Arthritis Care & Research
Vol. 66, No. 9, September 2014, pp 1403–1409
DOI 10.1002/acr.22311

ORIGINAL ARTICLE

Effectiveness of Rituximab for the Otolaryngologic Manifestations of Granulomatosis With Polyangiitis (Wegener's)

LINDSAY LALLY,[1] ROBERT S. LEBOVICS,[2] WEI-TI HUANG,[1] AND ROBERT F. SPIERA[1]

Objective. **Ear, nose, and throat (ENT) involvement is the most prevalent manifestation of granulomatosis with polyangiitis (Wegener's) (GPA) and correlates with permanent damage and decreased quality of life. Although prior studies have evaluated the efficacy of rituximab (RTX) for granulomatous features of GPA, none have evaluated its efficacy solely for ENT manifestations. We compared the effectiveness of RTX to other therapies for the ENT manifestations of GPA in a large, well-characterized cohort.**

Methods. **We performed a retrospective analysis of 975 visits from 99 GPA patients seen at a tertiary care ENT practice between 2003 and 2013. At each visit, subjects had a complete ENT examination, with ENT activity assessed by a single expert otolaryngologist. ENT disease activity during the observational period in subjects receiving RTX was compared to subjects receiving all other therapy.**

Results. **In total, 48 subjects had never received RTX and 51 received RTX at least once. There was no active ENT disease during 92.4% of the observational period (days) for subjects receiving RTX, compared with 53.7% of the observational period for subjects not receiving RTX (odds ratio 11.0 [95% confidence interval 5.5–22.0], $P < 0.0001$). Subjects receiving RTX, compared with those receiving methotrexate, azathioprine, cyclophosphamide, or trimethoprim-sulfamethoxazole, were significantly more likely to have no active ENT disease ($P < 0.0001$ for each comparison).**

Conclusion. **RTX is an effective treatment for ENT manifestations of GPA. Subjects treated with RTX were significantly less likely to have active ENT disease compared with those not receiving RTX. Patients being treated with RTX were 11 times less likely to have active ENT disease than patients being treated with other therapies.**

INTRODUCTION

Granulomatosis with polyangiitis (Wegener's) (GPA) is a multisystem autoimmune disease characterized by granuloma formation and necrotizing vasculitis of small- and medium-sized blood vessels with a predilection for the upper airway, lung, and kidneys. The majority of patients with GPA have serologically detectable antineutrophil cytoplasmic antibodies (ANCAs) directed against proteinase 3 (PR3) at some point during their disease course. Ear, nose, and throat (ENT) manifestations, including rhinosinusitis, serous otitis media, and subglottic inflammation, are present in an estimated 90% of patients with GPA, making this the most commonly involved organ system in GPA (1). ENT disease frequently leads to accrual of permanent damage; ENT damage is highly correlated with reduced quality of life in GPA (2).

Depending on the extent and pattern of organ involvement, GPA can be classified as limited or severe (3,4). Patients with limited GPA do not have rapidly progressive glomerulonephritis or other organ-threatening disease manifestations. Limited GPA commonly presents with granulomatous inflammation and encompasses the 5–10% of patients with localized disease confined to the upper airway without other evidence of systemic vasculitic manifestations (5). The granulomatous lesions of GPA, such as those found in the ENT domain, may be accompanied by evidence of small vessel vasculitis in approximately one-third to one-half of biopsies. Thus, labeling ENT manifestations as granulomatous disease does not exclude the presence of vasculitis in those organs. The distinction between limited and severe disease has important therapeutic implications. Rituximab (RTX) has been shown to

Supported by the NIH (grant T32-AR007517-30), the Hospital for Special Surgery Scleroderma, Vasculitis & Myositis Center, and the Vasculitis Clinical Research Fund.

[1]Lindsay Lally, MD, Wei-Ti Huang, MS, Robert F. Spiera, MD: Hospital for Special Surgery, New York, New York; [2]Robert S. Lebovics, MD: St. Luke's-Roosevelt Hospital Center, New York, New York.

