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Contents

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SYSTEMATIC REVIEWS

Eldew H, Soldera J. Evaluation of biological therapies in autoimmune hepatitis: A case-based systematic review. *World J Gastrointest Pathophysiol* 2025; 16(1): 101481 [DOI: 10.4291/wjgp.v16.i1.101481]

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Contents

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SYSTEMATIC REVIEWS

Evaluation of biological therapies in autoimmune hepatitis: A case-based systematic review

Haifa Eldew, Jonathan Soldera

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Abstract

BACKGROUND

Autoimmune hepatitis (AIH) is typically treated with immunomodulators and steroids. However, some patients are refractory to these treatments, necessitating alternative approaches. Biological therapies have recently been explored for these difficult cases.

AIM

To assess the efficacy and safety of biologics in AIH, focusing on patients unresponsive to standard treatments and evaluating outcomes such as serological markers and histological remission.

METHODS

A case-based systematic review was performed following the PRISMA protocol to evaluate the efficacy and safety of biological therapies in AIH. The primary focus was on serological improvement and histological remission. The secondary focus was on assessing therapy safety and additional outcomes. A standardized search command was applied to MEDLINE, EMBASE, and Cochrane Library databases to identify relevant studies. Inclusion criteria encompassed adult AIH patients treated with biologics. Data were analyzed based on demographics, prior treatments, and therapy-related outcomes. A narrative synthesis was employed to address biases and provide a comprehensive overview of the evidence.

RESULTS

A total of 352 studies were reviewed, with 30 selected for detailed analysis. Key findings revealed that Belimumab led to a favourable response in five out of eight AIH patients across two studies. Rituximab demonstrated high efficacy, with 41 out of 45 patients showing significant improvement across six studies. Basiliximab

was assessed in a single study, where the sole patient treated experienced a beneficial outcome. Additionally, a notable number of AIH cases were induced by anti-tumor necrosis factor (TNF) medications, including 16 cases associated with infliximab and four cases with adalimumab. All these cases showed improvement upon withdrawal of the biologic agent.

CONCLUSION

Belimumab and Rituximab show promise as effective alternatives for managing refractory AIH, demonstrating significant improvements in clinical outcomes and liver function. However, the variability in patient responses to different therapies highlights the need for personalized treatment strategies. The risk of AIH induced by anti-TNF therapies underscores the need for vigilant monitoring and prompt symptom recognition. These findings support the incorporation of biologic agents into AIH treatment protocols, particularly for patients who do not respond to conventional therapies.

Key Words: Autoimmune hepatitis; Biological therapies; Belimumab; Rituximab; Basiliximab; Infliximab; Adalimumab

Core Tip: This systematic review highlights the effectiveness of biologic therapies, such as Belimumab and Rituximab, in managing refractory autoimmune hepatitis (AIH) cases. Despite standard treatments with immunomodulators and steroids, some patients remain unresponsive, necessitating alternative options. The review found that Belimumab and Rituximab significantly improved clinical outcomes and liver function in these challenging cases. Additionally, anti-tumor necrosis factor therapies were associated with AIH induction, emphasizing the need for careful monitoring and early detection. These insights advocate for the inclusion of biologics in AIH treatment protocols for patients unresponsive to conventional therapies.

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INTRODUCTION

Autoimmune hepatitis (AIH) is a chronic inflammatory liver disease affecting all ethnicities, with higher prevalence in northern Europeans and those with certain HLA types on chromosome 6. AIH type 1 is associated with HLA-DR3 and HLA-DR4, while other types involve HLA-DQB1 and HLA-DRB[1,2]. The immune-mediated inflammation can result in fibrosis, cirrhosis, and hepatocellular carcinoma. The exact aetiology is unknown, but environmental and genetic factors are believed to trigger hepatocyte damage and chronic inflammation. These include viruses (Hep A, C, D, CMV), drugs (minocycline, methyldopa, ticrynafen), and herbal agents[1-4]. AIH commonly affects young females.

AIH is classified into two types based on specific autoantibodies[1,5]. Type 1 is more prevalent in females with a ratio of 1:4 compared to males, particularly affecting those aged 10-30 and 40-60 years[2,6]. In type 1, autoantibodies include antinuclear antibody (ANA), smooth muscle antibody (SMA), perinuclear antineutrophil, and anti-soluble liver antigen/liver pancreas (anti-SLA/LP) and/or cytoplasmic autoantibody[1,5]. Type 2 primarily affects children[1,2] and is characterized by positive autoantibodies such as anti-liver kidney microsomal-1 (anti-LKM type 1 or type 3) and/or anti-liver cytosol-specific[6]. To provide further context, the immunological basis of AIH involves the immune system targeting liver cells, leading to chronic inflammation. Biologic therapies aim to modulate this immune response, particularly in refractory cases where conventional treatments fail to control the disease effectively.

Another classification variant of AIH is based on overlap syndromes. The AIH-primary biliary cholangitis (PBC) overlap syndrome exhibits histological features of AIH and serological findings of PBC, including positive anti-mitochondrial antibodies (AMA). Conversely, the other variant shows histological features of PBC with serological markers of AIH, such as positive ANA and SMA, but is AMA-negative, sometimes termed autoimmune cholangitis or AMA-negative primary biliary cirrhosis. The AIH and sclerosing cholangitis overlap syndrome, which displays AIH serological features but primary sclerosing cholangitis characteristics on histology and cholangiography, has been well described[7]. Clinical presentation might range from asymptomatic cases to acute liver failure with jaundice, prolonged prothrombin time, and abnormal liver enzymes. Common symptoms include lethargy, anorexia, nausea, abdominal discomfort, pruritus, and arthralgia. Rare presentations may include encephalopathy, portal hypertension, and gastrointestinal bleeding[8-10].

