Treatment of refractory Wegener's granulomatosis with humanized monoclonal antibodies

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Received 23 August 1996

Summary

Conventional immunosuppression for systemic vasculitides is limited by substantial side-effects, cumulative drug toxicity and refractoriness in some patients. Six Wegener's granulomatosis patients who had been refractory to conventional therapy for at least 6 months, were treated with humanized monoclonal antibodies specific to lymphocyte CD52 or CD4 antigens. Diagnosis was on clinicopathological grounds, supported by the presence of autoantibodies to Proteinase 3. Histological evidence of persistent disease activity was obtained for each patient. Humanized monoclonal anti-CD52, with or without anti-CD4, was given intravenously up to 40 mg/day for up to 10 days. Remission, (programmed withdrawal of drug therapy without return of refractory disease) was achieved in all patients. Cytotoxic drugs were discontinued at the time of monoclonal antibody treatment and not used again; steroids were withdrawn gradually. Four patients relapsed at 1.5, 5, 10 and 18 months, and were treated successfully with further monoclonal antibody therapy alone. Three years after the study began, five patients are well; one patient died at surgery whilst in remission. Humanized monoclonal antilymphocyte antibodies may provide an effective treatment in patients with systemic vasculitis which is refractory to steroids or cytotoxic agents, or who are intolerant of these drugs.

Introduction

Conventional treatment for patients with primary multisystem vasculitis, such as Wegener's granulomatosis (WG) and microscopic polyangiitis (MP), has usually combined steroids and cytotoxic agents, most frequently cyclophosphamide (Cy) or azathioprine (Az), in a high-dose induction regimen to achieve remission, followed by a lower-dose maintenance regimen to safeguard remission in the long term.1,2 In a recent study of WG, which is one of the commoner and more easily recognizable vasculitides, although marked improvement was eventually achieved in 90% of patients, the median time to achieve remission on treatment was 12 months and relapses were frequent, occurring in up to 50% of patients during follow-up, necessitating further courses of therapy.1 Similar relapse rates were found in other series.3 Thus substantial morbidity has been encountered, due not only to poorly responsive disease but also to the hazards of long-term immunosuppression; for example, the incidence of bladder cancer after the first use of cyclophosphamide, currently the drug of choice for WG, has recently been reported to be 5.5% at 10 years and 16% at 15 years,4 after a cumulative dose of only 100 g.

This has led to attempts to develop alternative therapeutic strategies which, based on growing evidence that cellular autoimmunity is implicated in the pathogenesis of systemic vasculitis,5 specifically target the lymphocyte.6,7 We introduced humanized monoclonal antibody (mAb) therapy for certain rare...
patients with severe multisystem lymphocytic vasculitis, and this success led us to consider adoption of the same approach to other patients with commoner forms of autoantibody-associated vasculitis, such as WG or MP, also resistant to treatment. We describe in this paper the effects of mAb therapy on six patients with intractable WG, who were refractory to conventional immunosuppressive drug therapy or were unable to continue this because of risks from cumulative toxicity or unacceptable side-effects.

Methods

Monoclonal antibodies

Two humanized monoclonal antibodies were used in these studies. The first, hlgG1CD52 (CAMPATH 1H), was genetically engineered to have its rat hypervariable complementarity-determining regions grafted into a human immunoglobulin framework. The CD52 antigen is predominantly expressed on human lymphocytes, macrophages and monocytes but not on other cell types. Antibodies raised against this efficiently lyse lymphocytes, but not monocytes, in the presence of human complement, and are known to be lympholytic in vivo, probably through involvement of complement and cellular effector systems. Within the lymphocyte population, the major effect of anti-CD52 appears to be on T-cell numbers and T-cell function, with sustained depletion of both CD4+ and CD8+ subpopulations reported after its administration in man; a more transient depletion of B cells is also seen. The second monoclonal antibody, hlgG1CD4, a humanized anti-CD4 antibody, can interfere with the function of the CD4 antigen.

