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Original Article

Eight-year survival study of first-line tumour necrosis factor α inhibitors in rheumatoid arthritis: real-world data from a university centre registry

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Abstract

Objective. This study aimed to investigate the efficacy, safety and survival of TNF-α inhibitors in patients with RA.

Methods. A total of 178 patients >18 years of age were treated with TNF-α inhibitors. A total of 74 patients were treated with infliximab, 75 with adalimumab and 29 with etanercept. Each patient was followed-up for a period of 8 years.

Results. Anti-TNF-α therapy resulted in rapid clinical improvement. The rate of good/moderate response according to EULAR response criteria for the index 28-joint DAS with CRP in the first 6 months was 82% for infliximab, 89.6% for adalimumab and 95.6% for etanercept. The rate of withdrawal in 8 years was 80% for patients on infliximab, 61.4% for patients on adalimumab and 47.6% for patients on etanercept. The main reasons for discontinuation were allergic reactions for infliximab (rate of discontinuation 25.7%) and inefficacy for adalimumab and etanercept (17.5% and 23.8%, respectively). Systemic allergic reactions and infections were significantly more frequent in the infliximab group ($P < 0.05$ and $P < 0.001$, respectively). However, there was no significant difference among the three drugs concerning serious infections. According to Kaplan–Meier survival analysis, a significantly faster withdrawal for infliximab patients was depicted compared with adalimumab ($P = 0.003$) and etanercept ($P = 0.019$), while adalimumab and etanercept were not statistically different ($P = 0.089$).

Conclusions. TNF-α inhibitors establish an effective therapeutic option in RA showing an acceptable safety profile. Infections and allergic reactions appear more often with infliximab, while serious infections did not differ among them. RA patients treated with infliximab are more likely to discontinue treatment earlier compared with the other alternatives.

Key words: RA, TNF-α inhibitors, infliximab, etanercept, adalimumab, adverse events, drug survival

CLINICAL SCIENCE

Key messages

- Infections and allergic reactions in RA patients appear more often with infliximab.
- Serious infections in RA patients did not differ among the three drugs.
- RA patients treated with infliximab more often discontinue treatment earlier compared with etanercept and adalimumab.

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Introduction

RA is a chronic disease with the potential to cause substantial bone and cartilage damage as well as functional disability [1]. Synthetic DMARDs (sDMARDs), which constitute the traditional therapy for RA, influence the

disease process by slowing down the joint and bone destruction [2]. MTX is the DMARD of choice for patients with active RA, due to its long-term survival in clinical practice [3]. A combination of sDMARDs is often necessary to achieve disease remission [4, 5]. There is evidence that an aggressive combination of potent sDMARDs clearly improves clinical response and structural damage [5, 6]. However, there is a proportion of patients, especially in established RA, in whom sDMARDs can only partially control the disease course. Today, we have a large number of biologic agents that, together with DMARDs, or sometimes even as a monotherapy, can successfully be used to treat such difficult cases. These include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol, as TNF-α inhibitors; anakinra, an IL-1 receptor inhibitor; rituximab, a therapeutic monoclonal antibody that targets CD20 antigen in B lymphocytes; abatacept, a T lymphocyte co-stimulatory inhibitor; as well as tocilizumab and sarilumab, which inhibit the actions of IL-6 via binding to both soluble and membrane-bound IL-6 receptors. Recently, biosimilar molecules for many of the biologic agents and Janus kinase (JAK) inhibitors were also introduced as therapeutic options for RA. JAK inhibitors are small-molecule therapies that inhibit the activity of one or more of the JAK family of enzymes, which are intracellular, non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK–signal transducer and activator of transcription (STAT) signalling pathway. In order to achieve standard therapeutic goals, optimal use of all these therapeutic agents is demanded, which should be based in a targeted therapeutic strategy. Indeed, EULAR has developed a set of recommendations for the management of RA that summarize the current strategy [7].

Infliximab is the first anti-TNF-α monoclonal antibody that was approved for the treatment of RA, and it is provided intravenously. In contrast, adalimumab, a monoclonal human anti-TNF-α antibody, and etanercept, a recombinant version of the soluble p75 TNF-α receptor, are both administered subcutaneously. In the present long-term study, we investigated the efficacy, safety and survival of the above three anti-TNF-α agents in patients with established RA.

Although treatment with these agents was found to provide an acceptable safety profile, some concerns have been raised about the increased risk of serious infections and solid malignancy in a small percentage of patients [8–10]. In addition, in some cases of patients treated with infliximab, treatment had to be discontinued due to infusion allergic reactions [11]. Paradoxical autoimmune phenomena can also be induced by them [12]. The study attempts to answer these and other relevant queries, with observation over 8 years of treatment.

Methods

Patients

This is an observational retrospective study. Patients >18 years of age who fulfilled the ACR criteria for RA and gave informed consent participated in the study. A total of 178 patients diagnosed with active RA despite the use of sDMARDs were treated with TNF-α inhibitors for the first time and as the first type of biologic DMARD in a tertiary hospital centre during the time period 2000–2015. The period of enrolment was 7 years (between 2000 and 2007) and each patient was followed up for a period of 8 years. A total of 74 patients were treated with infliximab, 75 with adalimumab and 29 with etanercept.

