# Challenges in the use of corticosteroids in the management of autoimmune hepatitis


## ABSTRACT

Autoimmune hepatitis is widely assumed by health-care professionals to be a disease that is easily controlled through the use of corticosteroids and immunosuppressants but recent studies in the UK indicate highly variable treatment regimens and often unsatisfactory treatment outcomes, such as dependence on long-term high-dose steroids and ongoing need for liver transplantation in some cases. The therapeutic use of the systemically acting corticosteroid prednisolone results in unacceptable side effects in many patients. Recent evidence suggests that it is not always necessary to use high-dose steroids (>0.5 mg/kg/d) to attain remission; and side effects may also be minimised through more targeted therapy with the less systemically-absorbed corticosteroid, budesonide. The authors offer advice on the stratification of treatment for these patients and suggest changes to improve the services available for people with autoimmune hepatitis in the UK.


Autoimmune hepatitis is a rare form of autoimmune liver disease. The prevalence in northern Europe is 15–25 cases per 100 000 individuals but there evidence that the prevalence is increasing over recent decades (Manns et al, 2010a; European Association for the Study of the Liver, 2015).

Autoimmune hepatitis is more common in women with a 4:1 gender ratio. There is a bimodal age pattern at presentation with one peak in numbers presenting as children or adolescents and another in the 40–60-year-old age group. There is also evidence of a higher prevalence and more severe disease on presentation in certain ethnic groups such as African Americans and native Alaskan populations. Unusual variant forms of autoimmune hepatitis may occur during pregnancy or in recipients of liver transplants (European Association for the Study of the Liver, 2015).

The condition is a result of the loss of immunological tolerance to hepatic autoantigens. It may emerge following a range of different viral infections or after treatment with various drugs or supplements. There is a high prevalence of other autoimmune conditions in patients or their first-degree relatives.

Corticosteroid therapy has been the mainstay of autoimmune hepatitis treatment for the past 50 years. High-dose oral prednisolone is generally given to induce remission, followed by the introduction of steroid-sparing immunosuppressants such as azathioprine with tapering of the corticosteroid dose. UK and European guidelines recommend the use of azathioprine as long-term maintenance monotherapy or sometimes in combination with low-dose prednisolone (*Figure 1*). However, new pathways are being developed because of the challenges of treatment which are discussed in this article (Trivedi and Hirschfield, 2013).

Studies from specialist liver units suggest that biochemical remission, with normalized liver function tests and IgG levels, may be achieved within 3 years in up to 80% of patients using this approach (Czaja, 2010; Trivedi et al, 2019). The 20-year life expectancy for patients post diagnosis is more than 80% and the risk of liver transplantation or death from liver failure has been reduced to less than 5% (Czaja, 2010).

However, a recent study from the United Kingdom Autoimmune Hepatitis (UK-AIH) consortium involving 1249 adult patients revealed significant variation in the care received by patients with autoimmune hepatitis (Dyson et al, 2018). A high proportion of patients remain on long-term corticosteroid therapy (treatment lasting longer than 6 months) and significant treatment variability was reported. Its authors expressed profound dissatisfaction with the slow pace of improvements in this area, stating:

> **'The medical community seems comfortable in accepting both suboptimal patient outcomes and largely outmoded therapeutics for the disorder.'**

This article summarizes the findings of recent research and the discussions of an expert panel on the challenges in improving the management of autoimmune hepatitis in the UK, with particular emphasis on optimizing the use of corticosteroids in these patients.

## Clinical presentation in autoimmune hepatitis

Patients may present with non-specific signs of chronic liver disease such as fatigue, abdominal and joint pain, and general ill-health. A minority of patients will present with severe disease with signs of liver failure including fulminant disease.


