

Treatment of Giant Cell Arteritis Using Induction Therapy With High-Dose Glucocorticoids

A Double-Blind, Placebo-Controlled, Randomized Prospective Clinical Trial

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Objective. Glucocorticoid (GC) therapy for giant cell arteritis (GCA) is effective but requires prolonged administration, resulting in adverse side effects. The goal of the current study was to test the hypothesis that induction treatment with high-dose pulse intravenous (IV) methylprednisolone permits a shorter course of therapy.

Methods. Twenty-seven patients with biopsy-proven GCA were enrolled in a randomized, double-blind, placebo-controlled study to receive IV methylprednisolone (15 mg/kg of ideal body weight/day) or IV saline for 3 consecutive days. All patients were started on 40 mg/day prednisone and followed the same tapering schedule as long as disease activity was controlled. The numbers of patients with disease in remission after 36, 52, and 78 weeks of treatment and taking ≤ 5 mg/day prednisone were compared. Cumulative prednisone dose, number of relapses, and development of adverse GC effects were assessed.

Results. Ten of the 14 IV GC-treated patients, but only 2 of 13 control patients, were taking ≤ 5 mg/day

prednisone at 36 weeks ($P = 0.003$). This difference was maintained; there was a higher number of sustained remissions after discontinuation of treatment in the IV GC-treated group and a lower median daily dose of prednisone at 78 weeks ($P = 0.0004$). The median cumulative dose of oral prednisone, excluding the IV GC dose, was 5,636 mg in the IV GC-treated group compared with 7,860 mg in the IV saline-treated group ($P = 0.001$).

Conclusion. Initial treatment of GCA with IV GC pulses allowed for more rapid tapering of oral GCs and had long-term benefits, with a higher frequency of patients experiencing sustained remission of their disease after discontinuation of treatment.

In many populations, giant cell arteritis (GCA) is the most common form of vasculitis, especially in persons over the age of 50 years (1,2). The distribution of arterial inflammation is most prominent in the thoracic aorta and its primary and secondary branches (1,2). GCA may lead to serious outcomes, including loss of vision, ischemia of the extremities, stroke, aortic aneurysm, and death (1–8). High-dose glucocorticoid (GC) treatment effectively suppresses the systemic inflammatory processes of GCA and halts the progression of clinical symptoms (1,2). However, GCs must be given for 1–2 years or longer, and as a result, most patients develop GC-related complications that cause important morbidity and disability (9,10). Reliable GC-sparing drugs have not yet been identified (11–15).

Although many symptoms related to GCA start to improve within hours or days after starting GC treatment, the vascular inflammation appears to persist for an indeterminate time despite the use of these

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agents. Temporal artery biopsies and examination of other vessels after weeks of GC therapy show continued histologic arteritis (16,17). Studies in human temporal artery–mouse chimeras have confirmed the persistence of the vasculitis over several weeks even with “conventional” doses of GCs (18). In these experiments, SCID mice were engrafted with inflamed temporal arteries from patients with GCA and then treated with systemic GCs. Complete suppression of the transplanted vasculitis was possible but required GC doses up to 4–40 times higher than those used as standard therapy for GCA in human patients (18). These data suggest that the usual doses of GCs given to patients induce a rapid remission of the systemic inflammatory response, even though the local arteritis persists for a greater duration. Prolonged GC therapy is thus required while the disease runs its course for 1–2 years or more (9).

The purpose of this study was to determine whether induction treatment with high-dose pulse intravenous (IV) methylprednisolone suppresses the inflammatory processes of GCA more effectively than the usual oral therapy, thereby allowing for more rapid tapering of oral GC doses and, consequently, a smaller total dose of GCs and fewer side effects. The effect of IV GCs was assessed by comparing patients given IV GC pulses with those given saline injections for the rate of successful oral prednisone tapering without causing relapses.

PATIENTS AND METHODS

Patients. Inclusion criteria. The diagnosis of GCA was based on characteristic clinical findings and was confirmed by temporal artery biopsy (19). All consecutive newly diagnosed patients who had a positive biopsy result and met eligibility criteria were offered enrollment. The protocol was approved by the Mayo Clinic Rheumatology Research Committee and the Mayo Foundation Institutional Review Board. Written informed consent was obtained from all patients who participated.