Study protocol

Infliximab (3 mg/kg body weight) was administered intravenously at weeks 0, 2 and 6 and every 8 weeks thereafter. If there was an inadequate response to the treatment, the dose of infliximab was increased to 7.5 mg/kg body weight, keeping the same dosage interval. Adalimumab was applied in a dose of 40 mg subcutaneously, every 2 weeks. Etanercept was also given subcutaneously in a dose of 50 mg every week or in a dose of 25 mg twice a week. Before every intravenous infusion with infliximab, each patient was examined in our hospital. Complete clinical examination and laboratory testing (blood and urine tests, as well as any other examinations deemed necessary) were performed. Patients receiving a subcutaneous biologic agent were examined in our hospital every 3 months (clinical examination and laboratory testing). Each patient was studied over a period of 8 years. Data were collected at defined time points: baseline, every 6 months for the first 2 years and then annually. More specifically, at baseline, demographic and disease characteristics were recorded, such as age, sex, disease duration, seropositivity for RF, total tender and swollen joint count, ESR and CRP. All RA patients were tested for latent tuberculosis (TB) using the purified protein derivative (PPD) skin test as well as chest X-rays before entering anti-TNF-α therapy. In addition, all patients were screened for hepatitis B and C viruses and all had immunological tests, including ANA, ENA, ANCA etc. At each patient's follow-up, data concerning the efficacy, adverse events and cause of discontinuation of anti-TNF-α therapy were recorded. Furthermore, clinical and laboratory data and information on comorbidities, surgical interventions and immunosuppressive and other concomitant drugs were collected. Of note, all data were collected systematically in routine medical records.

The treatment response was assessed mainly by using the 28-joint DAS with CRP (DAS28-CRP) [13] or DAS28 with ESR (DAS28-ESR) [14–16] and the ACR response criteria for 20%, 50% and 70% (ACR20, ACR50, ACR70, respectively) improvement [17].

Patients who were lost to follow-up for unknown reasons without completing 8 years were excluded from the study.

The protocol was approved by the Institutional Scientific Committee of the University Hospital of Ioannina, Greece.

Statistical analysis

Categorical measurements were described as frequencies and percentages while the mean and S.D. were used for scale measurements. Chi-square tests were used to assess differences in the rates of serious infections and adverse events. Random effects repeated measures analysis was applied to detect changes in all efficacy indices. Logistic regression analysis was applied to examine the effect of treatment on complications adjusting for gender, age, MTX intake, steroid intake, age, duration of the disease and severity of the disease. A similar model was applied for the effect of treatment on allergies, but controlling for gender, MTX intake and steroid intake. Cox regression was applied for the differences in time to withdrawal among three TNF-α inhibitors. Survival analysis was adjusted for the presence of side effects, age, sex, RF positivity, disease duration, ESR and CRP at baseline, MTX and/or steroids intake and number of former failures of sDMARDs. *P*-values <0.05 were considered to indicate statistically significant differences. Analysis was conducted using SPSS version 22.0 (IBM, Armonk, NY, USA).

Results

Patient description and baseline characteristics

Of the 178 patients, 5 had a positive PPD skin test but normal chest X-rays and they were all treated with isoniazide 300 mg/day for a period of 9 months. One patient had hepatitis B–positive antibodies and received prophylactic antiviral therapy. None of our patients had positive ANAs, ENAs or ANCAs before the initiation of therapy. The study sample included 31 (17.4%) male and 147 (82.6%) female patients. Their mean age was 52 years (S.D. 15) for the male patients and 57 years (S.D. 12) for the female patients. Their mean disease duration was 14 years (S.D. 8.5). A total of 112 patients (63.8%) were positive for IgM RF and 177 patients (99.4%) had received DMARD treatment before entering the study—in particular 169 (95.5%) had received MTX. The baseline characteristics of the RA patients are presented in Table 1. It should be noted that all patients had active disease as evaluated by a high DAS28 score, the high number of tender and swollen joints and the high levels of ESR and CRP (Table 1).

Efficacy

Anti-TNF-α therapy resulted in rapid clinical improvement associated with a reduction in inflammatory markers in the first 6 months of treatment, which was sustained throughout the following years (Fig. 1). The rate of good/moderate response according to the EULAR response criteria for the index DAS28-CRP in the first 6 months was 82% for infliximab, 89.6% for adalimumab and 95.6% for etanercept. The respective rates in the following years are shown in Fig. 2.

Additionally, a significant percentage of patients achieved ACR20, -50 and -70 response criteria in the first 6 months. The respective percentages were reduced over time (Fig. 3).

