

Autoimmune hepatitis: A life-long disease

Christina Weiler-Normann, Ansgar W. Lohse*

1st Medical Department, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

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The immune system is built on the basis of genetic and epigenetic factors, and shaped by constant and repeated internal and external challenges. Autoimmune disease appears to arise as a consequence of unknown external triggers in a susceptible host. Susceptibility develops on a predetermined genetic background [1], and is probably influenced by multiple environmental factors and life events such as infections. Once clinically apparent autoimmune disease has developed, the predisposition is so strong that cure is very rare indeed. This applies to such diverse autoimmune diseases as multiple sclerosis [2], lupus [3], type 1 diabetes [4] or rheumatoid arthritis [5]. To an immunologist, it does therefore not come as a surprise that autoimmune hepatitis (AIH) behaves similarly, and that most patients require life-long treatment as reported in this issue of the *Journal* [6].

However, this message does come as a surprise to the patient. And it often also comes as a surprise to the treating hepatologist. Patients want diseases to disappear, and as physicians we like to share our patients' optimism. In case of autoimmune hepatitis, the mostly excellent response to immunosuppressive therapy [7] and the usually asymptomatic course of AIH in remission make it all the more tempting to try and withdraw treatment. Furthermore, the possible side effects of immunosuppressive drug treatment make a trial of treatment withdrawal even more attractive. Like in all other chronic diseases, it is difficult to know which drug schedule and which dosages should be applied and for how long. The published guidelines give only very little help in these decisions and the data on which these are based are scarce [8–10]. The study by van Gerven *et al.* [6] describing the relapse rate in a large group of patients observed in various centers in the Netherlands is therefore a very welcome addition to the literature, and the message is sobering: even when being selective in choosing patients in whom a trial of treatment withdrawal is undertaken, the vast majority relapse, and very few patients indeed maintain remission without continued therapy. Relapse is usually early, but may sometimes be late, and a longer observation period in this study might have increased this figure even further.

The study is based on a retrospective analysis of a national registry, and therefore has a number of almost inevitable methodologically weak points. Most importantly, parameters considered essential before trying to stop treatment were missing in many patients. Only 51% of these patients had received measurement of their IgG levels, and only 18% had received a liver biopsy prior to reduction of immunosuppression. IgG levels in particular are essential in defining remission [11], and only patients with repeatedly normal IgG can be considered to be in stable remission [12], thus potentially qualifying for a trial of drug withdrawal. Furthermore, the time in remission of patients withdrawn from treatment was in some patients shorter than generally recommended. In addition, almost half of these patients still had dual therapy (steroids plus azathioprine) when treatment withdrawal was started, while most textbooks and treatment guidelines [8] recommend stable remission on monotherapy (usually azathioprine) before trying to taper out all treatment. Finally, autoantibody testing was incomplete, and the given information limited: patients were apparently not tested for SLA/LP antibodies, and the number of LKM-positive patients is not shown. Both autoantibodies have been described as predictors of relapse [13], and most specialists would recommend life-long treatment in patients positive for either of these two characteristic autoantibodies.

At the same time, the study has some important strengths not to be found in earlier reports on this subject. The study is based on a large patient population of altogether 844 AIH cases collected from 21 Dutch treatment centers, mostly not highly specialized referral centers, and therefore is likely to reflect everyday practice quite well. It is therefore particularly sobering to see that out of this large group of patients so few could safely be withdrawn of all treatment: treatment withdrawal was only attempted in a selected 16% of the whole group; almost half of these developed a flare while still on a reduced dose of drugs and only 1.7% of the overall patient group ended up without drugs. The conclusion that with very few exceptions AIH is a chronic disease requiring long-term and mostly life-long treatment is thus very convincing.

