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ORIGINAL ARTICLE

Hepatology

B cell depletion for autoimmune liver diseases: A retrospective review of indications and outcomes

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Abstract

Objectives: Pediatric autoimmune hepatitis has an incidence of 0.23/100.000 children in North America, with a bleak prognosis if left untreated. Steroids are the therapy of choice but are not always effective. B cell depletion is a safe and effective therapy that allows for a steroid-sparing protocol, especially in patients who do not tolerate side effects.

Methods: We retrospectively reviewed rituximab-treated patients between 2017 and 2022. Demographics, previous treatments, reasons for B cell depletion, response, and adverse effects were noted.

Results: Six patients with a mean age of 10.2 years were included. All patients had comorbidities that rendered treatment with steroids unsuccessful or undesirable. Rituximab was started at a mean follow-up of 8 months. After 6 months, the mean alanine transaminase and aspartate transaminase levels decreased from 575 IU/L and 342 IU/L, respectively, to 28 IU/L ($p = 0.02$) and 36 IU/L ($p = 0.008$), respectively. Mean γ-glutamyl transpeptidase decreased from 105 to 25 IU/L ($p = 0.01$). Immunoglobulin G levels were normalized in all patients ($p = 0.01$). No severe adverse events were observed. One patient had persistent hypogammaglobulinemia, and another had lymphopenia.

Conclusion: B-cell depletion is an effective and safe treatment for autoimmune liver diseases and should be included as an option, particularly for relapsing patients in whom steroids are undesirable or have shown nonadherence.

KEYWORDS

children, effective, rituximab, safe, steroid-sparring

1 | INTRODUCTION

Pediatric autoimmune liver diseases (AILD) are divided into autoimmune hepatitis (AIH) and autoimmune sclerosing cholangitis (ASC).[1–4] AIH is a chronic hepatitis with elevated immunoglobulin G (IgG), autoantibodies, and lymphoplasmacytic infiltration of the parenchyma. It can be classified into type 1 (AIH-1), positive antinuclear (ANA) or anti-smooth-muscle (ASMA) antibodies, and type 2 (AIH-2), positive anti-liver-kidney microsomal type 1 (anti-LKM-1) or anti-liver cytosol type 1 (anti-LC-1). AIH-1 affects all ages, AIH-2 is predominantly diagnosed in pediatric female patients and has a more severe course.[5–7] ASC is a cholestatic disease characterized by bile duct inflammation and stricture development.[3] The International Autoimmune Hepatitis Group (IAIHG) described the diagnostic criteria[8–10] that were later validated for pediatric patients.[11,12]

If untreated, AIH has a 32% survival rate at 5 years.[13] Treatment consists of steroids with azathioprine, with excellent responses.[2,5,14] Side effects are frequent, with diabetes, hypertension, growth stunting, and osteoporosis having been described.[15] Treatment objective is normalization of transaminase and IgG levels, with autoantibody negativization.[9,13] Unfortunately, 20% of patients do not adequately respond, relapse during steroid withdrawal,[2,5] or present comorbidities that contraindicate steroid use.[13]

Biologic agents have gained popularity owing to their efficacy in other diseases, and rituximab,[16–19] a CD20 antibody, impairs B cell autoantigen presentation by blocking inflammatory responses.[20–23]

2 | PATIENTS AND METHODS

We conducted a retrospective review of patients with AILD diagnosed at Centre Hospitalier Universitaire (CHU) Sainte-Justine between 2017 and 2022. All rituximab-treated patients were included, but those who received other biological agents were excluded. The protocol consisted of 4 weekly doses of 375 mg/m^2 and then every 6 months. Perfusion was provided at the hospital under clinical surveillance. Demographic data, reasons for rituximab treatment, and side effects were also recorded. Liver enzymes, IgG, and autoantibody levels were measured before each dose. CD20+ cells were measured using flow cytometry to evaluate the treatment response and guide the best timing of the subsequent dose. Biopsy results were simplified according to the IAIHG score.[9] All patients were followed up at the outpatient clinic, with four visits per year and another four telephonic follow-ups by our team nurses. Furthermore, all patient information was strictly stored and updated in the electronic database. Control biopsies were not part of our protocol if remission was sustained.

Normality of the data was evaluated using the Kolmogorov-Smirnov test. Changes in transaminase levels were analyzed using One-Way analysis of variance or Friedman's test. Independent variables were compared using Fisher's Exact Test. Statistical significance was set at $p < 0.05$. This study was conducted using the STROBE guidelines for observational studies (see Supplementary STROBE Checklist).