Survival

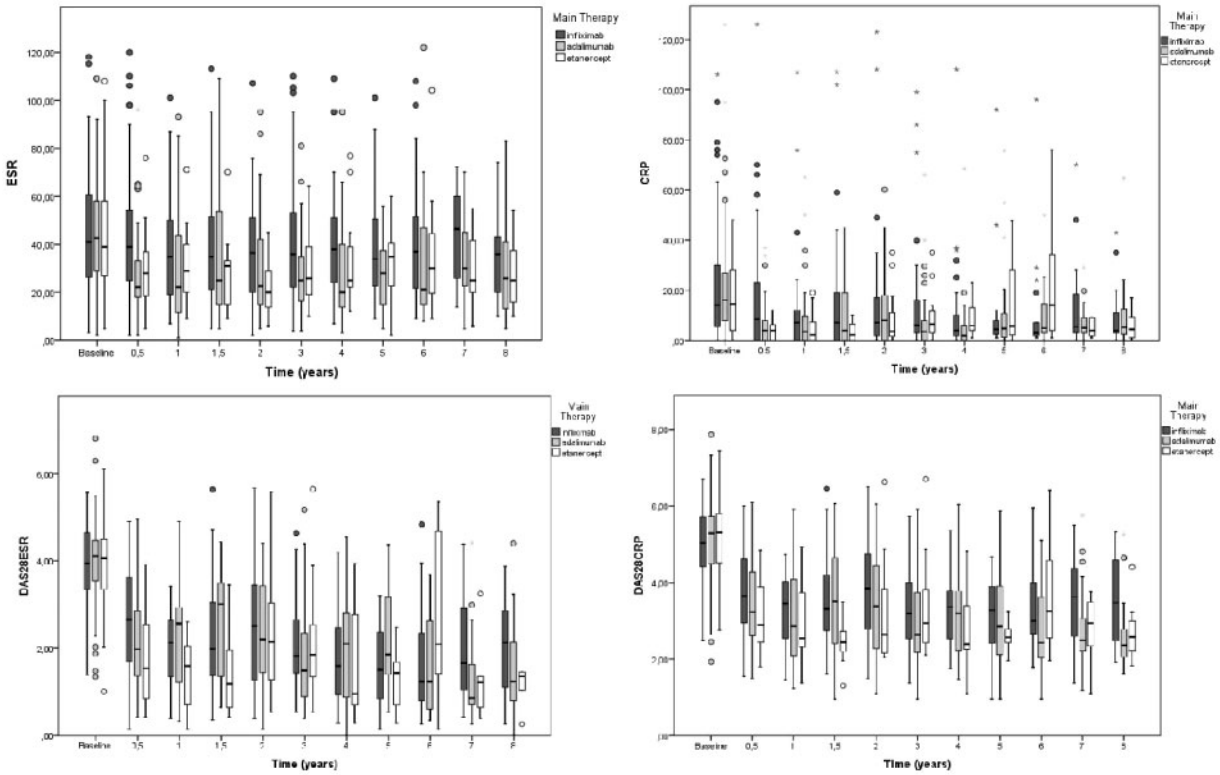
The rate of withdrawal in 8 years was 80% for patients on infliximab, 61.4% for patients on adalimumab and 47.6% for patients on etanercept. Supplementary Fig. S1, available at *Rheumatology* online, depicts withdrawals from

Table 1 Baseline characteristics of RA patients treated with TNF inhibitors

Parameters	Total	Infliximab	Adalimumab	Etanercept
RA patients, *n*	178	74	75	29
Female/male ratio	147/31	60/14	61/14	26/3
Age, mean (S.D.), years	55 (12)	57 (12)	54 (13)	55 (14)
Disease duration, mean (S.D.), years	14.07 (8.52)	13.85 (6.65)	13.48 (8.82)	16.14 (11.53)
RF positivity, *n* (%)	112 (63.8)	46 (62.16)	47 (62.66)	19 (65.51)
Painful joints, mean (S.D.)	9.13 (5.78)	8.95 (4.75)	9.05 (4.64)	9.75 (4.97)
Swollen joints, mean (S.D.)	3.58 (3.65)	2.90 (1.86)	4.02 (2.65)	4.17 (2.92)
ESR, mean (S.D.), mm/h	45.37 (24.33)	46.52 (24.56)	44.95 (21.80)	43.62 (20.11)
CRP, mean (S.D.), mg/l	20.89 (22.46)	22.00 (22.48)	21.55 (15.74)	16.52 (22.62)
DAS28-CRP, mean (S.D.)	5.10 (1.03)	5.12 (0.30)	5.2 (0.35)	5.20 (0.70)
DAS28-ESR, mean (S.D.)	3.92 (1.00)	4.20 (0.59)	4.09 (0.68)	3.53 (1.59)
Patients who received MTX previously, *n* (%)	169 (95.5)	69 (93.24)	72 (96.00)	28 (96.55)
Patients who received leflunomide previously, *n* (%)	41 (23.2)	13 (17.56)	19 (25.33)	9 (31.03)
Steroid intake, *n* (%)	139 (78.5)	58 (78.37)	59 (78.66)	22 (75.86)
Prior use of >3 DMARDs, *n* (%)	67 (37.64)	23 (31.08)	32 (42.67)	12 (41.38)

Comparison of the three groups did not reveal statistically significant differences regarding demographic and clinical parameters ($P > 0.05$).

Fig. 1 Reduction in inflammatory markers and clinical indices



Anti-TNF-α therapy resulted in a rapid clinical improvement associated with a reduction in all inflammatory markers and clinical indices.

