A double-blind placebo controlled trial of etanercept in patients with giant cell arteritis and corticosteroid side effects

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ABSTRACT

Objective: Open label studies have suggested that tumour necrosis factor (TNF) antagonists led to sustained improvement and corticosteroid sparing effect in patients with giant cell arteritis (GCA). To confirm these observations, we conducted a randomised, double-blind, placebo controlled trial with etanercept in patients with biopsy-proven GCA with side effects secondary to corticosteroids.

Methods: We randomly assigned patients with GCA to receive etanercept (n = 8) or placebo (n = 9) over 1 year together with corticosteroids that were reduced according to a predefined schedule. The primary outcome was the ability to withdraw the corticosteroid therapy and control the disease activity at 12 months.

Results: Baseline characteristics were similar in the two groups, although patients in the etanercept group showed higher levels of basal glycaemia (p = 0.02) and a higher erythrocyte sedimentation rate (ESR) (p = 0.01). After 12 months, 50% of the patients in the etanercept group and 22.2% in the placebo group were able to control the disease without corticosteroid therapy (p value not significant). Patients in the etanercept group had a significant lower dose of accumulated prednisone during the first year of treatment (p = 0.03). There were no differences in the number and type of adverse events.

Conclusion: The limited number of patients included in this study does not allow us to draw definitive conclusions. Etanercept therapy was well tolerated in this aged population. The therapeutic role of etanercept in patients with GCA should be evaluated in studies with a larger number of patients.

Giant cell arteritis (GCA) is the most frequent form of vasculitis affecting the elderly.[1] Clinically, it can manifest as local symptoms or signs related to the involved cranial vessels, by a systemic illness with fever, malaise and weight loss and/or by polymyalgia rheumatica.[2 3] Although in 1990 the American College of Rheumatology (ACR) developed classification criteria that emphasise the clinical hallmarks of the disease,[4] they were not intended for diagnostic purposes. Therefore, a definitive diagnosis of GCA requires the demonstration of the typical pathological findings on the temporal artery biopsy.[5 6]

The pathogenesis of GCA is not completely understood, although current data support a role for a localised antigen-driven T cell immune response,[7] in individuals with a genetic predisposition associated with certain alleles of the Human leukocyte antigen (HLA)-DRB1 molecule.[8–10] The CD4+ T cells are the dominant cell phenotype in the vasculitic lesions and activated macrophages, producing pro-inflammatory cytokines such as interleukin (IL)1 and IL6, that are readily demonstrated in the arterial wall infiltrate could serve as antigen presenting cells.[8 11–13]

By contrast, GCA is characterised by a prominent acute phase reaction expressed by a raised erythrocyte sedimentation rate (ESR) and increased serum levels of C-reactive protein (CRP).[1] It is well known than the acute phase response is induced by the pro-inflammatory cytokines, mainly IL1, IL6 and tumour necrosis factor (TNF)α.[14] Recently, using immunohistochemical techniques, the presence of TNFα and its receptors in endothelial cells and infiltration of mononuclear cells close to the internal elastic laminae of the inflamed vessels in patients with GCA has been reported.[15] The localisation of TNFα and its receptors in close proximity to the internal elastic laminae suggest that TNF could be involved in the leukocyte infiltration and arterial wall destruction characteristic of GCA.[15] In addition, a strong association of GCA with TNFα2 microsatellite polymorphism has been demonstrated.[16]

High dose corticosteroid is the only effective therapy in GCA.[1] Prednisone (45–60 mg daily) improves the clinical manifestations in most of the patients in less than 1 week. A month after beginning treatment, clinical and laboratory parameters show the acute phase reactants have mainly returned to normal, and tapering can begin.[17] In the majority of patients the corticosteroids can be withdrawn after 2 to 3 years of therapy.[3] Even tough corticosteroid therapy is clearly effective in GCA, but it is not an ideal therapy due to the following issues: (a) many of these elderly patients develop severe side-effects, such as diabetes or osteoporosis with vertebral compression fractures;[18 19] (b) corticosteroid therapy is not always able to prevent the development of either permanent visual loss or cerebrovascular accidents;[20] (c) despite corticosteroid therapy, some patients develop smouldering involvement of the aorta or other large vessels resulting in aortic aneurysm or aortic arch syndrome;[21–23] and (d) in some patients the disease remains active, requiring continued corticosteroid therapy. In these cases, the addition of immunosuppressive agents has not been proven to be clearly beneficial.[1 24 25]

