after 10 years despite immunosuppression, in 49% if there are persistent mild–moderate laboratory abnormalities and in 82% when bridging necrosis or multilobular necrosis is present [Feld *et al.* 2005; Schalm *et al.* 1977; De Groote *et al.* 1978]. Cirrhosis development is associated with liver-related death/transplantation (hazard ratio 9.96) and reduced 10-year survival (67% *versus* 94% in patients without

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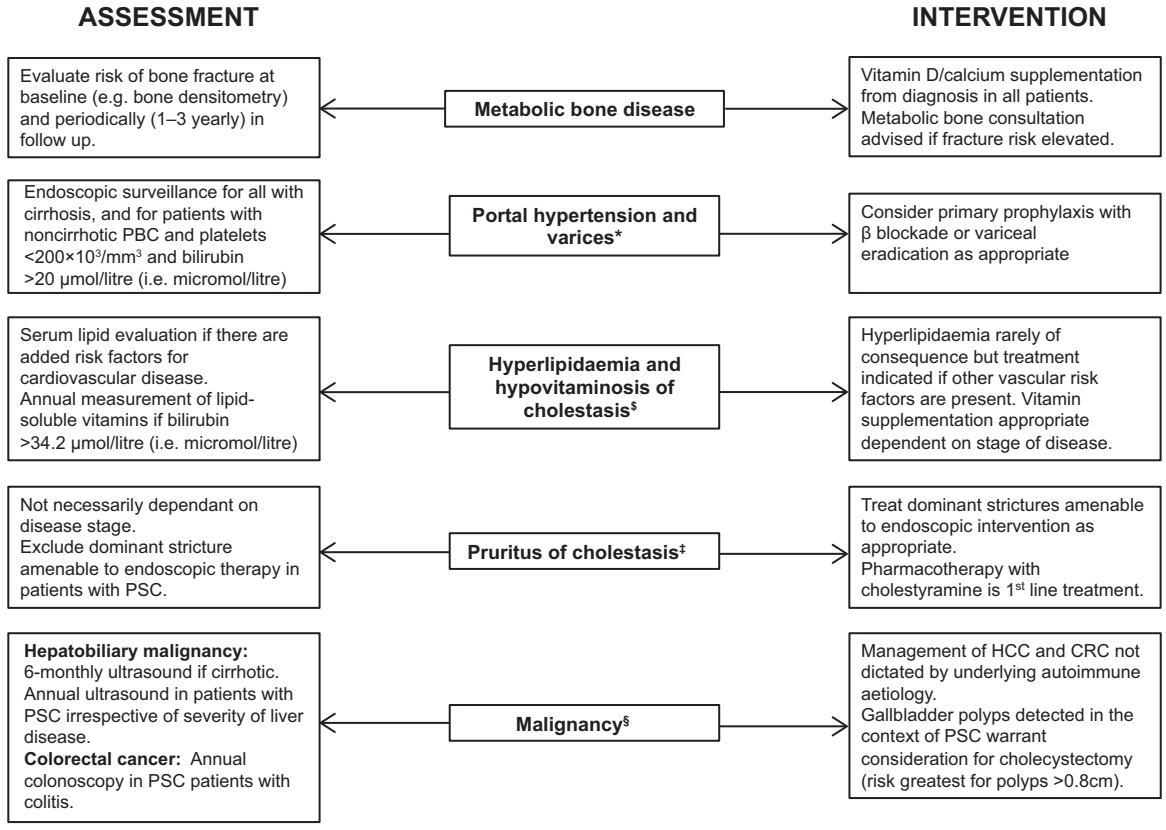

Figure 1. Extrahepatic manifestations, complications and surveillance strategies in autoimmune liver disease. The complete management of autoimmune liver disease should encompass early symptom recognition and surveillance of complications, whether they are related to the side effects from drug therapy (e.g. osteoporosis and prednisolone) or the underlying disease itself (e.g. metabolic osteopathy of cholestasis). Some complications may be evident only in patients with advanced fibrosis/cirrhosis [e.g. hepatocellular carcinoma (HCC)] whereas others are unrelated to disease severity [e.g. colonic cancer and biliary malignancies in primary sclerosing cholangitis (PSC); the pruritus of cholestasis].

*Obstruction to portal venous flow may also occur at a presinusoidal level in primary biliary cirrhosis (PBC), and nodular regenerative hyperplasia is found in up to 43%. Thus, given the risk of noncirrhotic portal hypertension in patients with PBC, additional parameters for variceal surveillance have been adopted [Bressler *et al.* 2005; Levy *et al.* 2007].

$Largely applies to PBC.

‡Cholestyramine is ineffective in around 20% of patients. Other bile-acid sequestrants (e.g. colesevelam) have not been shown to improve symptoms. Rifampicin use is supported by meta-analyses, although side effects remain a concern. Opioid antagonists can be used as a third-line treatment although there may be a risk of withdrawal-like reactions. Pilot studies report a subjective amelioration of itch using ondansetron and sertraline although patient numbers were small. Those with refractory pruritus can be treated with drugs having anecdotal support, or referred to specialized centres where more invasive or experimental approaches (e.g. extracorporeal albumin dialysis, ultraviolet B therapy) may be considered [Kremer *et al.* 2011].

§Effective surveillance strategies for cholangiocarcinoma (CCA) are currently lacking, although proteomic analysis of bile and urine could provide helpful as a future prospective [Lankisch *et al.* 2011; Metzger *et al.* 2013]. The risk of gallbladder cancer in PSC appears greatest with polyps over 0.8 cm [Eaton *et al.* 2012].

cirrhosis) [Gleeson *et al.* 2011; Feld *et al.* 2005; Verma *et al.* 2004]. However, 10-year survival of treated individuals in remission approaches 98% [Czaja, 2009a] and therapy should be considered in all patients having active inflammation and established (compensated) cirrhosis on biopsy, even those with milder biochemical abnormalities. The benefits of treatment in asymptomatic patients with mild interface hepatitis are less well established, as this group reportedly have a 10-year survival as high as 80% [Feld *et al.* 2005], whereas in another study the 10-year survival of eight untreated patients with mild disease was significantly lower than that of

treated patients with severe disease (67% *versus* 98%) [Czaja, 2009a]. The true natural history of mild AIH is unknown, although some patients in this category can do well without immunosuppression. However, untreated mild AIH does not have a uniformly benign prognosis and asymptomatic patients may become symptomatic, a group of patients with a 10-year mortality that exceeds 10% [Feld *et al.* 2005]. Mild disease activity can be interspersed with phases of severe activity that can be aggressive, and the available data indicate that histological stage, including the frequency of patients with cirrhosis, is similar between symptomatic and symptom-free patients, although those with symptoms may have higher inflammatory scores [Feld *et al.* 2005]. Moreover, between 26% and 70% of asymptomatic patients may go on to develop symptoms during follow up, with fluctuating histological inflammatory activity [Feld *et al.* 2005; Kogan *et al.* 2002]. Spontaneous recovery of AIH may occur; however, resolution of inflammatory activity occurs much less frequently in untreated patients (12% *versus* 63%). Moreover, the rapidity at which disease resolution takes place rather than its occurrence is an important factor in preventing disease progression [Czaja, 2009b]. If left untreated, patients with mild AIH should be closely monitored and reviewed clinically on a regular basis for signs to suggest progressive disease worthy of treatment. Conversely, patients with decompensated liver disease or fulminant hepatic failure represent populations which may not always benefit from immunosuppression (Table 1), and management in this setting should be in the context of access to transplantation if appropriate [Ichai *et al.* 2007].

