Effectiveness, Predictive Response Factors, and Safety of Anti-Tumor Necrosis Factor (TNF) Therapies in Anti-TNF-Naive Rheumatoid Arthritis

ANTONIO FERNÁNDEZ-NEBRO, MARÍA V. IRIGOYEN, INMACULADA UREÑA, MARÍA A. BELMONTE-LÓPEZ, VIRGINIA CORET, FRANCISCO G. JIMÉNEZ-NÚÑEZ, GISELA DÍAZ-CORDOVÉS, MARÍA A. LÓPEZ-LASANTA, ANTONIO PONCE, MANUEL RODRÍGUEZ-PÉREZ, ENRIQUE CALERO, and PEDRO GONZÁLEZ-SANTOS

ABSTRACT. ***Objective.*** To evaluate the effectiveness and safety of anti-tumor necrosis factor (anti-TNF) therapies in rheumatoid arthritis (RA), and to identify the factors involved in this response.

Methods. Dynamic prospective cohort study of patients with RA treated with anti-TNF under clinical practice conditions. Effectiveness was evaluated using Disease Activity Score (DAS) 28, European League Against Rheumatism (EULAR) response, Health Assessment Questionnaire (HAQ), and time to treatment failure. Prior adherence was evaluated retrospectively and safety was evaluated by adverse events (AE). The analysis was restricted to anti-TNF-naive patients.

Results. The study included 161 patients treated for RA during 6 years (60 infliximab, 79 etanercept, and 22 adalimumab). At 6 months, 15% reached a good EULAR response and 38% a moderate response. A mean decrease of –1.5 ($p < 0.0001$) was observed in the DAS28 and of –0.34 in the HAQ ($p < 0.0001$); however, women showed poorer progress in terms of DAS and HAQ. In the first year, 64.3% did not experience treatment failure and this figure was 50.5% after 2 years. In one-third, glucocorticoids were withdrawn and in the remainder the dose was reduced by 50%. Adherence to treatment, selection of etanercept, and intensification of infliximab were associated with a lower probability of premature failure in the multivariate model. AE were similar to those in other studies and no outstanding differences in safety were found between the 3 anti-TNF therapies.

Conclusion. Anti-TNF treatments are effective and safe, reducing the activity of the disease, disability, and the need for corticosteroids. Patients who displayed good adherence prior to the anti-TNF treatment and were treated with etanercept or with increasing doses of infliximab had the best chance of displaying a response. (First Release Nov 1 2007; J Rheumatol 2007;34:2334–42)

Key Indexing Terms:
RHEUMATOID ARTHRITIS INFLIXIMAB ETANERCEPT ADALIMUMAB
EFFECTIVENESS SAFETY COHORT STUDY

Rheumatoid arthritis (RA) is a chronic, progressive, destructive, and disabling disease with a prevalence of between 0.5% and 1% of the population[1]. Methotrexate (MTX), leflunomide, and sulfasalazine are the most recommended conventional disease modifying antirheumatic drugs (DMARD), and should be used as soon as the diagnosis is established. However, between 10% and 20% of patients are resistant to conventional treatment[2] and may require the use of alternative therapies, such as tumor necrosis factor-blocking agent (anti-TNF).

Anti-TNF drugs have been available in Europe for more than 5 years, since the principal clinical trials showed that they were effective and safe for the treatment of early[3-7] and longstanding RA[8-13]. However, the majority of patients undergoing anti-TNF therapy in clinical practice would not meet the criteria for inclusion in these clinical trials[14] and they may not respond as well to these treatments[15]. Therefore, 2 questions should be addressed: whether the effectiveness and safety of these agents is the same under real clinical practice conditions, and which factors influence the response to anti-TNF.

Our objective was to determine the effectiveness and safety of infliximab, etanercept, and adalimumab under normal clinical practice conditions and in a cohort of patients with RA; and to identify the factors involved in the response to anti-TNF.

From the Servicio de Reumatología, Hospital Regional Universitario Carlos Haya, and Departamento de Medicina, Facultad de Medicina de Málaga, Málaga, Spain.

A. Fernández-Nebro, MD, PhD, Servicio de Reumatologia, Hospital Regional Universitario Carlos Haya, Facultad de Medicina de Málaga; M.V. Irigoyen, MD; I. Ureña, MD, PhD; M.A. Belmonte-López, MD; V. Coret, MD; F.G. Jiménez-Núñez, MD, PhD; G. Díaz-Cordovés, MD; M.A. López-Lasanta, MD; A. Ponce, MD, PhD; M. Rodríguez-Pérez, PhD; E. Calero, MD, Servicio de Reumatología, Hospital Regional Universitario Carlos Haya; P. González-Santos, MD, PhD, Departamento de Medicina, Facultad de Medicina de Málaga.