Exclusion criteria. Patients with GCA who fulfilled any of the following criteria at the time of enrollment were excluded from the study: those taking GC therapy at doses equivalent to >10 mg/day of prednisone for >10 days prior to enrollment; patients with chronic inflammatory diseases other than GCA that are associated with an acute-phase response; patients with evidence of active systemic infection, poorly controlled diabetes mellitus, coronary artery disease with angina, and congestive heart failure; patients with recent vision loss, amaurosis fugax, or transient ischemic attacks; and patients unable to return for regular followup.

Study design. This was a double-blind, placebo-controlled, randomized prospective clinical trial. Once eligibility was determined and informed consent was obtained, each patient was randomly assigned to 1 of the 2 treatment arms of

the study after being stratified by sex, with blocks of 8 within each sex. Patient confidentiality was protected by the use of coded identifiers. Patients were seen every 4 weeks during the first year of therapy.

Patient assessment. Clinical and laboratory assessments were done at the start of the therapy, at 4-week intervals in the first year of treatment, at 2–3-month intervals in the second year, and at 3–6-month intervals in the third year or until the conclusion of the followup visits. Each patient assessment was done without reference to previous assessments.

A history was obtained and a physical examination was performed at the beginning of the study and during each visit thereafter. Particular attention was paid to possible signs and symptoms of GCA and polymyalgia rheumatica (PMR), such as headaches, scalp tenderness, fever, and musculoskeletal pains. Examination included auscultation of the heart and lungs and of the cervical, subclavian, axillary, and brachial areas for possible bruits, as well as palpation of the scalp for tenderness of temporal arteries or pulse abnormalities. Bilateral upper extremity blood pressures were monitored at each visit. The presence of signs or symptoms of GCA or PMR, with or without abnormalities in laboratory parameters, indicated GCA disease activity and required adjustments of the GC dose.

Treatment. Enrolled patients were randomly assigned to receive either pulse IV methylprednisolone (15 mg/kg of ideal body weight/day; equivalent to ~1,000 mg/day for an average 70-kg patient) or IV normal saline (as placebo) once a day for days 1, 2, and 3 of treatment. All patients also received oral prednisone daily from the first day of enrollment. Patients continued to take their regular medication, and no additional medications for the treatment of GCA were used (in particular, no other immunosuppressive agents, no additional methylprednisolone pulses during followup, and no aspirin).

The intravenous GC or placebo was administered uniformly in the Mayo General Clinical Research Center by the nursing staff. The physician who did the followup assessment was not involved in the administration of the medication, ensuring that he/she was completely blinded.

All patients were started on a single oral dose of 40 mg/day prednisone administered each morning. The dosage was reduced successively every 2 weeks as follows, if disease was controlled: 30 mg/day, 20 mg/day, 17.5 mg/day, 15 mg/day, 12.5 mg/day, and 10 mg/day. Below 10 mg/day, the dosage was reduced by 1 mg/day every 2 weeks. This treatment schedule, which is less intensive than the conventional treatment, both in terms of the daily prednisone dosages and in terms of the prednisone tapering, was chosen to avoid overtreatment and to be sensitive to treatment differences in the 2 treatment arms.

At the time of the first followup visit, which occurred 4 weeks after the initiation of therapy, a 50% reduction in the elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) level and the absence of clinically active disease were considered sufficient grounds for continuing with the reduction schedule. At all subsequent visits, the patient's disease had to remain in remission for prednisone to be further tapered. Remission was defined as the absence of clinical symptoms and normal values for the ESR and CRP.

Relapse of GCA was defined as the return of signs or symptoms and/or an increase in either the ESR or CRP level to

above normal after a reduction of the prednisone dosage, followed by the improvement of these signs or symptoms and/or laboratory parameters when the GC dosage was increased. When disease activity continued or relapsed, the dosage of prednisone was increased by 10 mg if the patient was taking ≥ 25 mg/day and by 5 mg if the patient was taking < 25 mg/day. Once administered, the new dosage was maintained for 2 weeks before it was again tapered per the scheduled protocol.

Recurrence was defined as the return of signs and/or symptoms and/or changes in laboratory parameters in a patient with GCA who had not been receiving GC therapy for at least 1 month. Treatment of recurrence was individualized and based on clinical presentation and laboratory findings, and reinitiation of moderate-dose prednisone and further tapering were left to the discretion of the treating physician.

