

Intravenous Immunoglobulins for Relapses of Systemic Vasculitides Associated With Antineutrophil Cytoplasmic Autoantibodies

Results of a Multicenter, Prospective, Open-Label Study of Twenty-Two Patients

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Objective. To evaluate at 9 months and 24 months the safety and efficacy of intravenous immunoglobulins (IVIgs) administered for 6 months to treat relapses of Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) occurring either under treatment or during the year following discontinuation of corticosteroids and/or immunosuppressants.

Methods. Patients received IVIgs (0.5 gm/kg/day for 4 days) as additional therapy administered monthly for 6 months and were assessed every 3–6 months. Corticosteroids could be maintained or reintroduced at

the time of relapse; immunosuppressants could be continued but could not be reintroduced. At months 9 (end point) and 24 (followup), the following information was collected: complete or partial remission, relapse as assessed with the Birmingham Vasculitis Activity Score (BVAS) 2005, and tolerance and safety of IVIG therapy.

Results. Twenty-two Caucasian patients (7 men and 15 women) were studied: 19 had WG, and 3 had MPA. Their median age was 53 years (range 19–75 years), and their median duration of systemic vasculitis was 27 months (range 7–109 months). Their median BVAS 2005 score was 11 (range 3–25). At study entry, 21 patients were ANCA positive, and 21 patients were taking steroids and/or immunosuppressants. All patients experiencing relapse were treated with the same drug(s) plus IVIgs. All patients initially responded to IVIG therapy. By month 9, 13 patients had complete remission, 1 had partial remission, 7 had relapse, and 1 had treatment failure. In 8 of the 14 patients who had remission, the response persisted at month 24. Seven patients experienced minor side effects.

Conclusion. IVIgs induced complete remissions of relapsed ANCA-associated vasculitides in 13 of 22 patients at month 9. Because of the good safety and tolerance profiles of IVIgs, these agents can be included in a therapeutic strategy with other drugs used to treat relapses of WG or MPA.

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS) are small-vessel vasculitides that are frequently associ-

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ated with antineutrophil cytoplasmic autoantibodies (ANCA) (1). Corticosteroids in combination with immunosuppressants, such as oral or pulse cyclophosphamide, are universally accepted as the standard treatment for inducing remission, preventing relapses, and sometimes curing these diseases (2–4). However, when therapy is reduced gradually and/or discontinued, relapses are common and are responsible for substantially more drug-related morbidity and mortality. Although cyclophosphamide can effectively manage relapses, repeated cycles of cyclophosphamide are associated with bone marrow suppression, myelodysplasia, infection, infertility, and transitional-cell carcinoma of the bladder, which may occur years after its initial use. Therefore, alternative therapies are needed to limit these adverse events.

Results of the European Vasculitis Study (EUVAS) Trial showed that azathioprine maintenance therapy enabled the reduction of cyclophosphamide exposure without increasing the relapse rate over 18 months (2). In addition, the safety and efficacy of agents involved in the immune response, such as intravenous immunoglobulins (IVIGs), are being increasingly investigated in vasculitis patients. For decades, IVIGs have shown potent therapeutic efficacy in patients with ANCA-positive vasculitides (5–9). The effectiveness of IVIGs alone (8,9) or as concomitant therapy has been evaluated in several types of ANCA-associated vasculitides, even though its mechanism(s) of action remains poorly understood (6,7,10,11). In small prospective studies on persistent ANCA-associated vasculitides, complete or partial responses were obtained in 45–75% of the patients given IVIG alone or in combination with other drugs (8,9,11–13). Moreover, IVIGs have an excellent therapeutic/side-effects index. However, the place of IVIG in the treatment regimen of ANCA-associated vasculitides remains unclear because few trials have evaluated its indication as first- or second-line treatment. The only placebo-controlled trial in patients with persistent ANCA-associated vasculitides published to date demonstrated regression of vasculitis at 3 months after a single dose of IVIG (11).

The present study was designed to evaluate at 9 and 24 months of followup the efficacy and safety of concomitant administration of IVIGs given monthly for 6 months to patients with relapses of ANCA-associated vasculitides (WG, MPA, or CSS) occurring during therapy with corticosteroids and/or immunosuppressants or during the year following their termination.