AIH may present alongside other autoimmune disorders, such as type 1 diabetes, ulcerative colitis (UC), coeliac disease, and thyroiditis[1,8]. Hepatocellular carcinoma can be a late manifestation, highlighting the need for timely diagnosis and treatment to reduce mortality. The initial diagnostic workup involves evaluating liver function tests (LFT), including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase, which can be

significantly elevated, ranging from 200-300 IU/L to thousands[11]. Elevated bilirubin levels may also indicate AIH with cholestasis.

Serological tests play a critical role in diagnosing AIH and its variants. For type 1 AIH, ANA are present in 43% of patients, and single-stranded and double-stranded DNA may also be detected. Anti-smooth muscle antibodies (ASMA), SMA, which target actin, are found in 41% of type 1 cases. Type 2 AIH is identified by anti-LKM-1[8]. Additionally, 10 to 30% of AIH patients have positive anti-SLA/LP[12]. Diagnostic scoring systems, like the International AIH Group's scoring system, are useful for diagnosing cases lacking characteristic features[8]. Imaging studies, including abdominal ultrasound, are performed to rule out other liver conditions such as tumors, fatty liver, cirrhosis, gallstones, and cholestasis, though they do not have specific features for AIH[13,14].

Liver histology is crucial before starting treatment for AIH to assess liver condition. A liver biopsy is highly recommended if not contraindicated, as it can reveal essential features of AIH, including plasma cell infiltrates, fibrosis, and bile duct abnormalities[8,12]. AIH management primarily involves corticosteroid monotherapy (Prednisolone, Budesonide), which can be used alone or combined with immunotherapy such as azathioprine (AZA) or mycophenolate (MMF)[8,12,15]. Corticosteroids are recommended as the initial treatment for AIH and for short courses (< 6 months), but caution is needed in cases of acute severe hepatitis or liver failure[8,12,15].

Corticosteroids combined with immunotherapy (AZA, MMF, ciclosporin) are preferred for treating AIH, especially for courses longer than six months[6]. While this therapy can control inflammation and achieve significant remission in some patients, others may experience disease recurrence or side effects. Continuous monitoring for potential complications is crucial, with monthly blood tests recommended for 3-6 months until AST and ALT levels normalize[12]. Biologics, including Rituximab, Rapamycin (Sirolimus), and Belimumab, are increasingly used for refractory AIH cases[16-18]. Unlike conventional treatments, which primarily focus on suppressing the immune response, biologic therapies target specific immune pathways involved in the pathogenesis of AIH, offering a more tailored approach for refractory cases.

This study aims to systematically review and analyse the existing literature on the efficacy and safety of biologics in AIH, focusing on patients unresponsive to standard treatments and evaluating outcomes such as serological markers and histological remission.

MATERIALS AND METHODS

This case-based systematic review evaluates the efficacy of biological therapies in AIH, using the PRISMA checklist[19] for data collection.

Inclusion and exclusion criteria

Included were studies on adults (> 18 years) diagnosed with AIH *via* serology, imaging, or histology, treated with biological therapies, either alone or in combination with corticosteroids or immunosuppressants. The PICO criteria used for the search include: Population (adults diagnosed with AIH), intervention (conventional therapies, corticosteroids, or immunosuppressants with biological therapies), comparison [biological therapies *vs* other treatments, such as anti-tumor necrosis factor (TNF) therapies], outcomes (control of disease activity).

Exclusion criteria were patients < 18 years, studies not focused on AIH or biological therapies, or those with significant methodological flaws.

Risk of bias assessment

The risk of bias in randomized controlled trials (RCTs) was assessed by the QUADAS-2 in observational studies[20], using the Cochrane Bias Assessment tool Robvis[21].

Study selection and data extraction

A comprehensive literature search was conducted using MEDLINE, EMBASE, Cochrane Library, and the University of South Wales databases, with no restrictions on publication type or language. The study, registered in the PROSPERO database (CRD42024524959), filtered relevant case reports, case series, observational studies, and RCTs.

The search command used in this review was: ("autoimmune hepatitis" [All Fields] OR "AIH" [All Fields] OR "autoimmune liver disease" [All Fields]) AND ("biological therapy" [All Fields] OR "biologic therapy" [All Fields] OR "monoclonal antibodies" [All Fields] OR "rituximab" [All Fields] OR "infliximab" [All Fields] OR "TNF inhibitors" [All Fields] OR "anti-TNF therapy" [All Fields]) AND ("case reports" [Publication Type] OR "case series" [Publication Type] OR "observational study" [MeSH Terms]).

The study selection followed three phases: (1) Screening titles and abstracts; (2) Retrieving full-text articles based on inclusion criteria; and (3) Reviewing and extracting data from selected papers.

Data processing and analysis

Data gathered from the included studies were organized into a preconceived form, allowing systematic extraction. The data was then analysed using frequencies, medians, and means, processed using Excel 365 to provide comprehensive insights into the study's outcomes.

RESULTS

The analysis of AIH treatment outcomes through various interventions is shown in Tables 1 and 2[22-42]. The studies were selected following specific eligibility criteria and using the PRISMA flow diagram, displayed in Figure 1. The bias assessment is displayed in Figure 2.

The literature search initially found 352 articles, and after removing duplicates, 350 articles remained. After screening titles and abstracts, 265 were excluded, including 17 without abstracts, 8 not involving anti-TNF therapy, and 47 deemed irrelevant or using different methodologies. A total of 85 studies were reviewed in detail. Of these, 30 were eligible for inclusion, while 55 were excluded due to age criteria (15), different methodologies (30), or insufficient data (10). The final quantitative synthesis included 30 articles. These were divided into two categories: Studies on biologics treating AIH (9, Table 1) and anti-TNF induced AIH (12, Table 2).

