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Comparative Overview of Azathioprine and Rituximab for Gastrointestinal IgG4 Disease

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Abstract

IgG4-related disease (IgG4-RD) is a chronic inflammatory condition marked by the infiltration of IgG4-positive plasma cells. The pancreas and biliary systems are commonly involved. Glucocorticoids (GCs) have been the mainstay of treatment for IgG4-RD, achieving a high initial response rate. Many patients experience relapses when the GC dose is reduced or discontinued, necessitating the need for effective steroid-sparing agents. Rituximab, a monoclonal antibody targeting CD20 on B-cells, has emerged as a promising alternative for patients with IgG4-RD. Similarly, other immunosuppressive agents such as Tacrolimus and Azathioprine are being evaluated for their potential to manage IgG4-RD. The studies for this review have been carried out in Italy, Sweden, Minnesota (USA), and Japan. Relapse rates were 21%, 0% (smaller number of patients), and 11% in the Rituximab trials, compared to 19% in the Azathioprine group, indicating similar results. Remission rates were not reported in the Azathioprine group, but remission rates in Rituximab studies were 89%, 99% (66 complete and 33 partial), and 86%, indicating high efficacy of Rituximab in inducing remission. Azathioprine shows promise as a maintenance therapy, lowering relapse rates compared to steroids alone, while Rituximab exhibits high remission rates but also a moderate relapse rate, especially in multi-organ involvement. The review concludes that while Rituximab is a good choice for steroid-resistant or intolerant cases, Azathioprine requires more research. However, Rituximab also had a higher incidence of adverse reactions, which mostly included infections, including a case of tuberculosis and borrelia, whereas Azathioprine had benign effects, including nausea, vomiting, and elevated

transaminases.

Keywords

IgG4 Pancreatitis, IgG4 Cholangitis, Rituximab, Azathioprine, Tocilizumab, Corticosteroids

1. Introduction

IgG4-related disease (IgG4-RD) is a chronic inflammatory condition marked by the infiltration of IgG4-positive plasma cells in various organs and elevated serum IgG4 concentrations. This disorder can affect multiple organ systems, including the pancreas, bile ducts, salivary glands, and kidneys, often mimicking malignancies and other inflammatory conditions. The disease's etiology remains unclear, but it is believed to involve a complex interplay of genetic, environmental, and immunological factors [1]. The clinical manifestations of IgG4-RD can be diverse, ranging from asymptomatic organ enlargement to severe organ dysfunction, underscoring the need for timely and accurate diagnosis and treatment [1].

Glucocorticoids (GCs) have been the mainstay of treatment for IgG4-RD, achieving high initial response rates and rapid symptom relief. However, long-term use of GCs is fraught with significant side effects, such as hyperglycemia, hypertension, osteoporosis, and increased susceptibility to infections, making prolonged therapy difficult. Moreover, many patients experience relapses when the GC dose is reduced or discontinued, necessitating the need for effective steroid-sparing agents. Therefore, exploring alternative treatments that can provide sustained disease control with fewer side effects is critical.

Rituximab, a monoclonal antibody targeting CD20 on B-cells, has emerged as a promising alternative for patients with IgG4-RD, particularly those who are refractory to or intolerant of GCs. Rituximab has shown efficacy in inducing and maintaining remission in IgG4-RD by depleting B-cells, which play a crucial role in the pathogenesis of the disease [2].

Similarly, other immunosuppressive agents such as Mycophenolate, Tacrolimus, and Azathioprine are being evaluated for their potential to manage IgG4-RD. Azathioprine, an immunosuppressant acting via inhibition of purine synthesis in actively dividing cells, is currently used in inflammatory bowel disease, lupus, and transplant. It may offer benefits as part of a steroid-sparing regimen in IgG4 disease through the same mechanism.

