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Long-term Outcomes of Rituximab Therapy in Ocular Granulomatosis with Polyangiitis

Impact on Localized and Nonlocalized Disease

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Purpose: To evaluate the long-term outcomes of rituximab (RTX) treatment in patients with ocular granulomatosis with polyangiitis (GPA) with localized or generalized disease.

Design: Retrospective cohort.

Participants: Thirty-seven patients with ocular GPA receiving RTX in a multidisciplinary vasculitis clinic between 2004 and 2013.

Methods: A total of 100 patients who received a course of RTX were identified, and notes were reviewed. Baseline demographic details, clinical characteristics (including organ involvement), drugs used, and outcome measures were recorded.

Main Outcome Measures: The percentage in remission (inactive disease with prednisolone $\leq$7.5 mg with or without maintenance treatment) at 6 months, time to remission, percentage relapsing, side effects, B-cell count, antineutrophil cytoplasm antibody titers, induction, and maintenance regimens.

Results: The median follow-up time after the first RTX course was 36.5 months. Twenty patients had scleritis, and 17 patients had orbital disease; 86% achieved remission at 6 months. The percentage in remission versus partial remission was not statistically significant between patients with scleritis and patients with orbital disease (85% vs. 15% with scleritis and 82% vs. 18% with orbital disease; $P = 1.00$). The percentage relapsing was not statistically significant ($P = 0.33$) between scleritis (60%) and orbital disease (41%). Localized disease (ocular $\pm$ ear-nose-throat/lung) was observed in 57%, and generalized disease (ocular plus other organs) was observed in 43%, the former having a median duration of disease of 40 months. There was no statistically significant difference ($P = 0.37$) in the percentage in remission between localized and generalized ocular disease. Relapses occurred in 51%, with localized disease being a significant risk factor for relapse. Fifty percent of patients with generalized disease versus none with localized disease received cyclophosphamide (CYP) as part of the induction regimen. Patients who received CYP during induction had significantly ($P = 0.027$) lower ratios of baseline 12-month proteinase 3 titers than patients who did not have CYP. Infections were observed in 16% of patients, with 8% requiring hospital admission.

Conclusions: Our long-term data suggest that RTX is effective for inducing disease remission in localized and generalized ocular GPA. Localized disease is a significant risk factor for relapse, which may be related to less use of CYP in the induction regimen. *Ophthalmology 2015;■:1–7 © 2015 by the American Academy of Ophthalmology.*

Antineutrophil cytoplasm antibody (ANCA)–associated vasculitis (AAV) includes granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, microscopic polyangiitis, eosinophilic GPA, and single-organ AAV.[1,2] Antineutrophil cytoplasm antibody–associated vasculitis has a presumed autoimmune cause and can be life-threatening. Classically, disease remission has been induced with high-dose corticosteroids and cyclophosphamide (CYP), and this approach has significantly improved survival. However, in some patients, disease remains refractory to this regimen and overall relapse rates remain high at approximately 50% over 5 years, with significant early and late treatment-related morbidity and mortality.[3,4] Ocular involvement in AAV includes orbital inflammation and scleritis, which can occur with (generalized disease) or without (localized) other organ involvement.[5,6] Truly localized AAV is not common and has been seen in only 5% of a large cohort of patients with GPA with long-term follow-up.[7]

Rituximab (RTX) is a chimeric monoclonal antibody that leads to the depletion of peripheral B cells, but not plasma cells, by targeting the B-cell–specific CD20 calcium channel.[8] Additional effects on T cells via interference in B- and T-cell interactions also may contribute to its effects.[9]

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Rituximab has been used successfully in treating a number of autoimmune diseases, including rheumatoid arthritis and GPA,[10–12] with good evidence from randomized controlled trials to prove its efficacy.[13,14]

The systemic small-vessel vasculitis seen in AAV (e.g., in scleritis) is thought to be mediated by ANCA produced by B cells,[15] whereas the granulomatous inflammation in GPA (e.g., in orbital disease) may be mediated more by CD4+ T cells with a T-helper 1 cytokine profile.[16–18] Several large case series have found that RTX is effective for the treatment of granulomatous and nongranulomatous manifestations of AAV.[19,20] In a recent survey of 59 patients, Holle et al[21] reported that granulomatous manifestations were more refractory to RTX than nongranulomatous disease, although outcomes were only measured at 4 months. We have previously reported that RTX can take up to 6 months to achieve complete remission in patients with GPA with scleritis or orbital disease.[20]

The aims of this study were to assess the long-term outcomes of RTX treatment in patients with ocular GPA and to determine whether there is a differential response of granulomatous (orbital) and nongranulomatous (scleritis) manifestations, as well as of localized and generalized disease. Long-term follow-up also allowed us to characterize predictors of relapse in these patients with GPA. Furthermore, our use of a standardized RTX dosing regimen for each cycle eliminates the variability that has been present in some previous case series.