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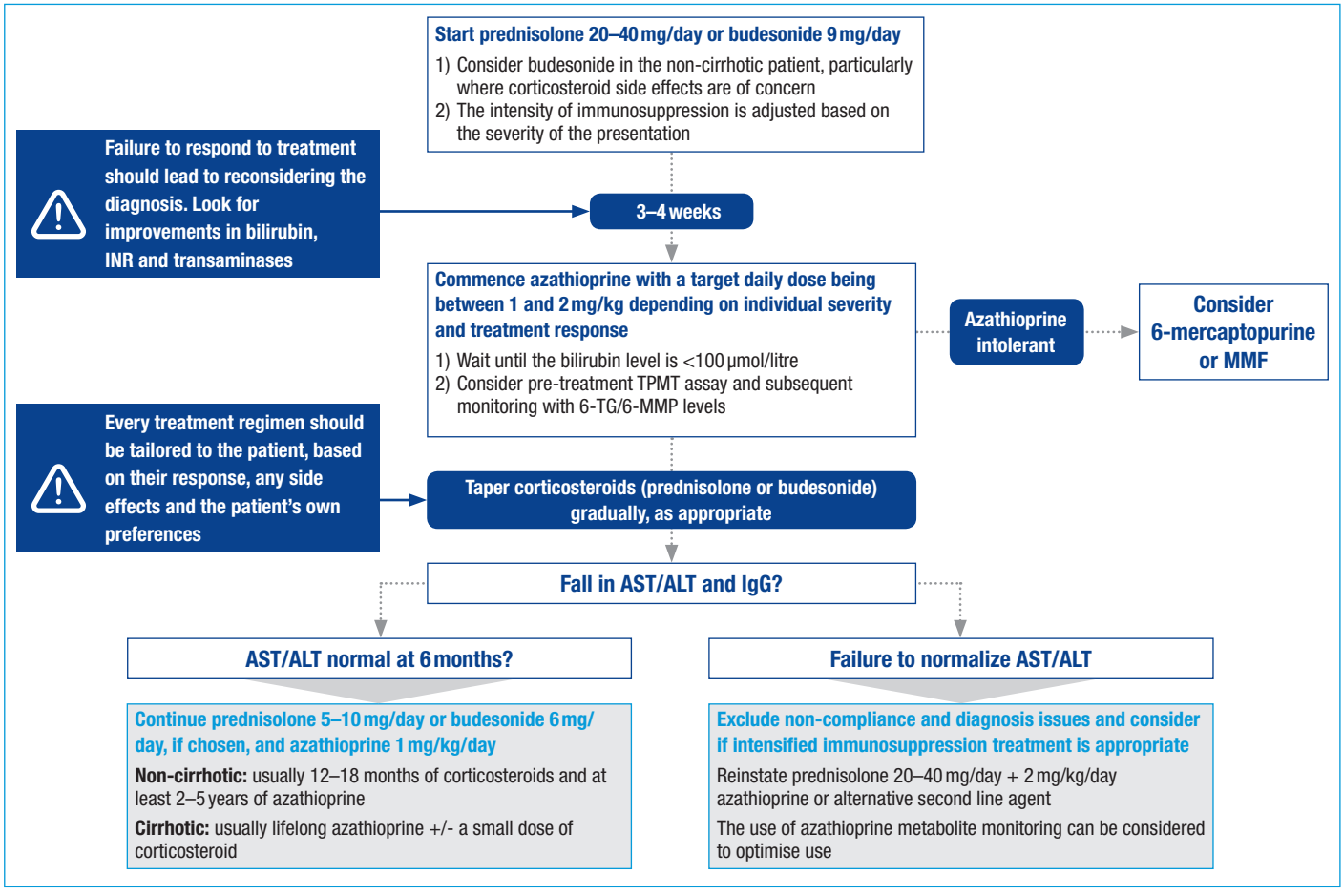


Figure 1. A practical approach to treating autoimmune hepatitis. ALT = alanine transaminase; AST = aspartate transaminase; IgG = immunoglobulin G; INR = international normalized ratio; MMF = mycophenolate mofetil; MMP = methyl mercaptopurine; TG = thioguanine; TMPT = thiopurine methyltransferase.

A diagnosis is made on the basis of elevated serum immunoglobulin IgG levels, serum autoantibodies including antinuclear antibodies, and compatible liver histological findings such as interface hepatitis. Liver biopsy should always be performed and is a prerequisite for the diagnosis of autoimmune hepatitis.

Autoimmune hepatitis is classified into two main variants. Type 1 is the dominant form, occurring in about 90% of cases. This is identified through the presence of antinuclear antibodies (ANA), smooth muscle antibodies (SMA) or soluble liver antigen (anti-SLA). Patients with type 2 disease have liver kidney microsome antibodies (LKM-1 or LKM-3) or liver cytosol antibodies (antiLC1). Theirs is generally a more severe form with a younger age of onset.

However, in clinical practice it can be difficult to differentiate patients with autoimmune hepatitis from those with drug-induced liver injury because of the variable clinical presentation (Liwinski and Schramm, 2017). Increasingly, there is also considerable overlap with metabolic syndrome and patients may illustrate overlap features with two other autoimmune liver conditions, primary biliary cholangitis and primary sclerosing cholangitis. The latter two are associated with poorer patient outcomes (Trivedi and Hirschfield, 2012).