This systematic review aims to evaluate and compare the efficacy and safety of Rituximab and Azathioprine currently used but not standardized in patients diagnosed with IgG4-RD. Specifically, we seek to assess clinical response, remission rates, relapse rates, and safety outcomes, including adverse events, in patients treated with these agents.

2. Methods

Priori protocol was created and is listed under PROSPERO CRD42024542454 in the International Prospective Register of Systematic Reviews. For this review, we followed Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting criteria, as mentioned in Figure 1.

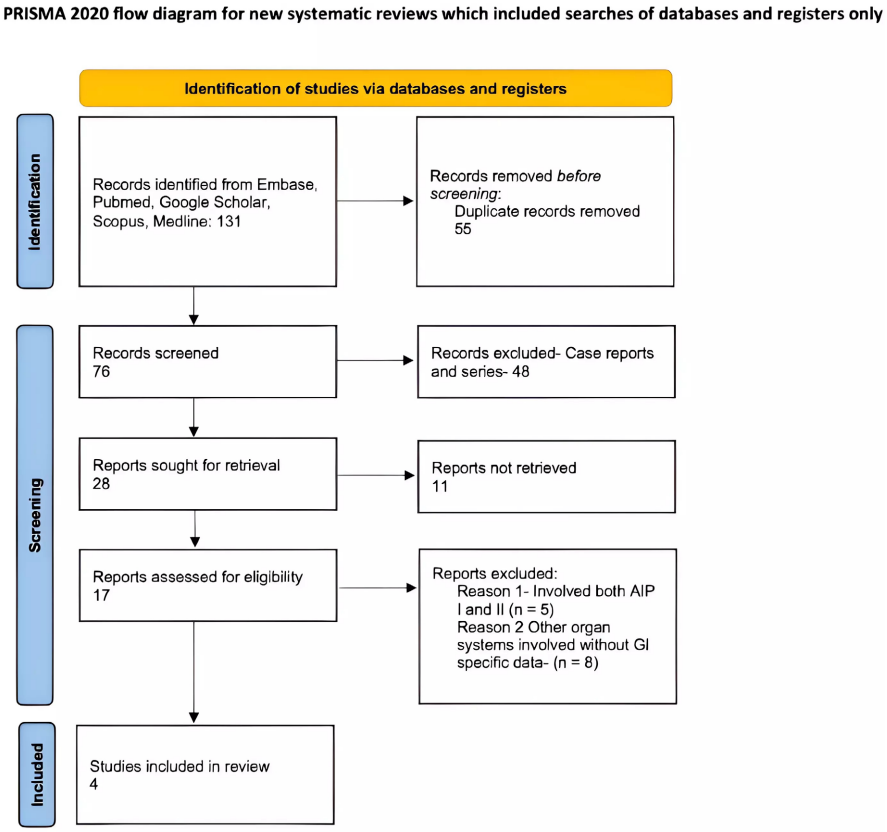

Figure 1. Prisma diagram for the systematic review.

2.1. Eligibility Criteria

Inclusion criteria for the studies were:

1) Studies published in English;

2) Studies including patients diagnosed with pancreatic or hepatobiliary IgG4 disease;

3) Studies assessing the use of Rituximab, Azathioprine, Tacrolimus, and Mycophenolate as therapeutic interventions;

4) Only systematic reviews and meta-analyses.

Exclusion criteria were:

1) Non-English publications;

2) Studies not exclusively including patients with IgG4 pancreatitis and cholangitis;

3) Studies published before 2015;

4) Studies that are not relevant to the research question.

2.2. Search Strategy and Study Selection

From 2015 to the present, a search of peer-reviewed papers and conference/abstract proceedings was carried out in the following electronic databases: PUBMED, Google Scholar, MEDLINE (the Cochrane library), EMBASE (the Ovid interface), and CENTRAL (the COVID interface). Search strategies were developed using keywords, their synonyms, abbreviations, and MeSH terms for "Immunoglobulin G4", "IgG4", "Azathioprine", "Rituximab", "Tacrolimus", "Mycophenolate", "Pancreatitis", "Autoimmune Pancreatitis", "Cholangitis", and "Biliary Disease". This was chosen to cover the sought-after therapeutic agents and gastrointestinal IgG4-related diseases.