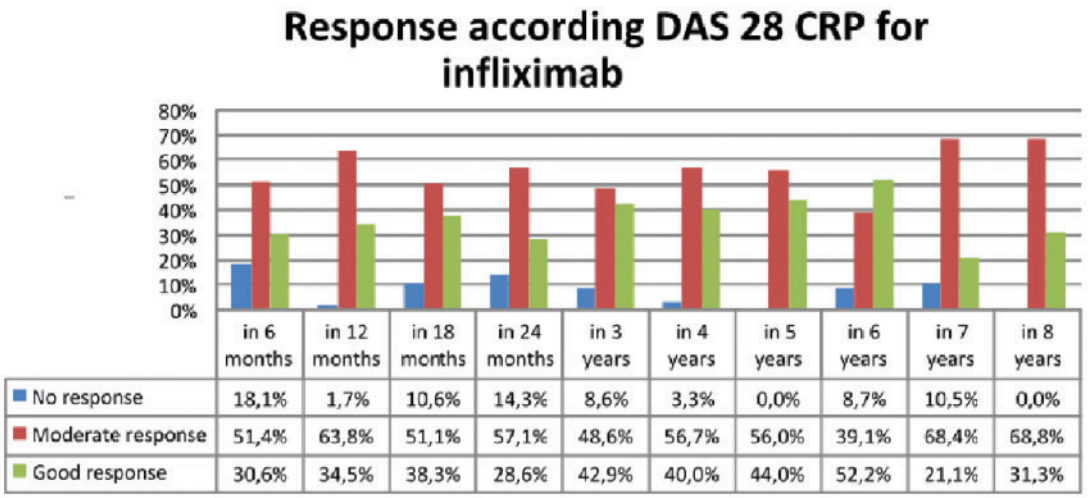
infliximab, adalimumab and etanercept therapy in an intention-to-treat analysis. Fig. 4 presents the survival rate of the three TNF-α inhibitors as well as the remaining number of patients on each therapy (at risk) at the different time points. According to Kaplan–Meier methods, the survival rate of infliximab after the first year of treatment was 79.0%, after the second year it was 55.5%, after the third year it was 44.9%, after the fourth year it was 38.3% and after the fifth, sixth and seventh years it was 36.4%, 30.0% and 22.5%, respectively. After 8 years of treatment the survival rate was 20.0%. After the first year of treatment with adalimumab, its survival rate was 88.2%, after the second year it was 73.8%, after the third year it was 65.9%, after the fourth year it was 62.0% and after the fifth, sixth and seventh years it was 58.1%, 52.7% and 46.0%, respectively. After 8 years of treatment the survival rate was 38.6%. After the first year of treatment with etanercept, its survival rate was 88.5%, after the second year it was 86.8%, after the third year it was 83.0%, after the fourth year it was 81.5% and after the fifth, sixth and seventh years it was 79.4%, 76.3% and 72.0%, respectively. After 8 years of treatment the survival rate was 52.4%.

The main reasons for discontinuation were allergic reactions for infliximab (rate of discontinuation 25.7%) and inefficacy for adalimumab and etanercept (17.5% and 23.8%, respectively). Kaplan–Meier curves (Fig. 4) showed a significantly faster withdrawal for infliximab patients compared with adalimumab ($P = 0.003$) and etanercept ($P = 0.019$), while adalimumab and etanercept were not statistically different ($P = 0.089$). The risk of discontinuation (hazard ratio) for infliximab patients *vs* etanercept patients was 4.48 (95% CI 1.69, 11.9). The corresponding risk for infliximab patients *vs* adalimumab patients was 1.92 (95% CI 1.11, 3.32). In order to correlate possible predisposing factors (such as age, sex, RF positivity, disease duration, ESR and CRP at baseline, MTX and/or steroids intake as well as the number of failures of DMARDs) to the final event (treatment discontinuation), we performed a Cox regression analysis. This analysis revealed two independent prognostic factors that influenced anti-TNF agent survival in a statistically significant manner. These were the number of prior failed sDMARDs and the absence of concomitant MTX intake. More specifically, biologic agent survival was significantly lower in RA patients who had failed more than three sDMARDs ($P = 0.022$) as well as in those who had not received MTX along with the biologic therapy ($P = 0.033$).

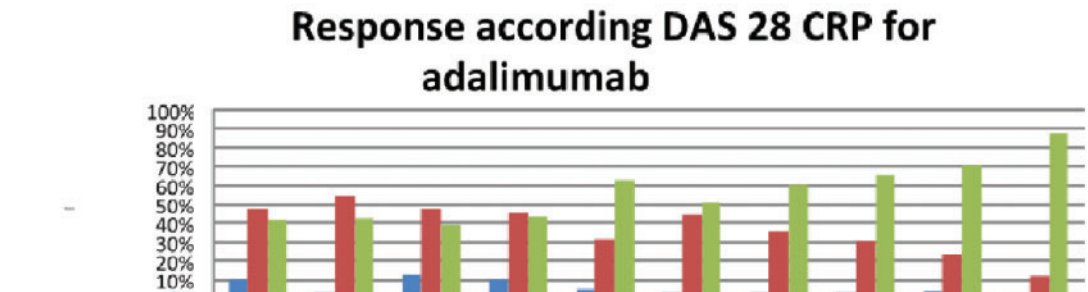
Safety

The most common serious adverse events for all three treatments were infections, occurring primarily in the

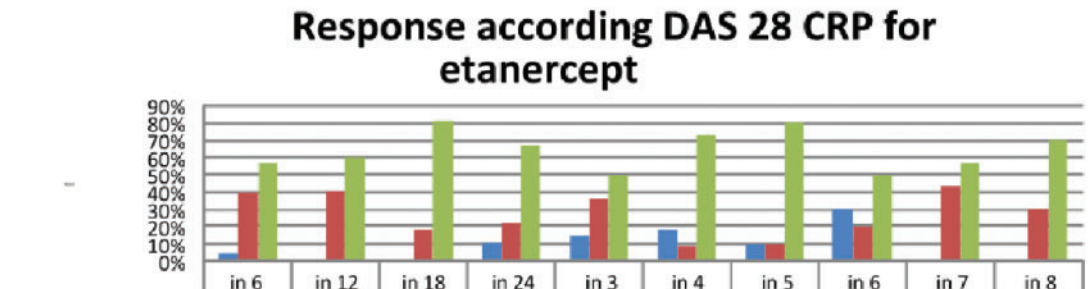
Fig. 2 Response according DAS28-CRP for RA patients



	in 6 months	in 12 months	in 18 months	in 24 months	in 3 years	in 4 years	in 5 years	in 6 years	in 7 years	in 8 years
No response	18,1%	1,7%	10,6%	14,3%	8,6%	3,3%	0,0%	8,7%	10,5%	0,0%
Moderate response	51,4%	63,8%	51,1%	57,1%	48,6%	56,7%	56,0%	39,1%	68,4%	68,8%
Good response	30,6%	34,5%	38,3%	28,6%	42,9%	40,0%	44,0%	52,2%	21,1%	31,3%



	in 6 months	in 12 months	in 18 months	in 24 months	in 3 years	in 4 years	in 5 years	in 6 years	in 7 years	in 8 years
No response	10,4%	3,3%	13,2%	10,4%	5,3%	3,2%	3,6%	3,8%	4,8%	0,0%
Moderate response	47,8%	54,1%	47,2%	45,8%	31,6%	45,2%	35,7%	30,8%	23,8%	12,5%
Good response	41,8%	42,6%	39,6%	43,8%	63,2%	51,6%	60,7%	65,4%	71,4%	87,5%

