Survival of TNF-alpha antagonists in rheumatoid arthritis: a long-term study

T.E. Markatseli[1], Y. Alamanos[2], I. Saougou[1], P.V. Voulgari[1], A.A. Drosos[1]

[1]Rheumatology Clinic, Department of Internal Medicine, Medical School, University of Ioannina, Ioannina, Greece, [2]Department of Public Health, Medical School, University of Patras, Patras, Greece.

Abstract

Objective

To investigate the efficacy, safety and survival of tumour necrosis factor (TNF) α antagonists in patients with rheumatoid arthritis (RA).

Methods

One hundred and fifty-one RA patients treated with TNF-α inhibitors during the time period 2000 to 2009 were studied. Kaplan-Meier statistic analysis was applied, in which discontinuation from anti-TNF-α therapy was used as the terminal event.

Results

Eighty-two patients received infliximab, 49 adalimumab and 20 etanercept: they were followed up over 7, 5 and 4 years, respectively. Anti-TNF-α therapy resulted in a rapid clinical improvement associated with a reduction in inflammatory markers in the first year of the treatment, which was sustained throughout the following years. Ninety (59.6%) patients were withdrawn during the observational period overall. The patients who discontinued infliximab, adalimumab and etanercept therapy were 55/82 (67.1%), 27/49 (55.1%) and 8/20 (40%) respectively. The main reasons for discontinuation were drug adverse events and inefficacy. According to Kaplan-Meier methods, the "survival rate" of infliximab after the first year of treatment reached 82.9%, while after 7 years the proportion was 32.9%. With regard to adalimumab, after the first year of treatment its "survival rate" was 83.7% and after 5 years it reached 44.9%. As far as etanercept is concerned, after the first year of treatment, the "survival rate" reached 70% and after 4 years it remained 60%.

Conclusions

TNF-α antagonists constitute an effective therapeutic option for patients with RA refractory to disease-modifying anti-rheumatic drugs. They demonstrate an acceptable safety profile. Their survival rate is high in the first years of treatment, while after the fifth year it decreases considerably.

Key words

rheumatoid arthritis, TNF-α antagonists

Theodora E. Markatseli, MD
Yannis Alamanos, MD, Assoc. Professor
Ioanna Saougou, MD
Paraskevi V. Voulgari, MD, Assist. Professor
Alexandros A. Drosos, MD, FACR, Professor

Please address correspondence to:
Alexandros A. Drosos, MD, FACR,
Professor of Medicine/Rheumatology,
Rheumatology Clinic,
Department of Internal Medicine,
Medical School,
University of Ioannina,
Ioannina, Greece.
E-mail: adrosos@cc.uoi.gr

Received on April 14, 2011; accepted in revised form on July 8, 2011.

Competing interests: none declared.

Introduction

Rheumatoid arthritis (RA) is the most common human autoimmune disease that results in substantial joint damage and disability. Although the precise etiology of RA remains unclear, there is evidence that proinflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-1, and interleukin-6 play a role in the RA pathogenesis (1, 2). Interfering with the activities of these molecules might, therefore, be useful for the treatment of RA.

Remission and retardation of radiographic progression are main goals in the treatment of RA. Disease-modifying anti-rheumatic drugs (DMARDs), which constitute the traditional therapy for RA, influence the disease process, by slowing down the joint and bone destruction (3, 4). Methotrexate (MTX) is the DMARD of choice for patients with active RA due to its long-term survival in clinical practice (5). Combination of DMARDs is very often needed for patients to achieve disease remission and it has been found to be safe and effective in the long-term management of RA (6, 7). However, there is a proportion of patients, especially in established RA, in whom DMARDs only partially can control the disease course. The development of the TNF-α inhibitors was evolutionary in the last decades. Therapies that target TNF have been successfully used to treat patients with Th1-mediated chronic inflammatory diseases and particularly patients with RA refractory or intolerant to at least two DMARDs (8). Plenty of studies – randomised or not – have demonstrated the efficacy of TNF-α antagonists in the treatment of RA (9-13). In most of these trials, patients receiving TNF-α antagonists achieved both disease remission and demonstrated a statistically significant delay in radiographic progression, compared with those receiving DMARDs. Infliximab is the first anti-TNF-α monoclonal antibody that was approved for the treatment of RA, and it is given intravenously in different administration schedules. On the other hand, adalimumab, a monoclonal human anti-TNF-α antibody, and etanercept, a recombinant version of the soluble p75 TNF-α receptor, are both administered subcutaneously.