Due to the above-mentioned considerations new therapeutic alternatives are needed in patients with GCA. In this regard, the recent availability of

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biological therapies with a remarkable efficacy for other inflammatory conditions has opened up new possibilities in the field of vasculitis. Several small series of patients and case reports have suggested the possible utility of TNF antagonists in patients with GCA refractory to corticosteroid therapy.[26–29] The same is true for polymyalgia rheumatica (PMR), a closely related syndrome,[30–33] and for other large vessel granulomatous vasculitis such as Takayasu arteritis.[34] Although these uncontrolled studies have shown a remarkable efficacy and safety in patients with refractory disease or those experiencing significant corticosteroid side effects, these data have not been confirmed in prospective controlled studies with infliximab performed in patients with recent onset GCA or PMR.[35 36]

The purpose of this multi-centre, double-blind placebo controlled study was to assess the potential efficacy of TNFα blocking therapy with etanercept in patients with biopsy-proven GCA and side effects secondary to corticosteroids.

METHODS

Patients

Patients were recruited at four hospital rheumatology divisions across Spain. Initially the study was designed with the participation of six additional centres, but was stopped before the inclusion of the initially calculated number of patients because of a low recruitment rate. Eligible patients needed to have biopsy-proven GCA controlled with corticosteroid therapy with side effects secondary to this therapy. They were clinically asymptomatic on a stable dose of corticosteroids (≥10 mg of prednisone during the previous 4 weeks), but with at least one of the following comorbidities: (1) corticosteroid-induced diabetes mellitus (fasting serum glucose levels ≥126 mg/dl) or an impaired glucose tolerance; (2) osteoporosis, defined by densitometric criteria or clinically by the presence of minimal trauma fracture; (3) high blood pressure, defined by a systolic blood pressure higher than 140 mmHg, a diastolic blood pressure higher than 90 mmHg, or the need of drug therapy for hypertension.

Patients were excluded if: (a) they had a clinical picture suggestive of GCA but did not have biopsy-proven arteritis, even if they meet the ACR classification criteria for GCA; (b) they had chronic infections such as HIV, hepatitis B or C, fungal or mycobacterial infections etc.; (c) they had neoplasm or a history of malignancy in the preceding 5 years; (d) they had multiple sclerosis or other demilinisating disorders; (e) they had cytopoenia: leucopoenia (leukocytes ⩽3.5×109/litre), thrombocytopoenia (platelets ⩽100×109/litre) and/or anaemia (haemoglobin⩽10 g/dl); (f) they had any other condition that contraindicates etanercept therapy.

The study was approved by the institutional review board and the ethics committee at each study centre. All patients gave written informed consent.

Study protocol

Study design

The study was divided in two phases. Phase I had a duration of 12 months and comprised the double-blind placebo controlled period. Thereafter, the study medication was stopped and the patients were followed over 3 additional months to evaluate the possible occurrence of relapse (phase II).

Study medications

Patients were randomly assigned in a 1:1 ratio to receive etanercept or placebo. Etanercept was administered at the standard dose of 25 mg twice weekly (subcutaneous injection).

Before screening, patients had to have been on stable dose of corticosteroids for at least 1 month. Etanercept or placebo was added to their current dose of corticosteroid, which was maintained at at stable level in all patients during the first month after randomisation. Thereafter, corticosteroids were tapered according to the following schedule: (a) if the patient was taking ⩾30 mg daily of prednisone, it was decreased by 10 mg/weekly until a daily dosage of 30 mg was reached; (b) if the patient was taking 30 to 15 mg daily of prednisone, it was decreased by 5 mg/weekly; (c) if the patient was taking 0 to 15 mg of prednisone, it was decreased by 2.5 mg/weekly. If the patient developed a relapse (first relapse), the prednisone was raised for 1 month to the previous dosage able to control the disease activity. Thereafter, the tapering of prednisone was resumed following the same schedule. In case of a second relapse, the prednisone was again raised for 1 month to the previous dosage able to control the disease activity, and then tapered at half the dosage on the same schedule. In cases of a third relapse, the patient was withdrawn from the study and treated according to the judgment of their doctor.

