

Current status of therapy in autoimmune liver disease

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Abstract: Therapeutic strategies for autoimmune liver diseases are increasingly established. Although proportionately uncommon, specialist centers have with time refined the best approaches for each disease, based on an improved understanding of the spectrum of presentation. The major treatment aims are to prevent end-stage liver disease and its associated complications. As a result of drugs such as ursodeoxycholic acid, predniso(lo)ne and azathioprine, both primary biliary cirrhosis and autoimmune hepatitis are now less commonly indications for liver transplantation. Unfortunately, the same inroads in treatment efficacy have as yet not been made for primary sclerosing cholangitis, although the recognition that a subset of patients may have a treatable secondary sclerosing cholangitis (IgG4 related) is helping a proportion. With better biological understanding, more specific interventions are expected that will benefit all those with autoimmune liver diseases.

Keywords: autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, secondary sclerosing cholangitis, autoimmune pancreatitis

Introduction

Autoimmune liver diseases are chronic inflammatory processes in which an immunological attack is directed against hepatocytes and/or the biliary epithelium [Kumagi *et al.* 2008]. Table 1 illustrates the presently recognized common disease divisions. Such divisions may be artificial since broadly it is suggested that 10% of those with primary biliary cirrhosis (PBC) will have features of autoimmune hepatitis (AIH) [Chazouilleres *et al.* 1998; Czaja, 1998], 10% of adults with AIH have radiological evidence for sclerosing cholangitis (SC) [Abdalian *et al.* 2008] and a similar number of those with primary sclerosing cholangitis (PSC) will have histological evidence of AIH [van Buuren *et al.* 2000]. The rate of overlap seems higher in children with AIH, in whom 50% will have sclerosing cholangitis on endoscopic retrograde cholangiopancreatography (ERCP) [Gregorio *et al.* 2001].

The diseases reflect a balance of environmental and genetic factors [Weismuller *et al.* 2008; Mackay, 2007] and whilst broadly autoimmune in etiology, both immune and nonimmune pathways are likely involved in tissue damage.

Once the balance is tipped towards tissue destruction a chronic process ensues and clinicians are now well placed to modify disease by direct immunosuppression (e.g. predniso(lo)ne/azathioprine) or indirect modification to the bile acid milieu (e.g. ursodeoxycholic acid [UDCA]). These diseases are uncommon, may progress slowly, and are recognized now to have a broad spectrum of presentation. Together these make clinical trial design and interpretation harder but herein we review the basis for the use of disease-modifying agents. Symptom control is covered more fully elsewhere [Hirschfield *et al.* 2008] and similarly the management of the poorly defined autoimmune overlap syndromes is also not detailed [Rust and Beuers, 2008].

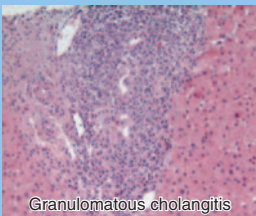
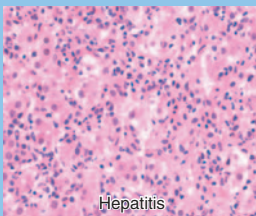


Autoimmune hepatitis

AIH is a chronic and relapsing necroinflammatory hepatitis accompanied by elevated immunoglobulins and autoantibodies that help serological classification [Krawitt, 2006; Manns and Vogel, 2006; Czaja and Freese, 2002]. Type 1 disease is associated with nonspecific antinuclear and/or antismooth muscle antibodies, occurs across all

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Table 1. Summary of pertinent features of autoimmune liver disease.

	Primary biliary cirrhosis	Autoimmune hepatitis	Primary sclerosing cholangitis	IgG4 associated autoimmune pancreatitis/sclerosing cholangitis
Examples of presentation	Asymptomatic cholestasis, fatigue/pruritus	Asymptomatic transaminitis, jaundice, arthralgia	Asymptomatic cholangitis, abdominal pain	Diabetes, jaundice, pancreatic mass, fleeting cholangiopathy
Specific investigations	Anti-mitochondrial antibodies (M2 fraction); liver biopsy showing active granulomatous duct lesions	Raised globulins; autoantibodies (ANA/SMA/LKM); liver biopsy showing interface hepatitis and lymphoplasmacytic infiltrate	Cholangiography; liver biopsy showing periductal sclerosis	Elevated IgG4 levels; pancreatic imaging changes; cholangiopathy; retroperitoneal fibrosis
Typical histological or radiological appearance	 Granulomatous cholangitis	 Hepatitis	 Periductal sclerosis	 Sclerosing cholangitis
Untreated natural history	Stable disease in some; progressive portal hypertension and/or chronic liver failure	Mild disease in some; liver failure (acute or chronic with portal hypertension)	Cholangitis; portal hypertension; biliary cirrhosis, portal hypertension and liver failure	Relapsing and remitting course; chronic pancreatitis; secondary biliary cirrhosis
Specific medical intervention	Ursodeoxycholic acid 13–15mg/kg/d	Prednisone (20–40 mg/d) and azathioprine (1–2 mg/kg/d)	Consider high dose (25–30 mg/kg/d) ursodeoxycholic acid but evidence lacking	Prednisone (20–40 mg/d) largely successful with optimal treatment to be defined

ages, in women more so than men, and associates in Caucasians with HLA-DR3 (DRB1*0301) and DR4 (DRB1*0401). Patients with the DRB1*0301 allele tend to be younger, with more severe relapsing disease and have a greater chance of treatment failure. Type 2 AIH, representing less than 10% of all AIH, is defined by the presence of specific liver–kidney microsomal antibodies, occurs more frequently in Europe and South America, and nearly always presents in childhood, often with more severe disease. As a diagnosis of exclusion the mimics of disease are important to consider before starting immunosuppression. Viral hepatitis must be ruled out but the other notable conditions include Wilson disease [Milkiewicz *et al.* 2000], alpha-1-antitrypsin deficiency [Lok *et al.* 1994] and drug-induced hepatitis [Liu and Kaplowitz, 2002]. Drug injury can replicate all features of AIH (Table 2) and stopping the offending medication usually, but not always, suffices in management.

