Efficacy of Rituximab in Limited Wegener's Granulomatosis with Refractory Granulomatous Manifestations

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ABSTRACT. ***Objective.*** Patients with limited Wegener's granulomatosis (WG) may experience a relapsing and remitting course. How such patients should be treated, particularly when they are refractory to standard of care therapies, is not clear. Rituximab is a monoclonal anti-CD20 antibody that has been used successfully to treat multiple forms of autoimmune and rheumatic diseases, but its role in the treatment of limited WG remains uncertain.

Methods. Eight patients with limited WG who were refractory to (or intolerant of) standard immunosuppressive therapies were evaluated at the Johns Hopkins Hospital or the Mayo Clinic Rochester, and were treated with rituximab using a standard lymphoma protocol.

Results. Four men and 4 women with limited WG were treated with rituximab. Patients' mean age was 39 years. All patients had predominantly necrotizing granulomatous disease manifestations, including chronic sinusitis, pulmonary nodules, orbital pseudotumor, and subglottic stenosis. Patients had failed an average of 3 immunosuppressive agents, not including glucocorticoids. Six patients had failed (or were intolerant of) therapy with cyclophosphamide; all 8 had failed therapy with methotrexate. At the time of treatment, 3 of the 8 patients were antineutrophil cytoplasmic antibody-negative. Rituximab successfully induced disease remission in all 8 patients. Three patients were retreated preemptively with rituximab after return of peripheral blood B-cells. Five patients were successfully retreated with rituximab after disease flare.

Conclusion. Rituximab is an effective therapy for patients with limited WG and may be sufficient to induce sustained remission, even among patients with refractory disease and predominantly necrotizing granulomatous disease manifestations. (First Release Aug 1 2008; J Rheumatol 2008; 35:2017–23)

Key Indexing Terms:
VASCULITIS WEGENER'S GRANULOMATOSIS RITUXIMAB

Wegener's granulomatosis (WG) is an idiopathic autoimmune disease characterized by the presence of necrotizing granuloma and vasculitis involving the small and medium-caliber blood vessels. Because WG is associated with the presence of circulating antineutrophil cytoplasmic antibodies (ANCA), it is also known as an ANCA-associated vasculitis, a rubric that includes microscopic polyangiitis and the Churg-Strauss syndrome[1]. In its generalized form, WG is associated with pulmonary capillaritis, glomerulonephritis, and other life-threatening disease manifestations[2].

In 1966, Carrington and Liebow described a series of 16 patients who had a "limited form" of WG[3]. These patients had the necrotizing granulomatous lesions characteristic of this disease, but only minimal vasculitic involvement and no evidence of glomerulonephritis. Since that time, other investigators have recognized that some patients have a form of WG that does not pose an immediate threat to life or the function of a vital organ[4-6]. This limited form of WG is characterized by the presence of necrotizing granulomatous inflammation that leads to chronic sinusitis, pulmonary nodules, subglottic stenosis, and orbital pseudotumor[7].

From a practical standpoint, recognizing this limited form of WG has important therapeutic implications. Since the 1970s, it has been standard care to treat WG with a cytotoxic agent such as cyclophosphamide[8]. Although this approach is effective, it is associated with significant treatment-related morbidity[9], prompting the search for alternative treatment strategies. Since the 1990s, it has been recognized that patients with WG that is not immediately life-threatening may be treated effectively with alternative agents, such as methotrexate (MTX)[10,11]. This approach was recently validated in a randomized controlled trial that demonstrated that MTX was effective for remission induction in patients with non-life-threatening forms of WG[12].

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For some patients, however, this approach may not be sufficient to achieve a lasting disease remission or to prevent relapse. This leaves clinicians in the position of choosing between using a cytotoxic agent for non-life-threatening disease or tolerating an incomplete response.

Rituximab is a monoclonal antibody that binds to CD20 and leads to prolonged B-cell depletion[13]. Rituximab has been used by several investigators for treatment of patients with severe WG who were ANCA-positive and refractory to standard therapies. All these patients had clinical features caused by small-vessel vasculitis such as necrotizing glomerulonephritis, pulmonary capillaritis, and other manifestations of severe WG[14-16].