PATIENTS AND METHODS

Study design and patient population. This multicenter, prospective, open-label study recruited patients from 20 French hospitals. The protocol was approved by the Institutional Review Board of Hôpital Pitié Salpêtrière for the Programme Hospitalier de Recherche Clinique. Study monitoring was sponsored and funded by the Assistance Publique Hôpitaux de Paris. Each patient gave written informed consent to participate in the trial.

Inclusion criteria were a previous diagnosis of WG, MPA, or CSS based on disease manifestations that met the criteria of the Chapel Hill Consensus Conference (14) and/or the American College of Rheumatology classification criteria for WG (15) or CSS (16); factor(s) of poor prognosis at the time of first diagnosis of MPA or CSS (17); vasculitis relapse occurring during treatment or during the year following treatment discontinuation; and age >18 years.

Patients were excluded for the following reasons: no treatment for >12 months; diagnosis of polyarteritis nodosa; MPA or CSS without factor(s) of poor prognosis at baseline, as defined by the Five-Factors Score (17); recent extracapillary glomerulonephritis or recent and active glomerulonephritis with renal insufficiency (serum creatinine >300 μ moles/liter, or 34 mg/dl); cancer, lymphoma, leukemia, or psychiatric disorders; age <18 years; or cutaneous vasculitis or vasculitis secondary to infectious agents.

Patients with renal involvement resulting from chronic extracapillary glomerulonephritis were eligible to participate. However, at the time of relapse, we excluded renal flares with rapid rises in serum creatinine levels for 2 reasons: immunoglobulins seemed unable to control severe renal failure and prevent renal deterioration, and immunoglobulins were inappropriate in this context because one of the side effects of high dose IVIG is impaired renal function.

All patients received IVIGs (Tegeline; Laboratoire Français du Fractionnement et des Biotechnologies, Courtaboeuf, France), which were infused at a dosage of 0.5 gm/kg/day for 4 consecutive days each month for 6 months. When relapse occurred during corticosteroid therapy, clinicians were allowed to increase the oral or pulse prednisone dosage for 8–21 days provided that the dosage was tapered within 3 weeks to the dosage the patient was taking before relapse occurred. Like other brands of IVIGs, Tegeline is derived from the blood of multiple donors. To prevent transmission of viral and prion infections, the product is prepared exclusively from selected donors who have no family history of transmissible spongiform encephalopathy (TSE) and no potential exposure to the risk of contracting iatrogenic TSE through neurosurgery, transfusion, or exposure to bovine spongiform encephalopathy-contaminated food in the UK. The isolation, purification, and preparation process consists of several steps that are able to inactivate/remove TSE infectivity, including ethanol precipitation, filtration, 35-nm nanofiltration, and sterilizing filtration.

Immunosuppressants being taken at the time of relapse had to be maintained at the same dosage during IVIG therapy and were then reduced, discontinued, or switched to a maintenance treatment if cyclophosphamide had been given. For patients who were off treatment at the time of relapse and study inclusion, short-term steroids were prescribed as described above, but no immunosuppressants were prescribed.

The steroid dosage was freely decided by the treating physician according to the disease severity, with the objective of returning the dosage to the pre-relapse levels within 3 weeks or to the minimal effective dosage. In addition, cotrimoxazole as prophylaxis against *Pneumocystis jiroveci* pneumonia was mandatory in patients with CD4 cell counts $<200/\text{mm}^3$, as well as in patients with WG to prevent relapse (18).

Clinical assessments. Patients' medical records were reviewed at study entry (maximum of 5 days before the first IVIG infusion), at the time of infusion, monthly during the 6-month IVIG treatment period, and at months 9, 12, 15, 18, and 24 of followup. The following items were recorded on a preestablished report form: clinical symptoms; current therapy; C-reactive protein (CRP) level; serum creatinine level; glomerular filtration rate; Karnofsky Index of performance/function; liver function test results; hemoglobin value; white blood cell, neutrophil, lymphocyte, and platelet counts; hematuria, proteinuria; results of ANCA testing; and adverse effects secondary to IVIG infusion. All patients were tested for human immunodeficiency virus and hepatitis B and C viruses.

