World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2024 February 27; 16(2): 135-139

DOI: 10.4254/wjh.v16.i2.135

ISSN 1948-5182 (online)

EDITORIAL

Advancements in autoimmune hepatitis management: Perspectives for future guidelines

Marcos Mucenic

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Mohammadi F, Iran

Received: December 3, 2023
Peer-review started: December 3, 2023
First decision: December 15, 2023
Revised: January 4, 2024
Accepted: January 23, 2024
Article in press: January 23, 2024
Published online: February 27, 2024

Marcos Mucenic, Liver Transplantation Group, Santa Casa de Porto Alegre, Porto Alegre 90035-070, RS, Brazil

Corresponding author: Marcos Mucenic, MD, PhD, Doctor, Medical Assistant, Liver Transplantation Group, Santa Casa de Porto Alegre, Independencia 75, Porto Alegre 90035-070, RS, Brazil. mmucenic@gmail.com

Abstract

The first-line treatment for autoimmune hepatitis involves the use of prednisone or prednisolone either as monotherapy or in combination with azathioprine (AZA). Budesonide has shown promise in inducing a complete biochemical response (CBR) with fewer adverse effects and is considered an optional first-line treatment, particularly for patients without cirrhosis; however, it is worth noting that the design of that study favored budesonide. A recent real-life study revealed higher CBR rates with prednisone when equivalent initial doses were administered. Current guidelines recommend mycophenolate mofetil (MMF) for patients who are intolerant to AZA. It is important to mention that the evidence supporting this recommendation is weak, primarily consisting of case series. Nevertheless, MMF has demonstrated superiority to AZA in the context of renal transplant. Recent comparative studies have shown higher CBR rates, lower therapeutic failure rates, and reduced intolerance in the MMF group. These findings may influence future guidelines, potentially leading to a significant modification in the first-line treatment of autoimmune hepatitis. Until recently, the only alternative to corticosteroids was lifelong maintenance treatment with AZA, which comes with notable risks, such as skin cancer and lymphoma. Prospective trials are essential for a more comprehensive assessment of treatment suspension strategies, whether relying on histological criteria, strict biochemical criteria, or a combination of both. Single-center studies using chloroquine diphosphate have shown promising results in significantly reducing relapse rates compared to placebo. However, these interesting findings have yet to be replicated by other research groups. Additionally, second-line drugs, such as tacrolimus, rituximab, and infliximab, should be subjected to controlled trials for further evaluation.

Key Words: Autoimmune hepatitis; Treatment; Immunosuppression; Relapse; Remission induction

©The Author(s) 2024. Published by Baishideng Publishing Group Inc. All rights reserved.

Core Tip: Autoimmune hepatitis guidelines consider corticosteroids as first-line treatment, including budesonide as an option in patients without cirrhosis. Azathioprine is recommended to reduce corticosteroid doses and side effects. Nevertheless, there are concerns regarding its long-term malignancy risks. Recent publications suggest that these guidelines may be outdated. The efficacy of budesonide can be limited to patients with lower aminotransferases levels. The potential superiority of mycophenolate mofetil to azathioprine is under scrutiny. Additionally, there are controversies regarding treatment suspension, with a potential role for chloroquine for long-term maintenance treatment. Other therapeutic agents are still in the initial stages of research.

Citation: Mucenic M. Advancements in autoimmune hepatitis management: Perspectives for future guidelines. *World J Hepatol* 2024; 16(2): 135-139
URL: https://www.wjgnet.com/1948-5182/full/v16/i2/135.htm
DOI: https://dx.doi.org/10.4254/wjh.v16.i2.135

INTRODUCTION

Autoimmune hepatitis (AIH) was the first chronic liver disease for which a treatment benefit was demonstrated in randomized studies, marking over 50 years since those pivotal clinical trials. Patients under treatment exhibited a survival rate of 85%-95%, a stark contrast to the 33%-44% observed with a placebo after 2.0 years to 3.5 years of follow-up [1-3].