2.3. Outcome

The primary outcomes of interest were the efficacy of steroid-sparing treatments regarding clinical/biochemical/radiological response, remission rates, and relapse rates.

Secondary outcomes included safety profiles, including adverse events, serious adverse events, and withdrawals due to adverse events.

2.4. Data Extraction and Risk of Bias Assessment

Duplicates were eliminated from the collection of articles by importing them all into the Endnote 20 (Clarivate, Boston, USA) program. Two independent authors then extracted data, evaluated the entire texts, checked the titles and abstracts, and determined the bias risk. Extracted data included study characteristics (author, year, study design, sample size, interventions, outcomes), patient demographics, and outcomes of interest. The length of therapy, primary and treatment outcomes, type and dose of accomplished interventional drugs/other conventional treatments for IBD/placebo regimens, and other study characteristics were considered.

Cochrane's Risk of Bias (RoB) tool 2.0, was used to evaluate bias resulting from the randomization process, bias resulting from intended intervention deviations, bias resulting from missing outcome data, bias in outcome measurement, bias in choosing the reported result, and overall bias in RoB. The reviewers would then resolve their points of conflict to an agreed point (Figure 2).

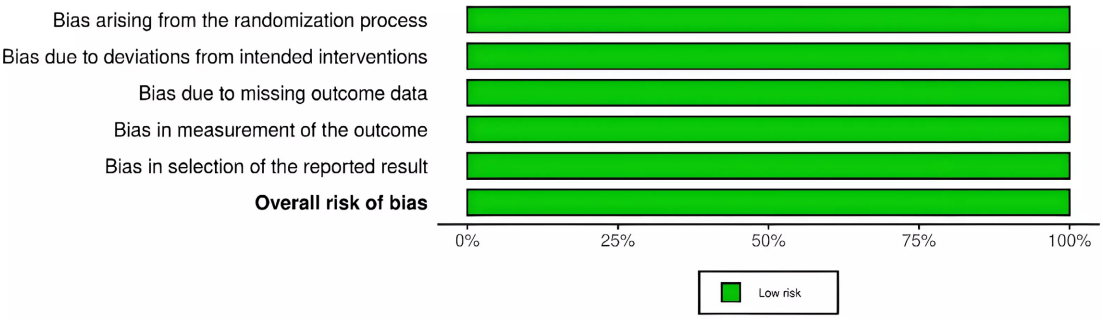

Figure 2. Risk of bias.

3. Results and Discussion

3.1. Study Characterization

Table 1 includes the characteristic features of the studies included in our study. The studies for this review have been carried out in Italy, Sweden, Minnesota, and Japan.

Table 1. Study characterization.

	Study	Type	Author	Year	Duration	Size
A	Efficacy and Safety of Rituximab for IgG4-Related Pancreato-Biliary Disease [2]	Systematic review and Meta-analysis	Marco Lanzillotta *et al.*	2021	19 months	101 receiving Rituximab; Rituximab administration was new disease onset (18.5%), disease flare after glucocorticoids (63.5%), and glucocorticoids intolerance (17.9%)
B	Efficacy and Safety of Rituximab in Autoimmune Pancreatitis Type 1: Our Experiences and Systematic Review of the Literature [3]	Systematic review	Sara Nikolic *et al.*	2021	17 months	103 (12 receiving Rituximab)
C	Rituximab Maintenance Therapy Reduces Rate of Relapse of Pancreaticobiliary Immunoglobulin G4-Related Disease [4]	Retrospective study	Shounak Majumder *et al.*	2018	34 months	43 Rituximab induction therapy (group 1, n = 14) and patients who received Rituximab induction followed by maintenance therapy (group 2, n = 29)
D	The Clinical Efficacy of Azathioprine as Maintenance Treatment for Autoimmune Pancreatitis: A Systematic Review and Meta-Analysis [5]	Systematic review and meta-analysis	Yoshiharu Masaki *et al.*	2022	24 months	4504 (346 receiving Azathioprine)

Further, Table 2 shows the drugs studied and the control group. Tables 3-5 show outcomes, including remission and relapse rates in Table 3, ADRs in Table 4 and result interpretation in Table 5.