Dr. Spiera has received research support from Roche-Genentech.

Address correspondence to Lindsay Lally, MD, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021. E-mail: lallyl@hss.edu.

Submitted for publication October 24, 2013; accepted in revised form February 11, 2014.

Significance & Innovations

- This is the largest cohort of granulomatosis with polyangiitis (Wegener's) (GPA) patients in whom the effectiveness of rituximab (RTX) for ear, nose, and throat (ENT) disease manifestations is reported. This differs from previous studies in that ENT disease activity was assessed by an expert otolaryngologist and that RTX was compared to other therapies.
- Patients who received RTX were more likely to have had ENT damage and severe disease, yet these same patients were significantly more likely to have no ENT disease activity compared to those not receiving RTX.
- Our findings suggest that RTX can be considered as a relevant therapeutic option for GPA patients with active ENT disease.

be noninferior to cyclophosphamide (CYC) for induction of remission in severe GPA (6,7). For limited disease, methotrexate (MTX) is often the first-line agent used for remission induction and maintenance (8). Despite these therapeutic regimens, refractory disease occurs in 15–20% of GPA patients and disease flares are common. In the Wegener's Granulomatosis Etanercept Trial (WGET), a randomized trial of 180 GPA patients comparing etanercept plus standard of care (MTX or CYC) to standard of care alone, flares were common in both groups. Of the 252 disease flares during the study, 80% were flares of limited disease (9). The presence of upper airway disease has been identified as a predictor of relapse in large cohorts of ANCA-associated vasculitis (AAV) patients (10). ENT damage is also very frequent; in the WGET cohort, the most numerous contributions to the Vasculitis Damage Index came from the ENT domains and accounted for 30% of reported damage (4). Determining an effective therapeutic strategy that controls limited GPA to prevent development of destructive ENT damage while limiting potential toxicities of potent immunosuppressive medications is needed.

The efficacy of RTX for granulomatous manifestations of GPA is debated. There have been a few small studies examining the use of RTX for granulomatous manifestations of GPA (11–14). These small case series classified all granulomatous manifestations together and reported variable outcomes regarding the effectiveness of RTX for granulomatous GPA. Each of these descriptive studies examined refractory patients who had failed or had contraindication to CYC therapy, and all studies were enriched with a high proportion of patients with orbital disease. Orbital masses in GPA are an exceptionally refractory disease feature, and radiographic differentiation between active disease and cicatricial change can be difficult to assess (15). The failure of several of these studies to demonstrate the efficacy of RTX for what has been defined as granulomatous GPA was driven mostly by failure to improve orbital disease. In this study, we examined the effectiveness of RTX compared with other therapies expressly for ENT manifestations in a large, well-characterized cohort of GPA patients.

PATIENTS AND METHODS

Patients. Subjects seen at a tertiary care ENT practice with an expertise in GPA between January 2003 and January 2013 were identified using the International Classification of Diseases, Ninth Revision (ICD-9) code for GPA (446.4). To be included in the cohort, subjects had to have a diagnosis of GPA by the treating physician and a biopsy with histopathologic findings consistent with GPA, ANCA positivity, or both. Charts were reviewed for demographics, organ involvement, ENT disease activity, medications, and procedures at each visit. All office visits included in the analysis had to include a complete ENT examination with direct endoscopic visualization of the nasal mucosa and tracheolaryngeal complex and an audiometric examination for those with otologic involvement. Office visits that did not include a complete ENT examination or documentation of ENT disease activity were excluded. Active disease was noted if there was evidence of sinorhinitis, tracheolaryngitis, subglottic inflammation, serous otitis, dacryocystitis, or new or worsening of conductive or sensorineural hearing loss. All ENT examinations were performed by a single otolaryngologist with an expertise in GPA (RSL).

Data were recorded systematically in a secure online database. Standardized data capture forms using ENT domains from the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) and the Vasculitis Damage Index were utilized. ENT procedures performed by the treating otolaryngologist, including tracheal dilation, myringotomy, dacryocystorhinostomy, and sinus surgery, were recorded; when available, histopathology from surgical specimens was used to corroborate the presence or absence of active ENT disease.