The first-line treatment of AIH involves the corticosteroids prednisone (PD) or prednisolone, either as monotherapy or in combination with azathioprine (AZA). Corticosteroids readily interfere with the immune system by affecting cytokine production and inhibiting T lymphocyte activation. AZA exerts its immunosuppressive effects by blocking the maturation of lymphocyte precursors, which may take at least 3 mo for the full effect to be accomplished[4].

In 2015, the European Association for the Study of Liver Diseases (EASL) published their practice guidelines on AIH diagnosis and management[5], followed by the American Association for the Study of Liver Diseases (AASLD) in 2019[6] and the Asian Pacific Association for the Study of the Liver in 2021[7]. Both the AASLD and EASL recommend delaying the introduction of AZA for the first 2 wk. This approach, though untested in clinical trials, may aid in distinguishing rare instances of AZA-induced hepatotoxicity from non-response. AZA is primarily employed for its steroid-sparing effect and for maintenance therapy since it is less effective in inducing a response. Once steroid responsiveness is confirmed and thiopurine methyltransferase deficiency is ruled out, AZA can be prescribed, according to these guidelines. Genetic mutations affecting thiopurine methyltransferase occur in up to 0.6% of the population, but the consequences of using AZA in these individuals can be severe[8].

For over 40 years, this was the standard first-line treatment. Randomized trials involving ursodeoxycholic acid and cyclosporine, as well as intermittent or pulse corticosteroid treatment, yielded negative results[9-13]. In 2010, a clinical trial suggested that budesonide (BD) might be more effective than PD in inducing a response, with the added advantage of causing fewer cosmetic side effects[14]. BD is a glucocorticosteroid with a potent topical effect and a high (> 90%) first-pass uptake[15]. However, this study faced criticism due to the rapid reduction in PD doses, irrespective of biochemical relapse or non-response, reaching 10 mg per day within 8 wk. Importantly, the effectiveness in the control group was much smaller than expected: Only 39% in 6 mo. Despite the criticism, the AASLD guidelines recommend BD as a first-line option for patients without cirrhosis, particularly those at risk of adverse corticosteroid-related side effects. Other medical societies take a more cautious approach, suggesting BD as an alternative pending further study.

A recent multicenter real-life study[16] that included treatment-naïve, non-severe AIH patients without cirrhosis revealed that clinicians prescribed BD in only 5% of cases. Notably, BD was more commonly used in patients with significantly lower liver test results (median alanine aminotransferase 198 IU/L *vs* 753 IU/L), with a relative risk of response of 0.20 compared to PD. However, effectiveness was similar in patients with alanine aminotransferase or aspartate aminotransferase levels < 2 times the normal limit. Complete biochemical response was 87% with PD and 51% with BD when equivalent initial doses were used (50 mg PD *vs* 9 mg BD), which was in contrast with the clinical trial favoring budesonide.

Current guidelines recommend mycophenolate mofetil (MMF) only for AZA-intolerant patients. MMF is the prodrug of mycophenolic acid. It exerts an antiproliferative action on lymphocytes by inhibiting inosine monophosphate dehydrogenase, the rate-limiting enzyme in de novo purine synthesis[15]. However, MMF has been found to be superior to AZA in renal transplant protocols, reducing acute rejection and graft loss[17,18]. Accordingly, two recent studies compared MMF to AZA on a head-to-head basis. The first was a Greek multicenter study published in 2022[19]. It was designed in a way that patients could choose whether to receive AZA (1-2 mg/kg/d up to 150 mg) or MMF (1.5-2.0 mg/d) in addition to a starting PD dose of 40 mg. Notably, the MMF group achieved greater rates of complete biochemical response (96% *vs* 87%) and smaller rates of therapeutic failures (8% *vs* 19%) or treatment modification due to incomplete response or intolerance (11% *vs* 44%) after 4.8 years of follow-up.

