

Infliximab plus Prednisone or Placebo plus Prednisone for the Initial Treatment of Polymyalgia Rheumatica

A Randomized Trial

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Background: A reliable alternative to steroids for treating polymyalgia rheumatica has not yet been identified. Although infliximab has been used occasionally in steroid-resistant cases, its efficacy has not been demonstrated in a controlled study.

Objective: To compare the efficacy of prednisone plus infliximab with that of prednisone plus placebo in patients with newly diagnosed polymyalgia rheumatica.

Design: Randomized, placebo-controlled trial.

Setting: 7 rheumatology clinics in Italy.

Patients: 51 patients with newly diagnosed polymyalgia rheumatica. Patients with associated giant cell arteritis and those who had been previously treated with steroids or biological or immunosuppressive agents were excluded.

Intervention: Initial therapy with oral prednisone tapered from 15 mg/d to 0 mg/d over 16 weeks according to a standard protocol, plus infusions of placebo or infliximab, 3 mg/kg of body weight, at weeks 0, 2, 6, 14, and 22.

Measurements: The primary efficacy end point was the proportion of patients without relapse or recurrence through week 52. Secondary outcomes were the proportion of patients no longer taking prednisone, the number of relapses and recurrences, the duration of prednisone therapy, and the cumulative prednisone dose.

Results: Four patients (3 in the infliximab group and 1 in the placebo group) did not complete the trial. The proportion of patients who were free of relapse and recurrence at 52 weeks did not differ between groups (6 of 20 patients [30%] in the infliximab group vs. 10 of 27 patients [37%] in the placebo group; adjusted risk difference, -3 percentage points [95% CI, -31 to 24 percentage points]; $P = 0.80$). In a sensitivity analysis that included dropouts, the best-case scenario yielded a difference of 5 percentage points (CI, -21 to 31 percentage points) between the groups. The secondary outcomes at weeks 22 and 52 did not differ between the groups.

Limitations: The study had a small sample and a short follow-up. A low dosage of infliximab was used, and the prednisone dosage was rapidly tapered.

Conclusions: Although too small to be definitive, the trial provides evidence that adding infliximab to prednisone for treating newly diagnosed polymyalgia rheumatica is of no benefit and may be harmful. If there is benefit, it is unlikely to be large.

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Polymyalgia rheumatica is a common clinical syndrome of unknown cause that is characterized by aching and morning stiffness in the shoulder girdle, pelvic girdle, and neck in persons 50 years of age or older (1, 2).

Glucocorticoids are the preferred treatment for polymyalgia rheumatica. Prednisone or its equivalent at an initial dosage of 12.5 to 25 mg/d is adequate for most patients with polymyalgia rheumatica who do not have associated giant cell arteritis, which is a closely related condition. Usually, the response to glucocorticoids is rapid, with complete resolution of symptoms after a few days of therapy (1, 2). Treatment for 1 to 2 years is usually required. However, a subset of patients tends to have a more chronic, relapsing course and requires low doses of steroids over a much longer time (3-7). Steroid-related adverse events are frequently observed during treatment (8).

Cytotoxic drugs have been used as glucocorticoid-sparing agents, with conflicting results. In particular, randomized, controlled trials on the potential efficacy of methotrexate for treating polymyalgia rheumatica and giant cell arteritis have been inconclusive (9-14). Only 2 randomized, placebo-controlled studies have evaluated the efficacy

of methotrexate for treating polymyalgia rheumatica when it is administered with oral prednisone.

van der Veen and colleagues (9) did not find a steroid-sparing effect of methotrexate at a dosage of 7.5 mg/wk in 40 patients with polymyalgia rheumatica (9). However, only 21 patients who had a complete 2-year follow-up or at least 1 year of follow-up after discontinuing prednisone therapy were evaluated. Therefore, the results were limited by the few patients analyzed. Caporali and colleagues (11) reported the efficacy of methotrexate as a steroid-sparing

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Context

Some patients with polymyalgia rheumatica have a chronic relapsing course and require long-term glucocorticoid therapy, which can lead to adverse effects. A small case series suggested that infliximab had a glucocorticoid-sparing effect.

Contribution

Researchers randomly assigned patients with newly diagnosed polymyalgia rheumatica to a prednisone taper plus placebo or infliximab, 3 mg/kg of body weight, at weeks 0, 2, 6, 14, and 22. They found no difference in relapse- and recurrence-free survival at 52 weeks.

