Clinical outcomes in a cohort of Colombian patients with rheumatoid arthritis treated with Etanar, a new biologic type rhTNFR:Fc

P.I. Santos-Moreno[1], G. Sánchez[2], D. Gómez[1], C. Castro[2]

[1]BIOMAB IPS: Rheumatoid Arthritis Center, Bogotá; [2]SIIES Research and Education in Health, Bogotá, Colombia.

Objective

To evaluate the clinical response at 12 month in a cohort of patients with rheumatoid arthritis treated with Etanar (rhTNFR:Fc), and to register the occurrence of adverse effects.

Methods

This is a multicentre observational cohort study. It included patients over 18 years of age with an active rheumatoid arthritis diagnosis for which the treating physician had begun a treatment scheme of 25 mg of subcutaneous etanercept (Etanar ® 25 mg: biologic type rhTNFR:Fc), twice per week. Follow-up was done during 12 months, with assessments at weeks 12, 24, 36 and 48. Evaluated outcomes included tender joint count, swollen joint count, ACR20, ACR50, ACR70, HAQ and DAS28.

Results

One-hundred and five (105) subjects were entered into the cohort. The median of tender and swollen joint count, ranged from 19 and 14, respectively at onset to 1 at the 12th month. By month 12, 90.5% of the subjects reached ACR20, 86% ACR50, and 65% ACR70. The median of DAS28 went from 4.7 to 2, and the median HAQ went from 1.3 to 0.2. The rate of adverse effects was 14 for every 100 persons per year. No serious adverse effects were reported. The most frequent were pruritus (5 cases), and rhinitis (3 cases).

Conclusion

After a year of following up a patient cohort treated with etanercept 25 mg twice per week, significant clinical results were observed, resulting in adequate disease control in a high percentage of patients with an adequate level of safety.

Key words

rheumatoid arthritis, disease-modifying anti-rheumatic drugs, anti-rheumatic agents, TNFR-Fc fusion protein, drug-related side effects, adverse reactions

Pedro I. Santos-Moreno, MD, MSc
Guillermo Sánchez, PhD
Danny Gómez, MD
Carlos Castro, MSc

Please address correspondence to:
Guillermo Sánchez, PhD,
SIIES Research and Education in Health,
Cr 8A, No 153-51,
110911 Bogotá, Colombia.
E-mail:
guillermosanchezvanegas@gmail.com

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Introduction

Rheumatoid arthritis is an inflammatory chronic disease, with marked effects with regards to quality of life and functional class (1). Treatments seek to control the inflammatory process, alleviate pain and avoid joint damage, maintaining or improving the functional state and the quality of life of those who suffer from this condition (2, 3). There are pharmaceuticals able to prevent joint destruction, which have been described as disease-modifying anti-rheumatic drugs (DMARDs) (4). In some cases, these drugs have not been effective, or the patients experience serious adverse effects (5-7). This situation has led to the development of a new generation of drugs which inhibit the tumour necrosis factor cytokine, which plays an important role in joint inflammation, and which has demonstrated to be effective in this disease control (7). These drugs are known as biological therapy or biological DMARDs, which promise better clinical results, but are not exempt from presenting adverse effects (8, 9). The fusion protein rhTNFR:Fc (recombinant tumour necrosis factor receptor:Fc) is a soluble protein which joins and deactivates the tumoural necrosis factor (TNF), resulting in a block of TNF-α, reducing inflammation and reducing the disease activity in rheumatoid arthritis patients (10-12). Etanar-25 mg is an rhTNFR.Fc, and it has the same structure as etanercept (10). This molecule is available in Colombia, and has been approved by regulatory agency (INVIMA: national institute for surveillance of medicines and food), based on preclinical and clinical studies conducted mainly in China (10, 13). This drug is usually prescribed when DMARDs such as methotrexate alone or in combination with other DMARDs have not presented favourable results (8).

Most studies on which the efficacy and safety of etanercept have been demonstrated have been controlled clinical trials, which may overestimate the effect, due to their being performed in controlled conditions under which patients adjust to strict administration regimens, based on the protocol (7, 8, 14). In spite of strengths in bias control, it is probable that in real life settings these drugs present different results in terms of disease control. Thus, a study with conditions similar to those in real life was performed, in order to assess the clinical response at 12 months and record the occurrence of adverse events in a cohort of patients with rheumatoid arthritis treated with rhTNFR:Fc (Etanar 25 mg).