Adverse effects of GCs. Adverse cardiovascular (hypertension, hyperlipidemia), musculoskeletal (steroid myopathy, osteoporosis, vertebral compression fractures, hip fractures, and aseptic necrosis of femoral and humeral heads), gastrointestinal (peptic ulcer disease, upper gastrointestinal bleed), endocrine (Cushingoid habitus, glucose intolerance, and exacerbation of diabetes mellitus), ophthalmic (cataracts, glaucoma), and other effects (increased risks of infections) were recorded during the study. A bone density measurement and a lipid profile were obtained at enrollment and at defined time intervals.

Osteoporosis preventive measures. All patients received calcium (1,200–1,500 mg) and vitamin D (400–800 IU) supplements daily. Therapy with bisphosphonates was initiated depending on bone densitometry findings.

Primary and secondary outcome measures. The primary outcome measure was met if a patient was taking ≤ 5 mg/day of oral prednisone 36 weeks after the initiation of GC therapy. Because this outcome variable is critically influenced by the diagnosis of a flare and this assessment is, at least in part, subjective, each patient was followed up by the same physician whenever possible, and this physician was not involved in the administration of the IV drug. If there was potential uncertainty in the diagnosis of a flare, a second physician was consulted. Secondary outcome measures included the percentages of patients taking ≤ 5 mg/day prednisone at 52 weeks and 78 weeks of therapy, the median daily dose of prednisone in the 2 groups, the total cumulative prednisone dose, the number of relapses, and the number of treatment-related adverse events at the conclusion of the study.

Statistical analysis. Sample size and power considerations for the primary outcome, remission at 36 weeks, were based on the comparison of 2 proportions. A sample size of 14 in each treatment group provided 80% statistical power to detect a difference of $\sim 50\%$ if the IV GC group's 36-week remission rate was between 50% and 90% (2-sided chi-square test with continuity correction and a significance level of 0.05). Baseline characteristics of the IV GC-treated and placebo-treated participants were compared with a *t*-test for continuous variables and with chi-square or Fisher's exact test for proportions. Remission rates and the median daily dose of prednisone at 36, 52, and 78 weeks were compared with chi-square or Fisher's exact test and the Wilcoxon rank sum test, respectively. Relapse rates per 100 person-months of followup were estimated and compared using exact methods based on the

Poisson distribution. Repeated-measures analyses using mixed linear models were performed for the ESR, CRP level, and hemoglobin value using SAS Proc Mixed, version 8 (SAS Institute, Cary, NC), thereby providing separate estimates of the means by time on study and intervention group. A compound symmetry variance-covariance form in repeated measurements was assumed for each outcome, and robust estimates of the standard errors of parameters were used to do statistical tests and construct 95% confidence intervals (95% CIs). Because the data for the ESR and CRP level were skewed to the right, a natural log transformation was performed prior to analysis. The model-based means are unbiased with unbalanced and missing data so long as the missing data are noninformative (missing at random). Statistical tests were 2 sided. *P* values less than 0.05 were considered significant.

RESULTS

Study population. Twenty-seven patients were enrolled in the study. There were 19 women and 8 men, with a mean age of 74 years on the entry date (range 57–89 years). Fourteen patients were randomly assigned to receive the 3-day course of IV methylprednisolone pulses in addition to the oral prednisone; 13 were randomly assigned to the placebo arm to receive normal saline infusions plus oral prednisone. In all patients, GCA was newly diagnosed, and the diagnosis was confirmed by biopsy. Six patients in the treatment group and 6 patients in the control group had received > 10 mg/day prednisone for at most 10 days prior to enrollment for their GCA-related symptoms. All other patients had not received prior treatment. The clinical findings and initial laboratory values in the 2 study groups at the initiation of treatment are shown in Table 1. The mean ages at diagnosis and the clinical features were typical of patients with GCA. There were no significant differences between the groups in terms of demographic data or clinical presentations.

Our study design used a less-immunosuppressive treatment algorithm of oral prednisone, and we therefore decided to exclude patients with GCA-related vision loss, amaurosis fugax, and cerebrovascular accidents for safety reasons. However, no patient had to be excluded because of these criteria during the enrollment period. The high frequency of patients with jaw claudication, both in the control group and in the treatment group, indicated that we did not select for patients with less severe GCA, but that we included a representative spectrum of GCA patients. All patients were followed up for at least 52 weeks. All but 1 patient in each group were followed up for 78 weeks.

