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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 TNF antagonists led to sustained improvement and corticosteroid sparing effect in patients with giant cell arteritis (GCA). To confirm these observations, we conducted a randomized, double-blind, placebo controlled trial with etanercept in patients with biopsy-proven GCA with side-effects secondary to corticosteroids.

*** Methods:** We randomly assigned GCA patients to receive etanercept (n=8) or placebo (n=9) during 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 controlling the disease activity at 12 months.

*** Results:** Baseline characteristics were similar in the 2 groups although patients in the etanercept group showed higher levels of basal glycemia (p=0.02) and a higher 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=NS). 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 to draw definitive conclusions. Etanercept therapy was well tolerated in this aged population. The therapeutic role of etanercept in GCA patients should be evaluated in studies with a larger number of patients.

INTRODUCTION

Giant cell arteritis (GCA) is the most frequent vasculitis affecting the elderly **(1)**. Clinically, it can be manifested by 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 developed classification criteria that emphasize 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 localized antigen-driven T-cell immune response **(7)**, in individuals with a genetic predisposition associated with certain alleles of the 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 IL-1 and IL-6, that are readily demonstrated in the arterial wall infiltrate could serve as antigen presenting cells **(8,11-13)**.

On the other hand, GCA is characterized 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 IL-1, IL-6 and TNFą **(14)**. Recently, using immunohistochemical techniques, it has been reported the presence of TNFa and its receptors in endothelial cells and infiltrating mononuclear cells close to the internal elastic laminae of the inflamed vessels in patients with GCA **(15)**. The localization of TNFa 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 TNFa2 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. One month after clinical and laboratory parameters, mainly the acute phase reactants, have returned to normal, tapering can begin **(17)**. In a majority of patients the corticosteroids can be withdraw after 2 to 3 years of therapy **(3)**. Even tough corticosteroid therapy is clearly effective in GCA, it is not an ideal therapy due to the following facts: 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 smoldering involvement of the aorta or other large vessels resulting in aortic aneurysm or aortic arch syndrome **(21-23)**. d) Finally, 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 biological therapies with a remarkable efficacy for other inflammatory conditions has open new spectations 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 in for PMR, a close-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 significant corticosteroids´ side effects, these data have not been confirmed in prospective controlled studies with infliximab done in patients with recent onset GCA or PMR (**35,36**).

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

METHODS

- Patients: Patients were recruited at four Rheumatology Divisions in Spain. Initially the study was designed with the participation of 6 additional Centers, but had to be 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 should be 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 mm Hg, a diastolic blood pressure higher than 90 mm Hg, or the need of drug therapy for hypertension.

Patients were excluded if: **a)** had a clinical picture suggestive of GCA but without biopsy-proven arteritis, even if they meet the ACR Classification Criteria for GCA. **b)** Chronic infections such as HIV, Hepatitis B or C, fungal or mycobacterial infections etc. **c)** Neoplasm or a history of malignancy in the preceding 5 years. **d)** Patients with multiple sclerosis or other demilinizating disorders. **e)** Patients with cytopenias: leukopenia (leukocytes ≤ 3.5x109/L.), thrombocytopenia (platelets ≤ 100x109/L.) and/or anemia (haemoglobin ≤ 10 g./dl.). **f)** Any other condition that contraindicates etanercept therapy.

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

- Study protocol:

*** Study design:** The study was divided in 2 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 during three 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 have to be on stable dose of corticosteroids for at least 1 month. Etanercept or placebo was added to the current dose of corticosteroid, which was maintained stable in all patients during the first month after randomization. Thereafter, the 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)** From 30 to 15 mg. daily of prednisone, it was decreased by 5 mg./ weekly. **c)** From 15 mg. of prednisone to complete withdrawal it was decreased by 2.5 mg./weekly. If the patient developed a relapse (first relapse), the prednisone was raised during one 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 during one month to the previous dosage able to control the disease activity and then tapered at half the dosage of the same schedule. In case of a third relapse, the patient was withdrawn from the study and treated according to the judgment of the physician.

