Table 1 Change in ASAS outcome domains

Outcome domain	Median (IQR)		p Value*
	Baseline	Six months	
BASFI	44.4 (60.8–22.3)	42.3 (53.3–34.4)	0.68
Pain VAS	58 (74–35)	47 (60.5–24.5)	0.09
Global assessment VAS	48 (77.5–32)	48 (61–30)	0.08
BASDAI morning stiffness	49 (63.3–27.5)	40 (45.5–25.3)	0.22

*Wilcoxon's matched pairs, signed ranks test.

documented a modest ASAS 20 response despite employing a more intensive regimen.⁸ Similarly, Cairns *et al* found only modest improvement in the BASDAI (6.8 to 5.75).⁹ A shorter disease duration (9.2 years present study *v* 15.1 years Maksymowych *et al*) as well as slightly lower disease activity cannot explain the observed lack of efficacy.

Adverse effects were seen in 16 patients, most of which were minor and well tolerated (post-infusion fever and myalgias in 12, mild uveitis in one). Three patients experienced serious adverse effects (renal disease in two, gastrointestinal problems in one) temporally related to the infusions. Renal adverse events included doubling of the serum creatinine levels and nephrotic range proteinuria, respectively. A relapsing form of glomerulopathy is a rare adverse effect of pamidronate infusions.¹⁰ Our patient did not consent to a renal biopsy, and the proteinuria gradually resolved. The third patient had severe diarrhoea and anorexia lasting for 2 months for which no alternative pathology could be found. One patient developed a severe disease flare after the third infusion (severe bilateral uveitis and peripheral arthritis requiring high dose steroid treatment). This patient had history of mild uveitis and peripheral arthritis 4 years ago. It cannot be ascertained whether pamidronate was responsible for the flare or this represented a lack of efficacy of the drug in this patient.

In conclusion, pamidronate infusions did not decrease disease activity significantly in patients with moderately active AS refractory to NSAIDs. The study raises questions about the efficacy of monthly pamidronate infusions as a treatment for AS.

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Glucocorticoid resistance in a girl with Takayasu's arteritis

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We report the case of a 16 year old girl with Takayasu's arteritis, which started with a bilateral neck pain associated with fever and a carotid murmur. A Doppler ultrasound of the neck showed a bilateral carotid involvement with thickened arterial walls and increased blood flow velocity, and a computed tomographic scan of the aorta showed involvement of the abdominal tract.

Treatment was started with oral prednisone and methotrexate, with a very poor clinical response (fig 1); acute phase reactants were significantly raised, recurrent fever persisted, and abdominal pain developed showing that the abdominal

aorta was affected. Treatment with intravenous boluses of high dose methylprednisolone gave transient benefit; treatment with glucocorticoids (GCs) was continued and additional immunosuppressant drugs were progressively added, still without any clinical and laboratory sign of remission. To confirm that the patient was taking her treatment, oral betamethasone was given under strict supervision during a period of admission in hospital, but still with no sign of clinical improvement. To obtain guaranteed steroid absorption, intravenous (IV) betamethasone was given in hospital for a 2 week period and for the following months at home, still without any benefit.

Figure 1 Erythrocyte sedimentation rate (ESR) over time in relation to the steroid and immunosuppressive treatment. Additional immunosuppressant drugs are indicated by numbers in the rectangles at the top of the figure: 1, methotrexate 0.5 mg/kg/day; 2, thalidomide 2.5 mg/kg/day; 3, infliximab 100 mg IV at weeks 0, 2, and 6; 4, azathioprine 2 mg/kg/day p.o. + cyclosporin p.o. targeted to a through plasma level of 200 ng/ml; 5, cyclosporin p.o. targeted to a through plasma level of 200 ng/ml. Inset: densitometric analysis of hsp90 and β -actin in peripheral blood mononuclear cells (PBMCs) of the patient and of one control. Serial dilutions of hsp90 and β -actin reverse transcription products were coamplified by polymerase chain reaction (PCR) in the same reaction, and the PCR products were separated by electrophoresis. Densitometric analysis of specific bands obtained with hsp90 primer sets were performed and optical densities were normalised with β -actin mRNA band intensities. Data are the means (SE) of the ratios obtained for each dilution. * $p < 0.05$ Student's t test for independent data.

GC resistance could be explained by the increased cytokine production seen in Takayasu's arteritis.^{1,2} However, after 1 year's treatment with high dose steroids, some unusual clinical and laboratory clues were evident: physical examination disclosed an extremely thin girl, with no signs of exogenous Cushing's syndrome. She had a normal blood pressure, a normal ocular tone, 3.8×10^6 red blood cells, $10\,800$ white blood cells with 70% polymorphonucleates, 0.3×10^9 eosinophils/l, 235×10^{12} platelets/l, haemoglobin 78 g/l, packed cell volume 0.23, normal mean corpuscular volume.