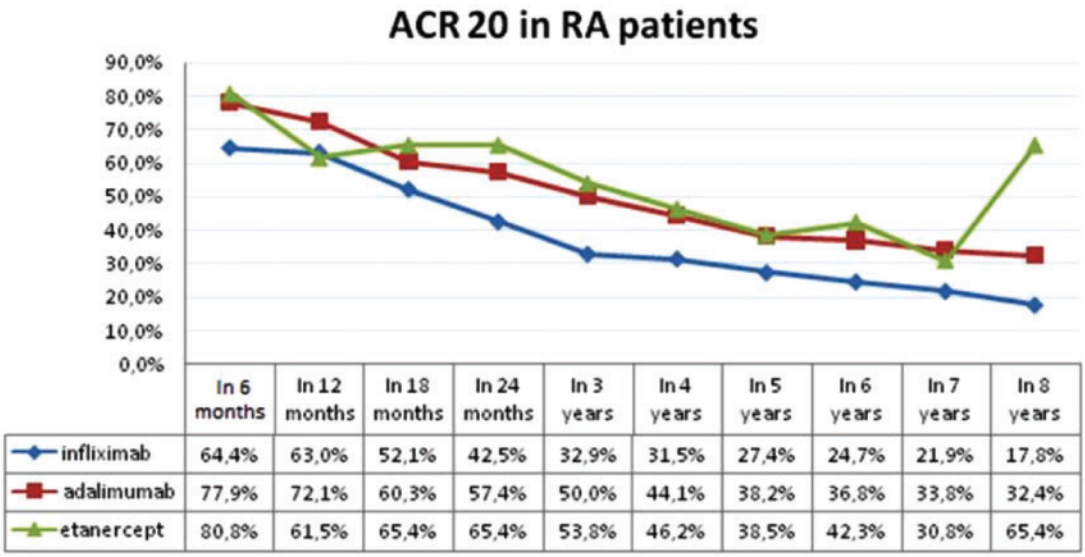


	in 6 months	in 12 months	in 18 months	in 24 months	in 3 years	in 4 years	in 5 years	in 6 years	in 7 years	in 8 years
No response	4,3%	0,0%	0,0%	11,1%	14,3%	18,2%	10,0%	30,0%	0,0%	0,0%
Moderate response	39,1%	40,0%	18,8%	22,2%	35,7%	9,1%	10,0%	20,0%	42,9%	30,0%
Good response	56,5%	60,0%	81,3%	66,7%	50,0%	72,7%	80,0%	50,0%	57,1%	70,0%

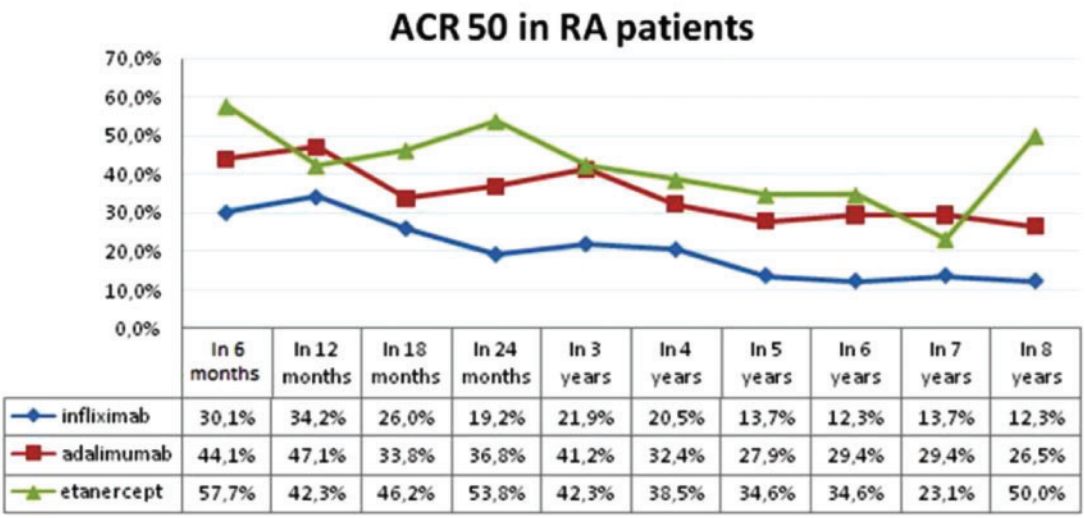
Moderate and good response rates were high in the first 6 months of treatment.

first year. The total number of adverse events was higher in the infliximab group compared with the two other treatments (Table 2). Additionally, infections as well as systemic allergic reactions were significantly more frequent in infliximab compared with the two other treatments, which did not differ statistically (Table 2). However, there was no significant difference among the three drugs concerning serious infections (infliximab *vs* adalimumab, $P = 0.3443$; infliximab *vs* etanercept, $P = 0.5325$; adalimumab *vs* etanercept, $P = 0.9466$).