Table 2. Drugs implicated in precipitating an autoimmune-like hepatitis.

Dihydralazine, halothane, indomethacin, interferon alpha, methyldopa, minocycline, miscellaneous herbal supplements, nitrofurantoin, orlistat, ramipril, statins, terbinafine, tumor necrosis factor alpha inhibitors

There is a wide spectrum of presentation from acute liver failure (rare; <10% of all acute liver failure), all the way through to asymptomatic transaminitis (perhaps 30–35% of cases) [Werner *et al.* 2008; Feld *et al.* 2005; Kogan *et al.* 2002]. One-third of patients can expect to be cirrhotic at presentation, yet decompensated disease can favourably respond to treatment, assuming active inflammation remains. It is now recognized that one in five adults who develop disease are over 60: treatment, the rate of remission and relapse being similar

[Al-Chalabi *et al.* 2006; Czaja and Carpenter, 2006]. Importantly the clinical presentation, disease behavior and treatment vary between racial groups. Black Americans, especially men, can have aggressive disease at presentation, are less likely to respond to conventional immunosuppressive therapy and have a higher mortality. As well they are younger and more likely to have a cholestatic variant of disease, which is not steroid responsive [Verma *et al.* 2007; D'Souza *et al.* 2005; Zolfino *et al.* 2002; Lim *et al.* 2001].

A number of scoring systems may help arrive at a diagnosis, although historically these originated for research, and are not prognostic [Alvarez *et al.* 1999]. The latest collaborative scoring system is appealing as it focuses on just autoantibodies, immunoglobulins, histology and exclusion of viral hepatitis [Hennes *et al.* 2008]. Liver biopsy is essential (assuming an appropriately sized biopsy), as biochemical markers need not correlate with histological severity. Despite this the classical features of a plasma cell infiltrate invading the limiting plate are not specific.

Immunosuppressive therapy in AIH

The major trials evaluating immunosuppressive therapy in AIH are relatively old, and focus on treating advanced disease. Since clinicians face treatment conundrums for patients with less advanced disease this does result in gaps in our knowledge. The studies nevertheless critically demonstrated that prednisone alone or in combination with azathioprine improved symptoms, laboratory tests, histologic findings and survival [Murray-Lyon *et al.* 1973; Soloway *et al.* 1972; Cook *et al.* 1971]. Importantly the trials do not demonstrate azathioprine monotherapy to be effective in inducing remission; its role is in maintenance therapy. Once remission has been obtained, the introduction of azathioprine permits the dose of corticosteroids to be reduced [Summerskill *et al.* 1975]. In one trial, azathioprine (75 mg/day) was stopped and prednisolone continued at a maintenance dose of 5–12.5 mg/day. The probability of relapse within three years was 32% in patients who stopped azathioprine compared with 6% in those who continued combination therapy [Stellon *et al.* 1985]. In a further study, patients were randomized to high dose azathioprine (2 mg/kg/day) after withdrawal of prednisolone or continued combination therapy (prednisolone 5–10 mg/day and azathioprine 1 mg/kg/day). There were no significant

differences between the two groups and no patient relapsed on azathioprine alone at one-year follow up [Stellon *et al.* 1988]. Biochemical and histological remission was subsequently sustained in 83% of patients on azathioprine over the longer term [Johnson *et al.* 1995].

Who and how to treat AIH

The absolute indications for treatment are based on the original studies of symptomatic patients and remain (1) serum aspartate aminotransferase (AST) greater than ten times upper normal, or (2) an AST greater than five-fold elevated with a greater than two-fold elevation in IgG, or (3) histological evidence of bridging or multiacinar necrosis. These criteria represent a severe end of the disease spectrum, in which untreated patients have a mortality of 40% within six months and ten-year survival of only 27% [Czaja and Freese, 2002; Soloway *et al.* 1972]. The absence of fibrosis or cirrhosis is not a relevant guiding factor. Patients outside such criteria are clearly still appropriate to treat but individual judgment is exercised, and a composite assessment made of symptoms, liver biochemistry and histology. The older literature suggests those with mild interface hepatitis have a normal five-year survival and a five-year progression to cirrhosis of around 20%, whilst mild-to-moderate laboratory abnormalities are associated with cirrhosis in 49% within 15 years but a ten-year survival of 90% [De Groote *et al.* 1978; Schalm *et al.* 1977; Baggenstoss *et al.* 1972]. Just as the magnitude of biochemical changes do not correlate with histological injury, nor is there any distinguishing feature between those with and without symptoms [Kogan *et al.* 2002]. The hope of treating more mild disease is to prevent progression of disease and cirrhosis because corticosteroids may prevent and reverse fibrosis [Czaja and Carpenter, 2004; Dufour *et al.* 1997] although this may not necessarily always be borne out [Roberts *et al.* 1996]. Not treating may also be valid: retrospectively in our practice, asymptomatic patients had lower serum aminotransferase, total bilirubin and IgG at baseline and half received no therapy and their survival was no different to those with symptoms [Feld *et al.* 2005]. Patients with an inactive cirrhosis are not candidates for medical therapy and in those progressing rapidly to acute liver failure transplantation is usually more appropriate than steroids [Ichai *et al.* 2007].

Two general approaches evolved: (1) prednisone monotherapy; and (2) combination therapy, either from the outset, or with addition of azathioprine (or 6-mercaptopurine if preferred) later (Table 3). Both strategies work but most clinicians now use a combination approach, since this is associated with a lower occurrence of corticosteroid-related side effects (10% *vs* 44%) [Summerskill *et al.* 1975]. These two agents clearly have side effects (Table 4) and the monitoring of patients is well established [Czaja, 2008]. UDCA has been used for patients with mild disease in Japan, but this is not widely practiced elsewhere [Nakamura *et al.* 1998].