Outcomes. The primary outcome of interest was ENT disease activity during the observational period (as measured in days) in subjects receiving RTX versus those receiving all other therapies. ENT disease activity was a dichotomous categorical measure of present or absent as determined by the examining otolaryngologist. RTX use was defined a priori as the most recent infusion within 6 months or continued B cell depletion at the time of the visit. The secondary outcomes were the comparison of ENT disease activity in subjects receiving RTX with those receiving MTX, azathioprine (AZA), CYC, or trimethoprim/sulfamethoxazole (TMP/SMX).

Statistical analysis. The demographic characteristics of subjects who ever received RTX were compared to those who never received RTX. A 2-tailed unpaired Student's *t*-test was used to compare continuous data and a chi-square test was employed to compare categorical data. Because the data for the primary and secondary outcomes were longitudinal in nature, a linear mixed-effects model

was used to analyze data and compare treatment groups. ENT disease activity during the observational period was analyzed with medication at the time of visit as the time-dependent variable. Observational time in the cohort was accounted for in this model as a continuous variable, and the mixed linear effects model can incorporate both irregularly spaced observations and nonuniform followup time. To assess the validity of the mixed-effects analyses, we adjusted for all the significant factors in the univariate analysis in addition to age, sex, and disease duration.

RESULTS

Clinical and demographic characteristics. In total, 137 subjects were identified via the ICD-9 code, of which 38 were excluded for having a diagnosis other than GPA. After excluding these patients, 99 subjects were included in the cohort and contributed 975 office visits to the analysis. The mean ± SD age was 49.8 ± 15.1 years and the mean ± SD disease duration was 8.1 ± 6.0 years; 68 subjects were women and 83 subjects were ANCA positive, with 76 subjects having PR3 positivity. Sixty subjects had limited disease and 96 had documented ENT manifestations during the study period.

In this cohort, 51 subjects had received at least 1 course of RTX and 48 subjects had never received RTX. Those who received RTX were more likely to have had severe GPA (48% versus 26%; $P = 0.027$) and were also more likely to have had ENT damage (94% versus 73%; $P = 0.004$). There were no other statistically significant differences between the 2 groups (Table 1). The mean number of days in the observational cohort did not vary between subjects receiving RTX and those who did not receive RTX. Those who received RTX contributed a mean ± SD of 1,570.7 ± 1,240.2 days observed and those not receiving RTX were observed for a mean ± SD of 1,352.3 ± 1,058.3 days ($P = 0.35$).

ENT disease activity. Active ENT disease was documented at 393 office visits; at the remaining 582 visits, ENT disease activity was absent. Subjects were receiving RTX at 144 visits, MTX at 197 visits, CYC at 55 visits, AZA at 98 visits, and TMP/SMX without other immunosuppressants at 113 visits. At 274 visits, subjects were not receiving any immunosuppressive therapy other than oral corticosteroids, which were being taken at 131 of these visits. In this cohort, there were no patients in whom RTX was administered concurrently with another immunosuppressive agent other than oral corticosteroids. There was no difference in mean prednisone dose between subjects receiving RTX and those receiving other therapy. Subjects receiving RTX were taking a mean ± SD prednisone dose of 7.7 ± 12.5 mg compared with those receiving other therapy, whose mean ± SD dose was 5.9 ± 9.2 mg ($P = 0.48$). This reflects the prednisone or prednisone-equivalent dose subjects were taking at the time of each office visit. Intravenous steroids given as premedication, inhaled or intralesional corticosteroids, were not able to be accounted for in these analyses, although the majority of subjects receiving RTX were routinely given methylprednisolone 100 mg intravenously as premedication prior to each infusion.