*** 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 appear during the study but 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 controlling the disease activity at 12 months, in patients who had developed side-effects secondary to corticosteroid treatment. The secondary outcomes were: 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 months follow-up phase of the study.

Clinical evaluations were performed at screening, baseline, every 2 weeks during the first 3 months of treatment and monthly thereafter. The following data were recorded at each visit: an structured questionnaire on symptoms of GCA, global evaluation of disease activity by the patient and physician (visual analogue scale, 0-100), laboratory evaluation (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 hospitalization or prolongation of existing hospitalization, 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 ischemic manifestations of GCA, such as diplopia, transient visual loss, jaw claudication or symptoms suggestive of cerebrovascular accidents, which should be immediately reported to the attending physician.

- Screening and treatment of latent tuberculosis infection: All patients had a chest X-rays and/or 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 $\geq$ 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.

- 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 of 75%, and the estimate efficacy in the placebo group of 15%. Assuming a 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 are reported as the mean (standard deviation) or, if skewed, as the median (interquartile range). Categorical variables were calculated as frequencies and percentages. The analysis was based on the intention-to-treat principle. Chi-squared and Fisher's exact tests have been used to check the association between categorical variables and treatment. Significant differences in numeric variables between treatment groups have been analysed using analysis of variance (ANOVA) in case of normally distributed variables, otherwise the Wilcoxon test has been

used. A *p* value less than 0.05 was considered as statistically significant. The SAS system has been used for data base design and for all statistical analysis.

RESULTS

- Baseline demographic and clinical characteristics of the patients: From April 14th 2003 to September 16th 2004, 8 patients were randomly assigned to and treated with etanercept and 9 patients were assigned and received placebo. The randomization, reasons for discontinuing treatment and the numbers of patients who completed the trial are shown in **Figure 1**. Baseline demographic and clinical characteristics were similar in the 2 groups (**Table 1**). The study group comprised typical GCA patients with a mean age of 74.5 ± 6.1 years and mostly females (82%). The median duration of GCA and previous corticosteroid therapy was almost 10 months, and despite this follow-up, patients were still on treatment with median prednisone dosage of 15 mg/day (**Table 2**). It is important to remark that all the patients had at least 1 comorbiditie, and a significant proportion of patients, especially in the etanercept group had 5 or more concomitant diseases. Patients in the etanercept group were more likely to have diabetes mellitus and showed a higher levels of basal glycemia 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 **Figure 2**, 50% of the patients in the etanercept group compared to 22.2% in the placebo group reached this end point (p=NS). 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 had also 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 (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% versus 50%) and the total number of relapses (14 versus 8) were higher in the placebo group, although the differences did not reach statistical significance (**Table 3**). Five patients entered the Phase II, 4 in the etanercept group and 1 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 (**Figure 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 DEXA values or in the number of new fractures between treatment groups. Only 2 patients had clinical symptoms suggestive of a fracture. One patient in the etanercept group had a fracture of the 5ª metatarsal bone at month 12, and 1 patient in the control group had axial pain highly suggestive of vertebral fracture that was not confirmed by plain x-ray. There were also no differences in the glycemic 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 of low severity and did not required their withdrawal 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 a gastrointestinal bleeding and other patient had two different traumatisms that were considered unrelated to the study medication.

According to the present recommendations of the Spanish Society of Rheumatology, eleven patients (5 in the etanercept group and 6 in the placebo group) received TB prophylaxis with isoniazide. Three out of the eleven patients 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 the increase in prednisone dose. Four patients (2 in each group) developed cephalea during the study period. There were no ischemic manifestations after the randomization 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 corticosteroids 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 age population despite the high frequency of comorbidities.