Belimumab

Kolev *et al*[22] reported a case series from Switzerland involving 6 patients aged 37-65 with type 1 AIH and other comorbidities. Belimumab was administered initially at 10 mg/kg IV, followed by 200 mg subcutaneously weekly. Results showed that 3 out of 3 patients responded well: One had normalized liver enzymes and Fibroscan, while two managed corticosteroid tapering successfully, with improved Fibroscan in all three. This study demonstrates the efficacy of Belimumab in complex cases of AIH, PBC, and Sjogren's syndrome.

Arvaniti *et al*[23] conducted a case series in Greece on two patients aged 27 and 58 with refractory AIH, systemic lupus erythematosus, and other conditions. Belimumab was given at 10 mg/kg every 28 days, later adjusted to 21-40 days. Both patients experienced significant improvements in liver stiffness and histology, achieving remission with normalized liver enzymes and reduced ALT. The flexible dosing approach was highlighted as useful.

Rituximab

Burak *et al*[24] conducted a case series in Canada with 6 patients (aged 36-68) diagnosed with refractory AIH and comorbidities like diabetes, hypertension, osteoporosis, and chronic kidney disease. Rituximab was given at 1000 mg, two weeks apart. All patients showed significant improvement in AST and immunoglobulin G (IgG), with 3/6 reducing prednisolone dosage. ANA and ASMAs decreased, and liver biopsies showed inflammation improvement. Rituximab proved effective for refractory AIH and reducing steroid dependence.

Carey *et al*[25] described a 44-year-old female with refractory AIH and Evan syndrome. Rituximab led to normalized platelets, hemoglobin, and aminotransferases, achieving sustained remission.

Al-Busafi *et al*[26] reported a 68-year-old woman with refractory AIH, hypertension, and Waldenstrom macroglobulinemia. Rituximab at 375 mg/m² resulted in significant clinical and biochemical improvements and sustained remission.

Barth *et al*[27] studied a 27-year-old female with B-cell lymphoma and AIH. Rituximab 375 mg/m² weekly for 8 weeks initially reduced aminotransferases and lymphadenopathy. After a relapse, an additional 4 weeks of treatment normalized enzymes and reduced IgG.

Riveiro-Barciela *et al*[28] analyzed 35 AIH patients (aged 19-73) from Spain's ColHai Registry. Rituximab, given in periodic or fixed doses, showed an 89% clinical benefit rate (CBR), with reduced corticosteroid use and no increased complications in cirrhosis patients. The study concluded Rituximab as an effective option, particularly in refractory cases.

Santos *et al*[29] presented a 52-year-old female with AIH, diabetes, and asthma. Rituximab normalized liver tests and stabilized platelet counts, achieving remission in both AIH and refractory immune thrombocytopenia (ITP).

Results of studies on Basiliximab

Zarrabi *et al*[30] presented a case review of a 22-year-old female with AIH, PBC overlap, and metastatic osteosarcoma. Basiliximab was administered at 20 mg weekly for 4 weeks, while other conventional treatments (steroids, tacrolimus, MMF) were paused. The treatment led to the normalization of liver enzymes (LFTs), suggesting the potential efficacy and safety of Basiliximab in complex cases.

Anti-TNF induced AIH

This section explores studies on the efficacy and safety of anti-TNF therapies like Infliximab and Adalimumab in AIH.

Jenkins *et al*[31] United States: A 31-year-old male with UC developed AIH after Infliximab. Liver enzymes normalized upon withdrawal, while UC was managed with Vedolizumab.

Wong *et al*[32], Canada: A 69-year-old male with AIH experienced severe liver impairment after Infliximab, requiring liver transplantation.

Mancini *et al*[33], Italy: A 33-year-old female with psoriasis developed AIH after Infliximab, which was managed with high-dose Prednisone.

Adar *et al*[34], Israel: A 36-year-old female with psoriasis, psoriatic arthritis, and Crohn's disease developed AIH after Infliximab.

Karanfilian *et al*[35], United States: A 37-year-old male with Crohn's and psoriasis developed AIH after Infliximab. Liver function improved after switching to Prednisone.

Rodrigues *et al*[36], Portugal: Eight patients with autoimmune conditions developed AIH after anti-TNF therapy. Steroid therapy post anti-TNF discontinuation led to improvement.

Yilmaz *et al*[37], United States: A 39-year-old woman with ankylosing spondylitis developed AIH after Infliximab. Liver function normalized after stopping treatment.