Caution

The study was too small to definitively identify harms or small benefits.

Implication

Infliximab is unlikely to cause large improvements in polymyalgia rheumatica outcomes when added to a glucocorticoid taper.

—The Editors

agent in a study of 72 patients with polymyalgia rheumatica (11), in which methotrexate was administered at a higher dosage (10 mg/wk). A steroid-sparing effect of methotrexate was observed after 1 year of treatment; however, the methotrexate group did not have fewer steroid-related adverse events.

Infliximab, a chimeric monoclonal antibody used against tumor necrosis factor (TNF)- α , has been used successfully in treating different rheumatic disorders. In a recent open-label pilot study (15), infliximab had a steroid-sparing effect in 4 patients with glucocorticoid-resistant polymyalgia rheumatica who had developed steroid-related side effects. The promising results of the pilot study led us to perform a randomized, double-blind, placebo-controlled, multicenter trial to evaluate the efficacy and safety of prednisone plus infliximab for the initial treatment of patients with polymyalgia rheumatica.

METHODS**Design Overview**

We conducted a 52-week multicenter, double-blind, prospective, randomized, placebo-controlled study comparing the efficacy and tolerability of oral prednisone plus infliximab versus oral prednisone plus placebo as first-line treatment for polymyalgia rheumatica. The ethics committees of the participating centers reviewed and approved the study protocol. Before entering the trial, patients were informed of the nature, duration, and purpose of the study and of the potential benefits and drawbacks that could be expected. All patients gave their written informed consent.

Setting

Seven rheumatologic centers in Italy (Genoa, L'Aquila, Modena, Parma, Perugia, Reggio Emilia, and Trent), which receive most of their referrals from general practitioners, participated in the study.

Participants

Consecutive patients with newly diagnosed polymyalgia rheumatica who were observed from January to December 2003 were eligible. We diagnosed polymyalgia rheumatica according to the Healey criteria (16). Inclusion criteria were age older than 50 years; erythrocyte sedimentation rate (ESR) greater than 40 mm/h; persistent pain (for at least 1 month) involving 2 of 3 areas (neck, shoulders, or pelvic girdle); morning stiffness lasting more than 1 hour; rapid response to prednisone, 20 mg/d or less; and absence of signs or symptoms of other musculoskeletal or connective tissue conditions. Exclusion criteria were previous treatment with steroids, biological agents, or immunosuppressive agents; clinical or histologic evidence of giant cell arteritis; fulfillment of the American College of Rheumatology 1987 revised criteria for rheumatoid arthritis (17); pleuritis, pericarditis, leukopenia, or thrombocytopenia and antinuclear antibodies indicating the presence of systemic lupus erythematosus or other connective tissue conditions (18); presence of myositis, hypothyroidism, and psoriatic arthritis; presence of uncontrolled diabetes or hypertension, infection, and neoplasm (including multiple myeloma); and presence of active or inactive (latent) tuberculosis, as evaluated by detailed medical history (including personal history of tuberculosis, possible previous contacts with tuberculosis, and family history of tuberculosis), chest radiography (performed within 2 months before study entry), and tuberculin purified protein derivative test.

Randomization and Intervention

We randomly assigned patients to treatment groups in a 1:1 ratio balanced in blocks by using central randomization by telephone. The randomization schedule was computer generated in blocks of 4 by Schering-Plough, Milan, Italy. Assignment was not stratified by center. For practicality, each center systematically received medication in lots for 4 consecutive patients and a pharmacist at each center dispensed it.

Patients were assigned to receive placebo or infliximab, 3 mg/kg of body weight, at weeks 0, 2, 6, 14, and 22. All patients received oral prednisone, 15 mg, at approximately 8.00 a.m. daily for the first 4 weeks. Daily dosages in the next three 4-week periods were 10 mg, 5 mg, and 2.5 mg. Prednisone treatment was discontinued thereafter if permitted by the patient's clinical conditions.

Patients followed the same tapering schedule as long as they fulfilled the clinical and laboratory definition of disease remission. If clinical and laboratory features indicated relapse, the previous dosage was resumed. If polymyalgia rheumatica recurred after prednisone therapy was withdrawn, oral prednisone therapy was restarted at the lowest

dosage that had previously controlled symptoms. In case of continuing disease activity, the dose of prednisone was increased by 5 mg daily until remission was achieved. The new dosage was maintained for 2 weeks and was followed by clinical and laboratory reassessment before reducing the dose on an individual basis.