Address reprint requests to Dr. A. Fernández-Nebro, Rheumatology Service, Hospital Regional Universitario Carlos Haya, Pabellón C: "Hospital Civil," Plaza del Hospital Civil s/n, 29009 Málaga, Spain. E-mail: afnebro@gmail.com

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MATERIALS AND METHODS

This non-random quasiexperimental study was carried out in a tertiary care center (reference population 628,912). From March 1999, all patients with RA [according to American College of Rheumatology (ACR) criteria[16]] who did not respond to at least 2 DMARD, including MTX, and who in the opinion of their doctors required biological therapy, were included in a structured clinical followup protocol. No formal level of activity was required for their inclusion.

Followup and treatment protocol. The protocol was approved by the center's Ethical Committee and included the collection of retrospective data related to disease diagnosis, its duration, and previous treatments. The timing of the reviews could vary, although the visits at 0, 3, 6, and 12 months and then annually were fixed.

At each visit, a complete examination was carried out and information was obtained on the treatment and any adverse effects. Similarly, information was gathered on the core set of variables recommended by the European League Against Rheumatism (EULAR)[17]. A visual analog scale of activity was assessed by the doctor, and patients completed a Spanish version of the Health Assessment Questionnaire (HAQ)[18]. Blood was extracted for routine laboratory tests that included assessment of acute-phase reactivity and the rheumatoid factor (RF).

Adherence was considered to be good if, in the doctor's opinion, the patients had demonstrated a willingness and the capacity to follow the recommendations indicated (treatments, appointments, other medications, etc.) at the visits up to the moment of entering the program. This dichotomous variable was recorded retrospectively and the adherence was taken into account only up to the moment that they commenced the anti-TNF treatment, but not after. Data for patients treated with infliximab was collected by the same rheumatologist (VC) just before each infusion at the day hospital, while the rest were collected by their respective doctors at their appointments at an external clinic.

From December 2000, all patients were evaluated and if necessary, treated for active or latent tuberculosis following the recommendations of the European and Spanish drug agencies[19]. The anti-TNF treatment was chosen by the doctor and depended, in part, on the availability of each formulation in our country at any given time (etanercept from 1999, infliximab from 2000, and adalimumab from 2003) and the preference of the patient for the route of administration. Infliximab (Remicade, Schering-Plough, SA, Madrid, Spain), etanercept (Enbrel, Wyeth Laboratories, Madrid) and adalimumab (Humira, Abbott Laboratories, Spain) were initially administered according to the technical data sheets. There were no restrictions on the use of DMARD, steroids, and nonsteroidal antiinflammatory drugs (NSAID). The treatments were readjusted or interrupted by the doctor according to the clinical response and/or adverse events (AE). After temporary interruptions, the patients were reincorporated into the same group, while after longer interruptions they could change to another anti-TNF.

Evaluation criteria. The effectiveness and safety outcomes were evaluated in all patients who received at least one dose of anti-TNF (intention to treat analysis). The primary efficacy endpoint was the time to treatment failure, defined as the definitive withdrawal of anti-TNF for any reason, or the substitution or addition of concomitant DMARD to maintain the efficacy of the anti-TNF. Changes in the dose of anti-TNF, DMARD, NSAID, or corticosteroids were not considered treatment failures.

The secondary efficacy endpoints were analyzed at the sixth month of treatment and included: EULAR criteria[20], change from the baseline value in the Disease Activity Score 28 (DAS28)[21-23], HAQ, and the minimal clinically important difference (MCID) in physical function (reduction in HAQ $\geq$ 0.22)[24].

Safety was evaluated by the information on AE obtained by examination and patient self-report at each visit. AE were graded as mild (easily tolerated, did not require specific treatment or prolong hospitalization, and did not require the drug to be withdrawn), moderate (interfered with activities without directly threatening the life of the patient, required drug treatment, and may or may not require withdrawal of the medication), and serious (life-threatening or caused death, required or prolonged hospitalization, caused significant permanent sequelae, or induced fetal alterations or malformations).

Statistical analysis. Patients were not excluded due to lack of data, and lost data were managed with the last-observation carried forward method. Since the order of prescription of the anti-TNF treatments may influence its efficacy[25], we restricted the analysis to anti-TNF-naive patients to improve the comparison between groups. The basal homogeneity between treatment groups was checked using one-way analysis of variance (ANOVA) — with Bonferroni post-hoc analysis — or the 2-tailed chi-squared test with a 0.05 significance level. The efficacy in terms of DAS28 and HAQ at 6 months and the comparison between sexes at 24 months was assessed using the repeated-measures ANOVA test, with Bonferroni post-hoc analysis. The EULAR response was evaluated using 2-tailed chi-squared and the use of glucocorticoids using the Wilcoxon signed-rank test.