The study group comprised only biopsy-proven GCA patients with a median disease duration of around 10 months, and despite this follow-up, patients were still on treatment 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 a 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, 3 out of the 8 patients in the etanercept group were still asymptomatic without treatment three months after the end of the double-blind phase, in comparison with none of them in the placebo group. Although these differences did not reach statistically significance, patients in the etanercept group had a lower number of relapses and also a significant lower dose of accumulated prednisone during the first year of treatment.

Another of the outcomes of the study was to evaluate the appearance of new side effects or worsening of previous corticosteroid side effects during the study. Despite a significant lower dose of accumulated prednisone during the first year of treatment**,** there were not significant differences between the two groups. This finding might be explained by at least to facts. First of all, patients were selected because of the presence of corticosteroid side effects, and therefore, most of them were already treated and strictly monitored for these complications. Second, in this selected population, a longer follow-up might be necessary to observed clinically important differences.

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 of them was accompanied by the withdrawal of the study. Due to the high prevalence of TB in our country, eleven patients received TB prophylaxis with isoniazide. It is interesting to remark that in two of them isoniazide was change to riphampicin because of a moderate increased in the 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 a polymyalgic syndrome that resolved in all cases with the increase in prednisone dose and none of the patients developed ischemic manifestations of the disease after the start of the study medication.

In previous studies, TNF antagonists have shown to be effective in several cases of GCA resistant to corticosteroid therapy alone (**27-29**) and also immunosupressive drugs (**26**). Infliximab has also been explored as monotherapy in patients with GCA (**38**). However, and 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 significant corticosteroids´ 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 can not 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 ten months, and despite this follow-up, the patients were still on treatment with a median dose of 15 mg/day of prednisone, indicating that these patients belong to a subgroup with refractory disease. Furthermore, patients were also selected because of the presence of corticosteroid side effects, a subgroup of patients that might obtain more benefit of corticosteroid-sparing agents. Finally, the duration of the present study was longer than the study by Hoffman and co investigators (**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, especially 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 be evaluated in studies with a larger number of patients.

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COMPETING INTEREST

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FIGURE LEGENDS

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

Figure 2.- GCA patients without corticosteroid therapy during the 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*=NS).

Figure 3.- Acute phase reaction in GCA patients during the Phase I of the study. Top figure: erytrocyte sedimentation rate (ESR)**. Botton figure:** C reactive protein (CRP). Data are shown as absolute number variation with respect to the baseline levels.

Table 1.- Selected demographic and clinical characteristics at baseline.

	Etanercept (n = 8)	Placebo (n = 9)	*p*
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 , 24.9]	8.3 [1 , 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	143.4 ± 10	149.7 ± 22.4	0.8
Diastolic blood pressure	80.1 ± 10.7	87.9 ± 7.9	0.1
Glycemia (mg/dl)	113.9 ± 44.1	84.7 ± 5.4	0.02
HbA1c (%)	8.9 ± 1.7	7.5 ± 1	0.3
ESR (mm/1 hr)	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 a mean ± standard deviation.

Normal value: CRP: < 0.5 mg/dl. ESR ≤ 15 mm/1 hour.

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*
Approximate accumulated Prednisone dose (g) previous to the study:			0.6
- Mean ± SD	5.4 ± 3.05	9.2 ± 7.3	
- Median [CI 95%]	5.6 [2.6 , 8.2]	6.5 [3.5 , 14.8]	
Initial Prednisone dose (mg):			0.9
- Mean ± SD	18.1 ± 8.8	17.5 ± 7.7	
- Median [CI 95%]	15 [10.7 , 25.5]	15 [11.6 , 23.4]	
Acumulated dose 1 year (g):			0.03
- Mean ± SD	1.5 ± 1	3 ± 1.5	
- Median [CI 95%]	1.3 [0.6 , 2.4]	3.2 [1.8 , 4.1]	

Table 3.- Relapses during the study period.

