Case Report

Effective therapeutic use of rituximab in refractory Wegener’s granulomatosis

Alistair J. Ferraro1*, Clara J. Day2*, Mark T. Drayson2 and Caroline O. Savage2

1Queen Elizabeth Hospital, Department of Nephrology, Birmingham, 2Birmingham University, Division of Immunity and Infection, Birmingham, UK

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Introduction

Wegener’s granulomatosis (WG) is a chronic, multisystem disease, characterized by a small vessel vasculitis. Whilst it previously carried a high early mortality (80% in 2 years) [1], the advent of cyclophosphamide therapy for the induction of remission has reduced this greatly. Despite the use of other immunosuppressive agents, including methotrexate, azathioprine and mycophenolate mofetil, to maintain remission, relapse often occurs – with many patients requiring further courses of cyclophosphamide over many years.

Despite its success at remission induction, cyclophosphamide therapy comes at a heavy price, with increased rates of infection resulting in significant morbidity and mortality, and dose-related increases in rates of haematological and solid organ malignancies [2]. As a result, alternative therapeutic strategies, for example directed against cytokines such as tumour necrosis factor (TNF), are also being tested with some success [3], but these also carry significant risks of opportunistic infection, especially with mycobacteria.

The association of WG with anti-neutrophil cytoplasm antibodies (ANCA) against the antigen proteinase-3 (PR3) has long been recognized. In vitro, ANCA causes neutrophil activation, resulting in a respiratory burst and the release of inflammatory cytokines. In a mouse model of a similar disease, transfer of ANCA alone causes the full disease phenotype [4]. In patients with WG, ANCA titres [5] and B-cell activation markers [6] often correlate with disease activity, suggesting that ANCA – and, by implication, B cells – may be directly involved in disease pathogenesis. Strategies to disrupt ANCA production more selectively would, thus, represent a therapeutic opportunity with fewer anticipated side effects. Such observations have led others to use rituximab (a monoclonal antibody causing profound B cell depletion) as adjuvant therapy in WG, with encouraging results [7–9]. Nevertheless, the continued use of other immunosuppressive agents in these cases raises some difficulties in interpreting the effects observed.

We report the case of a 53-year-old man with aggressive relapsing WG, which had caused significant morbidity and had required repeated courses of cyclophosphamide despite the use of other agents to try to maintain remission. He subsequently developed a high grade B-cell lymphoma that was successfully treated, but this meant that further cyclophosphamide therapy was precluded when his WG again reoccurred. That relapse, and another subsequent one, has been treated successfully with rituximab alone, without clinical or laboratory evidence of significant impairment in immunity.

Case

A 53-year-old male presented with dry gangrene of his right foot. Initial therapy with heparin, prostacyclin infusion and debridement was successful, but 4 weeks later he developed recurrent symptoms requiring forefoot amputation and had concurrent gangrene in two fingers on each hand. In the preceding few months, he had developed a left vocal cord palsy and a painful discharging left ear resulting in a mastoid exploration. Following persistent pain, and a computed tomography (CT) scan suggestive of a tumour in the left basal skull region, biopsies of the post-nasal space were taken but were not diagnostic. He also required a right popliteal–pedal arterial bypass following an acute popliteal artery thrombosis. He was in sinus rhythm and, although a smoker, he had no prior history of claudication, diabetes, hypertension,
cerebrovascular disease or ischaemic heart disease, but had lost 12 kg in weight in the preceding 3 months. All histology had been non-diagnostic and other investigations included a normal echocardiogram, chest X-ray, abdominal CT scan and bone scan. His creatinine was 77 µmol/l. His urine tested positive for blood and protein by dipstick. Further blood tests revealed a thrombocytosis of $943 \times 10^9/l$, elevated C-reactive protein (CRP) and positive c-ANCA by indirect immunofluorescence. A renal biopsy contained only medulla, but histological examination revealed arteritis and a diagnosis of WG was made. A week later, he underwent amputation of his affected finger tips and subsequent histology of these also showed evidence of previous arteritis.

