University of Groningen

Maintenance immunosuppressive therapy in autoimmune hepatitis

Stolk, Mark F. J.; van den Berg, Aad P.; van Erpecum, Karel J.

Published in:
European Journal of Internal Medicine

DOI:
[10.1016/j.ejim.2021.05.005](https://doi.org/10.1016/j.ejim.2021.05.005)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2021

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Stolk, M. F. J., van den Berg, A. P., & van Erpecum, K. J. (2021). Maintenance immunosuppressive therapy in autoimmune hepatitis: To stop or not to stop, that is the question. *European Journal of Internal Medicine*, 90, 25-26. <https://doi.org/10.1016/j.ejim.2021.05.005>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Commentary

Maintenance immunosuppressive therapy in autoimmune hepatitis: To stop or not to stop, that is the question.

Mark F.J. Stolk^{a,*}, Aad P. van den Berg^b, Karel J. van Erpecum^c

^a Department of Gastroenterology, St Antonius Hospital Nieuwegein, the Netherlands

^b Department of Gastroenterology and Hepatology and Institute for Organ Transplantation (GIOT), University Medical Center Groningen, Groningen, the Netherlands

^c Department of Gastroenterology and Hepatology University Medical Center Utrecht, Utrecht, the Netherlands

ARTICLE INFO

Keywords

Autoimmune hepatitis
Immunosuppression
Withdrawal
Relapse

Autoimmune hepatitis (AIH) is a rare and challenging disease. Its presentation ranges from mildly elevated transaminases to jaundice with decompensated liver disease. Blood tests often reveal elevated immunoglobulin G levels and several antibody tests like anti-smooth muscle antibodies, liver-kidney microsomal antibodies or soluble liver antigen antibodies can be positive. Viral hepatitis (including hepatitis E viral infection), drug-induced liver injury and (especially in young patients) Wilson disease should be excluded. A single reliable diagnostic test is lacking, but the (revised or simplified) AIH scoring system allows to establish a probable or definite AIH diagnosis [1]. A rapid and correct diagnosis of AIH is important, because if left untreated, AIH can lead to cirrhosis and even liver failure with need for transplantation or premature death. It is encouraging to recognize that the modern AIH population is quite different from those in the early years when Dame Sheila Sherlock treated AIH patients (generally icteric with often advanced liver disease) with prednisone monotherapy [2]. Currently, the diagnosis is established much earlier in most cases, and therapeutic options have expanded greatly. When therapy is initiated with high dose corticosteroids, transaminases often show a rapid response allowing to taper steroids and maintenance immunosuppressive therapy can then be prescribed. Usually azathioprine is used for long-term treatment, either alone or in combination with low-dose corticosteroids. In about 20% of cases, intolerance or insufficient treatment response necessitate second-line treatment with mycophenolate mofetil. Third-line treatment options include cyclosporine, tacrolimus and sirolimus. There is limited experience with infliximab or rituximab. Poor adherence to long-term

treatment for chronic diseases such as hypertension, hypercholesterolemia and human immunodeficiency virus (HIV) infection is a frequent phenomenon (especially in asymptomatic patients) with non-adherence rates of 50% or higher, and the same could apply to AIH patients. In general, the patient is happy because -at least according to liver tests- the enigmatic liver inflammation is under control. In the best case the patients asks after some time if therapy can be stopped and in the worst case the patient decides without consultation of the physician, to stop all medication. Unfortunately, relapse is very common after stopping immunosuppressive therapy in AIH patients (25– 89% in previous studies [3–7]), mostly within one year after withdrawal. Risk factors reported to be associated with high relapse rates are slow response to initial immunosuppression, shorter treatment duration, higher ALT and IgG levels at withdrawal, a history of previous relapse, a liver biopsy with residual inflammation at withdrawal, immunosuppressive combination therapy at withdrawal, older age, and concomitant other autoimmune diseases. Long-term treatment with nitrofurantoin, minocycline and Tumor Necrosis Factor alpha (TNF alpha) inhibitors and other medication can lead to drug-induced AIH [8]. Drug-induced autoimmune-like hepatitis shows a different natural history with very low risk of relapse after drug withdrawal (and often also temporarily prednisone treatment) and is not discussed further. There is no agreement on strict stopping rules for immunosuppression in AIH and reliable non-invasive markers to prove complete remission of AIH do not exist. Recent guidelines from the European Association for the Study of the Liver (EASL) advise that withdrawal could be considered after at least 3