	Etanercept (n = 8)	Placebo (n = 9)	*p*
Phase I (months 0 -12)			
- Patients with relapse (%)	50	77.8	NS
- Nº relapses	8	14	NS
	Etanercept (n = 4)	Placebo (n = 1)	*p*
Phase II (months 13 -15)			
- Patients with relapse (%)	25	100	NS
- Nº relapses	1	1	NS

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

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

Figure 1

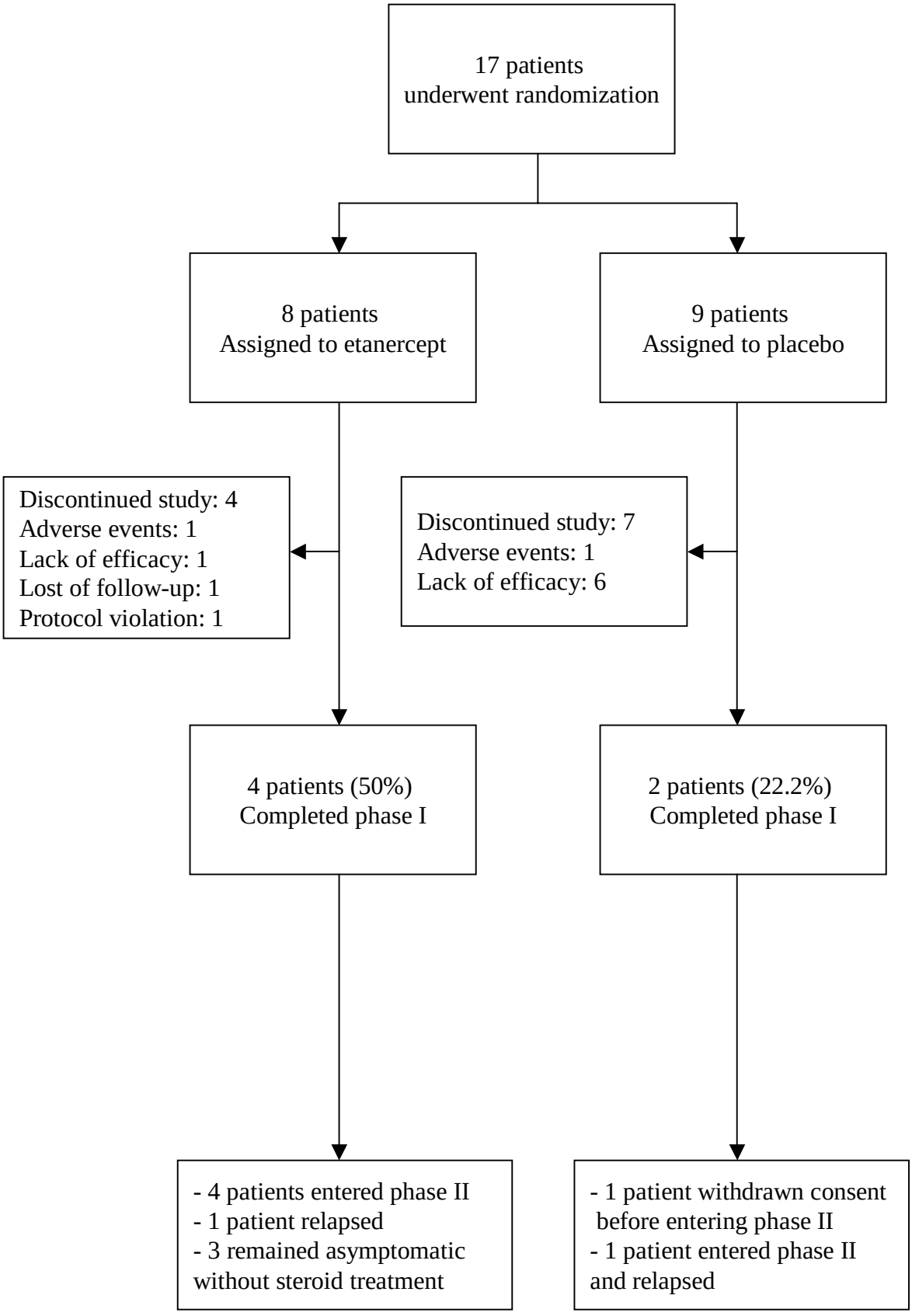


