Review Article

Rituximab: A Review of Use in Adult Rheumatology

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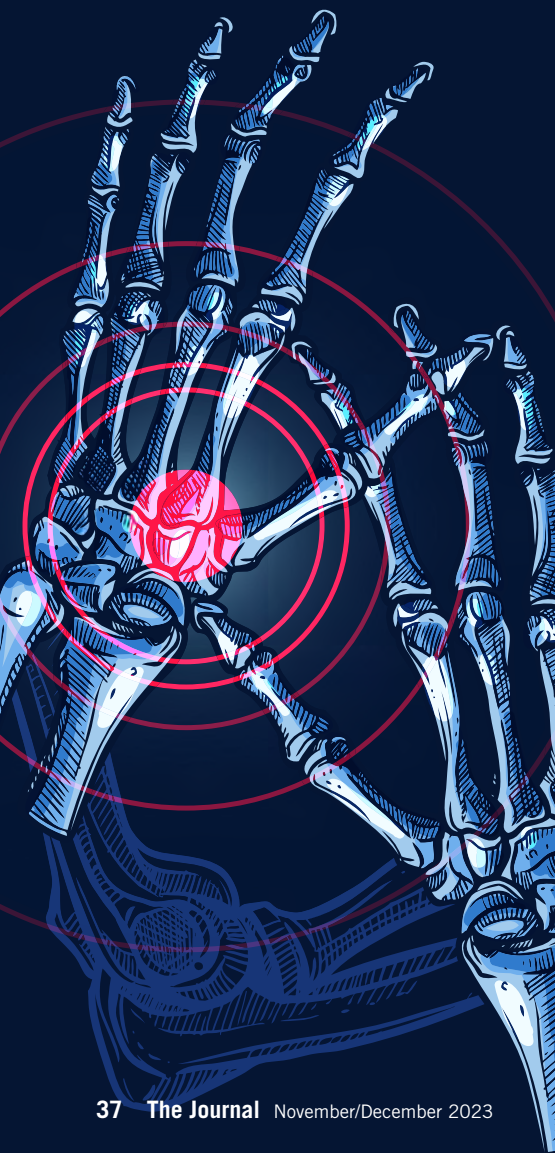

Though rituximab was originally approved for treating non-Hodgkin's lymphoma, its use has expanded to a variety of disease states, including immune-mediated rheumatic diseases.[1] This literature review aims to summarize recommendations for rituximab use in adults with rheumatic diseases that have American College of Rheumatology (ACR) or European Alliance of Associations for Rheumatology (EULAR) guidelines available. Additionally, this review aims to briefly summarize evidence and dosing for rituximab in each disease state, as well as the available formulations.

Introduction

Rituximab is a chimeric anti-CD20 monoclonal antibody (mAB) first approved for the treatment of non-Hodgkin's lymphoma in the US in 1997 under the brand name Rituxan®.[1] CD20 is a transmembrane protein expressed by the majority of pre-B and mature B-cells.[2,3] Rituximab, as an anti-CD20 mAB, depletes CD20+ B-cells through multiple mechanisms, including antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.[3]

Since 1997, rituximab has been used in numerous disease states, particularly finding use in immune-mediated rheumatic diseases, such as rheumatoid arthritis (RA), Felty syndrome, systemic lupus erythematosus (SLE), Sjogren's syndrome (SjS), and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides.[4] Of these disease states, rituximab is only FDA approved for rheumatoid arthritis and the Antineutrophil Cytoplasmic Antibody (ANCA)-associated vasculitides microscopic polyangiitis and granulomatosis with polyangiitis. Though not well elucidated, there are a variety of mechanisms thought to contribute to the efficacy of rituximab in immune-mediated rheumatic diseases, including the reduction of autoantibodies and the depletion of pathogenic subsets of CD20+ B-cells. For example, in RA, this includes the reduction of rheumatoid factor (RF) and the depletion of CD27+IgD- B-cells, which have a greater prevalence in the synovial fluid and are more prone to expressing the cytokine RANKL after activation, contributing to bone resorption.[5,6]