Antiglobulin and anti-idiotype responses to therapeutic monoclonal antibodies

Antibodies to the administered anti-CD52 and anti-CD4 antibodies were determined in double-capture ELISAs as previously described. The anti-CD52 assay was capable of detecting 2 µg of polyclonal goat antihuman IgG (Fc-specific, Sigma #12136) and 10 ng/ml of monoclonal anti-idiotype antibody YID 13.9 (which recognizes the anti-CD52 idiotype). The rat anti-CD4 assay could detect 250 ng/ml of the anti rat IgG2b mAb NORIG 7.16. Currently, there is no monoclonal anti-idiotype reagent recognizing human IgG1CD4.

T-cell subsets

These were determined as described previously.

Autoantibody assays

Both indirect immunofluorescence (IIF) assays and ELISAs were performed to detect anti-neutrophil cytoplasm antibodies (ANCA). Initially, the latter incorporated a crude extract of neutrophil cytoplasm containing the known ANCA antigens as solid-phase ligand. Subsequently, an antigen-specific ELISA, using the purified molecular species, either proteinase 3 (PR3) or myeloperoxidase (MPO), was developed. ELISA results were expressed as percentage binding of a reference positive control serum (normal <16%).

Autoantibody assays

These were performed as previously described. Briefly, 111Indium-labelled autologous polymorphonuclear leucocytes were injected intravenously. Imaging by gamma camera was carried out at 3 and 24 h. Abnormal uptake in the field of interest was recorded. The scans were reviewed by two specialists in nuclear medicine, unaware of the clinical details of the patients and graded according to a previously established scale.

Patients

The clinical presentations of the six patients are summarised in Table 1; their detailed case histories are shown in Appendix I. Their WG had been unresponsive to the treatments documented in Table 2 for at least 6 months, and no change in treatment had been made in the 4 weeks before mAb therapy was introduced. Histopathological evidence of WG had been obtained in five patients before referral for monoclonal antibody therapy; in the remaining patient a full course of radio- and chemotherapy for an intractable lesion made subsequent histology difficult to interpret. Each of the six patients was then re-biopsied immediately prior to commencement of treatment to determine whether histological evidence of vasculitis, as vessel-wall necrosis and an accompanying inflammatory cell infiltrate, was demonstrable in the organ thought to be the site of active disease; see Table 1.

Results

Response to treatment

The dates of treatment, doses of monoclonal antibody used, salient features relating to the individual's response to treatment, and current steroid therapy of the patients are detailed in Table 2. Despite the presence of intractable active disease in each patient, a measurable and sustained improvement occurred in all after relatively short-term treatment, usually 10 days at most, and periods of treatment-free remission of up to 18 months then occurred, (Figure 2). Each
Table 1  Assessment of disease extent, diagnostic pathology and treatment prior to mAb therapy

<table>
<thead>
<tr>
<th>Patient</th>
<th>Clinical features</th>
<th>Non-invasive studies</th>
<th>Pathology</th>
<th>Treatment before mAb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Paranasal scintiscan</td>
<td>Isotope GFR</td>
<td>Pulmonary imaging</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(normalized)</td>
<td>(post mAb treatment)</td>
<td>(resolution)</td>
</tr>
<tr>
<td>1</td>
<td>SKEN</td>
<td>(+ (+))</td>
<td>49 (86)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>SKL</td>
<td>(+)</td>
<td>RDT</td>
<td>C (+)</td>
</tr>
<tr>
<td>3</td>
<td>SK</td>
<td>(+ (+))</td>
<td>26 (130)</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>NE</td>
<td>- (ND)</td>
<td>NRF</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>SLKE</td>
<td>+ (ND)</td>
<td>31 (ND)</td>
<td>C, En (+)</td>
</tr>
<tr>
<td>6</td>
<td>SLK</td>
<td>+ (+)</td>
<td>NRF</td>
<td>C, En (+)</td>
</tr>
</tbody>
</table>

CSL, cytotoxic-sensitive leucopenia; HC, haemorrhagic cystitis; CXS, cumulative dose of Cy > 100g; ND, not done; RDT, renal dialysis therapy; NRF, normal renal function; C, cavitation; En, endobronchial extension; RT, radiotherapy; ATG, anti-thymocyte globulin; PE, plasma exchange; IVig, intravenous immunoglobulin.