Treatment effect of GC induction therapy. All patients in both groups improved after the initiation of

Table 1. Clinical findings in the methylprednisolone- and saline-treated patient groups at the initiation of therapy*

	Placebo group (n = 13)	IV GC group (n = 14)	P
Age, mean (range) years	71.4 (57–81)	75.9 (67–89)	0.11
No. of women/no. of men	9/4	10/4	1.00
Headaches	10 (77)	8 (57)	0.4
Jaw claudication	9 (69)	11 (79)	0.68
Scalp tenderness	8 (62)	5 (36)	0.18
PMR	4 (31)	7 (50)	0.31
Fever	5 (38)	3 (21)	0.42
Weight loss	5 (38)	3 (21)	0.42
Hemoglobin, mean (95% CI) gm/dl	11.4 (10.6–12.3)	11.6 (11.2–12.1)	0.69
ESR, mean (95% CI) mm/hour	67.9 (41.6–110.8)	66.9 (55.5–80.5)	0.96
CRP level, mean (95% CI) mg/dl	5.16 (2.67–9.96)	3.43 (2.04–5.76)	0.34

* Except where indicated otherwise, values are the number (%) of patients. IV GC = intravenous glucocorticoid; PMR = polymyalgia rheumatica; 95% CI = 95% confidence interval; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein.

GC therapy. Reversible manifestations resolved. None of the patients had the appearance of new vascular complications after the initiation of prednisone treatment. The mean ESR and CRP values had returned to normal by the first followup visit at week 4 (Figure 1). The study design required that prednisone dosages be adjusted if disease activity was not controlled and that the GC dosage necessary be used as the major outcome variable. Figure 1 shows that disease activity was equally well controlled in both treatment arms, and there was no difference in the acute-phase response markers.

The numbers of patients in each treatment group with disease in remission at the specified followup periods while receiving ≤ 5 mg/day prednisone is shown in Table 2. At 36 weeks of followup, 10 of 14 patients (71%) who received pulse GCs had achieved the primary outcome measure of reducing the daily prednisone dose to ≤ 5 mg while their disease was in remission. In contrast, only 2 of the 13 patients (15%) who received 3 days of saline infusions had reduced the prednisone dose to ≤ 5 mg/day. This difference of 56% (95% CI 19–76) was significant ($P = 0.003$).

At 52 weeks of followup, 11 of 14 IV GC-treated patients were receiving ≤ 5 mg/day prednisone, and 2 of 13 saline-infused patients were at this level ($P = 0.001$). At 78 weeks, 12 of 14 IV GC-treated patients were receiving ≤ 5 mg/day prednisone, and 4 of 12 patients in the saline group were at this same GC level ($P = 0.006$). One IV GC-treated patient who had been tapered off prednisone at week 36 without relapse or recurrence was

admitted to a nursing home after 60 weeks and was unable to return for clinic visits. Followup by verbal communication did not suggest any evidence of recurrence, and the patient was included in the results at 78 weeks. One patient in the placebo group who failed to reach the primary end point of ≤ 5 mg/day prednisone at 36 weeks, and who had continued to take prednisone up to the last visit at 76 weeks, decided to continue followup with a local physician and not to return to the Mayo General Clinical Research Center for further followup.

Cumulative GC doses. The median dosages of oral prednisone at the end of each of the followup periods of 36, 52, and 78 weeks were significantly lower