Given the anonymity and retrospective nature of this study, a waiver from the ethics committee of CHU Sainte-Justine the review of medical charts and publication of results was obtained.

3 | RESULTS

Eighty-six patients were diagnosed with AILD, and six were treated with rituximab (five females and one male). The mean age was 10.2 years (range, 14 months–15.4 years). The time to the first rituximab dose was 8 months (0–24 months, $\sigma^2 = 72.5$). The mean follow-up period after B cell depletion was 21.5 months (9–42 months, $\sigma^2 = 233$) (Table 1).

The mean pretreatment alanine transaminase (ALT) was 575 IU/L (range 116–2200), and 28 IU/L (range 16–51) at 6 months ($p < 0.001$). Four patients had normal ALT levels at 6 months. Changes in aspartate transaminase were similar, with a mean of 342 IU/L before treatment (range 100–966), and 36 IU/L (range 20–48) after 6 months ($p = 0.001$) (Figure 1). Mean pretreatment γGT was 105 IU/L (range 51–405), and 25 IU/L (range 16–56) at 6 months ($p = 0.03$). IgG and autoantibodies normalized in all patients ($p = 0.006$) (Figure 2).

Four patients received prednisone as first-line treatment, but none received prednisone after rituximab was started ($p = 0.015$). One patient continued to receive mycophenolate mofetil (MMF) and tacrolimus as part of the postliver transplant protocol. In another patient azathioprine was continued as it seemed to allow for a lower frequency of maintenance doses (Figure 3).

No severe complications, infections, or hospitalizations were recorded, although one patient required subcutaneous IgG replacement therapy, whereas the other had mild lymphopenia. No flareups occurred. All patients had an uneventful follow-up and were leading otherwise normal lives. A brief review of each case is provided in the following paragraphs:

The first patient had AIH-2 liver failure (anti-LKM 1:320; ASMA 1:160) and underwent liver transplantation. Biopsy-proven rejection during the first month was treated with tacrolimus, MMF, and intravenous steroids without improvement. A follow-up biopsy was compatible with de novo AIH and was treated with rituximab. Complete resolution followed without relapse to date. The patient received subcutaneous IgG for persistent hypogammaglobulinemia.

What is Known

- Pediatric autoimmune hepatitis has a poor prognosis if untreated, with 32% at 5 years.
- Steroids and azathioprine are the treatment of choice, with responses of up to 80%, but many patients do not tolerate the side effects, leading to nonadherence, particularly in adolescent patients.
- Nonadherence, mainly due to side effects, is the main reason for treatment failure, relapse, and mortality in these patients.

What is New

- Rituximab causes B cell depletion and decreases liver inflammation in pediatric patients.
- Rituximab appears to be safe and effective for the induction and maintenance of remission in adult patients, but pediatric data are scarce.
- Rituximab may be considered the first choice in selected cases that are either intolerant to steroid side effects, suffer from other autoimmune diseases, or when adherence cannot be ensured.

TABLE 1 Patients' demographics and descriptions.

Dx	Age Dx	Sex	IAIHG Score	Time to rituximab	Reason for B cell depletion	Complications
AIH-2	14 m	F	20	13 m	Liver transplantation Steroid-resistant acute rejection Warm autoimmune hemolytic anemia	Hypogammaglobulinemia
AIH-2	6 y 6 m	F	19	0 m	Chronic neutropenia LOF of IL17R	No
AIH-1	13 y 6 m	F	21	3 m	Steroid-dependence Hyper IgM and IgA Concomitant EBV infection Severe acne with steroids	No
AIH-1	15 y 4 m	F	19	0 m	Severe acne Incipient metabolic syndrome Family history of autoimmune diseases	No
ASC	14 y 2 m	M	20	24 m	First-line treatment failure Second-line treatment failure Possible nonadherence Growth stunt	Persistent lymphopenia
ASC	10 y 3 m	F	20	7 m	Psychiatric troubles with nonadherence	No

Abbreviations: AIH-1, autoimmune hepatitis type 1; AIH-2, autoimmune hepatitis type 2; ASC, autoimmune sclerosing cholangitis; EBV, Epstein-Barr virus; IAIHG, International Autoimmune Hepatitis Group; Ig, immunoglobulin; IL17R, interleukin-17R; LOF, loss of function; m, month; y, year.