Use of rituximab for treatment of the vasculitic manifestations of WG is gaining acceptance; however, its use for treatment of necrotizing granulomatous disease manifestations characteristic of limited WG is still controversial. Aries, *et al*[17] recently reported their experience using rituximab for the treatment of 8 consecutive patients with WG with refractory granulomatous manifestations (including lung nodules, orbital pseudotumor, and subglottic stenosis). Of these 8 patients, 5 failed to respond, indicating that rituximab may not be equally effective for all clinical manifestations associated with WG[17].

We describe our experience using rituximab for treatment of 8 patients with limited WG, 3 of whom were ANCA-negative at the time of therapy. These patients predominantly had the granulomatous manifestations of WG and were refractory to standard therapy for limited WG.

MATERIALS AND METHODS

Patients were diagnosed with limited WG at the Johns Hopkins Vasculitis Center or the Mayo Clinic Rochester. Limited disease was defined as not threatening either life or the function of a vital organ (Table 1)[7]. All patients met the modified American College of Rheumatology criteria for diagnosis of WG[18]. Before treatment with rituximab, each patient was tested for the presence of ANCA, and had failed at least one steroid-sparing agent. Rituximab was dosed using a standard lymphoma protocol (375 mg/m^2 intravenously weekly for 4 weeks) in all patients (although Patient 5 did not complete her first course), and patients were monitored with routine testing of peripheral blood B-lymphocyte counts by fluorescence-activated cell sorting. ANCA testing was performed by indirect immunofluorescence and ELISA for proteinase-3 ANCA (PR3-ANCA) and myeloperoxidase-ANCA (MPO-ANCA) using standard protocols at each institution. Data collection was censored on May 15, 2007.

RESULTS

Four men and 4 women with limited WG were treated with rituximab (Table 2). Patients' mean age at time of rituximab treatment was 39 years (range 19–58 yrs). Seven patients had chronic sinusitis; 6 patients had other manifestations associated with necrotizing granuloma, including pulmonary nodules (n = 5), orbital pseudotumor (n = 3), and subglottic stenosis (n = 1). Patients had failed an average of 3 immunosuppressive agents (range 1 to 6), not including glucocorticoids. Six patients had failed therapy with cyclophosphamide; all 8 had failed therapy with MTX. At the time of treatment, 3 of the 8 patients were ANCA-negative; one of these patients had never been ANCA-positive. Rituximab successfully induced disease remission in all 8 patients. Two patients were retreated preemptively with rituximab after return of peripheral blood B-lymphocytes. Five patients were successfully retreated with rituximab for disease recurrence; 4 of these patients were ANCA-positive at the time of disease flare. WG flares occurred a mean of 14 months after the first treatment with rituximab, and 5 months (range 0–10 mo) after reconstitution of B-cells. Brief case reports are provided below.

Patient 1. A 57-year-old woman was diagnosed with PR3-ANCA-positive WG in 1997. Her disease manifestations included chronic sinusitis, chronic rhinitis, nasal crusting, arthritis, purpura, and fatigue. She failed to respond to therapy with MTX and glucocorticoids. Treatment with daily oral cyclophosphamide (cumulative dose 6 g) caused hemorrhagic cystitis; she was transitioned to chlorambucil but continued to have active disease. Chlorambucil was discontinued and she was treated with rituximab 375 mg/m^2 weekly for 4 weeks and glucocorticoids. ANCA remained positive at a low titer, but her peripheral blood B-cells became undetectable, and she was successfully tapered off glucocorticoids without recurrence of disease. Her peripheral blood B-cells returned 8 months after treatment with ritux-

Table 1. Wegener's granulomatosis (WG): limited and severe disease definitions.

Term	Definition
Limited disease	Patient meets the modified American College of Rheumatology criteria for a diagnosis of WG but does not have disease that poses an immediate threat to either a critical individual organ or to patient's life. Specifically, this means: 1. Patient has no red blood cell casts in the urine 2. Serum creatinine must be ≤ 1.4 mg/dl and there must be no evidence of a rise in serum creatinine more than 25% above patient's baseline 3. Pulmonary involvement must be circumscribed such that room air pO_2 is > 70 mm Hg or room air O_2 saturation by pulse oximetry is > 92% No disease may exist within any other critical organ (e.g., gastrointestinal tract, eyes, central nervous system) that, without the immediate institution of maximal therapy (i.e., pulse methylprednisolone and daily cyclophosphamide), threatens the function of the organ and/or the patient's life
Severe disease	Any patient with WG whose disease is not classifiable as limited has, by definition, severe disease

Table 2. Clinical characteristics of the study population, including organ involvement and ANCA status at time of first treatment with rituximab. B-cells were recorded as present once their absolute number was 5, or 1% of total lymphocyte count.

