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Intravenous immunoglobulin for ANCA-associated systemic vasculitis with persistent disease activity

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Summary

Intravenous immunoglobulin (IVIg) is a potential alternative treatment for anti-neutrophil cytoplasm antibody (ANCA)-associated systemic vasculitis (AASV) with less toxicity than conventional immunosuppressive agents. This randomized, placebo-controlled trial aimed to investigate the efficacy of a single course of IVIg (total dose 2 g/kg) in previously-treated AASV with persistent disease activity in whom there was an intention to escalate therapy. Vasculitic activity was monitored by the Birmingham vasculitis activity score (BVAS), C-reactive protein (CRP) and ANCA levels. Treatment response was defined as a reduction in BVAS of more than 50% after 3 months, and there was an intention to keep doses of concurrent immunosuppressive drugs unchanged during this period; follow-up continued to 12 months. Seventeen patients were randomized to receive IVIg and 17 to receive placebo. Treatment responses were found in 14/17 and 6/17 of the IVIg and placebo groups, respectively ($p = 0.015$, OR 8.56, 95%CI 1.74–42.2). Following infusion of trial medication, greater falls in CRP were seen at 2 weeks ($p = 0.02$) and 1 month ($p = 0.04$) in the IVIg group. No differences were observed between ANCA levels or cumulative exposure to immunosuppressive drugs, and after 3 months there were no differences in CRP levels or disease activity between the IVIg and placebo groups. Seventeen adverse effects occurred after IVIg and six after placebo: they were mostly mild, although reversible rises in serum creatinine occurred in four from the IVIg group. A single course of IVIg reduced disease activity in persistent AASV, but this effect was not maintained beyond 3 months; mild, reversible side-effects following IVIg were frequent. IVIg is an alternative treatment for AASV with persistent disease activity after standard therapy.

Introduction

The small-vessel vasculitides such as Wegener's granulomatosis and microscopic polyangiitis are characterized by constitutional symptoms, accompanied by clinical signs resulting from focal multi-system inflammation, such as haemoptysis due to lung vasculitis or renal failure due to glomerulonephritis. The pathological hallmark of involvement of the vasculature is transmural infiltrates of

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leucocytes, with areas of segmental necrosis, sometimes associated with collections of lymphocytes and monocytes/macrophages, forming granulomata. The frequent presence of circulating autoantibodies to neutrophil cytoplasm antigens (ANCA) with antigenic specificity for proteinase 3 (PR3-ANCA) and myeloperoxidase (MPO-ANCA), suggests that autoimmune mechanisms underlie the pathogenesis of these disorders and has led to their description as ANCA-associated systemic vasculitides (AASV).[1–3]

Conventional therapy with a combination of steroids and cyclophosphamide controls disease activity in 90% of patients, but fewer than 60% have full resolution of their symptoms.[4,5] Therapy has to be sustained, since up to 50% relapse within 2 years of achieving remission. Such prolonged therapy leads to increasing risks from the cumulative toxicity of the drugs used in treatment.[5] Thus, added to the marked chronic morbidity caused by the disease, there is substantial drug-induced morbidity: in a study of 158 patients with Wegener's granulomatosis, cyclophosphamide led to infertility in 50% and bladder cancer in 15%, whereas steroids produced cataracts, osteopenic fractures and diabetes.[5,6]

Alternative agents to current therapy include sulfamethoxazole/trimethoprim, which reduces relapse rates in Wegener's granulomatosis, and lymphocyte depletion using polyclonal or monoclonal antibodies, which has produced treatment-free remission and suggested an important role for T-cells in the pathological autoimmune response.[7–10] A rationale for the use of intravenous immunoglobulin (IVIg) in AASV has been developed from experience in Kawasaki disease, a systemic vasculitis of young children.[11] This was supported by research which showed that IVIg could interfere with the binding of ANCA to their antigens through idiotypic mechanisms and from the ability of IVIg to inhibit ANCA-induced neutrophil activation.[12,13] Other diseases with a possible autoimmune basis have, in controlled studies, also been shown to be responsive to IVIg.[14–16] Two open studies of IVIg, involving 26 and 14 patients with persistent AASV, observed sustained reductions in disease activity in 75% and 40%, respectively.[17–19] When given alone without concurrent immunosuppression as first-line treatment for otherwise untreated AASV, four out of six patients had sustained remission of their symptoms.[20] This trial was designed to test the therapeutic efficacy of a single course of high-dose IVIg in reducing disease activity in previously treated patients with persistent AASV.