The rates were expressed per 100 patient-years with a 95% confidence interval (CI). Kaplan-Meier curves and the log-rank test were used to estimate the time to treatment failure and to compare the survival functions between groups, respectively. Cox regression was used to identify the prognostic factors of time to treatment failure in uni- and multivariate analysis. The baseline variables included in the univariate analysis were sex, age, duration of disease, Charlson comorbidity index, RF, DAS28, HAQ, erythrocyte sedimentation rate, C-reactive protein, good adherence, previous number of DMARD, corticosteroids, anti-TNF selected, and year of initiation of first anti-TNF treatment. All variables that reached a value of $p < 0.10$ were included in the Cox multivariate model (stepwise forward/Wald; p in 0.05 and p out 0.10). Statistical analysis was carried out using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

The 161 patients included in our study (81% women) from March 1999 to January 2006 had a mean age of 54 ± 12 years [± standard deviation (SD), range 27–81]. During the followup, 232 anti-TNF regimens were established (68 infliximab, 122 etanercept, and 42 adalimumab) and while 56 (35%) patients received more than one treatment, 15 (9%) received all 3. The mean followup time of the anti-TNF-naive patient cohort was 20.6 ± 16.8 months (± SD, range 0.0–62.2), with a median of 24 months and time of exposure to anti-TNF of 276.8 patient-years. The demographic and basal clinical characteristics of the 161 anti-TNF-naive patients were quite homogeneous between the groups, excluding the use of concomitant DMARD (Table 1).

Effectiveness. After 6 months (n = 158), 23 (15%) patients achieved a good EULAR response and 60 (38%) a moderate one, although only 13 (8%) reached clinical remission (DAS28 < 2.6). The mean reduction in DAS28 from the baseline value was –1.5 ± SD 1.4 ($p < 0.0001$) and that in the HAQ was –0.35 ± 0.54 ($p < 0.0001$). There were 78 (49%) cases that reached an MCID in HAQ (HAQ reduction $\geq$ 0.22), but only 3% reached a HAQ = 0. Etanercept produced a superior response to infliximab in terms of the DAS28, but not in HAQ or in the EULAR responses (Table 2).

There were essentially no differences between men and women in terms of age at diagnosis of arthritis, the age at which anti-TNF therapy was initiated, the doses of anti-TNF, the number of DMARD received previously, percentage concomitantly receiving DMARD and/or corticosteroids, doses of corticosteroids, and basal levels of the DAS28 and HAQ. In

Table 1. Patient demographic and baseline clinical characteristics.

	Infliximab, n = 60	Etanercept, n = 79	Adalimumab, n = 22
Age, yrs	54.0 ± 11.6	54.0 ± 12.4	54.0 ± 10.4
Age at diagnosis, yrs	44.4 ± 13.1	43.7 ± 13.0	44.6 ± 11.2
Women, %	88	76	82
Duration of disease, yrs	9.6 ± 7.9	9.9 ± 7.9	9.5 ± 8.3
Charlson's Comorbidity Index, 0–37	1.2 ± 0.5	1.4 ± 0.8	1.4 ± 0.9
Age adjusted Charlson's Comorbidity Index, 0–43	2.3 ± 1.2	2.4 ± 1.5	2.4 ± 1.3
Rheumatoid factor, %	78	77	81
Rheumatoid nodules, %	15	22	23
Adherence to treatments, %	87	86	84
No. of previous DMARD	3.8 ± 1.5	3.8 ± 1.5	3.6 ± 1.3
Concomitant DMARD, %*			
No DMARD	8	46	27
Methotrexate	83	52	50
Leflunomide	8	3	9
Sulfasalazine	0	0	5
Hydroxychloroquine	0	0	5
Methotrexate plus hydroxychloroquine	0	0	5
Corticosteroids, %	65	67	48
Prednisone (equivalent) dose mg/day	7.5 ± 4.4	8.9 ± 8.2	9.9 ± 5.9
Tender joints, 0–28	16.6 ± 8.3	13.6 ± 7.9	13.3 ± 6.2
Swollen joints, 0–28	11.1 ± 7.3	9.7 ± 6.7	9.5 ± 7.8
Duration of morning stiffness, min	73.0 ± 106.7	66.8 ± 89.2	60.7 ± 45.9
Pain, 0–100	63.7 ± 21.5	68.1 ± 20.8	69.5 ± 20.4
Patient's global assessment, 0–100	64.3 ± 21.7	71.4 ± 20.2	69.0 ± 20.0
Physician's global assessment, 0–100	64.0 ± 15.9	66.5 ± 15.0	68.2 ± 7.8
ESR, mm/h	33.3 ± 22.8	33.5 ± 25.1	41.1 ± 24.3
CRP, mg/l	23.7 ± 22.2	23.1 ± 18.4	17.4 ± 15.2
DAS28	6.2 ± 1.3	5.9 ± 1.4	6.2 ± 0.9
HAQ disability, 0–3	1.78 ± 0.56	1.71 ± 0.65	1.74 ± 0.71
Hemoglobin level, g/l	125 ± 24	123 ± 18	125 ± 14
Leukocyte count, $\times 10^3/\mu l$	7.8 ± 2.8	7.5 ± 2.3	8.8 ± 2.4
Platelet count, $\times 10^3/\mu l$	278 ± 80	275 ± 76	332 ± 85
Albumin, g/l	3.8 ± 0.5	3.6 ± 0.4	3.6 ± 0.3

