ACR Open Rheumatology
Vol. 4, No. 5, May 2022, pp 406–409
DOI 10.1002/acr2.11409

American College of Rheumatology
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JOURNAL CLUB

Journal Club Review of "Comparison of Two Rituximab Induction Regimens for Antineutrophil Cytoplasm Antibody–Associated Vasculitis: Systematic Review and Meta-Analysis"

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Objective. The objective of this study was to compare the efficacy and safety of two rituximab (RTX) regimens for the induction of remission in severe antineutrophil cytoplasm antibody-associated vasculitis (AAV): the four-dose (375 mg/m^2 intravenously weekly) versus the two-dose (1000 mg intravenously biweekly) regimen.

Methods. A systematic review was performed to identify studies using the four- and/or two-dose RTX regimens for induction of remission in severe AAV. Disease status 6 months after RTX infusion was required for inclusion. Patients were excluded if they received concomitant cyclophosphamide or plasma exchange. The primary end point was the proportion of patients in complete remission at 6 months. The pooled estimate was obtained by using meta-analysis methods for proportions with random effects. Secondary end points included antineutrophil cytoplasm antibody status, number of patients with B-cell depletion, mean prednisone dose, infections, and death.

Results. A total of 27 studies and 506 patients were included for analysis: 361 patients received the four-dose regimen, and 145 patients received the two-dose regimen. Most patients had relapsing disease at inclusion (83% and 92% of patients, respectively). There was no significant difference between the four- and two-dose regimens, with a complete remission achieved in 85% (95% confidence interval [CI]: 70-96) and 91% (95% CI: 79-99) of patients, respectively. At 6 months, both regimens were associated with a similar mean daily prednisone dose (8.1 mg), infections (12% in both), and death (1% vs. 0%, respectively).

Conclusion. No difference was found in terms of efficacy or safety between the four- and two-dose RTX regimens for induction of remission in severe AAV.

https://onlinelibrary.wiley.com/doi/10.1002/acr2.11274

Bénard V, Farhat C, Zarandi-Nowroozi M, Durand M, Charles P, Puéchal X, et al. Comparison of two rituximab induction regimens for antineutrophil cytoplasm antibody–associated vasculitis: systematic review and meta-analysis. ACR Open Rheumatol 2021;3:484–94.

INTRODUCTION

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis is a rare form of small vessel vasculitis with an incidence rate of around 3.3 per 100,000 population based on a population-based cohort from Olmsted County, Minnesota, in the United States (1). The same study also identified increased mortality in patients with ANCA vasculitis compared with the general population (1). Life-threatening complications, including renal failure, diffuse alveolar hemorrhage, and neurological involvement, can occur in patients with ANCA-associated vasculitis, requiring aggressive management (2).

Rituximab is an anti-CD20 monoclonal antibody that depletes B lymphocytes through various mechanisms, and it has been studied in different diseases (3). In 1997, rituximab was studied in patients with lymphoma with varying doses of 125 mg/m^2, 250 mg/m^2, and 375 mg/m^2 (4). This early landmark study included 20 patients of whom 10 were treated with the 375 mg/m^2 dose, and interestingly, the overall response in the three groups (ie, the 125 mg/m^2, 250 mg/m^2, and 375 mg/m^2 groups)

Author disclosures are available at https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Facr2.11409&file=acr211409-sup-0001-Disclosureform.pdf.

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No potential conflicts of interest relevant to this article were reported.

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Submitted for publication October 15, 2021; accepted December 10, 2021.

was exactly similar at 33%. After this trial, the 375 mg/m^2 dose was later used for phase 2 trial for patients with B-cell lymphoma and was later identified as the lymphoma protocol. Ultimately, further studies were done, and rituximab was approved for the treatment of lymphoma (3,5).

Interestingly, clinical investigators have used this protocol for other autoimmune diseases, although the pathogenesis and the degree of B-cell involvement in these diseases are different from lymphoma and, traditionally, oncology patients receive much more therapy in terms of immunosuppression as compared with patients with autoimmune diseases.

Rituximab was later used in a randomized, double-blind, controlled study in patients with rheumatoid arthritis with a fixed dose of 1 g every 2 weeks with good results (6). This led to the other known rituximab regimen—1 g every 2 weeks—known as the rheumatoid arthritis protocol. This protocol highlighted the ability to achieve clinical response despite giving a lower total dose of rituximab compared with the prior lymphoma protocol.

Rituximab continued to be used in various autoimmune diseases, including immune thrombocytopenic purpura (ITP), severe pemphigus vulgaris (PV), and ANCA-associated vasculitis (7–10). Interestingly, the lymphoma protocol, being older, was initially used in ITP and PV, whereas newer studies started using lower doses of rituximab or the rheumatoid arthritis protocol. Lower doses of rituximab were recommended because B-cell–depleting agents can cause hypogammaglobulinemia; therefore, using lower doses while maintaining clinical efficacy has been a topic of interest for clinicians (11).

Importantly, these two protocols are used in treating patients with ANCA-associated vasculitis. However, no head-to-head trials using these regimens have been performed in patients with ANCA-associated vasculitis owing to the paucity of patients with this disease and the challenges of recruiting patients to such a study. In an attempt to address this question, Bénard and colleagues conducted a systematic review and meta-analysis to compare the two rituximab regimens used for induction therapy in patients with ANCA-associated vasculitis with regard to efficacy in inducing remission in 6 months after therapy as well as safety and effect on mortality (12).