The Birmingham Vasculitis Activity Score (BVAS) 2005, which was adapted from BVAS 2 (19,20), was used to specifically evaluate vasculitis activity. This clinical index is based on symptoms and signs in 10 categories (systemic signs; skin; mucous membranes and eyes; ear, nose, and throat; chest; heart and vessels; gastrointestinal tract; kidney; nervous system; and others) divided into 60 predefined items. Each item is weighted (range 1–9), and an item is scored if the investigator thinks it is present and caused by active vasculitis. Higher scores indicate more active disease. For low-grade grumbling disease, but not new/worse signs, the BVAS 2005 was scored as persistent disease.

Complete remission was defined as the disappearance of clinical and biologic signs of vasculitis, as reflected by a BVAS 2005 score of zero. Partial remission was defined as attenuation of clinical and biologic symptoms that were present at the time of relapse, as reflected by $\geq 50\%$ decrease in the BVAS 2005 score obtained at study entry. Vasculitis sequelae (lasting >3 months) could be present at the time of evaluation and were not recorded as symptoms of disease activity, but as persistent damage (e.g., persistent proteinuria associated with the disappearance of hematuria, a stable serum creatinine level above the normal range, or persistent sinusitis). Worsening of symptoms was considered to represent relapse when new symptoms appeared after an initial complete remission or partial remission. Treatment failure was recorded when there were new symptoms or further deterioration of vasculitis symptoms that were present at trial entry.

The Medical Outcomes Study Short Form 36 (SF-36) health survey was completed at each assessment (21,22). The SF-36 evaluates 8 dimensions of health status (general and mental health, physical and social functioning, physical and emotional role, pain, and vitality), and it can be condensed into 2 scores, a physical component summary and a mental component summary. Scores for each dimension/summary range from 0 (worst) to 100 (best). A 5-point difference in the SF-36 score is considered clinically and socially relevant (23). Adverse events were graded according to predefined World Health Organization criteria as mild, moderate, severe, or life-threatening.

Statistical analysis. Our working hypothesis was that monthly administration of concomitant high-dose IVIG as an immunomodulatory agent would attenuate disease activity during relapses of ANCA-associated vasculitides. Given the exploratory nature of this study, we aimed at including 40 patients, with an intermediate analysis based on 20. End points were the numbers of complete remissions and partial remissions and the safety and efficacy of IVIGs. The objective was to have at least 20% of patients with complete remission or 50% of patients with partial remission at month 9 of followup. If this goal was reached at the time of the intermediate analysis corresponding to 20 patients included in the study, the inclusion of additional patients would be stopped.

Quantitative values are expressed as the mean \pm SD or as the median and range. Qualitative values are given as the number and percentage. Data were collected at the time of infusion, then monthly for 6 months, at month 9 (time of the intermediate statistical analysis), and at each followup visit thereafter (at months 12, 15, 18 and 24). Data were analyzed with the StatView program (1992–1998; SAS Institute, Cary, NC).

RESULTS

Characteristics of the patients at study entry.

Twenty-four Caucasian patients were screened, and 22 of them (7 men and 15 women) fulfilled the inclusion criteria: 19 had WG and 3 had MPA. Table 1 shows the patients' characteristics at study inclusion, by type of vasculitis. The median age of the 22 patients was 53 years (range 19–75 years), and the median duration of their vasculitis symptoms before study inclusion was 27 months (range 7–109 months). Thirteen patients had been smokers, and 6 had various allergies. The median BVAS 2005 score at study entry was 11 (range 3–25).

Before relapse of the vasculitis (prior to study inclusion), the median prednisone dosage was 4 mg/day (range 0–10). At study inclusion, corresponding to the first infusion of IVIG as concomitant therapy, 21 of the 22 patients were taking corticosteroids (dosage range 5–60 mg/day of prednisone in 19 patients and/or 1.2 mg/kg/day to a maximum dosage of 1 gm/day of pulse methylprednisolone in 6 patients) and/or immunosuppressants. One patient received a single pulse of corticosteroids at the time of the first IVIG infusion and then received IVIGs alone. Patients were taking the following immunosuppressants: cyclophosphamide in 7 (intravenous in 5 and oral in 2), azathioprine in 7, methotrexate in 3, and mycophenolate mofetil in 1. Cotrimoxazole had been prescribed for 12 WG patients to prevent relapse (800/160 mg of trimethoprim/sulfamethoxazole) (18) and for 1 MPA patient with severe lymphopenia to prevent *Pneumocystis jiroveci* pneumonia (400/80 mg of trimethoprim/sulfamethoxazole). Cotrimoxazole was started before relapse occurred and before study inclusion.