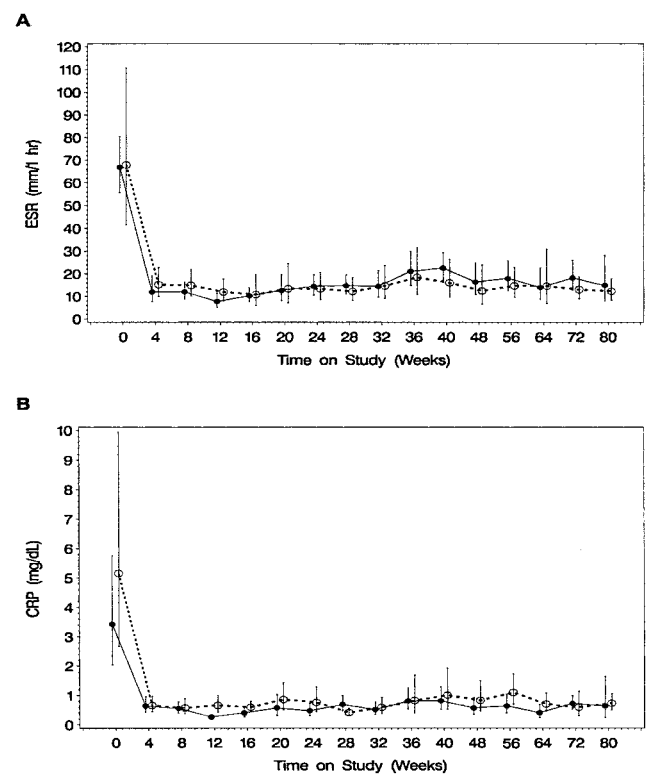


Figure 1. Longitudinal monitoring of disease activity. All patients were monitored for disease activity using the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level as laboratory indicators. Results are shown as the mean and 95% confidence interval after back transformation of the log values to the arithmetic scale. The study design required treating physicians to adjust treatment to control disease activity and to use the amount of treatment necessary as the major outcome variable. Data for the ESR (A) and the CRP level (B) document that treatment was successfully adjusted in both treatment arms to control disease activity. There was no difference between the placebo (○) and the intravenous pulse glucocorticoid (●) treatment groups.

Table 2. Remission rates and median daily dose of prednisone at 36, 52, and 78 weeks according to intervention*

Weeks treated, treatment group	No. of patients with disease in remission and receiving ≤5 mg/day prednisone	Prednisone dosage, median (IQR) mg/day
36		
Placebo	2 of 13	7 (6–9)
IV GC	10 of 14	2 (0–7)
<i>P</i>	0.003	0.007
52		
Placebo	2 of 13	9 (8–11.5)
IV GC	11 of 14	3.5 (0–5)
<i>P</i>	0.001	0.0004
78		
Placebo	4 of 12	7 (5–9)
IV GC	12 of 14	0.5 (0–4)
<i>P</i>	0.006	0.0004

* IQR = interquartile range; IV GC = intravenous glucocorticoid.

in the patients treated with IV methylprednisolone than in those treated with saline (Table 2). The course of GC withdrawal therapy in the 2 groups is shown in Figure 2. In the initial weeks, the disease was equally well controlled in the treatment and control arms. The curves started separating at 4 months, when the patients were receiving ≤10 mg/day prednisone. At all subsequent visits for the remainder of the followup, the dosages in the saline (placebo)-treated patients were higher.

The median total cumulative oral prednisone dose taken by the IV GC-treated patients by week 78 was 5,636 mg (interquartile range [IQR] 4,050–6,690),

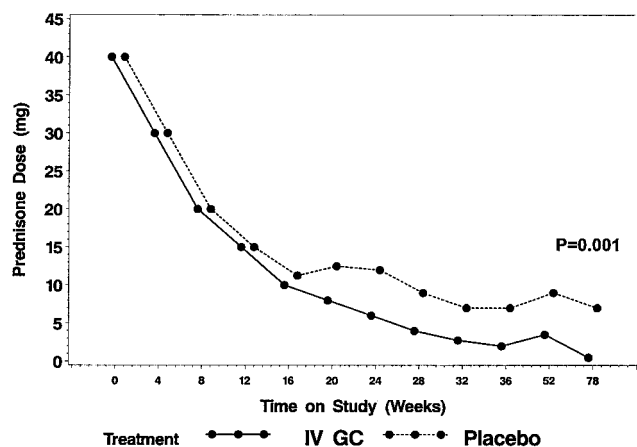


Figure 2. Effect of initial high-dose steroid pulse on subsequent treatment response. The prednisone dosage was rapidly tapered and adjusted to control disease activity. Median daily doses are shown. The disease was initially equally well controlled both in the treatment arm and in the control arm. The curves started separating at 4 months, with the intravenous glucocorticoid (IV GC) treatment arm requiring lower doses than the placebo arm.

while the median total cumulative oral prednisone dose taken by week 78 in the IV placebo-treated group was 7,860 mg (IQR 7,373–9,005) ($P = 0.001$). In this analysis, the IV GC dose was excluded because pulse steroids may have different biologic effects from those of long-term oral steroids.