Methods

Patients were enrolled from five hospitals in England between 1991 and 1995. The study protocol was approved by the Local Research Ethical Committee in each hospital and prior to entry the study was explained to all patients and written, informed consent obtained.

Study design

A prospective, double-blind, placebo-controlled, multicentre, randomized study, with reduction of disease activity as the primary end-point.

Inclusion criteria

Inclusion required: (i) prior diagnosis of Wegener's granulomatosis or microscopic polyangiitis, the disease definitions satisfying the criteria of the Chapel Hill Consensus conference;[21] (ii) ANCA positivity at diagnosis; (iii) active vasculitis with a requirement for further therapy; (iv) at least 2 months treatment with prednisolone and cyclophosphamide or azathioprine; and (v) age 18 years or over.

Exclusion criteria

Patients were excluded for the following reasons: (i) IVIg therapy during the previous 3 months; (ii) history of anaphylaxis to properly matched blood products; (iii) selective IgA deficiency; (iv) rapidly progressive glomerulonephritis, (20% rise in serum creatinine within 2 weeks) or severe pulmonary haemorrhage.

Treatment protocol

Similar therapeutic regimens for AASV were used in participating centres, with the combination of prednisolone and cyclophosphamide for remission induction, and azathioprine with continued prednisolone for remission maintenance. After entry into the trial and a 2-week observation period, patients were randomly assigned to receive IVIg 0.4 g/kg/day for 5 days (total dose 2 g/kg) (Sandoglobulin, Novartis) or placebo. Randomization and distribution of trial medication was centrally controlled by Novartis UK who prepared the placebo, identical in appearance to IVIg; patients and physicians were blinded to the treatment limb. Prophylactic hydrocortisone was not used but chlorpheniramine could be administered as required. It was intended to keep doses of immunosuppressive drugs unchanged until 3 months after the trial infusion; at this time treatment was changed according to local practise.

Assessment of disease activity

Items representing vasculitis activity during the preceding month were recorded according to previously agreed definitions and scored in the BVAS system.[22] In addition to clinical history and examination, BVAS

includes data from specialist opinions, radiology and urine analysis. C-reactive protein (CRP) estimation was performed in local laboratories and sera were frozen in aliquots and stored at $-20\,^{\circ}C$. Sequential sera were tested at the end of the study for total IgG levels and by antigen-specific ELISA for PR3-ANCA and MPO-ANCA.[23]

Trial assessments

Patients were reviewed at entry, at the time of infusion, at 2 weeks, and monthly until 12 months. The following items were documented: vasculitis activity score, weight, current immunosuppressive therapy, CRP, serum creatinine, liver function tests, haemoglobin, white cell, neutrophil, lymphocyte and platelet counts, haematuria, proteinuria and adverse effects to the trial medication. In view of earlier reports of viral transmission following IVIg, hepatitis C serology was tested if rises in alanine transaminase were detected. White cell scans and chest radiology were performed at entry and repeated after 3 months if vasculitic activity was observed.

Statistical analysis

It was hypothesized that high-dose IVIg was an immunomodulatory agent which reduced disease activity in AASV. The primary end-point, treatment response, was defined as a reduction in BVAS by $>50\%$ between entry and 3 months after infusion. A previous study had indicated a response rate of 75% in those receiving IVIg; assuming a response rate of 25% in those receiving placebo, at least 16 patients were required for each limb in order to detect an effect of IVIg with a power of 0.8 and significance level of 0.05 in a two-tailed study.[18]

Secondary end-points were: fall in BVAS, CRP and ANCA levels, relapse frequency between 3 and 12 months, reduction in immunosuppressive drug doses and adverse-effect rates. The χ^2 test with Yates correction was used for dichotomous variables, e.g. treatment response and relapse. BVAS scores and demography were expressed as mean and standard deviation, and compared by two-tailed Students-t-test. CRP levels were abnormally distributed, normal <10, range 1–300, and were expressed as median and range and compared by two-tailed Student's-t-test after logarithmic conversion. Differences between BVAS and CRP levels following infusion were expressed as falls in BVAS or CRP calculated by subtracting the BVAS or CRP level at the time of assessment from the level immediately prior to infusion. Data analyses were performed at entry (-2 weeks), time of infusion, 2 weeks, and 3, 6, 9 and 12 months.

Results

Of 39 patients approached to enter the study, four chose not to participate and 35 were entered. One withdrew consent before starting treatment, thus 17 were randomized to the IVIg and 17 to the placebo groups.