Materials and methods

Study design, patients and outcomes

An observational cohort study was carried out in 13 Colombian reference centres, including patients over 18 years of age with an active rheumatoid arthritis diagnosis in spite of being under treatment with DMARDs. Patients who had begun a treatment scheme with 25 mg of subcutaneous etanercept, twice per week (Etanar® 25 mg, approved for using in Colombia) were included. Follow-up was done over 12 months, with evaluations performed at weeks 12, 24, 36 and 48. Outcomes evaluated included: tender joint count (TJC), swollen joint count (SJC), Health Assessment Questionnaire (HAQ), Disease Activity Score 28 (DAS28), and American College of Rheumatology response criteria (ACR20, ACR50, ACR70).

ACR calculus was made in accordance with the ACR guidelines, including the evaluation of painful and oedematous joints, along with the assessment of the following five criteria: evaluation of the overall condition by the physician, self-report of physical function, degree of pain and overall condition (visual analogue scale from 0 to 10), added to the assessment of an acute-phase reactant (ESR) (15). Specifically, the assessments of ACR20, ACR50, and ACR70, are clinical improvement measurements that have been widely accepted (15, 16). ACR20 represents the percentage of patients who achieve at least a 20% improvement in their painful and oedematous joint count, and in three of the five criteria described (overall assessments by the doctor and patient, functional state, and ESR). Threshold was also assessed for 50% and 70% (ACR50 and ACR70, respectively).

The safety evaluation included the search for signs or symptoms suggestive of adverse effects at the physical exam, and the performance of biochem-

ical and haematological tests. Adverse effects were defined as those injuries that occurred during the study, or when the severity or frequency of a pre-existing injury increased during the study. A serious adverse effect was defined as an effect that caused death, constituted a threat to the patient's life, generated or prolonged hospitalisation, were cause for a surgical intervention, or produced disability, cancer, or an infection associated with death or hospitalisation.

Statistical analyses

Analyses included the general description of clinical and demographic variables. The distribution of numerical variables was evaluated using the Shapiro Wilk test. The behaviour of TJC, SJC, DAS28 and HAQ were evaluated using the median of each follow-up point, and was contrasted using the Friedman's non-parametric test for related samples. The proportions of subjects that reached the threshold of ACR (20, 50, and 70) were compared throughout the follow-up employing Cochrane's Q statistic. For hypothesis contrast a *p*-value <5% was considered.

Ethical considerations

This study meets the international guidelines related to the recommendations for research with human beings set forth in the Nuremberg Code, the Helsinki Declaration (latest revision Brazil 2013), and the Belmont Report; likewise, it follows the recommendations raised in the Resolution 8430 of 1993 of the Colombian Health Ministry. It was approved by an independent ethics committee and each patient granted his or her consent for the use of their information.

Results

This cohort included 105 subjects, 88.5% were women (93/105), 100% of which completed a six-month follow-up. Of these, 80% (84/105) had follow-up at 9 and 12 months. The median duration of the disease was 9.6 months. At the outset of the cohort 66% were seropositive (69/105) and the average prior use of DMARDs was of 2.9. These were used in the doses and recommended schemes. The patients' characteristics at the outset are described in Table I.

Table I. General population characteristics at the beginning of the cohort.

Variable	Min	p25	Median	p75	Max
Age	26	50	56	61	77
Time of disease – years	0.27	4.5	9.6	14.6	54.2
TJC	0	11	19	40	68
SJC	0	10	14	26	50
HAQ	0.05	1.1	1.3	1.8	2.55
DAS28	0.8	2.6	4.7	5.3	6.3
ESR	1	23	30	40	71

Min: minimum value; p: percentile; Max: maximum value; TJC: tender joint count; SJC: swollen joint count; HAQ: Health Assessment Questionnaire; DAS28: Disease Activity Score; ESR: erythrocyte sedimentation rate.

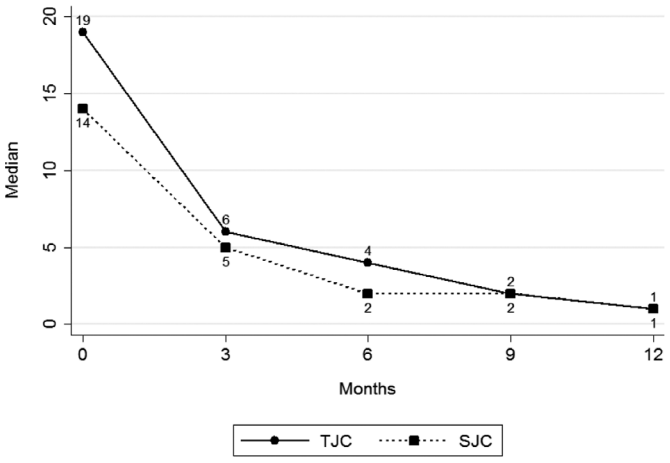

Fig. 1. Joint count median: 12-month follow-up. TJC: tender joint count; SJC: swollen joint count.