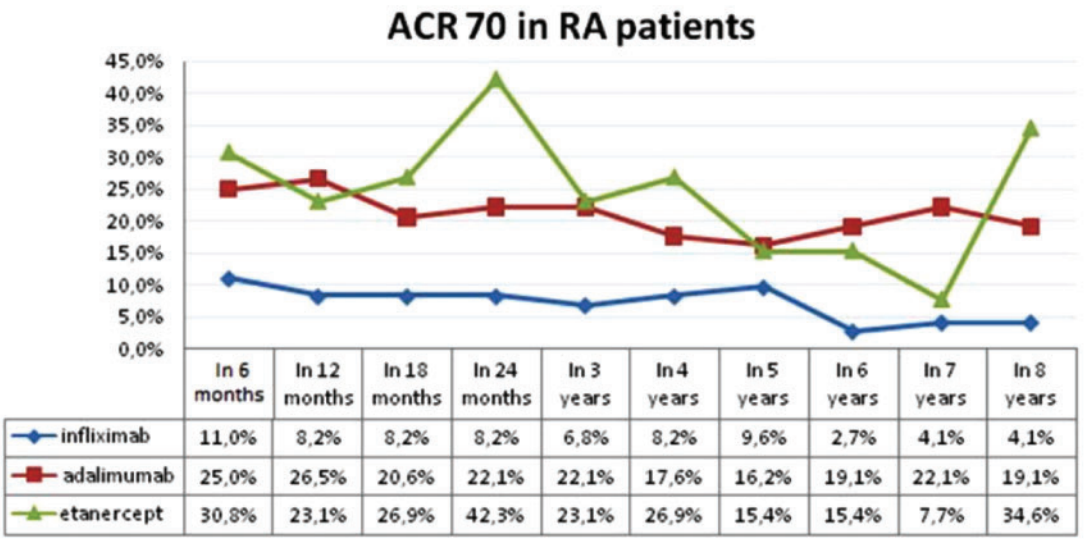
Fig. 3 Response to anti-TNF-α treatment according ACR criteria



	In 6 months	In 12 months	In 18 months	In 24 months	In 3 years	In 4 years	In 5 years	In 6 years	In 7 years	In 8 years
infliximab	64,4%	63,0%	52,1%	42,5%	32,9%	31,5%	27,4%	24,7%	21,9%	17,8%
adalimumab	77,9%	72,1%	60,3%	57,4%	50,0%	44,1%	38,2%	36,8%	33,8%	32,4%
etanercept	80,8%	61,5%	65,4%	65,4%	53,8%	46,2%	38,5%	42,3%	30,8%	65,4%



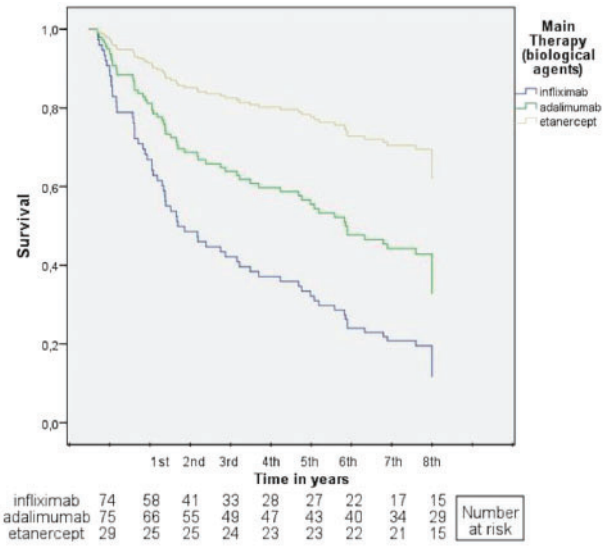
	In 6 months	In 12 months	In 18 months	In 24 months	In 3 years	In 4 years	In 5 years	In 6 years	In 7 years	In 8 years
infliximab	30,1%	34,2%	26,0%	19,2%	21,9%	20,5%	13,7%	12,3%	13,7%	12,3%
adalimumab	44,1%	47,1%	33,8%	36,8%	41,2%	32,4%	27,9%	29,4%	29,4%	26,5%
etanercept	57,7%	42,3%	46,2%	53,8%	42,3%	38,5%	34,6%	34,6%	23,1%	50,0%



	In 6 months	In 12 months	In 18 months	In 24 months	In 3 years	In 4 years	In 5 years	In 6 years	In 7 years	In 8 years
infliximab	11,0%	8,2%	8,2%	8,2%	6,8%	8,2%	9,6%	2,7%	4,1%	4,1%
adalimumab	25,0%	26,5%	20,6%	22,1%	22,1%	17,6%	16,2%	19,1%	22,1%	19,1%
etanercept	30,8%	23,1%	26,9%	42,3%	23,1%	26,9%	15,4%	15,4%	7,7%	34,6%

A significant percentage of patients achieved the ACR20, -50 and -70 response criteria.

Fig. 4 TNF-α inhibitor survival in patients with RA



Kaplan–Meier curves show a significantly faster withdrawal for infliximab patients compared with adalimumab and etanercept.

The predisposing factor for significantly more frequent infections was the intake of steroids, but only for the infliximab group.