* Corresponding author at: Department of Gastroenterology, St Antonius Hospital Po Box 2500, 3430EM Nieuwegein, the Netherlands
E-mail address: m.stolk@antoniusziekenhuis.nl (M.F.J. Stolk).

<https://doi.org/10.1016/j.ejim.2021.05.005>

Received 29 April 2021; Accepted 1 May 2021

Available online 21 May 2021

0953-6205/© 2021 European Federation of Internal Medicine. Published by Elsevier B.V. All rights reserved.

years treatment, including at least two years with normal transaminases and IgG [1]. In this issue of the Journal, van den Brand *et al.* present the first prospective study on drug withdrawal with adherence to a strict protocol in patients with AIH in long-term remission [9]. Although small, this study provides some valuable insights for the clinician. In addition to the EASL criteria, their inclusion criteria were histological activity index (HAI) ≤ 3 , absence of cirrhosis and immunosuppressive monotherapy. Of note, persistent histological activity precluded drug withdrawal in 30% of cases (5 of 17 patients). One of these patients had progressed from F0 (no fibrosis) to incomplete cirrhosis (stage 5) with HAI=10 compared to the baseline biopsy. A total of eight patients (67%) remained in treatment-free remission during a median follow-up of 62 (range: 13–75) months. A relapse occurred in four patients (33%).

The value of a liver biopsy prior to decide on discontinuation of immunosuppressive therapy is controversial, and patients are generally not very eager to undergo this procedure. The current work of van den Brand *et al.* underscores that a significant number of AIH patients may need a more intense immunosuppressive regimen despite apparent disease remission according to the liver tests. Transient elastography (Fibroscan®) measures liver stiffness in a patient-friendly, non-invasive way within a few minutes and correlates reasonably well with degree of fibrosis in viral and cholestatic liver diseases. Fibroscan® could be of value in selecting those AIH patients on maintenance immunosuppressive therapy who could benefit from liver biopsy to decide on treatment withdrawal or on even more intensive immunosuppression [3]. Liver stiffness values measured by transient elastography increase not only with progressive fibrosis, but also with ongoing intrahepatic inflammation. This is a significant disadvantage in case of viral hepatitis, but could be an advantage in AIH where we want to detect not only fibrosis, but also unexpected ongoing inflammation under maintenance immunosuppression. Interestingly, in the study of van den Brand *et al.*, patients who were in histological remission had significantly lower median levels of ALT (16 vs. 25 U/L; $p = 0.01$) and AST (22 vs. 26 U/L; $p = 0.01$) compared with patients who were not eligible for withdrawal, in line with previous reports [10]. One should also realise in this respect, that in autoimmune hepatitis, histological improvement after institution of immunosuppressive therapy lags behind clinical and laboratory improvement by 3–8 months [11,12].

Van den Brand *et al.* report that 67% (95% C.I. 40–93%) of their patients remained in treatment-free remission, whereas relapse occurred in 33% (95% C.I. 7–60%) of cases. These results suggest (albeit patient numbers are limited), that in a highly selected patient group there is a reasonable chance of persistent remission after withdrawal of immunosuppression. Limitations of the study are that no detailed histological data from the time of initial AIH diagnosis are provided and that baseline data on auto-antibodies are incomplete.