Demography and diagnosis

The baseline characteristics of the two groups together with details of their previous treatment are summarized in Table 1. There were no significant differences between any of the characteristics, including previous drug exposure. The diagnosis was supported by confirmatory histology in 30/34 (88%), 26 (76%) had C-ANCA and 8 (24%) P-ANCA at presentation. The distribution of disease activity at the time of trial entry is summarized in Figure 1. One patient, who met the entry criteria with vasculitis on a tissue biopsy, and was entered into the IVIg group had the diagnosis revised after the end of the study to hepatitis-C-associated cryoglobulinaemic vasculitis, but remained in the analysis.

Therapeutic response at 3 months (primary end-point)

A therapeutic response, defined as a 50% reduction in BVAS, was observed in 14/17 and 6/17 of the IVIg and placebo groups, respectively, ($p=0.015$, OR 8.56, 95%CI 1.74–42.2). Two patients in the placebo group died before 3 months, one of viral pneumonitis and one of gastrointestinal haemorrhage caused by peptic ulceration; in a censored analysis, 14/17 IVIg-treated vs. 6/15 placebo-treated patients responded to the trial medication ($p=0.035$, OR 6.1, 95%CI 1.1–50.4).

Disease activity

BVAS at the time of infusion was 6.1 (SD 1.56) and 5.4 (SD 1.8) for the IVIg and placebo groups, respectively. Following infusion, the fall in BVAS was greater in the IVIg than the placebo group when compared at 1 month (fall in BVAS of 3.2 (SD 1.9) vs. 0.87 (SD 1.6), $p<0.001$), and 3 months (fall in BVAS of 4.1 (SD 2.3) vs. 2.3 (SD 2.0, $p<0.01$) (Figure 2). There were no significant differences in BVAS after 3 months, or in the frequency of relapse, 5/16 for IVIg and 4/15 for placebo, between the two groups. Vasculitis activity demonstrated by chest radiology or white-cell scanning was present before infusion in 9/17 and 12/17 of the IVIg and placebo groups. After 3 months, active lesions were seen in 3/12 and 7/12 of the IVIg and placebo groups who underwent repeated examination. No significant

Table 1 Baseline characteristics of 34 patients with ANCA-associated systemic vasculitis according to treatment group

	IVIg ($n=17$)	Placebo ($n=17$)	Both ($n=34$)
Age (years)	57.1	50.4	53.8
SD	10.5	19.9	16.0
Range	36–74	21–79	21–79
Sex (M/F)	10/7	9/8	19/15
Diagnosis (Wegener's granulomatosis/microscopic polyangiitis)	13/4	11/6	24/10
Duration (months)	60.8	43.2	52.5
SD	51.6	46.3	50.0
Range	14–230	3–192	3–230
Number of systems involved at presentation	4.9	5.1	5.0
Cumulative prednisolone dose (g)	13.9	8.4	11.1
SD	9.6	4.8	7.8
Range	3–36.6	0–18	0–36.6
Cumulative cyclophosphamide dose (g)	30.1	46.9	38.0
SD	30.7	49.5	42.0
Range	0–99	0–180	0–180
Cumulative azathioprine dose (g)	53.2	39.5	47.0
SD	77.5	52.9	65.1
Range	0–250	0–200	0–250
Number of patients who had received other vasculitis treatments	5	7	12

changes in serum creatinine were seen during the study between the treatment limbs, apart from the reversible nephrotoxicity of IVIg (see below). Systems demonstrating the largest change, i.e. loss of disease activity, following IVIg were: constitutional 10/17, with control of arthralgia/arthritis in 9/12; ENT 6/9; lung 6/13; and neurology 5/7, all peripheral neuropathy.

During longer-term follow-up in 15 patients (median 18 months, range 13–48 months), five received open-label IVIg every 3 months as part of their remission maintenance regimen with apparent good effect.

C-reactive protein

Sequential CRP levels are shown in Figure 3. The falls in CRP (CRP at time of infusion minus CRP at follow-up time point) following infusion were higher in the IVIg group than in the placebo group: at 2 weeks, fall in CRP (median and range) 3.5 (−66 to 95) mg/l vs. −3.8 (−56 to 54) mg/l ($p<0.05$), and at 1 month, fall in CRP 4.0 (−26 to 96) mg/l vs. 0.0 (−32 to 20) mg/l ($p<0.05$). No differences between the falls in CRP levels were observed after 1 month.

ANCA and IgG levels

At the time of infusion, seven were positive for PR3-ANCA and three for MPO-ANCA. No differences were observed in PR3-ANCA or MPO-ANCA positivity after infusion between the two groups. Prior to infusion, total IgG levels were 9.9 (SD 3.4) g/l and 9.2 (SD 3.6) g/l for the IVIg and placebo groups; 2 weeks after infusion IgG levels had risen in the IVIg group to 17.7 (SD 2.6) g/l and were unchanged in the placebo group 9.4 (SD 3.3) g/l.