Table 2. Treatment and control groups in the studies.

	Interventional group	Control group
A	Rituximab	
B	Rituximab	Glucocorticoids
C	Rituximab induction only	Rituximab induction and maintenance
D	Azathioprine	Glucocorticoids

Table 3. Outcomes of the studies.

	Primary outcome	Secondary outcome
A	High remission rate (88.9% at 6 months), moderate relapse rate (21% overall, 35.9% with multiorgan involvement)	Limited adverse events (25%)
B	Complete remission in 66.7%, partial remission in 33.3%	Low relapse rates during a median follow-up of 17 months
C	86% in steroid-free remission 6 months after Rituximab initiation. 3-year relapse rate, 45% in no maintenance group compared to 11% in maintenance (P = 0.034)	Infections developed in 6 of 43 patients, all in group 2 (P = 0.067 vs group 1); all but 1 occurred during maintenance therapy
D	Improvement in symptoms, prevention of relapse (19.2% relapse rate); 29.8% patients without Azathioprine experienced relapse	Effective as maintenance therapy, reduced need for corticosteroids

Table 4. Adverse drug reactions in the studies.

	ADR
A	25% adverse event rate
B	One patient had TB reactivation and one had Borrelia infection
C	Infections developed in 6 of 43 patients, all in group 2 (P = 0.067 vs group 1); all but 1 occurred during maintenance therapy
D	Non-remarkable

Table 5. Results.

	Results
A	Treatment of IgG4-related pancreato-biliary disease with Rituximab is associated with high remission rate, a higher relapse rate in the presence of multiorgan involvement, and limited AEs
B	Rituximab is efficacious in the treatment of AIP type 1 by inducing remission and preventing relapse apart from few adverse effects
C	Statistically significant reduced relapse in Rituximab maintenance group
D	Demonstrated the efficacy of Azathioprine in preventing relapse of AIP, which supports the use of Azathioprine as a maintenance treatment in patients with AIP who relapse upon withdrawal of glucocorticoids therapy

IgG4-related disease (IgG4-RD) is frequently associated with multi-organ involvement, extending beyond the pancreas. The disease has a predilection for males and often occurs in individuals over the age of 50. This is reflected in the study, with patients being 65% men and an average age between 55 and 60 years. The exact etiology of IgG4-RD remains unclear, but it is believed to involve an aberrant immune response, possibly triggered by environmental factors in genetically susceptible individuals [1]. This study deals with IgG4 pancreatitis and cholangitis.

2020 revised guidelines to diagnose IgG4 pancreatitis include:

1) Clinical or radiological features—one or more organs show diffuse or localized swelling or mass or nodule characteristic of IgG4-related disease;

2) Serological diagnosis—serum IgG4 level of more than 135 mg/dL;

3) Pathological diagnosis—2/3 of the following criterion—dense lymphocytic and plasma cell infiltration, IgG4 positive plasma cells at greater than 10 per field, typical strobili form fibrosis or obliterative phlebitis.

Diagnosis is definite if all criteria are met, probable if the first and third criteria are met, and possible if the first and second are met [1]. IgG4-related disorders are sometimes aided by the efficacy of steroid therapy.