Patient	Age, yrs	Sex	Organ Involvement	Other Immunosuppressive Therapies	ANCA Status	Time to B-cell Return, mo	Time to First Flare
1	43	F	E, A, S	MTX, CYC, chlorambucil	PR3-ANCA	8	18 mo
2	50	M	E, OP, A	MTX, CYC	PR3-ANCA	11	18 mo
3	32	M	E, L, OP	CYC, chlorambucil, MTX, MMF, ETA, IFX, ADA	PR3-ANCA	12	13 mo
4	36	M	E, L	ETA, MTX	Negative	7	NA[a]
5	26	F	E, L, J	CYC, MTX, AZA	Negative	6	6 mo
6	46	M	E, L, OP	CYC, AZA	PR3-ANCA	9	16 mo
7	58	F	E, SGS	CYC, MTX	PR3-ANCA	4	NA[a]
8	19	F	L	MTX, ADA	Negative	NA[b]	NA[c]

[a] Retreated with rituximab prior to first flare; [b] B-cells remain undetectable; [c] patient has not experienced flare 5 months after initial treatment with rituximab. A: arthritis; E: ear, nose, and throat; L: lung; OP: orbital pseudotumor; SGS: subglottic stenosis; J: joints; MTX: methotrexate; CYC: cyclophosphamide; MMF: mycophenolate mofetil; ETA: etanercept; IFX: infliximab; ADA: adalimumab; AZA: azathioprine; NA: not applicable.

imab, but she remained symptom-free without maintenance glucocorticoids for a total of 18 months. She subsequently experienced a limited disease flare (characterized by migratory arthralgias) and was retreated with rituximab using the same dosing protocol, which led again to symptom resolution. She has remained in remission since 2005.

Patient 2. A 60-year-old man was diagnosed with PR3-ANCA-positive WG in 1999 based on chronic sinusitis, nasal crusting, orbital pseudotumor, fever, migratory arthralgias, hemoptysis, and pulmonary infiltrates; diagnosis was confirmed by open lung biopsy. He was initially treated with MTX and glucocorticoids but was switched to cyclophosphamide because of persistent proptosis. Rituximab 375 mg/m^2 was added to his regimen of cyclophosphamide 2 mg/kg and prednisone 10 mg daily. His peripheral blood B-cell levels were undetectable after the first dose of rituximab; he received weekly rituximab infusions for an additional 3 weeks, with clinical resolution of all symptoms. Treatment with cyclophosphamide was discontinued 2 weeks after his last dose of rituximab. His peripheral blood B-cells returned 11 months after he completed treatment with rituximab. He remained in remission for a total of 18 months, when he again developed proptosis. He was retreated with rituximab and high-dose glucocorticoids, which led to clinical improvement and partial regression of the proptosis. He remains asymptomatic taking prednisone 5 mg daily, for chronic maintenance.

Patient 3. A 44-year-old man was diagnosed with PR3-ANCA-positive WG in 1984. Disease manifestations included chronic sinusitis, orbital pseudotumor, and pulmonary nodules; diagnosis was confirmed by open lung biopsy. He was initially treated with cyclophosphamide (cumulative dose 5.6 g) but developed hemorrhagic cystitis. Subsequent treatment with chlorambucil caused pancytopenia. He was treated with a succession of alternative steroid-sparing agents including MTX, azathioprine, mycophenolate mofetil, etanercept, and infliximab, none of which controlled his symptoms. Treatment with rituximab 375 mg/m^2 weekly for 4 weeks led to clinical remission. Twelve months after treatment with rituximab, his proptosis had completely resolved. At the same time, however, his peripheral blood B-cells had returned, and 1 month later, he experienced a WG flare that included recurrence of his orbital pseudotumor and arthritis. He was retreated with rituximab and high-dose glucocorticoids. Because his orbital pseudotumor was slow to respond to therapy, 2 months after his last infusion of rituximab, he was also treated with adalimumab. His orbital pseudotumor gradually demonstrated evidence of improvement; however, 4 months after his second course of rituximab, he developed shortness of breath and was subsequently diagnosed with an adenoviral pneumonitis. He was intubated and treated with cidofovir, but his cardiopulmonary function continued to decline, and he subsequently died.