Formulations

Since the approval of Rituxan®, biosimilars have come to market, such as Truxima® (rituximab-abbs) in 2018, Ruxience® (rituximab-pvvr) in 2019, and Riabni® (rituximab-arrx) in 2020.[7] Biosimilars are copies of biological drugs, though molecular identity cannot be established as it can be with generics of chemical drugs.[8] These biosimilars are commonly used in practice in lieu of Rituxan®, often depending on insurance coverage, and may offer substantial cost savings for patients, which can be expanded through co-pay assistance programs. A subcutaneous formulation, Rituxan Hycela®, was approved in 2017 for several types of cancer after at least one IV infusion of rituximab, though it has not yet been studied in rheumatic disease.[9] Further research is needed to compare the efficacy and tolerability of the subcutaneous formulation in this patient population, as it could increase patient convenience and decrease time for treatment and monitoring.

Rheumatoid Arthritis

RA is a chronic, inflammatory autoimmune disease that principally affects the joints, though it can progress to systemic effects. Damage to the joints often results in bone erosion and deformities which are associated with significant pain.[10]

Rituximab is categorized as a biologic disease-modifying anti-rheumatic drug (DMARD) which was first approved in 2006 for use in RA. The 2022 EULAR and the 2021 ACR guidelines on the treatment of RA generally recommend the addition of a biologic DMARD after failure to achieve goals of treatment on at least one conventional synthetic DMARD, such as methotrexate or leflunomide, with short-term glucocorticoids.[11,12] The decision to try more than one conventional synthetic DMARD is typically dependent on treatment cost and whether poor prognostic factors are present, such as high disease activity or high levels of RF.[11,12] The choice of biologic DMARD is largely based on patient-specific factors, with rituximab being preferred in patients with a history of a lymphoproliferative disorder where rituximab is an approved treatment. In this patient population, rituximab can be considered earlier in therapy if disease activity is moderate to high.[11]

When rituximab was approved for RA in the US, dosing recommendations for one course were two 1,000 mg doses separated by two weeks, with subsequent courses given every 24 weeks or as clinically indicated, but no sooner than 16 weeks.[3] The EULAR guideline, based on the most recent expert consensus in 2011, prefers a low-dose regimen of either a single 1000 mg IV infusion or two 500 mg IV infusions separated by two weeks.[12,13] This is reinforced by a more recent meta-analysis comparing the efficacy of initiating low-dose (1 x 1000 mg or 2 x 500 mg) versus high-dose (2 x 1000 mg) rituximab in patients with RA. Primary endpoints included ACR criteria for 20% improvement (ACR20), ACR50, and ACR70, in disease activity, as well as the Disease Activity Score in 28 joints (DAS28) at both 24 and 48 weeks. Non-inferiority criteria were met for low-dose rituximab for the ACR20, ACR50, and DAS28 at 24 and 48 weeks. There were no significant differences between the primary endpoints.[14]

However, per the expert consensus, in patients with a history of TNF-inhibitor failure, the FDA-approved high dose is preferred. Monitoring for radiographic progression with the low-dose regimen was not evaluated in this population, while the higher-dose regimen has shown efficacy in slowing radiological damage at both one and two years of treatment per the REFLEX trial.[13,15,16]

Though the optimal strategy for dosing frequency is not clearly defined, the ACR and EULAR guidelines generally recommend the treat-to-target strategy over regular re-treatment, with goals of sustained clinical remission or low disease activity.[11-13] The treat-to-target strategy is preferred to optimize therapy, prevent over- or under-treatment, and improve patient outcomes.[13,14]

Felty Syndrome

Felty syndrome is an uncommon condition characterized by a triad of RA, splenomegaly, and neutropenia that most commonly affects patients with severe, erosive, long-standing, seropositive arthritis.[17]

Based on limited case studies, there is best evidence for the use of the DMARDs methotrexate and rituximab, both of which have shown the potential to improve neutrophil counts in this subset of patients. Rituximab is recommended to be added after insufficient response to methotrexate, a conventional synthetic DMARD, per the EULAR and ACR guidelines outlined above.[12,13,17,18]