Relapses during followup. The total number and rate of relapses in the 2 treatment arms are shown in Table 3. Fewer relapses were seen in the IV GC-treated group than in the control group (21 in 14 patients versus 37 in 13 patients; $P = 0.028$). All diagnoses of a flare were reviewed at the end of the study to examine the validity of the diagnosis. One investigator who was not involved in the followup assessments performed this review. All diagnoses of flares appeared to be retrospectively legitimate; only 4 of the 58 flares were based entirely on patients’ symptoms, 30 flares met laboratory and clinical criteria, and 24 flares were diagnosed based on elevated acute-phase response markers without unequivocal worsening of clinical symptoms. There was no obvious bias in the diagnosis of a flare in the placebo treatment arm.

Treatment-related adverse effects. Complications that were potentially treatment related are summarized in Table 4. All exacerbations of underlying conditions or new conditions occurring in the followup period were recorded. There were no significant differences in the occurrence of adverse events, including osteoporosis,

Table 3. Relapse rates according to intervention group*

No. of flares	Placebo group		IV GC group	
	No. of patients†	Total flares	No. of patients†	Total flares
0	1	0	4	0
1	1	1	2	2
2	2	4	5	10
3	5	15	3	9
4	3	12	0	0
5	1	5	0	0
Total	13	37	14	21

* Fewer relapses were seen in the intravenous glucocorticoid (IV GC)-treated group than in the placebo-treated group (21 in 14 patients versus 37 in 13 patients; $P = 0.028$). In the group receiving placebo, 2 flares were determined on the basis of clinical symptoms, 16 on the basis of laboratory tests only, and 19 on the basis of clinical and laboratory findings. In the group receiving IV GCs, 2 flares were determined on the basis of clinical symptoms, 8 on the basis of laboratory tests only, and 11 on the basis of clinical and laboratory findings. In the group receiving placebo, the number of relapses per 100 person-years was 189.7 (95% confidence interval [95% CI] 133.6–261.5). In the group receiving IV GCs, the number of relapses per 100 person-years was 101.6 (95% CI 62.9–155.3).

† Number of patients with the given number of flares.

Table 4. Summary of treatment-related adverse effects*

	All patients (n = 27)	IV GC-treated patients (n = 14)	Placebo-treated patients (n = 13)
Cardiovascular			
Hypertension	6	3	3
Hyperlipidemia	6	3	3
Other			
Angina, coronary artery disease	1	0	1
Fluid retention	1	1	0
Palpitations/tachycardia	2	0	2
Gastrointestinal			
Peptic ulcer disease	0	0	0
Upper gastrointestinal bleed	0	0	0
Other			
Abdominal bleeding	1	0	1
Rectal outlet bleeding	1	0	1
Musculoskeletal			
Steroid myopathy	0	0	0
Osteoporosis	6	3	3
Hip fracture	0	0	0
Pelvis fracture	1	0	1
Aseptic necrosis (AVN)	0	0	0
Vertebral compression fractures	0	0	0
Endocrine			
Cushingoid habitus	21	11	10
Glucose intolerance	3	1	2
Exacerbation of diabetes mellitus	0	0	0
Ophthalmic			
Cataracts	1	1	0
Glaucoma	1	1	0
Central serous chorioretinopathy secondary to steroids	1	0	1
Subconjunctival hemorrhage	1	1	0
Infections			
Herpes zoster	1	1	0
Upper respiratory tract infection	5	3	2
Urinary tract infection	5	3†	2‡
Pneumonia	3	1	2‡
<i>Candida</i> esophagitis	1	0	1
Other			
Depression	1	0	1
Dizziness/lightheadedness	3	3	0
Deep venous thrombosis	1	0	1
Colon cancer (hemicolectomy)	1	1	0
Sleep apnea	1	1	0
Total events	75	38	37

* IV GC = intravenous glucocorticoid; AVN = avascular necrosis.

† One patient who had 3 episodes in the 18-month followup period.