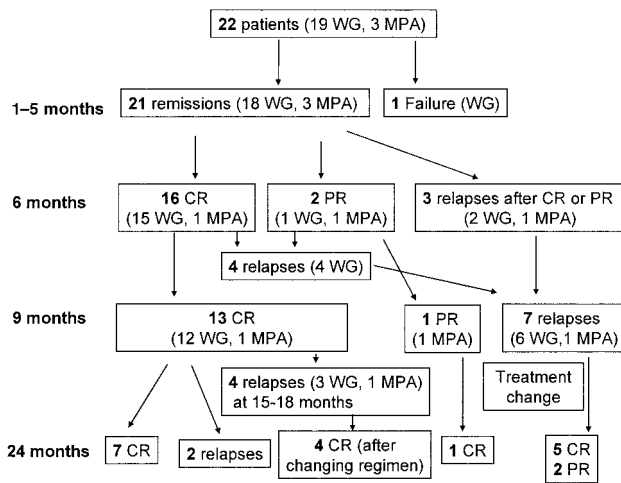


Figure 1. Outcomes throughout 24 months of followup in patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides treated with intravenous immunoglobulins (IVIG) as additional therapy. Twenty-two patients with ANCA-associated vasculitis, consisting of either Wegener’s granulomatosis (WG) or microscopic polyangiitis (MPA), were treated for 6 months with monthly infusions of IVIGs. Assessments were performed at 6 months, 9 months (study end point; 3 months after cessation of IVIG infusions), and 24 months, and determinations of complete remission (CR) or partial remission (PR) were then made.

All but 1 of the patients were ANCA-positive by indirect immunofluorescence analysis at the time of vasculitis diagnosis and relapse: 2 had perinuclear ANCA, 18 had cytoplasmic ANCA, and 1 had ANCA of undetermined pattern. Enzyme-linked immunosorbent assay showed that the ANCA were myeloperoxidase-specific in 3 patients, proteinase 3-specific in 16 patients, and of undetermined specificity in 2 patients. All patients were seronegative for human immunodeficiency virus (HIV) and hepatitis B and C viruses. Five patients had antibodies to hepatitis B surface antigen as a consequence of vaccination. All patients with granulomatous ear/nose/throat lesions also had generalized symptoms.

Outcomes. Clinical outcomes in the 22 study patients at months 6, 9, and 24 of followup are shown in Figure 1.

Initial responses (0–6 months). One WG patient developed renal insufficiency after the first IVIG infusion and was considered to have failed therapy. Twenty-one patients achieved remission between month 1 and month 5. After 6 months of IVIG therapy, complete remission occurred in 16 of the 22 patients (72.7%; 15 with WG and 1 with MPA), partial remission occurred in 2 patients, and relapse occurred in 3.

Subsequent course (6–24 months). At the study end point at month 9, complete remission persisted in 13 of the 16 patients who were in complete remission at month 6. Seventeen of the 22 study patients (77.3%) were in complete remission at month 24, and 2 patients were still in partial remission. Between months 5 and 9 of followup, 7 patients experienced a relapse despite their initial responses to IVIGs (5 had complete remission and 2 had partial remission initially). Their therapy was modified at the discretion of the treating physician, and 5 achieved complete remission and 2 achieved partial remission by the end of the study.

For the 13 patients in complete remission at month 9, the steroid dosage could be reduced in 9 of them and stopped in 4 of them. Moreover, dosages of immunosuppressants were lowered in 4 other patients. One patient received a corticosteroid pulse only with the first IVIG infusion (at the time of relapse and therefore entry into the study); thereafter, no oral drugs were combined with IVIGs in this patient. His complete remission was maintained until month 18 of followup, when he experienced a relapse.