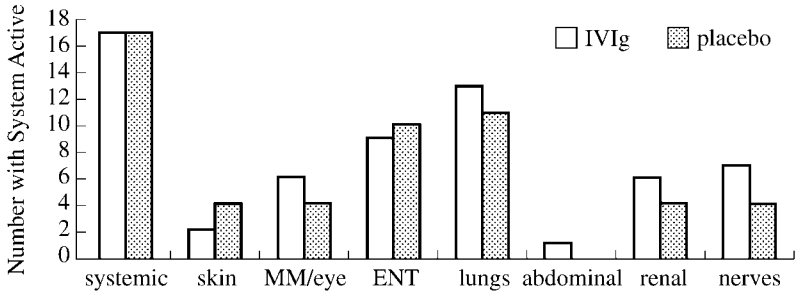

Figure 1. Distribution of system involvement, by vasculitis activity, at the time of entry. Number with activity in each system, $n=17$ for IVIg and 17 for placebo.

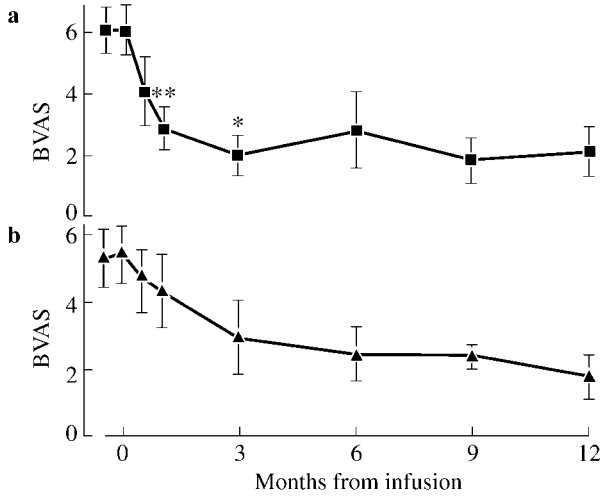

Figure 2. Sequential Birmingham Vasculitis Activity Scores (BVAS) for (**a**) ■ IVIg group and (**b**) ▲ placebo group (mean and 95%CI). A difference in the fall in BVAS following IVIg or placebo was observed at one month (**$p=0.001$) and three months (*$p=0.01$).

Immunosuppressive drugs

Daily prednisolone doses before infusion were 14.1 (SD 8.7) vs. 11.4 (SD 9.7) mg/day for the IVIg and placebo groups. At the time of infusion, 12/17 and 15/17 of the IVIg and placebo groups, respectively, were receiving continuous oral cyclophosphamide or azathioprine, daily dose 77.9 (SD 61.1) mg/day vs. 91.1 (SD 53.7) mg/day. No differences were observed for subsequent prednisolone or cytotoxic exposure between the two groups. Two from the placebo group had escalation of therapy within the first 3 months for worsening vasculitis, with re-introduction of cyclophosphamide in one and open IVIg in the other. After three months, five from the IVIg group had escalation of therapy with cyclophosphamide re-introduced in two, two received open IVIg and one monoclonal anti-T-cell therapy with CAMPATH 1-H.[10] During the same period in the placebo group, one had cyclophosphamide re-introduced, one open IVIg and one CAMPATH 1-H.

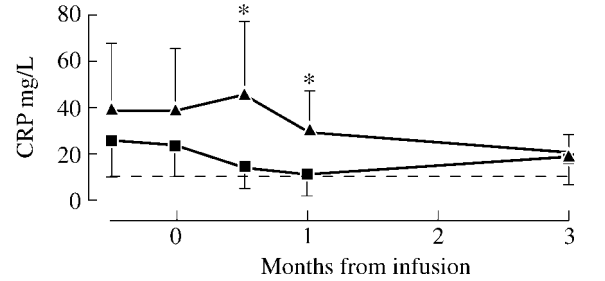

Figure 3. Sequential C-reactive protein (CRP) levels between entry and 3 months (median and 95%CI, ■ IVIg group, ▲ placebo group). A difference in the fall in CRP following IVIg or placebo was observed at 2 weeks and at 1 month (*$p<0.05$).