Patient 4. A 39-year-old man was diagnosed with PR3-ANCA-positive WG in 1997; disease manifestations included chronic sinusitis and lung nodules, and diagnosis was confirmed by lung biopsy. He subsequently developed type 1 diabetes mellitus and rheumatoid factor-positive rheumatoid arthritis, which was treated with leflunomide, then etanercept. Treatment with MTX and prednisone controlled his WG, but his lung lesions failed to resolve and ultimately MTX was felt to be ineffective for his pulmonary disease. His condition remained relatively stable for years under treatment with a combination of trimethoprim/sulfamethoxazole and low-dose prednisone, until 2004, when he developed a disease flare that included sinusitis, bloody crusts, hemoptysis, and worsening lung lesions (although he was ANCA-negative at the time). Cyclophosphamide was contraindicated due to aspergillus colonization and probable aspergilloma. He was treated with rituximab 375 mg/m^2 weekly for 4 weeks and glucocorticoids, with resolution of symptoms and shrinkage of lung nodules (Figure 1). He has been retreated with rituximab preemptively for asymptomatic B-cell reconstitution 4 times. Using this treatment strategy, he has remained in remission without the use of glucocorticoids since 2004.

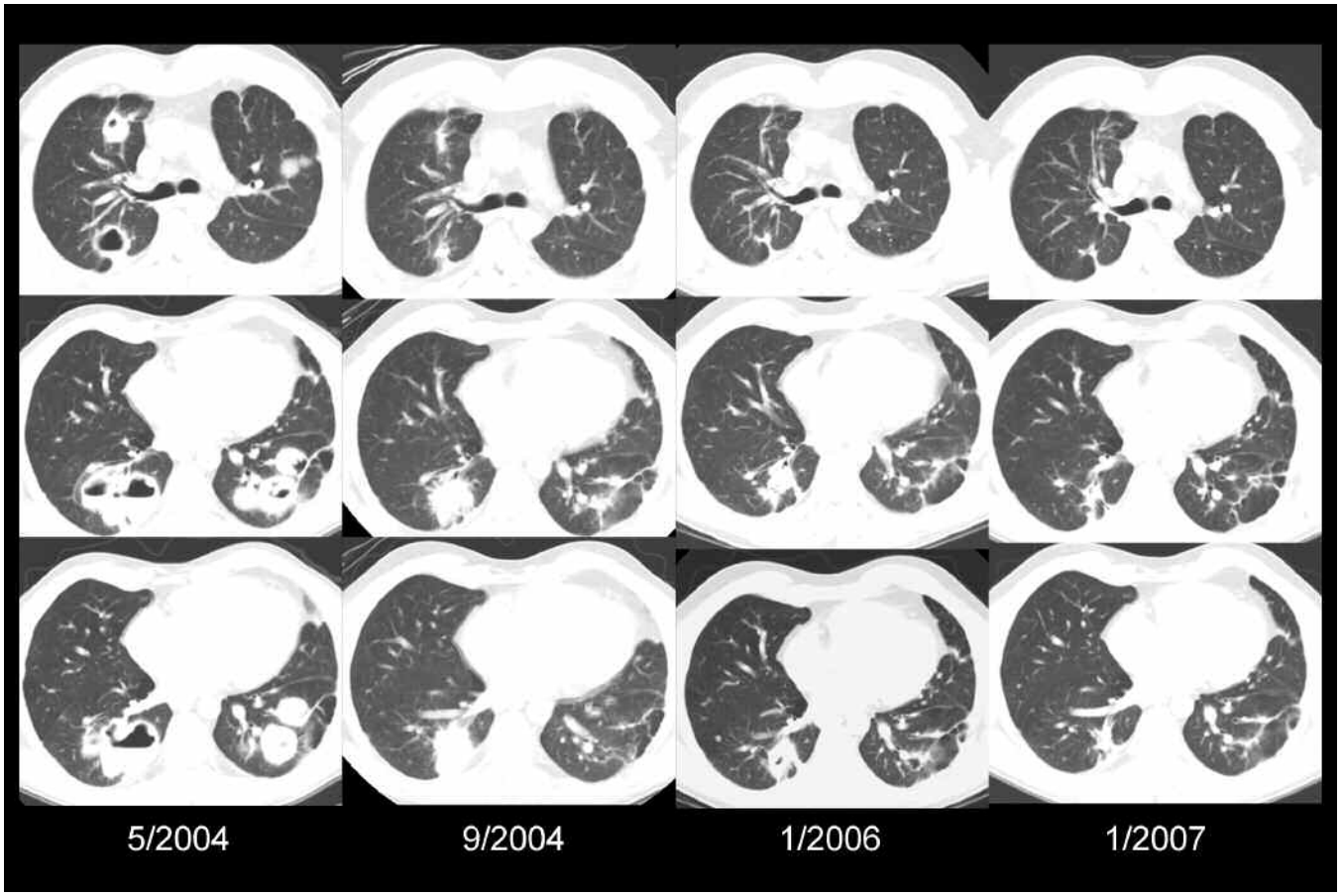

Figure 1. Resolution of pulmonary lesions after treatment with rituximab in an ANCA-negative patient with WG. Patient 4 was initially treated with rituximab in 2004, and was retreated with rituximab after return of peripheral blood B-cells a total of 3 times, with gradual resolution of pulmonary lesions.

Patient 5. A 29-year-old woman was diagnosed with PR3-ANCA-positive WG in 1995. Her disease has been characterized by chronic sinusitis and pulmonary nodules; diagnosis was confirmed by lung biopsy. Initial treatment with intravenous cyclophosphamide at another institution (approximate cumulative dose 2 g) was complicated by hemorrhagic cystitis. MTX stabilized her disease but led to pancreatitis. She was switched to azathioprine but experienced a disease flare of nasal inflammation, fatigue, night sweats and arthralgias; she was ANCA-negative at that time. Since further treatment with cyclophosphamide was contraindicated, she was treated