Although the TNF-α blocking agents have been relatively safe in the short- and long-term management of RA, some concerns have been raised about the increased risk of serious infections and solid malignancy in a small percentage of patients treated with these agents (14). Less severe, but quite often, autoimmmmune phenomena can also be induced by them (15). In addition, in some cases of patients treated with infliximab, treatment has to be discontinued due to infusion allergic reactions.

In the present long-term open label study, we investigate the efficacy, safety and survival of the aforementioned anti-TNF-α agents in anti-TNF-α naïve patients with RA.

Materials and methods

One hundred and fifty-one anti-TNF-α naïve RA patients, who were enrolled between March 2000 and March 2005, were treated with TNF-α inhibitors and were followed-up at predefined times according to a standardised protocol. The protocol had been approved by the Institutional Scientific Committee of the University Hospital of Ioannina, Greece. All patients fulfilled the American College of Rheumatology (ACR) criteria for RA (16). Before initiation of anti-TNF-α treatment all patients were screened for latent tuberculosis. Ten patients had positive purified protein derivative skin test for tuberculosis and were treated with isoniazide 300mg/day for a period of 9 months. Patients with evidence of active tuberculosis, chronic or clinically significant infection, malignancy or congestive heart failure were not eligible for the study.

All patients met criteria for administration of α biologic agent. They had active disease which was included: tender or swollen joint count ≥6, disease activity score for the 28 joint indices (DAS-28) ≥3.2 (17) and erythrocyte sedimentation rate (ESR) ≥28 mmHg/1st hour or C-reactive protein (CRP) ≥10 mg/l. Additionally, they were all refractory to at least 2 DMARDs. Patients were not randomised to receive a specific TNF-α inhibitor. They were treated as regular clinical patients. The

decision to start a specific anti-TNF-α biologic agent was made according to patients' preference for intravenous infusions or self-injections. Although this was not a sponsored trial, the costs of the different biologic agents did not influence this decision, since in our country patients receive biologics for free as their costs are covered by patients' life insurance. Infliximab (3 mg/kg body weight) was administered intravenously at weeks 0, 2, 6 and every 8 weeks thereafter. If there was an inadequate response to the treatment, the intervals between infusions were shortened to 6 or to 4 weeks or, alternatively, the dose of infliximab was increased to 5mg/ kg body weight keeping the same dosage interval. Insufficient response was defined as patients not fulfilling the ACR 20% criteria or the DAS-28 score improvement >1.2. Adalimumab was applied in patients with RA in a dose of 40 mg subcutaneously, every 2 weeks. If adalimumab therapy failed to result in an acceptable response, the injections were conducted every week. Etanercept was also given subcutaneously. In all patients, it was administered as a 25 mg subcutaneous dose twice a week. Approximately three years later, when the once week injection of 50 mg of etanercept was available, all patients switched to the later administration scheme.

Data concerning the efficacy, tolerability, adverse events as well as the cause and the exact date of discontinuation from the anti-TNF-α therapy were recorded. In addition, clinical and laboratory data, parallel medical diseases, immunosuppressive and other concomitant drugs were recorded. Clinical improvement according to the ACR 20%, 50% and 70% response criteria, as well as the DAS-28 score were calculated. Reasons for discontinuations included failure of drug treatment due to lack of efficacy, adverse events – either life-threatening or intolerance – comorbidity and loss from follow-up. All patients had their last follow-up examination by March 2009.

Statistical analysis

The data were analysed in order to estimate the survival of TNF-α inhibitors in patients with RA. Kaplan-Meier statistic analysis was applied, in which discontinuation from anti-TNF-α therapy was taken as the terminal event. Cox regression models were used to compare discontinuation rates between the three treatment groups as well as to adjust for the following independent factors: drug, sex, age, disease duration and MTX intake. Comparisons between the three treatment groups were applicable at year 4, while comparisons between infliximab and adalimumab group were also possible at year 5. The treatment response according to the ACR criteria was analysed in an intention to treat analysis. Statistical analysis was performed using SPSS Statistics, version 17.0.

Table I. Baseline characteristics of the 151 RA patients treated with TNF inhibitors.