Last year in the EASL Liver Meeting, a randomized control trial (the CAMARO trial) was presented[20]. Patients in the AZA arm received a maximum daily dose of 100 mg, while patients in the MMF arm were treated with up to 2000 mg daily, per protocol. In treatment-naïve patients, MMF was superior to AZA for induction of remission (55.3% *vs* 25.8%) with less cessation due to adverse effects (5.1% *vs* 25.8%). Some may argue that the AZA maximum dose was not equivalent to that of MMF, but the magnitude of the difference between the treatment arms was relevant, and an increase of the AZA dose would lead to even greater side effect rates.

After 50 years, an important modification in the first-line treatment of AIH is anticipated, as MMF could be considered an alternative to AZA. Second-line or third-line drugs such as tacrolimus, rituximab, and infliximab need controlled trials for further evaluation, requiring a multicentric effort due to the large sample sizes needed.

Regarding long-term therapy, the prolonged use of corticosteroids is associated with well-established side effects, while maintaining monotherapy with AZA carries risks such as skin cancer and lymphoma[21]. It is recommended to consider suspending treatment upon achieving a complete response. However, the suspension of treatment remains a topic of controversy in the management of AIH. Historical data has shown that relapses can lead to the progression of AIH to cirrhosis, liver failure, and even death. Nevertheless, recent publications with closer follow-up have not found these serious complications. A consolidation period of at least 18 mo is recommended, considering that histological remission typically lags behind biochemical remission[6,22].

Plasma cell infiltrates and interface hepatitis have been associated with relapse after treatment suspension[23,24], but those publications defined response as a reduction to less than twice the upper limit of liver tests. It was later demonstrated that complete biochemical normalization, including aminotransferases and gamma globulin levels, correlated with more favorable clinical outcomes. Unfortunately, even using these criteria, relapses still occurred in 46%-81% of patients after 3 years of follow-up[25,26]. However, these publications evaluating relapse risk are potentially biased because of their retrospective nature. Indeed, there is currently no controlled trial to support any treatment withdrawal strategy. A prospective trial in this regard would be invaluable, but it would need to be multicentric to include a sufficient sample size. There is a need to evaluate prospectively whether a liver biopsy is needed before treatment suspension, or if strict biochemical criteria alone are sufficient.

Encouraging results have emerged from single-center studies involving the use of chloroquine diphosphate, demonstrating a significant reduction in relapse rates compared to a placebo. Chloroquine plays an established role in the treatment of autoimmune rheumatic diseases, potentially by interfering with lysosomal phagocytic function, antigen presentation, cytokine production, and other immunoregulatory effects. However, it is important to note that these intriguing findings have yet to be independently replicated by other research groups[27-29].

Promising therapeutic agents, such as those acting on cytokine, chemokine, and signaling pathways, cell-based therapy, microbiome modulation, or nanomedicine, are still in the early stages of research[30].

CONCLUSION

The clinical management of autoimmune hepatitis is primarily rooted in landmark clinical trials conducted over 50 years ago. While certain aspects of this management have evolved, recent research has provided data that hold the potential to refine our current guidelines. Nonetheless, achieving optimal strategies for response induction, treatment maintenance, and suspension will require ongoing research and efforts.

FOOTNOTES

Author contributions: Mucenic M wrote and revised the manuscript.

Conflict-of-interest statement: The author declares having no conflicts of interest.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: https://creativecommons.org/Licenses/by-nc/4.0/

Country/Territory of origin: Brazil

ORCID number: Marcos Mucenic 0000-0001-9389-2236.