Clinical features: prominent clinical involvement of S, sinus/nasal/paranasal tissue; K, kidney; L, lung; N, nerve, E, eye. Pathology: △, vasculitis on biopsy immediately prior to mAb treatment; ▽, rebiopsy failed to show vessel-wall necrosis; (however, evidence of chronic inflammatory cell infiltrates, absence of infection and ready response to treatment were compatible with vasculitis as relevant diagnosis).

patient was followed up for at least 6 months after mAb treatment. The failure of conventional therapy was underscored by the fact that the further use of cyclophosphamide, the preferred agent for active WG, was precluded in four of the six patients, because of previous chemical cystitis, current leucopenia or the risk of cumulative toxicity (>100 g ingested). The impact of the mAb seemed to have no adverse effect on the host resistance to infection. The only death (patient 2, who died at another hospital after surgery to resect a bulla left at the site of a previous chest drain) would seem to be unrelated to this treatment. Relapses, which occurred in four patients (1, 2, 3 and 5), occurred despite a reduced CD4 population in two (1 and 2), (Figure 3). Patients 2 and 3 had detectable circulating ANCA at the time of first relapse as did patient 1 at the time of her fourth relapse.

**Antiglobulin titre**

In a previous study, one patient with lymphocytic vasculitis did develop an antiglobulin response after mAb therapy. However, none of the patients with WG described here produced antiglobulins in a similar fashion.

**Lymphocyte depletion**

The effect of monoclonal antibody therapy on peripheral CD4 populations is shown in Figure 3. There was substantial and sustained depletion of the CD4 cells, measured as a percentage total of circulating lymphocytes (normal range >25%). Despite this, systemic opportunistic infections were not seen in these patients, although patient 5 developed herpetic oral ulceration 3 weeks post-treatment, which responded to appropriate antiviral treatment. However, this patient had previously received anti-thymocyte globulin, as well as conventional immuno-suppressive drugs for 15 years, prior to humanized monoclonal antibodies. Local intercurrent bacterial or fungal infections, arising on a presumably multifactorial basis, responded appropriately to the relevant antimicrobial therapy. Of note, patient 4 had herpes zoster in sacral S4 distribution, at the time monoclonal antibody treatment was given: there were no unexpected or untoward sequelae related to this mAb intervention, necessitated by the severity of the vasculitis.

**Autoantibody titres**

Although all six patients had positive ANCA serology at some stage during their disease, by the time they were referred for treatment, circulating ANCA were detected in only one patient (patient 3). This patient remained ANCA-positive throughout the period of study, with relapse being better predicted by serial scintiscans and isotope GFR studies, see Figure 1.

**Autologous leucocyte scans**

This technique was helpful in showing abnormal foci of labelled white-cell accumulation close to the nasal or paranasal air spaces in five of the six patients. In none of these did ENT examination reveal that the abnormalities could be accounted for by the presence of infection, and the response to
therapy, which did not include antibiotics, was further evidence against infection being a major factor contributing to the localization. In a separate study of 50 patients with systemic vasculitis, such leucocyte imaging was found to be useful for detecting unsuspected sites of disease and for monitoring disease activity, being superior to conventional radiography or CT scanning for lesions in or near upper or lower airways. 16

Discussion

Our findings suggest that patients with Wegener’s granulomatosis who are refractory to conventional therapy can be brought into remission by monoclonal antibody treatment. The progression of active disease was reversed, as judged by clinical assessment and paired objective non-invasive studies, such as leucocyte scintiscans (three patients) radiological resolution of structural lung abnormalities (three patients) isotope measurements of glomerular filtration rate (two patients) and nerve conduction studies (one patient). More impressively, cytotoxic therapy, escalation of which was contraindicated in more than half the patients for reasons of leucopenia, haemorrhagic cystitis or risk of cumulative toxicity, was not required once the monoclonal antibody therapy was started and was not used again. Steroid treatment was tapered slowly in all patients to 10 mg by 2 months after the monoclonal regimen was

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**Table 2** Details of mAb treatment and outcome, as well as current therapy at latest follow-up