Similarly, IgG4-associated cholangitis is diagnosed with similar histology, IgG4 levels > 135 mg/dL, intra or extrahepatic strictures, and steroid response. Serum IgG4 cut-off levels greater than ×2 ULN may be helpful in more accurately distinguishing IgG4-sclerosing cholangitis (SC) from primary sclerosing cholangitis or cholangiocarcinoma [1]. Between 80 and 90% of IgG4-SC cases are linked to AIP.

Treatment of IgG4-RP primarily involves glucocorticoids, typically prednisone. The response to glucocorticoids is often dramatic, with rapid improvement in symptoms and imaging findings [3]. The proposed therapeutic regimen entails the administration of prednisone at a dosage of 40 mg per day, to be sustained for an initial duration of 4 weeks. Subsequently, a meticulously designed 7-week prednisone taper is recommended, wherein the dosage is gradually reduced by 5 mg per week until complete cessation, resulting in an overall treatment duration of 11 weeks. Despite this approach, a staggering 50% of patients experience relapse.

Definitions of remission and relapse are subjective. Mostly, clinical, biochemical, and radiologic parameters are improved without ongoing steroid requirements. Any recurrence of parameters or steroid requirements denotes relapse. IgG5-RI is also used [4].

Less than one-third of patients who receive steroid induction therapy face recurrence. Risk factors for relapse are elevated IgG4 levels, icterus, and retroperitoneal involvement [6]. Japanese guidelines recently recommended the extension of steroid therapy to 3 years [7]. For individuals facing recurrent or refractory disease, particularly those undergoing steroid tapering or discontinuation, the therapeutic landscape expands to encompass second-line agents. Among these options, Rituximab, Azathioprine, Mycophenolate mofetil, methotrexate, and

even Tacrolimus enter the therapeutic arsenal, although it is crucial to note that the efficacy of these agents lacks confirmation from randomized controlled studies [8].

3.2. Rituximab

Rituximab (RTX) is a monoclonal antibody that depletes B-cells by targeting antigen CD-20. Due to better remission in studies and a more direct effect, RTX should be considered in steroid-resistant or intolerant patients [2].

3 studies with Rituximab are included in this review. Subjects were predominately male. The patient population was mostly Caucasian, even in the Japanese study. The first review and meta-analyses by Lanzillotta *et al.* pooled data from 7 cohort studies and included 101 patients. Rituximab was given at disease onset to 18.5% of the patients, 63.5% times it was a flare-up after steroids, and 18% of the patients had contraindications to steroids. A total of 19-month follow-up was done with a complete response amongst 89% of the cases. It was noted that the relapse rate was 21%, higher percentage 36% with multi-organ involvement [2]. High remission rate (88.9% at 6 months) was also noted.

The second study is Swedish. It comprised a total of 103 patients. A total of 11 patients received Rituximab, and 1 received siltuximab (anti-IL-6) due to Castleman's disease but was included due to similarities. Seven people got treatment after endoscopy, 2 during relapse off steroids, and three as a third line option. Of 12, 8 patients achieved complete remission and 4 partial remission. Dosages used were either 375 mg/m2 weekly for 4 weeks and then 3 monthly OR 1000 mg every 15 days for two doses repeated six months. There was no relapse in 17 months. One of the patients developed tuberculosis and one Borrelia skin infection [3].

The last study focused on induction only versus maintenance therapy. It was a retrospective study with 14 patients in an induction-only group, 29% had RTX as the first line, 21% as the second line after steroids, and 50%, as the second line after steroids with immunomodulators. 5 people in the induction-only group relapsed, whereas 4 in the maintenance group had a relapse. One of the relapses was during the maintenance infusions. The difference was significant with $P = 0.037$ [4].

So, Rituximab showed benefits as first-line and second-line therapies both. It even showed benefits with continued maintenance. However, given the ADR profile and initial steroid response, our recommendation is Rituximab use for relapses, steroid resistance, or intolerance. Maintenance in people with multiple relapses has also been shown to be beneficial and hence would be recommended. The latter is limited by a small study design.