Inducing remission

Prednis(ol)one (20–30 mg/day) is the mainstay for inducing remission and in most cases is combined with azathioprine. Hepatotoxicity secondary to the latter is rare and in part dose dependent, being more common in those with decompensated liver disease [Lohse and Mieli-Vergani, 2011]. Therefore azathioprine can either be instituted from the outset (50 mg/day) or within a few weeks following steroid response at a dose of 1–2 mg/kg/day (Figure 2). Delaying introduction of azathioprine can be pragmatically helpful in managing and avoiding side effects of treatment. 6-Mercaptopurine as an alternative therapeutic option may be reserved for patients intolerant to azathioprine, although evidence for its efficacy in treating patients whose disease does not respond to azathioprine is lacking and largely anecdotal [Pratt *et al.* 1996].

The American Association for the Study of Liver Diseases guidelines include an option for starting with prednisone at 1 mg/kg/day (maximum 60 mg/day) [Manns *et al.* 2010a] during the induction phase, although such high doses are rarely necessary and are associated with side effects. However, in patients without cirrhosis, this may result in a more rapid normalization of serum transaminases [Schramm *et al.* 2010].

Maintaining remission

Remission is defined as a complete normalization of all inflammatory parameters, including AST, alanine transaminase (ALT) and bilirubin (biochemical remission); immunoglobulin G (IgG) (immunological remission); and histologically active inflammation. Remission is achievable in around 75–80% of patients after 24 months of treatment (including those with cirrhosis) and associated with around 80% patient survival at 10 years [Montano-Loza *et al.* 2007a; Johnson *et al.* 1995]. Normalization of serum aminotransferase levels within 3 months of starting therapy is highly predictive for sustained biochemical remission at 2 years [Wang *et al.* 2011]. Remission is usually maintained with prednisolone at around 7.5–12.5 mg/day alongside azathioprine 1–2 mg/kg/day (2 mg/kg/day when using azathioprine monotherapy or if previous relapses). A thioguanine nucleotide (TGN) concentration greater than 220 pmol/8×10^8 erythrocytes is predictive of remission [odds ratio 7.7], although there does not appear to be an association between TGN or methylmercaptopurine nucleotide concentration, or thiopurine methyltransferase activity and the development of leucopenia [Dhaliwal *et al.* 2012]. The optimum duration of therapy is controversial, but for patients without cirrhosis with type I AIH, a finite therapy with steroids for 12–18 months and azathioprine for 2–5 years, prior to a single trial off therapy, assuming all inflammatory parameters remain normal, is quite reasonable. Maintenance treatment with prednisolone and azathioprine has not been proven to be superior to azathioprine alone; however, monotherapy with azathioprine has only been systematically evaluated following histological confirmation of disease remission [Stellon *et al.* 1988; Johnson *et al.* 1995]. Nevertheless, tapering of steroids is commonly performed in clinical practice without repeat liver biopsy, provided full biochemical and

Table 1. Autoimmune hepatitis – treatment considerations in special populations [Czaja, 2011].

Acute, fulminant disease onset	Patients with acute, fulminant hepatitis at presentation have a less favourable response to corticosteroids and should be managed in the context of needing likely transplant
	Patients with an acute but not fulminating disease onset may respond favourably to standard corticosteroid therapy. However, a failure of clinical and biochemical improvement after 1–2 weeks of therapy warrants careful review. A fall of less than two points in UKELD score after 7 days predicts treatment failure with 85% sensitivity [Yeoman *et al.* 2011]
Pregnancy*	Pregnancy is generally uneventful in AIH, although can be associated with a lower live birth rate, maternal death, hepatic decompensation and need for transplant if the mother has cirrhosis
	AIH flares are more common in the absence of immunosuppressive therapy although azathioprine is largely safe in pregnancy and no complications have been documented in the IBD literature in pregnant women. However, traces of azathioprine may be found in breast milk [Habal and Huang, 2012]
Age >60 years	At presentation, disease is frequently indolent and aggressive with advanced liver fibrosis/cirrhosis and hepatic decompensation being common manifestations
	Older patients respond very well to low doses of prednisolone (~10 mg) and improve more rapidly compared with individuals <40 years of age (24-month biochemical response 94% *versus* 64%); however, the risks of sepsis in decompensated patients require careful consideration
	Bone protection and maximizing the dose of azathioprine (to minimize corticosteroid use) are strongly encouraged
Asymptomatic patients and mild disease[$]	The decision whether to treat all in this group is controversial
	10-year survival of untreated patients is significantly lower than that of treated patients with severe disease, and taking the decision to refrain from treatment based on an assumption that mild disease does not progress may unnecessarily risk the development of adverse consequences
Seronegative disease	10–54% of patients with cryptogenic cirrhosis have AIH despite the absence of conventional autoantibodies
	19% of patients with AIH lack detectable autoantibodies at presentation
	Absence of autoantibodies should not delay the institution of immunosuppression in the patient with otherwise compatible features

*Liver disease may actually improve in pregnancy as the high oestrogen levels favour an anti-inflammatory cytokine shift. However, as blood oestrogen levels fall peri partum, AIH may be exacerbated.
[$]Although the features of AIH may spontaneously resolve, rates are much less frequent in untreated individuals (12% *versus* 63%). The frequency of cirrhosis is similar between symptomatic and symptom-free patients, although those with symptoms may have higher inflammatory scores.
IBD, inflammatory bowel disease; UKELD, UK model for End-stage Liver Disease.

immunological remission has been attained. Follow-up biopsies should however be considered given that 5% of patients per year develop cirrhosis, a rate much higher in those with ongoing inflammation. Moreover, relapse and progression to fibrosis are almost universal when immunosuppression is stopped in the presence of residual interface hepatitis [Carpenter and Czaja, 2002; Montano-Loza *et al.* 2007b; Czaja and Carpenter, 2003]. The combination of normal IgG and transaminase levels together correlates with lower histological inflammatory scores (Knodell index <4) [Lüth *et al.* 2008] in around 90% of cases, although histological remission may lag 3–6 months behind biochemical remission. Treatment until normal liver AST, ALT, bilirubin and