Systemic Lupus Erythematosus

SLE is a heterogeneous autoimmune disease with a wide array of systemic manifestations; two of the most common are acute cutaneous lupus and arthritis.[19] Due to this heterogeneity, treatment is largely dependent on symptoms, organ involvement, and level of severity.[19,20]

The 2019 EULAR guideline for the management of SLE recommends rituximab in severe, refractory cases of organ-threatening, non-renal SLE. For SLE with renal involvement, rituximab can be considered in relapsing or refractory disease.[20] These recommendations are based on a lack of evidence for efficacy earlier in the disease process (e.g. less severe disease) or not having failed first-line options.[20-23]

The randomized-controlled EXPLORER trial in patients with moderate-to-severe non-renal SLE found no significant differences in clinical response between rituximab and placebo when added to the standard of care.[21-22] In Hispanic and Black patients, however, a significant difference was found in both partial and complete clinical response with rituximab versus placebo ($p = 0.04$).[22] The randomized-controlled LUNAR trial in patients with class III or IV lupus nephritis found no significant differences in clinical renal response between rituximab and placebo when added to the standard of care.[23] Despite the findings in these two trials, retrospective studies have found benefit in using rituximab in more severe, refractory cases of both renal and non-renal SLE.[21]

In studies, rituximab regimens have included two 1000 mg doses two weeks apart as well as four doses of 375 mg/m2/week.[21] Though not formally compared, differences in response have not been noted between the two regimens.[24] As with RA, a treat-to-target strategy may offer greater benefits in decreasing the frequency and severity of flares.[19]

Sjogren's Syndrome

SjS is a systemic autoimmune disease leading to dysfunction of secretory glands, causing mucosal dryness, particularly in the eyes and mouth, known as sicca symptoms. Approximately 50% of those affected may develop extra-glandular involvement with a wide spectrum of clinical manifestations, affecting a multitude of organ systems. A variety of autoantibodies are also associated with SjS, including antinuclear antibodies, anti-Ro/SS-A, and cryoglobulins. Additionally, SjS often occurs with other systemic autoimmune diseases, including RA and SLE.[25,26]

While therapy is primarily directed at symptomatic relief of sicca symptoms, systemic therapies can be considered in patients with active systemic disease. The 2019 EULAR guideline for the management of SjS developed algorithms through task force clinical experience and largely retrospective studies based on domains affected and disease severity.[26] To briefly summarize the place of rituximab in these algorithms, rituximab is considered a second-line option in SjS with the following: cutaneous vasculitis with high activity (diffuse purpura covering ≥18% of the body surface area or the presence of ulcers), renal involvement with a high EULAR Sjögren's syndrome disease activity index (ESSDAI) domain score (≥15), multineuritis, and hemolytic anemia with hemoglobin levels <8 g/dL. Rituximab is considered as rescue therapy, after first- and second-line treatments, for SjS with the following: acute glandular involvement, arthritis with synovitis and high severity (ESSDAI domain score >5 or severe widespread tenosynovitis), interstitial lung disease with symptoms present with ordinary activity or at rest, and central nervous system (CNS) vasculitis or neuromyelitis optica spectrum disorder. Though algorithms vary based on organ involvement, generally, glucocorticoids are first-line, with other oral immunosuppressants second-line, or as second-line options. Rituximab may be preferred over alternative second-line therapies, such as oral immunosuppressants, or other rescue therapies in patients with cryoglobulinemic-associated vasculitis (CV).[26]

While most uncontrolled trials for the use of rituximab in SjS have demonstrated

benefit in either global response, organ-specific response, or reduction of prednisone, two major randomized-controlled trials, the TEARS and TRACTISS trials, exhibited underwhelming results.[27,28] The TEARS trial found no significant differences between placebo and rituximab in the primary outcome of ≥30 mm improvement in two out of four visual analog scales (VAS) for global disease, fatigue, pain, and dryness at 6 months.[27] Notably, at baseline, patients had only moderate global disease activity with an average ESSDAI score of 10.1. The TRACTISS trial also found no significant differences between placebo and rituximab in the primary outcome of a decrease in ≥30% in VAS assessments of fatigue or oral dryness at week 48.[28] However, there was a significant difference in EEDAI scores at week 36. At baseline, patients had low global disease activity with an average ESSDAI score of 5.7.