Results are expressed as mean ± standard deviation unless otherwise indicated. * $p < 0.001$. DMARD: disease modifying antirheumatic drugs; DAS: Disease Activity Score; HAQ: Health Assessment Questionnaire.

Figure 1A, the evolutionary profile of DAS28 can be seen according to sex in a general linear model over 24 months (median followup of the cohort). For both sexes, the DAS28 decreased with time ($p < 0.0001$), but while in women it stabilized from the third month onwards, in men it continued to decrease until the end of the first year ($p < 0.0001$). A similar, although more gradual, phenomenon was observed with the evolution of HAQ at 24 months ($p < 0.0001$) and with the time/sex interaction ($p = 0.017$).

The failure rate of anti-TNF was 35.4 per 100 patients/year (95% CI 34.7–36.2) and the median time to failure was 24.1 months (95% CI 12.0–36.3). The probability of remaining without any treatment failure was 64.3% in the first year and 50.5% in the second year (Kaplan-Meier method). The patients who received etanercept remained for longer without treatment failure than those treated with infliximab during the first 24 months (log-rank test, $p = 0.032$: Figure 1B and Table 3), and they had a lower failure rate throughout the followup period [rate ratio 0.6 (95% CI 0.4–0.9)].

Anti-TNF dose and concomitant medication. In 33 (55%) patients administered infliximab, the treatment was intensified by scaling up the dose to a mean of 4.9 ± 0.3 mg/kg/infusion (range 4–6) and/or cutting the interval to 6 weeks ($p < 0.0001$). The most common scale-up regime was 5 mg/kg/8 weeks, which was used in 23 (38%) patients. These patients remained longer without treatment failure (median 37.7 mo; 95% CI 18.5–56.9) than the rest of the cohort (28 mo; 95% CI 8.3–28.9; $p = 0.0434$) without suffering more AE. In the etanercept group, the administration interval was extended in 8 patients (10%) to 25 mg/week and in 4 (5%) to 25 mg/2 weeks, without increasing the risk of failure ($p = 0.3232$). The administration guidelines were not modified in the adalimumab group.

Of the 161 patients included, 113 (70%) took some con-

Table 2. Response to infliximab or etanercept at 6 months (intention to treat analysis).

	Infliximab	Etanercept	p
No. of patients	60	78	
DAS28 at 6 mo, mean ± SD*			0.030
Baseline	6.2 ± 1.3	5.9 ± 1.4	
6 mo	5.0 ± 1.5	4.3 ± 1.5	
Absolute change	–1.3 ± 1.2	–1.7 ± 1.5	
Percentage change	21	29	
DAS28 at 6 mo < 2.6, %†§	4	14	0.045
EULAR response at 6 mo, %†			0.152
Good response	11	25	
Moderate response	49	43	
No response	40	32	
HAQ at 6 mo, mean ± SD††			0.218
Baseline	1.77 ± 0.58	1.72 ± 0.66	
6 mo	1.45 ± 0.60	1.27 ± 0.74	
Absolute change	–0.32 ± 0.37	–0.46 ± 0.63	
Percentage change	18	27	
MCID HAQ, %†	58	57	0.951
HAQ = 0, %†	2	4	0.448

* Repeated-measures ANOVA at 0, 3, and 6 months (Pilai-trace test): Intrasubject effect of time ($p < 0.0001$) and intersubject effect of type of anti-tumor necrosis factor ($p = 0.030$). Infliximab vs etanercept; Bonferroni test, $p = 0.002$. † Chi-square. § Infliximab vs etanercept, $p = 0.045$. †† Repeated-measures ANOVA at 0, 3, and 6 months (Pilai-trace test): intrasubject effect of time ($p < 0.0001$) and intersubject effect of type of anti-TNF ($p = 0.218$). Infliximab vs etanercept; Bonferroni test, $p = 0.218$. DAS: Disease Activity Score; EULAR: European League Against Rheumatism; HAQ: Health Assessment Questionnaire; MCID: minimal clinically important difference.