Table 1 Biologics for the treatment of autoimmune hepatitis

Ref.	Country	Age	Patient-comorbidity	Type of AIH	Previous intervention	Intervention	Comparison	Study design	Outcomes measured	Result
Kolev *et al*[22]	Switzerland	37-65 (6 pt)	There were 3 patients with AIH and 3 with PBC. Pt 1: AIH, Sjögren's disease; Pt 2: AIH, PBC, Coeliac, Asthma; Pt 3: AIH, Autoimmune thyroiditis	3 patients with type 1 AIH	Pt 1: Prednisolone, AZA, rituximab, MMF, UDCA; Pt 2: Prednisolone, AZA, UDCA, MMF, CyA; Pt 3: Prednisolone, AZA, MMF, budesonide, CyA	Belimumab 200 mg SC weekly	No comparison	Case series	Improvement of Fibroscan and normalization of AST and ALT	3/3 patients respond positively to Belimumab
Arvaniti *et al*[23]	Greece	27 and 58	Pt 1: AIH, SLE, Hypergammaglobulinemia; Pt 2: Acute severe hepatitis	Refractory AIH	Pt 1: Prednisolone, AZA; Pt 2: Prednisolone, AZA and MMF	Belimumab: 10 mg/kg initially every 28 days	No comparison	Case series	Improvement of Fibroscan, Histology and normalization of AST and ALT	Both patients (2/2) achieved and maintained complete response to Belimumab
Burak *et al*[24]	Canada	36-68 (6 pt)	Pt 1: T2DM, HTN; Pt 2: Osteoporosis; Pt 3: Asthma; Pt 4: None reported; Pt 5: CAD; Pt 6: CKD	Refractory AIH	Pt 1: Prednisone; Pt 2: Prednisone; Pt 3: Prednisone; Pt 4: AZA + MMF; Pt 5: Prednisone; Pt 6: Prednisone + AZA + MMF	Rituximab 1000 mg given each two weeks day 1 and 15 over 72 weeks	No comparison	Case series	Improvement of liver histology and of AST and ALT levels and reduction of steroids dose	All 6 patients had significant improvement histology: 4/6 improved inflammation grades in all and 2/6 patients improved fibrosis stages
Carey *et al*[25]	Arizona-United States	44	Several autoimmune disorders including Evan syndrome	Refractory AIH	Prednisolone and AZA	Rituximab for 375 mg/m^2 once a week /four weeks	No comparison	Case report	Normalization of haemoglobin, platelets, AST and ALT	Complete response
Al-Busafi *et al*[26]	Canada	68	Hypertension, osteoporosis and a Waldenström macroglobulinemia	Refractory AIH	Prednisone	Rituximab given as high-dose-rituximab four weekly 375 mg/m^2 rituximab	No comparison	Case report	Histological, AST and ALT improvement	Partial responde, demanding the use of prednisone and AZA
Barth *et al*[27]	United States	27	B cell lymphoma	AIH intolerance to steroid	Prednisone	Rituximab 375 mg/m² weekly for 8 weeks and extra four weeks upon relapse	No comparison	Case report	Improvement in AST and ALT	Complete remission, with a relapse which responded to an increase of rituximab frequency
Riveiro-Barciela *et al*[28]	Barcelona	19-73 (32 pts)	10 patients with cirrhosis, 4 patients with overlap with PBC or PSC	Refractory AIH	Corticosteroids and immunosuppressive medications	Rituximab 1 g/2 weeks in (9%) patients, periodical doses in 32 (91%), fixed/6 months in 16 (46%) and 16 (46%) in periods	No comparison	Case series	Improvement in AST and ALT	Biochemical response in 31.89% patients, discontinuation of ≥ 1 immunosuppressive drugs in 47%, significant reduction in corticosteroid dose in most patients; safe even in cirrhotic patients
Santos *et al*[29]	United States	52	Asthma, DM, ITP	Refractory AIH	Methylprednisolone, prednisone, IV immune globulin (IVIG), anti-D immune globulin, danazol	Rituximab administration: 375 mg/m^2 IV weekly for 4 weeks	No comparison	case report	Normalization of AST and ALT	Complete laboratorial remission
Zarrabi *et al*[30]	United States	22	PBC overlap, recurrent metastatic osteosarcoma	Refractory AIH	Steroids, tacrolimus and MMF	Basiliximab six doses of 20 milligrams/dose, then weekly for four weeks	No comparison	Case report	Normalization of AST and ALT	Complete and sustained response

AIH: Autoimmune hepatitis; Pt: Patient; PBC: Primary biliary cholangitis; AZA: Azathioprine; MMF: Mycophenolate mofetil; UDCA: Ursodeoxycholic acid; CyA: Cyclosporine A; SLE: Systemic lupus erythematosus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; HTN: Hypertension; T2DM: Type 2 Diabetes mellitus; IV: Intravenous; SC: Subcutaneous; ITP: Immune thrombocytopenia; CKD: Chronic kidney disease; CAD: Computer-aided detection.

Dang *et al*[38], Australia: A 47-year-old female with plaque psoriasis developed AIH after Infliximab, with improvement after discontinuation.

van Casteren-Messidoro *et al*[39], Netherlands: Two females, 46 and 30, with Crohn's disease and UC, developed AIH after Infliximab, showing improved liver function after withdrawal.

Cravo *et al*[40], Portugal: A 38-year-old female with Crohn's experienced AIH after Infliximab. Transitioning to Adalimumab improved liver function.

Grasland *et al*[41], France: A 35-year-old female with seronegative RA developed AIH after Adalimumab, with normalization of liver enzymes after switching to Abatacept.

Petríková *et al*[42], Slovakia: A 33-year-old female with Sjögren's syndrome and RA developed AIH after Infliximab, Etanercept, and Adalimumab. AIH was managed with immunosuppressive therapy after discontinuation.

DISCUSSION

AIH is an autoimmune condition that targets liver cells, causing inflammation that can lead to either chronic damage or acute liver failure. While not all AIH patients require treatment, those with severe active disease should be treated. Severe AIH, as defined by Mack *et al*[8], involves high aminotransferase levels (over tenfold the normal range) and histological evidence such as multi-acinar or bridging necrosis. Acute or chronic AIH, particularly when marked by jaundice and a prolonged international normalised ratio of 1.5 to 2, but without encephalopathy, also warrants treatment[7,12].