The second patient, known for chronic neutropenia secondary to interleukin-17R loss-of-function, was referred for hypertransaminemia. AIH-2 was diagnosed, with hyper-IgG, anti-LC1 (1:80), and lymphoplasmacytic infiltration in biopsies. Treatment with rituximab was initiated as a first-line treatment to control both conditions, with liver enzymes and neutrophil count normalizing quickly. No complications were observed.

The third patient presented with elevated transaminases and serum immunoglobulins with ANA (1:160) positivity. IgM against the Epstein-Barr virus-viral capsid antigen (EBV-VCA) was noted; therefore, bystander hepatitis was suspected. After spontaneous initial improvement, deterioration occurred. Steroids and azathioprine were started with excellent results; however, severe acne developed, and the disease relapsed with steroid withdrawal. Biopsies were compatible with AIH, and rituximab was initiated considering active EBV replication. Enzymes and IgG normalized quickly. No complications or relapses were noted, and acne resolved rapidly. Azathioprine was continued as it seemed to decrease the frequency of maintenance doses.

Fourth had hypertransaminasemia, severe acne, and metabolic syndrome. Elevated IgG, ANA (1:5120), and anti-deoxyribonucleic acid (DNA) (1:640) were present, with biopsies confirming AIH-1. Rituximab was started as the first-line therapy together with azathioprine due to great concern for steroid-related side effects. The enzymes normalized after induction, and the patient remained in remission without complications. Azathioprine was discontinued after the first maintenance dose, with no apparent change in the biochemical results.

The fifth patient was referred for hypertransaminasemia and jaundice, with ANA positivity (1:320). Biopsy showed lympho-plasmacyte infiltration and ductular changes, with magnetic resonance showing bile ducts irregularities, confirming the diagnosis of ASC. Steroids and azathioprine were initiated; however, severe acne and growth stunt developed. Furthermore, disease relapse was noted when steroids were tapered. Tacrolimus was administered without success; therefore, rituximab was initiated. Enzymes normalized quickly, and remission was maintained without complications, except for mild lymphopenia.

The last patient was referred to our hospital for cholestasis and hypertransaminasemia. ANA (1:160) positivity, biopsies with lymphoplasmacytic infiltration and neoductular formation, and magnetic resonance imaging with bile duct irregularities confirmed the diagnosis of ASC. Steroids and azathioprine were effective; however, the patient developed steroid-related metabolic syndrome. The patient developed psychiatric problems with treatment adherence becoming impossible; therefore, rituximab was started and other treatments were stopped. Enzyme normalization was observed after induction, and no relapses or complications were observed.

4 | DISCUSSION

AIH was described in 1950, when Waldenström reported a chronic hepatitis with elevated IgG levels affecting women that led to cirrhosis and liver failure.[24] Although advances have been made, several steps in its pathogenesis remain to be elucidated. Treatment