with rituximab and glucocorticoids. She received only 2 of 4 rituximab infusions due to the development of anterior neck swelling several hours after the second infusion. This event was transient, resolved spontaneously, and no etiology was established. Despite this abbreviated course, her peripheral blood B-cell levels became undetectable and her symptoms resolved. Six months later, her peripheral blood B-cells were detectable again, and she experienced a second limited WG flare, retreated successfully with a full course of rituximab. Since then, she has received 2 additional courses of rituximab at the time of B-cell reconstitution without adverse events or recurrence of previous symptoms. She has been in a glucocorticoid-free remission since 2006.

Patient 6. A 48-year-old man was diagnosed with PR3-ANCA-positive WG in 2002; disease features included chronic sinusitis, pulmonary nodules, endobronchial involvement, orbital pseudotumor, and subcutaneous nodules (Churg-Strauss granulomas)[19]; his diagnosis was confirmed by sinus biopsy. He was transitioned to azathioprine, but experienced a disease flare. Retreatment with cyclophosphamide failed to induce remission. He was therefore treated with a course of rituximab and glucocorticoids, with resolution of symptoms. Sixteen months after he was treated with rituximab, he had a disease flare that consisted of arthralgias, hemoptysis, rash, and eye pain. This occurred 8 months after the return of peripheral blood B-cells, and was accompanied by a rising ANCA titer. He again responded to treatment with rituximab (with some radiographic improvement in orbital involvement), and has remained in glucocorticoid-free remission since 2006.

Patient 7. A 60-year-old woman was diagnosed with PR3-ANCA-positive WG in 2004; symptoms included chronic sinusitis, serous otitis media, and subglottic stenosis; diag-

nosis was confirmed by sinus biopsy. She experienced progression of her sinus disease while on therapy, first with MTX, then with cyclophosphamide. She was successfully treated with rituximab and glucocorticoids for refractory disease. Four months later, after return of her peripheral blood B-cells, she was preemptively retreated. She has remained in a glucocorticoid-free remission since 2006.