Untreated, autoimmune hepatitis will normally lead to cirrhosis, liver failure and death. About one third of adults and one in two paediatric patients already show evidence of cirrhosis at presentation (Kirstein et al, 2015). About 40% of those in whom treatment fails to achieve remission will develop progressive liver disease.

The highly heterogenous presentation may create diagnostic challenges, exacerbated by the shortage of expertise in interpreting serological and histopathological findings. This may result in delays in the introduction of appropriate treatment for many patients.

## Problems with current care of patients with autoimmune hepatitis

The UK-AIH study involved similar numbers of patients being treated within the district general hospital system and specialist transplant centres (614 and 635 respectively), although as there were 37 non-specialist centres involved, greater heterogeneity of treatment might be expected in patients treated in the non-specialist centres. Remission rates were significantly higher in the transplant centres than in district general hospitals (62% *vs* 55%) despite treating a higher proportion of the patient population with more advanced disease. Nevertheless, the 'real

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world' remission rates for patients with autoimmune hepatitis treated throughout the UK health service were 59%, which is much lower than those claimed in earlier studies (Dyson et al, 2018; Theocharidou and Heneghan, 2018). This may be partly explained by changes in the criteria for attaining remission, from an improvement in serum aminotransferase levels to less than two times normal levels in the 2002 American Association for the Study of Liver Disease guidelines (Czaja and Freese, 2002) to a stricter requirement for full normalization of serum aminotransferase levels (Manns et al, 2010a).

There is a lack of consistency among clinicians on the use of the appropriate therapy for particular patient groups. The UK-AIH study found that 29 different treatment regimens were currently in use, even before taking account of differences in dosage. There were no significant differences between transplant and non-transplant sites with regard to numbers of different treatment regimens, use of maintenance corticosteroids or numbers of disease flares. However, patients managed in transplant centres were more likely to receive triple immunosuppressive therapy or be administered a calcineurin inhibitor.

In general, induction of remission is through treatment with corticosteroids and azathioprine. For those with mild disease who are intolerant to azathioprine, prednisolone monotherapy may be considered, and continued at a low dosage (e.g. ≤7.5 mg daily) as maintenance once remission has been attained. In all other patients, monotherapy with azathioprine is the goal of maintenance treatment (European Association for the Study of the Liver, 2015). Patients who develop side effects or intolerance to azathioprine and corticosteroids are treated with a range of second-line drugs such as mercaptopurine, mycophenolate mofetil or calcineurin inhibitors; however, there are no randomized controlled trial data to support their use currently, with existing evidence limited to observational cohort studies and case series from high-volume liver units.

While current European Association for the Study of the Liver (2015) guidelines advise against the use of prednisolone for long-term maintenance therapy, except in patients with mild disease and intolerant of azathioprine, the UK-AIH study showed that 55% of patients were receiving this drug as part of their treatment regimen and 9% were being maintained on prednisolone monotherapy (Dyson et al, 2018). Sustained exposure to systemic corticosteroids produced a high incidence of adverse effects, notably weight gain (75%), sleep disturbances (70%), changes in physical appearance (59%), mood swings (55%) and stomach pain or disturbances (28%) while only 3% of those in the cohort reported no significant side effects (Corrigan et al, 2017).

Systemic corticosteroid use in patients with autoimmune hepatitis is also strongly associated with detrimental effects on patients' quality of life, independent of remission status, notably as a cause of lower levels of utility, i.e. mobility and ability to perform usual activities (Wong et al, 2018). In another study, a high proportion of patients with autoimmune hepatitis reported significant impairment of mental health components of their quality of life, i.e. depression and chronic fatigue, that was not associated with any clinical or biochemical features of the disease (Janik et al, 2019).

## Recommendations on use of steroids in autoimmune hepatitis

The 2015 European guidelines suggest using 0.5–1 mg/kg of prednisolone per day to induce remission. For a 60 kg adult, this equates to a starting dose ranging from 30–60 mg daily – reduced to 7.5 mg/day if aminotransferase levels return to normal (and further reduced to 5 mg/day after 3 months and then tapered out according to the patient's risk factors and response (European Association for the Study of the Liver, 2015)). However, superiority data to support high dose (>0.5 mg/kg/day) *vs* conventional dose (<0.5 mg/kg/day) corticosteroid induction therapy is lacking. Indeed, a recent international study found no significant difference in the rate or likelihood of normalization of transaminase levels between study groups (Pape et al, 2019).

Budesonide is suggested as an alternative to prednisolone in current autoimmune hepatitis guidelines, but currently appears to be underused in clinical practice. Only 9% of patients in the UK-AIH study cohort received budesonide as induction therapy. Yet budesonide offers potential advantages over prednisolone. It has a higher steroid receptor affinity and much lower systemic bioavailability. As about 90% of the dose is retained in the liver, with less spill over into the systemic circulation, there is a reduced risk of steroid-related side effects.