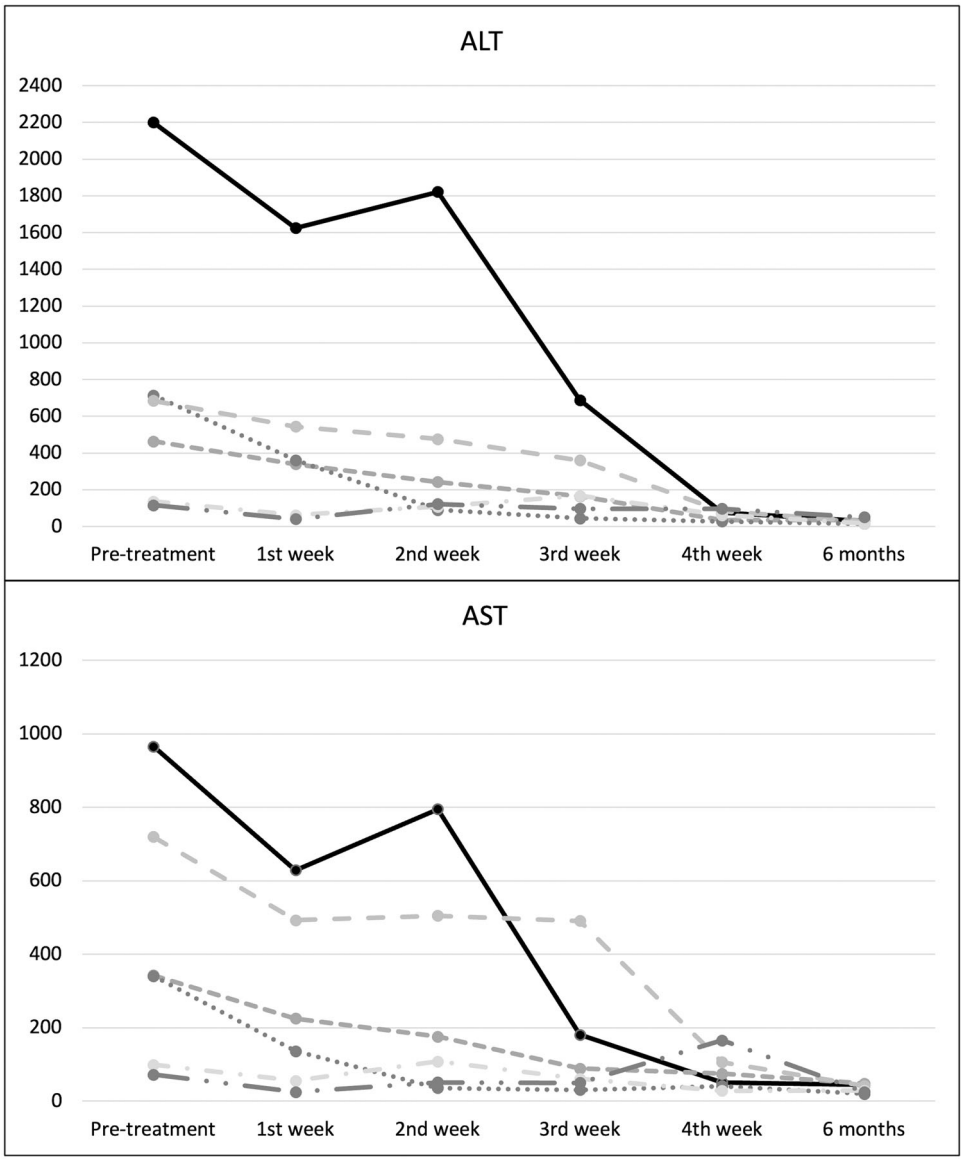

FIGURE 1 ALT and AST levels before and after rituximab treatment. ALT, alanine transaminase; AST, aspartate transaminase.

guidelines rely on broad immunosuppression[1,25,26]; however, side effects remain a major problem for patients. In pediatrics, biological and sociological factors must be considered. Not only must the risk of developing hypertension, diabetes, and glaucoma be considered; however, hirsutism, acne, and weight gain are reasons for nonadherence, especially in adolescents.[15,27–31] Calcineurin inhibitors have been successful; however, frequent control of the trough levels is necessary. Moreover, treatment adherence is variable because of frequent side effects.[26,32]

Newer medications capable of targeting specific steps in the immune response have made the search for alternative therapies fruitful. Biological agents may be effective, and reports of success with infliximab have been published.[33] Similar agents have been proposed.[34,35]

We successfully used rituximab in six patients with AILD, either due to treatment failure, development of side effects, concomitant autoimmune diseases, or avoidance of complications from pre-existing conditions.

Rituximab is an antibody against CD20 that causes B cell depletion. Despite being a T cell-mediated disease, B cells are still required for the maintenance of the immune reaction. B cells function not only as immunoglobulin-producing cells but also as antigen-presenting cells for T lymphocytes. Moreover, cytokines secreted by B cells determine the fate of T helper cells (T_h1 and T_h17). These B-T cell interactions are central to providing the costimulation needed for immune reactions to be sustained.[35–39] Furthermore, the existence of CD20+ T cells implicates previously unknown pathophysiological pathways.[40,41] Although it has proven effective in animal models,[36] it is not

FIGURE 2 IgG levels before and after B cell depletion therapy. *The line marks the 1.1 times the upper limit of the normal serum IgG values*. IgG, immunoglobulin G.