Can we predict in whom withdrawal of immunosuppressive treatment might be successful? There are hints in this study, and there are hints in the literature [13–17]. New in the present study is that younger age correlated with relapse, as did the presence of extra-hepatic autoimmune disease. Both findings are not surprising. Pediatric hepatologists have always recommended

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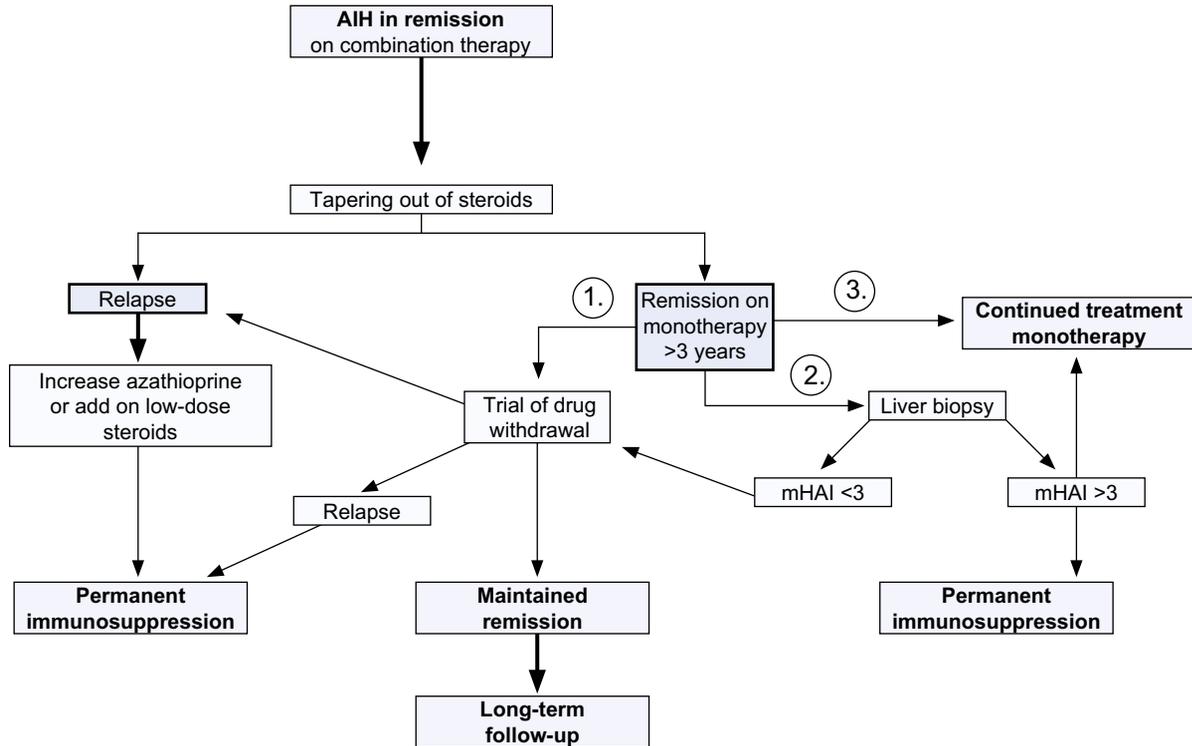
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* Corresponding author. Address: 1st Department of Medicine, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany. Tel.: +49 40 741053910; fax: +49 40 741058531.

E-mail address: alohse@uke.de (A.W. Lohse).



ELSEVIER



1. A trial of treatment withdrawal can be offered to patients with normal ALT and IgG levels for more than three years under close supervision, if patients opt against a liver biopsy
2. Liver biopsy prior to an attempt of treatment withdrawal is considered standard best practice, but the degree of inflammation to be tolerated has not been validated. A HAI of 3 as cut-off seems prudent
3. In high-risk patients life-long treatment without a trial of treatment withdrawal is probably appropriate. Risk-factors could be for example manifestation in childhood, presence of LKM or SLA/LP antibodies

Fig. 1. Possible treatment algorithm for treatment decisions in AIH. After information and education of the patient, several possibilities can be considered when sustained remission on monotherapy is established: (1) A trial of drug withdrawal can be undertaken after having informed the patient of a high probability of relapse. (2) Liver biopsy can be performed and results can be used to influence further treatment, especially in patients <45 years old and with concomitant autoimmune diseases. (3) In older patients or those unwilling to undergo liver biopsy or experimental treatment withdrawal, immunosuppressive therapy can be continued.