He consented to be included in the CYCLOPS trial (a trial of daily oral vs intermittent pulse cyclophosphamide, organized by the European Vasculitis Study Group) and, thus, received high-dose prednisolone, intravenous pulses of cyclophosphamide every 2 weeks for 6 weeks followed by pulses of oral cyclophosphamide every 3 weeks and a reducing course of oral prednisolone as per protocol. Three months after diagnosis, he relapsed with symptoms of fatigue and episcleritis, associated with a rising PR3–ANCA titre (Bindazyme™ Human anti-PR3 Enzyme Immunoassay Kit; Binding Site, Birmingham, UK). He responded rapidly to daily oral cyclophosphamide (2 mg/kg/day) and prednisolone (40 mg). In the following 4 months, his prednisolone dose was reduced slowly as his ANCA titres and CRP were falling and he felt well. However, 2 weeks after substituting cyclophosphamide with oral azathioprine (2 mg/kg/day) daily, he developed severe headaches and fatigue. A cranial CT scan and lumbar puncture were normal, but his PR3–ANCA titre was high and another relapse was diagnosed. He was treated with plasma exchange, increased prednisolone and reinstatement of the oral cyclophosphamide, resulting in a good response in his clinical condition and laboratory markers. Over the subsequent few months, his symptoms and serology remained quiescent, except for mild dyspnoea partially relieved by inhaled salbutamol. His prednisolone was again tailed down, but the cyclophosphamide was continued. The WG relapsed again with upper respiratory symptoms and fatigue, so he received a further seven sessions of plasma exchange in addition to continued cyclophosphamide and prednisolone (≤60 mg/day). Due to increasing concern about his cumulative cyclophosphamide dose, alternative strategies were attempted despite incompletely suppressed disease: mycophenolate mofetil failed to confer benefit, so a course of infliximab (anti-TNF monoclonal antibody) was undertaken, but a relapse during therapy again necessitated use of adjuvant oral cyclophosphamide. Although his ANCA titres remained high, clinical improvement was achieved. A few weeks later, methotrexate (≤15 mg/week) was substituted for cyclophosphamide; clinical remission lasted 5 months despite persisting high ANCA titres. His fifth relapse was characterized by arthralgia, rash and maxillary sinus inflammation. Mycophenolate mofetil 1 g b.d. had no effect on his symptoms, so high-dose prednisolone (0.5 mg/kg/day) and infliximab (in association with the ACTIVE pilot study [3]) was given. Soon after, however, when his vasculitis seemed quiescent, he developed night sweats. Investigations revealed a large hepatic mass and biopsy confirmed high-grade B cell non-Hodgkin’s lymphoma. All immunosuppression except 10 mg oral prednisolone was discontinued. He was treated to good effect with six cycles of CHOP chemotherapy (cyclophosphamide, prednisolone, daunorubicin, vincristine) during which his WG remained in remission.

Soon after stopping chemotherapy, mild nasal symptoms reoccurred and 2 months later, he complained of epistaxis, headaches and fatigue, associated with a rising ANCA titre. Further cyclophosphamide therapy was precluded, so rituximab (anti-CD20 monoclonal antibody) was used. Three infusions (375 mg/m² each) were given at weekly intervals with concurrent dexamethasone 4 mg. Prednisolone 20 mg daily was continued. When attending for a fourth dose, he complained of recurrent sweats, fatigue, dyspnoea and nasal stuffiness, but no active disease could be identified, his ANCA titre was falling and no peripheral blood B cells were detectable (Figure 1). The dose was withheld. He was maintained on prednisolone, reducing to 12.5 mg daily, but had no other additional immunosuppression and he remained asymptomatic. After 11 months, his B lymphocyte levels began to recover, with an associated climb in ANCA titre. Six weeks later, clinical symptoms of WG reoccurred. There was no evidence of recurrence of the lymphoma on abdominal CT scan. He received a further three doses of rituximab before developing transient symptoms similar to those suffered after the previous course of therapy, but B-cell depletion was achieved. Ten months later, he remains in remission, on prednisolone 5 mg daily. B cells remain undetectable in peripheral blood and his ANCA titre is 7 units (normal range: <10 units). He has suffered no significant intercurrent infections and immunoglobulin titres remain stable. A summary of the course of the disease and its treatments is found in Figure 2.