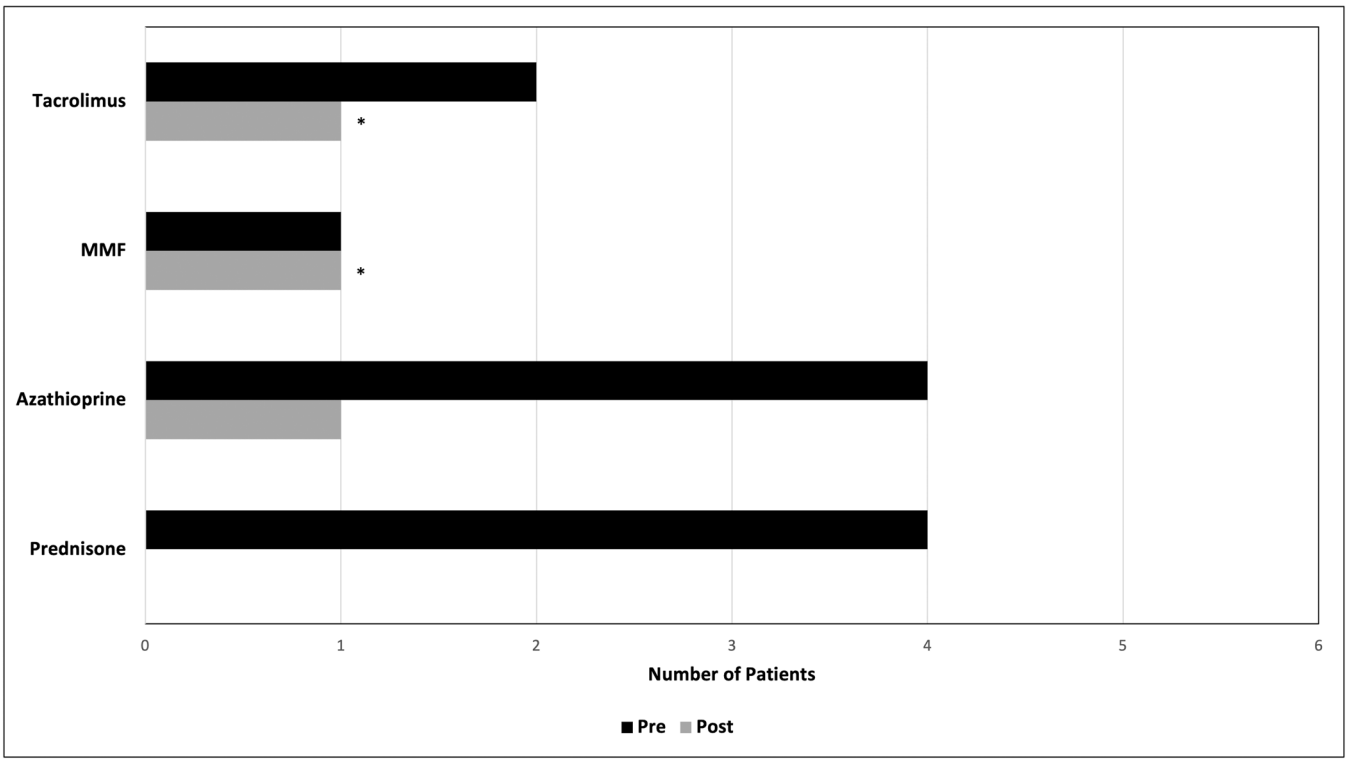

FIGURE 3 Medications used before and after rituximab induction. *One patient continued to receive treatment with tacrolimus and MMF as the usual posttransplantation protocol for autoimmune hepatitis. MMF, mycophenolate mofetil.

formally approved as an option owing to lack of data,[34] despite favorable experiences having been published and scientific societies suggesting its use when other medications fail.[13,16,19,42–45] Nonetheless, information regarding its long-term safety profile is lacking. The effects of chronic B cell depletion, an increased risk of infections, and hypogammaglobulinemia development are some of the questions. However, most data are from its use in hematologic diseases, which are already associated with most of these complications.[46,47] In our series, one patient developed hypogammaglobulinemia, and another chronic lymphopenia, but none had severe infections nor had to be hospitalized. Other studies have reported similar results.[16,19,42] Although perfusion reactions are possible,[19] our patients did not experience them.

All our patients had normalized liver enzymes after induction. They all required maintenance doses every 6 to 12 months to prevent relapses, which appeared to be preceded by CD20+ cell recovery. None of the patients lost response to rituximab, which has been reported by some authors.[38,48,49] These differences might be due to the small sample size or the use of maintenance doses, keeping CD20+ cells and IgG in the lower limits of normal.

Steroid withdrawal was achieved in our patients, particularly beneficial in those with nonadherence secondary to their side effects. In one patient, the development of psychiatric problems made conventional treatment impossible. However, remission was achieved with rituximab and adherence was no longer a concern (Table 1, Figure 3).