Response to immunosuppression therapy is assessed clinically, biochemically and by histology. In general a biochemical response (a decrease in serum aminotransferase and globulins), occurs within one to three months. A complete biochemical response is the aim, and a failure to see this

should always lead to reappraisal (assuming compliance). Remission is considered normalization of transaminases, IgG, and histological activity and around two-thirds of patients will enter remission within 18 months and nearly 90% will achieve this after 3 years of treatment [Czaja *et al.* 1984, 1983; Soloway *et al.* 1972]. Histological remission lags behind clinical and biochemical remission by three to six months explaining prolonged maintenance therapy and the use of histology by some as the final endpoint. In general, patients with mild or asymptomatic disease have better responses, although patients with established cirrhosis at presentation, can achieve remission successfully with a ten-year life expectancy of at least 90% [Roberts *et al.* 1996]; almost all require life-long therapy as treatment withdrawal invariably leads to relapse in this context.

With remission, tapering of immunosuppression is appropriate; for example, if by two to three

Table 3. Broad overview of initial regimens for treating autoimmune hepatitis.

	High-dose monotherapy	Initial monotherapy with subsequent azathioprine		Combination therapy from outset	
	Prednisone mg	Prednisone mg	Azathioprine	Prednisone mg	Azathioprine mg
Week 1*	60	20	X	30	50
Week 2	40	20	X	20	50
Week 3	30	20	X	15	50
Week 4	30	20	1–2 mg/kg if	15	50
Early maintenance until endpoint agreed with patient	20	Tapering dose to 5–10 mg by 1 year	responding and bilirubin < 100 µmol/l	10	50

*Although some guidance, e.g. the American Association for the Study of Liver Diseases, suggests how to taper treatment, this is best defined on an individual basis according to the biochemical response to treatment.

Table 4. Notable side effects of the common medications used in autoimmune liver disease.

Corticosteroids	Azathioprine/mercaptopurine*	Mycophenolate mofetil*	Ursodeoxycholic acid
Weight gain/cushingoid	Cytopenias	Cytopenias	Weight gain
Diabetes	Pancreatitis/pneumonitis	Diarrhea/gastrointestinal upset	Hair loss
Cataract	Nausea/vomiting/flu-like syndrome	Headache	Diarrhea
Hypertension/fluid retention	Hepatotoxicity	Rare colitis	Flatulence
Poor wound healing	Possible long-term malignancy risk	Possible long-term malignancy risk	
Osteoporosis	Impaired response to vaccination		
Adrenal suppression	Susceptibility to infection		

*Monitoring including regular hematology and biochemistry required.

months serum aminotransferase levels are normal, the prednisone dose can be decreased by 2.5–5 mg every two to four weeks. The precise strategy is center- and patient-specific, and in part relates to the initial dose of corticosteroid chosen. One typical approach [Johnson *et al.* 1995] has been the achievement of complete clinical, biochemical and histologic remission with prednisolone (5–15 mg/day) and azathioprine (1 mg/kg/day; traditionally not initiated until serum bilirubin < 100 µmol/l) for at least one year before the prednisolone is withdrawn. Long-term remission is maintained by low-dose corticosteroid alone [Cook *et al.* 1971], or in combination with azathioprine (1 mg/kg/day) [Stellon *et al.* 1985]. Maintenance with azathioprine monotherapy is well established and once complete remission has been induced and sustained the majority of patients will remain in remission with azathioprine at a slightly higher dose (2 mg/kg) given alone [Johnson *et al.* 1995]. After a further period of remission it is possible to maintain remission at a dose of 1 mg/kg/day, and indeed many simply use 1 mg/kg from the outset. Some patients may need low-dose prednisone with the azathioprine or the higher azathioprine dose to maintain remission.

Although a chronic relapsing disease, there is a natural desire for discontinuing treatment and there is no agreement as to how long to treat, particularly with azathioprine once prednisone has been withdrawn. For a few there will be no relapse off all treatment, but over 80% will eventually biochemically relapse [Hegarty *et al.* 1983]. Some of the factors that predict relapse are a failure to maintain consistently normal transaminases during therapy, time to initial biochemical remission, high IgG at entry and marked portal cell infiltrate [Miyake *et al.* 2005; Verma *et al.* 2004]. Most recently Montano-Loza demonstrated that relapse is less likely if the AST, gamma globulins and IgG are normal prior to withdrawal of treatment [Montano-Loza *et al.* 2007b]. A main factor distinguishing patients who relapse is the duration of therapy preceding withdrawal of immunosuppression: sustained remission was obtained in 67% of patients treated for less than four years prior to cessation of therapy, in contrast to only 10% of those treated for one to two years [Kanzler *et al.* 2001]. Additionally it is recognized that over 80% of patients on an indefinite azathioprine strategy (2 mg/kg) will remain in remission over a five-year period [Johnson *et al.* 1995].

Although relapse typically responds quickly and completely to retreatment, such patients are at increased risk of further relapse, and poorer outcomes, if drug withdrawal is reattempted [Montano-Loza *et al.* 2007a]. If relapse occurs, prednisone will be needed for remission, and azathioprine (or equivalent) is usually given on lifelong basis.