Monthly IVIG therapy was reintroduced in 3 WG patients who were in complete remission at month 9. The first patient relapsed at 10 months, and the treatment regimen was intensified with the use of corticosteroids and various immunosuppressants, but there was no clinical benefit. The second patient had vasculitis that was refractory to conventional therapy. Monthly IVIG infusions were reintroduced in this patient, and a new complete remission was obtained until the end of followup. The third patient was in sustained complete remission as of the fourth IVIG infusion; IVIGs were continued after the 6 planned cycles because of severe hypogammaglobulinemia, but the dosage was lowered to 1 gm/kg/day administered for 2 days each month.

Corticosteroid dosage. In the entire group of study patients, the median oral prednisone dosage prescribed at study inclusion was 20 mg/day (range 5–1,000), corresponding to the highest dosage during followup, and was given in combination with pulse methylprednisolone (n = 6 patients) at that time. During followup, the median oral prednisone dosage was decreased to 15 mg/day (range 0–60) by the second IVIG infusion (4 weeks), 10 mg/day (range 0–70) by month 9, and 10 mg/day (range 0–17) by month 24.

In patients who achieved complete or partial remission, the median oral prednisone dosage at study inclusion was 20 mg/day (range 5–500), corresponding to the highest dosage during followup. This dosage was gradually lowered during followup, to a median of 15

Table 1. Characteristics of patients with Wegener's granulomatosis (WG) or microscopic polyangiitis (MPA) at study inclusion

	WG patients (n = 19)	MPA patients (n = 3)
Age, years		
Median	56	50
Range	19–75	48–52
Sex, no. (%) female	12 (63.2)	3 (100)
Weight, kg		
Median	71	60
Range	47–90	59–65
Karnofsky Index		
Median	80	80
Range	70–100	80–90
Duration of vasculitis since first symptoms, months		
Median	27	15
Range	7–109	11–19
No. of relapses before study inclusion		
Median	1	1
Range	1–3	1–2
Renal involvement, no. (%)	9 (47.4)	3 (100)
Ear, nose, and throat involvement, no. (%)	15 (79)	1 (33)
Lung involvement, no. (%)	8 (42.1)	3 (100)
Birmingham Vasculitis Activity Score 2005		
Median	10	15
Range	3–25	11–19
Glomerular filtration rate, ml/minute		
Median	78	62
Range	28–146	40–68
C-reactive protein, mg/liter		
Median	8	5
Range	3–115	1–8
Leukocyte counts, gm/liter		
Median	8,000	6,300
Range	3,100–17,100	5,100–7,800
Lymphocyte counts, gm/liter		
Median	960	1,156
Range	40–3,127	680–1,300
Hemoglobin, gm/dl		
Median	11.8	11.8
Range	10.1–15.1	10.4–12.7
Platelet count, gm/liter		
Median	273,000	310,000
Range	94,000–667,000	274,000–430,000

mg/day (range 0–30) by the second IVIG infusion, 8 mg/day (range 0–12) by month 9, and 3.25 mg/day (range 0–10) by month 24.

No difference in response rates according to the different organ manifestations was observed. Because IVIGs were able to induce complete remission in 13 of the 22 patients (59.1% [95% confidence interval 0.39–0.79]) and partial remission in 1 patient (4.5%) by month 9, the objective of the study had been reached at the intermediate analysis, and study inclusions were therefore stopped according to the study protocol.

BVAS 2005 and SF-36 scores. As shown in Figure 2, the median BVAS 2005 score dropped from 11 (range

3–25) at study inclusion to 0 (range 0–13) at month 9 and 0 (range 0–12) at month 24.

The mean physical component summary score on the SF-36 remained unchanged during followup, with a mean \pm SD of 39.11 ± 8.51 at study inclusion, 42.02 ± 11.74 at month 9, and 39.94 ± 8.45 at month 24. The mental component summary score on the SF-36 improved from study entry to month 9 and then remained stable until month 24, with mean \pm SD values of 37.12 ± 11.67 , 43.27 ± 10.00 , and 43.82 ± 9.91 , respectively. Compared with the values at study inclusion, some scores were markedly improved at month 9: physical role improved from a mean score of 26.25 to a score of 61.36,