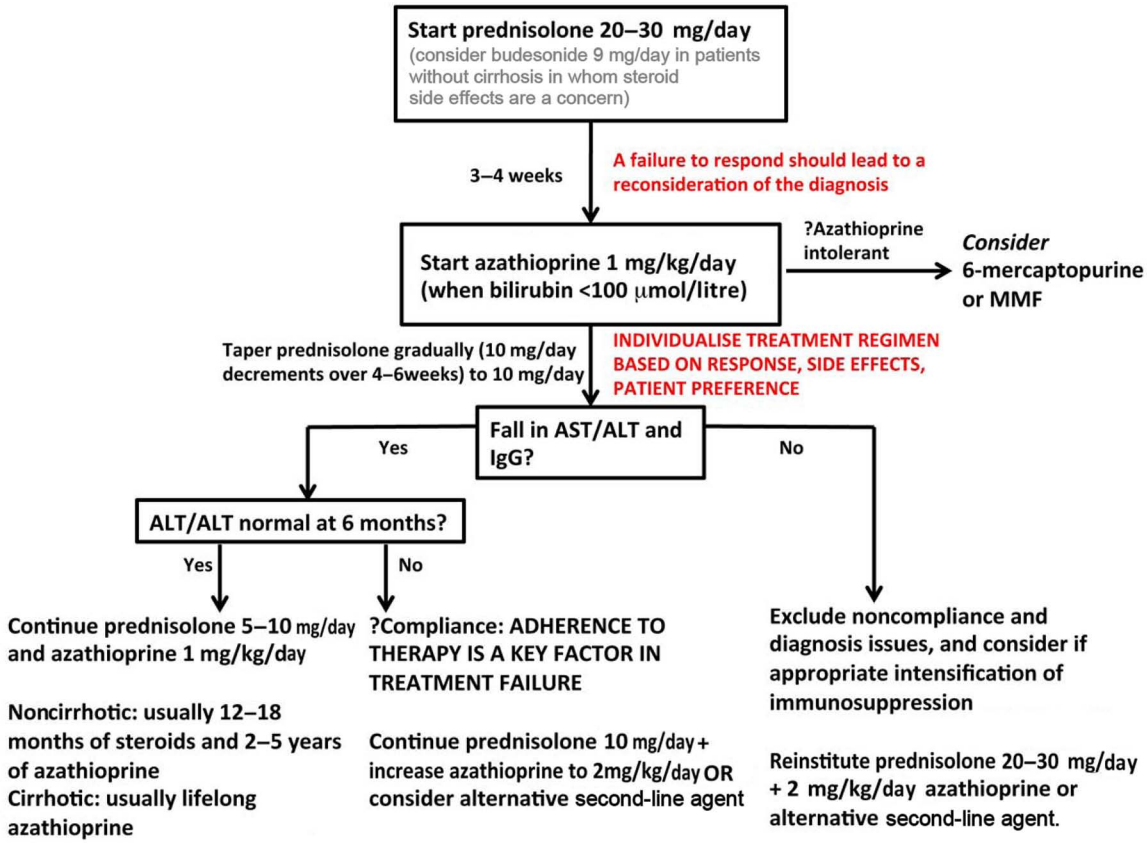

Figure 2. Suggested induction regimen for autoimmune hepatitis (AIH). A stratified, personalized approach to patient management is best achieved through good continuity of care, and it is rare that rapid decisions need to be made; guidelines exist purely as a framework from which to base care. Adherence to therapy is as important as anything clinical in AIH treatment. Budesonide in combination with azathioprine is emerging as an alternative frontline agent to prednisolone for patients without cirrhosis and ought to be considered for patients with comorbidities that might be exacerbated by prednisolone treatment. Patients who receive a lower maintenance dose of prednisolone (~10 mg/day) in combination with azathioprine (50 mg/day) respond similarly to those who receive prednisolone alone (≥20 mg/day) albeit with fewer side effects (10% *versus* 44%). Therefore, a combination maintenance regimen is preferred. Bone protection in those with prolonged steroid use is strongly recommended. Given the perceived hepatotoxicity of azathioprine, particularly in patients with pre-existing jaundice, individuals are normally initiated on steroids first, monitored, and azathioprine added when disease response (e.g. bilirubin <100 μmol/litre) has been confirmed.
ALT, alanine transaminase; AST, aspartate transaminase; IgG, immunoglobulin G; MMF, mycophenolate mofetil; ULN, upper limit of normal.

γ-globulin levels, and normal liver histology is ideal as this reduces the frequency of relapse after drug withdrawal from 86% to 60% [Montano-Loza *et al.* 2007c].

Disease relapse

Relapse is characterized by an increase in aminotransferase levels (>3 × ULN) while under therapy (poor drug compliance being the first consideration) [Sockalingam *et al.* 2012], following tapering of steroid doses or after a complete withdrawal of immunosuppression [van Gerven *et al.* 2013], and can still occur despite the prior attainment of complete remission, including a histologically inactive follow up biopsy. Most relapses (Table 2) occur within 12 weeks of stopping treatment and up to 80% of patients relapse around 3 years following treatment withdrawal. Disease relapses are associated with progression to cirrhosis (38%), liver failure (14–20%), an increasing frequency of subsequent relapse (86% after the third round of treatment), reduced transplant-free survival, hepatocellular carcinoma (HCC) and all-cause mortality [Hoeroldt *et al.* 2011; Montano-Loza *et al.* 2007b; Yoshizawa *et al.* 2012]. Relapse

Table 2. Factors predictive of poor outcome in autoimmune hepatitis.

	At presentation	During the treatment phase	On treatment withdrawal
Relapse when off treatment (50–90% of patients)	Prolonged symptomatic course Anti-LKM-1 positive* Anti-SLA/LP positive Nonconventional antibodies (anti-ASPGR, chromatin) Male sex HLA *DRB1*03*	Treatment nonadherence Short treatment duration Prolonged time to achieve remission Persistent portal inflammation or interface hepatitis Azathioprine-free maintenance regimens	Increasing duration since stopping treatment (50% relapse at 6 months; 80% at 3 years)
Progressive fibrosis/cirrhosis (10–50%)	Hypoalbuminaemia[$] Coagulopathy[$] Confluent necrosis	Treatment nonadherence Persistent inflammatory change on biopsy Increasing time to biochemical remission (>24 months) Persistently abnormal liver biochemistry Number of relapses per decade (>4)	Multiple relapses (38% progress to cirrhosis)
Liver-related death or OLT (10–20%)	Fulminant presentation Confluent necrosis Cirrhosis Female sex Anti-LKM-1, LC-1 or SLA/LP positive	Treatment nonadherence Poor responders (failure of transaminases to fall after 6 months; persistently raised ALT or AST) Frequent relapses Nontreatment with azathioprine	Multiple relapses Development of cirrhosis

Modified from Gleeson *et al.* [2011].
*Relapse is near universal in type-II/anti-LKM-1 positive patients without corticosteroids, and these patients often require low-dose, maintenance prednisolone.
[$]May reflect the presence of cirrhosis at baseline rather than risk of development.
ALT, alanine transaminase; ASPGR, asialoglycoprotein receptor; AST, aspartate transaminase; LC, liver cytosol; HLA, human leukocyte antigen; LKM, liver kidney microsomal; SLA/LP, soluble liver/pancreas antigen.

is treated by reinstituting corticosteroids (20–30 mg) and optimizing the dose of azathioprine (2 mg/kg/day). Patients who have relapsed once, or who have cirrhosis, must not be given an opportunity for future relapse and should receive lifelong therapy, usually the goal being monotherapy with azathioprine if tolerated.

Treatment failure

Assuming compliance and a correct diagnosis, patients who do not show clinical or laboratory improvement within 6 months of starting therapy (13%) may be incompletely responsive, whereas those whose condition deteriorates by any clinical or laboratory parameter despite compliance (~9%) are considered treatment failures [Montano-Loza *et al.* 2007b]. Such situations justify the reinstitution of prednisolone (variable dose depending on clinical setting) alone or in conjunction with azathioprine (2 mg/kg/day). High-dose steroids, if chosen, are maintained for at least 1 month. Thereafter, the steroid dose may be reduced according to the clinical response. Continued deterioration despite the above measures may be an indication for alternative therapies or transplantation, but histological evidence of ongoing inflammatory disease should be considered to

ensure accurate diagnosis and exclusion of confounders, such as drug-induced liver injury. The development of cholestasis can be a feature of azathioprine hepatotoxicity but should also prompt a search for overlapping PSC, particularly if the patient has coexistent inflammatory bowel disease (IBD) or a resistance to conventional therapy.

Alternative treatments

Alternative therapies are typically applied following the development of side effects/complications while on standard immunosuppression, or due to a failure of standard therapy to induce or maintain remission. Many early pharmacological trials defined biochemical remission as achieving serum transaminase levels up to 2 × ULN. It was not until the publication of more recent studies that the importance of complete normalization of aminotransferase levels became fully appreciated, albeit this is context specific (e.g. age and severity being relevant) [Manns *et al.* 2010a]. Further discussions in this section will therefore classify ALT or AST up to 2 × ULN as 'biochemical response' and normalization of ALT or AST as 'biochemical remission.'

Budesonide. Budesonide has a higher affinity for the glucocorticoid receptor than prednisolone but undergoes over 90% hepatic first pass metabolism with the resulting catabolites being devoid of glucocorticoid activity, potentially limiting steroid-related side effects. Until recently, evidence supporting the use of budesonide in AIH was reliant on small case series, with some suggesting that budesonide was effective at achieving biochemical response in less than one-third of patients, whereas in others, figures for complete remission approached 58–83% [Danielsson and Prytz, 1994; Czaja and Lindor, 2000]. These preliminary results implied that, at best, budesonide was noninferior to prednisolone but with possible improved tolerability. More recently a multicentre double-blind study randomized 203 patients with AIH to receive either budesonide or prednisone (both in combination with azathioprine) and observed biochemical remission at 6 months in 60% of the budesonide group *versus* only 38.8% with prednisone [Manns *et al.* 2010b]. In the open-label extension, whereby patients in the prednisone arm were switched to budesonide, biochemical remission was again more frequently attained in the cohort originally randomized to budesonide (68.2% *versus* 50.6%). Although promising, the overall proportion achieving remission on prednisone was clearly below that reported in historical case series. Moreover, histological correlates were not provided due to the short follow-up period, and prospective evaluation of repeat liver biopsy specimens following the attainment of biochemical and immunological remission while on budesonide would be potentially informative.

