Otolaryngological Progression of Granulomatosis with Polyangiitis after Systemic Treatment with Rituximab

Ian-James Malm1, David J. Mener, MD, MPH1, Jean Kim, MD, PhD1, Philip Seo, MD2, and Young J. Kim, MD, PhD1

Abstract

Objective. Rituximab is used for the treatment of granulomatosis with polyangiitis (GPA), historically known as Wegener's granulomatosis. However, the otolaryngological progression of GPA after systemic treatment with rituximab (Rituxan) is unclear. We therefore examined the disease sequelae of patients with GPA who were treated with rituximab.

Study Design. Case series with chart review.

Setting. Tertiary care medical center.

Subjects and Methods. Patients with a diagnosis of GPA who were treated with rituximab between 2006 and 2012 were included in this study. Systemic and otolaryngological symptomatology, prednisone usage, and procedural interventions following B-cell depletion were analyzed.

Results. We identified 11 patients who met our inclusion criteria. The average length of follow-up after treatment with rituximab was 23.5 months. After treatment with rituximab, there was a significant decrease in daily prednisone dose at 3, 12, and 18 months postinfusion (P < .05). However, there was no observed improvement in patients' otolaryngological complaints as measured by the Birmingham Vasculitis Activity Score. Furthermore, patients treated with rituximab underwent numerous otolaryngological interventions during follow-up. Patients with a history of subglottic stenosis (n = 6) underwent an average of 3.40 laryngoscopies and 0.58 dilations per year during rituximab remission, and patients with sinusitis also underwent multiple nasal endoscopies (4.54 per year, n = 9) and nasal debridements (1.34, n = 9).

Conclusions. While rituximab has been shown to be noninferior to cyclophosphamide with respect to remission from systemic GPA, these patients continue to have chronic otolaryngological manifestations of their disease. Otolaryngologists must continue to play a supportive role throughout their maintenance period.

Keywords
Wegener's granulomatosis, granulomatosis with polyangiitis, rituximab

Received June 17, 2013; revised September 30, 2013; accepted October 1, 2013.

Granulomatosis with polyangiitis (GPA), historically known as Wegener’s granulomatosis, is a systemic vasculitis that affects small and medium vessels predominately in the kidneys, lungs, and the mucosa of the upper respiratory tract.1 This ANCA (antineutrophil cytoplasmic antibody)–associated disease is characterized by the histological presence of granulomatosis, vasculitis, and necrosis.2 The reported prevalence of GPA in the United States is 3 per 100,000 people, predominately in whites, with an equal sex distribution and is, on average, diagnosed in the fifth decade of life.3-5 Otolaryngological manifestations of the disease have been well documented in the literature and are found in up to 90% of patients with GPA.4-6 Granulomatosis with polyangiitis most commonly affects the sinus and nasal mucosa, which leads to epistaxis, chronic sinusitis, and rhinosinusitis. This chronic inflammatory injury may progress to septal perforations and saddle nose deformities. Subglottic stenosis is also an important sequela of GPA, found in up to 16% to 23% of patients, and often requires multiple operative dilations.5,6 Furthermore, chronic serous otitis media secondary to eustachian tube dysfunction and sensorineural hearing loss are both frequently observed in patients with GPA.2 Otolaryngologists, therefore, play an integral role in the management and surveillance of patients with GPA.

In 2010, the RAVE trial showed that rituximab was noninferior to cyclophosphamide in inducing remission in patients with GPA, with the primary end point being disease flares.7 Since then, rheumatologists have begun using
rituximab, and in some cases as maintenance therapy, for patients who are unresponsive or with contraindications to classic treatments such as cyclophosphamide and methotrexate. There is, however, a paucity of data regarding the clinical course of patients treated with rituximab from the otolaryngologist’s standpoint. In this report, we characterized the progression of otolaryngological manifestations in patients with GPA after treatment with rituximab.

Methods

In accordance with a Johns Hopkins institutional review board–approved protocol, we performed a retrospective study at 2 tertiary hospitals (Johns Hopkins Hospital and Johns Hopkins Bayview Medical Center) on patients who were identified through a query of the otolaryngology departmental billing records for a diagnosis of GPA (International Classification of Diseases, Ninth Revision, code 446.4). Included were patients with GPA who were treated with rituximab and followed by the Department of Otolaryngology and the Division of Rheumatology for at least 6 months after their last infusion. We excluded patients with incomplete records, those who were treated (rituximab) at outside institutions, or patients without otolaryngological manifestations of their GPA disease as determined by history and examination.