3.3. Azathioprine

Azathioprine inhibits purine synthesis. It is currently extensively used in inflammatory bowel disease, vasculitis, lupus, and post-transplant patients.

Trials for use in IgG-4 disease are limited, and most of the data comes from case

reports. Relapse rates are harder to track, given pancreatitis in itself is a side effect. However, a Japanese systematic review based on 10 articles containing both eastern and western populations, with 4504 patients, 346 of which were on Azathioprine at doses of 2 mg/kg - 2.5 mg/kg. Of the 346, at least 187 had confirmed IgG-4 pancreatitis; relapse was defined as radiological in 3 studies, both clinical and radiological in 12, and unclearly defined in the rest 11. Average follow-up was slightly higher than 2 years. A relapse was seen in 19% of the patients on Azathioprine versus 30% on steroids at therapeutic doses.

Commonly associated adverse reactions were nausea, vomiting, and elevated transaminases and occurred at a higher incidence than the steroid-only group. The integrated odds were in favor of steroids with Azathioprine versus steroids alone. The study is observational and has shortcomings requiring more studies for standardization of therapy [5].

Other therapies are not included in the review.

3.4. Cyclophosphamide

Exclusive gastrointestinal IgG4 reports were not available. However, a study with IgG4 disease, on comparison between steroid only and combination therapy with cyclophosphamide, showed 38% relapse in steroid alone versus 12% in combination therapy, indicating benefit [9].

3.5. Mycophenolate

Similar to Cyclophosphamide, groups had steroids alone or in combination with mycophenolate. The relapse rate during 1 year of therapy was much higher in the former group than in later II (40.00 vs 20.59%). The remission rate was lower in the former group (51.42 vs 76.47%).

The total response in groups I and II was 98.15 and 96.3%, respectively, and within 12 months, the cumulative relapse rate in group II was significantly higher than that in group I (14.8 vs. 3.7%, P = 0.046). Recurrence occurred at the paranasal sinus, lacrimal glands, skin, lung, pancreas, and bile ducts, and the relapsed patients achieved remission after switching immunosuppressants or/and increasing the GC dose [10].

In a comparative study, the total response in Cyclophosphamide and Mycophenolate groups was 98.15 and 96.3%, respectively, and the first-year relapse rate with MMF (14.8 vs. 3.7%, P = 0.046) [11].

3.6. Tacrolimus

One study abstract was available, checking Tacrolimus effectiveness in IgG4 and other forms of autoimmune pancreatitis, AIP-1, and AIP-2. Data revealed type 1 was 69.5%, with male gender present in 65.8% of cases and 65.8.% concurrent autoimmune cholangitis (AIC). A high rate of relapse in AIP1 patients (43.9% in AIP1 vs. 27.7% in AIP2) prompted further escalation to Tacrolimus. Notably, use of Tacrolimus was very effective for clinical and biochemical remission [12].

3.7. Tocilizumab

Among 29 people with 14 on tocilizumab, at 6 months, tocilizumab demonstrated its effect, with 50% of patients achieving clinical remission in the Tocilizumab group versus 20% in the Cyclophosphamide group (P = 0.128) [13].

3.8. CD-19 Inhibitors

CD-19 inhibitors recently approved in the US after phase 3 trials. Not included in the study due to lack of post-marketing studies [14].

4. Conclusion

IgG4 disease is a multiorgan disease with excellent steroid response initially. GI involvement commonly includes the pancreas and biliary system. Progression is complicated by relapse in a third of patients, prompting a 3-year steroid taper at places. However, to avoid the effects of steroid overuse, resistance, or intolerance, Rituximab is an excellent choice being studied in small studies both for induction and maintenance. Other modulators are not exclusively studied on GI population but have been shown to decrease relapse overall. Azathioprine has one study backing its use, but limitations warrant further studies. Novel therapies, including complement targeting tocilizumab or recent CD-19 inhibitor, are promising and shall be explored in the future.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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