‡ One patient who had 2 episodes in the 18-month followup period.

osteopenia, hypertension, hyperlipidemia, or hyperglycemia. There were no documented cases of avascular necrosis in either group. One successfully treated patient in the IV GC group required outpatient treatment for pyelonephritis 11 days after enrollment. This patient had frequent urinary tract infections including 2 more during followup. There were no other adverse events that may have been related to the IV GC administration.

Outcome. Six IV GC-treated patients had ceased treatment and had disease in remission at the end of 18

months compared with none in the control group. Three of these 6 patients had ceased prednisone since week 36, 1 since week 40, and 2 since week 68. Further followup was available on 5 of the 6 patients, and all 5 continued without prednisone for at least 6 more months. Although there were a number of relapses during the course of the study, especially in the control patients, there were no important vascular complications in any patient during the course of the investigation. All patients survived during the study period.

DISCUSSION

This study shows that the majority of patients with GCA responded to treatment with an initial daily dose of 40 mg of prednisone (23 of 27 patients) and tolerated tapering during a period of 9 months to <10 mg/day of prednisone. The initial IV pulse GC therapy allowed for a more rapid tapering, and a significantly greater number of patients who received initial pulses could reduce their oral GC dosage to ≤ 5 mg/day by 36 weeks, without recurring disease activity, compared with those given control saline infusions. Possibly more importantly, this difference was maintained at the 52-week and 78-week followup visits, thereby documenting the long-term benefits of the initial pulse in controlling the vascular inflammation. The median oral prednisone dose taken by the patients given IV pulse GCs was also lower than the median dose in the control group at each of the followup visits. Correspondingly, the median total oral GC dose taken during the study period by those given IV GC pulses was significantly lower than that taken by patients given saline infusions. There were fewer relapses in the IV pulse GC group. These results suggest that an initial 3 days of pulse GCs in addition to oral therapy is not only more effective than oral therapy alone in suppressing the inflammatory processes of GCA at the start of therapy, but also confers the long-term benefits of lower oral doses being required to maintain the suppression. This benefit even extends into the second year of treatment and, perhaps, longer.

Two previous investigations have used pulse methylprednisolone as initial therapy in GCA; both studies used lower doses than those used here. One study (20) was a retrospective evaluation of 15 patients with GCA who had been given pulses of 500 mg of methylprednisolone for 3 days followed by an oral dosage of 20 mg/day of prednisolone. Two of the 15 patients had relapses of their disease within the first month of therapy and were given higher oral doses. Of the 13 patients whose disease was controlled with 20 mg/day of oral prednisolone, no sequelae of GCA or side effects from the GCs were observed. The authors concluded that initial pulse treatment may help reduce oral prednisolone doses; however, because of the uncontrolled nature of the study, definite conclusions are not possible.

While the second study was a controlled treatment trial, the researchers' study design was substantially different from our own. Chevalet et al (21) randomly assigned 164 patients to receive 1 of 3 regimens: a 240 mg IV pulse of methylprednisolone followed by 0.7

mg/kg/day oral prednisone, a 240 mg IV pulse of methylprednisolone followed by 0.5 mg/kg/day oral prednisone, or 0.7 mg/kg/day oral prednisone without an IV pulse. Oral GC dosages were tapered when clinical disease activity and laboratory markers of inflammation improved. After 1 year, the cumulative doses of GCs were identical in all 3 groups. The authors concluded that the methylprednisolone pulse had no long-term effect. One possible explanation for the different results between that study and ours is that Chevalet et al used a much smaller induction dose given as a single infusion. GCs at this dose mainly function by repressing cytokine transcription, particularly that of NF- κ B-regulated genes, which is readily reversible, and it may require more than 1 day of cytokine repression to induce lasting effects. Moreover, the transcription of key cytokines, such as interferon- γ , in the tissue appears to be relatively GC resistant, and GCs at higher dosages may act through additional mechanisms (18).