that immunosuppression should not be stopped in children with AIH [18], and that first manifestation of the disease in childhood usually requires life-long therapy. The co-existence of other autoimmune diseases in the same patient is likely to indicate a stronger susceptibility for autoimmunity. Scientifically, these findings may not come as a surprise, but clinically, they can be very helpful in the daily management of AIH patients, as they warn us to be particularly hesitant with a trial of drug withdrawal in these two patient groups. It should also warrant an active search for concomitant autoimmune diseases.

Even if drug withdrawal appears to be successful and the patient is in biochemical remission more than 1 year later, the patient remains an AIH patient: late relapse can occur. Relapse more than 20 years after successful drug withdrawal has been described in the literature [19], and we have observed similar cases. Frequent laboratory controls will be necessary in the first years after treatment withdrawal [1], and regular (at least yearly) testing of both transaminases and IgG levels thereafter is essential. The threshold to reinstitute immunosuppression should be low. In particular so, because AIH may run a subclinical course, and cirrhosis may progress without symptoms [1] – this preventable complication should not occur. Attention should be paid to rising IgG levels even within the normal limit, as a clear increase

for example from low normal to high normal values is likely to indicate renewed disease activity.

What are the scientific questions arising from this study? We should try to understand better the underlying susceptibility factors that cause AIH, and that might predict who has a chance of a stable drug-free remission. We should try to identify predictors beyond those discussed in this study: disease presentation, time to remission, drug-dosage required for remission induction, auto-antibody profiles and titres, IgG levels and ALT levels, including variations in the normal range, histological features at presentation and during treatment, remission duration, etc. In addition to these more biological factors, we need to address the psychological features of managing this chronic disease: compliance with the recommended treatment was recently shown to be an important factor [20], and treatment adherence in a chronic disease requiring daily medication with potentially toxic drugs may be very difficult. In managing patients wishing to withdraw treatment, different approaches may be appropriate and should be adapted to the individual wishes and fears of the patient (Fig. 1). Textbooks and guidelines [6,8–10] recommend liver biopsy prior to a trial of treatment withdrawal, and no such trial if the biopsy shows relevant inflammatory activity (usually a hepatitis activity index (HAI-Score) of 3 or more).

However, in daily practice we often take another approach after careful discussion with the patient: as most patients strongly wish to try treatment withdrawal, and as we prefer to undertake such a trial under our supervision rather than the patient doing it secretly (or not coming back), we discuss such a trial after a minimum of 3 years of stable remission. We strongly discourage such a trial in patients requiring dual immunosuppression or experiencing flares during maintenance therapy, as failure is certain. In all other patients, we discuss the option of biopsy or a trial of treatment withdrawal without biopsy, and insist on close monitoring. The majority of patients opt for a trial of treatment withdrawal without biopsy. In most patients, relapse tends to occur early, and if treatment withdrawal is undertaken slowly and stepwise, relapse occurs gradually. As soon as a relapse is definite (in some patients this may require biopsy to demonstrate relapse beyond doubt), immunosuppression is reinstated, usually with a short course of dual therapy, going back to monotherapy within 3 months. The approach may be less scientific, but very effective: we find that patient compliance is greatly improved by such a trial, and the acceptance for a long-term, usually life-long immunosuppression at the lowest effective dose is greatly enhanced after such a failure of treatment withdrawal. The most important message is, as clearly shown by the present study: AIH is a chronic disease, no matter how acute the first presentation, close medical supervision is essential, and the vast majority of patients require permanent treatment. Communicating the high probability of a long-term, perhaps life-long need for immunosuppressive medication early on when diagnosis is established may not please the patient but ultimately will help develop a trusting relationship between patient and physician [21]. Assisting the patient to accept this need, finding the lowest effective dose of the drugs tolerated best by this individual patient and motivation for the necessary drug-adherence will improve life expectancy, long-term outcome and patient satisfaction.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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