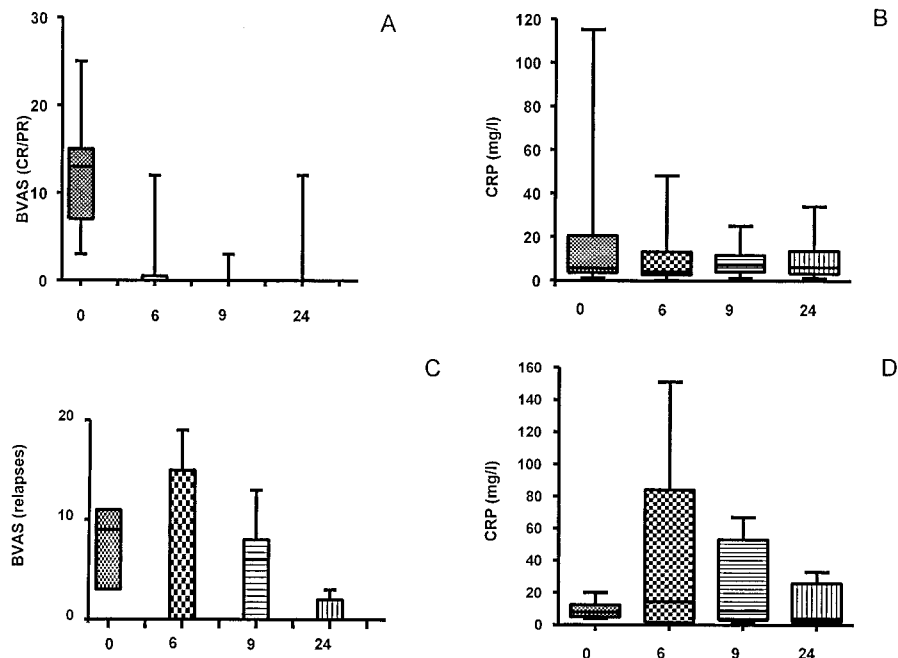


Figure 2. Changes in the Birmingham Vasculitis Activity Score (BVAS) 2003 (A and C) and the C-reactive protein level (B and D) in patients with Wegener's granulomatosis and microscopic polyangiitis in whom complete remission (CA) or partial remission (PR) (A and B) or relapse (C and D) occurred after or during 6 months of intravenous immunoglobulin infusions added to their existing therapy. Data are presented as box plots. Boxes represent the 25th and 75th percentiles, lines within the boxes represent the median, and lines outside the boxes represent the range.

pain improved from 47.05 to 63.50, emotional role improved from 35.00 to 63.64, social functioning improved from 51.88 to 62.50, vitality improved from 38.00 to 53.75, and health transition improved from 51.25 to 58.33. No relationship was found between the BVAS 2005 scores at study inclusion and the scores for the quality-of-life components.

Safety and adverse events. One patient developed renal insufficiency after the first IVIG infusion (considered to have failed therapy). This was recorded as a serious adverse event. Moderate and transient adverse effects of IVIG treatment were reported in 7 of the 22 patients (31.8%): 1 patient experienced nausea and/or vomiting at each infusion, 1 patient experienced nausea only during the first infusion, and 5 patients had headaches after the first infusion, which was associated with fever at only the first infusion in 1 of them, with arthralgias at only infusion 4 in 1 of them, and with influenza-like symptoms at only infusion 2 in 1 of them. No severe or life-threatening events were reported.

IVIG therapy was maintained in all patients who experienced an adverse event, and the infusion flow rate was adapted to the individual patient's tolerance level.

Three infections developed in 2 patients during followup. One patient developed a staphylococcal infection in the arteriovenous fistula without septicemia. The other patient developed Kaposi's sarcoma, which was related to prior immunosuppressive therapy, and a urinary tract infection identified as *Escherichia coli*.

Evolution of ANCA. Among the 13 patients who were in complete remission at month 9 of study, 5 were negative for ANCA during followup (months 9–18), 6 were positive for ANCA, and data were missing for the other 2 patients. After 24 months of followup, 4 of the 9 patients who were in complete or partial remission and underwent ANCA determinations at this time were ANCA-positive. The patient who was in partial remission at month 9 remained ANCA-positive during followup. Among the 7 patients who were experiencing a relapse at month 9 of study, 2 remained ANCA-positive,

3 were ANCA-negative since month 2, and 1 was ANCA-negative at month 2 but became ANCA-positive during followup.