Concomitant medications

Patients were allowed to continue with all other medications for previous comorbidities or to initiate new drugs for side effects or new diseases that appeared during the study but were not related to GCA. Concurrent treatment with any other medications for GCA different from corticosteroids or the study medications (etanercept or placebo) was prohibited.

Clinical outcome measures

The primary outcome was the ability to withdraw the corticosteroid therapy and control the disease activity at 12 months in patients who had developed side effects secondary to corticosteroid treatment. The secondary outcomes were to study: (a) cumulative dosage of prednisone during the phase I of the study; (b) number of relapses during the active phase of the study; (c) new side effects or worsening of previous corticosteroid side effects during the study; and finally (d) number of relapses during the 3 month follow-up phase of the study.

Clinical evaluations were performed at screening, baseline and every 2 weeks during the first 3 months of treatment, then monthly thereafter. The following data were recorded at each visit: a structured questionnaire on symptoms of GCA; global evaluation of disease activity by the patient and doctor by visual analogue scale (VAS), 0–100; laboratory evaluation of complete blood count (CBC), ESR (Westergren method) and CRP (nephelometry), blood urea, glucose and liver enzymes; presence of relapse; and side effects with special emphasis in new or worsening of previous corticosteroids side effects, or side effects related to etanercept therapy. A relapse was considered in the presence of symptoms and/or signs of GCA together with elevations in at least one of the acute phase reactants, either ESR and/or CRP.

Adverse events

As stated above, adverse events were recorded at each visit. A serious adverse event was defined as an event that was fatal, life-threatening, required hospitalisation or extention of existing hospitalisation, resulted in persistent or substantial disability or incapacity, or was medically significant or required intervention to prevent any of the outcomes mentioned. In addition, the patients were instructed to the possible development of ischaemic manifestations of GCA, such as diplopia, transient

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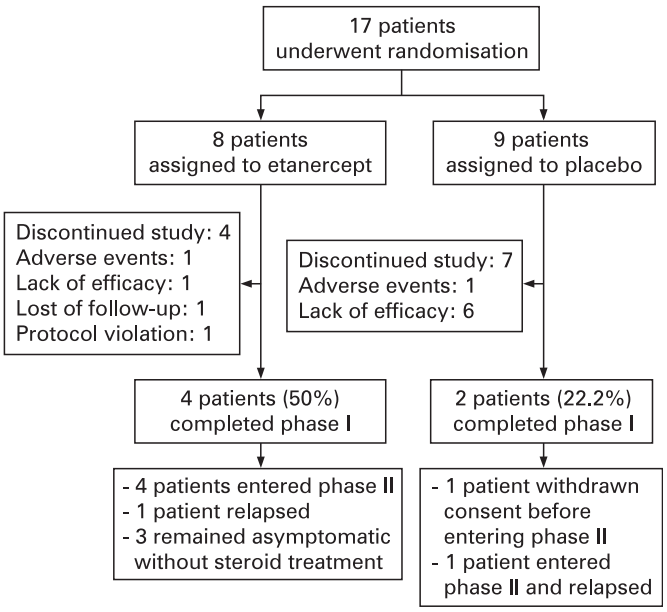

Figure 1 Flow of participants through the study. Randomisation, reasons for discontinuing treatment, and the numbers of patients who completed the trial are shown.

visual loss, jaw claudication or symptoms suggestive of cerebrovascular accidents, which patients were told should be immediately reported to the attending doctor.