Patient 8. A 21-year-old woman with a history of Crohn's disease was previously treated with infliximab, azathioprine, and more recently with MTX and adalimumab. She was diagnosed with ANCA-negative WG based on video-assisted thoracoscopic biopsy of lung nodules, which were her only disease manifestation. She was treated with glucocorticoids and MTX 25 mg/week; despite this, her lung nodules continued to grow, and new lung nodules began to develop. Because of fertility concerns, she declined therapy with cyclophosphamide. She was instead treated with rituximab and glucocorticoids. As her lung lesions resolved, she discontinued glucocorticoids following a steady dose taper, and her disease has remained in remission since December 2006.

DISCUSSION

Several investigators have successfully used rituximab to induce sustained remission in ANCA-positive patients with refractory severe WG, which is characterized by capillaritis-associated disease manifestations. Recent reports, however, have suggested that rituximab may be less effective for the treatment of the necrotizing granulomatous lesions associated with limited disease.

We describe successful use of rituximab for induction of remission in 8 consecutive patients with WG whose disease features were characterized by the effects of necrotizing granulomatous inflammation. All patients had previously failed at least one standard therapy for WG; 6 patients had been treated with cyclophosphamide, which was either ineffective or led to unacceptable morbidity. After treatment with rituximab, all 8 patients achieved a remission that typically lasted for 1 year; 6 patients remain in a glucocorticoid-free remission using rituximab alone for maintenance.

In this series, there was one death due to a fulminant adenoviral infection in a patient with a long history of refractory WG. Fatal adenoviral pneumonitis is a known complication of chronic immunosuppression[20]; it therefore seems reasonable to suspect that his exposure to multiple immunosuppressive drugs (including 2 alkylating agents and 4 biologics) may have contributed to his overall susceptibility to infection. As well, at the time of his death, he was being

