Role of mycophenolate mofetil in the treatment of autoimmune hepatitis

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More than 30 years ago controlled clinical trials demonstrated that treatment with steroids improves the outcome of patients with autoimmune hepatitis (AIH) decisively. Azathioprine was soon found to add benefit in the therapy of AIH and was shown to be the drug of choice for maintenance therapy. Since then, corticosteroid monotherapy and the combination of steroids with azathioprine have become the standard of treatment for AIH [1,2]. The excellent response rates and the fact that AIH is a rare disease requiring multicenter efforts on the one hand and limited commercial benefit on the other hand have led to a lack of larger controlled clinical trials evaluating alternative first line treatment options thereafter.

Using high dose prednisolone initially (0.5–1 mg/kg/d) in combination with azathioprine at a dose of 1–1.5 mg/kg/d in patients not severely jaundiced leads to complete and partial biochemical response rates in over 90% of patients within the first year of treatment and to an excellent long term survival [3,4]. This regimen is frequently used in European countries. One could, therefore, argue that there is no need for alternative first line treatments of AIH. However, up to 10% of patients do not respond sufficiently to the combination of prednisolone and azathioprine and another 5–10% experience side effects requiring treatment modification [1,5]. Side effects include the more frequent gastrointestinal complaints induced by azathioprine but also serious toxicity such as pancreatitis, cholestatic hepatitis, and neutropenia. Steroid related side effects include the multiple short term effects of high dose steroid therapy such as weight gain, diabetes, and psychosis and the long term effects on bone, eyes, and skin among others [1]. Budesonide has recently been demonstrated as a potential alternative for prednisolone with possibly less steroid side-effects in the so far largest controlled clinical trial of AIH [6], but the clinical value of budesonide remains controversial [2].

In this context, the study by Zachou et al. reported in this issue of the Journal [7] evaluated mycophenolate mofetil (MMF) in combination with prednisolone as an alternative to azathioprine in the first line treatment of AIH. MMF is a prodrug of mycophenolic acid, which is an inhibitor of inosine monophosphate dehydrogenase, the rate limiting enzyme in the de novo purine synthesis which is required for the proliferation of B- and T-lymphocytes [8]. Lymphocytes do not possess an alternative pathway of purine synthesis and, therefore, MMF targets preferentially the cells involved in the pathogenesis of AIH. MMF has widely replaced azathioprine in solid organ transplantation, mainly due to its faster onset of action and potentially greater immunosuppressive capacity reducing rejection episodes as seen after cardiac and renal transplantation, albeit at the cost of a higher rate of infections [9,10]. In liver transplantation, the superiority of MMF over azathioprine is less clear [11]. Moreover, the exact role of MMF as compared to azathioprine in the treatment of autoimmune diseases and vasculitis syndromes still has to be defined [12] and a recent controlled treatment trial of ANCA associated vasculitis concluded that MMF was inferior to azathioprine for the maintenance of remission [13].

To date, there have been no controlled clinical trials evaluating MMF in treatment naïve or treatment experienced patients with AIH. Although the study presented by Zachou et al. is a case series and not a controlled trial comparing azathioprine and MMF, the data were acquired prospectively according to a treatment protocol. Treatment consisted of prednisolone at a median initial dose of 0.5–1 mg/kg/d in combination with MMF at a median dose of 1.5–2 g/d. Biochemical response rates were excellent, with 88% of the 59 patients included achieving a complete biochemical remission within the first year of treatment and the other 12% achieving a partial remission. Seventy percent of those patients treated for more than one year were off steroids. Of note, only 3.4% of patients had to discontinue treatment due to MMF related side effects, which is considerably lower than the numbers reported for azathioprine [1] and for the use of MMF as second line treatment of AIH [14,15]. However, this may be confounded by the fact that patients had to take MMF for more than three months in order to be included into the study.

This study represents the first larger series of patients in whom an alternative to azathioprine as first line treatment of AIH has been investigated prospectively. The authors should be applauded for that. The strengths of the study are the prospective design and the large number of patients included from a single center. Also, the strict criteria applied for the definition of a biochemical remission, namely normalization of transaminases as well as immunoglobulins need to be mentioned. Other trials have used less stringent criteria (e.g. normalization of transaminases only [6] making a direct comparison of case series and controlled...
trials of AIH difficult. This is important because achieving a biochemical remission influences long term outcome and the combination of normal transaminases and normal IgG/gamma-globulins may best predict the lack of histological activity [3,16,17]. Obviously, the major weakness of the study is the lack of a direct or historical comparison with azathioprine from the same center. From the data presented, MMF seems to compare favorably with other reports using azathioprine with regard to its efficacy and seems to have considerably less side effects, but this may be a too optimistic interpretation of the data. 

So, should we use MMF as first line treatment of patients with AIH? In the direct comparison of the two drugs, MMF has several disadvantages. The first major disadvantage concerns treatment costs. Since maintenance treatment may be life long for the majority of patients with AIH, treatment costs have clearly to be taken into consideration [18]. The costs of MMF would be around 15 times higher than those of azathioprine. Since azathioprine is an efficient drug for most patients with AIH, these incremental costs would be hard to justify. The second disadvantage is that MMF has been associated with first trimester pregnancy loss and fetal malformations and is, therefore, contraindicated in pregnancy. Azathioprine on the other hand seems to be rather safe, although prematurity may be an issue [19]. This is relevant since many female patients with first presentation of AIH will be in child bearing age. Thirdly, long term side effects of MMF in patients with AIH are not known. Whether these disadvantages would be outweighed by the efficacy and side effect profile of MMF cannot be answered from the data available. Clearly it would be desirable to answer this question in a controlled clinical trial. However, the chances for such a trial to be performed are low.

If not using MMF first line, is there a role for MMF in the second line treatment of patients with AIH? There are several small case series describing the usefulness of MMF in patients intolerant to azathioprine or with insufficient response to the drug [14–16]. Response rates in this setting may be as high as 30–80% but are difficult to interpret since the patient populations are heterogeneous as is the definition of response. Two studies may give us clues as to the target population best suited for second line MMF treatment. In the study by Hennes et al., 12/27 patients intolerant to azathioprine entered remission under MMF in contrast to only 2/9 patients with prior insufficient response to azathioprine [15]. In the recent study of Sharzehi et al., none of the 12 patients with azathioprine non-response entered remission under MMF whereas 8/9 patients with prior azathioprine intolerance maintained remission under MMF [20]. This indicates that, in patients with prior insufficient response to azathioprine, more potent immunosuppressive drugs preferably with an alternative mode of action, such as cyclosporine A, tacrolimus, cyclophosphamide, or infliximab may be used [1,2].

In rare and heterogeneous clinical conditions such as AIH, medical progress is often made by a thoughtful combination of case series, clinical experience, and some clinical trials. This process has helped many of our patients. The present case series in conjunction with the other case series to MMF in AIH are the basis for a sensible clinical recommendation: MMF appears safe and effective in AIH, but there is no reason to make it the first-line drug in patients who could be managed by relatively low doses of azathioprine. However, in patients with limiting side-effects on azathioprine, MMF should be tried. The best alternative in patients, whose disease is not sufficiently controlled with azathioprine and steroids, remains open to future studies.

Conflict of interest

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References