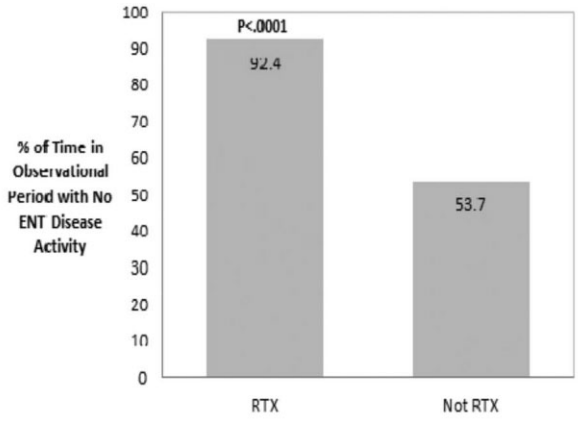
Table 1. Demographics*

Variable	RTX never (n = 48)	RTX ever (n = 51)	*P*
Age, mean ± SD years	52.4 ± 15.5	47.3 ± 14.4	0.1
Sex			0.38
Male	13 (27)	18 (35)	
Female	35 (73)	33 (65)	
Extent of disease			0.027
Limited	34 (74)	26 (52)	
Severe	12 (26)	24 (48)	
ANCA			0.39
PR3	38 (88)	38 (79)	
MPO	3 (7)	4 (8)	
Negative	2 (5)	6 (13)	
Disease manifestations			
General	8 (17)	17 (33)	0.06
Skin	5 (11)	4 (8)	0.63
Eye	14 (30)	25 (29)	0.97
ENT	45 (94)	51 (100)	0.7
Lung	24 (50)	34 (67)	0.09
Renal	7 (15)	14 (27)	0.12
ENT manifestations			
Bloody nasal discharge	22 (46)	31 (61)	0.14
Sinusitis	35 (73)	39 (76)	0.68
Subglottic inflammation	28 (58)	26 (51)	0.46
Conductive hearing loss	14 (29)	19 (37)	0.39
Sensorineural hearing loss	2 (4)	7 (14)	0.1
ENT damage	35 (73)	48 (94)	0.004

* Values are the number (percentage) unless indicated otherwise. RTX = rituximab; ANCA = antineutrophil cytoplasmic antibody; PR3 = proteinase 3; MPO = myeloperoxidase; ENT = ear, nose, and throat.

Subjects receiving RTX had no active ENT disease for 92.4% of the observational period compared with subjects not receiving RTX who had no active ENT disease for 53.7% of the observational period (odds ratio [OR] 11.0 [95% confidence interval (95% CI) 5.5–22.0], $P < 0.0001$). Adjusting for age, sex, disease duration, extent of disease, and ENT damage, subjects receiving RTX remained significantly more likely to have absent ENT disease activity compared with those not receiving RTX (OR 12.0 [95% CI 5.9–24.3], $P < 0.0001$) (Figure 1). All subjects who received RTX during the observational period had documented disease activity in the ENT domain prior to RTX administration. At the time of RTX treatment, 19 subjects (37%) had only ENT disease; this number would rise to 53% of subjects if the 7 subjects with ENT disease plus only fatigue or arthralgia were included. Only 3 subjects in this cohort received RTX for active nephritis during the observational period. When receiving RTX, 17 subjects (33%) had concurrent pulmonary or endobronchial disease; the majority of subjects with pulmonary involvement had pulmonary nodules (see supplementary Table 1, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22311/abstract).

The majority of subjects had at least partial improvement in all manifestations of ENT disease following RTX.



ENT Disease Activity	Medication		P value	OR, 95% CI	Adjusted OR*, 95% CI
	RTX	Not RTX			
% Observed Days with No Active ENT Disease	92.4	53.7	<.0001	11.0 (5.5–22.0)	12.0 (5.9–24.3)
% Observed Days with Active ENT Disease	7.6	46.3			

Figure 1. Ear, nose, and throat (ENT) disease activity by rituximab (RTX). OR = odds ratio; 95% CI = 95% confidence interval; * = adjusted for age, sex, disease duration, severity, and ENT damage.