Despite improved tolerability with budesonide, the presence of advanced liver disease or portosystemic shunts poses a risk for corticosteroid-induced side effects as a result of altered hepatic clearance and increased systemic availability. For this reason budesonide is not suitable for patients with cirrhosis and concern also exists for its use in those with a severe presentation [Mederacke *et al.* 2012]. Furthermore, switching prednisolone to budesonide in individuals already established on the former can be problematic because of severe steroid withdrawal symptoms, and budesonide has proven ineffective as a salvage agent for steroid-refractory or steroid-dependent AIH [Czaja and Lindor, 2000]. Nevertheless budesonide in combination with azathioprine is emerging as a promising alternative for induction in treatment-naïve patients without cirrhosis with uncomplicated AIH and may be especially appropriate for those with obesity, metabolic bone disease, diabetes, hypertension or when concern exists over the cosmetic side effects of prednisolone.

Mycophenolate mofetil. Mycophenolate mofetil (MMF) is a potent immunosuppressive agent, although side effects include diarrhoea and bone marrow suppression, which may necessitate discontinuation in some patients [Hlivko *et al.* 2008]. In one small study, five of seven patients with AIH with persistently active inflammation and either intolerance or resistance to azathioprine who were treated with MMF achieved normal transaminases, a fall in hepatic activity index and required steroid dose within 3–9 months [Richardson *et al.* 2000]. However, results from a multicentre European study (n = 37) were more sobering, with MMF inducing a biochemical response in only 43% of cases, any benefit largely being restricted to patients intolerant of azathioprine [Hennes *et al.* 2008]. More favourable reports from Greece (n = 59) and the Netherlands (n = 45) found that 67–88% of patients taking MMF as an alternative to azathioprine achieved biochemical remission [Zachou *et al.* 2011; Baven-Pronk *et al.* 2011].

Furthermore, 37% in the former study achieved complete remission off prednisolone. Data from the paediatric population have also been encouraging [Aw *et al.* 2009]. MMF represents a possible alternative, although its role has largely been reserved for instances when patients are intolerant of azathioprine/6-mercaptopurine as opposed to being nonresponders. Of practical concern is its reported teratogenicity, which precludes use in women planning pregnancy.

Calcineurin inhibitors. Cyclosporine A (CyA) has been shown to be beneficial in inducing and maintaining remission, particularly for children with AIH [Alvarez *et al.* 1999; Sciveres *et al.* 2004; Cuarterolo *et al.* 2006]. The rapid onset of induction is a theoretical advantage over azathioprine, although relapses occur on dose reduction [Sherman *et al.* 1994; Jackson and Song, 1995]. Tacrolimus has greater immunosuppressive potency than CyA, and in one study the average AST fell in 11 patients with steroid-refractory AIH treated with tacrolimus with no related adverse events [Aqel *et al.* 2004]. Larsen and colleagues also observed a marked improvement in ALT, IgG as well as hepatic necro-inflammatory score in nine patients taking low-dose tacrolimus for steroid-refractory AIH [Larsen *et al.* 2007], whereas high rates of biochemical remission were recently reported in 12 of 13 patients from Virginia treated with tacrolimus [Tannous *et al.* 2011]. These preliminary findings suggest that tacrolimus is probably safe and offers promise to those whose condition is nonresponsive to standard therapy. However, longer-term follow up and safety data from larger studies are needed.

Other agents. Ursodeoxycholic acid (UDCA) has not been systematically evaluated in AIH, although in early trials patients did demonstrate a clinical and biochemical improvement [Czaja *et al.* 1999] with a reduction in histological inflammation. However, the severity of fibrosis was unaffected and UDCA did not permit a reduction in corticosteroid dose. A group from Denmark recently treated seven patients with AIH with everolimus and after 3–5 months, all had ALT levels less than 1.2 × ULN [Ytting and Larsen, 2011]. Cyclophosphamide has been evaluated in small case series and may prove useful as a salvage therapy for problematic patients [Kanzler *et al.* 1997]. Isolated case reports exist reporting responsiveness of AIH to rituximab [Santos *et al.* 2006] and the anti-tumour necrosis factor α (TNFα) agent etanercept [Goldenberg and Jorizzo, 2005]; however, infliximab and adalimumab have been reported to induce and exacerbate AIH [Subramaniam *et al.* 2011; Doyle *et al.* 2011]. Nevertheless, a marked biochemical and immunological response was observed in 11 patients with AIH (six with azathioprine intolerance or side effects and five with AIH refractory to conventional therapy) treated with infliximab, although infectious complications developed in over 63% from this group [Weiler-Normann *et al.* 2012]. Methotrexate may be effective as a steroid sparing agent, although given its potential hepatotoxicity and the efficacy of azathioprine, a widespread role has never materialized.

Therapy with regulatory T cells

The putative role of regulatory T cells (T_{reg}) in the pathogenesis of AIH [Longhi *et al.* 2004, 2007, 2011] represents an attractive target for immune intervention aimed at reconstituting self tolerance. However, treatment has the potential to fail if adoptively transferred T_{reg} are inhibited or trans differentiate into an effector pathway, although drugs that maintain T_{reg} differentiation may help facilitate functional stability [Goodyear *et al.* 2012]. Another important factor is whether T_{reg} therapy needs to be antigen specific [Peiseler *et al.* 2012], in which case treatment would currently only be possible in type II AIH when the antigen is known (CYP450IID6). Nevertheless the advent of cell-based therapy for AIH is being actively pursued by a number of groups.

Primary biliary cirrhosis

The median survival of untreated patients with PBC is approximately 9–10 years from presentation, with 26% developing liver failure during this time [Prince *et al.* 2002]. In the absence of effective therapy the median time to develop extensive fibrosis is around 2 years, with a probability of remaining in early stage disease being 29% over 4 years [Christensen *et al.* 1980; Locke *et al.* 1996; Corpechot *et al.* 2000]. Over recent years, UDCA has demonstrated consistent evidence in improving liver biochemistry in PBC, with patients also showing improved transplant-free and overall survival [Lindor *et al.* 1996]. The 4-year risk of developing varices is lower for UDCA-treated patients (16% *versus* 58%) [Lindor *et al.* 1997], and UDCA therapy is associated with a fivefold lower progression rate (7%) from early stage disease to extensive fibrosis/cirrhosis compared with placebo (35%) [Corpechot *et al.* 2000].

When evaluating the UDCA trial data, note must be taken of the treatment dose used because some earlier studies applied lower than optimal treatment paradigms [Gong *et al.* 2008]. In PBC a dose of 13–15 mg/kg/day has been shown to be superior to 5–7 mg/kg/day or 23–25 mg/kg/day [Angulo *et al.* 1999]. The Barcelona study was able to demonstrate that patients with PBC achieving an alkaline phosphatase (ALP) reduction of at least 40% from baseline 1 year after being started on UDCA therapy had a survival akin to that of the control population, and of 192 patients treated in their cohort, 61% demonstrated a biochemical improvement falling within these parameters ('UDCA responders'). Conversely, nonresponders were more likely to progress to liver transplantation (relative risk 7.47) [Parés *et al.* 2006]. The more recent 'Paris' criteria (ALP < 3 × ULN, AST< 2 × ULN and serum bilirubin<1 mg/dl after 1 year of UDCA therapy) have also been shown to predict a 10-year transplant-free survival of 90% (*versus* 51% in nonresponders), with patients being less well discriminated by the Barcelona criteria (79% *versus* 63%) [Corpechot *et al.* 2008]. Moreover, patients with stage I/II PBC achieving an AST and ALP less than 1.5 × ULN, and normal bilirubin 12 months after starting UDCA therapy had an outcome free of liver-related death, transplantation, progression to cirrhosis or liver failure [Corpechot *et al.* 2011]. These studies highlight that absence of a biochemical response to UDCA has clear prognostic implications, and additionally failure to respond biochemically is associated with histologic progression [Kumagi *et al.* 2010]. UDCA is widely used and shown to reduce mortality, adverse events and need for transplantation in PBC [Lee *et al.* 2007]. It is therefore advocated as first-line therapy [Lindor *et al.* 2009; Beuers *et al.* 2009].