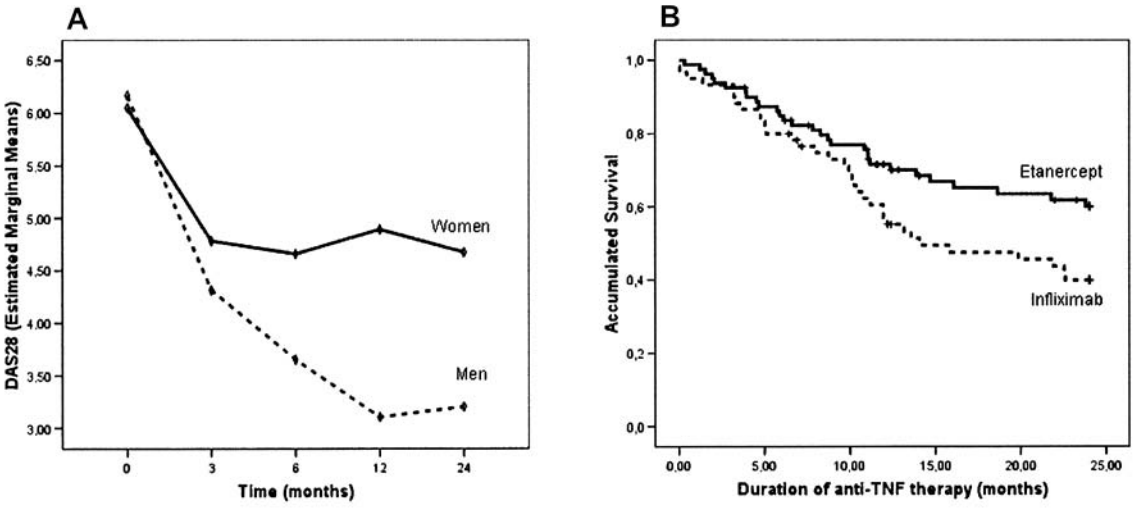

Figure 1. A. Progress of DAS28 scores over time, adjusted for sex (repeated-measures ANOVA). B. Kaplan-Meier survival functions to treatment failure for patients starting infliximab or etanercept.

comitant DMARD and had been taking such medication for a mean of 34 ± 35 months (range 0–167) when they started the anti-TNF therapy. Only 4 (2.5%) patients changed or added a new DMARD during the followup period. MTX was the most commonly used DMARD (90%), particularly with infliximab. The mean dose of MTX on starting anti-TNF treatment was 12.7 ± 5.0 mg/week (range 5–25, Table 1).

At the start of anti-TNF treatment, 95 (59%) patients took a mean dose of a prednisone equivalent of 8.5 ± 6.7 mg/day (range 2–40), while 9.5% took more than 10 mg/day. During followup, 33 (35%) were able to abandon this treatment and the remaining 62 reduced the mean dose to 4.4 ± 5.1 mg/day ($p < 0.0001$). Only 5 (3%) patients who initially did not take corticosteroids required such medication during the followup.

Table 3. Survival times and failure rates for anti-TNF-naive patients starting infliximab, etanercept, or adalimumab from March 1999 to January 2006.

Therapy Group	Patients' Survival Time, median (95% CI), mo	Time to Failure, Patient-yrs	No. Failures	Failure Rate per 100 Patient-yrs (95% CI)†
Infliximab, n = 60	14.1 (2.9–25.2)	105.7	43	40.7 (28.5–52.8)
Etanercept, n = 79	40.0 (16.9–63.2)	145.5	37	25.4 (17.2–33.6)
Adalimumab, n = 22	13.2*	23.1	9	39.0 (13.5–64.4)

* 95% CI could not be calculated (the median of survival time was not reached). † Rate ratio (etanercept/infliximab) 0.62 (95% CI 0.40–0.96).

No differences were noted between anti-TNF drugs in the reduction (p = 0.655) or withdrawal of corticosteroids (p = 0.571).

Factors related to failure of anti-TNF treatment. The factors that predict the time to failure of anti-TNF in the Cox regression models are shown in Table 4. Because the majority of patients were followed for less than 3 years and given the reduced size of the adalimumab group, survival was analyzed only for infliximab and etanercept during the first 24 months. The multivariate model showed that the probability of premature failure of the anti-TNF was 61% less in patients with good adherence, 65% less if there was an increment in the doses of infliximab, and 66% less when etanercept was chosen. Neither the year of initiation of treatment, age, nor the use of anti-TNF monotherapy influenced failure, not even when adjusted for adherence, anti-TNF dose escalation, or the anti-TNF drug employed.

Reasons for withdrawal and adverse events. Of the 161 patients included, the treatment was interrupted in 88 patients (55%). In 51 (58%), the anti-TNF therapy was interrupted due to toxicity with no evident differences between the 3 groups (p = 0.5479). At least one AE was suffered by 113 patients (70%) during the followup (77 per 100 patient-yrs). Serious AE occurred in 24 (15%) patients (9 per 100 patient-yrs) and they resulted in definitive withdrawal of treatment in 13 of them (54%). The life-threatening AE involved a glottis edema, which occurred in a 45-year-old woman during her second infliximab infusion, and an anaphylactic reaction, which occurred in a 70-year-old man on the tenth day of treatment with etanercept. Patients with infliximab suffered more AE (p = 0.005) although at the expense of mild AE and infusion reactions (Table 5).