The best evidence for use of rituximab is for patients with CV. In a retrospective trial of patients with cryoglobulinemia or vasculitis, there was a significant change in ESSDAI score from baseline to six months, with an average baseline ESSDAI score of 24 and average score at six months being 14.5 ($p = 0.008$), which aligned with results of previous studies in this population.[26,29]

The 2019 EULAR guideline recommends two 1000 mg doses two weeks apart for induction, as that dosing was used in the majority of studies.[26] However, no recommendations are made regarding maintenance use of rituximab or dosing. There is a paucity of data examining maintenance dosing and frequency of rituximab in patients with SjS.

Antineutrophil Cytoplasmic Antibody-Associated Vasculitides

ANCA-associated vasculitides are a rare group of autoimmune, necrotizing vasculitis with systemic, heterogeneous effects. This group includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA).[30] While GPA and MPA are classified as different diseases, they are often combined in guideline recommendations due to pivotal trials investigating these diseases jointly.[31]

For induction of remission for patients with active GPA or MPA that is not organ- or life-threatening, the 2022 EULAR guideline on the management of ANCA-associated vasculitides recommends glucocorticoids in combination with rituximab first-line.[32] This recommendation is extrapolated from trials that included patients with non-organ-threatening vasculitides, showing similar efficacy and safety to those with more severe disease at baseline. No randomized controlled trials have been performed comparing rituximab to other agents in patients with non-organ- or non-life-threatening vasculitides.[32] In contrast, the 2021 ACR guideline on the management of ANCA-associated vasculitides recommend methotrexate preferentially over rituximab in combination with glucocorticoids due to the reported greater body of evidence and clinical experience with methotrexate, noting clinical trials are needed to compare their efficacy.[31]

For induction of remission in organ- or life-threatening GPA or MPA, the EULAR guideline recommends either rituximab or cyclophosphamide in addition to glucocorticoids, with rituximab preferred in relapsing disease.[32] The EULAR guideline also notes rituximab is often preferred over cyclophosphamide in practice due to the risks of infertility, malignancies, and bone marrow failure associated with cyclophosphamide. For these reasons, the ACR guideline explicitly recommends rituximab over cyclophosphamide for induction therapy in patients with organ- or life-threatening GPA or MPA.[31]

In maintaining remission of GPA or MPA, the EULAR guideline recommends rituximab for all patients.[32] The ACR guideline recommends rituximab for maintenance in patients with organ- or life-threatening disease.[31] However, in patients with non-organ- or non-life-threatening GPA, rituximab is only recommended as an option for maintenance in patients who received either rituximab or cyclophosphamide for induction therapy.

Due to a lack of trials involving rituximab in the treatment of EGPA, rituximab is used less frequently. The EULAR guideline recommends rituximab as a second-line alternative to cyclophosphamide in inducing remission in organ-threatening disease and as an option for maintaining remission.[32]

For EGPA, the ACR guideline recommends rituximab or cyclophosphamide for induction in organ- or life-threatening disease, with preference for cyclophosphamide in patients with active cardiac involvement.[31] This is due to the increased risk of mortality in this population and greater evidence for cyclophosphamide. In patients with non-organ- or non-life-threatening EGPA, rituximab is only recommended

to be considered for induction after failure of preferred agents, which include mepolizumab, methotrexate, azathioprine, and mycophenolate mofetil. For all patients with EGPA, the ACR guideline only recommends considering rituximab for maintenance therapy if remission was induced with rituximab.[31]

Induction dosing is recommended as a course of four 375 mg/m2/week doses or a course of two 1000 mg doses 14 days apart.[31,32] A recent meta-analysis of retrospective studies found no difference in safety or efficacy between these doses.[32,33] For maintenance of remission, a single dose of 500 mg every 6 months is generally recommended. In patients who relapse on this maintenance regimen, an increase in dose to 1000 mg or an increase in frequency to every 4 months can be considered.[31]

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