Treatment challenges and alternative agents

Very few patients fail therapy assuming good compliance. Ethnicity, onset at an early age, hyperbilirubinemia, HLA DRB1*03 and a presentation MELD score of over 12 [Montano-Loza *et al.* 2007c; Verma *et al.* 2007] are important. The choice of intervention in treatment 'resistant' patients is arbitrary. As the numbers are small, data are limited, and sometimes extrapolated from studies focusing on new primary steroid-sparing treatments. Some try a higher dose of prednisone but alternative agents, such as calcineurin inhibitors, budesonide, mycophenolate mofetil (MMF) and rapamycin have all been suggested. Cyclosporin has been used successfully as primary treatment in pediatric and adult patients, and can act as a steroid-sparing agent [Cuarterolo *et al.* 2006]. Similar studies have focused on the related agent, tacrolimus [Larsen *et al.* 2007; Aqel *et al.* 2004]. For both agents if chosen the clinician must carefully appraise the risk from renal and neurological toxicity.

The potential for side effects from prednisone has driven interest in alternative steroid agents, particularly budesonide with its 90% first-pass hepatic metabolism (except in cirrhosis or portal hypertension [Danielsson and Prytz, 1994; Hempfling *et al.* 2003]). A large randomized trial of budesonide versus prednisone in new onset noncirrhotic AIH has been presented [Manns *et al.* European Association for Study of the Liver, 43rd Annual Meeting, 2008]. Patients were randomized for 6 months to either prednisone 40 mg/day (40 mg for the first 4 weeks, and then tapered down to 10 mg/day by week 9; tapering was allowed from week 3 if in remission) or budesonide 3 mg three times per day (upon biochemical remission budesonide dose was reduced to 3 mg b.i.d.). All patients received azathioprine at a dose of 1–2 mg/kg/day. Biochemical remission was defined as AST and alanine aminotransferase (ALT) within normal range and a complete response as biochemical remission as well as a lack of steroid side effects throughout the treatment period. Budesonide was shown to be superior in achieving

biochemical remission over the study period (60% *vs* 38.8%) with significantly fewer steroid side effects (72% *vs* 46.6%), and greater efficacy at achieving the primary endpoint of a complete response. However this trial lasted only six months and notably there was no difference in the total number of patients achieving a normal bilirubin or IgG. The dose of prednisone at 40 mg is higher than many use and thus whilst this study verifies the principle that budesonide is effective in inducing remission of previously untreated patients (if noncirrhotic), the issues over relevant side effects, long-term therapy, and particularly cost efficacy remain debatable. In contrast, the studies of budesonide for nonresponders have been disappointing, although this population will include cirrhotics [Czaja and Lindor, 2000].

MMF is free of nephrotoxicity with its side effects being similar to azathioprine; in addition some report diarrhea and headaches. For those intolerant of azathioprine there is a role [Chatur *et al.* 2005], and additionally MMF may be more potent for those with a poor response to therapy [Richardson *et al.* 2000; Devlin *et al.* 2004; Czaja and Carpenter, 2005]. Finally analogous to their use in other autoimmune/transplant settings, agents such as the anti-CD20 monoclonal antibody rituximab [Santos *et al.* 2006] may prove beneficial for selected patients.

Pregnancy is a frequent concern for young women with AIH. Disease flares may occur during and immediately after pregnancy [Werner *et al.* 2007; Schramm *et al.* 2006; Buchel *et al.* 2002; Heneghan *et al.* 2001] but no factors are predictive, so monitoring is required for all. Management is individualized in terms of the stage of disease and the degree of liver injury. In essence ongoing use of either prednisone and/or azathioprine is considered acceptable. Although azathioprine crosses the placenta there is a lack of teratogenicity in newborns and little evidence to suggest that there should be a dose reduction or drug withdrawal in patients who become pregnant while taking azathioprine. Supplemental or *de novo* prednisone use may be required but counter intuitively perhaps, most physicians shy away from *de novo* administration of azathioprine until after delivery.

Primary biliary cirrhosis

PBC is a chronic nonsuppurative granulomatous cholangitis of the small interlobular bile ducts,

seen most frequently in middle aged women [Gershwin and Mackay, 2008; Kumagi and Heathcote, 2008]. Historic data showed the natural history of histological changes in PBC to be progression to biliary cirrhosis: development of cirrhosis (Ludwig's stage 4 of PBC) over 4 years can be expected in 31%, 50%, and 68% of patients who start respectively from stage 1 (early), 2 or 3 disease [Locke *et al.* 1996]. Many patients remain asymptomatic whilst others have, or subsequently develop, fatigue and/or pruritus, which can be very distressing. With earlier diagnosis, contemporary series demonstrate most patients have no fibrosis (or symptoms) at presentation. Specific antimitochondrial antibodies (AMA) are found over 95% of the time, such that the combination of cholestatic liver biochemistry and AMA has a very high predictive power and routine liver biopsy has decreased in popularity [Zein *et al.* 2003]. An isolated observation of AMA conversely need not equate with PBC, nor be a need for treatment [O'Brien *et al.* 2008; Leung *et al.* 2007].

UDCA and PBC

Japanese researchers first isolated UDCA, the 7- β epimer of chenodeoxycholic acid from bear bile, itself a choleric in traditional medicine [Makino and Tanaka, 1998] and the prevailing view is that UDCA changes the natural history of PBC [Silveira and Lindor, 2008b; Lindor, 2007]. It is less hydrophobic and more hydrophilic than other bile acids, with apparently less toxicity towards the hepatobiliary epithelium. Its therapeutic mechanism of action includes expansion of the hydrophilic bile acid pool, a direct choleric effect (bicarbonate-rich choleresis and modulation of biliary transporter proteins), anti-inflammatory effects (interacts with the glucocorticoid receptor *in vitro*) and anti-apoptotic effects on hepatic epithelia. Cessation of therapy with UDCA leads to a rapid return of abnormal liver biochemistry in those with PBC who respond, demonstrating that the initiating and perpetuating factors remain unresolved.