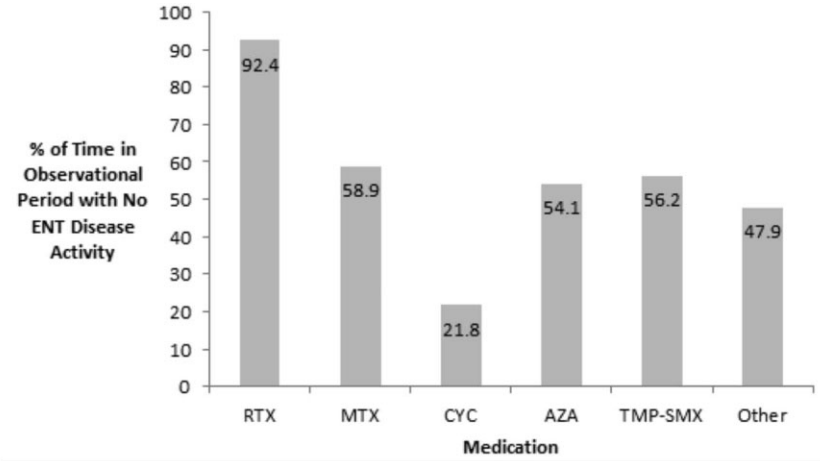
This cohort was enriched for subjects with subglottic disease, which can be particularly resistant to immunosuppressive therapy, especially once frank subglottic stenosis has developed. While subjects with subglottic involvement in this cohort demonstrated response to RTX, nearly half (46%) underwent concurrent endoscopic intervention. There were a similar number of surgical procedures performed in subjects with subglottic disease not receiving RTX.

When subjects receiving RTX were compared with those receiving MTX, which is widely accepted as the standard of care for limited GPA, those receiving RTX had active ENT disease during 7.6% of the observational period compared with 41.1% of the observational period for those receiving MTX (adjusted OR 11.5 [95% CI 6.4–24.8], $P < 0.0001$). The mean ± SD MTX dose was 20.8 ± 4.6 mg (range 10–30 mg). Comparing those receiving RTX with those receiving AZA, CYC, TMP/SMX, or other immunosuppressive therapy, those receiving RTX were significantly more likely to have absent ENT disease activity than those receiving any of the other therapies (Figure 2).

DISCUSSION

This study represented the largest reported experience with RTX versus other therapies for the ENT manifestations of GPA. There are many important differences in study design between our study and prior studies addressing this topic, most notably in the size of our cohort, the focus only on ENT disease (which was objectively assessed), and the use of a comparator group of similar subjects not receiving RTX. Aries et al reported a lack of efficacy of RTX for granulomatous GPA; however, their cohort consisted of 8 patients who had active disease despite treatment with CYC, corticosteroids, and anti–tumor necrosis factor therapy, making this a highly refractory group (11). Five of these patients had orbital disease, which is notoriously refractory to therapy and difficult to distinguish active disease from necrotic tissue. Furthermore, RTX was dosed at 375 mg/m^2 every 4 weeks, which is a lower dose than generally used for AAV. Seo et al subsequently reported a positive experience with RTX for granulomatous-limited GPA in a cohort of 8 patients (12). Again, all patients in this study were refractory to multiple other therapies, and there was no comparison group of similar patients who did not receive RTX. Holle and colleagues compared the efficacy of RTX in refractory GPA patients with vasculitic versus granulomatous manifestations and included 9 patients with limited ENT disease in their cohort of 59 patients (14). The authors concluded that most of the failure to respond to RTX was due to limited efficacy in granulomatous disease; however, this result was again largely driven by lack of response of orbital masses and pachymeningitis. The largest study to date reporting on the use of RTX for granulomatous GPA examined a British cohort of 34 patients with refractory ENT or orbital disease (13). At 6 months, 88% of patients had achieved partial or complete response, including 4 of the 5 patients with orbital masses; changes in the protocol during the study period resulted in different dosing regimens of RTX and repeated RTX administration every 6 months, regardless of disease activity, in a subset of 15 patients. The authors did not have a comparison group of similar patients with ENT disease receiving other therapies.

