CASE REPORT

Two Cases of Refractory Wegener’s Granulomatosis Successfully Treated with Rituximab

Naoto Tamura¹, Ran Matsudaira¹, Mika Hirashima¹, Makoto Ikeda¹, Michiko Tajima¹, Masuyuki Nawata¹, Shinji Morimoto¹, Kazuhiko Kaneda¹, Shigeto Kobayashi⁲, Hiroshi Hashimoto² and Yoshinari Takasaki¹

Abstract

Conventional therapy for Wegener’s granulomatosis, steroid and cyclophosphamide, fails to control disease activity in some refractory patients and has treatment-related toxicity. B cell depletion therapy using rituximab, a chimeric anti-CD20 monoclonal antibody, has been shown to be effective for certain autoimmune diseases including antineutrophil cytoplasmic antibody (ANCA) -associated systemic vasculitis. We report two refractory cases of Wegener’s granulomatosis: one with bronchial and pulmonary involvement and retroorbital granuloma, the other with retroorbital granuloma and hypertrophic pachymeningitis causing severe headache. Rituximab was effective in both cases, with diminished granuloma and reduced ANCA titers, allowing steroids to be tapered. No adverse effects were detected.

Key words: Wegener’s granulomatosis, anti-neutrophil cytoplasmic antibody (ANCA), rituximab, therapy, capture ELISA

(DOI: 10.2169/internalmedicine.46.6156)

Introduction

Wegener’s granulomatosis (WG) is a systemic autoimmune disorder of unknown etiology. Usually the disease progresses from a limited necrotizing granulomatosis in the respiratory tract to a generalized phase characterized by small vessel vasculitis, with antineutrophil cytoplasmic antibody (ANCA) playing a pathogenic role in this process (1). Most patients with WG are positive for proteinase 3 (PR3) -ANCA, detected by the cytoplasmic staining pattern on indirect immunofluorescence (IIF). Cyclophosphamide and glucocorticoids remains the first choice, for the treatment of generalized WG, but this conventional therapy is not sufficient in refractory cases and has potentially severe adverse side effects.

Rituximab, a monoclonal anti-CD20 chimeric antibody, has successfully been used to treat B cell lymphoma, and has recently shown to be effective for the treatment of autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (2-4). Efficacy of B cell depletion therapy with rituximab has also been reported in patients with WG or other ANCA-associated systemic vasculitis (5-8).

We present two cases of WG with retroorbital granuloma refractory to conventional therapy and other immunosuppressive drugs who were treated with rituximab, resulting in clinical improvement without any adverse effects.

Case Report

Case 1

A 15-year-old female presented in 2000 with episcleritis and pupura on both legs. The following year she was referred to hospital with episcleritis, headache and a mucopurulent nasal discharge. Laboratory testing showed a high PR3-ANCA titer (>300 EU), and nasal mucosa biopsy revealed chronic inflammatory changes compatible with WG. These clinical features fulfill the criteria for a diagnosis of WG by

¹Department of Internal Medicine and Rheumatology, Juntendo University School of Medicine, Tokyo  and  ²Department of Internal Medicine, Juntendo Koshigaya Hospital, Koshigaya

Received for publication July 31, 2006; Accepted for publication October 26, 2006

Correspondence to Dr. Naoto Tamura, tnaoto@med.juntendo.ac.jp
both the Chapel Hill Consensus Conference definitions (9) and the Research Committee of Intractable Vasculitis, Ministry of Health, Labor and Welfare in Japan (10). Therapy with prednisolone (50 mg/day) and intravenous cyclophosphamide pulse (IVCY) (500 mg/month for 7 months) reduced her symptoms and resulted in a reduction of her PR3-ANCA titer. After IVCY was discontinued and 7.5 mg/week of methotrexate was commenced, she continued to experience intermittent and occasionally bloody nasal discharge.

In September 2004 she was admitted to hospital following several months of cough and hemoptysis. She had shortness of breath and stridor, with wheeze audible on auscultation. Her height was 143.0 cm and weight was 64.0 kg. Laboratory testing showed a white blood cell count of 9,700 x 10⁶/l and CRP of 1.1 mg/dl. PR-3 ANCA was negative. Serum creatinine level was normal and no urinary protein was detected. Culture and stains of the nasal discharge and sputum were negative. Inhaled corticosteroids were started but were not effective. Bronchoscopy showed bronchial stenosis and erosive, hemorrhagic mucosa. Small pulmonary nodules were detected on computed tomography (CT) scan. Prednisolone was increased from 15 to 50 mg/day, IVCY was restarted (500 mg/month) and methotrexate was discontinued. However, she developed progressive left ophthalmalgia and headache in the middle of December, three weeks after the second administration of IVCY. Gadolinium (Gd) -enhanced magnetic resonance imaging (MRI) revealed a granuloma of the left retroorbit and hypertrophic pachymeningitis. Oculomotor disturbance and visual loss progressed rapidly over a few days despite steroid pulse therapy, resulting in irreversible blindness in the left eye.