The standard initial treatment for severe AIH includes corticosteroids and immunosuppressive agents such as AZA or MMF. However, some patients exhibit intolerance or resistance to these therapies. Evidence suggests that certain cases are refractory, necessitating alternative treatments. This study aims to explore the efficacy and safety of biologics, specifically Rituximab and Belimumab, in comparison to anti-TNF agents such as Infliximab and Adalimumab, particularly for cases where standard therapies are insufficient.

The studies reviewed provide strong evidence for the effectiveness of biologics, such as Rituximab, Belimumab, and Basiliximab, in managing refractory AIH. Significant improvements were observed in histological markers and liver function among patients receiving liver biopsies, alongside notable clinical symptom relief. The findings indicate that biologics can successfully treat AIH with minimal side effects.

On the other hand, anti-TNF therapies like Infliximab and Adalimumab were found to induce AIH in patients treated for conditions such as UC, Crohn's disease, psoriasis, and rheumatoid arthritis (RA). Patients often present elevated liver enzymes (AST, ALT) and positive autoimmune markers, such as ANA, ASMA, and dsDNA, with liver biopsies revealing typical AIH features, including inflammatory infiltrates and fibrosis.

In most cases, discontinuing the causative anti-TNF therapy led to normalization of liver enzymes and symptom improvement. Corticosteroids and alternative biologics, such as Vedolizumab and Abatacept, were effective in managing liver inflammation without triggering new episodes of AIH. For instance, Vedolizumab successfully managed UC after Infliximab was discontinued, Adalimumab was used effectively for Crohn's disease, and Abatacept improved liver function in seronegative RA. The long-term safety profile of biologics other than anti-TNF agents appears superior, with

Table 2 Anti-TNFα induced autoimmune hepatitis

Ref.	Country	Age	Comorbidities	AIH type	Previous intervention	Intervention	Comparison	Type of the study	Outcome	Result
Jenkins *et al* [31]	United States	31	UC	AIH induced by infliximab	Mesalamine, prednisone, adalimumab, Clostridioides difficile colitis	Suspension of Infliximab and use of Vedolizumab	None	Case report	AST and ALT improvement -AIH; Clinical and endoscopic improvement - UC	UC was controlled with the use of Vedolizumab AST and ALT normalized after infliximab was withdrawn
Wong *et al* [32]	Canada	69	AIH, HTN, diverticular disease	AIH induced by infliximab	Prednisolone	Infliximab	No comparison	Case report	Elevated AST and ALT, with elevated INR and positive ASMA and ANA. Liver biopsy showed multiacinar hepatocyte necrosis and interface hepatitis	Infliximab led to deterioration in liver markers compared to baseline instead of improvement
Mancini *et al* [33]	Italy	33	Psoriasis	AIH induced by infliximab	Methotrexate	Infliximab and prednisone	No comparison	Case report	Elevated AST and ALT levels, positive ANA and anti-dsDNA	Infliximab induced AIH
Adar *et al*[34]	Israel	36	Psoriasis and psoriatic arthritis, hypothyroidism, Crohn's disease	AIH induced by adalimumab	AZA, methotrexate and prednisolone	Adalimumab	No comparison	Case report	Elevated AST and ALT and IgG levels, positive ANA and anti-DNA. Liver biopsy showed fibrosis, inflammatory cell infiltrate, interface hepatitis, and hepatic rosettes	Adalimumab induced AIH, which was discontinued due to adverse effects
Karanfilian *et al*[35]	United States	37	Crohn's disease, psoriasis	AIH induced by infliximab	Prednisone	Infliximab	No comparison	Case report	Elevated AST and ALT, positive ANA and weakly positive smooth muscle antibody Liver biopsy showed active hepatitis with moderate interface activity, cholestasis, and infiltrate of eosinophils and plasma cells	Severe drug-induced autoimmune hepatitis secondary to infliximab and discontinuation of infliximab led to improvement in liver function tests
Rodrigues *et al*[36]	Portugal	22-69 year (8 pts)	Ulcerative colitis, Ankylosing spondylitis, Psoriatic arthritis, Rheumatoid arthritis; Crohn's disease, Palmoplantar pustular psoriasis	AIH induced by infliximab	Prednisone administered all AIH patients	Infliximab administered in 7 cases. Adalimumab administered in 1 case	No comparison	Case series	Infliximab: Six patients developed AIH and one patient developed DILI and cirrhosis	Normalisation of the liver function testes after discontinuation of anti-TNF
Yilmaz *et al* [37]	United States	39	Ankylosing spondylitis	AIH induced by infliximab	Methotrexate, sulfasalazine, hydroxychloroquine	Infliximab	No comparison	Case report	ALT and AST elevated with positive ANA. Liver biopsy showed an acute autoimmune hepatitis with a lymph plasmatic infiltration	Normal liver function tests two months after discontinuation of the anti-TNF drug
Dang *et al*[38]	Australia	47	Chronic plaque psoriasis	AIH induced by infliximab	Methotrexate	Infliximab	No comparison	Case report	Elevated AST, ALT and IgG levels. Liver biopsy indicated acute AIH	Infliximab discontinued and liver condition improved
van Casteren-Messidoro *et al*[39]	Netherlands	46 and 30	Case 1: Crohn's disease, erythema nodosum; Case 2: UC	AIH induced by infliximab	Prednisone and AZA	Case 1: Infliximab; Case 2: Pregnant, infliximab and azathioprine	No comparison	Case series	Case 1: After the fourth infliximab dose, positive ANA and IgG; liver biopsy indicated acute AIH; Case 2: Elevated AST and ALT; liver biopsy showed hepatitis	In both cases liver enzymes improved after infliximab was withdrawn