Adverse effects

Adverse effects were classified as mild, symptomatic treatment only, moderate, required modification of disease medication, or severe, required hospitalization. Seventeen adverse effects were seen in 12 patients from the IVIg group as compared to six adverse effects in four patients in the placebo group (Table 2). Four from the IVIg group had reversible rises in serum creatinine ranging from 31 to 422 μmol/l; all had previously impaired renal function with glomerular filtration rates under 40 ml/min. Creatinine values returned to baseline after 10–14 days. An unexplained rise in alanine transaminase occurred in one from the placebo group; subsequent hepatitis C serology was negative. Analysis of historical samples from the case re-classified as cryoglobulinaemia confirmed hepatitis C antibody positivity before IVIg infusion; this patient did not experience adverse-effects after IVIg, nor did he exhibit a therapeutic response to IVIg.

Discussion

This study has demonstrated that a single course of high-dose IVIg reduces disease activity in AASV where active vasculitis persists despite conventional therapy. The difference in clinical disease activity between the IVIg and placebo groups was present up to the analysis at 3 months. Subsequently, vasculitis activity, frequency of relapse and exposure to

Table 2 Frequency of adverse effects following infusion of trial medication according to treatment group

	IVIg ($n=17$)	Placebo ($n=17$)
Mild		
Headache	3	1
Fatigue	5	0
Rise in creatinine	1	0
Backache	1	0
Fever/chills	1	1
Rise in ALT	0	1
Polyarthralgia	0	1
Moderate		
Headache	2	0
Rise in creatinine	1	0
Severe		
Fluid overload/dyspnoea	0	2
Rise in creatinine	2	
Aseptic meningitis	1	0
Total	17	6

immunosuppression was the same in both limbs, indicating that the benefit of IVIg was not maintained beyond 3 months. Objective improvement from baseline in six patients from the placebo group could be attributed to the effect of continued immunosuppression, despite the lead-in time, or to a placebo effect, and similar effects would have contributed to the improvements in disease activity in the IVIg group. Patients entered into the study had a long disease duration, mean 52.5 months, and were selected by their poor response to standard therapy. Therapeutic responses to IVIg might be different in new patients or those with a shorter disease duration.

Adverse effects were frequent in the IVIg limb but all had subsided within 2 weeks; headaches and reversible rises in serum creatinine were a notable feature in this group. The headaches may have been related to the presence of inflammation in the head and neck in Wegener's granulomatosis. Nephrotoxicity after IVIg has been associated with previously impaired renal function, and linked to the presence of sucrose as a component of the IVIg product.[24] The IVIg used in this study contained sucrose, and rises in serum creatinine were only seen in patients with impaired renal function. However, most adverse effects were mild and did not preclude the subsequent use of open IVIg in any patient.

CRP is a useful marker of inflammation in systemic vasculitis, which is not influenced by anaemia or renal failure but elevated values can be caused by infection. CRP levels were elevated in most patients prior to infusion and greater falls were found at 2 weeks and 1 month in the IVIg-treated group.[25] Changes in CRP corresponded to changes in BVAS, and support the findings of the study which suggest that IVIg has a beneficial effect on the level of vasculitic inflammation in systemic vasculitis.

The lack of an effect of IVIg on ANCA levels, unlike reports from previous uncontrolled studies, was due in part to the small number (10/34) who had circulating ANCA detectable at the time of infusion. Many of the patients had already received substantial periods of immunosuppression likely to suppress antibody synthesis, and those who remained positive may have had titres falling on account of this prior treatment or rising as their disease was relapsing.[26]

The potential therapeutic mechanism of IVIg in vasculitis is unclear. IVIg contains antibodies which bind to the variable regions of ANCA autoantibodies and inhibit their binding to autoantigen, and IVIg inhibits ANCA-induced neutrophil activation and cytokine release *in vitro*.[12,13] IVIg has non-specific effects on cytokine release from macrophages and T-cells: in particular, it reduces TNFα and IL-1 release, which would contribute to the anti-inflammatory effects of IVIg in vasculitis.[27] As most cases here were ANCA-negative at the time of IVIg treatment, effects on cytokines, or possibly on T-cell surface receptors or complement activation may have been more important.[16,28]

Finally, further clinical studies are required to determine whether repeated courses of IVIg are also beneficial and allow reduced exposure to immunosuppressive drugs; this study would support an interval between courses of 3 months. It would also support the use of IVIg as an adjunctive treatment to immunosuppression, possibly allowing reduced steroid and cytotoxic doses, for example, in the elderly. No dose titration of IVIg in vasculitis has been performed, and multiple doses with a short time interval may be more effective than the single-dose regimen used here; also, smaller doses may be equally effective. We have addressed a subgroup of AASV with persistent disease and these results do not allow generalization to other subgroups of vasculitis, for example the use of IVIg in primary induction regimens. IVIg is expensive, and a cost-benefit argument must be satisfied should subsequent studies support its routine use.

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