Patients, investigators, and study personnel other than the pharmacist were unaware of the initial assignments throughout the study.

Infliximab (Remicade, Centocor, Inc., Malvern, Pennsylvania) was supplied in 20-mL vials containing 100 mg of lyophilized concentrate. Placebo was identically formulated but did not contain infliximab. Blinded personnel administered infusions over 2 hours by using an infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter through a peripheral venous access site.

Outcomes and Measurements

The predefined primary efficacy end point was the proportion of patients without relapse or recurrence through week 52. Secondary outcomes were the proportion of patients free of relapse or recurrence through week 22, the proportion of patients no longer taking steroids at weeks 22 and 52, the total number of relapses or recurrences, the duration of prednisone therapy, the cumulative dose of prednisone, and the number of patients with adverse events.

We defined disease remission as the disappearance of signs and symptoms of polymyalgia rheumatica with normalization of ESR. We defined relapse of polymyalgia rheumatica as the return of signs and symptoms (aching and stiffness at shoulder, hip girdle, or both) accompanied by an increased ESR (>30 mm/h) or a C-reactive protein (CRP) level greater than 5 mg/L (upper limit of normal reference range, 5 mg/L) as measured by nephelometry (NA latex CRP kit, Behringwerke, Marburg, Germany) during steroid-dosage tapering, followed by improvement of these signs or symptoms when the dose of steroids was increased. We defined recurrence of polymyalgia rheumatica as the return of signs and symptoms accompanied by changes in laboratory values more than 1 month after discontinuation of therapy.

We measured patients' assessment of disability by using the validated Italian version of the Health Assessment Questionnaire Disability Index (HAQ-DI) (19). Patients reported adverse events, which we defined as a new diagnosis or incidence of any condition during the scheduled visits or at any time throughout the study. At each visit, patients were asked which adverse events (from a predefined list of possible adverse events that was read to them) they had experienced. In addition, they were instructed during the first visit to voluntarily report to the investigator any adverse events that might occur during the study.

Follow-up Procedures

Clinical and laboratory assessments were performed before therapy began, every 2 weeks for the first 4 weeks, and then every 4 weeks from weeks 4 to 52.

Each visit included a complete physical examination and administration of a questionnaire to assess symptoms and health status, including the HAQ-DI. Adverse events and concomitant therapy were also recorded. We assessed complete blood count, antinuclear antibody status, and renal and liver function at baseline and at the last visit. We measured ESR and the CRP level at baseline and at each visit.

The principal investigator at each center assessed clinical evaluations and outcomes, and a co-investigator monitored adverse events and drug delivery. The principal investigator assessed relapses and recurrences at every follow-up visit or at unscheduled visits that were requested by patients.

Statistical Analysis

We chose the sample size on the basis of the proportion of patients without relapse or recurrence through week 52 in recently published case series from centers involved in our clinical trials (20–22). By pooling these data, we expected that approximately 40% of patients in the placebo group would be free of relapse or recurrence through week 52. Therapy had to perform at least twice as well in the treatment group as in the placebo group to be considered to have a clinically important effect. Therefore, we assumed that 80% of patients in the active treatment group would be without relapse or recurrence through week 52. A 2-group chi-square test with a 2-sided significance of 0.05 would have 80% power to detect an assumed difference of 40 percentage points between the placebo and treatment groups when the sample size in each group is 22 participants or more. We increased the total sample size to 51 participants, assuming a dropout rate of 15%.