Alternative and adjuvant therapies

Approximately one-third of patients with PBC may not respond to UDCA, remain at risk of progressive liver disease and are candidates for alternative therapy. The biochemical criteria provided by the Paris, Barcelona and related studies provide good correlation to long-term outcome for UDCA-treated patients and have been adopted by international bodies for assessing the efficacy of new treatments in PBC [Lindor *et al.* 2009; Beuers *et al.* 2009]. Although these criteria facilitate small-scale pilot studies of short duration, it remains unclear whether an improvement in liver biochemistry induced by agents other than UDCA has a true beneficial effect on PBC disease progression. An additional group to target are perhaps those with disease-specific antinuclear antibody (e.g. anti-gp210, anti-centromere) reactivity patterns [Bogdanos and Komorowski, 2011], individuals who are highly fatigued [Jones *et al.* 2010], patients with the rare premature ductopenic variant of PBC [Vleggaar *et al.* 2001] and those with interface hepatitis, as these also represent subgroups of patients with a poorer outcome, even when considering UDCA response.

Corticosteroids. In patients with PBC with 'florid' interface hepatitis on biopsy, there are anecdotal data demonstrating the efficacy of budesonide in improving liver histology and biochemistry when used in combination with UDCA [Chazouilleres *et al.* 2006; Poupon, 2011; Rautiainen *et al.* 2005; Rabahi *et al.* 2010; Leuschner *et al.* 1999]; the premise is in part a reflection of the association between AST and interface hepatitis with disease progression in PBC. Many of these studies are not yet supported by well controlled trials, and have been of too short duration to show any real survival benefit. However, it should be noted that transaminitis in PBC may in part be a feature of hepatocyte injury from the effects of cholestasis. Of note, portal vein thrombosis has been reported as a complication in up to 29% of patients with advanced liver fibrosis [Hempfling *et al.* 2003], precluding budesonide use in patients with cirrhosis. Due to concerns over side effects, evidence supporting the benefit of prednisolone is lacking, and although some restitution in serum and histological markers of liver inflammation has been documented [Mitchison *et al.* 1992], these findings have not translated into improved patient outcomes.

Colchicine. Colchicine has a historical role in the treatment of PBC and several double-blind prospective trials have found that colchicine decreased serum ALP, ALT and AST, although not as effectively as UDCA [Kaplan *et al.* 1986; Vuoristo *et al.* 1995]. The addition of colchicine to UDCA has also been reported to improve liver histological necroinflammatory score over a 10-year follow up but with little/no effect on histological stage or predicted patient survival [Almasio *et al.* 2000; Kaplan *et al.* 2004; Leung *et al.* 2011]. In many of these preliminary studies, patients were not receiving the optimum dose of UDCA, thus making it difficult to draw firm conclusions regarding the true efficacy of combination therapy.

Fibric acid derivates. The first studies to evaluate the use of fibrates for PBC appeared in Japanese journals in the late 1990s. Broadly speaking, a normalization of serum ALP has been observed in around 45% of UDCA nonresponders with the addition of a fibric acid derivative (*versus* ~18% taking placebo) [Kanda *et al.* 2003]. A recent prospective multicentre study ($n = 66$) demonstrated that bezafibrate monotherapy was at least as effective as UDCA in improving biochemical indices in PBC, whereas combination fibrate/UDCA therapy was effective in improving and maintaining normal biliary enzymes when the ineffectiveness of UDCA monotherapy was confirmed [Iwasaki *et al.* 2008]. These positive results have been replicated in numerous other pilot studies [Ohira *et al.* 2002; Levy *et al.* 2011]. Despite improving surrogate markers of long-term prognosis, the depth of evidence supporting fibrates in PBC remains small, with many trials employing undefined biochemical endpoints as a measure of treatment success, and only a few applying standardized criteria with relatively short duration (<1 year). The effects on histological progression are also unclear; some studies reporting improvement whereas others a deterioration [Yano *et al.* 2002; Kurihara *et al.* 2002]. Given that preliminary data have been promising, further studies should be encouraged. Of note, in the authors' experience, use of fenofibrate in patients with advanced PBC (jaundice) was not associated with benefit.

Other drugs. A number of studies have evaluated methotrexate as an immunomodulatory treatment, although in most the number of patients assessed was too small and trial duration too short to draw any firm conclusions. The largest ($n = 265$) randomized controlled trial (methotrexate/UDCA *versus* UDCA alone) did not find any significant differences in the rates of transplantation, transplantation-free survival, development of hepatic decompensation, biochemical deterioration or histological progression over a median study time of 7.6 years [Combes *et al.* 2005]. Azathioprine has very little effect on improving serum liver biochemistry or hepatic histology in PBC [Heathcote *et al.* 1976; Wolfhagen *et al.* 1998] and although early trials suggested a tendency toward improved survival [Christensen *et al.* 1985], this failed to reach statistical significance. Randomized trials have shown that cyclosporine had some effect on slowing biochemical and histological progression [Wiesner *et al.* 1990; Lombard *et al.* 1993]. Due to an increased rate of side effects, there has been little enthusiasm for further study on this drug, although it may protect against recurrent PBC post transplant, a complex area some relate to its potential antiviral properties [Neuberger *et al.* 2004]. Studies of MMF in addition to UDCA have not yielded beneficial results, although 6 of 15 UDCA nonresponders treated with the addition of budesonide and MMF had normalized liver biochemistry with the remainder achieving partial resolution. Histological activity and fibrosis were markedly improved in all patients [Rabahi *et al.* 2010]. Antiretroviral therapy (combivir) has also been trialled, largely stemming from the proposed viral aetiology of PBC [Mason, 2011]. Preliminary results have been mixed, although some patients did demonstrate minor improvements in hepatic biochemistry, symptoms and histological features [Mason *et al.* 2004, 2008]. A recent pilot study ($n = 6$) demonstrated an improvement in IgM titre and an increase in intrahepatic regulatory T-cell number using the anti-CD20 antibody rituximab [Tsuda *et al.* 2012]. Copper chelation therapies (D-pencillamine, tetrahydromolybdate), silymarin, moexipril or atorvastatin have not been shown to be effective in PBC.

Future therapeutic prospects

Farnesoid-X-receptor agonists. Farnesoid X receptor (FXR) is a nuclear receptor expressed at high levels in the liver and intestine. One of the primary functions of FXR activation is the suppression of cholesterol 7α hydroxylase-1 (CYP7A1), the rate-limiting enzyme in the synthesis of bile acids from cholesterol. Obeticholic acid (OCA) is a primary agonist for FXR and evidence from animal models supports the role of such agents in protecting the liver from cholestatic injury [Fiorucci *et al.* 2005; Modica *et al.* 2012]. Phase II clinical studies in PBC have recently reported that OCA significantly lowered ALP by around 40% compared with placebo (21–24.7% *versus* 7%) in UDCA nonresponders; however, some patients had to stop therapy due to severe pruritus [Mason *et al.* 2010; Kowdley *et al.* 2011]. A multicentre phase III trial is currently underway. Given the promising results thus far, exploring the therapeutic potential of manipulating other nuclear receptors involved in bile salt metabolism (e.g. liver X receptor, vitamin D receptor) may also prove beneficial in PBC.