The importance of B cells in the pathogenesis of GPA is widely accepted and has been bolstered by the clinical efficacy of RTX for induction and maintenance of severe AAV. B cells are implicated in the pathogenesis of AAV by giving rise to autoantibody-producing plasma cells, contributing to local cytokine production, and acting as antigen-presenting cells, and also through the T cell costimulatory pathway. The success of B cell depletion therapy in patients who are serologically ANCA negative suggests that B cells are important for more than just autoantibody production (16). CD20+ B cells are present in the inflammatory milieu of granulomatous lesions of GPA, where



Medication	% Observed Days with No ENT Disease Activity	P value	Adjusted OR*, 95% CI
RTX	92.4		
MTX	58.9	<.0001	11.5 (6.4-24.8)
CYC	21.8	<.0001	52.8 (19.1-145.9)
AZA	54.1	<.0001	8.1 (3.3-19.7)
TMP-SMX	56.2	<.0001	13.4 (5.9-30.6)
Other	47.9	<.0001	17.0 (6.9-41.6)

Figure 2. Ear, nose, and throat (ENT) disease activity by all medications. RTX = rituximab; MTX = methotrexate; CYC = cyclophosphamide; AZA = azathioprine; TMP/SMX = trimethoprim/sulfamethoxazole; OR = odds ratio; * = adjusted for age, sex, disease duration, severity, and ENT damage; 95% CI = 95% confidence interval.

macrophages, giant cell neutrophils, and CD4+ T cells are also found. Aggregates of B cells forming germinal center-like lymphoid follicles have been identified in endonasal biopsies of patients with GPA (17). PR3-expressing neutrophils and macrophages and high levels of B cell survival factors (BAFF and APRIL) have been demonstrated in close proximity to these B cell follicles in the granuloma (18). An analysis of the gene repertoire of the antibody-producing immunoglobulin heavy chain of these B cells demonstrated a higher frequency of mutations than healthy controls, suggesting antigen-driven selection and affinity maturation. Some authors have suggested that the microenvironment of the endonasal granuloma may be responsible for PR3-driven B cell maturation and selection, break of tolerance, and development of overt autoimmunity (19,20). Targeting of these autoreactive B cells that may play a role in GPA pathogenesis might explain the observed effectiveness of RTX for granulomatous ENT disease in our study.

Our study has numerous strengths that allow these findings to enrich the current literature. This is the largest cohort of GPA patients with well-documented ENT disease. A further strength of this study resides in the meticulously characterized ENT examinations by a single experienced otolaryngologist. A recent study reported high intrarater reliability in assessing endonasal disease activity in GPA (21). While the ENT assessor in our study was not blinded to medication use, the decision to prescribe or change therapeutic regimens was at the discretion of the patient's rheumatologist and not the otolaryngologist. Although the BVAS/WG includes 5 ENT items in the measurement of disease activity, direct otolaryngologic visualization and audiometric assessment are not required to assess manifestations such as subglottic disease or hearing loss (22). Therefore, the assessment of ENT disease activity with otolaryngologic examination at each visit in this study was more stringent and objective than the BVAS/WG, which is widely accepted as the gold standard of disease activity measurement in GPA (23). The importance of objective assessment of ENT disease activity in GPA has recently been espoused by Del Pero et al, who created an ENT disease activity score based on endoscopic and audiometric examination (24). While this activity score needs to be further validated and tested for interobserver reliability, its creation highlights the importance of collaborative, multidisciplinary care for GPA patients to guarantee accurate disease activity assessment to both guide therapy in clinical practice and assess outcomes in clinical trials.

Because of our ascertainment of subjects from a tertiary care ENT practice, our cohort was enriched for refractory ENT disease and ENT damage. Subjects receiving RTX were more likely to have ENT damage, suggesting that these patients may have had more extensive or refractory ENT disease at baseline. Despite this difference, patients receiving RTX were still far less likely to have active ENT disease at the time of examination, even though all those who received RTX had active ENT manifestations prior to treatment. While the overall generalizability of this cohort receiving specialized ENT care is unknown, the finding that those receiving RTX had more previous ENT damage and active ENT disease prior to treatment but were more likely to have no ENT disease activity during the observa-

tional period further bolstered our findings in support of RTX.