Table 4. Basal predictive variables of time to treatment failure in 161 patients with RA who received at least one dose of anti-TNF.

Predictor	Univariate Hazard Ratio (95% CI)*	Multivariate Hazard Ratio (95% CI)*
Adherence	0.46 (0.23–0.92)	0.39 (0.18–0.86)
Dose escalation of infliximab	0.53 (0.29–0.96)	0.35 (0.18–0.71)
Anti-TNF drug		
Infliximab	Reference	Reference
Etanercept	0.58 (0.36–0.96)	0.34 (0.18–0.61)
Adalimumab†	—	—

* Cox regression models were restricted to the first 2 years. † Adalimumab was not analyzed. RA: rheumatoid arthritis; TNF: tumor necrosis factor.

Two patients died during the followup period, which situates the mortality rate of the cohort at 0.7 per 100 patient-years (95% CI –0.2 to 1.7). A 67-year-old woman with a history of bronchial asthma died suddenly at her home 4 days after her eighth infliximab infusion and a 53-year-old man died due to metastatic carcinoma of the pancreas, which was diagnosed after 44 months taking etanercept.

A total of 62 infections were suffered by 46 patients (29%), the majority mild or moderate. Only 6 serious infections were recorded, 3 with infliximab (1 brucellosis, 1 ganglionar tuberculosis, and 1 urological sepsis), 2 with etanercept (1 septic arthritis on a prosthetic joint and 1 urological sepsis), and 1 pneumonia with adalimumab. The case of tuberculosis was detected in a woman who had had a negative pretreatment tuberculosis screening test and had been taking infliximab for 2 years. Allergic or pseudoallergic symptoms were reported in 23 patients (14%), many not checked by a doctor. Similarly, 7 (12%) infusion reactions were recorded with infliximab, 2 (3%) local reactions with etanercept, and 1 (5%) with adalimumab. Moreover, 7 patients treated with etanercept repeatedly complained of intense worsening of ocular and oral dryness, which did not occur with the other treatments.

During followup, 7 tumors or proliferative disorders were recorded. In the infliximab group, a pulmonary carcinoid tumor with a solitary pulmonary nodule was detected 3 days after the first infusion in the pretreatment chest radiograph of a 35-year-old woman and for this reason this patient was withdrawn from treatment. The following were found in the etanercept group: 1 pancreatic carcinoma (44th month of treatment); 1 basocellular carcinoma of the nasal dorsum (third month of treatment); 2 cases of monoclonal lymphoproliferation of B cells, the first of these with an inversion of the CD4/CD8 ratio and a monoclonal gamma peak (14th month of treatment), and the other with no monoclonal peak (11th month of treatment); and 1 IgG-kappa monoclonal gammopathy of uncertain significance (from the 30th month of treatment). In the adalimumab group, only 1 case of cutaneous basocellular carcinoma was recorded (30th month of treatment).

Table 5. Number and adverse event rates per 100 patient-yrs (95% CI) for anti-TNF-naive patients starting infliximab, etanercept, or adalimumab.

	Infliximab, N Rate (95% CI)	Etanercept, N Rate (95% CI)	Adalimumab, N Rate (95% CI)
Time at risk (patient-yrs)	106.03	145.8	24.96
Total adverse events	112	84	19
	105.7 (86.1–125.2)	57.6 (45.3–69.9)	76.1 (41.9–110.3)
Mild	67	40	13
	63.2 (48.6–78.3)	27.4 (19.0–36.0)	52.0 (23.8–80.4)
Moderate	39	35	4
	36.8 (25.2–48.3)	24.0 (16.1–32.0)	16.0 (0.3–31.7)
Serious	11	12	2
	10.4 (4.2–16.5)	8.2 (3.6–12.9)	8.0 (–3.1–19.1)
Life-threatening	1	1	0
	0.9 (–0.9–2.8)	0.7 (–0.7–2.0)	
Fatal	1	1	0
	0.9 (–0.9–2.8)	0.7 (–0.7–2.0)	
Total infections	30	24	8
	28.3 (18.2–38.4)	16.5 (9.9–23.0)	32.0 (9.8–54.3)
Serious infections	3	2	1
	2.8 (–0.4–6.0)	1.4 (–0.5–3.3)	4.0 (–3.8–11.9)
Soft tissue infections	3	3	1
	2.8 (–0.4–6.0)	2.0 (–2.7–4.4)	4.0 (–3.8–11.9)
Herpes zoster	0	2	1
		1.4 (–0.5–3.3)	4.0 (–3.8–11.9)
Increase transaminases	9	2	0 (0.0)
	8.5 (2.9–14.0)	1.4 (–0.5–3.3)	
Infusion reactions	7	0	0
	6.6 (1.7–11.5)		
Injection-site reaction	0	2	1
		1.4 (–0.5–3.3)	4.0 (–3.8–11.9)
Rash	7	5	1
	6.6 (1.7–11.5)	3.4 (0.4–6.4)	4.0 (–3.8–11.9)
Dryness symptoms worsening	0	7	0
		4.8 (1.2–8.4)	
Tumor/cell proliferation	1	5	1
	0.9 (–0.9–2.8)	3.4 (0.4–6.4)	4.0 (–3.8–11.9)
Cardiovascular events	1	4	0
	0.9 (–0.9–2.8)	2.7 (0.0–5.4)	
Onset or worsening of high blood pressure	6	3	1
	5.6 (5.2–6.1)	2.1 (–2.7–4.4)	4.0 (–3.8–11.9)
ANA	6	4	1
	5.6 (5.2–6.1)	2.7 (0.0–5.4)	4.0 (–3.8–11.9)
Anti-DNA-positive	5	0	1
	4.7 (4.3–5.1)		4.0 (–3.8–11.9)

