B-cell depletion therapy in patients with refractory Wegener's granulomatosis with head and neck manifestations

Evaluation of: Martínez Del Pero M, Chaudhry A, Jones RB *et al.*: B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study. *Clin. Otolaryngol.* 34(4), 328–335 (2009). In this study, Martínez del Pero *et al.* examined the effects of rituximab therapy in patients with head and neck manifestations of Wegener's granulomatosis that were refractory to treatment with standard therapies. Rituximab was overall well tolerated and effective. At 6 months, rituximab induced disease remission in 88% of patients (62% complete and 26% partial remission). All patients who did not respond to the first course achieved remission after a second course of rituximab. Four out of five patients with ocular masses showed a good response to rituximab.

KEYWORDS: B-cell depletion ■ biologic therapy ■ rituximab ■ vasculitis ■ Wegener's granulomatosis

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The efficacy of rituximab for refractory head and neck manifestations of Wegener's granulomatosis (WG) was analyzed by Martínez del Pero *et al.* in a retrospective study of 34 patients [1].

Rituximab has recently demonstrated non-inferiority to cyclophosphamide in inducing remission in severe (or generalized) antineutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV) in a multicenter, randomized, double-blind, placebo-controlled trial of 197 patients that included 148 patients with WG [2]. Rituximab-treated patients also experienced fewer adverse events than patients who received cyclophosphamide [2]. However, there is uncertainty regarding the usefulness of rituximab in the particular setting of patients with 'granulomatous' manifestations, such as those affecting the ear, nose and throat (ENT) and the orbit [3–7]. Thus far, this experience is confined to retrospective studies analyzing small numbers of refractory cases [3–7].

Summary of methods & results

■ Methods

This study was a retrospective chart review of 34 patients with WG with refractory ENT and/or ocular involvement treated with rituximab. Two different regimens of rituximab were used: 375 mg/m^2 weekly for 4 weeks ('lymphoma regimen'; n = 14; 41%); and two doses of 1000 mg 2 weeks apart ('rheumatoid arthritis regimen'; n = 20; 59%). A total of 19 (56%) patients were retreated during the first year because of disease relapse or persistent active disease. Rituximab courses were systematically administered every 6 months to 15 patients regardless of disease activity.

Follow-up visits were at least every 3 months. Disease activity was assessed by an adapted Birmingham Vasculitis Assessment score (BVAS). Outcome items were defined as follows: disease remission required a BVAS of 0 and prednisolone dose of 10 mg/day or less, maintained for at least 1 month; partial response required a BVAS reduction of 50% or more regardless of prednisolone dose; and relapse was considered as the return or first appearance of one major (life- or organ-threatening disease) or three minor BVAS items. Classical/protoplasmic (C/P)-staining ANCA were determined by immunofluorescence and proteinase 3 (PR3)/myeloperoxidase (MPO)-ANCA levels by ELISA.

Primary end points of the study were: proportion of patients achieving complete remission and partial response at 6 months; proportion of patients having relapses at 12, 18 and 24 months and at last follow-up; and proportion of patients suffering adverse events. Secondary end points included: PR3-ANCA change and prevalence at the different time points; and change in use of immunosuppressants other than prednisolone.

■ Results

The 34 patients had a median disease duration of 81 months (range: 41–131 months) and had received a median of five immunosuppressant medications (range: three to eight). The median follow-up period of the study was of 25 months (range: 7–65 months).

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Primary end points

After the first rituximab course, disease remission was achieved by 30 out of 34 (88%) patients at 6 months (62% complete and 26% partial remission). All four (12%) patients who did not respond to the first course of rituximab achieved complete remission after a second course.

Total BVAS had a statistically significant decrease after rituximab treatment from pretreatment values at all time points. ENT manifestations and ENT components of BVAS improved and remained lower than at baseline during all follow-up. However, patients who continued with active disease after rituximab treatment were those whose disease affected the nasal cavity.