Among severe infections, those of specific interest were two cases of pulmonary TB, which were recorded in patients receiving infliximab therapy, and one case of extrapulmonary TB in a patient receiving adalimumab. One of these patients (infliximab) had a normal chest X-ray and negative PPD skin test before anti-TNF-α therapy, while the other two patients had a positive PPD skin test and normal chest X-rays. In these three cases anti-TNF-α therapy was discontinued and the patients received triple anti-TB therapy for 9 months, with full recovery. All cases of TB occurred in the first 18 months after the initiation of anti-TNF-α treatment.

As regards systemic allergic reactions, these were more frequent in the infliximab group ($P < 0.001$ for comparison with each of the other two treatment agents). Severe systemic allergic reactions were also more frequent in patients under infliximab therapy. Severe systemic allergic reactions were characterized as those that demanded permanent discontinuation of the current anti-TNF-α therapy. Eleven cases of serious systemic allergic reactions were recorded (10 in infliximab and 1 in adalimumab). Most of these occurred in the first year of biologic treatment.

In our study, 11 cases of malignancy were recorded: 7 in the infliximab group [malignant lymphoma (1 case), lung cancer (2 cases), laryngeal cancer (1 case), breast cancer (1 case), basal cell carcinoma of the skin (2 cases)] and 4 in the adalimumab group [malignant lymphoma (1 case), liver cancer (1 case), prostate cancer (1 case), papillary thyroid carcinoma (1 case)]. The respective comparisons between groups were not statistically significant.

Paradoxical autoimmune phenomena as well as positive autoantibodies without a compatible clinical picture were also recorded in our study. These are also shown in Table 2.

Discussion

The aim of the present study was to investigate long-term efficacy, safety, survival and reasons of discontinuation of TNF-α inhibitors in patients with RA.

The results of this study showed that all three biologic agents (infliximab, adalimumab and etanercept) proved to be effective in RA patients. More particularly, a very good response was found in the first 6 months for all three treatments, which was maintained until the end of the study. Anti-TNF-α therapy resulted in rapid clinical improvement associated with a reduction in all inflammatory markers. The efficacy of the three drugs was comparable, as was reflected in a previous study from our department [18]. Good/moderate response rates according to the DAS28 in the first year were higher compared with those of the Hellenic Registry of Biologics, and remission in the first year was relatively higher [19]. A meta-analysis by Alonso-Ruiz et al. [20] showed an ACR response in the first year of treatment similar to our results.

With regard to safety, our study demonstrated an acceptable toxicity profile of anti-TNF-α therapy similar to that described by other investigators [21]. The greatest percentage of patients who experienced at least one adverse event was in the infliximab group (98.65%). The most frequently reported adverse event for all three drugs was infection, with the highest observed rate in the infliximab group (70.27%). Systemic allergic

Table 2 Adverse events in RA patients

Adverse events	Biologic agents			*P*-values
	Infliximab (n = 74 patients)	Adalimumab (n = 75 patients)	Etanercept (n = 29 patients)	
Total number of adverse events	73 (98.65)	58 (77.33)	22 (75.86)	• inf *vs* ada: 0.001 • inf *vs* eta: 0.001 • ada *vs* eta: NS
Infections	52 (70.27)	36 (48.00)	14 (48.28)	• inf *vs* ada: 0.006 • inf *vs* eta: 0.036 • ada *vs* eta: NS
Severe infections	13 (17.6)	10 (13.3)	4 (13.8)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Systemic allergic reactions	29 (39.19)	2 (2.67)	0 (0.00)	• inf *vs* ada: $<$0.001 • inf *vs* eta: $<$0.001 • ada *vs* eta: NS
Severe systemic allergic reactions	10 (13.51)	1 (1.33)	0 (0.00)	• inf *vs* ada: $<$0.001 • inf *vs* eta: $<$0.001 • ada *vs* eta: NS
Local allergic reactions	9 (12.16)	8 (10.67)	0 (0.00)	• inf *vs* ada: NS • inf *vs* eta: 0.049 • ada *vs* eta: NS
Malignancies	7 (9.46)	4 (5.33)	0 (0.00)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Haematological malignancies	1 (1.36)	1 (1.33)	0 (0.00)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Solid malignancies	4 (5.40)	3 (4.00)	0 (0.00)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Basic cell carcinomas	2 (2.70)	0 (0.00)	0 (0.00)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Autoimmune phenomena[a]	8 (10.81)	9 (12.00)	3 (10.34)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Positive autoantibodies (i.e. ANA, ANCA) without compatible clinical picture	2 (2.70)	2 (2.67)	1 (3.45)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Other adverse events				
General disorders	26 (35.14)	10 (13.33)	5 (17.24)	• inf *vs* ada: 0.019 • inf *vs* eta: NS • ada *vs* eta: NS
Blood and lymphatic system disorders	25 (33.78)	11 (14.67)	5 (17.24)	• inf *vs* ada: 0.006 • inf *vs* eta: NS • ada *vs* eta: NS
Nervous system disorders	20 (27.03)	11 (14.67)	5 (17.24)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Skin and subcutaneous tissue disorders	19 (25.68)	21 (28.00)	7 (24.14)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Hepatobiliary disorders	14 (18.92)	9 (12.00)	3 (10.34)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Musculoskeletal and connective tissue disorders	13 (17.57)	5 (6.67)	0 (0.00)	• inf *vs* ada: 0.041 • inf *vs* eta: 0.016 • ada *vs* eta: $<$0.001

(continued)