<table>
<thead>
<tr>
<th>Patient</th>
<th>Start date</th>
<th>Dose in mg (days)</th>
<th>Outcome</th>
<th>Current prednisolone (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD52</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>June 92</td>
<td>4(10)</td>
<td>-</td>
<td>Non-sinus disease inactive after treatment in June 92. GFR improved and stabilized at &gt;80 ml/min for 3 years. Lesions in left maxillary and ethmoid sinuses responded to local artery perfusion via maxillary (max) and ophthalmic (op) arteries, respectively, as well as local brachytherapy to the ethmoid lesion.</td>
</tr>
<tr>
<td></td>
<td>Nov 92</td>
<td>20, 40(3)</td>
<td>20(5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jan 93</td>
<td>10 art(max)</td>
<td>20(2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dec 93</td>
<td>10 art(op)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Apr 93</td>
<td>10 art(max), 40(5)</td>
<td>20(5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dec 94</td>
<td>10 art(op), 40(5)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Feb 93</td>
<td>4, 10, 40(3)</td>
<td>-</td>
<td>Cavitation in lungs replaced by small line shadows, compatible with scar formation. Pulmonary relapse at 10 m successfully treated with mAb. Died at 14 m after surgery (disease inactive). No return of renal function (on RDT for 2 years before mAb therapy).</td>
</tr>
<tr>
<td></td>
<td>Dec 93</td>
<td>10, 40(4)</td>
<td>20(5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Jan 94</td>
<td>4, 10, 40(3)</td>
<td>-</td>
<td>Nasal symptoms resolved and GFR improved, see Figure 1. Serial scintiscans and isotope GFR’s indicated relapse (Oct 94), before symptoms (Jan 95).</td>
</tr>
<tr>
<td></td>
<td>June 95</td>
<td>4, 10, 40(3)</td>
<td>20(5)</td>
<td>Nasal symptoms resolved again after further mAb therapy.</td>
</tr>
<tr>
<td>4</td>
<td>Jan 94</td>
<td>4, 10, 40(3)</td>
<td>10(5)</td>
<td>Persistent left ptosis, indicative of early orbital pseudotumour became undetectable at 2 m, peripheral nerve lesions resolved in 6 m.</td>
</tr>
<tr>
<td>5</td>
<td>Aug 94</td>
<td>2, 10, 40(5)</td>
<td>20(5)</td>
<td>Cinebronchoscopy 2 w post treatment showed disappearance of tracheal and endobronchial ulceration; cavitation resolved on CT at 3 m. Plasma creatinine remained unchanged.</td>
</tr>
<tr>
<td>6</td>
<td>Jan 95</td>
<td>4, 10, 40(3)</td>
<td>-</td>
<td>Stridor due to stenosing tracheal lesion resolved after 2 w. Nasal symptoms resolved by 6 w. Cavitating pulmonary nodules required two further courses of mAb before control of that disease was achieved.</td>
</tr>
<tr>
<td></td>
<td>March 95</td>
<td>4, 10, 40(3)</td>
<td>20(5)</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>May 95</td>
<td>4, 10, 40(3)</td>
<td>20(5)</td>
<td></td>
</tr>
</tbody>
</table>
Humanized monoclonal antibody therapy

140
120
100
80
60
40
20
0
January 94
May 94
Aug 94
Oct 94
Feb 95
MAb Therapy

ANCA % & GFR ml/min

ANCA (PR3)
ANCA (NR <16%)

Figure 1. Serial 111Indium-labelled autologous polymorphonuclear leucocyte scans, showing a abnormal paranasal uptake, and b GFR measurements in patient 3. Note normalization of leucocyte distribution to spleen and liver after mAb treatment (May 1994), and improvement in GFR. Scans become abnormal again in Oct 1994, as GFR diminishes.

The mechanism by which monoclonal antibody therapy engages the autoimmune response to achieve its beneficial effect is not clear. Since the patients were refractory to conventional therapy, and yet they, and a small group of patients with a more striking lymphocytic contribution to their vasculitis,8 responded rapidly to the mAb regimen, the balance of opinion must favour the engagement of some novel immunotherapeutic pathway, eventually affecting the lymphocyte. That the lymphocyte may play an active role in vasculitis, both by being directly cytotoxic as well as orchestrating the B-cell response has been argued before. If so, it would seem possible that the debulking of the lymphocyte pool, creating a relative deficit in the peripheral CD4 population of cells, is sufficient to have a substantial effect on the disease itself, an effect sustained for long periods after treatment. One further benefit may be that the mAb therapy is delivered directly to the site of the pathology, since intravenous infusion...
allows direct access to the vessel wall, a primary site of vasculitic injury.