Normally UDCA accounts for about 4% of bile acids but with pharmacotherapy it becomes the predominant bile acid. Over time studies confirmed a correlation between the degree of bile enrichment and improvement in liver biochemistries and PBC Mayo risk score (age, bilirubin and albumin levels, prothrombin time, and presence or absence of peripheral edema), and overall in

PBC the data suggest that the effective dosage for UDCA is 13–15 mg/kg per day, commonly, but not necessarily, as a single daily dose [Angulo *et al.* 1999; Poupon *et al.* 1997]. Sideeffects are minimal and include weight gain (3 kg in the first 12 months), hair loss, and rarely GI upset [Siegel *et al.* 2003]. Additionally nothing suggests UDCA is teratogenic but it is usually stopped before and during the first trimester, and restarted subsequently, with there being a good safety profile from its use in intrahepatic cholestasis of pregnancy.

Justifying UDCA use

Many studies have attempted to demonstrate clinical efficacy for UDCA, particularly following work demonstrating a fall in bilirubin values in patients with PBC, with most trials showing beneficial effects of UDCA on biochemical parameters in particular (but not symptoms) [Poupon *et al.* 1994, 1991, 1987; Heathcote *et al.* 1994]. With such a slow natural history any individual trial inevitably lacks the power to address endpoints such as death or liver transplantation. The cumulative evidence thus comes from individual and pooled analysis. Of note the Mayo Clinic [Lindor *et al.* 1996, 1994; Jorgensen *et al.* 2002] followed up patients with PBC treated with UDCA and have demonstrated a treatment-related prolongation in transplant free survival. French cohorts with long-term follow-up similarly demonstrate survival benefit [Poupon *et al.* 1999; Corpechot *et al.* 2005] and this was reiterated by a Spanish cohort including nearly 200 patients treated for a mean of 6.7 years [Pares *et al.* 2006]. In those with early stage disease, a biochemical response to UDCA (normalization or a 40% reduction from baseline) after 1 year was associated with a similar survival to the matched control population. ter Borg and colleagues in the Netherlands [2006] were able to show a survival benefit without transplant for low-risk patients compared to survival predicted by the Mayo risk model; moreover overall survival was nearly the same as for a control population. A recent publication [Corpechot *et al.* 2008] looked at defining the biochemical response a year after treatment, to identify UDCA-treated patients at risk of death or transplant. Reiterating the value of a response to UDCA, those with an ALP < 3 ULN and AST < 2 ULN and bilirubin $\leq 17.1 \mu\text{mol/l}$ after 1 year of UDCA had a ten-year transplant-free survival rate of 90% (compared with 51% for those who did not). Histological progression may

therefore be halted (but not reversed) by UDCA [Poupon *et al.* 2003; Corpechot *et al.* 2000], and studies show that after five years of UDCA treatment the incidence of cirrhosis is only 4%, 12%, and 59% respectively among patients followed-up from Ludwig stages 1 to 3 [Corpechot *et al.* 2002]. Therapy also appears to reduce the onset and severity of portal hypertension [Lindor *et al.* 1997].

Overall a combined analysis of three trials (548 patients) [Poupon *et al.* 1997] showed a one-third reduction in the risk of death or transplant, for patients with moderate-to-severe PBC. However meta-analyses have been inconsistent. Some conclude no beneficial effect on the incidence of death and/or transplant despite improvements in serum bilirubin, jaundice, and ascites [Gong *et al.* 2008; Goulis *et al.* 1999]. This contrasts with others showing that long-term treatment with the optimal dose of UDCA could improve survival free of transplant [Shi *et al.* 2006]. One needs to appreciate the varying, and often inadequate sample size and treatment duration of several studies, as well as inclusion of data from trials using suboptimal doses.

Finally, strong surrogate support for a long-term beneficial effect is available from trends in mortality for PBC [Mendes *et al.* 2008; Jackson *et al.* 2007] as well as liver transplantation: for the latter the proportion, as well as absolute number, of patients transplanted for PBC is decreasing [Lee *et al.* 2007], something not noted for PSC.

Traditional immunosuppression and PBC

Classical immunosuppression has been disappointing. A small three-year randomized control trial of prednisolone showed a significant reduction in the serum bilirubin level; however osteoporosis was an issue [Mitchison *et al.* 1992]. Benefits are unlikely from short-term therapy and although agents for osteoporosis are available, there has been little enthusiasm for further long-term studies. It was envisaged that budesonide could benefit patients with PBC and in the first trial improvement in liver biochemistry, IgM values and liver histology was observed for the few patients investigated (most had early disease) [Leuschner *et al.* 1999]. A later study (most had advanced disease) found no benefit [Angulo *et al.* 2000], although subsequent work from Finland has alluded to a histological benefit when

combined with UDCA [Rautiainen *et al.* 2005]. The observation that interface hepatitis on baseline biopsy is predictive of outcome in PBC (as well as a failure to normalize transaminases with UDCA) does suggest a subgroup may benefit from immunosuppression [Corpechot *et al.* 2004] and interest remains in using budesonide adjunctively in those with more florid hepatitic features.

Other trials of immunosuppressive therapy in PBC have employed azathioprine, cyclosporin and methotrexate in particular. Neither of the two trials of azathioprine showed benefit [Heathcote *et al.* 1976] [Crowe *et al.* 1980], and several small trials and one large trial (349 patients) of cyclosporin therapy have been published without good outcome data to support its use [Lombard *et al.* 1993]. Methotrexate similarly was championed by some studies [Kaplan *et al.* 2004, 1999] but when studied in randomized controlled studies is ineffective [Combes *et al.* 2005; Hendrickse *et al.* 1999].