Cravo *et al* [40]	Portugal	38	Crohn's disease	AIH induced by infliximab	Azathioprine and prednisolone	Infliximab and Adalimumab	Infliximab *vs* Adalimumab	Case report	AIH induced by Infliximab and switched to adalimumab. Elevated AST and ALT and IgG with positive ANA, anti-dsDNA, and antihistone antibodies. Liver Biopsy showed chronic hepatitis and mild periportal fibrosis	Infliximab discontinued and with adalimumab liver function normalized
Grasland *et al* [41]	France	35	Hypertension, obesity	AIH induced by adalimumab	Methotrexate, prednisone, NSAIDs, paracetamol and etanercept	Adalimumab	Adalimumab *vs* Abatacept	Case report	AIH induced by Adalimumab - AST and ALT elevated	Adalimumab was discontinued and liver function improved Abatacept was restarted and liver enzymes normalized
Petríková *et al*[42]	Slovakia	33	Sjögren syndrome, rheumatoid arthritis	AIH induced by adalimumab	Etanercept, certolizumab and anakinra	Adalimumab	No comparison	Case report	Increased AST, ALT, IgG and positive ASMA and AMA. Liver biopsy showed chronic hepatitis suggestive of AIH	Adalimumab induced autoimmune hepatitis and liver enzymes improved with withdrawal of adalimumab

AIH: Autoimmune hepatitis; Pt: Patient; UC: Ulcerative colitis; HTN: Hypertension; DILI: Drug-induced liver injury; AZA: Azathioprine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ANA: Antinuclear antibodies; ASMAs: Anti-smooth muscle antibodies; INR: International normalised ratio; IgG: Immunoglobulin G; NSAID: Non-steroidal anti-inflammatory drug; AMA: Anti-mitochondrial antibodies; TNF: Tumor necrosis factor.

no recurrence of AIH reported.

Belimumab

Belimumab is a monoclonal antibody that binds to the B lymphocyte stimulator protein (BLys or BAFF), inhibiting B cell activity and reducing survival. While primarily indicated for systemic lupus erythematosus and lupus nephritis[43,44], data suggests potential efficacy in treating AIH. A study by Kolev *et al*[22] evaluated six patients, three of whom had AIH, with positive outcomes in those who previously failed conventional treatment. Two patients achieved complete response with normalized liver enzymes and improved FibroScan results, while the third patient experienced partial response, reducing prednisolone to 5 mg/day and showing improved liver function.

Another study by Arvaniti *et al*[23] focused on two patients with refractory AIH, who had partial responses to conventional treatments like corticosteroids and MMF. Both patients achieved complete remission following Belimumab treatment, with liver enzymes normalizing and improved liver stiffness noted on scans.

Belimumab demonstrated reduced inflammatory activity and histological improvement in these cases, highlighting its potential in managing AIH, especially in patients unresponsive to standard therapies.

Rituximab

Rituximab is an anti-CD20 monoclonal antibody used to treat autoimmune disorders such as RA, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris, as well as lymphoproliferative diseases like chronic lymphocytic leukemia[45-47]. Rituximab works by targeting CD20 on B cells, reducing their activity, which is key in autoimmune diseases like AIH[46,47]. Administered intravenously, its dosing depends on the condition. Common side effects include cardiovascular issues, infections, and infusion reactions, which range from mild to severe[48,49].

Burak *et al*[24] conducted a case series involving six patients (aged 36-68) with refractory AIH who failed conventional treatments like corticosteroids and AZA. Rituximab, given at 1000 mg every two weeks, showed significant impro-