In January 2005 she developed right ophthalmalgia and visual loss. Repeat MRI demonstrated the progression in pachymeningitis. Prednisolone was increased to 100 mg/day and plasmapheresis was started. Her right eye symptoms improved gradually, but her respiratory symptoms continued and new pulmonary nodules were detected on CT scan. PR-3 ANCA was still negative with routine direct ELISA, but positive with an increased titer of 1,059.8 units (normal range <20.0) with capture ELISA (Wielisa-kit, Wieslab, Lund, Sweden). Rituximab was started with a regimen of four weekly infusions of 375 mg/m² of body surface area (5-8), commencing on February 17 (Fig. 1). Prior to the administration, this treatment was approved by the Institutional Review Board, and written informed consent was given by her and her parents. B cells were completely depleted after the second administration, as determined by CD19-positive cells analyzed with flow cytometry. Her clinical symptoms started to improve gradually two weeks after the last administration of rituximab. Her Birmingham Vasculitis Activ-
ity Score (BVAS) (11) decreased from 19 before rituximab administration to 5 points four weeks after the last administration, and 2 points twelve weeks after the last administration. Her bronchial erosions and pulmonary nodules disappeared, and PR3-ANCA titer decreased concomitantly. Prednisolone was tapered to 10 mg/day.

In September 2005 a small number of CD19-positive cells were detected, and on October 19 her PR3-ANCA titer had increased to 181.5 units with capture ELISA. In November, she relapsed with nasal bleeding, and on December 5 her PR3-ANCA titer had increased to 248.8 units. Prednisolone was increased to 30 mg/day, and rituximab was administered using the same regimen as previously. The retreatment induced another remission and her ANCA titers decreased to the normal range in February 2006.

Case 2

A 35-year-old woman with otitis media, mastoiditis, granuloma of the right antrum auris and positive PR3-ANCA was diagnosed with WG in April 2004 using the criteria described above. Her granuloma enlarged in spite of treatment with 30 mg/day of prednisolone, and she was referred to hospital for treatment. Her height was 150.6 cm and weight was 48.5 kg. She developed severe headaches, and hypertrophic pachymeningitis was demonstrated on Gd-enhanced MRI. Other organs, including her lungs and kidneys, were not affected. Treatment with IVCY (500 mg/month for 4 months) and steroid pulse therapy followed by 50 mg/day of prednisolone normalized her PR3-ANCA titer, but the effect on the pachymeningitis was transient. Addition of methotrexate (7.5 mg/week for 4 months) or cyclosporine A (150 mg/day for 6 months) did not change the clinical course. The hypertrophic pachymeningitis could potentially have been caused by infection, but culture of cerebrospinal fluid was negative and antibiotics and antituberculosis drugs failed to resolve dural thickening.

In April 2005 she developed right ophthalmalgia and proptosis, and MRI demonstrated a right retroorbital granuloma. Since the granuloma and pachymeningitis did not respond to IVCY (500 mg once, 750 mg twice) and steroid pulse therapy followed by 50 mg/day of prednisolone, rituximab was started at the end of September using the same regimen as for the first case (Fig. 2). Written informed consent was provided by her in advance of using rituximab. PR3-ANCA was persistently negative at disease flare using routine direct ELISA, but increased to 4,846.7 units when measured using capture ELISA. The orbital granuloma started to resolve one week after the last administration and had obviously decreased on MRI after 4 months (Fig. 3). The dural thickening due to hypertrophic pachymeningitis.
also decreased. Her PR3-ANCA titer decreased to 118.7 units on November 28, and became negative (18.0 units) in March 2006. Her BVAS decreased from 13 to 3, and prednisolone was tapered to 10 mg/day.

Discussion

Combination therapy with corticosteroids and daily oral cyclophosphamide, which is the standard of care for patients with active generalized WG, induces disease remission in approximately 90% of patients by 6 months (12). However, at least 25% experience severe drug-induced adverse effects, and 50% have disease relapse, resulting in cumulating damage from the disease and treatment (13). Clinical trials have been conducted to investigate ways of reducing the duration of exposure to cyclophosphamide by using IVCY or other immune suppressive drugs. IVCY appeared to be similarly effective to daily oral cyclophosphamide in inducing remission, with fewer adverse events (14), and periods of remission did not differ between patients receiving daily oral cyclophosphamide and IVCY according to the recent preliminary analysis of large randomized control trial (15). Methotrexate was less effective for the induction of remission in patients with extensive disease, with a high rate of relapse compared with cyclophosphamide (16). The substitution of azathioprine for cyclophosphamide after remission did not increase the rate of relapse and resulted in a lower rate of severe adverse events (12). It is therefore still necessary to determine a more effective and less toxic therapeutic regimen.