DISCUSSION

Conventional treatment of ANCA-associated vasculitides consists of corticosteroids, usually in combination with immunosuppressants. Maintenance therapy typically consists of azathioprine or methotrexate, which is prescribed for at least 12–18 months (2,24,25). Despite optimal treatment regimens, relapses occur in ~50% of WG patients and in <50% of MPA patients after 5 years of followup (2–4,25–29). Depending on the maintenance agent prescribed, relapses have been reported in 33–52% of patients given azathioprine, methotrexate, leflunomide, or mycophenolate mofetil (30–34); hence, no single drug seems to be better than the others.

IVIGs are prepared from normal human IgG obtained from pooled blood samples from >1,000 healthy blood donors, and they exert their immunomodulatory effects on a wide range of autoimmune and/or systemic inflammatory diseases. IVIGs have been shown to be effective in the treatment of Kawasaki disease (35) and to prevent the development of coronary aneurysms. They appear to be effective against ANCA-associated vasculitides (6–8). The efficacy of IVIGs prescribed alone (8,9) or as concomitant therapy has been evaluated in several types of ANCA-associated vasculitides (2,10,36,37). Treatment with IVIGs alone or in combination with other drugs achieved responses in 45–75% of patients with persistent ANCA-associated vasculitides included in small prospective studies (8,11–13).

The results of a placebo-controlled trial of IVIGs in patients with relapsing ANCA-positive vasculitides demonstrated better control of the vasculitis with IVIGs after standard therapy (11). That study was designed to investigate the efficacy of a single course of IVIGs (2 gm/kg) administered to previously treated patients with persistent disease activity in whom intensification of therapy was needed. Seventeen patients were randomized to receive IVIGs and 17 to receive placebo and were followed up for 12 months: 14 of the 17 patients given IVIGs and 6 of the 17 given placebo responded to treatment (11). That study opened the way for the use of IVIGs according to a single course of infusions protocol (2 gm/day for 4 days) and showed reduced disease activity for 3 months (11), which is consistent with the short half-life of IVIGs.

The results of our study confirm previously pub-

lished results, with 59.1% of the patients experiencing complete remission, 4.5% experiencing treatment failure, and 31.8% experiencing relapse at month 9 of followup. Therapy with IVIGs added to conventional treatments was able to induce remission in patients who were already being treated and to facilitate a reduction in the dosages of steroids and/or immunosuppressants. An increased steroid dosage was permitted for 3 weeks to “kick-start” a response in our patients, all of whom were experiencing relapse of their vasculitis at study entry. The strategy of briefly increasing the steroid dosage was to obtain rapid control of the disease while waiting for the effects of the IVIGs to begin, with the requirement that the steroid dosages be returned to the pre-relapse or minimal effective dosage within 3 weeks. We believe that the long-term results of IVIG treatment were not attributable to the limited and temporary increase in the steroid dosage. Followup of our study patients continued for 24 months, whereas in the placebo-controlled study (11), followup continued for 12 months. Although in several open-label studies, followup continued for 4 weeks to 5 years, too few patients were included to draw definitive conclusions about the results (8,11–13).

Our study is the first multicenter, prospective, open-label trial designed to evaluate the long-term effects of 6 courses of IVIG therapy in patients with ANCA-associated vasculitides. IVIGs have a place in the therapeutic approach to relapsing or refractory ANCA-associated vasculitides, but there were no previously published data concerning the persistence of the positive effect of IVIGs as additional therapy. Our study excluded patients with active crescentic glomerulonephritis, which requires other treatments, such as high-dose steroids, cyclophosphamide, and sometimes plasma exchanges. However, patients with preexisting glomerulonephritis that was controlled at the time of study entry were included in the trial.