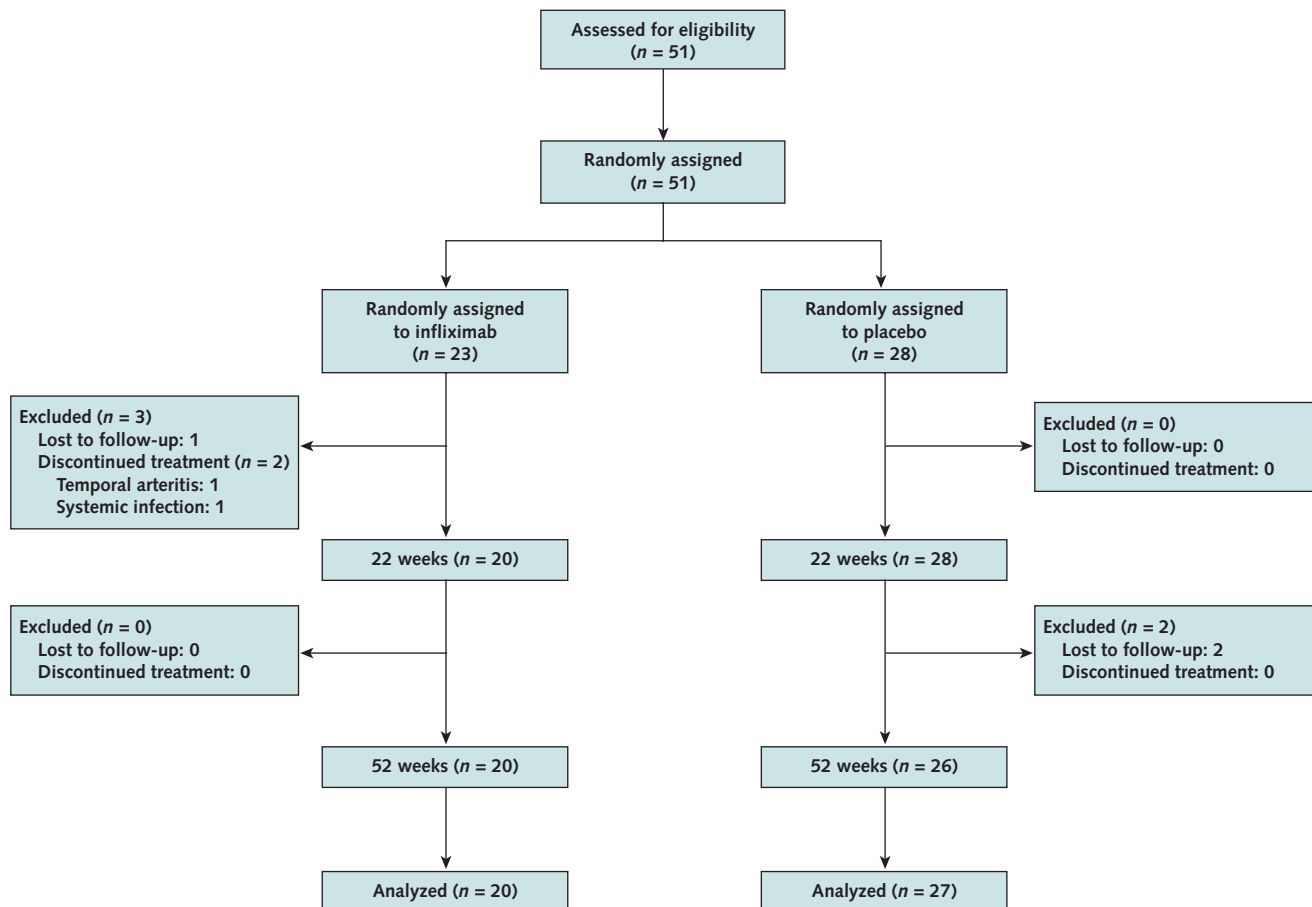
We reported continuous variables as the mean (SD) or, if skewed, as the median (interquartile range). We calculated frequencies and percentages for categorical variables. We based all analyses on the intention-to-treat principle. We did not perform an interim analysis.

Two-sided *P* values less than 0.05 indicated statistical significance. We used Stata software, version 9 (Stata Corp., College Station, Texas), for all analyses.

Primary End Point

We first compared the proportion of patients without relapse or recurrence through week 52 according to treatment group by using the Fisher exact test and then by using the conditional fixed-effects logistic model, with conditioning on study center. We assessed the confounding role on treatment effect of duration of symptoms, HAQ-DI score, and CRP level in separate logistic models because of the small sample. We compared models containing the treatment and confounding terms with the model containing the treatment term only, and we found no evidence of confounding. We reported treatment effects as differences in proportions (crude risk difference) and corresponding 95% CIs (23). We also computed the ad-

Figure 1. Study flow diagram.