Molecular therapies. A number of novel molecular therapies are also currently undergoing

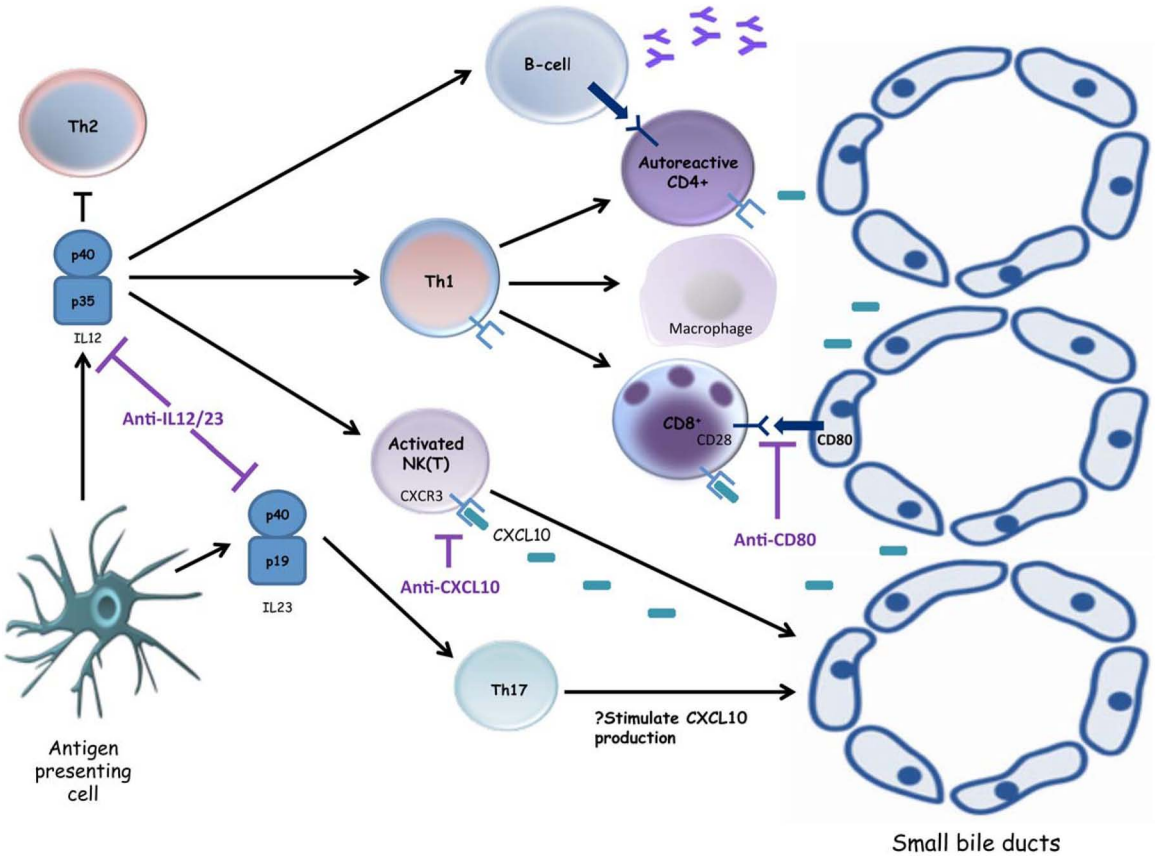

Figure 3. Emerging small-molecule inhibitors in primary biliary cirrhosis. Interleukin (IL)-12 secretion by an activated antigen presenting cell leads to natural killer (NK) cytotoxicity, macrophage activation and T helper 1 (Th1) differentiation, with subsequent activation of cytotoxic $CD8^+$ T cells as well as antibody-secreting B cells, all of which potentiate the destruction of cholangiocytes. The p40 subunit of IL12 is also a component of IL23, an essential cytokine for the differentiation of Th17 cells. Targeting the p40 subunit has been shown to ameliorate experimental immune-mediated cholangiopathy, and it is hoped these promising results can be translated into clinical practice. The immune-mediated destruction of small-sized bile ducts in primary biliary cirrhosis (PBC) is predominantly cell mediated, characterized by Th1 cells, $CD8^+$ T cells, NK cells and NKT cells which express CXCR3. Neutralizing antibodies to CXCL10, a ligand for CXCR3, may offer the possibility to interfere with one of the key inflammatory processes contributing to immune-mediated biliary destruction in PBC. Blockade of costimulatory signals between T cells expressing CD28 and antigen-presenting cells expressing CD80 (e.g. cholangiocytes, antibody-secreting B cells) could also represent an important approach for the treatment of autoimmune diseases.

clinical trials in PBC (Figure 3), having arisen as our understanding of disease aetiopathogenesis improves [Trivedi and Cullen, 2012].

CXCL10 monoclonal antibodies. In PBC, liver-infiltrating $CD8^+$ T cells, T helper 1 cells and natural killer cells express the chemokine receptor CXCR3, and murine models have demonstrated that knockout of CXCR3 results in amelioration of hepatic disease [Zhang *et al.* 2011]. One of the natural ligands for CXCR3 is the chemokine CXCL10, which is induced in damaged bile ducts and elevated in the serum of patients with PBC, with levels increasing as disease progresses [Chuang *et al.* 2005]. Anti-CXCL10 antibodies have also been shown to ameliorate lymphocyte-mediated damage and dramatically reduce liver fibrosis [Hintermann *et al.* 2010] thus may offer the possibility to interfere with one of the key inflammatory processes contributing to disease pathogenesis in PBC. A multicentre phase II trial using an anti-CXCL10 monoclonal antibody in PBC is currently in progress.

Anti-interleukin 12/interleukin 23. Interleukin (IL)-12 and IL23 are heterodimeric cytokines,

sharing the p40 subunit, and play critical roles in linking innate and adaptive immune responses [Lleo *et al.* 2012]. Genome-wide association studies (GWAS) have identified components of the IL12 signalling pathway as potential players in the effector mechanisms leading to biliary destruction in PBC [Hirschfield *et al.* 2009], and deletion of the p40 subunit of IL12 in mouse models has been shown to modify murine autoimmune cholangiopathy [Yoshida *et al.* 2009]. A human monoclonal antibody directed against IL12/IL23 has shown success in the treatment of psoriasis and Crohn's disease [Sandborn *et al.* 2008], and a phase II study in PBC has begun recruiting.

Anti-CD80. Polymorphisms in CD80 have been identified as conferring an increased susceptibility to PBC in a recent UK GWAS [Mells *et al.* 2011]. CD80 and CD86 represent potent costimulatory signals for T-cell activation and are, for example, expressed on small-duct cholangiocytes in PBC. This interaction confers an increased susceptibility to apoptosis and is also involved in activation of the nuclear factor κB pathway, which modulates the balance of survival and apoptosis in activated hepatic stellate cells. Blockade of costimulation between T cells and antigen-presenting cells through CD80 could represent an important therapeutic approach for the treatment of PBC and a phase II trial of an oral anti-CD80 agent has been proposed.

Primary sclerosing cholangitis

Up to 44% of patients with PSC may be asymptomatic at presentation, being diagnosed following the detection of cholestatic liver biochemistry in the context of pre-existing IBD [Broomé *et al.* 1996]. In some patients with previously stable disease can rapidly progress following the development of septic biliary complications (recurrent ascending cholangitis) due to impeded biliary drainage. Dominant strictures (DSt) are the principal cause of such complications, with 11.7–35.9% of patients with PSC presenting with DSt at diagnosis [Gotthardt *et al.* 2010]. Improved transplant-free survival may be achieved when endoscopic biliary or surgical intervention is performed [Gotthardt *et al.* 2010; Tsai and Pawlik, 2009]; however, given a paucity of randomized controlled trials in the area, the optimal approach for treating DSt remains unclear and the mainstay of treatment in PSC remains largely pharmacological. However, as the pathogenesis remains largely undefined, a causal therapeutic approach has yet to be developed and no currently identified medical treatment has been consistently shown to improve outcome free of liver transplantation in PSC.