Administration of the monoclonal antibodies proved to be safe, and side-effects were restricted to minor clinical disturbances, usually only on the first day of treatment, such as fever, chills and occasional rigors, which could be circumvented by slowing the infusion, and/or a single dose of 100 mg hydrocortisone. Although many of the patients had received considerable immunosuppression before, none have developed lymphoma, a recognized complication of immunosuppressive drug therapy. Nor have any of the patients developed a systemic opportunistic infection, and the incidence of other intercurrent bacterial or viral infections did not appear to be either more frequent or of greater severity than in other patients with WG receiving conventional immunosuppression.

Treatment could safely be given on repeated occasions. This advantage of the humanized version of an antilymphocyte globulin is important in the context that such treatment may eventually be the preferred approach for dealing with relapses, some of which are multiple and occur in up to 50% of patients with WG followed-up long term. Of interest is patient 5, who had been given anti-thymocyte globulin on compassionate grounds for intractable disease: this was successful initially, but further treatments were hindered because of serum sickness reactions, brought about by cross-species sensitiza-
Humanized monoclonal antibody therapy

Figure 3. Peripheral CD4 populations (% circulating lymphocytes) before and after mAb therapy. Note relapse occurred in two patients, 1 and 2, as the proportion of CD4 cells returned towards normal (>25% of circulating lymphocytes).

- **Acknowledgements**

We are indebted to the following physicians and surgeons who referred the patients included in this study and allowed us to report our findings: Dr DB Evans, Dr P Williams, Mr G Shone, Professor L van Es, Dr C Hagen, and Dr ICM Patterson. Gratitude is also expressed to the following physicians and surgeons, medical ophthalmologist (PM) and radiologist (CDRF) at Addenbrooke’s Hospital, who provided advice at various times invaluable to the management of the patients: Dr DBG Oliveira, Dr JR Bradley, Dr DRW Jayne, Dr P Meyer, Mr D Moffat, Dr CDR Flower, Dr T Higenbottam, Mr D Adlam, Dr Huw Jones, Dr GR Park and Professor DK Peters. The technical accomplishment of Peppy Rebello and Philip Ball is also gratefully acknowledged, as is that of staff of the Therapeutic Antibody Centre, University of Cambridge, who produced the anti-CD52 and anti-CD4 humanized monoclonal antibodies used in this study. This work was supported by the Medical Research Council, the Wellcome Trust, the Wellcome Foundation, the Gilman Foundation, and the Stuart Strange Trust.

**References**


- **Text**

...monoclonal antibody therapy was successful and uneventful.

In previous studies of certain patients with rare lymphocytic, non-Wegener’s vasculitis, combination therapy consisting of anti-CD52 together with anti-CD4 monoclonal antibodies seemed to be more effective than a broadly lympholytic approach with anti CD52 alone.\(^8\) Synergy has been demonstrated in an experimental model of autoimmune arthritis, wherein monoclonal antibodies, similar in specificity to those used for the patients with vasculitis, were capable of arresting an ongoing autoimmune response when used together, whereas neither alone could affect the progression (although either alone would block the induction).\(^17\) Such a combination regimen could prove useful for other reasons, since serial studies suggested that the concomitant use of CD4 may enhance tolerance to coadministered antibodies,\(^16\) thus avoiding the risks that anti-idiotypic responses might complicate repeated mAb treatments. However, since the role of anti-CD4 therapy is not yet established, our current policy is to use CD52 as the primary agent and to use anti-CD4 as adjunctive therapy if CD52 proves to have only a temporary effect, or if, for other reasons, such as the patient’s domiciliary location, this is not practicable (patients 4 and 5).