justed risk difference (95% CI) while conditioning on the study center, according to the Mantel–Haenszel method. We excluded treatment-by-center interaction by using the likelihood ratio test. We included all patients who completed follow-up. Because of missing data, we did not include 3 of 23 patients in the infliximab group and 1 of 28 patients in the placebo group in the analysis that compared the percentages of patients without relapse or recurrence. To determine the sensitivity of the results to these missing data, we performed a sensitivity analysis by using 2 scenarios: best-case scenario (all treatment successes in the infliximab group and all nonresponders in the placebo group) and worst-case scenario (all nonresponders in the infliximab group and all treatment successes in the placebo group). We performed a secondary analysis of the primary end point by plotting cumulative flare-free survival curves, according to the Kaplan–Meier method, and comparing them with a Cox model, which included the treatment effect only and was stratified by study center. We tested the proportional hazard assumption on the basis of Schoenfeld residuals.

Secondary End Points

We used the Fisher exact test to assess the association between infliximab treatment and the proportion of patients without relapse or recurrence through week 22 and the proportion of patients who were no longer receiving steroids and the proportion of patients with adverse events. We compared the number of relapses and recurrences, duration of prednisone therapy, and cumulative dose of prednisone by using the Mann–Whitney U test. We also used that test to compare intermediate assessments (at 22 weeks) of cumulative doses of prednisone between groups. We reported treatment effects as differences in proportions (95% CI) or as mean differences (95% CI).

We included all patients who completed follow-up in the evaluation of secondary end points. For adverse events, we considered all patients who were randomly assigned.

Role of the Funding Source

Infliximab and placebo were provided by Centocor Research and Development, Inc., Malvern, Pennsylvania. Centocor Research and Development, Inc., had no role in

the design, analysis, or interpretation of the study or in the decision to submit the manuscript for publication.

RESULTS

Baseline Characteristics and Follow-up

We enrolled 51 patients with newly diagnosed polymyalgia rheumatica during 1 year (January to December 2003). We randomly assigned 23 patients to receive prednisone plus infliximab and 28 patients to receive prednisone plus placebo. Forty-six patients (91%) completed the study through week 52 (Figure 1). Baseline characteristics for the 2 groups were similar (Table 1). In the first 22 weeks of the study, 3 patients in the infliximab group withdrew: 1 developed giant cell arteritis, 1 was lost to follow-up, and 1 developed systemic infection. Two patients in the placebo group were lost to follow-up after 22 weeks. However, 1 of them had already reached the primary end point by week 9 and thus was included in the analysis set. At the end of the 52-week follow-up, 20 patients (87%) in the infliximab group and 27 (96%) in the placebo group were available for clinical examination. Table 2 shows the changes in outcome measures during follow-up and at the end of the study.

Efficacy

Primary End Point

Forty-seven patients were available for analysis of the primary end point. The proportion of patients who were free of relapse or recurrence at 52 weeks did not differ between groups: 6 of 20 patients (30%) in the infliximab group and 10 of 27 (37%) in the placebo group. The infliximab–placebo risk difference, adjusted for center, was –3 percentage points (95% CI, –31 to 24 percentage points; *P* = 0.80). In sensitivity analyses, the risk difference was –11 percentage points (CI, –37 to 14 percentage points; *P* = 0.38) for the worst-case scenario and 5 percentage points (CI, –21 to 31 percentage points; *P* =

0.73) for the best-case scenario. Results from an analysis that did not stratify by center were similar. The crude infliximab–placebo difference in the proportion of patients without relapse or recurrence at 52 weeks was –7 percentage points (CI, –34 to 20 percentage points; *P* = 0.76). Results from worst-case and best-case scenario sensitivity analyses were –13 percentage points (CI, –39 to 12 percentage points; *P* = 0.38) and 3 percentage points (CI, –23 to 30 percentage points; *P* = 1.0), respectively. Finally, the groups did not differ in cumulative flare-free survival (hazard ratio, 1.25 [CI, 0.62 to 2.54]; *P* = 0.53) (Figure 2).

Secondary End Points

The groups did not differ in the proportion of patients without relapse or recurrence through week 22 (55% in the infliximab group vs. 54% in the placebo group). The proportion of patients who were no longer taking steroids at week 22 (55% in the infliximab group vs. 64% in the placebo group) and at week 52 (50% vs. 54%, respectively) did not differ between the groups. The total number of relapses and recurrences was 22 in the infliximab group and 32 in the placebo group. Sixteen episodes in the infliximab group and 25 in the placebo group were relapses, whereas 6 and 7 episodes, respectively, were recurrences. The median number of episodes per patient did not differ between the groups, both in all patients and in patients with flares only. The duration of prednisone therapy and the total cumulative prednisone dose did not differ between the groups at weeks 22 and 52.