Screening and treatment of latent tuberculosis infection

All patients had a chest *x* ray and/or purified protein derivative (PPD) skin test performed at screening according to the Spanish recommendations for the use of biologic agents for the detection of latent tuberculous infection (TB).[37] Those patients with chest *x* ray images showing calcified or scarred lesions consistent with latent tuberculosis or patients with a PPD skin test ⩾5 mm, had prophylactic treatment with isoniazid, 300 mg daily during 9 months or in the case of toxicity or intolerance riphampicin 600 mg daily for 4 months.

Table 1 Selected demographic and clinical characteristics at baseline

	Etanercept (n = 8)	Placebo (n = 9)	p Value
Age, years	74.5 (5.7)	74.4 (6.8)	0.8
Sex, % females	75	88.9	0.6
Time from GCA diagnosis (months):			
Median (CI 95%)	9.9 (2.7 to 24.9)	8.3 (1 to 53.4)	0.7
Comorbidities, %:			0.2
1	12.5	0	
2	0	11.1	
3	25	55.6	
4	12.5	22.2	
⩾5	50	11.1	
Systolic blood pressure, mmHg	143.4 (10)	149.7 (22.4)	0.8
Diastolic blood pressure, mmHg	80.1 (10.7)	87.9 (7.9)	0.1
Glycaemia, mg/dl	113.9 (44.1)	84.7 (5.4)	0.02
HbA1c, %	8.9 (1.7)	7.5 (1)	0.3
ESR, mm/h	21.2 (9.6)	12.1 (10.6)	0.01
CRP, mg/dl	1.4 (1.8)	0.8 (1.1)	0.4

Except for time from diagnosis, values are expressed as mean (SD). Normal value of CRP: <0.5 mg/dl ESR ⩽15 mm/h.
CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GCA, giant cell arteritis.

Statistical analysis

In order to calculate the sample size, we estimated that the percentage of patients in clinical remission without corticosteroid therapy at 12 months in the etanercept arm would be 75%, and the estimate efficacy in the placebo group 15%. Assuming an α risk of 0.05, a statistical power of 90%, and 10% drop-out rate during the study, the minimum sample size for the study should be 14 patients in each treatment arm.

Continuous variables were reported as the mean (SD) or, if skewed, as the median (interquartile range (IQR)). Categorical variables were calculated as frequencies and percentages. The analysis was based on the intention-to-treat principle. The χ^2 and Fisher exact tests were used to check the association between categorical variables and treatment. Significant differences in numeric variables between treatment groups were analysed using analysis of variance (ANOVA) in case of normally distributed variables, otherwise the Wilcoxon test was used. A p value less than 0.05 was considered as statistically significant. The SAS system was used for database design and for all statistical analysis.

RESULTS

Baseline demographic and clinical characteristics of the patients

From 14 April 2003 to 16 September 2004, eight patients were randomly assigned to the test group and treated with etanercept and nine patients were assigned to the control group and received placebo. The randomisation, reasons for discontinuing treatment and the numbers of patients who completed the trial are shown in fig 1. Baseline demographic and clinical characteristics were similar in the two groups (table 1). The study group comprised typical patients with GCA with a mean age of 74.5 (6.1) years and were mostly female (82%). The median duration of GCA and previous corticosteroid therapy was almost 10 months, and despite this follow-up, patients were still being treated with median prednisone dosage of 15 mg/day (table 2). It is important to note that all the patients had at least one comorbidity, and a significant proportion of patients, especially in the etanercept group, had five or more concomitant diseases. Patients in the etanercept group were more likely to have diabetes mellitus and showed a higher levels of basal glycaemia compared to the control group (p = 0.02). Although clinically asymptomatic at baseline, patients in the etanercept group had a higher ESR at baseline (p = 0.01).

Clinical efficacy

The primary outcome was the ability to withdraw the corticosteroid therapy and controlling the disease activity at the end of the 12 months of the double-blind phase of the study. As shown in fig 2, 50% of the patients in the etanercept group compared to 22.2% in the placebo group reached this end point (p value not significant). During the complete duration of the study more patients in the etanercept group had a good control of the disease without corticosteroids compared with placebo.

As expected with a better control of the disease in the etanercept group, patients in this group also had a significant lower dose of accumulated prednisone during the double-blind phase of the study. In fact, the accumulated dose of prednisone at 1 year was half in the etanercept group compared to placebo (mean (SD) of 1.5 (1) g vs 3 (1.5) g, p = 0.03; table 2).