S-Editor: Liu JH
L-Editor: A
P-Editor: Cai YX

REFERENCES

1 **Cook GC**, Mulligan R, Sherlock S. Controlled prospective trial of corticosteroid therapy in active chronic hepatitis. *Q J Med* 1971; **40**: 159-185 [PMID: 4933363 DOI: 10.1093/oxfordjournals.qjmed.a067264]

2 **Soloway RD**, Summerskill WH, Baggenstoss AH, Geall MG, Gitnick GL, Elveback IR, Schoenfield LJ. Clinical, biochemical, and histological remission of severe chronic active liver disease: a controlled study of treatments and early prognosis. *Gastroenterology* 1972; **63**: 820-833 [PMID: 4538724]

3 **Murray-Lyon IM**, Stern RB, Williams R. Controlled trial of prednisone and azathioprine in active chronic hepatitis. *Lancet* 1973; **1**: 735-737 [PMID: 4121073 DOI: 10.1016/s0140-6736(73)92125-9]

4 **Heneghan MA**, McFarlane IG. Current and novel immunosuppressive therapy for autoimmune hepatitis. *Hepatology* 2002; **35**: 7-13 [PMID: 11786954 DOI: 10.1053/jhep.2002.30991]

5 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: Autoimmune hepatitis. *J Hepatol* 2015; **63**: 971-1004 [PMID: 26341719 DOI: 10.1016/j.jhep.2015.06.030]

6 **Mack CL**, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, Vierling JM, Alsawas M, Murad MH, Czaja AJ. Diagnosis and Management of Autoimmune Hepatitis in Adults and Children: 2019 Practice Guidance and Guidelines From the American Association for the Study of Liver Diseases. *Hepatology* 2020; **72**: 671-722 [PMID: 31863477 DOI: 10.1002/hep.31065]

7 **Wang G**, Tanaka A, Zhao H, Jia J, Ma X, Harada K, Wang FS, Wei L, Wang Q, Sun Y, Hong Y, Rao H, Efe C, Lau G, Payawal D, Gani R, Lindor K, Jafri W, Omata M, Sarin SK. The Asian Pacific Association for the Study of the Liver clinical practice guidance: the diagnosis and management of patients with autoimmune hepatitis. *Hepatol Int* 2021; **15**: 223-257 [PMID: 33942203 DOI: 10.1007/s12072-021-10170-1]

8 TPMT testing before azathioprine therapy? *Drug Ther Bull* 2009; **47**: 9-12 [PMID: 19129430 DOI: 10.1136/dtb.2008.12.0033]

9 **Nasseri-Moghaddam S**, Nikfam S, Karimian S, Khashayar P, Malekzadeh R. Cyclosporine-A Versus Prednisolone for Induction of Remission in Auto-immune Hepatitis: Interim Analysis Report of a Randomized Controlled Trial. *Middle East J Dig Dis* 2013; **5**: 193-200 [PMID: 24829691]

10 **Cuarterolo ML**, Ciocca M, López S, Araujo M, Álvarez F. Autoimmune Hepatitis in Children: Prednisone Plus Azathioprine Versus Cyclosporine: A Randomized Trial. *J Pediatr Gastroenterol Nutr* 2020; **71**: 376-380 [PMID: 32520828 DOI: 10.1097/MPG.0000000000002776]

11 **Czaja AJ**, Wang KK, Shiels MT, Katzmann JA. Oral pulse prednisone therapy after relapse of severe autoimmune chronic active hepatitis. A prospective randomized treatment trial evaluating clinical, biochemical, and lymphocyte subset responses. *J Hepatol* 1993; **17**: 180-186 [PMID: 8445231 DOI: 10.1016/s0168-8278(05)80035-2]

12 **Czaja AJ**, Carpenter HA, Lindor KD. Ursodeoxycholic acid as adjunctive therapy for problematic type 1 autoimmune hepatitis: a randomized placebo-controlled treatment trial. *Hepatology* 1999; **30**: 1381-1386 [PMID: 10573515 DOI: 10.1002/hep.510300603]

13 **Summerskill WH**, Korman MG, Ammon HV, Baggenstoss AH. Prednisone for chronic active liver disease: dose titration, standard dose, and combination with azathioprine compared. *Gut* 1975; **16**: 876-883 [PMID: 1104411 DOI: 10.1136/gut.16.11.876]