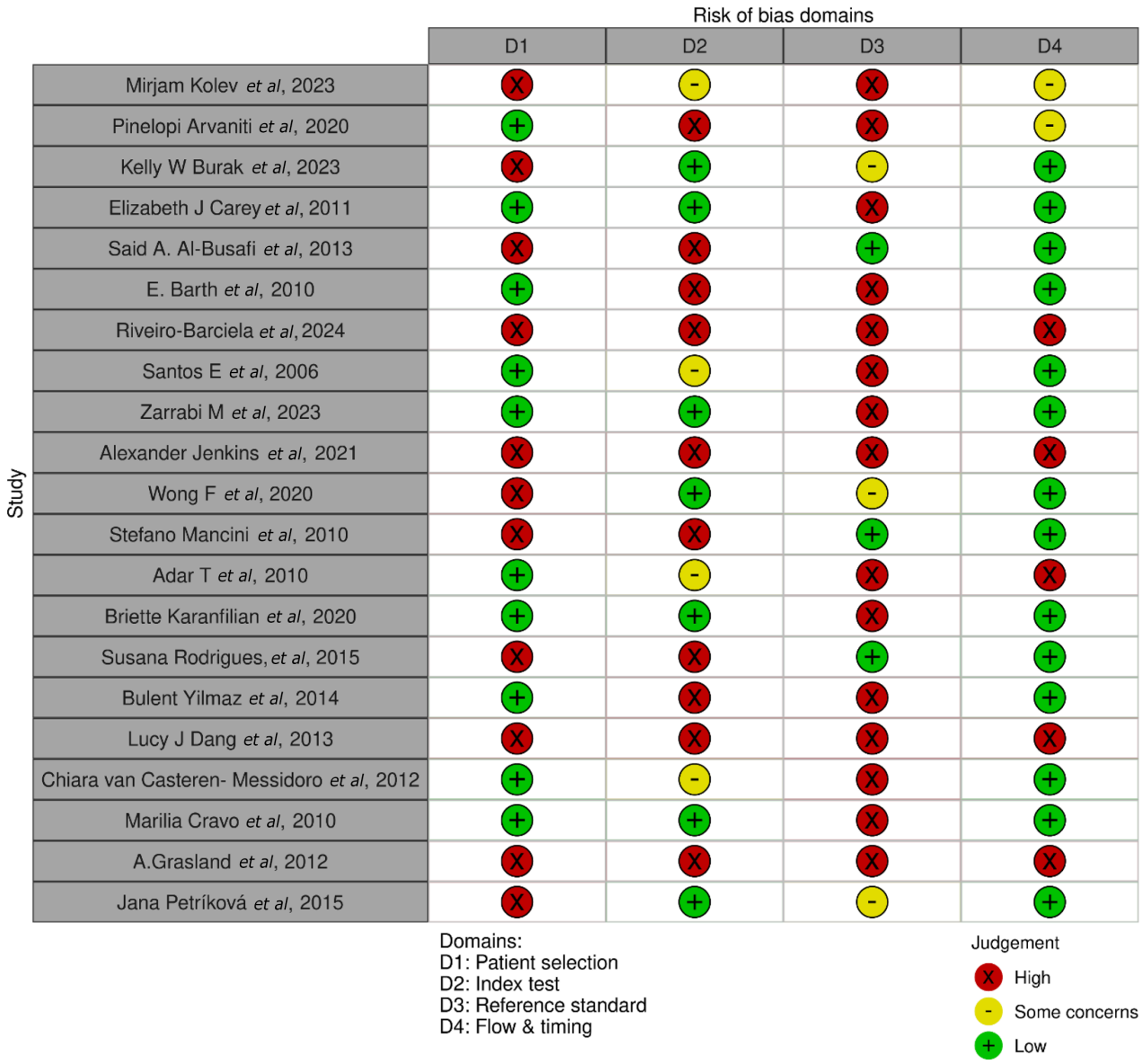

Figure 1 Prisma search strategy for systematic review.

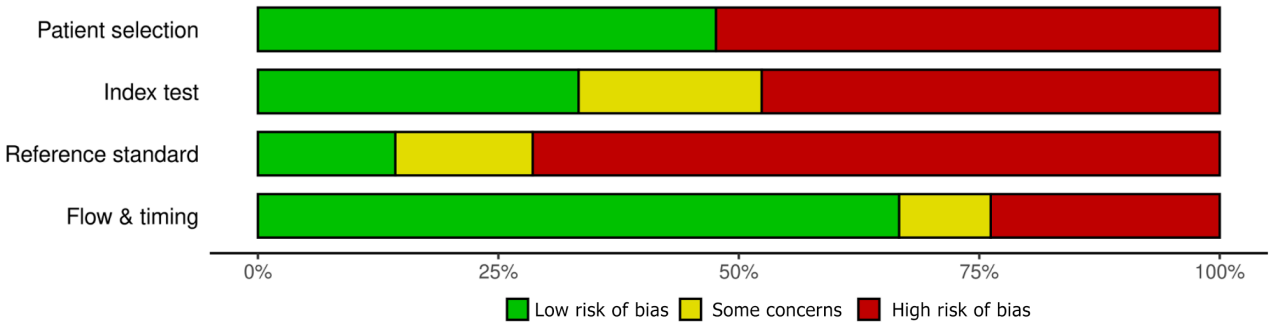

Figure 2 Bias assessment of the included studies.

vements by week 24 in IgG and AST levels. ANA and ASMA titers decreased, and four out of six patients had improved liver inflammation in biopsies by week 48. Two patients also showed fibrosis improvement. Overall, the study demonstrated that Rituximab is safe, well-tolerated, and improves histological and biochemical liver function in AIH.

In another case, a 44-year-old female with Evans syndrome and refractory AIH responded well to Rituximab after failing conventional therapies. After four weeks, she showed normalization of hemoglobin, platelets, and aminotransferases, with sustained remission for over a year[25]. Similarly, Al-Busafi *et al*[26] described a 68-year-old woman with

refractory AIH and Von Willebrand Disease who also achieved stable remission with Rituximab. Another case, reported by Barth *et al*[27], involved a 27-year-old woman with AIH and B cell lymphoma who experienced resolved lymphadenopathy and decreased aminotransferase levels after Rituximab treatment.

The Coihai registry, the largest study on Rituximab in AIH, included 35 patients. It found that 31 of them, including 12 with refractory AIH, achieved CBR. Rituximab helped reduce or discontinue other immunosuppressive drugs, such as reducing Prednisolone from 20 mg to 5 mg/day. Notably, patients with cirrhosis showed no difference in CBR rates compared to those without cirrhosis (P = 0.319). The study highlighted the safety and efficacy of Rituximab, with fewer infusion reactions[28].

Santos *et al*[29] reported on a 52-year-old woman with AIH and ITP who achieved AIH remission and normalized liver enzymes with Rituximab, further supporting its effectiveness in managing AIH alongside other autoimmune conditions.

Basiliximab in AIH and PBC

Basiliximab, a monoclonal antibody, acts as an immunosuppressant, primarily used to prevent organ rejection in kidney transplant patients. Its mechanism of action involves binding to the interleukin-2 receptor alpha chain (CD25) on T lymphocytes, inhibiting T cell activation and reducing the immune response, which is crucial in preventing organ rejection and disease activation[50].

Basiliximab is administered intravenously in single-dose vials of 10 or 20 mg. It is approved for preventing acute kidney transplant rejection and is also considered off-label for heart, lung, and liver transplants. Furthermore, it is being evaluated for treating autoimmune disease[51]. Side effects of Basiliximab include gastrointestinal symptoms such as nausea, hypersensitivity reactions, and infections[51].

A case study by Zarrabi *et al*[30] showed promising results for using Basiliximab in AIH. A 22-year-old woman with AIH, PBC overlap, and metastatic osteosarcoma experienced normalization of LFT with no major side effects after Basiliximab treatment, indicating its potential in managing overlapping autoimmune liver diseases.