The limited number of studies that have been carried out comparing the effects of budesonide with prednisolone in patients with autoimmune hepatitis appear to confirm this assertion. The largest study to date recruited 207 non-cirrhotic patients and compared the effects of an induction dose of budesonide 9 mg/day with azathioprine 1–2 mg/kg day *vs* prednisolone 40 mg/day tapered to 10 mg/day with a similar dose of azathioprine (Manns et al, 2010b). After 12 months' treatment the incidence of steroid-related side effects was 26.4% in patients receiving budesonide *vs* 44.8% in the standard treatment group ($P<0.002$). A more recent study by Janik et al (2019) showed that patients given budesonide had reduced side effects and improved quality of life scores compared with those given prednisolone.

The panel therefore propose that budesonide should be considered as a first-line initial treatment in non-cirrhotic patients with autoimmune hepatitis, those without portosystemic shunts or portal hypertension, non-icteric presentations and in patients with a normal

prothrombin time and international normalized ratio. It should also be considered for patients where there are concerns about comorbidities, such as unstable diabetes mellitus or osteoporosis. It is particularly recommended for younger patients with milder forms of the disease in whom compliance with prednisolone treatment may be poor, mainly as a result of the effects of prednisolone on body weight and facial appearance. In this context, the panel propose that mild disease would be defined as alanine transaminase levels below 300–400 U/litre and aspartate transaminase levels below 300 U/litre, together with an international normalized ratio of less than 1.3.

As a clinically effective and readily titratable treatment, prednisolone should remain the first-line therapy in certain patients with autoimmune hepatitis, including severely affected patients with acute severe disease, cirrhotic or cholestatic presentations and those with extrahepatic symptoms such as arthralgia.

In a subset of patients, it may be appropriate to initiate therapy with prednisolone and then switch to budesonide. A study by Peiseler et al (2018) investigated the use of budesonide in 60 patients previously receiving prednisolone who had developed severe side effects or who were prednisolone-dependent and unable to reduce the dose below acceptable levels. Favourable biochemical responses to budesonide were reported in 55% of patients after 6 months, rising to 70% at 12 months follow up and 67% after 2 years. In a subset of 15 patients who were showing evidence of osteopenia as a result of their previous exposure to prednisolone, there was an improvement in bone mineral density in six cases, stable findings in eight and a further deterioration in just one patient.

There are few data available on comparative dosages of the two glucocorticoids in autoimmune hepatitis but experience in treating other autoimmune conditions, such as inflammatory bowel disease, suggests that a 9 mg dose of budesonide is equivalent to between 45 and 50 mg prednisolone.

## Patient perspectives

Adverse effects of treatment on the quality of life of patients with autoimmune hepatitis would be expected to impact on their compliance with treatment. In published reports, 25% of non-responders to initial treatment with corticosteroids are non-adherent with therapy because of side effects (Sockalingam et al, 2010).

A more recent study (Corrigan et al, 2017) identified a proportion (18/133; 14%) of patients with autoimmune hepatitis whose treatment was stopped or altered in response to severe adverse effects. While 61% of those questioned recalled having the potential side effects of steroids explained to them when they began treatment, 31% claimed that they were unaware of those risks, with the remaining 8% unsure what they had been told. In this survey, 97% of respondents felt that information about patient support groups would help them deal with drug-related side effects and other aspects of their treatment.

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Feedback from patients has highlighted the need to provide better information about the diagnosis and treatment of autoimmune hepatitis (Corrigan et al, 2017). Some have complained that they do not know which medical professionals to approach for guidance in dealing with their condition. Given the rare nature of the condition, GPs may be unfamiliar with current treatment options, particularly with regard to azathioprine therapy and the need for monitoring with blood tests. There is anecdotal evidence from hepatologists that as a result of a lack of guidance from health-care professionals, patients with autoimmune hepatitis may self-adjust their treatment in order to gain some control over the troublesome side effects.

## Options for improving services for patients with autoimmune hepatitis

In the UK, the vast majority of patients (66%) attend university teaching hospitals, with approximately 50% overall cared for in liver transplant centres (Gordon et al, 2018). However, remission rates appear to be lower in non-transplant units.