The only published series of rituximab-treated patients comes from the IAIHG, which reported 22 successfully treated adults.[36] Although our group reported the first two cases,[16] after proving its effectiveness in murine models,[37] pediatric data are scarce with one other published article with six pediatric patients.[17] In this study, the authors also found that rituximab was safe and effective for the treatment of these diseases.

The limitations of our findings should be mentioned, as the retrospective and single-center nature of this study makes variable isolation and bias avoidance difficult. These limitations are particularly true for rare diseases, where the number of patients is small. Nonetheless, despite the inherent differences between our patients, all of them were diagnosed, treated, and followed by the same hepatologist, which allowed for an important degree of standardization.

We found that rituximab is effective and safe for AILD, and we believe that it should be the first-line treatment in cases where steroids may be dangerous. Moreover, in patients with nonadherence due to steroid-related side effects, treatment should be started early to avoid relapse. However, validation through larger prospective studies is required to further support our conclusions.

AUTHOR CONTRIBUTIONS

Dr Guillermo Costaguta and Dr Fernando Álvarez conceptualized and designed the study, collected data, carried out the initial analyses, drafted the initial manuscript, and critically reviewed and revised the manuscript. Both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Identified individual participant data will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form. The data will be made available upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. Proposals should be submitted to gcostaguta5@gmail.com.

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REFERENCES

1. Lohse AW, Dalekos G, Drenth J, et al. EASL Clinical Practice Guidelines: autoimmune hepatitis. *J Hepatol*. 2015;63:971-1004. doi:10.1016/j.jhep.2015.06.030
2. Alvarez F. Autoimmune hepatitis and primary sclerosing cholangitis. *Clin Liver Dis*. 2006;10:89-107. doi:10.1016/j.cld.2005.10.009
3. Maggiore G, Riva S, Sciveres M. Autoimmune diseases of the liver and biliary tract and overlap syndromes in childhood. *Minerva Gastroenterol Dietol*. 2009;55(1):53-70.
4. Jiménez-Rivera C, Ling SC, Ahmed N, et al. Incidence and characteristics of autoimmune hepatitis. *Pediatrics*. 2015;136:e1237-e1248. doi:10.1542/peds.2015-0578
5. Cuarterolo M, Ciocca M, Álvarez F. Hepatitis autoinmune en niños. Perspectivas actuales. *Arch Argent Pediatr*. 2014;112(2):169-175. doi:10.5546/aap.2014.169
6. Ramonet M, Ramirez-Rodriguez N, Álvarez Chávez F, et al. Autoimmune hepatitis in pediatrics, a review by the working group of the Latin American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (SLAGHNP). *[Hepatitis autoinmune en pediatría, una revisión del Grupo de Trabajo de la Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición Pediátrica (SLAGHNP)]*. *Arch Argent Pediatr*. 2022;120(4):281-287. doi:10.5546/aap.2022.eng.281
7. Lapierre P, Alvarez F. Type 2 autoimmune hepatitis: genetic susceptibility. *Front Immunol*. 2022;13:1025343. doi:10.3389/fimmu.2022.1025343
8. Johnson PJ, McFarlane IG, on behalf the panel. Meeting report: international autoimmune hepatitis group. *Hepatology*. 1993;18:998-1005. doi:10.1002/hep.1840180435