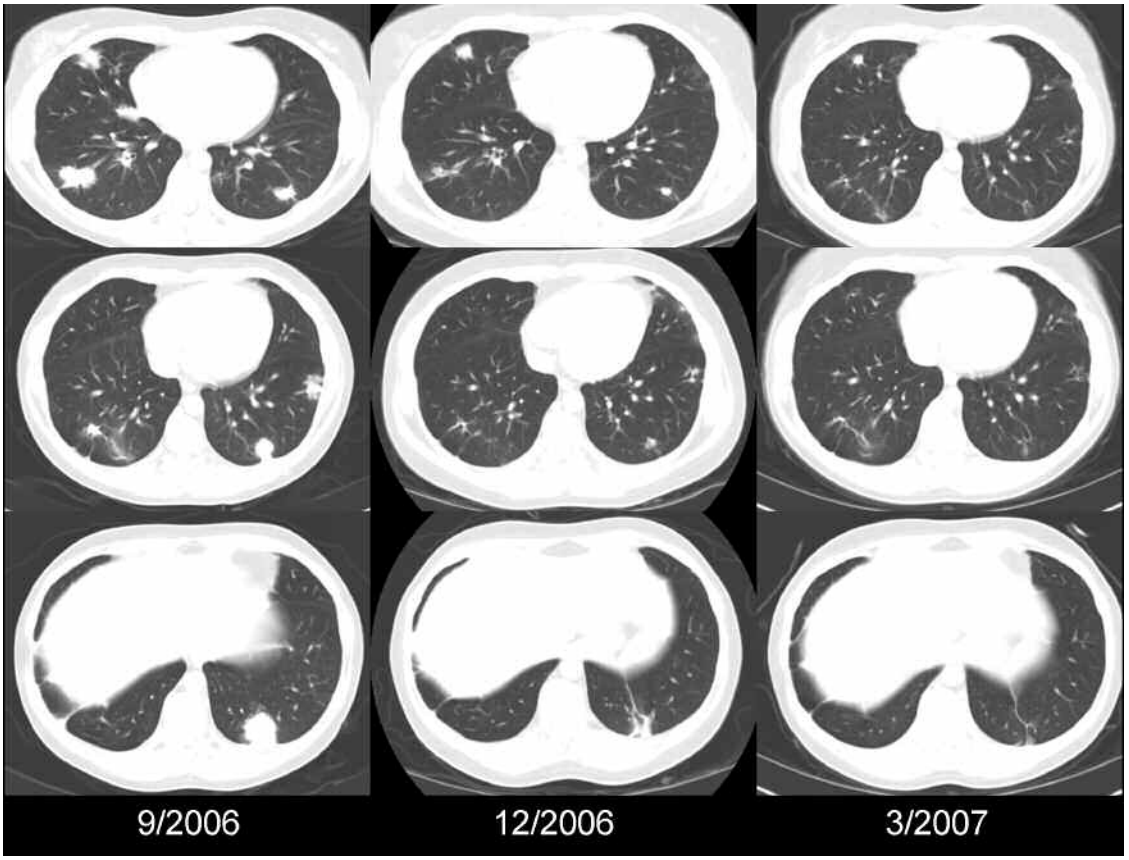

Figure 2. Resolution of pulmonary lesions in an ANCA-negative patient with WG, 6 months after treatment with rituximab. The pulmonary lesions continued to resolve as glucocorticoids were tapered; prednisone was discontinued at the time the last set of images was taken (March 6, 2007).

treated with adalimumab. Tumor necrosis factor-α (TNF-α) plays a crucial role in clearance of adenoviral infection from the lungs[21]. Although an increase in adenoviral infections has not been associated with clinical use of these agents, TNF inhibition could significantly impair adenoviral clearance in a patient with a long history of immunocompromise, and the combined use of anti-TNF and anti-B-cell therapy may potentiate the toxicity of each individual agent. A recent metaanalysis of 6 randomized clinical trials of patients with non-Hodgkin's lymphoma indicates that the addition of rituximab to standard chemotherapeutic regimens does not lead to an increase in infectious complications[22]. Recent reports suggest, however, that rituximab may induce reactivation of latent viral infections[23]. This possibility warrants careful scrutiny in future studies.

Rituximab was introduced for treatment of autoimmune disease under the assumption that it would target the production of pathogenic autoantibodies[24-26]. It is therefore interesting that 3 patients in this series were ANCA-negative at the time of treatment. This suggests that the role of B-cells in the pathogenesis of the disease goes beyond being responsible for ANCA production.

Other investigators have not experienced similar levels of success using rituximab for treatment of the necrotizing granulomatous manifestations of WG[17]. There are 3 factors that may contribute to this discrepancy. First, without serial biopsies, the granulomatous manifestations of WG may be difficult to differentiate from progressive scarring (which would not be expected to respond to immunosuppressive therapy). Second, these lesions are histologically heterogeneous and vary substantially in size[27]. Consequently, tissue penetration by the drug may be a factor, and some granulomatous lesions may require prolonged B-cell depletion for complete resolution (Figure 1). Finally, dosing of rituximab may be an issue. One report of unsatisfactory results of rituximab therapy concerned a monthly dose of 375 mg/m^2, and while peripheral blood B-cell depletion was noted, this may not necessarily reflect adequate tissue B-cell depletion[4]. Our experience suggests that rituximab given at a dose of 375 mg/m^2 weekly for 4 weeks is a reasonable option for treatment of the granulomatous manifestations associated with limited WG when standard immunosuppressive agents have failed. We chose to repeat this protocol with subsequent treatment courses, as our experience to date in patients with severe manifestations of WG has been with this protocol. Alternative dosing regimens, such as the lower-dose regimen of 1000 mg infused at Day 1 and Day 15 reported in patients with rheumatoid arthritis[28], are to date untested in ANCA-associated vasculitis. Given the refractory expression of these patients' disease, we decided to retreat with rituximab to maintain remission. The optimal strategy for maintenance of remission after it is induced with rituximab needs further investigation. Given the limitations of current standard-of-care therapies, the use of rituximab for this patient population warrants further study.