METHODS

The authors conducted a systematic review of the literature that included randomized studies, nonrandomized studies, cohort studies, case–control studies, and case series that assessed the efficacy of rituximab as the four-dose (lymphoma protocol) or the two-dose (rheumatoid arthritis protocol) regimen. The authors excluded single case reports as well as systematic reviews and meta-analyses if present.

The criteria for inclusion were receiving a recent diagnosis, having relapsing disease or severe disease, having a minimum of 6 months' follow-up, and having remission data. The authors excluded patients who received concomitant cyclophosphamide and/or plasma exchange. These criteria seem to be reasonable; however, later in the results section, the authors mentioned that some data for remission were not completely available for review and several patients did not have Birmingham Vasculitis Activity Score (BVAS) scores at the 6-month follow-up, which the authors acknowledged as a limitation of the study.

The authors then conducted a literature review that included several sources (PubMed, Cochrane, clinialtrials.gov, Medline, and others), which is valuable in capturing studies for review. The authors identified a reasonable timeframe from 1 January 2000 until 7 October 2019 for their literature review. The authors searched studies published in English and French, which they acknowledged as a limitation in the discussion section in that it limits the generalizability of the study, especially in the Asian population among which ANCA vasculitis exhibits different features compared with the White population (13).

The authors outlined a reasonable and well-structured algorithm that they followed during their study. Two reviewers were assigned to screen studies, and a third reviewer was identified in case of doubt or disagreement. The authors expressed that the senior author was consulted if further uncertainty was encountered. Furthermore, the authors identified one author for abstraction in order to minimize a potential abstraction inconsistency.

The authors assigned two reviewers to assess for publication bias using a specific tool that they outlined. The authors outlined their primary outcome as a BVAS score of 0, which is commonly used in clinical trials, but also included the absence of disease activity on clinical assessment as defined by each study, which is a rather nonspecific term and could have been used because of a lack of availability of BVAS scores, as mentioned in the results section.

The secondary outcome mentioned included ANCA positivity, B-cell depletion status (ie, number of patients with depleted B cells), mean prednisone daily dose, and mean time to remission. It is worth noting that the secondary outcomes were not met due to data unavailability, which the authors acknowledged in their discussion section.

The authors conducted testing for heterogeneity for the included studies as well as sensitivity analyses, which is a reasonable and standard approach for meta-analysis studies to ensure the validity of the results.

RESULTS

The authors identified 3,619 studies in their initial search, which was further narrowed down to 27 studies that included 759 patients, from which the final cohort of patients (N = 506) was extracted. The authors outlined their process in a graphical chart explaining how the studies were selected and how the final patient cohort was obtained. Similarly, they outlined in their supplemental material how they graded the studies with a reasonable grading system.

The total number of patients in the four-dose regimen was higher, with 361 patients, compared with the two-dose regimen, which had 145 patients. The majority of patients were granulomatosis with Polyangiitis in both groups (90% in the four-dose regimen compared with 92% in the two-dose regimen), which is also a limitation that the authors acknowledged and is secondary to the selection of the studies originating more from Europe and the US. Moreover, relapsing disease was dominant in both cohorts, with 83% in the four-dose regimen and 92% in the two-dose regimen, a limitation that the authors acknowledged, but it is worth noting that clinical trials usually include new-onset and relapsing disease owing to the paucity of cases with new-onset ANCA vasculitis.

The four-dose regimen was also noted to have a slightly higher percentage of patients with cyclophosphamide exposure compared with the two-dose regimen with 23% versus 18%, respectively. Moreover, ANCA positivity was higher in the group with a four-dose regimen with 88% compared with 77% in the two-dose group.

The authors reported an overall percentage of complete remission around 88%. The authors mentioned that no significant difference in remission was identified between the four-dose regimen and the two-dose regimen. However, they mentioned that significant heterogeneity was identified in the studies, which is a limitation that the authors acknowledged.

The authors were able to report comparable percentages of patients with ANCA positivity at 6 months: 44% of patients who had the four-dose regimen and 35% of patients who had the two-dose regimen. Moreover, the percentages of patients with B-cell depletion were comparable, with a slightly higher percentage in the four-dose regimen compared with the two-dose regimen (80% vs. 70%, respectively). The percentages of patients with infections were similar in both groups, at 12%.

As previously mentioned, the lack of BVAS scores at 6 months and mean time to remission limited the authors' ability to achieve their secondary outcome; however, they were able to report on the percentage of patients with infections and able to report on mortality (which are of clinical significance) while assessing the safety of the therapy.

CRITIQUE

In this meta-analysis, the authors investigated the currently used regimens of rituximab in the management of ANCA-associated vasculitis. The authors reported that there was no significant difference regarding clinical efficacy as well as safety at 6 months between the four-dose regimen and the two-dose regimen. This finding can be of clinical and practical significance; however, structured studies are needed before firm conclusions are drawn. The limitations in the study secondary to data unavailability and heterogeneity in the studies may also have an impact on the applicability of these findings.

As the authors described in the discussion section, the two-dose regimen delivers a lower total dose of rituximab to patients, which is an important socioeconomic factor to be considered. This would decrease health care use by decreasing the number of visits to infusion centers by 50%. Moreover, decreasing the total rituximab delivered might have less impact on the development of hypogammaglobulinemia experienced by patients on rituximab, although this remains to be systematically studied.

Lastly, the coronavirus disease 2019 (COVID-19) pandemic had a major impact on health care, and worse adverse patient outcomes were associated with rituximab use, so using the lower dose of rituximab might be a reasonable alternative during the COVID-19 pandemic or in patients with an increased risk of infection (14).

AUTHOR CONTRIBUTIONS

Dr. Elfishawi drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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