9. Álvarez F, Berg PA, Bianchi FB, et al. International autoimmune hepatitis group report: review criteria for diagnosis of autoimmune hepatitis. *Journal Hepatol*. 1999;31:929-938.
10. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology*. 2008;48(1):169-176. doi:10.1002/hep.22322
11. Mileti E, Rosenthal P, Peters MG. Validation and modification of simplified diagnostic criteria for autoimmune hepatitis in children. *Clin Gastroenterol Hepatol*. 2012;Apr 10(4):417-421.e2. doi:10.1016/j.cgh.2011.11.030
12. Ferri PM. Diagnostic criteria for autoimmune hepatitis in children: a challenge for pediatric hepatologists. *World J Gastroenterol*. 2012;18(33):4470-4473. doi:10.3748/wjg.v18.i33.4470
13. Mieli-Vergani G, Vergani D, Baumann U, et al. Diagnosis and management of pediatric autoimmune liver disease: ESPGHAN hepatology committee position statement. *J Pediatr Gastroenterol Nutr*. 2018;66(2):345-360. doi:10.1097/MPG.0000000000001801
14. Mieli-Vergani G, Vergani D. Autoimmune paediatric liver disease. *World J Gastroenterol*. 2008;14(21):3360-3367. doi:10.3748/wjg.14.3360
15. Beretta-Piccoli BT, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. *World J Gastroenterol*. 2017;23(33):6030-6048. doi:10.3748/wjg.v23.i33.6030
16. D'Agostino D, Costaguta A, Álvarez F. Successful treatment of refractory autoimmune hepatitis with rituximab. *Pediatrics*. 2013;132(2):e526-e530. doi:10.1542/peds.2011-1900
17. Wennmann M, Kathemann S, Kampmann K, et al. A retrospective analysis of rituximab treatment for B cell depletion in different pediatric indications. *Front Pediatr*. 2021;9:651323. doi:10.3389/fped.2021.651323
18. Chung Y, Rahim MN, Graham JJ, Zen Y, Heneghan MA. An update on the pharmacological management of autoimmune hepatitis. *Expert Opin Pharmacother*. 2021;22(11):1475-1488. doi:10.1080/14656566.2021.1895747
19. Carey EJ, Somaratne K, Rakela J. Successful rituximab therapy in refractory autoimmune hepatitis and Evans syndrome. *Rev Med Chil*. 2011;139:1484-1487.
20. Mix H, Weiler–Normann C, Thimme R, et al. Identification of CD4 T-Cell epitopes in soluble liver antigen/liver pancreas autoantigen in autoimmune hepatitis. *Gastroenterology*. 2008;135:2107-2118. doi:10.1053/j.gastro.2008.07.029
21. Than NN, Jeffery HC, Oo YH. Autoimmune hepatitis: progress from global immunosuppression to personalised regulatory T cell therapy. *Can J Gastroenterol Hepatol*. 2016;2016:1-12. doi:10.1155/2016/7181685
22. Liberal R, Grant CR, Yuksel M, et al. Regulatory T-cell conditioning endows activated effector T cells with suppressor function in autoimmune hepatitis/autoimmune sclerosing cholangitis. *Hepatology*. 2017;66(5):1570-1584. doi:10.1002/hep.29307
23. Weiler-Normann C, Sebode M, Lohse AW. Autoimmune hepatitis 2013 and beyond. *Minerva Gastroenterol Dietol*. 2013;59(2):133-141.
24. Waldenström J. Leber. Blutproteine und Nahrungseiweisse. *Dtsch Gesellsch Verd Stoffw*. 1950;15:113-119.
25. de Boer YS, Liberal R, Vergani D, Mieli-Vergani G. Real-world management of juvenile autoimmune liver disease. *United European Gastroenterol J*. 2018;6(7):1032-1038. doi:10.1177/2050640618768922
26. Cuarterolo ML, Ciocca M, López S, Araujo M, Álvarez F. Autoimmune hepatitis in children: prednisone plus azathioprine versus cyclosporine. *J Pediatr Gastroenterol Nutr*. 2020;71:376-380. doi:10.1097/MPG.0000000000002776
27. Wellen BCM, Lin HC, Stellway JE. Psychosocial considerations in pediatric autoimmune liver disease. *Clinical Liver Disease*. 2022;20:124-129. doi:10.1002/cld.1238
28. Bozzini AB, Neder L, Silva CA, Porta G. Decreased health-related quality of life in children and adolescents with autoimmune hepatitis. *J Pediatr*. 2019;95(1):87-93. doi:10.1016/j.jped.2017.10.013
29. Takahashi A, Moriya K, Ohira H, et al. Health-related quality of life in patients with autoimmune hepatitis: A questionnaire survey. *PLoS One*. 2018;13:e0204772. doi:10.1371/journal.pone.0204772
30. Kerkar N, Annunziato RA, Foley L, et al. Prospective analysis of nonadherence in autoimmune hepatitis: a common problem. *J Pediatr Gastroenterol Nutr*. 2006;43:629-634. doi:10.1097/01.mpg.0000239735.87111.ba