Figure 2

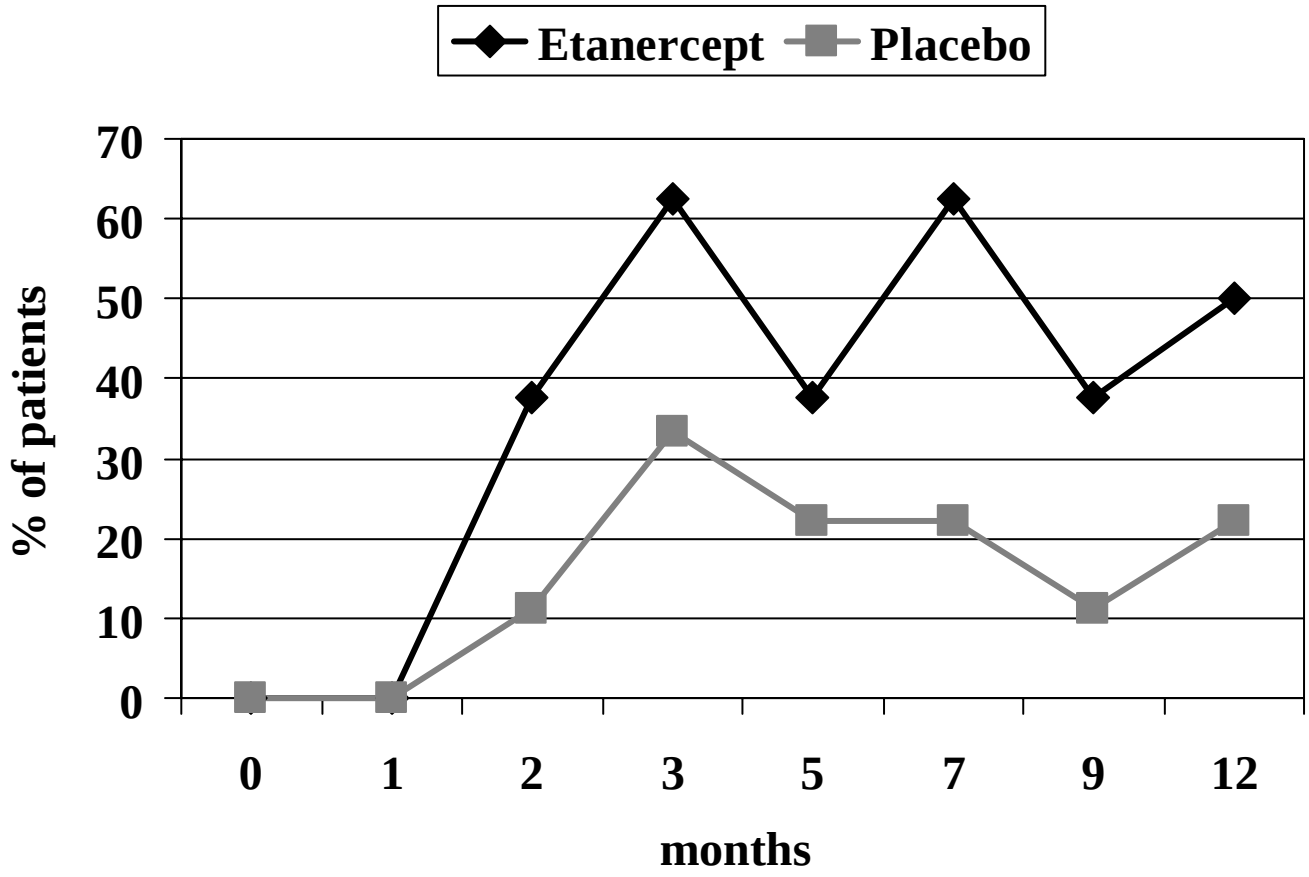
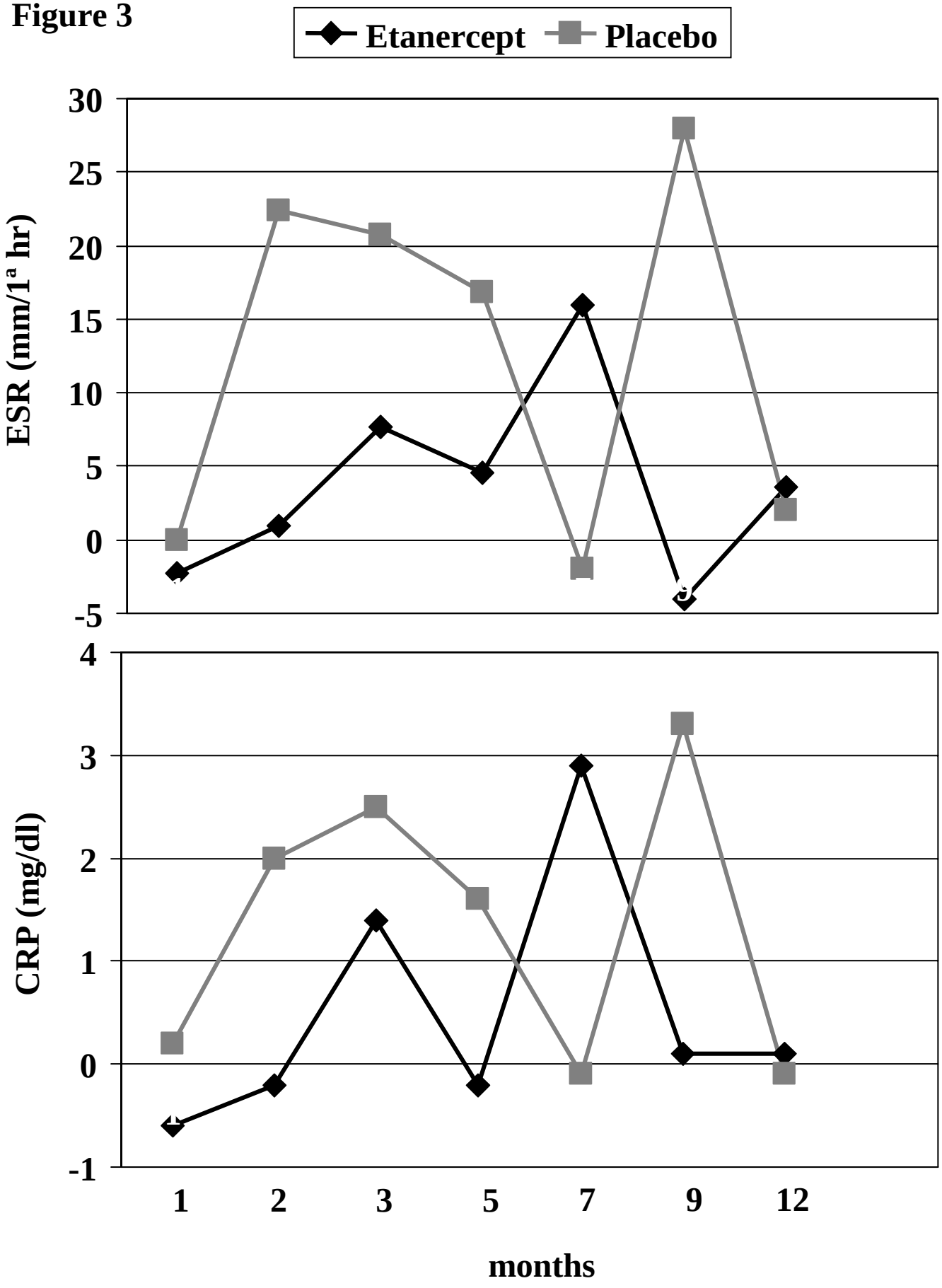


Figure 3



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

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