A total of 11 patients had ocular involvement. The six patients with episcleritis, conjunctivitis, blepharitis and/or keratitis improved after treatment. Among five patients with retro-orbital masses, four responded well to rituximab. Three patients had significant residual fibrotic tissue, which may explain the suboptimal response in one of them.

During the first year, 19 (56%) patients were retreated because of relapse occurrence (n = 3) or incomplete response (n = 16) and all entered remission after a second course of rituximab. Relapse rate fluctuated between 11 and 17% at 12, 18 and 24 months and at the end of follow-up. At the end of the study, only 2 of 13 (15%) patients failed treatment and the remaining 13 (85%) continued in remission.

Adverse events developed in 19 out of 34 (56%) patients. A total of ten (30%) patients suffered infections, but only four (12%) of them required admission and responded well to intravenous antibiotics. Three (9%) patients had leukopenia with lymphopenia or neutropenia, which was attributed to the administration of other immunosuppressants in two of them. A further five (15%) patients had infusion reactions and four (12%) had other medical conditions.

Secondary end points

Antineutrophil cytoplasmatic antibodies were positive before treatment in 15 out of 34 (44%) patients for PR3-ANCA and 23 out of 34 (68%) patients for C-ANCA. P- and MPO-ANCA were detected in three patients. ANCA were negative in nine patients. The response rates to rituximab did not differ between ANCA-positive and ANCA-negative patients at any time point. PR3-ANCA levels significantly decreased at 6 months. A rise in PR3-ANCA could predict a disease relapse with a good specificity (range: 83–90%), but demonstrated unreliable sensitivity (range: 20–100%). In the three patients with MPO-ANCA, levels remained negative during the follow-up, even in one patient who had a relapse.

The proportion of patients receiving immunosuppressants before starting rituximab (30 out of 34 patients; 88%) was reduced to 15% at 6 months, 25% at 12 months, 14% at 18 months, and 24% at 24 months or longer follow-up. The median prednisolone dose was significantly reduced from 10 mg/day before starting rituximab to 7.75 mg/day at 6 months, 6 mg/day at 12 months, and 5 mg/day at later follow-up.

Discussion

This study comprises the largest series of WG patients with refractory head and neck involvement treated with rituximab. Rituximab was well tolerated and provided a good response after the initial course and after retreatment during the first year in these patients. A total of 56% of patients were retreated owing to persistent disease activity or disease relapse [1]. These results are concordant with the findings of a recent multicenter survey of rituximab as treatment in 65 patients with refractory AAV (46 WG patients) [8]. In this study, after rituximab administration, 98% of patients responded (75% complete and 23% partial remission) and relapse occurred in 57% of patients who achieved full remission [8]. After a second rituximab course, 31% of relapsing patients suffered a new relapse [8].

The reasons for using different initial and retreatment rituximab regimens were not fully detailed in the present study, but come from studies of the same group of investigators:

- Patients initially received two rituximab regimens (the lymphoma and rheumatoid arthritis regimens). Although clinical response was not analyzed in accordance to the type of regimen used, both have been demonstrated to induce depletion of peripheral blood B cells in all patients and to produce similar remission rates (81 and 75%, respectively), without differences in duration of B-cell depletion or the duration of disease remission [8];
- A second course of rituximab was guided by the return of symptoms of active disease. These patients were also retreated every 6 months regardless of disease activity. The rationale for using the 6-monthly regimen was based in a previous study of 11 patients with AAV in

which patients had a median duration of B-cell depletion of 8 months after rituximab infusion, and relapses, which occurred in 60% of them, were developed on or after the return of circulating B cells [9]. In this regard, B-cell depletion, which is achieved in all patients with vasculitis after rituximab therapy [3,5–11], appeared to be a good marker of remission since relapses were thought to be preceded by the return of peripheral B cells [5,6,9–11]. However, Jones *et al.* demonstrated that approximatley 50% of patients suffered a relapse while being B-cell depleted [8]. Early relapses, occurring at a median interval of 2 months, have also been communicated in WG patients following rituximab treatment, despite persistent peripheral B-cell depletion [12]. In a study of 77 patients with AAV, the 6-monthly protocolized rituximab retreatment regimen showed lower relapse rates than retreatment based on the occurrence of relapse (10 vs 73%; $p < 0.01$) [13]. Owing to these differing results in retreatment modalities, future trials should use the same retreatment regimens for all patients.