Follow-up to clinical outcomes

At the moment of entering the cohort, the median of TJC was 19, and SJC was 14, respectively. These counts were reduced progressively, reaching, by month 12, a median of one for both TJC and SJC. The median count behaviour at the time of each follow-up is illustrated in Figure 1.

The DAS 28 median at the moment of joining the cohort was 4.7, and reached 2 by the final visit (month 12). Likewise, HAQ went from a median of 1.3 to 0.2 in the fourth follow-up visit. Significant differences were established in the behaviour of DAS 28 throughout the follow-up (*p*-value = 0.000), as well as for HAQ (*p*-value = 0.000). The descriptive statistics and the behaviour of the distribution along the follow-up are presented in Table II, and the behaviour of the DAS28 and HAQ are illustrated in Figure 2.

The ACR 20 results showed that 74% of the patients (78/105) reached an improvement of at least 20% by the third month, and 90.5% (76/84) of the patients reached that level of improvement by month 12 (*p*-value = 0.000). The assessment of the percentage of patients who reached responses of 50% and 70%, along with ACR 20 behaviour are presented in Figure 3.

Adverse events report

During the 12-month follow-up, in the group of 105 patients 15 adverse events were reported (adverse events rate: 14 events per 100 people per year). There were no reports of serious adverse events. In two cases the physician ordered patients to suspend the medicine (leukopenia and pruritus). The adverse events reported are described in Table III.

Discussion

The follow-up of this cohort showed an adequate response from the patients to the treatment with Etanercept, with a marked improvement during the first trimester of treatment, and a sustained effect over 52 weeks of clinical evaluation. Different authors have reported similar results, confirming the effectiveness of etanercept (17, 18). TJC and SJC evidenced a significant reduction dur-

Table II. DAS28 and HAQ behaviour. Follow-up to 12 months.

		n	Min	p25	p50	p75	Max	*p*-value (Friedman)
DAS28	Baseline	105	0.8	2.6	4.7	5.3	6.3	0.000
	Month 3	105	0.5	2.1	3.1	4.2	6.5	
	Month 6	105	0.8	2	3	3.5	5.1	
	Month 9	84	0.5	2	3	3.4	4.7	
	Month 12	84	0.5	2	2	3.0	4.2	
HAQ	Baseline	105	0.1	1.1	1.3	1.8	2.6	0.000
	Month 3	105	0	0.3	0.7	1.2	2.4	
	Month 6	105	0	0.1	0.4	0.9	2.4	
	Month 9	84	0	0.1	0.3	0.7	2	
	Month 12	84	0	0	0.2	0.6	1.7	

n: number of subjects; Min: minimum value; p: percentile; Max: maximum value: DAS28: Disease Activity Score; HAQ: Health Assessment Questionnaire.

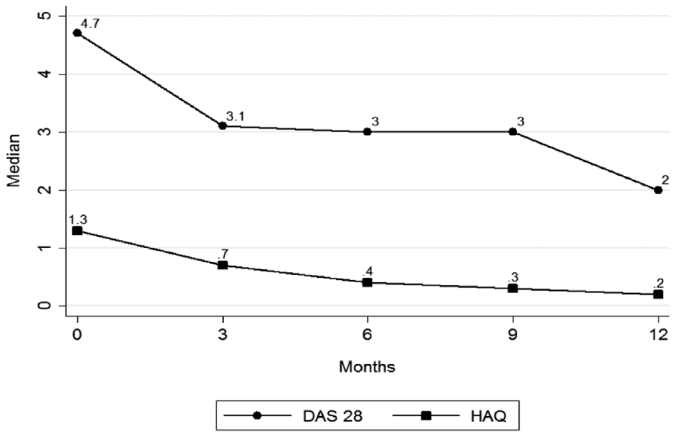

Fig. 2. DAS28 and HAQ median: 12-month follow-up. DAS28: Disease Activity Score, HAQ: Health Assessment Questionnaire.

ing the first and second trimester, and a stable behaviour over the following six months. These findings are consistent with those given by Larry *et al*. who described a reduction at the sixth month of 56% in the mean of TJC. Our study reported a reduction at the sixth month of 79% in the median number of TJC.

Most of the studies which have evaluated the efficacy or effectiveness of etanercept have done through comparison of improvement with the ACR20, ACR50, and ACR70 indices (8). In this study the results showed an excellent behaviour of these indicators during the first and second trimesters, after which a plateau of effectiveness is reached in which at least 90% of the cases reach an improvement of 20%. The study by Klareskog reported that at the third month more than 70% of the patients reached ACR20, and those results were maintained over 26 months of follow-up (18). The systematic review by Wiens and collaborators showed an ACR20 of 55% at the sixth month and of 77% at the first year (17).