During the active phase of the study the proportion of patients with relapses (77.8% vs 50%) and the total number of relapses (14 vs 8) were higher in the placebo group, although the

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Table 2 Approximate accumulated corticosteroid therapy previous to the inclusion in the study and during the study period

	Etanercept (n = 8)	Placebo (n = 9)	p Value
Approximate accumulated prednisone dose previous to the study, g:			0.6
Mean (SD)	5.4 (3.05)	9.2 (7.3)	
Median (CI 95%)	5.6 (2.6 to 8.2)	6.5 (3.5 to 14.8)	
Initial prednisone dose, mg:			0.9
Mean (SD)	18.1 (8.8)	17.5 (7.7)	
Median (CI 95%)	15 (10.7 to 25.5)	15 (11.6 to 23.4)	
Accumulated dose at 1 year, g:			0.03
Mean (SD)	1.5 (1)	3 (1.5)	
Median (CI 95%)	1.3 (0.6 to 2.4)	3.2 (1.8 to 4.1)	

CI, confidence interval.

differences did not reach statistical significance (table 3). Five patients entered the phase II, four in the etanercept group and one in the placebo group. Three of the four patients in the etanercept group remained asymptomatic without any therapy and one of them relapsed. The patient in the placebo group that entered phase II also relapsed. The most frequent clinical manifestation of relapse was a polymyalgic syndrome. The clinical relapse was associated with an increase in the acute phase reactants (fig 3).

Another of the secondary outcomes was to evaluate the appearance of new side effects or worsening of previous corticosteroid side effects during the study. There were no differences in dual energy x ray absorptiometry (DEXA) values or in the number of new fractures between treatment groups. Only two patients had clinical symptoms suggestive of a fracture. One patient in the etanercept group had a fracture of the fifth metatarsal bone at month 12, and one patient in the control group had axial pain highly suggestive of vertebral fracture that was not confirmed by standard *x* ray. There were also no differences in the glycaemic and hypertension control during the study period.

Safety

The two study groups did not differ significantly with regard to either the overall rate of adverse events or the rates of specific events (table 4). The most common adverse events were infections, mostly upper respiratory tract infections and lower urinary tract infections. All of them were considered by the investigators to be of low severity and did not require withdrawal of the patient from the study. Two patients in each group developed a total of six serious adverse events. One patient in the etanercept group developed a cardiac failure and another patient developed nausea and weight loss that were attributed to the study medication. In the placebo group one patient developed gastrointestinal bleeding and another patient had two different traumatisms that were considered unrelated to the study medication.

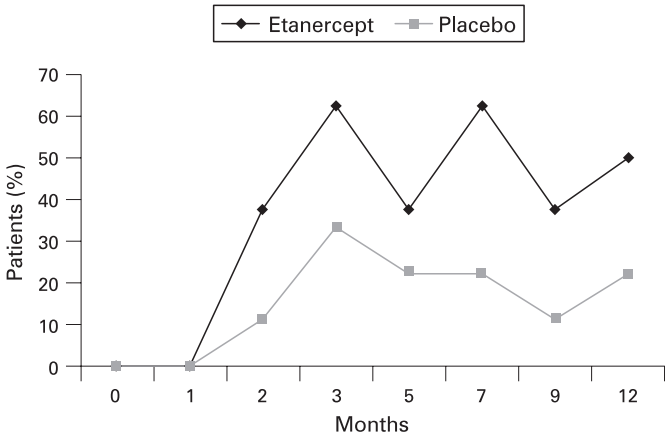

Figure 2 Patients with giant cell arteritis (GCA) without corticosteroid therapy during phase I of the study. At the end of the 12 months of the double-blind phase of the study, 50% of the patients in the etanercept group compared to 22.2% in the placebo group were able to control disease activity without corticosteroid treatment (p value not significant).