The mean time from diagnosis to death/liver transplantation ranges from 9.6 to 12 years, whereas there also lies a 10–15% lifetime risk of cholangiocarcinoma (CCA) [Broomé *et al.* 1996; Ponsioen *et al.* 2002], the risk being greatest in patients with a dominant stricture (>25%) [Chapman *et al.* 2012]. Furthermore, up to 5% of patients develop CCA within 12 months of PSC diagnosis [Bergquist *et al.* 1998, 2002; Tischendorf *et al.* 2007]. 'Small-duct PSC' has a considerably better outcome than the classical form, with a longer transplant-free and overall survival (29 years *versus* 17 years) [Björnsson *et al.* 2002, 2008; Broomé *et al.* 2002; Angulo *et al.* 2002]. Although these patients do not develop CCA, approximately 28% progress to the large duct variant over a median of 7.4 years.

Patients with PSC with IBD (>75%) appear to have a shorter transplant-free and overall survival, as well as an increased risk of CCA compared with patients without IBD [Trivedi and Chapman 2012]. IBD is diagnosed at least 1 year before PSC, more often among patients with CCA (90%) compared with those without (65%), and the duration of IBD before diagnosis of PSC is also significantly longer in patients who develop CCA (17.4 years *versus* 9.0 years) [Boberg *et al.* 2002]. In a 20-year prospective follow up of 171 patients with PSC, all who developed CCA in the context of DSt had evidence of concurrent IBD, whereas no CCA was found in patients with PSC without IBD. The 18-year transplant-free survival for those with IBD was also considerably lower than those without (23% *versus* 77.8%) [Rudolph *et al.* 2010].

Identifying endpoints of therapy

Adverse endpoints like malignancy, death or transplantation are impractical for evaluating new therapies in PSC given the long duration of disease. Moreover, the heterogeneity of PSC makes accurate patient selection and stratification for clinical trials difficult, particularly with regard to cholangiographic pattern of disease, the presence and influence of coexisting IBD, and in those having overlapping features with AIH/IgG4-associated cholangitis.

Despite there being some evidence that patients who achieve (and sustain) a completely normal serum ALP have a good prognosis [Stanich *et al.* 2011], there has historically been little support to the notion that merely improving liver biochemistry translates into better long-term clinical outcome in PSC. However, this paradigm has recently been challenged following the publication of a study by Al-Mamari and colleagues ($n = 139$) in which patients who attained a reduction in serum ALP up to 1.5 × ULN over 24 months were observed to have a significantly better outcome than individuals with a persistently elevated ALP [Al-Mamari *et al.* 2012]. In this observational study, biochemical improvement within these parameters was achieved by 40% of patients over a median of 2 years, of which only 6% ($n = 3$) of individuals developed a clinical endpoint (hepatic decompensation or liver transplantation) *versus* 38% in the group without an ALP reduction ($p < 0.0001$). The end point free survival was also significantly longer in patients with an ALP improvement ($p < 0.0001$). Moreover, no patient in the group achieving an ALP less than 1.5 × ULN developed CCA or liver-related death *versus* 15% and 23% ($p = 0.002$) respectively in the group with persistently raised ALP. Similar results were observed in a population of 198 patients from Sweden in which a reduction in serum ALP by 40% from baseline was found to correlate with better long-term patient survival [Lindström *et al.* 2012a]. In both of these studies, improvement in serum ALP within the aforementioned parameters identified patients more likely to experience a benign clinical outcome irrespective of whether ALP reduction was achieved whilst taking UDCA or off therapy. Taken together, these findings may help in the design of future clinical trials, provided the results can be validated by other centres.

Ursodeoxycholic acid

Numerous studies have endeavoured to address the efficacy of UDCA in PSC; however, due to relatively small patient numbers, suboptimal doses and short follow-up periods, results have been inconsistent. Most demonstrated some improvement in liver biochemistry [Poropat *et al.* 2011; Harnois *et al.* 2001; O'Brien *et al.* 1991; Lindor 1997; van Hoogstraten *et al.* 1998], but few suggest an improvement in histological features [Mitchell *et al.* 2001; Beuers *et al.* 1992; Stiehl *et al.* 1994; Cullen *et al.* 2008]. Some data also point to an improvement in the cholangiographic appearances of PSC [Mitchell *et al.* 2001], degree of liver fibrosis [Mitchell *et al.* 2001; Cullen *et al.* 2008] and survival [Cullen *et al.* 2008; Olsson *et al.* 2005]. Enrichment of bile with UDCA is dose dependant, reaching a plateau between 22 and 25 mg/kg/day. Higher doses (28–30 mg/kg/day), although associated with improvements in liver biochemistry, appear to confer harm to patients, with greater numbers developing endpoints including death and transplantation [Lindor *et al.* 2009; Imam *et al.* 2011]. This may be due to larger quantities of unabsorbed UDCA entering the colon, being subsequently modified to hepatotoxic bile acids or perhaps the antiapoptotic activity of UDCA preventing apoptosis of activated stellate cells, thereby promoting fibrogenesis [Lindor *et al.* 2009; Benedetti *et al.* 1997; Fickert *et al.* 2002]. In sum, the available data suggest that UDCA at doses of 17–20 mg/kg/day improves liver biochemistry, although transplant-free survival does not appear to be affected [Triantos *et al.* 2011], with higher doses leading to adverse consequences. Therefore, it is quite reasonable to not prescribe UDCA to patients with PSC.

Ursodeoxycholic acid and chemoprevention

Nontreatment with UDCA has previously been identified as an independent predictor of hepatobiliary malignancy in PSC [Brandsaeter *et al.* 2004]; however, actual benefit is difficult to demonstrate as around 50% of CCA occur within the first year after diagnosis of PSC. One randomized controlled trial did not find any significant difference comparing UDCA with placebo over a 5-year period [Olsson *et al.* 2005], although conflicting results were obtained from a German study in which no cases of CCA were detectable in 150 patients with PSC taking UDCA for longer than 8 years [Rudolph *et al.* 2007].

The estimated risk of colorectal cancer in patients with PSC with ulcerative colitis is approximately 30% over 20 years, despite colitis activity being quiescent in most [Trivedi and Chapman 2012]. Several studies have found a significantly reduced prevalence of colonic dysplasia in patients taking 'standard-dose' UDCA [Pardi *et al.* 2003]. Although some describe this chemoprotective effect as being relatively modest [Wolf *et al.* 2005], the cumulative mortality did appear better

in those taking UDCA. However, a recently published follow-up study to a clinical trial of UDCA (17–23 mg/kg/day) in PSC reported no difference in the frequency of colorectal dysplasia, cancer or dysplasia/cancer-free survival over a 5-year period [Lindström *et al.* 2012b]. Moreover a study from the Mayo Clinic found a greater association of colonic dysplasia in patients with PSC/IBD taking UDCA compared with those receiving placebo (hazard ratio 4.44) [Eaton *et al.* 2011], although these patients were receiving high doses (28–30 mg/kg/day).

Immunosuppression

A host of immunomodulatory agents have been evaluated in PSC. Although they may induce an improvement in biochemical indices, these therapies have proven largely disappointing and fail to slow disease progression or improve prognosis, with the possible exception of carefully selected patients having overlapping features with AIH [Trivedi and Hirschfield, 2012]. Moreover, in individuals with suspected PSC and markedly elevated serum IgG4 levels, or an IgG4-positive plasma cell infiltrate evident histologically, treatment with corticosteroids may be considered [Webster *et al.* 2009]. In such a situation, the diagnosis of PSC should be questioned since an autoimmune cholangiopathy might be present. A form of sclerosing cholangitis associated with florid autoimmune features has also been described in children [Gregorio *et al.* 2001], where despite the parenchymal liver damage responding well to immunosuppression, biliary disease progresses in around 50% of patients.