The findings in our study are consistent with the hypothesis that it is useful to distinguish the systemic inflammatory response associated with GCA from the local immune response in medium-sized and large arteries (22,23). These 2 processes appear to be driven by different pathogenetic mechanisms and responses to treatment. The systemic immune response that can occur without vasculitic inflammation in patients with PMR is highly responsive to GCs, and this systemic element is readily suppressed certainly in patients with PMR, but also in patients with GCA. This systemic inflammatory response may set the stage for vasculitic inflammation by stimulating pattern recognition receptors and thereby activating vascular dendritic cells (23,24). Activation of dendritic cells is sufficient to initiate a T cell response with subsequent recruitment of immune effector populations (25). The incurred inflammatory lesion, including granuloma formation and vascular remodeling, develops its own dynamics (26–29). The persistent vasculitis after treatment observed in previous artery biopsy studies (16,17), the elevations of interleukin-6 levels during GC withdrawal (30,31), and the experimental human temporal artery–SCID mouse chimera investigations showing that large doses of GCs are necessary to obliterate the vasculitis (18) all serve as evidence that this local vascular inflammatory component is more resistant to GCs.

The results of the present study suggest that daily 40-mg doses of prednisone followed by a relatively rapid diminishment was sufficient to allow for satisfactory clinical control of the systemic inflammation. However, the disease is clearly smoldering, as evidenced by the

frequent relapses and the difficulties associated with reducing the prednisone dosage after the first year of treatment or below the level of 10 mg/day. Clinical relapses of GCA often present with rather vague and nonspecific symptoms, and it should be noted that objective laboratory evidence of an acute-phase response was emphasized in our study design more than is recommended in clinical practice. This definition of flare may have resulted in a high estimate of disease flares, although the earlier treatment of laboratory flares may have also prevented the occurrence of clinical flares. The principal results, however, remained the same and similar trends were obtained when only combined laboratory and clinical flares were included in the analysis (Table 3). Even in the pulse GC group, only 6 of the 14 patients had completely discontinued treatment after 18 months, consistent with our previous notion that the term "cure" should be used in GCA only with great caution. Initial IV pulse methylprednisolone appears to improve this long-term outcome because it was not only more effective in early suppression of GCA, but it also allowed for a lower oral dose to maintain the suppression, or even induced sustained remissions in a subset of patients.

It should be noted that the placebo group received significantly less prednisone than is generally recommended in current clinical practice. Most treatment algorithms recommend an initial daily dose of 60 mg oral prednisone followed by a slow taper to ~10 mg/day prednisone after 9–12 months. The long-term clinical implications of smoldering disease are unclear, and as a result, it is uncertain whether the majority of patients would do fine with substantially less aggressive treatment than is currently recommended. Alternatively, the long-term outcome of GCA may depend on optimal disease control. In this case, it is possible that initially higher doses of oral prednisone and more prolonged treatment would have improved the results in the second year of followup, would have reduced the frequency of relapsing disease, and would therefore have been equally as effective as the initial pulse treatment followed by lower oral prednisone doses. However, this better disease control would have come at the cost of a much higher cumulative prednisone dose.

Larger oral doses of GCs are more often associated with an increased rate of adverse events (8,9). Thus, a more rapid withdrawal of GCs and a smaller total dose is likely to be a safer regimen and associated with fewer adverse side effects (8,9). We chose not to include the IV pulse methylprednisolone amounts in calculating the total GC dose because the pulses were given only at the

initiation of therapy. Because of the short half-life of GCs, this form of treatment may not have the same toxicity profile as long-term treatment. Our study population was too small to allow for the detection of a difference in steroid-related adverse events in the 2 groups. One of the reasons is that our control group received substantially less prednisone than is commonly used in clinical practice. Another reason is that we aggressively treated osteoporosis in all patients and may have thus prevented fractures in some patients during the study. A further potential limitation of the present investigation is the duration of followup. Any changes in GC dosage requirements after 18 months were not included in our analysis. At the last followup visit in the study, most patients were taking relatively low and stable doses of prednisone, and a late important change in dosage requirements for one group or the other would seem to be an unlikely event. However, 3 patients in the placebo group still needed ≥ 10 mg/day to control disease activity, and a longer followup period may demonstrate differences in the long-term toxicity of steroid treatment.

In conclusion, initial pulses of methylprednisolone suppressed GCA inflammatory processes effectively, thereby allowing for a lower oral dose of GCs and a more rapid reduction of oral prednisone therapy than current guidelines recommend. Study of additional patients and longer followup are needed to determine whether this mode of treatment also reduces common and serious adverse side effects associated with long-term GC therapy and decreases the risk of late vascular complications of GCA, such as aortic aneurysms.

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