The results of ACR50 and ACR70 demonstrate an excellent response from the patients. It is worth it to highlight that during the first semester only 13.3% and 41% reached ACR70 and ACR50, respectively. However, by month 12 this result reached 65% for ACR70 and 86% for ACR50. These results are markedly superior to those reported in Klareskog's study, who reported at month 12 an ACR50 of 45%, and ACR70 of 22%. In general, despite finding results that are consistent with the literature, the patients of our cohort reached better clinical results, given that a considerable number of patients achieved improvements above 70%. These results can be explained because it is a cohort of patients with a median of 9.6 months duration (early arthritis cohort), which implies a better prognosis. However, it is important to take into account that these results have been documented in an observational setting, under real life conditions, in which it is undeniable that potential observer and observed biases may be present, as described in what has been described as the Hawthorne effect (19). Despite the recognition of the possibility of and overestimated effect by the patient and the treating physician, the important number of clinical measures and the consistence of the findings allow for concluding that the rhTNFR:Fc (Etanar) molecule produces a significant clinical improvement, which is sustained over 12 months of follow-up.

The assessments of HAQ and DAS28 showed a remarkable improvement, which coincides with the outcomes estimated with the ACR and the joint counts. This presents a marked improvement during the first trimester, and maintained throughout the follow-up.

The adverse events described for this cohort allow for appreciating an adequate safety profile for etanercept, without having documented deaths or serious adverse events. The events that arose in this study are similar to the habitual literature reports (8, 17). Pruritus and rhinitis were predominant, and they are amply described as possible associated events. Although in the literature there have been descriptions of increases in the rates of infection, in this cohort there was only one documented case of herpes labialis. It is important to take into account that the present study used doses of 25mg twice a week, as was administered in the study by Hu *et al*. (10), in which rhTNFR:Fc was compared to methotrexate, documenting a low rate of adverse effects, with a safety profile similar to the one reported by this research.

Notwithstanding the obvious benefits derived from treatment with a molecule such as rhTNFR:Fc (Etanar), it is important to note that the management of this type of patient must always be given in the framework of strategies of the treatment by therapeutic targets (T2T: Treat to target), given that the clinical results in the context of a comprehensive programme based on targets allow the physician to offer the patients care that guarantees a reduction in the disease progression, improving their adherence to the treatment and having an effect on their quality of life. (20, 21).

The limitations of this study are those inherent to observational studies, in which, as was previously described, a

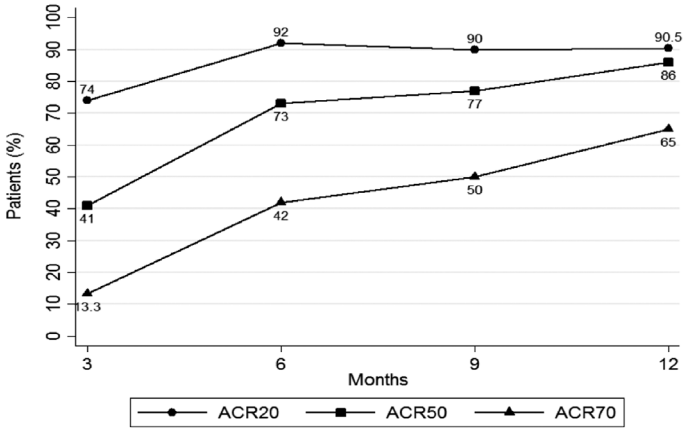

Fig. 3.
Clinical improvement: ACR 20, ACR 50 and ACR 70: 12-month follow-up. ACR: American College of Rheumatology response criteria.

Table III. Frequency of adverse events.

Event	n	%
Pruritus	5	33.3
Rhinitis	2	13.3
Leukopenia	1	6.7
Peripheral neuropathy	1	6.7
Cephalea	1	6.7
Lower member oedema	1	6.7
Diarrhoea	1	6.7
Vascular ulcer	1	6.7
Herpes labialis	1	6.7
Injection site reaction	1	6.7
Total	15	100.0

n: number of subjects.

bias may be present in the observer who knows the intervention and at the same time is the person tasked with evaluating outcomes. Having outcomes that can be evaluated with simple counts can minimise, to some degree, the existence of measurement bias. Even with these difficulties, the results obtained are consisted with previous studies and have the strength of originating in uncontrolled scenarios, which may resemble conditions nearing habitual practice.

The results here presented are relevant to the clinical practice, in the context of a country such as Colombia, where patients and institutions face the high cost of biological DMARDs, and where different alternatives to etanercept may be found in the market place, in price ranges that may be an average of 27% above that of a drug that clinically effective and safe such as Etanar (22).

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