The retrospective nature of this study poses certain limitations. We were unable to systematically capture data on potential adverse events. RTX is generally safe and well tolerated in GPA; a recent retrospective cohort from the Mayo Clinic characterizing patients receiving at least 2 courses of RTX over a decade concluded that repeated B cell depletion was associated with low risk of infectious complications (25). ANCA titers and B cell levels were not measured at standard intervals in our cohort. Similarly, the time between followup visits varied for each subject. The mixed linear effects model used to analyze these longitudinal data is a robust model for this study because it incorporates observational time in the cohort while accounting for irregularly spaced measurements, and subjects are not presumed to contribute the same number of measurements to the analysis (26). However, this nonuniform followup time prevented accurate determination of time to response to RTX and other therapies.

There were secular changes in the patterns of RTX use throughout the period studied (2003–2013). The first studies of successful use of B cell depletion therapy with RTX in GPA were published in 2001 (27). After these initial studies, increasing evidence about the efficacy of RTX in AAV became available, culminating in 2 randomized controlled trials published in 2010 illustrating noninferiority of RTX to CYC for remission induction in severe disease (6,7). Despite the increased widespread use of RTX during the study period, in our cohort, there were no differences in patient demographics or outcomes in those treated with RTX prior to 2011 compared with after 2011, when Food and Drug Administration approval of RTX for severe GPA was granted.

RTX may be an effective treatment for the ENT manifestations of GPA. Patients treated with RTX were far less likely to have active disease in the ENT domain than patients treated with other immunosuppressives, including MTX, AZA, or CYC. These data suggest that RTX may be a valuable alternative to conventional immunosuppressive therapies for the treatment of ENT manifestations of GPA. The findings of this retrospective study will ultimately need to be verified in prospective controlled clinical trials.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Lally had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Lally, Spiera.
Acquisition of data. Lally, Lebovics, Spiera.
Analysis and interpretation of data. Lally, Huang, Spiera.