For patients in this study with intractable vasculitis, humanized monoclonal antibody therapy appears to provide an alternative to conventional regimens incorporating steroids and cytotoxic agents, both of which themselves contribute a separate and substantial iatrogenic morbidity. Even short-term therapy can produce long-term remissions. As the growing understanding of the pathogenesis of the vasculitides points to autoimmune mechanisms, the introduction of specific immunotherapy offers the opportunity for safer and more selective treatment than available hitherto. Our experience of using humanized monoclonal antibodies with specificity for lymphocytes, particularly T cells, suggests that this might be a suitable strategy not only for patients with refractory vasculitis, but eventually perhaps for the treatment of vasculitis at an earlier stage in relapse, if conventional management with cytotoxic and steroid drugs is not speedily effective.


**Appendix I: Details of patients**

**Patient 1**

This 30-year-old woman developed a persistent oral-antral fistula after failed intranasal antrostomy for recurrent sinusitis at the age of 16, in 1979. Biopsies of the oral lesions did not yield a histological diagnosis. In 1981, she developed episodes of weakness, night sweats and headaches and intermittent iritis of the left eye. She was given a full course of radiotherapy to the palatal lesion, followed by a full systemic course of chemotherapy. Although responding initially, the disease again relapsed and, on this occasion, the symptoms were accompanied by episcleritis and proteinuria. In 1991, she was treated with further Cy and prednisolone. But after 2 months these were discontinued because of marrow suppression, which proved to be long-lasting. She was then referred for further management. A conclusive histological diagnosis of WG proved difficult to reach at this stage, possibly because of the effects of previous radiochemotherapy; repeated antihistoplasms eventually revealed evidence of a chronic inflammatory infiltrate with multinucleated giant cells, but without outright vasculitis manifested by vessel-wall necrosis; however, ANCA with specificity for PR3 were detected. The disease progressed, with an enlarging ulcerating granulomatous maxillary sinus lesion, development of a peripheral sensory neuropathy and increased urinary protein excretion, isotope CFR 49 ml/min despite prednisolone 60 mg/day. She was then referred for consideration of monoclonal antibody therapy.

**Patient 2**

This 65-year-old man was admitted to another hospital in 1989 with pneumonia and a right retrocardiac shadow seen on chest xray. He had normal renal function at that time. Bronchoscopy and biopsy of the lung lesion suggested a diagnosis of squamous carcinoma of the lung. Later, he was found to have renal impairment and managed conservatively. Renal failure progressed and, in Sept 1990, he was readmitted, whereupon a renal biopsy and review of the lung biopsy showed granulomatous vasculitis, compatible with a diagnosis of WG; anti-PR3 antibodies were also detected. He was treated with Cy and prednisolone, and with this his ANCA titre became negative. His chest X-rays also became normal and despite now being on renal dialysis therapy (RDT) he remained well until Jan 1992. At that time he developed haemorrhagic cystitis and a small contracted bladder. During 1992, two new lesions appeared on the chest X-ray, his ANCA titre became positive and the pulmonary changes progressed.
despite increasing the prednisolone to 30 mg/day, as well as a course of Az, eventually discontinued because of leucopenia, and treatment with high-dose pooled intravenous immunoglobulin (IVIg). With increasing malaise and dyspnoea, he was referred for further management in Feb 1993. Serial diagnostic imaging showed marked multiple bilateral enlarging ill-defined cavitating pulmonary nodules. CT of the chest showed irregular cavitating masses in both lungs, particularly affecting the upper lobes; lung biopsy showed areas of active vasculitis, compatible with a diagnosis of WG.

**Patient 3**

This 40-year-old man was referred in Jan 1994 for assessment of his WG. His disease had started in 1983 with persistent epistaxis, which led to the diagnosis by nasal septal biopsy, which showed granulomatous lesions with giant cells, in Aug 1984. He received chemotherapy for his WG, followed by a course of radiotherapy to the nose. His hearing deteriorated in 1985 with ‘glue’ ear requiring grommets bilaterally. In 1988 he underwent reconstructive surgery to his nose after the development of ‘saddle’ deformity. During the 6 months prior to referral he had been troubled by recurrent chest infections, migratory arthralgias and stuffy nose; his isotope GFR had deteriorated to 26 ml/min. His medication had consisted of Cy, Az and steroids, but he had had to discontinue Cy because of cystitis and on admission he was taking Az 150 mg od and prednisolone 10 mg od. Of interest was that his brother had also developed WG.