Discussion

As early survival from WG improves, patients now often suffer a protracted, relapsing disease. Repeated courses of cyclophosphamide are, thus, often needed, carrying significant risks of iatrogenic disease – either infective or neoplastic. This patient had suffered frequent repeated relapses that were refractory to other therapies and which occurred despite substantial maintenance immunosuppression. His disease reoccurred soon after successful chemotherapy for lymphoma at which point treatment options were limited severely. Therapy with rituximab resulted in the depletion of B cells from peripheral blood, associated with a prolonged clinical response and a
fall in ANCA titre, but with preservation of immunoglobulin levels. B-cell recovery was followed rapidly by re-emergence of symptoms and ANCA antibody titres, but retreatment with rituximab was again effective.

Rituximab is a chimeric monoclonal antibody to CD20 and its administration results in profound systemic depletion of cells expressing CD20 (B cells and pre-B cells). Early progenitor cells and differentiated

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Fig. 1. Plot of B cell count, PR3 titre and total immunoglobin levels, during rituximab therapy.

Fig. 2. Timeline plot of ANCA titre, prednisolone dose and use of other agents during course of therapy. C – Cyclophosphamide. AZA – Azathioprine. MMF – Mycophenolate mofetil. MTX – Methotrexate. P. Ex – Plasma Exchange. CHOP – chemotherapy for lymphoma (see text).
plasma cells do not express the antigen, which may
account for the apparent preservation of previously
acquired immunity seen here and elsewhere [10].
Nevertheless, it is paradoxical that established
autoimmune responses in a variety of diseases, includ-
ing WG, rheumatoid arthritis [10], systemic lupus
erythematosus [11] and acquired haemophilia [12],
should appear disproportionately sensitive to ritux-
imab therapy. The precise role of B cells in the
pathogenesis of WG remains elusive at present, but
several possibilities exist. B cells can act as antigen-
presenting cells to T cells or provide additional
co-stimulatory signals for them. Another possibility is
that self-reactive B cells, derived from unusual B cell
subsets [13], may follow an alternative maturation
process, including the continued expression of CD20
during antibody production.

In conclusion, rituximab appears to offer therapeutic
promise in WG and may be used when other treat-
ments are precluded or unsuccessful. A randomized
prospective controlled trial would be a worthwhile
development. The effects of rituximab on pre-existing
acquired immunity appear to be limited, reducing
the likelihood of opportunistic infection. The reason
for its efficacy is not well understood, but it offers
additional insights into the pathophysiology of the
disease.

Conflict of interest statement. None declared.

References

1. Walton EW. Giant-cell granuloma of the respiratory tract
2. Hoffman GS, Kerr GS, Leavitt RY. Wegener’s granulomatosis:
TNFa blockade with infliximab in ANCA-associated systemic
4. Xiao H, Heeringa P, Hu P et al. Antineutrophil cyto-
plasmic autoantibodies specific for myeloperoxidase cause
glomerulonephritis and vasculitis in mice. J Clin Invest 2002;
110: 955–963
5. Gaskin G, Savage COS, Ryan JJ et al. Anti-neutrophil
cytoplasmic antibodies and disease activity during long term
follow up of 70 patients with systemic vasculitis. Nephrol Dial
Transplant 1991; 6: 689–694
6. Popa ER, Stegeman CA, Bos NA, Kallenberg CG,
Tervaert JW. Differential B- and T-cell activation in Wegner’s
7. Specks U, Ferenza FC, McDonald TJ, Hogan MC. Response
of Wegener’s granulomatosis to rituximab therapy. Arthritis
Rheum 2001; 44: 2836–2840
8. Eriksson P. Short term outcome and safety in 5 patients
with ANCA-positive vasculitis treated with rituximab: 11th
International Vasculitis and ANCA Workshop 2003. Kidney
Blood Press Res 2003; 26: 294
9. Jayne D, Burns S, Smith K. A prospective, open label trial of
B-cell depletion with rituximab in refractory systemic vasculitis;
11th International Vasculitis and ANCA Workshop 2003. Kidney
Blood Press Res 2003; 26: 294
of B-cell targeted therapy with rituximab in patients with
of B-lymphocyte depletion in systemic lupus erythematosus.
Arthritis Rheum 2002; 46: 2673–2677
12. Wiestner A, Cho HJ, Asch AS et al. Rituximab in the
treatment of acquired factor VIII inhibitors. Blood 2002; 100:
3426–3428
13. Chumley MJ, Dal Porto JM, Cambier JC. The unique Ag receptor
signalling phenotype of B-1 cells is influenced by locale, but

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