ANA: antinuclear antibodies.

Some type of cardiovascular problem was suffered by 15 patients (9%) during the followup period: 10 developed arterial hypertension or decompensation, 2 a cardiac rhythm disorder (supraventricular tachycardia and atrial fibrillation), 1 acute myocardial infarction with rhythm disorders, 1 deep vein thrombosis, and 1 cardiac insufficiency.

DISCUSSION

Pragmatic or "naturalistic" studies give a good idea of the effectiveness of treatments because they reflect how such therapies work in the "real world," far from the optimal conditions of clinical trials. Our study analyzes the effectiveness and safety of infliximab, etanercept, and adalimumab in a cohort of patients with RA resistant to multiple DMARD. Unlike others, our study presents the longterm experiences of a single center, directly comparing 3 anti-TNF treatments under clinical practice conditions.

Patients treated with anti-TNF in clinical practice have a severity and comorbidity profile that could make these drugs seem less effective and more toxic than expected[15]. Despite this, at 6 months our patients reached a clinical response that, while slightly more modest, was quite close to that observed

in clinical trials with ACR20 on physical function[8,12,13]. Although the EULAR and ACR response criteria are not absolutely comparable, there is a good level of agreement between ACR20 and the moderate and good EULAR responses together[26]. In contrast, the EULAR responses and improvement in DAS28 that we observed were not as good as those obtained in some observational studies[27,28].

Our primary effectiveness outcome was the time to treatment failure, since as a function of survival it is the most suitable method to analyze the results in a dynamic cohort that covers a period greater than 5 years. Although the time that a patient continues taking treatment is used more frequently as a measure of effectiveness[29], it may be affected by some confusing factors[30]. Nevertheless, the duration of treatment and the time to failure were almost identical in our study because only 2.5% of cases changed or added a new DMARD during their progress, and because treatment with 4 DMARD had previously failed in the majority of patients. Comparing this outcome, we obtained results that were comparable with some but not all similar studies[27,31-34]. These discrepancies can be attributed to methodological differences, particularly in terms of the analysis according to the intention to treat, the different severity and populations examined, or the different management strategies of concomitant therapy, to name but a few. For example, the proportion of patients taking glucocorticoids and the basal doses taken were very different from one study to another, and only one of these analyzed its development[31]. Changes in the dose of anti-TNF during development were also not well analyzed in previous studies. Intensification of treatment with infliximab could increase the costs less than expected[35] and result in moderate effectiveness[36], although some authors suggest that this improvement is only a consequence of the statistical effect known as regression towards the mean. Normally, intensification results from insufficiency in the clinical response or duration of the response. Although in our study the intensification of the treatment with infliximab reduced the risk of failure by 65% at 2 years without an increment in AE, a metaanalysis indicated that it could increase the risk of neoplasia and serious infections[37]. The intensification of treatment with etanercept or adalimumab is much less common in clinical practice[36] and was not undertaken in our study. In contrast, the interval between etanercept doses increased in 15% of patients without any loss of efficacy, a practice that has been little reported but that may be possible in a proportion of patients with a good response to etanercept[38]. Adherence to the recommendations is another aspect that has been examined little in the various studies carried out to date[35], and that we found may have a significant influence on effectiveness. Adherence is an important factor — perhaps the most important in our society with universal and free access to the health system — within a model of the effectiveness of a medicine in the community[39]. We subjectively and extensively evaluated the adherence deliberately, and not other stricter indices that above all evaluate compliance. Poor adherence is the result of many factors such as lack of compliance, AE, comorbidities, economic cost, etc. Thus the variable that we selected best sums up the disposition and capacity of patients to follow the recommendations made by their rheumatologist throughout their followup. Accordingly, adherence forms part of their history and is not limited to the treatment to be analyzed, but also to the appointments, other medication, etc. Therefore, this concept could be more suited to chronic illnesses where compliance is generally rather low[40], although more than 80% of our patients were classified by their doctor as adherent to the recommendations.