14 **Manns MP**, Woynarowski M, Kreisel W, Lurie Y, Rust C, Zuckerman E, Bahr MJ, Günther R, Hultcrantz RW, Spengler U, Lohse AW, Szalay F, Färkkilä M, Pröls M, Strassburg CP; European AIH-BUC-Study Group. Budesonide induces remission more effectively than prednisone in a controlled trial of patients with autoimmune hepatitis. *Gastroenterology* 2010; **139**: 1198-1206 [PMID: 20600032 DOI: 10.1053/j.gastro.2010.06.046]

15 **Terziroli Beretta-Piccoli B**, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: Standard treatment and systematic review of alternative treatments. *World J Gastroenterol* 2017; **23**: 6030-6048 [PMID: 28970719 DOI: 10.3748/wjg.v23.i33.6030]

16 **Díaz-González Á**, Hernández-Guerra M, Pérez-Medrano I, Sapena V, Riveiro-Barciela M, Barreira-Díaz A, Gómez E, Morillas RM, Del Barrio M, Escudé L, Mateos B, Horta D, Gómez J, Conde I, Ferre-Aracil C, El Hajra I, Arencibía A, Zamora J, Fernández A, Salcedo M, Molina E, Soria A, Estévez P, López C, Álvarez-Navascúes C, García-Retortillo M, Crespo J, Londoño MC; ColHai Registry. Budesonide as first-line treatment in patients with autoimmune hepatitis seems inferior to standard predniso(lo)ne administration. *Hepatology* 2023; **77**: 1095-1105 [PMID: 36626622 DOI: 10.1097/HEP.0000000000000018]

17 **van Gelder T**, Hesselink DA. Mycophenolate revisited. *Transpl Int* 2015; **28**: 508-515 [PMID: 25758949 DOI: 10.1111/tri.12554]

18 **Knight SR**, Russell NK, Barcena L, Morris PJ. Mycophenolate mofetil decreases acute rejection and may improve graft survival in renal transplant recipients when compared with azathioprine: a systematic review. *Transplantation* 2009; **87**: 785-794 [PMID: 19300178 DOI: 10.1097/TP.0b013e3181952623]

19 **Dalekos GN**, Arvaniti P, Gatselis NK, Gabeta S, Samakidou A, Giannoulis G, Rigopoulou E, Koukoulis GK, Zachou K. Long-term results of mycophenolate mofetil vs. azathioprine use in individuals with autoimmune hepatitis. *JHEP Rep* 2022; **4**: 100601 [PMID: 36411768 DOI: 10.1016/j.jhepr.2022.100601]

20 **Snijders R**, Stoelinga A, Gevers T, Pape S, Biewenga M, Tushuizen M, Verdonk R, De Jonge HM, Vrolijk JM, Bakker S, Vanwolleghem T, de Boer Y, Baven-Pronk M, Beuers U, der Meer AV, van Gerven N, Sijtsma M, Verwer B, van IJzendoorn M, van Herwaarden M, van den Brand F, Korkmaz KS, van den Berg A, Guichelaar M, Levens A, Van Hoek B, Drenth JPH. Abstract LBO-06: A controlled randomized trial of azathioprine vs. mycophenolate mofetil for the induction of remission in treatment-naive autoimmune hepatitis (CAMARO trial). EASL Congress; June 21-24, 2023; Vienna (hybrid meeting) [DOI: 10.1016/s0168-8278(23)00457-9]

21 **Kotlyar DS**, Lewis JD, Beaugerie L, Tierney A, Brensinger CM, Gisbert JP, Loftus EV Jr, Peyrin-Biroulet L, Blonski WC, Van Domselaar M, Chaparro M, Sandilya S, Bewtra M, Beigel F, Biancone L, Lichtenstein GR. Risk of lymphoma in patients with inflammatory bowel disease treated with azathioprine and 6-mercaptopurine: a meta-analysis. *Clin Gastroenterol Hepatol* 2015; **13**: 847-58.e4; quiz e48 [PMID: 24879926 DOI: 10.1016/j.cgh.2014.05.015]