**Patient 4**

This 40-year-old woman was referred in Jan 1994, with a 7 yr history of episodic bursitis and tenosynovitis, affecting predominantly the shoulders until 1992 and thereafter the elbows, hips, ankles and dorsum of the feet. From April 1993 she noted arthritis and fusiform swelling of the small joints in the hands. In June 1993 evidence of peripheral neuropathy became manifest as decreased sensation over the lateral border of the left foot, then, two days later, over the right foot, extending gradually to the ankle on the left, to mid calf on the right. Two weeks later Raynaud’s phenomenon started in the hands and then the feet. There was accompanying constitutional disturbance with night sweats and weight loss of 8 kg in 3 weeks. Sural nerve biopsy revealed vasculitis. The vasculitis was treated with prednisolone 100 mg od and Cy 150 mg od. Ischaemic patches on the digits, nailfold infarcts and splinter haemorrhages complicated the early course and herpes zoster of the ophthalmic branch of the right trigeminal occurred in Aug 1993 and was treated with acyclovir. Attempts to lower the steroid dose below 50/35 on alternate days in Sept, and below 50/5 in Dec were accompanied by a rise in markers of inflammation (ESR and CRP) as well as evidence of clinical deterioration (arthralgias, extension of numbness and in Dec, ptosis of the left eye and early orbital pseudotumour formation). There was some response of the ptosis to intermittent plasmapheresis. However, the prednisone had to be increased to 50 mg daily in Jan 1994, and a further episode of zoster occurred, affecting the perineal distribution of S4 on the left side, necessitating reintroduction of acyclovir 4 g daily. At the time mAb treatment was introduced there was a left ptosis, advancing paraesthesia in both hands and decreasing sensation over the fingers of both hands, the left foot to the ankle and the right leg to mid thigh. Nerve conduction studies confirmed an axonal neuropathy and biopsy the presence of vasculitis. She had zoster in the region of the left S4 dermatome, was markedly cushingoid and had livedo reticularis affecting the lower limbs. Treatment at this stage was prednisolone 50 mg od, Cy 150 mg od as well as acyclovir 4 g daily.

**Patient 5**

This 43-year-old woman developed WG in 1980 involving the nose, sinuses and skin (cutaneous vasculitis). She was treated with prednisolone, Cy and Az. She subsequently collapsed the bridge of her nose, had pulmonary and renal involvement, (biopsy proven focal necrotizing glomerulonephritis) as well as episcleritis, despite continued cytotoxic drugs and steroids. In July 1992, she developed haemorrhagic cystitis caused by the Cy. In 1993, the WG progressed: there was an enlarging pseudotumour in the left orbit, which also involved the parotid gland and was accompanied by episcleritis. She responded to antithymocyte globulin (ATG) but this was complicated by serum sickness: she later proved refractory to two further courses of ATG, also complicated by serum sickness. Serial chest CT showed substantial increase in the number, size and cavitation of the chest lesions, which on biopsy 2 months before referral revealed a severe granulomatous vasculitis. Cinebronchoscopy in July 1994 showed the CT lesions to have extended to produce multiple ulcerations in the trachea and upper bronchi.

**Patient 6**

This 50-year-old woman presented in Nov 1989 with malaise, pain in both ears, red eyes, sinusitis, nasal discharge, headaches, a dry non-productive cough
and dyspnoea at rest. A chest CT showed a cavity in the left upper lobe of the lung. A nasal biopsy from the right middle turbinate showed changes consistent with WG. She was commenced on Cy 200 mg and prednisolone 60 mg in Feb 1990, which produced a remission. In July 1993 the Cy was substituted by Az, but after 2 months there was relapse—worsening cough, malaise, headaches and sinusitis. Az was stopped and Cy recommenced. IVlg, 2 g/kg was used to try to spare the Cy dose, now cumulatively >100 g. This produced a remission of clinical symptoms. The IVlg was subsequently administered every 3 months. Although responding to these, after the third course symptoms of malaise, cough, dyspnoea and nasal discharge returned, complicated by severe inspiratory stridor which prompted referral for mAb therapy. Bronchoscopy revealed tracheal stenosis with granulomatous ulcerating lesions.