The decision to use rituximab therapy was made on a case-by-case basis by the senior rheumatologist (P.S.), with indications including failure to respond or contraindications to classic immunosuppressive therapies. In general, patients underwent a weekly infusion of rituximab with 375 mg/m² for 4 weeks, along with intravenous solumedrol, followed by tapering doses of oral prednisone. Patients were maintained on a variety of additional maintenance therapies after induction with rituximab. Serology was followed with ANCA titers, CD19/CD20 B-cell percentage, and erythrocyte sedimentation rate (ESR). All patients were successfully depleted of circulating B-cells after rituximab treatment, and there were no significant adverse events associated with infusion. We reviewed all clinical notes 12 months after the last infusion of rituximab or until the re-emergence of B-cell populations, whichever came first. Many patients were redosed with rituximab after 8 to 12 months to maintain B-cell depletion, and records were reviewed for that extended time of treatment. Patients had follow-up with a rheumatologist at each designated time point.

We analyzed both systemic as well as otolaryngological manifestations after rituximab treatments. Within this time, we surveyed the number of office nasal endoscopies and debridements, total laryngoscopies, and operative subglottic stenosis dilations.

To assess global symptomatology, the Birmingham Vasculitis Activity Score (BVAS) was employed. This is a validated 9-organ grading system that provides quantitative assessment of active vasculitis. Otolaryngological manifestations are classified according to 5 subcategories in this instrument. The authors retrospectively scored the patients at various time points according to clinical notes and documented examinations. We also recorded the daily prescribed prednisone at each time point.

Statistical analyses of prednisone dosage were calculated using a 2-tailed paired t test (GraphPad Software, La Jolla, California) with $P < .05$ denoting significance.

Results

We identified 17 patients who were treated with rituximab at our institution between 2006 and 2012. Of the 17 patients, we excluded 6 because they were treated initially at an outside institution or they were lost to follow-up. A total number of 11 patients met our selection criteria, 5 women and 6 men. The mean age at diagnosis in our cohort was 30 years, and the mean age at last follow-up was 40.9 years. Following the first rituximab infusion, each patient was deemed therapeutic and followed for an average of 23.5 months (range, 6-48 months). There was 1 mortality from a severe GPA sequela.

Symptomatic syndromes at diagnosis are shown in Figure 1. Sinusitis was the most commonly reported sequela, seen in 55% of the patients ($n = 6$). The 2 systemic manifestations of GPA, renal and pulmonary involvement, were observed to occur at presentation rather than later in the disease course. Other otolaryngological manifestations, including saddle nose deformities ($n = 5$), septal perforations ($n = 6$), and hearing loss ($n = 8$), were noted later in the course of disease. Likewise, subglottic stenosis ($n = 6$) developed throughout the disease course and was not a presenting symptom in any of our patients.

Most patients in our cohort were treated with multiple different immunosuppressive regimens prior to receiving rituximab (Table 1). The most commonly used agents were glucocorticoids (11 patients) followed by cyclophosphamide (10 patients) and methotrexate (10 patients). One patient had a history of treatment with etanercept and infliximab several years prior to referral to our institution. In our cohort, 70% of patients cited the BVAS symptom “bloody nasal sinus discharge, nasal crust, ulcers, and/or granulomas” at the initiation of rituximab therapy. We did not observe a significant drop in BVAS scores at each follow-up time point after treatment with rituximab due to lack of power from our small sample size. There was, however, a trend suggesting a positive response to rituximab treatment (Figure 2). There was also a statistically significant drop in daily prednisone dose at 3 months ($P = .002$), 12 months ($P = .002$), and 18 months ($P = .047$).

The most frequently performed procedures were nasal endoscopy and nasal debridement. On average, nasal endoscopies were performed 4.54 times per year per patient (median, 2.0; range, 0-20.0), and debridements were performed at a rate of 1.34 times per year per patient (median, 0; range, 0-6.0) after rituximab initiation in patients with a history of sinusitis ($n = 9$). Of note, 1 patient had frequent otolaryngology visits and endoscopies for sphenopalatine injections to treat facial pain (10 endoscopies in a 6-month period). We included this patient in our cohort because the
Table 1. Patient population.