REFERENCES

1. Seo P, Stone JH. The antineutrophil cytoplasmic antibody-associated vasculitides. Am J Med 2004;117:39-50.
2. Walton EW, Leggat PO. Wegener's granulomatosis. J Clin Pathol 1956;9:31-7.
3. Carrington CB, Liebow A. Limited forms of angiitis and granulomatosis of Wegener's type. Am J Med 1966;41:497-527.
4. DeRemee RA, McDonald TJ, Harrison EG Jr, Coles DT. Wegener's granulomatosis: anatomic correlates, a proposed classification. Mayo Clinic Proc 1976;51:777-81.
5. Hoffman GS, Leavitt RY, Kerr GS, Fauci AS. The treatment of Wegener's granulomatosis with glucocorticoids and methotrexate. Arthritis Rheum 1992;35:1322-9.
6. MacFarlane DG, Bourne JT, Dieppe PA, Easty DL. Indolent Wegener's granulomatosis. Ann Rheum Dis 1983;42:398-407.
7. The WGET Research Group. Design of the Wegener's Granulomatosis Etanercept Trial (WGET). Control Clin Trials 2002;23:450-68.
8. Fauci AS, Katz P, Haymes BF, Wolff SM. Cyclophosphamide therapy of severe systemic necrotizing vasculitis. New Engl J Med 1979;301:235-8.
9. Hoffmann GS, Kerr GS, Leavitt RY, et al. Wegener's granulomatosis: an analysis of 158 patients. Ann Intern Med 1992;116:488-98.
10. De Groot K, Mühler M, Reinhold-Keller E, Paulsen J, Gross WL. Induction of remission in Wegener's granulomatosis with low dose methotrexate. J Rheumatol 1998;25:492-5.
11. Langford CA, Talar-Williams C, Sneller MC. Use of methotrexate and glucocorticoids in the treatment of Wegener's granulomatosis. Arthritis Rheum 2000;43:1836-40.
12. De Groot K, Rasmussen N, Bacon PA, et al. Randomized trial of cyclophosphamide versus methotrexate for induction of remission in early systemic antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:2461-9.
13. Golbin JM, Specks U. Part 2: Synopsis of B-lymphocyte targeted therapy of ANCA associated vasculitis. Clin Exp Rheumatol 2007;25:S74-76.
14. Keogh KA, Ytterberg SR, Fervenza FC, Carlson KA, Schroeder DR, Specks U. Rituximab for refractory Wegener's granulomatosis: Report of a prospective, open-label pilot trial. Am J Respir Crit Care Med 2006;173:180-7.
15. Eriksson P. Nine patients with anti-neutrophil cytoplasmic antibody-positive vasculitis successfully treated with rituximab. J Intern Med 2005;257:540-8.
16. Omdal R, Wildhagen K, Hansen T, Gunnarsson R, Kristoffersen G. Anti-CD20 therapy of treatment-resistant Wegener's granulomatosis: favourable but temporary response. Scand J Rheumatol 2005;34:229-32.
17. Aries PM, Hellmich B, Voswinkel J, et al. Lack of efficacy of rituximab in Wegener's granulomatosis with refractory granulomatous manifestations. Ann Rheum Dis 2006;65:853-8.
18. Leavitt RY, Fauci AS, Bloch DA, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum 1990;33:1101-7.
19. Gibson LE, Specks U, Homburger H. Clinical utility of ANCA tests for the dermatologist. Int J Dermatol 2003;42:859-69.
20. Ardehali H, Volmar K, Roberts C, Forman M, Becker LC. Fatal disseminated adenoviral infection in a renal transplant patient. Transplantation 2001;71:998-9.
21. Minter RM, Rectenwald JE, Fukuzuka K, et al. TNF-alpha receptor signaling and IL-10 gene therapy regulate the innate and humoral immune responses to recombinant adenovirus in the lung. J Immunol 2000;164:443-51.
22. Rafailidis PI, Kakisi OK, Vardakas K, Falagas ME. Infectious

complications of monoclonal antibodies used in cancer therapy: A systematic review of the evidence from randomized controlled trials. Cancer 2007;109:2182-9.
23. Freim Wahl SG, Folvik MR, Torp SH. Progressive multifocal leukoencephalopathy in a lymphoma patient with complete remission after treatment with cytostatics and rituximab: Case report and review of the literature. Clin Neuropathol 2007;26:68-73.
24. Edwards JC, Cambridge G. B-cell targeting in rheumatoid arthritis and other autoimmune diseases. Nat Rev Immunol 2006;6:394-403.
25. 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.
26. Keogh KA, Wylam ME, Stone JH, Specks U. Induction of remission by B lymphocyte depletion in eleven patients with refractory antineutrophil cytoplasmic antibody-associated vasculitis. Arthritis Rheum 2005;52:262-8.
27. Katzenstein AL, Locke WK. Solitary lung lesions in Wegener's granulomatosis. Pathologic findings and clinical significance in 25 cases. Am J Surg Pathol 1995;19:545-52.
28. Edwards JCW, Szczepanski L, Szechinshi J, et al. Efficacy of B-cell targeted therapy with rituximab in patients with rheumatoid arthritis. New Engl J Med 2004;350:2572-81.