	Infliximab (n=82)	Adalimumab (n=49)	Etanercept (n=20)
Sex (male/ female), n (%)	14/68 (17/83)	6/43 (12/88)	1/19 (5/95)
Age (yeas), mean (SD)	55.8 (12)	54.2 (14)	53.5 (13.1)
Disease duration (years), mean (SD)	13 (7)	15.1 (8.4)	12.9 (12.6)
RF positive, n (%)	52 (63.4)	30 (61.2)	13 (65)
MTX intake, n (%)	65 (79)	30 (61)	14 (70)
CsA intake, n (%)	49 (60)	3 (6)	13 (65)
Steroid intake, n (%)	72 (88)	42 (85.7)	15 (75)
DAS-28, mean (SD)	5.55 (0.91)	5.87 (0.83)	6.09 (1.08)
ESR (mm/1st hour), mean (SD)	49 (28)	48.6 (23.5)	49.6 (24.4)
CRP (mg/l), mean (SD)	26.5 (27.3)	21.6 (16.8)	22.3 (15.2)

Results

A total of 151 patients with established RA refractory to at least 2 DMARDs were eligible for anti-TNF-α therapy. Of these, 130 (86.1%) were women and 21 (13.9%) men, with a mean age of 55±12.8 years and mean disease duration 13.7±8.4 years. Ninety-five (62.9%) patients were positive for IgM rheumatoid factor (RF). The baseline characteristics of the RA patients are presented in Table I. It is of note that all patients had active disease as it is evaluated by the high DAS-28 score and the high levels of ESR and CRP. As it is depicted in Table I, at baseline a significant proportion of the 151 patients were under therapy with combination of two DMARDs and steroids without improvement. The fact that these 151 patients with established RA were refractory or intolerant of the majority of DMARDs also explains the high percentage of patients in concomitant cyclosporine A (CsA) intake particularly in infliximab group. The majority of patients (88.4%) did not substantially modify their concomitant therapy with DMARD while under anti-TNF-α treatment.

Infliximab was administered to 82 patients, while 49 patients received adalimumab and 20 etanercept. In 32 patients (39%) of those receiving infliximab the dose was increased to 5 mg/kg, since they did not respond to the initial dose of infliximab. In addition, in 18 patients (34%) the dosage interval was shortened. On the other hand, 7 (14.3%) among the 49 patients who were treated with adalimumab, did not respond sufficiently to the therapy and thus, the interval between injections was also shortened. The duration of the observational period for all patients who did not drop out and who were treated with infliximab, adalimumab and etanercept lasted 7, 5 and 4 years respectively.

Anti-TNF-α therapy resulted in a rapid improvement in the DAS-28 score and in the inflammatory markers in the first year of the treatment, which was sustained throughout the following years (Figure 1). Additionally, a significant percentage of patients achieved the ACR 20, 50 and 70 response criteria. The overall clinical response is shown in Figure 2.

Figure 3 presents the survival of the three TNF-α inhibitors. According to Kaplan-Meier methods, the "survival rate" of infliximab after the first year of treatment reached 82.9%, after the second year it was reduced to 63.4%, after the third year it was 50%, after the fourth year it was further reduced to 43.9%, while after the fifth and the sixth year this rate was 37.8% and