The safety profile of IVIGs was good, with only moderate and transient adverse reactions and a positive impact on the quality-of-life scores, as assessed with the SF-36 health survey. Side effects of IVIG therapy in patients with various autoimmune diseases as well as vasculitides have been reported to occur in 0–36% of patients; most were mild, transient, and completely reversible (5,8,36,38–40). These values are consistent with the 31.8% rate of moderate side effects observed in our patients. Our patients were tested serologically for antibodies to HIV, hepatitis C virus, and hepatitis B surface antigen, none of which were detected. One patient developed renal insufficiency after the first IVIG

infusion, with rapid deterioration. Because of the presence of microscopic hematuria and proteinuria, we believe this was probably glomerulonephritis and was not caused by IVIG; however, it was recorded as a serious adverse event of IVIG therapy, since the treatment was considered to have played a partial role in the renal function impairment.

To date, no cases of variant Creutzfeldt-Jakob disease related to a plasma-derived product have been reported, and the risk of transmission by these products is considered to be very low. Indeed, specific precautionary measures in the preparation of plasma-derived products have been adopted in France to prevent this risk. The IVIG preparation used in the present study was subjected to these precautionary measures in order to prevent the transmission of viral and prion infections, and the donors had no family history of TSE and no potential exposure to the risk of contracting iatrogenic TSE through neurosurgery, transfusion, or exposure to bovine spongiform encephalopathy-contaminated food in the UK.

The good safety and tolerance profiles of IVIG could place them in the potential key role as the treatment of choice for ANCA-associated vasculitides. Unlike in other studies, we chose 9 months as the study end point because we wanted to evaluate responses to IVIGs not only immediately postinfusion, but also at 3 months after treatment cessation (i.e., 9 months after initial infusion) as well as later (at 12 and 24 months) in order to assess their long-term impact, if any. Because IVIGs are an uncommon and expensive treatment, their widespread use is a concern. For this reason, we recommend treatment with IVIG infusions only in patients with refractory and/or relapsed ANCA-associated systemic vasculitides, which represents only a limited number of patients.

Different mechanisms of action have been proposed to explain the beneficial effects of IVIGs on autoimmune diseases, including modulation of Fc γ receptor expression on leukocytes and endothelial cells, interaction with complement proteins, modulation of the synthesis and release of cytokines and chemokines, modulation of cell proliferation and apoptosis, remyelination, neutralization of circulating antibodies, selection of immune repertoires, and interaction with other cell surface molecules expressed on lymphocytes and monocytes (41). However, the pathogenesis of ANCA-positive systemic vasculitides is not completely understood. In vitro, anti-proteinase 3-specific ANCA are able to activate murine and human neutrophils primed by tumor necrosis factor α and contribute to the formation of

vasculitic lesions. It is pertinent that the ability of IVIGs to produce lasting disease remissions has been associated with decreased ANCA levels (6). Such mechanisms could be at work in the positive effects observed in our patients; however, antiidiotype antibodies to ANCA were not monitored. The evolution of ANCAs in our patients showed that the clinical response was not associated with the appearance or disappearance of ANCAs. Some patients who were in complete or partial remission became ANCA-negative, but some remained ANCA-positive.

Our findings confirm that IVIGs are a safe, well-tolerated, and effective concomitant treatment for relapses of WG and MPA. We believe that because of these qualities, IVIGs should be included in the therapeutic approach to ANCA-associated systemic vasculitides. Our observations also indicate that relapses were frequent after stopping IVIG infusions, suggesting that they can temporarily hold the disease at bay, but maintenance therapy remains necessary after IVIGs are discontinued or IVIGs should be continued over the long-term. Prospective studies are needed to evaluate the indication(s) of IVIGs for use as steroid-sparing and immunosuppressant-sparing therapy, which was only partially demonstrated in our studies. Because relapses frequently occur in patients with WG and MPA, other prospective trials are warranted to determine the optimal duration of IVIG administration and their use in place of, or in addition to, steroids and immunosuppressants.

AUTHOR CONTRIBUTIONS

Dr. Guillevin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Pagnoux, Mouthon, Guillevin.

Acquisition of data. Martinez, Cohen, Pagnoux, Mahr, Mouthon, Delaunay, Sadoun, Guillevin.

Analysis and interpretation of data. Martinez, Vinzio, Sadoun, Guillevin.

Manuscript preparation. Martinez, Mouthon, Sailler, Guillevin.

Statistical analysis. Martinez, Vinzio, Mahr, Guillevin.

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APPENDIX A: THE FRENCH VASCULITIS STUDY GROUP

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