New approaches for PBC

The group of patients most appropriate for new agents are those who fail to respond to UDCA (around 40%) and a number of agents are worthy of comment. The addition of bezafibrate (which may increase phospholipid translocation into the bile) has been investigated, but the results to date are early and a well-powered study is needed [Iwasaki *et al.* 2008]. Atorvastatin with many anti-inflammatory properties beyond its lipid

lowering effect was recently shown not to be of value for PBC [Stojakovic *et al.* 2007]. In view of the cloning of a human retrovirus from a cDNA library derived from PBC biliary epithelia cells, antiretrovirals have been investigated, but convincing data is still awaited [Mason *et al.* 2008, 2004]. More selective immunosuppression (e.g. rituximab) is being studied as well as approaches focusing on fibrosis modulation. Finally other ways of targeting the bile acid pathway are being pursued. Modifications to UDCA (e.g. nor-UDCA) may appeal as well as interfering with nuclear hormone receptors [Zollner *et al.* 2006]. The Farnesoid X receptor (FXR) is a bile acid-activated nuclear receptor highly expressed in both the liver and gastrointestinal tract. It has a role in regulating bile and cholesterol metabolism and FXR agonists (e.g. novel bile acids or small molecule agonists such as INT-747) may have a role in the future.

Primary sclerosing cholangitis

Sclerosing cholangitis is a broad description for a group of disorders in which the biliary tree is damaged by chronic inflammation with subsequent fibrosis and obstruction to free biliary drainage [Weismuller *et al.* 2008; LaRusso *et al.* 2006]. This scarring leads to beading and dilatation of the bile ducts, cholestasis, secondary biliary cirrhosis and infectious complications. The term is broad as many different injuries result in the same endpoint (Figure 1), hence when using the term PSC, it is assumed that secondary causes are absent [Abdalian and Heathcote, 2006].

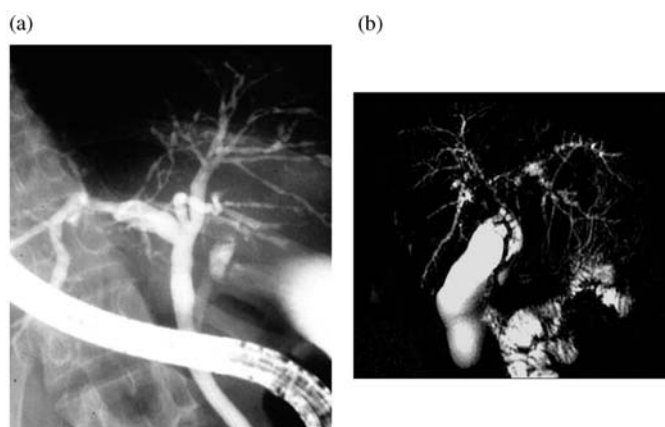


Figure 1. Sclerosing cholangitis – equivalent biliary imaging between primary and secondary disease: (a) classical appearance of primary sclerosing cholangitis by ERCP; (b) portal biliopathy secondary to portal vein thrombosis giving equivalent imaging by MRI.

The original descriptions of PSC required clear exclusion of obstruction by stones or malignancy [Chapman *et al.* 1980], and prior to readily available cholangiography, surgery was often involved in evaluation. Although percutaneous biopsy may show the diagnostic periductal sclerosis, the patchy nature of disease means more often nonspecific biliary changes are described. Radiological assessment of the biliary tree therefore remains clinically the most common diagnostic modality, and this has until recently been by endoscopic or percutaneous cholangiography. With increasingly sophisticated MRI there is a noninvasive and safe imaging modality that is now the initial investigation of choice [Meagher *et al.* 2007]. This is benefiting those with inflammatory bowel disease (IBD) who still represent a significant cohort at risk for PSC, even when they have normal liver biochemistry: a recent study found MRCP evidence of disease in 20% [Bungay *et al.* 2008]. Small duct PSC (a variant that progresses over time to large duct PSC in 20% of individuals [Bjornsson *et al.* 2008]) is the term used for patients with classic histological findings but a normal cholangiogram. Its presence supports broadly the concept of an evolving disease: (a) small duct cholangitis, (b) progressive cholestasis, (c) cirrhosis and (d) decompensation.

In the classic descriptions, the majority of patients had ulcerative colitis and were more often men presenting in their 40s [Bambha *et al.* 2003]. Symptomatically fatigue, right upper quadrant pain, pruritus and jaundice are common and since the clinical course of PSC is typically one of insidious worsening of cholestasis, end-stage liver disease inevitably develops; prior natural history studies show average survival at 12 to 17 years from symptom onset [Kim *et al.* 2000]. Bacterial cholangitis, especially after intervention, is seen in about one in three patients, and cholangiocarcinoma develops in as many as 10–20% of patients (commonly presenting within the first year of diagnosis of PSC [Bergquist *et al.* 2002]).

In interpreting studies, one must first recall that the inclusion criteria have traditionally been stringent with classically all three of abnormal biochemistry, cholangiography and histology being required. This skews enrollment. Although alternative etiologies have been sought, this refers to the traditional etiologies: chronic obstruction by stones, vascular disease

(portal vein thrombosis, hepatic artery loss), recurrent cholangitis and cholangiocarcinoma. It has not included IgG4 associated sclerosing cholangitis a steroid-responsive disease. Endpoints for treatment intervention are troublesome with the dilemma of including patients with such advanced disease that efficacy of any treatment is unlikely. As a surrogate outcome measure, the Mayo PSC risk score has frequently been applied, as it predicts the probability of survival (based on age, bilirubin, albumin, AST and the presence/absence of variceal bleeding). Lastly assessing the stage, and progression, of disease by use of serial liver biopsy, as has been common, is limited by sampling errors.

UDCA and PSC – herbal choloretic or proven pharmaceutical?

The use of UDCA was naturally studied after the successful studies in PBC, and remains a popular agent [Silveira and Lindor, 2008a]. Indeed its use demonstrates how prescribing habits are a balance of evidence and perceived benefit, and that modern medical practice can be as 'unscientific' as traditional medicine.