Table 2 Continued

Adverse events	Biologic agents			*P*-values
	Infliximab ($n = 74$ patients)	Adalimumab ($n = 75$ patients)	Etanercept ($n = 29$ patients)	
Otorhinolaryngeal system disorders	11 (14.86)	4 (5.33)	2 (6.90)	• inf *vs* ada: 0.041 • inf *vs* eta: 0.016 • ada *vs* eta: <0.001
Urogenital system disorders	10 (13.51)	4 (5.33)	3 (10.34)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: <0.001
Cardiovascular system disorders	7 (9.46)	6 (8.00)	1 (3.45)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Respiratory, thoracic and mediastinal disorders	6 (8.11)	4 (5.33)	2 (6.90)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Gastrointestinal disorders	6 (8.11)	6 (8.00)	1 (3.45)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Reproductive system disorders	5 (6.76)	3 (4.00)	1 (3.45)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Psychiatric disorders	4 (5.41)	5 (6.67)	1 (3.45)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Endocrine system disorders	2 (2.70)	0 (0.00)	0 (0.00)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS
Eye disorders	2 (2.70)	1 (1.33)	1 (3.45)	• inf *vs* ada: NS • inf *vs* eta: NS • ada *vs* eta: NS

All values presented as n (%).
[a]One case of autoimmune hepatitis (infliximab), one case of optic neuritis (adalimumab), nine cases of granuloma annulare (seven with adalimumab, one with infliximab, one with etanercept), seven cases of psoriasiform rash (six with infliximab, one with etanercept), one case of discoid rash (adalimumab) and one case of butterfly rash (etanercept).
ada, adalimumab; eta, etanercept; inf, infliximab; NS, not significant.

reactions were significantly more frequent in the infliximab group (39.19%) compared with adalimumab (2.67%), while in the etanercept group, no allergic reactions were observed. However, the number of RA patients treated with etanercept was lower. These observations are confirmed by other Greek studies [11, 18, 19]. In line with our results, a recent systematic review highlighted that the risk of treatment discontinuation due to adverse events was greater for infliximab than for adalimumab or etanercept in RA patients [22]. The same review revealed a greater risk for serious infections with infliximab than with the other two therapeutic choices, while we showed that rates of serious infections did not differ statistically among the three drugs. A higher rate of antibodies against infliximab compared with the two other drugs may explain the higher incidence of allergic reactions. The higher incidence of infections may be attributable to structural and pharmacological properties among the three drugs. Adverse events occurred frequently during the first year of biologic treatment, requiring attention by physicians during this period. The number of malignancies reported in our study seems to be rather higher than what is expected in the general population. However, the small sample size (178 patients) does not allow us to draw safe conclusions on whether these malignancies were provoked by anti-TNF-α therapy or were just random events. Similarly, it would not be safe to generalize from these observations.

Survival for all three treatments was satisfactory. However, as far as infliximab is concerned, survival was significantly lower compared with adalimumab and etanercept, while there was no statistical difference between them. A 5 year drug survival for RA patients was 31% in the infliximab group, 43% in the adalimumab group and 49% in the etanercept group [19]. However, the Italian Group for the Study of Early Arthritis registry showed a 5 year survival for infliximab of ~40% [23]. Our study showed 8 year drug survival rates moderately lower for infliximab and adalimumab, while for etanercept the percentage was slightly higher. In the literature, almost all studies show a significantly lower survival for

infliximab compared with adalimumab and etanercept [24–29]. The possible explanation is the high incidence of antibodies against infliximab compared with the other two drugs, leading to a higher rate of allergic reactions and inefficacy [30]. Indeed, ADAs not only neutralize the activity of TNF inhibitors, but can provoke serious adverse events, including allergic reactions and vasculitis [31]. Although IgG1 and IgG4 are the main types of ADAs and are not involved in allergic reactions, IgA, IgM and IgE ADAs have also been detected [31]. Interestingly, researchers have described the presence of IgE infliximab ADAs in patients who had a hypersensitivity reaction to infliximab [32, 33]. Furthermore, IgE-mediated reactions were more severe than non-IgE-mediated events [34]. Of note, several patients who suffered an allergic reaction and simultaneously had IgE infliximab ADAs also displayed positive skin testing when commercial infliximab was injected [32, 33]. Side effects, especially infections, are a second cause of the lower survival of infliximab compared with adalimumab and etanercept and etanercept has a lower percentage of discontinuation. This is in agreement with other studies [35, 36] and with a recent meta-analysis that included >200 000 RA patients [37]. Nevertheless, a similar persistence rate among infliximab, etanercept and adalimumab has also been described [38, 39].

In our study, concomitant use of MTX significantly increased anti-TNF-α survival, as has been reported in other studies [35–37]. In addition, failure of more than three sDMARDs is associated with decreased drug survival and is in line with previous results [35].

There are some limitations in our study. It has a limited number of patients, especially in the etanercept group. In Italy, infliximab was the first anti-TNF-α drug commercially released. Several years later adalimumab was also commercially available and later etanercept became available. Thus, initially, many patients eligible for this kind of treatment were received infliximab therapy. Later, the other two drugs were used in our clinic. That is why our patients are not well balanced across the different TNF inhibitors. After all the drugs were commercially available, the drug choice was based on each patient's preference for intravenous or subcutaneous treatment. The present observational study is one of the longest found in the literature. We evaluated survival, efficacy and safety of anti-TNF-α treatment in RA and included patients from everyday clinical practice.

In conclusion, anti-TNF-α therapy is effective in improving signs and symptoms of patients with established RA refractory to conventional treatment with sDMARDs. TNF-α inhibitors demonstrate an acceptable safety profile. RA patients treated with infliximab are more likely to discontinue treatment earlier comparing with the two alternatives. Infections and allergic reactions appear more often with infliximab, but serious infections did not differ among the three drugs.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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