The hypothesis of a primary steroid resistance was therefore considered; this is a rare syndrome, characterised by a generalised reduced sensitivity to GCs, hypercortisolism, resistance to dexamethasone suppression test, and no sign or symptoms of Cushing's syndrome.² Serum cortisol levels were measured and an ACTH stimulation test with tetra-cosactide was performed four times and always tested normal. Unexpectedly, hypercortisolaemia was not present. However, normal cortisol levels have been seen previously in

patients with generalised GC resistance,³ and the complete absence of side effects despite prolonged treatment with high doses of GCs, prompted us to exclude a mosaic problem of resistance only within immune cells.

The whole cell [3 H]dexamethasone binding assay was performed on PBMCs. In comparison with 10 patients, treated with GCs and responsive to treatment, and six healthy controls, a reduced number of receptors per cell in the patient's PBMCs was seen. Binding affinity (Kd) was, on the contrary, not modified (table 1).

Abnormalities of the receptor number have been described in primary resistance, and have been related to gene mutations.^{2,4} DNA was extracted from PBMCs; PCR amplification of the gene was carried out with primers for exons 4, 5, 7, 8, and 9 α , and the PCR products digested with specific restriction enzymes,⁵⁻⁷ but no mutation was identified.

Other important determinants of GC sensitivity are hsp90 proteins, which stabilise the receptor in a conformation that is necessary for ligand binding,⁸ and increased levels of hsp90 mRNA are associated with GC receptor defects.⁹ Total RNA was extracted, reverse transcribed, and a semiquantitative PCR protocol was applied to quantify and compare the expression of hsp90 and β -actin mRNAs.¹⁰ An increased expression of hsp90 mRNA in the patient's PBMCs was evident (fig 1, inset), which suggests that there may be a molecular explanation for the GC resistance.

Table 1 Sites of receptors in each cell and binding affinity (Kd) for dexamethasone in PBMCs

	Patients	Responders (n = 10)	Controls (n = 6)
Receptors/cell	1799	3884 (305.8)	3601.5 (355)
Kd (nmol/l)	3.01	3.40 (0.44)	2.54 (0.70)

Results are shown as mean (SD).

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Successful treatment of meningeal involvement in Wegener's granulomatosis with infliximab

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Meningeal involvement in Wegener's granulomatosis (WG) is rare and only 32 cases have been reported by Reinhold-Keller and coworkers.^{1,2} The outcome of the disease has improved with the institution of cytotoxic agents.³ We report on a patient with WG and progressive pachymeningitis despite treatment with cyclophosphamide (CyC) and glucocorticoids who responded well to infliximab treatment.

In December 2003 a 34 year old male chemist was diagnosed with localised WG, according to the American College of Rheumatology criteria and the Capel Hill Conference criteria, on the basis of granulomatous nasal inflammation, left-sided otitis media, and the detection of proteinase-3-antineutrophilic cytoplasmic antibodies (PR3-ANCA) >100 U/ml (normal <5 U/ml).^{4,5} Because of progressive hearing loss oral prednisolone (1 mg/kg body wt) and intravenous CyC 0.8 g/m²/month were started.

After 3 months when prednisolone was tapered to 15 mg/day the patient developed headache, bilateral paresis of the abducens nerve, and paresis of the left oculomotor nerve. Magnetic resonance imaging (MRI) disclosed dural thickening with enhanced gadolinium uptake across both cerebral hemispheres and the basal region (fig 1A), and another increase of PR3-ANCA (46 U/ml) supported the suspicion that WG had spread to the meninges and had become generalised. Methylprednisolone pulse therapy and oral CyC (2 mg/kg body wt) were successfully started.

After prednisolone was tapered to 50 mg/day the patient again complained of headache and incapacitating bilateral diplopia. MRI findings had remained virtually unchanged; the modified Birmingham Vasculitis Activity Score (BVAS/WG)⁶ was 9 (BVAS1 = 4; BVAS2 = 5), and the PR3-ANCA level 18 U/ml.

Because oral CyC and prednisolone could not control the disease this led us to examine reports that infliximab might be effective in treating refractory WG.⁷ After written informed

consent was obtained and no signs of infection were found, infliximab (5 mg/kg body wt) at weeks 0, 2, and 6, and thereafter at 8-weekly intervals was started. After 2 weeks clinical symptoms of cerebral involvement had subsided, the BVAS/WG had fallen to 4, and the PR3-ANCA level was 10 U/ml. Oral CyC was reduced to 1 mg/kg body wt and prednisolone to 5 mg/day within 3 months. Over the following 12 months, the patient remained free of clinical symptoms and MRI findings improved impressively (fig 1B), indicating that infliximab was effective in controlling meningeal involvement.

Granuloma formation is a hallmark in localised WG. These granulomas consist predominantly of tumour necrosis factor α (TNF α) expressing T cells and macrophages, and different groups have shown that infliximab, a TNF α neutralising agent, was effective in refractory WG.^{7,8} Our patient originally presented with localised WG that generalised and spread to the meninges despite immunosuppressive treatment. Infliximab induced and maintained remission in our patient with no side effects reported to date. This shows a difference between infliximab and etanercept, which could not prevent relapses in a recently published placebo-controlled trial.⁹

To our knowledge, ours is the first report demonstrating that infliximab may be a viable treatment option in generalised WG not responding to oral CyC and glucocorticoids.

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