REFERENCES

1. Hoffman GS, Kerr GS, Leavitt RY, Hallahan CW, Lebovics RS, Travis WD, et al. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488–98.
2. Seo P, Min YI, Holbrook JT, Hoffman GS, Merkel PA, Spiera R, et al, for the WGET Research Group. Damage caused by Wegener's granulomatosis and its treatment: prospective data from the Wegener's Granulomatosis Etanercept Trial (WGET). Arthritis Rheum 2005;52:2168–78.
3. Bacon PA. The spectrum of Wegener's granulomatosis and disease relapse. N Engl J Med 2005;352:330–2.
4. The Wegener's Granulomatosis Etanercept Trial Research Group. Limited versus severe Wegener's granulomatosis: baseline data on patients in the Wegener's Granulomatosis Etanercept Trial. Arthritis Rheum 2003;48:2299–309.
5. Holle JU, Gross WL, Holl-Ulrich K, Ambrosch P, Noelle B, Both M, et al. Prospective long-term follow-up of patients with localised Wegener's granulomatosis: does it occur as persistent disease stage? Ann Rheum Dis 2010;69:1934–309.
6. Stone JH, Merkel PA, Spiera R, Seo P, Langford CA, Hoffman GS, et al. Rituximab versus cyclophosphamide for ANCA-associated vasculitis. N Engl J Med 2010;363:221–32.
7. Jones RB, Tervaert JW, Hauser T, Lugmani R, Morgan MD, Peh CA, et al. Rituximab versus cyclophosphamide in ANCA-associated renal vasculitis. N Engl J Med 2010;363:211–20.
8. De Groot K, Rasmussen N, Bacon PA, Tervaert JW, Feighery C, Gregorini G, et al, for the European Vasculitis Study Group. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody–associated vasculitis. Arthritis Rheum 2005;52:2461–9.
9. Wegener's Granulomatosis Etanercept Trial (WGET) Research Group. Etanercept plus standard therapy for Wegener's granulomatosis. N Engl J Med 2005;352:351–61.
10. Hogan SL, Falk RJ, Chin H, Cai J, Jennette CE, Jennette JC, et al. Predictors of relapse and treatment resistance in antineutrophil cytoplasmic antibody-associated small-vessel vasculitis. Ann Intern Med 2005;143:621–31.
11. Aries PM, Hellmich B, Voswinkel J, Both M, Nolle B, Holl-Ulrich K, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006;65:853–8.
12. Seo P, Specks U, Keogh KA. Efficacy of rituximab in limited Wegener's with refractory granulomatous manifestations. J Rheumatol 2008;35:2017–23.
13. Martinez DP, Chaudhry A, Jones RB, Sivasothy P, Jani P, Jayne D. B-cell depletion with rituximab for refractory head and neck Wegener's granulomatosis: a cohort study. Clin Otolaryngol 2009;34:328–35.
14. Holle J, Dubrau C, Herlyn K, Heller M, Ambrosch P, Noelle B, et al. Rituximab for refractory granulomatosis with polyangiitis: comparison of efficacy in granulomatous versus vasculitic manifestation. Ann Rheum Dis 2012;71:327–33.
15. Holle JU, Voigt C, Both M, Holl-Ulrich K, Nolle B, Laudien M, et al. Orbital masses in granulomatosis with polyangiitis are associated with a refractory course and a high burden of local damage. Rheumatology (Oxford) 2013;52:875–82.
16. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. N Engl J Med 2013;369:417–27.
17. Voswinkel J, Mueller A, Kraemer JA, Lamprecht P, Herlyn K, Holl-Ulrich K, et al. B lymphocyte maturation in Wegener's granulomatosis: a comparative analysis of VH genes from endonasal lesions. Ann Rheum Dis 2006;65:859–64.
18. Zhao Y, Odell E, Choong LM, Barone F, Fields P, Wilkins B, et al. Granulomatosis with polyangiitis involves sustained mucosal inflammation that is rich in B-cell survival factors and autoantigen. Rheumatology (Oxford) 2012;51:1580–6.
19. Muller A, Holl-Ulrich K, Lamprecht P, Gross WL. Germinal centre-like structures in Wegener's granuloma: the morphological basis for autoimmunity? Rheumatology (Oxford) 2008; 47:1111–3.
20. Thurner L, Muller A, Cerutti M, Martin T, Pasquali JL, Gross WL, et al. Wegener's granuloma harbors B lymphocytes with specificities against a proinflammatory transmembrane protein and a tetraspanin. J Autoimmun 2011;36:87–90.
21. Garske U, Haack A, Beltran O, Flores-Suarez LF, Bremer JP, Lamprecht P, et al. Intra and inter-rater reliability of endonasal activity estimation in granulomatosis with polyangiitis (Wegener's). Clin Exp Rheumatol 2012;30 Suppl 70:S22–8.

22. Stone JH, Hoffman GS, Merkel PA, Min YI, Uhlfelder ML, Hellmann DB, et al. A disease-specific activity index for Wegener's granulomatosis: modification of the Birmingham Vasculitis Activity Score. Arthritis Rheum 2001;44:912–20.
23. Merkel PA, Aydin SZ, Boers M, Direskeneli H, Herlyn K, Seo P, et al. The OMERACT core set of outcome measures for use in clinical trials of ANCA-associated vasculitis. J Rheumatol 2011;38:1480–6.
24. Del Pero MM, Chaudhry A, Rasmussen N, Jani P, Jayne D. A disease activity score for ENT involvement in granulomatosis with polyangiitis (Wegener's). Laryngoscope 2013;123:622–8.
25. Cartin-Ceba R, Golbin JM, Keogh KA, Peikert T, Sanchez-Menendez M, Ytterberg SR, et al. Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener's): ten-year experience at a single center. Arthritis Rheum 2012;64:3770–8.
26. Gibbons RD, Hedeker D, DuToit S. Advances in analysis of longitudinal data. Ann Rev Clin Psychol 2010;27:79–107.
27. Specks U, Fervenza FC, McDonald TJ, Hogan MC. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. Arthritis Rheum 2001;44:2836–40.