<table>
<thead>
<tr>
<th>Age at Diagnosis, y</th>
<th>Sex</th>
<th>Presenting Symptomatology</th>
<th>Previous Therapies</th>
<th>Age at First Infusion, y</th>
<th>Months of Follow-up after Rituximab</th>
</tr>
</thead>
<tbody>
<tr>
<td>41</td>
<td>M</td>
<td>Lung</td>
<td>CPM, MTX, Pred</td>
<td>54</td>
<td>12</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>Kidney, MSK</td>
<td>CPM, Pred, AZA</td>
<td>73</td>
<td>12</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>Cutaneous, kidney, MSK, sinusitis</td>
<td>CPM, MTX, Pred</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>Lung, MSK, SND, sinusitis</td>
<td>MTX, Pred, AZA</td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>Lung, sinusitis</td>
<td>CPM, MTX, Pred</td>
<td>32</td>
<td>42</td>
</tr>
<tr>
<td>31</td>
<td>M</td>
<td>Cutaneous, eye, MSK</td>
<td>CPM, CSP, MTX, Pred, AZA, etanercept, infliximab</td>
<td>36</td>
<td>48</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>Lung, MSK</td>
<td>CPM, MTX, Pred, MM</td>
<td>45</td>
<td>24</td>
</tr>
<tr>
<td>19</td>
<td>F</td>
<td>Kidney, sinusitis</td>
<td>CPM, MTX, Pred, MM, HCQ</td>
<td>44</td>
<td>12</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>Sinusitis, SP, otitis media, hearing loss</td>
<td>CPM, MTX, Pred, AZA</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>26</td>
<td>M</td>
<td>Sinusitis, hearing loss</td>
<td>CPM, MTX, Pred, AZA</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>18</td>
<td>M</td>
<td>Lung</td>
<td>CPM, MTX, Pred, AZA</td>
<td>23</td>
<td>48</td>
</tr>
</tbody>
</table>

Abbreviations: AZA, azathioprine; CPM, cyclophosphamide; CSP, cyclosporine; HCQ, hydroxychloroquine; MM, mycophenolate mofetil; MSK, musculoskeletal; MTX, methotrexate; Pred, prednisone; SND, saddle nose deformity; SP, septal perforation.

Figure 1. Longitudinal symptoms and signs of the patient population in our series. Patients were retrospectively assessed for each otolaryngological manifestation at their initial presentation and during the course of their disease. The y-axis represents the percentage of the total cohort displaying disease manifestations during this study. MSK, musculoskeletal.

Figure 2. Percentage of patients with otolaryngological Birmingham Vasculitis Activity Score (BVAS) symptomatology at follow-up. Patients were scored for the presence of BVAS symptoms at various time points. The percentage was calculated by dividing the number of patients with each symptom by the total number of patients seen at each time point.
facial pain was a sequela of GPA, and the patient was placed on rituximab for treatment of the ongoing midface destruction. Other upper respiratory procedures were performed in patients with a history of subglottic stenosis (n = 6). These patients received laryngoscopies at a rate of 3.40 per year (median, 3.57; range, 0.75-6.50) and dilations at a rate of 0.58 per year (median, 0.38; range, 0-1.71).

**Discussion**

In our series, induction therapy with rituximab was effective in allowing patients to taper off prednisone while maintaining controlled symptoms. However, many of our patients continued to experience low-level disease manifestations, such as nasal crusting, sinus pressure, and chronic otitis media despite B-cell depletion. Similar to previously published case cohorts, we used the BVAS assessment tool to quantify symptomatology after treatment with rituximab. The BVAS scoring system is a validated standardized assessment tool for GPA, giving a point for the presence of signs and symptoms attributable to active vasculitis.5-10,12

The patients in our cohort were able to taper off of prednisone after treatment with rituximab, and we observed a trend suggesting a decrease in otolaryngological BVAS scores. However, while patients’ overall symptoms improved, they continued to have significant otolaryngological morbidities such as sinusitis, nasal crusting, and subglottic stenosis. These symptoms rarely required increases in immunotherapy maintenance but did require close observation and management by otolaryngologists. They also underwent numerous interventional procedures, even though these patients would otherwise be categorized as “in remission.”

Treatment for GPA has evolved considerably since the disease was first described in the 1930s when the 1-year mortality was reported to exceed 80%.13 With the introduction of cyclophosphamide and glucocorticoids in the 1970s, GPA has been transformed into a chronic disease characterized by flares, interspersed with periods of remission and “grumbling” low-level disease activity.13 Based on the correlation between disease activity and ANCA titers, B-cell depletion was thought to be an effective strategy to induce remission. Since then, several case-controlled cohorts and randomized controls trials have demonstrated the efficacy of rituximab for systemic GPA.7,8,11-12

The efficacy of rituximab for otolaryngological manifestation of the disease, however, has been more equivocal. In 2009, a retrospective study of 38 patients with refractory otolaryngological sequelae for GPA showed a significant decrease in disease activity, with 88% of patients achieving a complete or partial response.10 The outcome measurements in this study were otolaryngological BVAS scores, prednisone dose, and PR3-ANCA levels. However, in another case cohort study with refractory GPA, rituximab was not associated with improved clinical response as measured by BVAS scores.15 In this cohort, the patients notably had the necrotizing granulomatous manifestations of this disease, including orbital pseudotumor, subglottic stenosis, and lung nodules.