Effectiveness of rituximab on granulomatous head and neck manifestations has been previously reported with conflicting results. As in the study by Martínez del Pero *et al.*, other series of eight [6] and ten [7] WG patients with refractory granulomatous manifestations, including three and seven patients with orbital masses, respectively, have demonstrated good results with rituximab. However, other individual cases [4,5] and a series of eight patients [3] showed poor response to rituximab. In the latter, only three of eight patients responded to rituximab, and the five patients with ocular masses did not improve (three showed mass progression and two did not change) [3]. Discrepancies in these results may be related to:

- Different rituximab dosage and retreatment regimens: patients in whom retreatment was not given [3] or was administered in a lower/incomplete dose [5] had worse outcomes than patients who were retreated with full doses after the occurrence of disease relapse [1,6], after B-cell reconstitution (while asymptomatic) [6,7], or, as in this study, when given at regular 6-monthly intervals [1].
- Different disease extent: most of the studies treating granulomatous manifestations with rituximab included patients with both localized and generalized disease [1,7,14]. Of note, disease extent in itself has clinical and therapeutic implications, as localized forms can generally be initially treated with immunosuppressants less aggressive than cyclophosphamide (e.g., methotrexate) [15], but may require a longer duration of therapy, since localized forms appear to have a more relapsing course than generalized forms [16]. While disease extent/severity could have an impact on the efficacy of rituximab for WG overall, whether the response of ENT and orbital manifestations is influenced by the extent/severity of the disease is not known.
- Histological features: while ENT and orbital manifestations have been more frequently associated with lesions in which granuloma is the major component, vasculitis may also be observed in pathologic specimens from these lesions. Variation in degree or pattern of inflammation could conceivably influence the response to rituximab treatment. In the particular setting of ocular masses, subglottic stenosis and endobronchial disease, fibrotic lesions cannot be expected to respond to immunosuppressive therapy or rituximab [17]. Therefore, caution should be exercised in determining success or failure of a particular treatment when such lesions do not respond to therapy, especially if their disease is otherwise quiescent.

Future perspective

This study strongly supports the use of rituximab in patients with WG and refractory ENT and ocular manifestations. While additional

Executive summary

- Rituximab used in patients with Wegener's granulomatosis and refractory head and neck manifestations led to disease remission in 88% of patients (62% complete and 26% partial) within 6 months of starting therapy.
- Patients who did not respond to the first rituximab course (12%) and those requiring a second treatment owing to relapse or persistent disease activity during the first year (56%) also achieved disease remission.
- After rituximab, the proportion of patients on immunosuppressants and median prednisolone dose were significantly reduced at 6 months and during follow-up.
- Among patients with ocular manifestations, all presenting with episcleritis, conjunctivitis, blepharitis and/or keratitis (n = 6) improved after treatment. Five patients had ocular masses, of whom four responded well to rituximab.
- Antineutrophil cytoplasmatic antibody detection did not influence the response to rituximab during the period of the study.
- Adverse events developed in 56% of patients, most commonly infections and infusion reactions.

studies are required to confirm these findings and answer the questions that remain, including how best to use this medication, especially in terms of retreatment schedule, and to better define potential long-term toxicities, it appears to be a valuable addition to the therapeutic armamentarium for patients with WG.

Financial & competing interest disclosure

José Hernández-Rodríguez is supported by the Ministerio de Ciencia e Innovación and Fondo Europeo de Desarrollo Regional (FEDER; SAF 08/04328), Spain; and Marató TV3 (06/0710), Spain. Curry L Koening is supported by the Public Health Services research grant numbers UL1-RR025764 and C06-RR11234 from the National Center for Research Resources. Eamonn S Molloy is supported by the RJ Fasenmeyer Center for Clinical Immunology, Cleveland Clinic, OH, USA. He has participated in a scientific advisory board for Genentech. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

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