Methods

Inclusion Criteria and Data Collection

We retrospectively reviewed the notes of 100 patients with GPA who received RTX between December 2004 and January 2013, identified in a pharmacy dispensing database. Of these, 37 were found to have ocular disease. Ethical approval for this study was obtained from the Hammersmith, Queen Charlotte's, and Chelsea Research Ethics Committee. All patients were followed up in a multidisciplinary clinic at a single tertiary referral center, and all fulfilled the definitions of the Revised Chapel Hill Consensus Conference for GPA.[1,2] Patients underwent regular clinical, serologic, and immunologic examinations for disease activity and extent, as well as treatment-related side effects.

Investigators with experience in diagnosing and managing GPA completed a customized computer database for patients who met the inclusion criteria. Data collection included information on demographics, previous/current immunosuppression, disease activity, and adverse events at the time of each RTX course and at specified time points thereafter. Long-term disease activity/damage, relapse occurrence, and steroid dose were also recorded every year after the first RTX course. For patients receiving multiple courses of RTX, the response to therapy (disease activity and prednisolone dose) and laboratory results were recorded at specified time points for the first 12 months after each course.

Treatment Protocol

Rituximab (MabThera; Hoffman-LaRoche Ltd, Hertfordshire, UK) was given as 2 intravenous doses of 1 g 2 weeks apart, in addition to standard treatment. The corticosteroid tapering regimen varied depending on the organs involved. In the majority of patients, repeat courses of RTX were given when disease relapse occurred.

Clinical Assessments

We used European League Against Rheumatism (EULAR) definitions to define remission and relapse.[22] Remission was defined as the absence of disease symptoms and signs with a reduction in prednisolone to $\leq$7.5 mg. The definition of partial remission was a >50% reduction in Disease Extent Index score.[23] In addition, we further specified the proportion of patients achieving inactive disease for $\geq$3 months after discontinuing prednisolone and all immunosuppressive agents.[24] Relapse was defined as recurrence of disease activity or new onset of disease manifestations. In view of these definitions, although grading systems for scleritis activity exist, scleritis was graded as being present or absent. Orbital inflammation is a more difficult entity to grade but was graded as being present or absent on the basis of clinical and radiographic information.

Patients were also defined according to their EULAR disease stage (localized and generalized) based on their entire follow-up period.[5,6] In view of our previous experience,[20,25] localized disease was defined as that restricted to the eye or the ear-nose-throat/lung. Generalized disease was that involving other organs or the kidney.

Laboratory Assessments

The ANCA status was tested by indirect immunofluorescence and antibody specificity (proteinase 3 [PR3]-ANCA, myeloperoxidase [MPO]-ANCA, or ANCA-negative) by antigen-specific assay. A change in the ANCA status to ANCA negativity (MPO-ANCA or PR3-ANCA normal range) after each RTX course was also recorded.

Circulating B-cell numbers were assessed by fluorescence-activated cell sorting analysis. B-cell depletion was defined as a count of $<0.02\times10^9$/L, with subsequent B-cell repopulation being defined as a count of $\geq0.02\times10^9$/L.[19]

Statistical Analysis

Rates were reported as the rate of patients being affected (e.g., relapse and adverse event) and event rates (e.g., adverse events), where appropriate.[26] Analyses and graphs were constructed using GraphPad Prism version 5.01 (GraphPad Software Inc, La Jolla, CA) and PASW Statistics 18 (version 18.0.0; SPSS Inc, Chicago, IL). A P value $\leq$0.05 was accepted as statistically significant. Changes in variables were compared by Wilcoxon and Mann–Whitney tests; proportions between groups were compared using the chi-square test or Fisher exact test. Logistic regression was used to evaluate potential risk factors for relapse, generating odds ratios. Relapse and remission times were analyzed by Kaplan–Meier survival analysis, and differences between groups were compared using the log-rank test.

Results

Characteristics of Patients with Ocular Disease and Treatment Protocol

Of a total of 100 patients with GPA who received 152 RTX courses between December 2004 and January 2013, 37 received RTX for ocular disease. For patients with ocular disease, the median follow-up time after the first RTX course was 36.5 months (range, 6–56 months). All these patients had a diagnosis of GPA, with 20 patients having scleritis and 17 patients having orbital disease. The