31. Schramm C, Wahl I, Weiler-Normann C, et al. Health-related quality of life, depression, and anxiety in patients with autoimmune hepatitis. *J Hepatol*. 2014;60:618-624. doi:10.1016/j.jhep.2013.10.035
32. Alvarez F, Ciocca M, Cañero-Velasco C, et al. Short-term cyclosporine induces a remission of autoimmune hepatitis in children. *J Hepatol*. 1999;30:222-227. doi:10.1016/s0168-8278(99)80065-8
33. Weiler-Normann C, Schramm C, Quaas A, et al. Infliximab as a rescue treatment in difficult-to-treat autoimmune hepatitis. *J Hepatol*. 2013;58:529-534. doi:10.1016/j.jhep.2012.11.010
34. Gottenberg JE, Morel J, Perrodeau E, et al. Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study. *BMJ*. 2019;364:l67. doi:10.1136/bmj.l67
35. Halliday N, Dyson JK, Thorburn D, Lohse AW, Heneghan MA. Review article: experimental therapies in autoimmune hepatitis. *Aliment Pharmacol Ther*. 2020;52:1134-1149. doi:10.1111/apt.16035
36. Liossis SNC, Sfikakis PP. Rituximab-induced B cell depletion in autoimmune diseases: potential effects on T cells. *Clin Immunol*. 2008;127:280-285. doi:10.1016/j.clim.2008.01.011
37. Béland K, Marceau G, Labardy A, Bourbonnais S, Alvarez F. Depletion of B cells induces remission of autoimmune hepatitis in mice through reduced antigen presentation and help to T cells. *Hepatology*. 2015;62(5):1511-1523. doi:10.1002/hep.27991
38. Sakamoto S, Akamatsu N, Hasegawa K, Ohdan H, Nakagawa K, Egawa H. The efficacy of rituximab treatment for antibody-mediated rejection in liver transplantation: a retrospective Japanese nationwide study. *Hepatol Res*. 2021;51:990-999. doi:10.1111/hepr.13643
39. Than NN, Hodson J, Schmidt-Martin D, et al. Efficacy of rituximab in difficult-to-manage autoimmune hepatitis: results from the International Autoimmune Hepatitis Group. *JHEP Reports*. 2019;1:437-445. doi:10.1016/j.jhepr.2019.10.005
40. Böhmig GA, Halloran PF, Feucht HE. On a long and winding road: alloantibodies in organ transplantation. *Transplantation*. 2023;107(5):1027-1041. doi:10.1097/TP.0000000000004550
41. Vlaming M, Bilemjian V, Freile JÁ, et al. CD20 positive CD8 T cells are a unique and transcriptionally-distinct subset of T cells with distinct transmigration properties. *Sci Rep*. 2021;11(1):20499. doi:10.1038/s41598-021-00007-0
42. Santos ES, Arosemena LR, Raez LE, O'Brien C, Regev A. Successful treatment of autoimmune hepatitis and idiopathic thrombocytopenic purpura with the monoclonal antibody, rituximab: case report and review of literature. *Liver Int*. 2006;26:625-629. doi:10.1111/j.1478-3231.2006.01262.x
43. Barth E, Clawson J. A case of autoimmune hepatitis treated with rituximab. *Case Rep Gastroenterol*. 2010;4:502-509. doi:10.1159/000322693
44. Burak KW, Swain MG, Santodomino-Garzon T, et al. Rituximab for the treatment of patients with autoimmune hepatitis who are refractory or intolerant to standard therapy. *Can J Gastroenterol*. 2013;27(5):273-280. doi:10.1155/2013/512624

45. Saul SA, Taylor SA, Mohammad S. Treatment of refractory pediatric autoimmune hepatitis with rituximab. *JPGN Reports*. 2021;2(3):e069. doi:10.1097/PG9.0000000000000069
46. Chiou FK, Beath SV, Patel M, Gupte GL. Hypogammaglobulinemia and bacterial infections following pediatric post-transplant lymphoproliferative disorder in the rituximab era. *Pediatr Tranplant*. 2019;23:e13519. doi:10.1111/petr.13519
47. Labrosse R, Barmettler S, Derfalvi B, et al. Rituximab-induced hypogammaglobulinemia and infection risk in pediatric patients. *J Allergy Clin Immunol*. 2021;148(2):523-532.e8. doi:10.1016/j.jaci.2021.03.041
48. Randall KL. Rituximab in autoimmune diseases. *Aust Prescr*. 2016;39(4):131-134. doi:10.18773/austprescr.2016.053
49. Li T, Zhang LJ, Zhang QX, et al. Anti-Rituximab antibody in patients with NMOSDs treated with low-dose rituximab. *J Neuroimmunol*. 2018;316:107-111. doi:10.1016/j.jneuroim.2017.12.021.

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