Subsequent debate has centered on the seemingly discordant data regarding the efficacy of rituximab for vasculitic vs granulomatous manifestations of GPA.16 Aouba et al16 simplified GPA manifestations as either predominately vasculitis related (eg, renal disease, alveolar hemorrhage, constitutive symptoms) or necrotizing granuloma related (eg, subglottic stenosis, upper airway and ear, orbital pseudotumor, lung nodules) and suggested that the granulomatous manifestations of this disease may be relatively refractory to rituximab treatment as they may represent a later manifestation of disease progression. A recently published report by Holle et al11 attempted to answer this question by subdividing their cohort into patients with vasculitic or granulomatous manifestations. They noted a statistically significant difference in the response rate, with an 89.2% response rate for patients with renal disease and a 44.4% response rate in patients with orbital granulomas.

A recently published report on the progression of otolaryngological manifestations of GPA with standard treatment (antimetabolites, steroids) reported a yearly procedure rate of 0.63 procedures per patient year among all patients,17 which is within the range of our observed rates. Unfortunately, we were not able to significantly compare the rate of procedural interventions before and after B-cell depletion due to the absence of medical records as many of our patients were referred from outside hospitals for treatment. Our data, nonetheless, are in line with previously published case cohorts demonstrating the efficacy of rituximab to induce remission and allow for prednisone taper.5,10,11

Our analysis suggests that otolaryngological manifestations of GPA, such as sinusitis, chronic otitis media, and subglottic stenosis, are more refractory to rituximab treatments and require close otolaryngological follow-up and interventional procedures in the setting of B-cell depletion. The incomplete otolaryngological responses we observed may be due to the fact that the granulomatous manifestations may take longer to respond to immunosuppressive therapy, as these lesions are often a mix of inflammatory infiltrates and fibrosis.2,16 Our study does not exclude the possibility that continued B-cell depletion over several years might have a substantial impact on the otolaryngological manifestation of GPA. We are continuing this study to determine whether rituximab has a differential response depending on disease severity at the time of B-cell diffusion. Furthermore, it is unclear whether rituximab prevents development of new otolaryngologic manifestations of GPA or if it is simply controlling preexisting injury to the mucosa.

There are inherent limitations to our study because it is a chart review in which we are retrospectively quantifying disease activity using self-reported patient complaints and physical examination findings. As a tertiary care center, we are caring for patients who have been managed by multiple physicians and are referred to our hospital after failing numerous therapies. This introduces a potential selection bias as we may be preferentially observing patients with late-stage GPA with preexisting damage to their aerodigestive mucosa.
A weakness of the BVAS system is that it is a qualitative tool that uses clinical judgment to determine whether a symptom is due to active vasculitis or chronic damage. There is significant variability in what is considered “active vasculitis,” especially in the absence of serial biopsies. Manifestations such as nasal crusting and sinusitis have been described as “grumbling” disease, which has been defined as disease activity with minor symptoms that do not require a change in immunosuppressive treatments but warrant close follow-up and symptomatic treatment. It is unclear whether grumbling disease is due to active inflammation, chronic infection, or chronic damage, as there is a paucity of biopsy-driven observations for patients in this disease setting. Furthermore, symptoms that may have begun as active vasculitis, such as hearing loss, may over time become characterized as “chronic damage.” In this case, the clinical note would reflect the presence of hearing loss, but it would not be recorded on the BVAS score. In short, the BVAS scoring system, although validated, is an imperfect tool for the otolaryngologist as it does not account for the heterogeneity of the disease process in our patients. Despite this, our analysis is important in that it highlights the limitations of rituximab to fully control otolaryngological manifestations of GPA.

**Conclusion**

In our cohort, we have shown that induction therapy with rituximab is sufficient to allow patients with GPA to taper off prednisone. However, our patients continued to experience low-level disease manifestations that warranted close follow-up and interventions from an otolaryngologist. Despite the ability of rituximab to deplete B cells, our data highlight the limitations of this therapy from an otolaryngology treatment perspective. We recommend close and continued follow-up of patients with GPA who are treated with rituximab due to its seemingly incomplete effect on the mucosal tissue in the upper aerodigestive tract.

**Author Contributions**

Ian-James Malm, collected data, analyzed data, wrote article; David J. Mener, analyzed data, revised article, final approval; Jean Kim, analyzed data, revised article, final approval; Philip Seo, analyzed data, revised article, final approval; Young J. Kim, designed study, revised article, final approval.

**Disclosures**

**Competing interests:** Young J. Kim received a sponsored grant for cancer vaccine adjuvant research from Aduro Biotech, Inc.

**Sponsorships:** None.

**Funding source:** National Institute of Dental and Craniofacial Research, National Cancer Institute, and the Alpha Omega Alpha Carolyn L. Kuckein Student Research Fellowship.

**References**