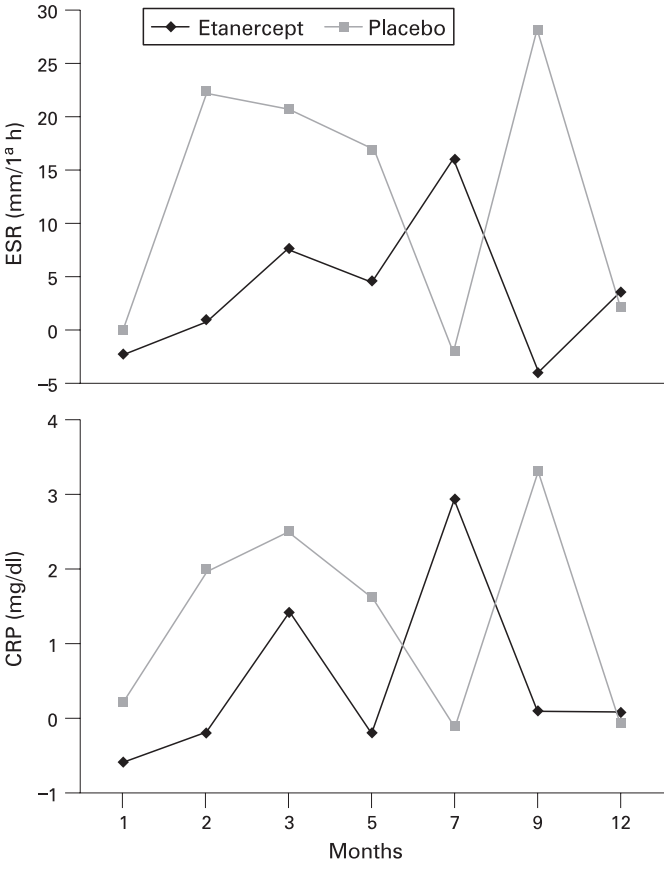

Figure 3 Acute phase reaction in patients with giant cell arteritis (GCA) during phase I of the study. Top panel: erythrocyte sedimentation rate (ESR). Bottom panel: C-reactive protein (CRP). Data are shown as absolute number variation with respect to the baseline levels.

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Table 3 Relapses during the study period

	Etanercept*	Placebo*	p Value
Phase I (months 0–12):			
Patients with relapse (%)	50	77.8	NS
No. of relapses	8	14	NS
Phase II (months 13–15):			
Patients with relapse (%)	25	100	NS
No. of relapses	1	1	NS

*For phase I: etanercept n = 8, placebo = 9; for phase II: etanercept n = 4, placebo = 1.
NS, not significant.

According to the present recommendations of the Spanish Society of Rheumatology, 11 patients (5 in the etanercept group and 6 in the placebo group) received TB prophylaxis with isoniazide. Of the 11 patients, 3 had a mild to moderate increased in the liver function test, and in 2 of them isoniazide was change to riphampicin for 4 months.

As stated above, the most frequent clinical manifestation of the relapse was a polymyalgic syndrome that resolved in all cases with an increase in prednisone dose. Four patients (two in each group) developed cephalea during the study period. There were no ischaemic manifestations after the randomisation process.

DISCUSSION

This is the first prospective double-blind placebo controlled study of etanercept therapy in patients with GCA. Due to the high efficacy of corticosteroid therapy in GCA and the lack of well demonstrated corticosteroid-sparing alternatives in patients with this type of vasculitis, we chose to include only patients with toxicity secondary to steroid therapy. The results of the present study are clearly limited by the sample size. Etanercept therapy was well tolerated in this aged population despite the high frequency of comorbidities.

The study group comprised only biopsy-proven patients with GCA with median disease duration of around 10 months, and despite this follow-up, patients were still being treated with prednisone doses over 15 mg/day. The study group was also selected because of the presence of toxicity secondary to corticosteroids in an attempt to explore the steroid-sparing effect of etanercept in a very well defined population that can benefit from a biologic agent.