Adverse Events

We included all 51 patients who were randomly assigned in the analysis of adverse events. Apart from relapses, 8 adverse events (Table 3) occurred in both groups (7 patients in the infliximab group and 5 in the placebo group), with no statistical difference between groups. Two

Table 1. Baseline Characteristics*

Variable	Infliximab Group (n = 23)	Placebo Group (n = 28)
Demographic characteristics		
Mean age (SD), y	70.9 (7.6)	70.7 (7.4)
Women, n (%)	16 (70)	15 (54)
Clinical features		
Median duration of symptoms before therapy (IQR), wk	11.0 (6.0–18.0)	10.0 (7.5–14.5)
Systemic symptoms or signs (fever, anorexia, weight loss), n (%)	10 (43)	14 (50)
Mean Health Assessment Questionnaire score (SD)	1.65 (0.6)	1.43 (0.7)
Peripheral arthritis, n (%)†	3 (13)	8 (29)
Laboratory features		
Mean erythrocyte sedimentation rate (SD), mm/h	69.3 (20.9)	69.8 (24.4)
Median C-reactive protein level (IQR), mg/L‡	58.0 (27.0–83.0)	50.3 (25.0–80.8)

* IQR = interquartile range.

† Defined as the presence of joint swelling and tenderness.

‡ C-reactive protein was measured by nephelometry (upper value of the normal reference range, 5 mg/L).

patients in the infliximab group withdrew from the treatment protocol, 1 because of giant cell arteritis proven by biopsy and 1 because of systemic infection. No patient in the placebo group withdrew because of adverse events. Four patients in the infliximab group had infusion reactions, but they did not need to discontinue treatment. Two other patients in the infliximab group had 1 episode of pancreatitis and cholecystitis and increased fasting plasma glucose levels, which were treated by diet and glibenclamide, respectively. The most frequently reported adverse events in the placebo group were hypertension and exacerbation of hypertension (5 patients), followed by cataract (1 patient), dyspepsia (1 patient), and bladder cancer (1 patient).

DISCUSSION

The results of our randomized, double-blind, placebo-controlled study suggest that adding infliximab to prednisone does not substantially affect the course of polymyalgia rheumatica when the effect is defined as the proportion of patients without relapse or recurrence through the first 52 weeks of therapy. The confidence intervals encompass a range of possible true effects, from benefit to harm. Results of our sensitivity analysis supported our main analysis. Similarly, the 2 groups did not differ in the proportion of patients no longer taking prednisone, the numbers of relapses and recurrences, the duration of prednisone treatment, and the cumulative prednisone dose.

Glucocorticoids have been the treatment of choice for polymyalgia rheumatica for many years. However, the

course of polymyalgia rheumatica is heterogeneous, often with a variable glucocorticoid requirement. Some evidence suggests that there are 2 subsets of patients with polymyalgia rheumatica, 1 with a mild, self-limiting disease requiring 1 to 2 years of treatment and another with a more chronic relapsing course of disease that may require steroid treatment for several years or indefinitely (1–7). Previous investigations have shown that 65% of patients with polymyalgia rheumatica who have been treated with prednisone have at least 1 serious glucocorticoid-related adverse event, and the risk for vertebral fractures is 5 times greater among women (8). Steroid-related adverse events are strictly related to the cumulative dose (8). Efforts have been made to find drugs that permit use of lower doses of prednisone in polymyalgia rheumatica for the shortest time.

Methotrexate is the most studied steroid-sparing agent in polymyalgia rheumatica. However, evidence that methotrexate is effective in treating polymyalgia rheumatica is inconclusive (9–14). Recently, a double-blind, placebo-controlled study showed that prednisone plus methotrexate was associated with a shorter duration of prednisone treatment (11). However, because the effect of methotrexate was evident only after 1 year of treatment, the patients treated with methotrexate were also exposed to high cumulative prednisone doses, and they did not have less steroid-related morbidity. Given these findings, the advantage of adding methotrexate to prednisone treatment is unclear.