Ideally, all patients with autoimmune hepatitis would be under the care of a specialist hepatologist or at least a gastroenterologist dealing mainly with liver disease. But autoimmune hepatitis is a relatively uncommon disease and there is variation in access to specialist services around the country. One option would be to develop clinical networks linking district general hospitals with specialist units. In this model after an initial assessment to identify more severely affected patients, the majority would receive ongoing treatment at their local hospital by a specialist in liver disease but could be referred for further investigations at the specialist unit with acute-severe presentations, after failure to attain remission after 6 months, or when azathioprine fails to maintain remission.

Given the competing demands on consultants' time, acute hospitals should consider expanding the role of specialist nursing staff in monitoring patients with autoimmune hepatitis. A suitable model for the training and deployment of nurses would be the services provided for the treatment of viral hepatitis and more common autoimmune conditions, such as inflammatory bowel disease. Specialist hepatology disease nurses trained in autoimmune liver diseases can facilitate monitoring blood results between clinic visits and be able to implement changes to the treatment plan after discussions with the lead consultant. Importantly, nurses would be able to provide continuity of care, a key factor for optimal outcomes. Patients should be given a card with the contact details

## KEY POINTS

- Disappointingly low numbers of patients with autoimmune hepatitis in the UK are in remission (defined as normalization of serum transaminase and IgG levels).
- A wide range of unvalidated treatment regimens is being used.
- Prednisolone remains the best currently available initial treatment for patients with autoimmune hepatitis who present with acute severe disease and cirrhosis.
- A significant proportion of patients who receive prednisolone maintenance therapy experience serious side effects with detrimental effects on their quality of life.
- The rates and likelihood of normalization in transaminase levels are no different between patients treated with high-dose prednisolone (>0.5 mg/kg/day) *vs* doses <0.5 mg/kg/day.
- Data from a high-quality randomized controlled trial and several observational cohort studies indicate that budesonide is as clinically effective as prednisolone in selected patients but with fewer side effects.
- Remission rates may be higher for patients with autoimmune hepatitis who are treated at specialist centres.
- More hepatology nurse specialists should be appointed to enable better monitoring of patients with autoimmune hepatitis.
- More high-quality clinical research is needed to optimize the long-term management of patients with autoimmune hepatitis with budesonide and alternative second-line therapies to azathioprine.

for staff able to offer advice. Patients would also benefit from being able to access more up-to-date information sheets on issues such as the main medications used to treat autoimmune hepatitis and the role of other medical treatments, such as vaccinations and antibiotics in the management of respiratory infections.

The panel believe that encouraging a more active role for specialist hepatology nurses could reduce demand and average waiting times in consultant clinics, while facilitating on-demand access for patients. Improved monitoring and more timely decisions on changes to treatment protocols may allow considerable progress towards a more cost-effective service and improve key metrics such as the ratio of new to follow-up appointments. Consideration should also be given to maximizing the potential value of on-line consultation technologies to reduce time and travel costs for patients. There is also a need to develop a database of patients with autoimmune hepatitis listing their current treatment protocol and disease status.

In some centres, secure and confidential, web-based systems have been introduced for patients to access blood results and, where appropriate, be copied in to communications between medical staff. Early identification of patients who are struggling to comply with their current treatment regimen is vital in improving outcomes for patients with autoimmune hepatitis. Improving patient understanding of the correlation between their test results and their physical experiences may help improve compliance. In many cases, patients may feel more confident in seeking advice from nursing staff, particularly on quality of life issues.

## Research goals

In view of the serious consequences of progressive disease in autoimmune hepatitis, there is a pressing need for new therapeutic approaches. There has been considerable progress in developing disease-modifying agents and novel antibodies for other autoimmune conditions such as multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis, but there have been few equivalent studies in patients with autoimmune hepatitis. The clinical network model discussed above may facilitate the recruitment of patients into future clinical trials.

The panel also identified a need for more information on currently available therapies. A key aim of future studies will be to gather better quality data on the use of budesonide in maintenance therapy. Research is also needed on the use of the various second-line treatments in patients unsuited to long-term azathioprine therapy.

## Conclusions

There is an assumption from some health-care professionals that autoimmune hepatitis is a disease that is easily controlled through the use of corticosteroids and immunosuppressants. Recent data from the UK have shown this assumption to be incorrect, demonstrating highly variable treatment regimens and unsatisfactory treatment outcomes in many.

The therapeutic use of the systemically acting corticosteroid prednisolone results in unacceptable side effects in many patients. However, these side effects can be minimized in a high proportion of patients with autoimmune hepatitis through more targeted therapy with an alternative steroid, budesonide and steroid-sparing agents such as azathioprine. Organizational changes are suggested to improve the services available for managing patients with autoimmune hepatitis in the UK. **BJHM**


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