During the complete duration of the study more patients in the etanercept group had good control of the disease compared with placebo. In fact, at the end of the 12 months of the double-blind phase of the study 50% of the patients in the etanercept group compared to 22.2% in the placebo group were able to control the disease activity without corticosteroid therapy. Furthermore, three out of the eight patients in the etanercept group were still asymptomatic without treatment 3 months after the end of the double-blind phase, in comparison to none in the placebo group. Although these differences did not reach statistical significance, patients in the etanercept group had a lower number of relapses and also a significantly lower dose of accumulated prednisone during the first year of treatment.

Another of the study outcomes was to evaluate the appearance of new side effects or worsening of previous corticosteroid side effects during the study. Despite a significantly lower dose of accumulated prednisone during the first year of treatment, there were no significant differences between the two groups. This finding might be explained by at least two points. First of all, patients were selected because of the presence of corticosteroid side effects, and therefore, most of them were already being treated and strictly monitored for these complications. Second, in this selected population, a longer follow-up might be necessary to observed clinically important differences.

Table 4 Frequency and types of adverse events (AE) during the study period

	Etanercept (n = 8)	Placebo (n = 9)	p Value
Patients with AE (%)	100	77.8	NS
No. of AE	23	23	NS
No. of serious AE	3	3	NS
Severity of AE:			
Low	62.5	33.3	NS
Moderate	25	33.3	NS
Severe	12.5	11.1	NS
Type of AE:			
Infections	4	4	NS
Injection site reaction	1	2	NS
Cardiac failure	1	0	NS
Abnormal liver function test	2	1	NS

NS, not significant.

The two study groups did not differ significantly with regard to either the overall rate of adverse events or the rates of specific events. The most common adverse events were infections, mostly upper respiratory tract infections, considered by the investigators as mild and none were accompanied by withdrawal from the study. Due to the high prevalence of TB in Spain, 11 patients received TB prophylaxis with isoniazide. It is interesting to note that in two of them isoniazide was changed to riphampicin because of a moderate increased in liver function test. Nevertheless, none of the patients presented with clinical signs or symptoms suggestive of tuberculosis during the study period. The most frequent clinical manifestation of the relapse was polymyalgic syndrome that resolved in all cases with the increase in prednisone dose; none of the patients developed ischaemic manifestations of the disease after the start of the study medication.

In previous studies, TNF antagonists have been shown to be effective in several cases of GCA resistant to corticosteroid therapy alone[27–29] and also immunosuppressive drugs.[26] Infliximab has also been explored as monotherapy in patients with GCA.[38] However, although the patients had a clear initial response, this was not followed by a sustained improvement. The authors suggested that infliximab should be used in GCA only for patients who are unresponsive to, or intolerant of, corticosteroids.[38] Despite the reported efficacy and safety of TNF antagonists in patients with refractory disease or patients experiencing significant corticosteroid side effects in open studies, these data have not been confirmed in a prospective controlled study with infliximab in patients with recent onset GCA.[35]

However, the results of the present study cannot be compared with the infliximab trial. Besides the use of a different TNF antagonist, we only included patients with biopsy-proven GCA. Patients in the etanercept trial had a median duration of GCA of around 10 months, and despite this follow-up, the patients were still being treated with a median dose of 15 mg/day of prednisone, indicating that these patients belonged to a subgroup with refractory disease. Furthermore, patients were also selected because of the presence of corticosteroid side effects, hence were a subgroup of patients that might obtain

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more benefit from corticosteroid-sparing agents. Finally, the duration of the present study was longer than the study by Hoffman *et al*.[35]

It is reasonable to assume that, in a condition like GCA in which the response to corticosteroids is a hallmark of the disease, it will be difficult to obtain a significant advantage for any treatment and especially so in trials with a short-term follow-up. Nevertheless, the identification of genetic, clinical or laboratory markers that can predict toxicity of corticosteroids or a subgroup with refractory GCA might help to select patients that can benefit from steroid-sparing agents, including biologicals.

The limited number of patients included in this study does not allow us to draw definitive conclusions. The therapeutic role of etanercept in patients with GCA and toxicity secondary to corticosteroid therapy should therefore be evaluated in studies with a larger number of patients.

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Ethics approval: The study was approved by the institutional review board and the ethics committee at each study centre.

Patient consent: All patients gave written informed consent.

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