Treatment of autoimmune hepatitis

Following uncontrolled studies of immunosuppressive therapy for autoimmune chronic active hepatitis (AIH) in the 1960s, three controlled clinical trials in the early 1970s formed the basis of, and justification for, current immunosuppressive regimens. Taken together, they suggested that treatment with prednisolone improved liver function tests, ameliorated symptoms and prolonged survival. Azathioprine seemed to have no role in inducing remission but could be used for maintenance of prednisolone induced remission, allowing a lower dose of prednisolone to be used. These studies were undertaken at a time when the controlled clinical trial was not a standard approach to investigating therapeutic efficacy and were, in their own way, landmark studies.

Looking back with nearly a quarter of a century's hindsight, it is easy to pick holes in their design and interpretation. The number of patients was small, and some of their conclusions have not stood the test of time. For example, it was suggested that the steroid medication should be given for the shortest possible time to control symptoms and then withdrawn, whereas we are now confident that treatment must be prolonged. Likewise, it was implied that it would generally take up to two years to achieve remission, whereas we now know that biochemical and histological remission can usually be attained within six months. None the less, the trials did confirm prolongation of survival, and were a major advance on the previous anecdotal reports.

A more serious flaw, and one to which all clinical trials are, to some extent, open to, was the question of whether or not the sample studied was genuinely representative of the population of patients with AIH as a whole. Here, the answer is probably no. Firstly, patients entered into the initial trials had severe symptomatic disease and had been referred to the centres carrying out the trials for this very reason. Nowadays, with the increasing use of auto- analysers, an increasing percentage of patients is detected incidentally, and they have a much milder form of the disease. Secondly, it is now recognised that there are several other causes of the histological picture of "chronic active hepatitis" that will not benefit from immunosuppressive treatment and yet may have been entered into these initial studies. For example, chronic viral hepatitis B and C, and drug related cases were not always screened for, and Wilson's disease and α1-antitrypsin deficiency were not well recognised as causes of this clinical picture.

More specific diagnostic procedures have not always helped the situation. For example, matters were only complicated when, in 1989, antibodies to the hepatitis C virus (HCV) were detected, using the first available anti-HCV screening tests. In a high percentage of patients with AIH, it was suggested that HCV may be the main aetiological factor in this disease. However, subsequent studies showed that many of these results were, in fact, false positives, particularly in the United Kingdom and United States, although in European patients with so-called type II AIH (anti-LKM positive) a strong association between HCV and AIH persists even with highly specific HCV tests. Indeed, it was problems of assessing the importance of HCV in patient groups from different countries that led to the formation of the International Autoimmune Hepatitis Study Group, which derived a consensus statement on criteria for diagnosis and response to treatment.

In a second generation of studies the use of azathioprine and prednisolone to maintain remission has been redefined. The first problem to be tackled was whether or not immunosuppressive treatment could be withdrawn once remission has been maintained for a year or so. Two studies showed that the great majority of cases would relapse rapidly. Secondly, Stellon et al confirmed the steroid sparing role of azathioprine as when it was withdrawn from patients in stable remission on prednisolone and azathioprine combined, there was a significantly higher relapse rate than when the initial treatment was maintained. This led to a controlled study of the maintenance of remission by azathioprine alone in which the dose of azathioprine was increased to 2 mg/kg/day and the prednisolone withdrawn completely. Surprisingly, there were no relapses among the group in which prednisolone was withdrawn and a subsequent long term follow up has confirmed the safety of the regimen and its efficacy in maintaining steroid free remission for up to 10 years. The benefits were a notable reduction in weight and steroid side effects, particularly Cushingoid features. Although severe arthralgia and myalgia were common, they were usually transitory and may be ameliorated by a slower withdrawal of the steroid component.

So, what conclusions can we arrive at? Firstly, the benefits of immunosuppressive treatment are only clear for those with severe symptomatic diseases, particularly if bridging necrosis is present, and after a firm diagnosis has been made. As it is now possible to establish the diagnosis with a much higher degree of confidence, as many forms of viral hepatitis can now be excluded, it is no longer necessary to wait for the customary six month period before initiating treatment. As nearly 90% of patients with severe AIH, but without cirrhosis, will survive for 10 years, it is unlikely that further trials of treatment are going to be undertaken if the end point is death. More likely we will have to use some surrogate marker such as remission and relapse rates. Those with severe and symptomatic disease, especially if they have a biopsy diagnosis of bridging necrosis, should receive immunosuppressive treatment. Most will enter remission on 30 mg prednisolone daily for one month, after which azathioprine can be introduced at 1 mg/kg/day and the dose of prednisolone reduced to 5–15 mg/day to maintain the aminotransferase activity within the normal range. If the patient develops steroid side effects, the option of increasing the dose of azathioprine to 2 mg/kg/day and withdrawing the steroids completely can be exercised. The optimal duration of treatment is unknown. Certainly, attempting withdrawal of immunosuppressive therapy before two years should be...
avoided and five years is probably reasonable. However, during any attempt at withdrawal, very close monitoring is essential as relapse may be rapidly fatal. Even if successful, long term follow up at three monthly intervals is required as we have seen major relapses occurring up to 11 years after withdrawal.

For patients with mild forms of the disease, including those middle aged and elderly men and women who are detected asymptomatically, the situation is far less clear. This group of patients will probably form the bulk of referrals to gastroenterologists and the therapeutic approach is still contentious. There is clearly an urgent need for a trial here but in view of the survival figures quoted above it is unlikely that such a study will be undertaken. One approach is to prescribe a small dose of prednisolone (5 mg/day) on the grounds that there may be an insidious onset of fibrosis/cirrhosis or that the disease may have subclinical periods of increased activity with histological assessment after five years of treatment. The second is a careful “watch and see” policy but with more frequent histological assessments perhaps every 18 months. However, there is clearly no justification for any treatment that causes significant side effects.

Finally, the quality of life for most patients, even with severe AIH is, on modest doses of azathioprine and prednisolone combined, or azathioprine alone, very high. Many will be completely asymptomatic, have normal liver function tests and have an excellent prognosis. In this situation, while an improved understanding of the pathogenesis of AIH may permit the development of more “specific” therapies, it is unlikely that current regimens will be superseded for many years to come.

PHILIP J JOHNSON

Department of Clinical Oncology,
The Chinese University of Hong Kong,
Prince of Wales Hospital,
Shatin, Hong Kong