Antibiotics

In advanced stages of PSC, patients have recurrent episodes of bacterial cholangiosepsis which itself can lead to disease progression. Such patients may benefit from prophylactic antibiotics whereas other approaches have sought to identify their efficacy longer term. Metronidazole together with UDCA (compared with UDCA alone) was shown to significantly improve serum ALP in PSC; however, an impact on liver histology or cholangiography was not found to be statistically significant in a randomized controlled study of 80 patients conducted over 36 months [Farkkila *et al.* 2004]. Similar results have been found using minocycline [Silveira *et al.* 2009]. A paediatric study (n = 14) evaluating the efficacy of vancomycin also found an improvement in biochemical parameters as well as symptom profile after 2 months of therapy [Davies *et al.* 2008]. This was particularly marked in patients without cirrhosis.

Emerging therapeutic candidates

24-norUrsodeoxycholic acid. 24-norUrsodeoxycholic acid (norUDCA) is the C23-homologue of UDCA, largely being secreted in an unchanged or glucuronidated form. Because of cholehepatic shunting, norUDCA increases the flow of a bicarbonate-rich choleresis. In animal models of PSC, norUDCA has been shown to exhibit anti-inflammatory, antifibrotic and antiproliferative effects, increasing the hydrophilicity of biliary bile acids whilst stimulating bile flow [Fickert *et al.* 2006]. These encouraging results can hopefully be extrapolated to human PSC and clinical trials are currently being planned.

Adhesion molecule/chemokine manipulation. In adults, the liver and gut have distinct endothelial phenotypes whereby vascular adhesion protein 1 (VAP-1) expressed on hepatic sinusoids is implicated in lymphocyte recruitment to the liver, and similarly mucosal addressin cell adhesion molecule 1 (MAdCAM-1) and the chemokine CCL25 are expressed on intestinal mucosal vessels where they are involved in the recruitment of lymphocytes expressing the integrin $\alpha4\beta7$ and chemokine receptor CCR9. However, VAP-1 expression becomes induced on mesenteric vessels in IBD, whereas MAdCAM-1 and CCL25 are increased on hepatic endothelium in PSC where they support the recruitment and adhesion of $\alpha4\beta7^{hi}CCR9^{+}$ intestinal mucosal lymphocytes [Adams *et al.* 2008]. As well as being an adhesion molecule, VAP-1 is an enzyme possessing amine oxidase activity, and deamination of the dietary constituent methylamine by VAP-1 has been recently shown to induce the expression of functional MAdCAM-1 on hepatic endothelium in the presence of TNFα [Liaskou *et al.* 2011]. Although trials of anti-TNFα therapy did not show benefit in treating patients with PSC, the availability of enzyme inhibitors and neutralizing antibodies against VAP-1 are potentially attractive as future therapeutic agents. Monoclonal antibodies targeting $\alpha4\beta7$, MAdCAM-1 and CCR9, which are currently undergoing clinical trials in IBD, may also represent potential for future treatment in PSC (Figure 4).

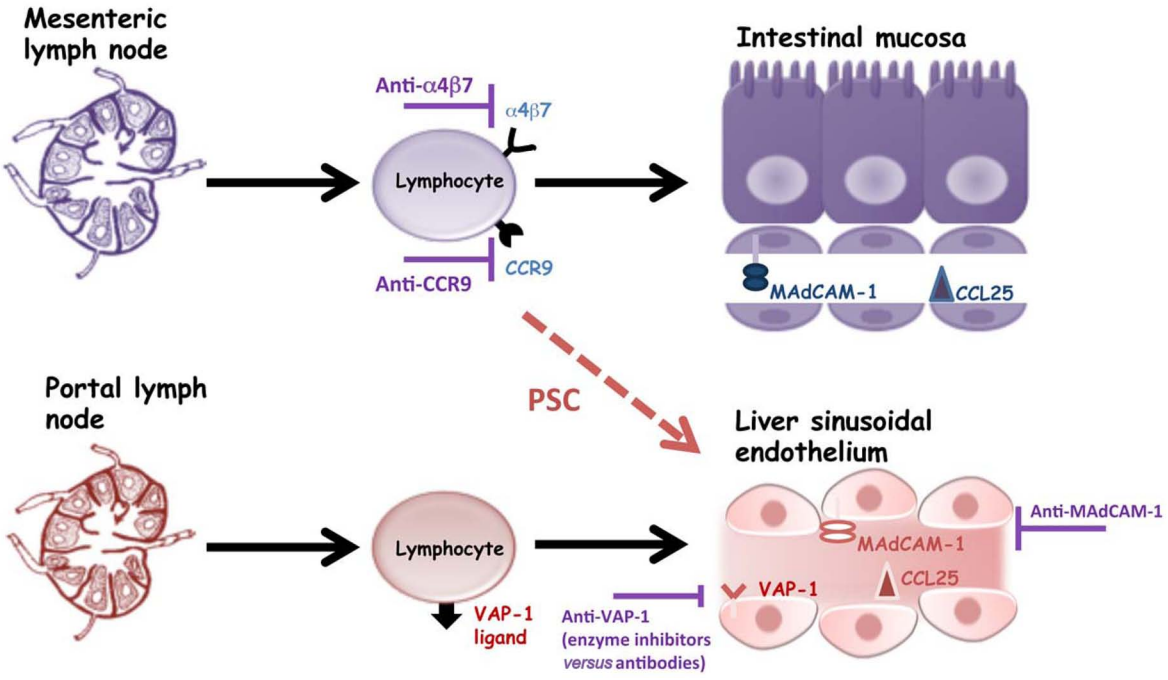

Figure 4. Therapeutic manipulation of adhesion molecules in primary sclerosing cholangitis (PSC). In PSC, hepatic vascular adhesion protein 1 (VAP-1) expression is upregulated and its inherent enzymatic properties enable the generation of mucosal addressin cell adhesion molecule 1 (MAdCAM-1) on liver sinusoidal endothelium. Hepatic CCL25 expression is also upregulated in the PSC liver, although the reasons for this are unclear. The end result is that lymphocytes that have been generated to recognize gut antigens in the setting of inflammatory bowel disease are now misdirected to the liver where they contribute to inflammation and biliary destruction. There are now several available agents targeting these adhesion molecule and chemokine interactions which may represent viable therapeutic options for investigation in PSC.

Other agents. The antiproliferative effects of sirolimus were recently shown to improve liver fibrosis and inflammation in bile duct ligated rats [Patsenker *et al.* 2011] and represent an avenue to be explored further in human studies. In *cftr*$^{-/-}$ knockout mice, supplementation of the fatty acid docosahexaenoic acid (DHA) was shown to reverse the development of bile duct injury. In a recent pilot study (n = 23) the mean ALP significantly improved after 12 months of DHA treatment [Martin *et al.* 2012]. Fibric acid derivates stimulate biliary phospholipid secretion via the peroxisome proliferator-activated receptor α–multi-drug resistance protein 3 (MDR3) pathway and may also represent putative therapeutic agents in carefully selected patients [Kita *et al.* 2002].

Conclusion

When managing patients with autoimmune liver disease, a long-term, longitudinal approach to care must be adopted that focuses on clarity, accuracy and rationale for intervention. In the majority of patients with AIH and PBC, remission can be obtained with currently available pharmacotherapy yielding a favourable patient outcome. However, in one-third of patients with PBC and the majority of those with PSC there exists a shortfall of available medical therapies. This void may hopefully be overcome with the advent of molecular-targeted agents. However, the slow natural history exhibited by these diseases and the fact that patients are being diagnosed at a much earlier stage represents a clinical hurdle when choosing surrogate endpoints for clinical studies.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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