Biliary enrichment of UDCA increases with increasing dose and reaches a plateau at a daily dose of 22–25 mg/kg in the bile of patients with PSC [Rost *et al.* 2004]. Various trials investigated UDCA treatment in PSC after Hayashi's and Chazouilleres' first open label studies in, 1990 [Chazouilleres *et al.* 1990; Hayashi *et al.* 1990]. The initial double-blind placebo controlled trial of standard dose UDCA by Beuers and colleagues [1992] demonstrated an improvement in serum liver tests and a histological score. Similar results were described by Stiehl and colleagues [1994]. A larger controlled trial from the Mayo with longer follow up confirmed the effects of UDCA on serum liver biochemistry, but without a survival benefit. This important effort was randomized, double-blinded (UDCA at 13–15 mg/kg/day *vs* placebo) and involved 105 patients (half with advanced PSC), with a median follow up of 2.2 years [Lindor, 1997]. Most subsequent studies have similarly confirmed an improvement in serum liver biochemistry but not more tangible endpoints.

Harnois assessed the tolerability and effectiveness of UDCA at 25–30 mg/kg/day in a pilot study of patients with PSC [Harnois *et al.* 2001]. Changes in the Mayo risk score after one year of treatment

and projected survival at four years of treatment were compared with prior data. High-dose UDCA was well-tolerated, associated with improvement in liver biochemistries, and led to a significant improvement in the Mayo risk score. Other encouraging results with high-dose UDCA were seen in a two-year double-blind, placebo-controlled study conducted by Mitchell and colleagues in which 26 patients with PSC were randomized to 20 mg/kg/day of UDCA or placebo [Mitchell *et al.* 2001]. Further work recently published [Cullen *et al.* 2008] also points towards benefit from high-dose therapy and this is similar to a, 2005 randomized, placebo-controlled study by Olsson and colleagues (UDCA at 17–23 mg/kg/day) [Olsson *et al.* 2005]. They found significantly improved liver biochemistry but no significant difference for the combined endpoint of death or liver transplantation.

Thus, overall the studies to date support an effect of UDCA on liver tests, demonstrate no harm, but lack robust data for the hard endpoints patients want to see. Other considerations are relevant. PSC is a premalignant condition and some studies suggest UDCA may counteract this. PSC is associated with a 10–20% lifetime risk for the development of cholangiocarcinoma, and patients with ulcerative colitis and PSC are at a higher risk for colonic dysplasia and colon cancer (0.5–1% per year of disease, explaining the recommendation for regular colonoscopy in those with IBD and PSC, including post-transplant). Gallbladder malignancy is also a concern [Buckles *et al.* 2002]. There are a few publications supporting the notion that UDCA use is associated with a lower prevalence of colonic neoplasia in patients with PSC and concomitant ulcerative colitis, and this parallels *in vivo* experimental data [Rudolph *et al.* 2007; Pardi *et al.* 2003].

Alternative and innovative approaches to medical therapy in PSC

Numerous other agents (e.g. prednisone, budesonide, azathioprine) have been used with the hope of improving medical care in PSC, but without positive outcomes. The combination of an antibiotic with UDCA is very attractive and a study with 80 patients with PSC randomized to either UDCA alone or the combination of metronidazole and UDCA did find that combination therapy improved serum alkaline phosphatase and Mayo Risk Scores, but without significant

effect on disease progression compared to UDCA alone [Farkkila *et al.* 2004]. In view of the possibility that biliary infection may contribute to the cholangitis, trials of antibiotics continue to be of interest – for example, vancomycin [Davies *et al.* 2008] and azithromycin [Boner *et al.* 2007]. Other possible treatments include antifibrotics such as rapamycin or angiotensin converting enzyme inhibitors. The role of cystic fibrosis transmembrane conductance regulator (CFTR) as an important ion channel in biliary biology has led to an ongoing trial of docosahexaenoic acid which improves CFTR function [Blanco *et al.* 2004]. Disappointedly despite its role in IBD, tumor necrosis factor alpha (TNF alpha) inhibition does not seem to directly help PSC [Hommes *et al.* 2008]. Perhaps the most exciting agent at present is an inhibitor of toxic bile formation, 24-norursodeoxycholic acid (a homologue of UDCA with one fewer methylene group in its side chain). Multidrug resistance gene 2 knockout mice represent a well-characterized model for sclerosing cholangitis and the novel bile acid 24-norursodeoxycholic acid appears to ameliorate the cholangiopathy [Fickert *et al.* 2006].

Supportive care in PSC

A few important concepts merit discussion. Bacteriobilia is found in the majority of patients with PSC, but clinically apparent cholangitis does not commonly manifest unless intervention has occurred, or the disease has advanced significantly. There is therefore a move away from ERCP unless it is with clear therapeutic intent (i.e. dominant stricture, in which case repeated balloon dilatation may be better than stenting [Kaya *et al.* 2001]) or there is a raised suspicion for malignancy. Biliary surgery in patients with PSC, other than simple cholecystectomy (surprisingly frequent [Said *et al.* 2008]), should be minimized and reserved for the selected rare noncirrhotic patients who have marked cholestasis or recurrent cholangitis caused by a dominant extrahepatic or hilar stricture not amenable to endoscopic therapy. PSC is an important indication for liver transplantation, reflecting the present inadequacies of medical treatment [Schreuder *et al.* 2008]. The use of MELD scores is appropriate but some specific circumstances including recurrent bacterial cholangitis despite therapy, severe extrahepatic biliary obstruction that precludes operative repair, and uncontrolled peristomal variceal bleeding

may not be adequately addressed by MELD. Post-transplant outcome is good for PSC but recurrent disease is worrying at up to 20% by five years, and may be a greater concern in living related donation. Of the many proposed risk factors for recurrent PSC, the presence of an intact colon in those with colitis is one that has potential for modification, by appropriately timed colectomy [Vera *et al.* 2002].