Anti-TNF induced AIH

While biologics show promising results, anti-TNF agents in AIH carry significant risks, including the induction of AIH itself.

Infliximab, a purified DNA-derived chimeric IgG monoclonal antibody, inhibits TNF-alpha, which is active in acute phase reactions and systemic inflammation. It is produced by lymphocytes, NK cells, neutrophils, macrophages, mast cells, and neurons[52]. By blocking TNF-alpha, Infliximab halts the inflammatory cascade, improving conditions like Crohn's disease and psoriasis[53]. Infliximab can be administered intravenously or subcutaneously and is linked to common side effects like headaches, rashes, and infusion reactions. More severe risks include tuberculosis, necessitating TB screening before treatment[53]. AIH has also been reported as a side effect.

Several case reports and studies support this finding. Jenkins *et al*[31] reported a case of a 31-year-old man treated with infliximab for UC who developed AIH. Discontinuing infliximab and switching to vedolizumab, alongside budesonide and AZA, normalized liver enzymes. Wong *et al*[32] discussed a 69-year-old man who developed AIH after three doses of infliximab, requiring a liver transplant due to hepatocyte necrosis. Mancini *et al*[33] described a 33-year-old woman with psoriasis who developed infliximab-related hepatitis, requiring prednisone for recovery. Additional studies by Karanfilian *et al*[35] and Rodrigues *et al*[36] highlighted similar cases, confirming AIH development following infliximab or adalimumab treatment. Liver recovery was achieved by discontinuing the drug[37-39].

Adalimumab, another anti-TNF therapy, has been used since 2002 for autoimmune conditions like plaque psoriasis, ankylosing spondylitis, RA, UC, and Crohn's disease[54]. Administered *via* subcutaneous injection, it carries side effects, including respiratory infections and headaches. It also increases lymphoma risk[54]. Our study examined Adalimumab induced cases of AIH.

Grasland *et al*[41] described a 35-year-old woman with RA who developed AIH after adalimumab treatment. Liver enzymes normalized after switching to abatacept. Similar findings were reported by Petríková *et al*[42] and Cravo *et al*[40], where patients with Sjögren's syndrome, RA, and Crohn's disease developed AIH after adalimumab use, confirmed by liver biopsies[42]. However, Cravo *et al*[40] highlighted a full recovery from AIH after infliximab discontinuation, with adalimumab successfully controlling the patient's intestinal disease without AIH recurrence.

The varying outcomes of biologics and anti-TNF agents may be due to differences in their mechanisms of action. Belimumab targets BLyS, reducing B-cell activity and autoantibody production, addressing AIH's autoimmune processes. Rituximab depletes B-cells by targeting CD20, also lowering autoimmune activity. In contrast, TNF-alpha inhibitors like infliximab and adalimumab disrupt immune responses, potentially triggering AIH, underscoring the complexity of immune modulation in AIH management.

Among reviewed articles, nine studies reported improvement of AIH using biologics like Rituximab, Belimumab, and Basiliximab, while twelve highlighted the development of AIH linked to anti-TNF therapies, specifically infliximab and adalimumab, when used for other autoimmune conditions[40].

Nevertheless, the use of anti-TNF therapies, particularly infliximab, has been explored as a potential treatment for refractory AIH in cases where standard or second-line therapies fail. A recent study demonstrated that infliximab can induce a complete biochemical response in up to 65% of patients with active AIH, which might support its role as a rescue therapy for those unresponsive to conventional treatments[55]. However, the presence of concomitant metabolic-associated liver disease significantly impacts the progression of liver fibrosis in AIH. A study by Liu *et al*[56] highlighted that patients with both AIH and MASLD, particularly those with diabetes mellitus, have a higher risk of developing severe fibrosis, further complicating disease management and increasing the likelihood of cirrhosis development. Thus, addressing steatosis and metabolic syndrome in AIH patients may be crucial for improving long-term liver outcomes and preventing fibrosis progression.

This study encountered several limitations related to the rarity of AIH. The small sample sizes in the available studies on biologics and anti-TNF therapies hinder the ability to detect significant differences, reducing the generalizability of the findings across larger populations. Genetic variability among patients further complicates treatment outcomes, making it difficult to predict responses accurately. Additionally, the high cost of biologics and anti-TNF agents limits their accessibility, potentially skewing the results towards patients who can afford these treatments. The lack of large-scale RCTs weakens the evidence base for biologic treatments in AIH, while heterogeneity in study design also limits the consistency of findings, and impaired our ability to run a meta-analysis. Thus, despite the promising results from biologics like Belimumab and Rituximab, the existing data remain constrained by these significant factors, and future research, such as RCTs, is crucial to overcome these challenges. Moreover, as our study is a systematic review, the sample size and patient heterogeneity is inherently constrained by the availability of published data, which may not fully capture the diversity of AIH presentations and treatment responses.

CONCLUSION

In conclusion, while biologics such as Belimumab and Rituximab show promise in treating AIH, anti-TNF therapies like Infliximab and Adalimumab may exacerbate or even induce AIH. Careful patient selection is essential, particularly for those with refractory AIH who fail to respond to standard treatments. Personalized approaches using genetic and biomarker analyses offer a pathway to optimize treatment and mitigate risks. However, the limitations surrounding small sample sizes, cost barriers, and genetic variability underscore the need for further research, especially large-scale RCTs, to solidify the efficacy and safety of biologics in AIH treatment. Such studies are also needed to explore why anti-TNF therapies lead to adverse effects while biologics have a more favorable profile.

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