22 **Bittencourt PL**, Cançado EL, Couto CA, Levy C, Porta G, Silva AE, Terrabuio DR; Brazilian Society of Hepatology on the Diagnosis and Management of Autoimmune Diseases of the Liver, Carvalho Filho RJ, Chaves DM, Miura IK, Codes L, Faria LC, Evangelista AS, Farias AQ, Gonçalves LL, Harriz M, Lopes Neto EP, Luz GO, Oliveira P, Oliveira EM, Schiavon JL, Seva-Pereira T, Parise ER. Brazilian society of hepatology recommendations for the diagnosis and management of autoimmune diseases of the liver. *Arq Gastroenterol* 2015; **52** Suppl 1: 15-46 [PMID: 26959804 DOI: 10.1590/S0004-28032015000500002]

23 **Czaja AJ**, Davis GL, Ludwig J, Taswell HF. Complete resolution of inflammatory activity following corticosteroid treatment of HBsAg-negative chronic active hepatitis. *Hepatology* 1984; **4**: 622-627 [PMID: 6745850 DOI: 10.1002/hep.1840040409]

24 **Czaja AJ**, Carpenter HA. Histological features associated with relapse after corticosteroid withdrawal in type 1 autoimmune hepatitis. *Liver Int*

2003; **23**: 116-123 [PMID: 12654134 DOI: 10.1034/j.1600-0676.2003.00810.x]

25 **Hartl J**, Ehlken H, Weiler-Normann C, Sebode M, Kreuels B, Pannicke N, Zenouzi R, Glaubke C, Lohse AW, Schramm C. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. *J Hepatol* 2015; **62**: 642-646 [PMID: 25457202 DOI: 10.1016/j.jhep.2014.10.018]

26 **van Gerven NM**, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, Beuers U, van Buuren HR, de Man RA, Drenth JP, den Ouden JW, Verdonk RC, Koek GH, Brouwer JT, Guichelaar MM, Mulder CJ, van Nieuwkerk KM, Bouma G; Dutch Autoimmune Hepatitis Working Group. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. *J Hepatol* 2013; **58**: 141-147 [PMID: 22989569 DOI: 10.1016/j.jhep.2012.09.009]

27 **Mucenic M**, Mello ES, Cançado EL. Chloroquine for the maintenance of remission of autoimmune hepatitis: results of a pilot study. *Arq Gastroenterol* 2005; **42**: 249-255 [PMID: 16444381 DOI: 10.1590/s0004-28032005000400011]

28 **Raquel Benedita Terrabuio D**, Augusto Diniz M, Teofilo de Moraes Falcão L, Luiza Vilar Guedes A, Akeme Nakano L, Silva Evangelista A, Roberto Lima F, Pires Abrantes-Lemos C, José Carrilho F, Luiz Rachid Cancado E. Chloroquine Is Effective for Maintenance of Remission in Autoimmune Hepatitis: Controlled, Double-Blind, Randomized Trial. *Hepatol Commun* 2019; **3**: 116-128 [PMID: 30619999 DOI: 10.1002/hep4.1275]

29 **T de Moraes Falcão L**, Terrabuio DRB, Diniz MA, da Silva Evangelista A, Souza FG, R Cancado EL. Efficacy and safety of chloroquine plus prednisone for the treatment of autoimmune hepatitis in a randomized trial. *JGH Open* 2019; **4**: 371-377 [PMID: 32514439 DOI: 10.1002/jgh3.12258]

30 **Snijders RJALM**, Assis DN, Oo YH, Sebode M, Taubert R, Willemse J, Tomsin B, Lohse AW, Drenth JPH, Gevers TJG; International Autoimmune Hepatitis Group (IAIHG) collaborators and the European Reference Network for Rare Liver Diseases (ERN RARE-LIVER). Research gaps and opportunities in autoimmune hepatitis-Results of the international autoimmune hepatitis group research workshop 2022. *Liver Int* 2023; **43**: 1375-1384 [PMID: 37035872 DOI: 10.1111/liv.15573]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com

© 2024 Baishideng Publishing Group Inc. All rights reserved.