The rationale for choosing infliximab as adjunctive therapy for polymyalgia rheumatica was based on the results of a recent open-label pilot study showing that inflix-

Table 2. Treatment Effect on the Primary and Secondary End Points*

Characteristic	Infliximab Group	Placebo Group	Infliximab–Placebo Difference (95% CI), percentage points	P Value
Primary end point				
Patients without relapse or recurrence at 52 weeks, <i>n/n (%)</i>	6/20 (30)	10/27 (37)	–3 (–31 to 24)†	0.80†
Best-case scenario, <i>n/n (%)</i> ‡	9/23 (39)	10/28 (36)	5 (–21 to 31)†	0.73†
Worst-case scenario, <i>n/n (%)</i> §	6/23 (26)	11/28 (39)	–11 (–37 to 14)†	0.38†
Secondary end points				
Patients without relapse or recurrence at 22 weeks, <i>n/n (%)</i>	11/20 (55)	15/28 (54)	1 (–27 to 30)	1.00
Patients not receiving PDN at 22 weeks, <i>n/n (%)</i>	11/20 (55)	18/28 (64)	–9 (–37 to 19)	0.56
Patients not receiving PDN at 52 weeks, <i>n/n (%)</i>	10/20 (50)	14/26 (54)	–4 (–33 to 25)	1.00
Total relapses and recurrences, <i>n</i>	22	32		
Median relapses and recurrences (IQR), <i>n</i>				
All patients	1 (0 to 2)	1 (0 to 2)	–0.18 (–0.8 to 0.6)	0.69
Patients with relapses or recurrences	1.5 (1 to 2)	1 (1 to 2)	–0.3 (–1.1 to 0.5)	0.95
Median cumulative duration of PDN therapy (IQR), <i>wk</i>	26 (16 to 52)	22 (16 to 51)	4.7 (–9.8 to 9.0)	0.93
Median cumulative dose of PDN (IQR), <i>g</i>				
At 22 weeks	0.9 (0.9 to 13.6)	0.9 (0.91 to 11.9)	0.9 (–57.4 to 229.6)	0.78
At 52 weeks	17.1 (0.9 to 2.6)	12.2 (0.91 to 2.3)	4.9 (–5.0 to 14.9)	0.31
Patients with adverse events, <i>n/n (%)</i>	7/23 (30)	5/28 (18)	12.6 (–10.9 to 36.1)	0.34

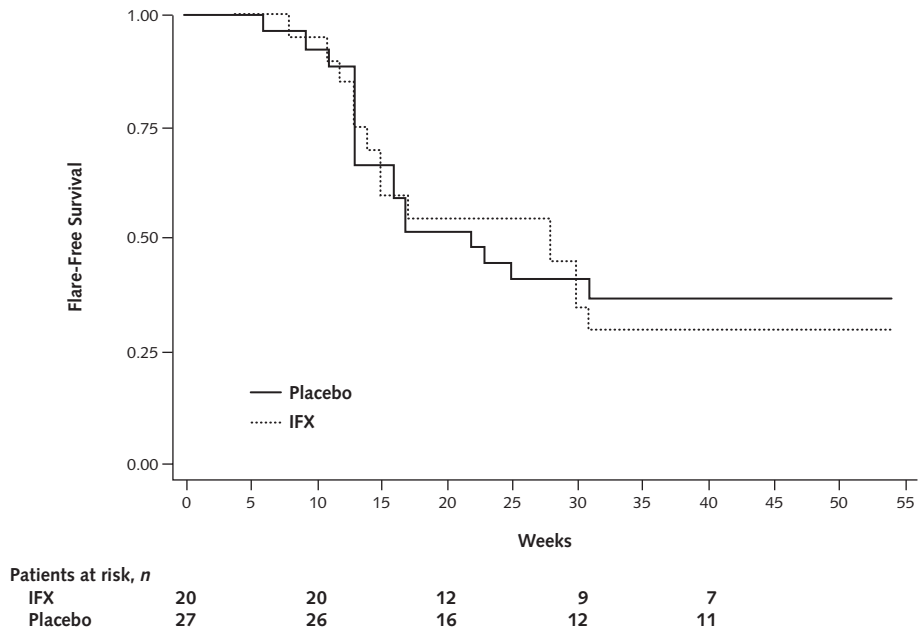
* IQR = interquartile range; PDN = prednisone.