What could be the advice for physicians caring for AIH patients who want to stop maintenance immunosuppressive therapy? Certainly, the requirements of the EASL guidelines should be taken into account (i.e. at least 3 years immunosuppressive treatment, including at least two years with normal transaminases and IgG). Cirrhosis could be a reason not to pursue withdrawal, considering the chance of deleterious outcome in case of relapse. Repeated relapses often lead to progressive fibrosis and

poor outcome [6]. Subsequently, the known risk factors for relapse should be evaluated. Then a liver biopsy should strongly be considered, and the patient should be aware that the results of the biopsy could even lead to the advice of increasing dosages of immunosuppressive medication. In conclusion, the publication by van den Brand *et al.* [9] can be viewed as a relevant step towards better identification and selection of AIH patients who might benefit from maintenance drug treatment withdrawal. This work also points to the importance of new research efforts into the factors that predict or might be related to relapse. One might think here of the role of elastography, the importance of reaching a deep remission, the type of drug and drug levels during remission and genetic factors as potential approaches to patient-tailored therapy in order to improve prognosis in AIH.

Declaration of Competing Interest

None.

References

- [1] Lohse AW, Chazouillères O, Dalekos G, Drenth J, Heneghan M, Hofer H, et al. EASL clinical practice guidelines: autoimmune hepatitis. *J Hepatol* 2015;63:971–1004. <https://doi.org/10.1016/j.jhep.2015.06.030>.
- [2] Cook GC, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q J Med* 1971;40:159–85. <https://doi.org/10.1093/oxfordjournals.qjmed.a067264>.
- [3] Hartl J, Ehlken H, Sebode M, Peiseler M, Krech T, Zenouzi R, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. *J Hepatol* 2018;68:754–63. <https://doi.org/10.1016/j.jhep.2017.11.020>.
- [4] Van Gerven NMF, Verwer BJ, Witte BJ, Van Hoek B, Coenraad MJ, Van Erpecum KJ, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *J Hepatol* 2013;58:141–7. <https://doi.org/10.1016/j.jhep.2012.09.009>.
- [5] Czaja AJ, Ludwig J, Baggenstoss AH, Wolf A. Corticosteroid-treated chronic active hepatitis in remission: uncertain prognosis of chronic persistent hepatitis. *N Engl J Med* 1981;304:5–9. <https://doi.org/10.1056/NEJM198101013040102>.
- [6] Montano-Loza AJ, Carpenter HA, Czaja AJ. Consequences of treatment withdrawal in type 1 autoimmune hepatitis. *Liver Int Off J Int Assoc Study Liver* 2007;27: 507–15. <https://doi.org/10.1111/j.1478-3231.2007.01444.x>.
- [7] Zachou K, Gatselis NK, Arvaniti P, Gabeta S, Rigopoulou EI, Koukoulis GK, et al. A real-world study focused on the long-term efficacy of mycophenolate mofetil as first-line treatment of autoimmune hepatitis. *Aliment Pharmacol Ther* 2016;43: 1035–47. <https://doi.org/10.1111/apt.13584>.
- [8] Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, et al. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. *Hepatology* 2010;51:2040–8. <https://doi.org/10.1002/hep.23588>.
- [9] van den Brand FF, Snijders RJALM, de Boer YS, Verwer BJ, van Nieuwkerk CMJ, Bloemena E, et al. Drug withdrawal in patients with autoimmune hepatitis in long-term histological remission: a prospective observational study. *Eur J Intern Med* 2021. <https://doi.org/10.1016/j.ejim.2021.03.024>.
- [10] Hartl J, Ehlken H, Weiler-Normann C, Sebode M, Kreuels B, Pannicke N, et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. *J Hepatol* 2015; 62:642–6. <https://doi.org/10.1016/j.jhep.2014.10.018>.
- [11] Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al. Diagnosis and management of autoimmune hepatitis. *Hepatology* 2010;51: 2193–213. <https://doi.org/10.1002/hep.23584>.
- [12] Soloway RD, Summerskill WH, Baggenstoss AH, Geall MG, Gitnick GL, Elveback IR, et al. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology* 1972;63:820–33.