IgG4 associated sclerosing cholangitis/ autoimmune pancreatitis – a steroid responsive cholangiopathy

Atypical presentations of syndromes including sclerosing cholangitis have been recognized for some time [Toosi and Heathcote, 2004] and the Japanese-defined steroid responsive autoimmune pancreatitis (AIP) that, in its spectrum, includes a sclerosing cholangiopathy (AIP/SC) [Kamisawa and Okamoto, 2008]. Elevated serum IgG4 levels were found to be associated with sclerosing pancreatitis and treatment with corticosteroids decreased levels [Hamano *et al.* 2001]. Thus, it is now recognized that IgG4-associated cholangitis is the biliary manifestation of a multisystem fibro-inflammatory disorder in which affected organs have a characteristic lymphoplasmacytic infiltrate rich in IgG4-positive cells [Bjornsson *et al.* 2007; Gardner and Chari, 2008]. Specific diagnostic criteria for AIP have emerged over time and one recent example is based on histologic, imaging, serologic characteristics and extra-pancreatic involvement as well as a response to corticosteroids [Chari, 2007]. With greater awareness of disease, it is also clear that IgG4 levels can be normal in a proportion of patients. Other organs are often involved in AIP and their involvement may be diagnosed before, simultaneous with, or after the diagnosis of AIP – for example, in 64 patients who had AIP [Hamano *et al.* 2006] the most frequent extrapancreatic lesion was hilar lymphadenopathy (80.4%), followed by extrapancreatic bile duct lesions (73.9%), lacrimal and salivary gland lesions (39.1%), hypothyroidism (22.2%), and retroperitoneal fibrosis (12.5%). Both intrinsic (tubulointerstitial fibrosis) and extrinsic (hydronephrosis secondary to retroperitoneal fibrosis) renal disease have been associated with AIP, as has inflammatory pneumonitis and inflammatory pseudotumor of the liver. Biliary tract involvement of both intra- and extrahepatic bile ducts is seen, with the distal common bile duct being the most common site. Patients may also present

following surgical exploration for presumed malignancy that turns out to be benign.

It is likely that a proportion of patients previously labeled as PSC have a variant of this disease, suggesting a subgroup that might require different therapy. Furthermore, is the quandary as to the observation that 9% of patients enrolled into a clinical trial of PSC were retrospectively found to have elevated IgG4 levels and these patients appeared to fare worse [Mendes *et al.* 2006]. AIP/SC differs from PSC in that there is generally less intrahepatic involvement and segmental strictures can be transient; IBD, which is present in two-thirds of those with PSC, is less common (6%) in AIP/SC.

This disease can be spontaneously relapsing and remitting, but the use of steroids (Table 5) predictably induces remission including resolution of pancreatic ductal abnormalities or masses and of extra-pancreatic manifestations (biliary strictures, retroperitoneal fibrosis, salivary gland enlargement). Adjunctive treatment by biliary stenting may still be needed. Whether to treat PSC patients found to have a raised IgG4 level (without other features of AIP/SC) is not resolved nor is there is consensus on steroid regimens or the duration of treatment [Church and Webster, 2008; Ghazale and Chari, 2007]. Starting prednisone doses range from 30 to 40 mg in most studies, although lower doses may be effective. An initial high-dose therapy is usually given for three to four weeks followed by a reducing course – for example, prednisone 40 mg daily for four weeks followed by tapering of 5 mg per week. Such a course allows for assessment of response to therapy, which is typically fast with significant radiological improvement at around two weeks; a fall in serum IgG4 levels and liver enzymes also guides response. In patients who experience a complete radiological response, normalization of imaging findings typically occurs within just over one month. Where needed biliary stent removal can usually occur within 2 months of treatment, although if there are fibrotic changes in the biliary tree or retroperitoneally radiological resolution may be limited. Recent data suggest that relapse is likely in 70% of patients who have proximal extrahepatic or intrahepatic biliary strictures. Chronic immunosuppression achieved by the use of long-term low-dose steroids or by addition of immunomodulatory medications such as azathioprine or mycophenolate mofetil may therefore be

Table 5. Features of autoimmune pancreatitis/sclerosing cholangitis (AIP/SC).

Clinical features aiding the diagnosis of AIP/SC	Examples of presentation prompting treatment		
	Pancreatic presentation – acute	Pancreatic manifestations – late	Extra-pancreatic presentation
Classical imaging findings for AIP/SC e.g. focal pancreatic mass, focal pancreatic duct stricture, fleeting/migrating biliary strictures Elevated serum IgG4 Other organ involvement e.g. kidney, salivary/lacrimal gland, retroperitoneal fibrosis, hepatic pseudotumors Positive histology with lymphoplasmocytic infiltrate Response to steroid therapy	Obstructive jaundice with focal or diffuse pancreatic enlargement	Radiological evidence of persistent pancreatic mass or enlargement and/or distal biliary strictures	Biliary strictures Interstitial nephritis Retroperitoneal fibrosis

appropriate and rituximab may be an option for a few [Ghazale *et al.* 2008; Topazian *et al.* 2008; Church *et al.* 2007; Hirano *et al.* 2007].

Conclusions

In predicting the emerging treatments for this field, it is hoped that the combined efforts of genetic analysis (association studies, gene expression, copy number variation, methylation), proteomics, imaging and animal models will lead to new drug targets. The slow natural history exhibited by these diseases and the fact that patients are being diagnosed at much earlier stages of disease will remain challenges for those designing studies. Regardless, the prospects for avoiding liver failure is excellent for those diagnosed today with autoimmune liver disease.

Conflict of interest statement

Both GM Hirschfield and EJ Heathcote have received research support from Axcan Pharma, and are recruiting patients to an ongoing trial of INT-747 supported by Intercept Pharmaceuticals.

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