A relevant finding in our study, which has not been previously reported with anti-TNF treatment, was that women showed a more unfavorable provisional response than men in terms of the DAS28 and HAQ. Undoubtedly, this reinforces the female sex as a factor of poor prognosis in RA[41].

The 3 anti-TNF drugs analyzed here have not been compared in clinical trials, although indirect comparison by systematic review failed to identify differences between them[42]. A direct comparison has been made in a few observational studies[31-33,43], although only one compared these 3 treatments at the same time exclusively in patients with RA[33]. Among the studies that compared 2 of these agents[31,32], only Geborek, *et al*[31] found better results in DAS28 and ACR20 with etanercept at 3 and 6 months, despite the fact that the duration of the treatment was similar after a followup of 20 months. However, in that study the same patient could be included in various treatment groups, introducing a corresponding intrapatient correlation and influence of the order of treatment on effectiveness[25]. In addition, they included patients from 6 centers with a different population source, and with different experiences and treatment availabilities. In our study, all 3 biological agents showed excellent drug survival but unfortunately, we were not able to compare the 3 anti-TNF treatments in the survival analysis with the drug, as there were few patients that received adalimumab in the study and their followup was generally short. When etanercept and infliximab were compared, we did not find any relevant differences at 3 or 6 months, unlike at 2 years. The differences observed favored the use of etanercept in terms of maintenance of efficacy and suggest that infliximab but not etanercept frequently required a readjustment of the doses, probably due to an initially suboptimal dose but also due to the development of drug resistance. However, we recognize that our study possesses some limitations that make it difficult to compare the anti-TNF, such as lack of randomization, different numerical composition of the groups, short-term use of adalimumab, and different data collection sites for patients treated with infliximab when compared with the other 2 treatments.

With reference to safety, we observed that the total rate of AE and the percentage of patients that abandoned treatment due to toxicity were greater than those in clinical trials, although the serious and fatal AE were similar[44]. The rate of AE was quite similar between treatment groups, except with

infliximab, which produced milder AE as a consequence of infusion. The milder AE may also reflect the means in which the data were collected since these patients were seen at a day hospital and interacted with the attending rheumatologist for the 2 hours that the infusion lasted. This is reinforced by the fact that the incidence of local reactions for etanercept or adalimumab that we observed is lower than that described in the literature[45,46].

Our total infection rate was also the same as that observed in registers from other countries, although in terms of serious infections it was lower than the German[47] and British[48] registers, and more similar to that of the clinical trials[45]. The differences with regard to these registers are probably due to the selection bias introduced by the registers, different number of patients, the definition of serious infection, and differences in concomitant therapies. While 5% of German patients received 2–3 concomitant DMARD and 20% took more than 10 mg/day of prednisone, none of our patients took 3 DMARD concomitantly and only 9.5% received more than 10 mg/day of prednisone. The failure to communicate serious infections by patients or their doctors may also affect these figures. This latter reason seems to explain that only 0.7 serious infections/100 patient-years were published after the commercialization of etanercept[45].

The most common infections in patients treated with anti-TNF are usually respiratory and the majority are mild. However, we observed an increase in infections of soft tissues in our patients similar to that of the German register[47]. It was also notable that although the majority of cases of tuberculosis occur during the first 12 weeks[46], one of our cases suffered ganglionar tuberculosis after 2 years with infliximab, while the pretreatment tuberculosis screening was negative. Without doubt this is due to a new infection rather than reactivation, and it underlines the necessity for antituberculosis vigilance during the whole treatment.

We did not observe any demyelinating disease or lymphomas, and the incidence of allergic reactions, hepatic toxicity, cardiac insufficiency, myocardial infarction, arrhythmias, venous thrombosis, solid tumors, and lymphoproliferative syndromes did not increase. Nevertheless, the duration and the number of patients in our study did not permit us to extract conclusions regarding the risk of developing neoplasias or adverse effects, with a prevalence < 1%. In contrast, in 10 of our patients there was an onset or worsening of arterial hypertension, and 7 cases treated with etanercept in which symptoms of xerophthalmia and xerostomia were aggravated, although an etiopathogenic relationship with these drugs was not established.

Anti-TNF agents are effective and safe under clinical practice conditions, reducing the activity of RA disease, disability, and the need for corticosteroids. Good adherence to the therapeutic recommendations prior to anti-TNF treatment and the selection of etanercept or escalation of the doses of infliximab are factors that predict a good response to treatment.

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