† Mantel–Haenszel analysis, stratified by center.

‡ Assumes 3 infliximab group dropouts are treatment successes and 1 placebo group dropout is a nonresponder.

§ Assumes 3 infliximab group dropouts are nonresponders and 1 placebo group dropout is a treatment success.

Figure 2. Flare-free survival.



The cumulative probability of not having relapse or recurrence over time did not statistically differ between the groups ($P = 0.53$, Cox regression stratified by study center). IFX = infliximab.

imab reduced glucocorticoid requirements in 4 patients with polymyalgia rheumatica who were glucocorticoid resistant and who had side effects to these drugs (15).

Tumor necrosis factor- α may play a major role in the inflammatory response in polymyalgia rheumatica or giant cell arteritis, or both conditions. Elevated circulating levels of TNF- α are present in both conditions (24–26). Furthermore, Hernández-Rodríguez and colleagues (25, 26) showed that tissue expression of TNF- α was elevated in patients with giant cell arteritis who had a strong systemic inflammatory reaction, and that high TNF- α production was associated with longer steroid requirements and relapsing disease (25, 26).

The frequency of relapse and recurrence of polymyalgia rheumatica in our study was high (70% in the infliximab group and 63% in the placebo group) but was similar to the rates reported in 2 recent double-blind, placebo-controlled studies on polymyalgia rheumatica and giant cell arteritis (11, 12). Older studies described the frequency of flare-ups as approximately 30% (27–29). A recent prospective Italian study (30) reported a relapse frequency of 50% among patients with polymyalgia rheumatica who were followed for a mean of 39 months. A population-based study (31) from the Mayo Clinic showed a similar percentage of flare-ups (55%). The study clearly demonstrated that rapid tapering of prednisone is a substantial predictor of relapse, regardless of the current dose. Therefore, the higher rate of flare-ups observed in our study and in the 2 previous double-blind, placebo-controlled studies

(11, 12) is probably related to the rapid prednisone tapering schedule.

Our study has several limitations. First, we enrolled only patients with newly diagnosed polymyalgia rheumatica. The pilot study showed some efficacy of infliximab in patients with more severe chronic relapsing disease (15). Furthermore, pathophysiologic studies (25, 26) have shown an association between high production of TNF- α and steroid-resistant, relapsing disease. Different patterns of inflammation may be present in patients with polymyalgia rheumatica or giant cell arteritis who require differentiated therapeutic approaches. Second, we followed patients for only 1 year. Longer follow-up may be needed to evaluate the efficacy of infliximab. Third, we used a low

Table 3. Adverse Events

Adverse Event	Infliximab Group (<i>n</i> = 23), <i>n</i>	Placebo Group (<i>n</i> = 28), <i>n</i>
Diabetes mellitus	1	0
Cataract	0	1
Dyspepsia	0	1
Hypertension	0	2
Exacerbation of hypertension	0	3
Bladder cancer	0	1
Infusion reaction	4	0
Giant cell arteritis	1	0
Systemic infection	1	0
Pancreatitis or cholecystitis	1	0

dose of infliximab (3 mg/kg of body weight). Thus, the negative results of our study could be related to dose inadequacy. Fourth, we used a relatively low starting dose of prednisone and tapered it rapidly over 16 weeks, which may have contributed to the high frequency of flare-ups. Fifth, 5 of 51 patients (9.8%) discontinued treatment or were lost to follow-up. Finally, the CIs for the treatment effect were too wide to allow definite conclusions. This is associated with the sample size, which was targeted to a much larger effect of treatment.

A study by Hoffman and colleagues (32) on giant cell arteritis provides additional support of our negative results on the efficacy of TNF- α blockade in polymyalgia rheumatica. The design of that trial is very similar to ours. Patients with newly diagnosed disease were randomly assigned to receive steroids plus placebo or steroids plus infliximab, 5 mg/kg, which were administered by using the same schedule as that in our study. During the 22-week treatment period, the groups did not differ in the proportion of patients without relapse or in cumulative steroid dose.

Our study was not designed to evaluate the efficacy of infliximab in treating chronic relapsing polymyalgia rheumatica. Our conclusions can thus only be applied to newly diagnosed disease. A larger controlled trial is needed to make definite conclusions.

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