This report confirms the efficacy and safety of rituximab therapy in Japanese patients with WG. The use of rituximab resulted in clinical improvement in these refractory cases. Although there was no evidence of renal involvement in the present two cases, previous reports have shown efficacy of rituximab for patients with active kidney disease (5-8). It is notable that there was no treatment-related infection with this agent in our cases or in previous reports (5-8), whereas the conventional immunosuppressive therapy regimen has the potential to cause life-threatening infections. Although rituximab depletes B cells, the level of serum immunoglobulin is usually maintained (5).

The central concept of rituximab therapy is the removal of B cells, the cellular source of ANCA. The pathogenesis of ANCA in developing systemic vasculitis has been well established (1). PR3-ANCA has been reported to be associated with disease activity and is a predictable marker of relapse in patients with WG (17). In our cases, PR3-ANCA detected by capture ELISA was likely to be related to the active disease.

Compared with systemic vasculitis, the pathogenesis of granuloma is obscure and various cell types are involved in the granulomatous lesion (1). Aries et al (18) reported a lack of efficacy of rituximab for eight cases of WG with refractory granulomatous manifestations. In particular, all four patients with retroorbital granuloma did not respond to rituximab. They speculated that rituximab might be effective for vasculitis but not for granuloma. However, the retroorbital granulomata in our cases were diminished by rituximab. They did not disappear completely on MRI, but this may indicate post-inflammatory fibrosis which is commonly observed in retroorbital lesions (19). Furthermore, rituximab was also effective for hypertrophic pachymeningitis which occasionally accompanies WG or other systemic vasculitides and possibly causes headache and cranial nerve involvement (20).

Long-term observation of ten patients with ANCA-associated vasculitis treated with rituximab, with a median follow-up of 35.5 months, showed relapse in three patients after the first treatment but no relapses after a second treatment (5). All of the cases were associated with increasing ANCA titers. Likewise, a mild relapse observed in our first
case was controlled with a medium dose of prednisolone and retreatment with rituximab. Interestingly, only a small number of B cells were detected compared to increased ANCA titers in Case 1 at the time of relapse. Voswinkel et al (21) recently reported that selection and affinity maturation of potential PR3-ANCA producing B cells started in granulomatous lesions. Although in our case immunofluorescence staining of the biopsy specimen for CD20-positive cells was not performed, B cells in the granuloma were possibly the source of PR-3 ANCA.

Capture ELISA was helpful in monitoring the disease activity in our cases, as has previously been reported in other cases (22, 23). PR3-ANCA was positive at diagnosis, but persistently negative by usual direct ELISA during disease flare in both cases. Capture ELISA demonstrated high levels of PR3-ANCA associated with disease activity, although we do not have measurements for the time of disease onset or the time of initial referral. In addition, the PR3-ANCA titer of Case 2 in December 2004, prior to development of the retroobtital granuloma, was measured retrospectively by capture ELISA. The titer (58.0 units) was much lower than at the time of initial referral. In addition, the PR3-ANCA titer of PR3-ANCA associated with disease activity, although we do not have measurements for the time of disease onset or the time of initial referral. In addition, the PR3-ANCA titer of Case 2 in December 2004, prior to development of the retroobtital granuloma, was measured retrospectively by capture ELISA. The titer (58.0 units) was much lower than at disease flare (4,846.7 units). The most commonly used retroortbital granuloma, was measured retrospectively by capture ELISA. The titer (58.0 units) was much lower than at disease flare (4,846.7 units). The most commonly used ANCA test assays worldwide are IIF and direct ELISA. In Japan, direct ELISA is usually used. Capture ELISA differs from direct ELISA in that an anti-PR3 monoclonal antibody is precoated to avoid denature of the PR3 antigen. It is likely that the epitope recognized by PR3-ANCA changed during the course of the disease, but the reason for this discrepancy between the methods should be further investigated.

Rituximab was a safe and effective treatment for refractory WG. Since it induces B cell depletion, which is quite a different mechanism of action compared to other immune suppressive agents, it may be a useful alternative when other drugs prove to be ineffective in refractory cases. A randomized, double-blind trial to determine the effectiveness of rituximab in treating adults with WG and microscopic polyangiitis is now under way in the United States (WWW.clinicaltrials.gov).

We would like to thank Dr. David RW Jayne for his kind advice regarding the treatment of these cases (Vasculitis and SLE unit, Department of Medicine, University of Cambridge School of Clinical Medicine, UK). This report was supported by the Japan Health Sciences Foundation with a grant for “Research on Health Sciences focusing on Drug Innovation, International Collaborative Research,” and by the Ministry of Health, Labor and Welfare in Japan with grants for “Research on Regulatory Science of Pharmaceuticals and Medical Devices” and “Research on Intractable Vasculitis.”

References