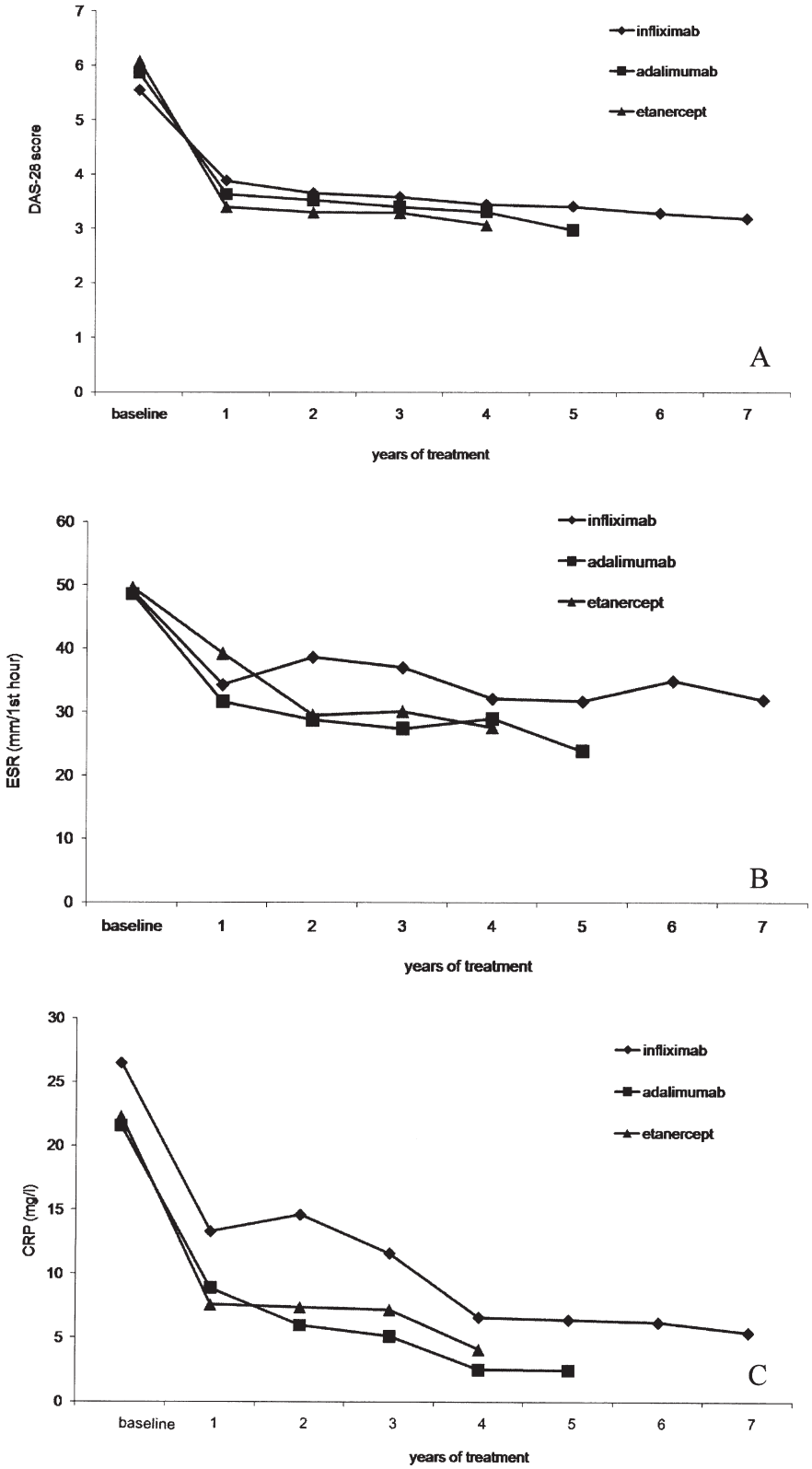

Fig. 1. Improvement of DAS-28 score (**A**), ESR (**B**) and CRP (**C**) in the three groups of RA patients.

35.4% respectively and after 7 years of treatment the survival rate was 32.9%. After the first year of treatment with adalimumab, its "survival rate" was 83.7%, after the second year it was lessened to 69.4%, after the third year this rate was 63.3%, after the fourth year it was further decreased to 51%, while after 5 years of treatment it was maintained to these levels (44.9%). In relation to the etanercept group, after the first year of treatment the "survival rate" reached the proportion of 70%, after the second and third year it remained high (65% and 60% respectively) and as we completed 4 years of treatment we noticed that the drug survival was 60%. The comparison of the three anti-TNF agents' survival did not reveal statistically significant differences at year 4 (p=0.57). Similarly, the difference in survival rate at year 5 between infliximab and adalimumab group of RA patients did not reach the level of statistical significance (p=0.69).

A total of 90 (59.6%) patients were withdrawn during the observational period. Fifty-five patients (67.1%) discontinued infliximab therapy, 27 patients (55.1%) ceased adalimumab therapy, while 8 (40%) discontinuations in the etanercept group of patients were recorded. More specifically, among the patients who were treated with infliximab, 23 (28%) terminated the study due to adverse drug reactions, 14 (17.1%) due to lack of efficacy, 9 (11%) due to comorbidity, while 9 (11%) were lost from follow-up. As severe adverse drug reactions demanding the permanent discontinuation of the current anti-TNF-α therapy were considered the immediate hypersensitivity reactions and infections. These occurred in 15 (18.3%) and 8 (9.8%) patients who received infliximab therapy respectively. In all patients, who experienced immediate hypersensitivity reactions, the infusion was immediately ended and appropriate drugs were administered. The permanent discontinuation of infliximab therapy was decided in cases of serious acute infusion reactions (9 patients), as well as in cases of recurrence of clinical symptoms in subsequent infusions despite the administration of premedication and the maintenance of a slow infusion rate (6 patients). Two cases of pulmonary tuberculosis (TB) and one of TB spondylitis were recorded. None of these patients had positive purified protein derivative skin test. As regards the outcome, all severe infections were resolved after appropriate treatment. The main reason for discontinuation due to comorbidity was cardiovascular disease. Additionally, two cases of

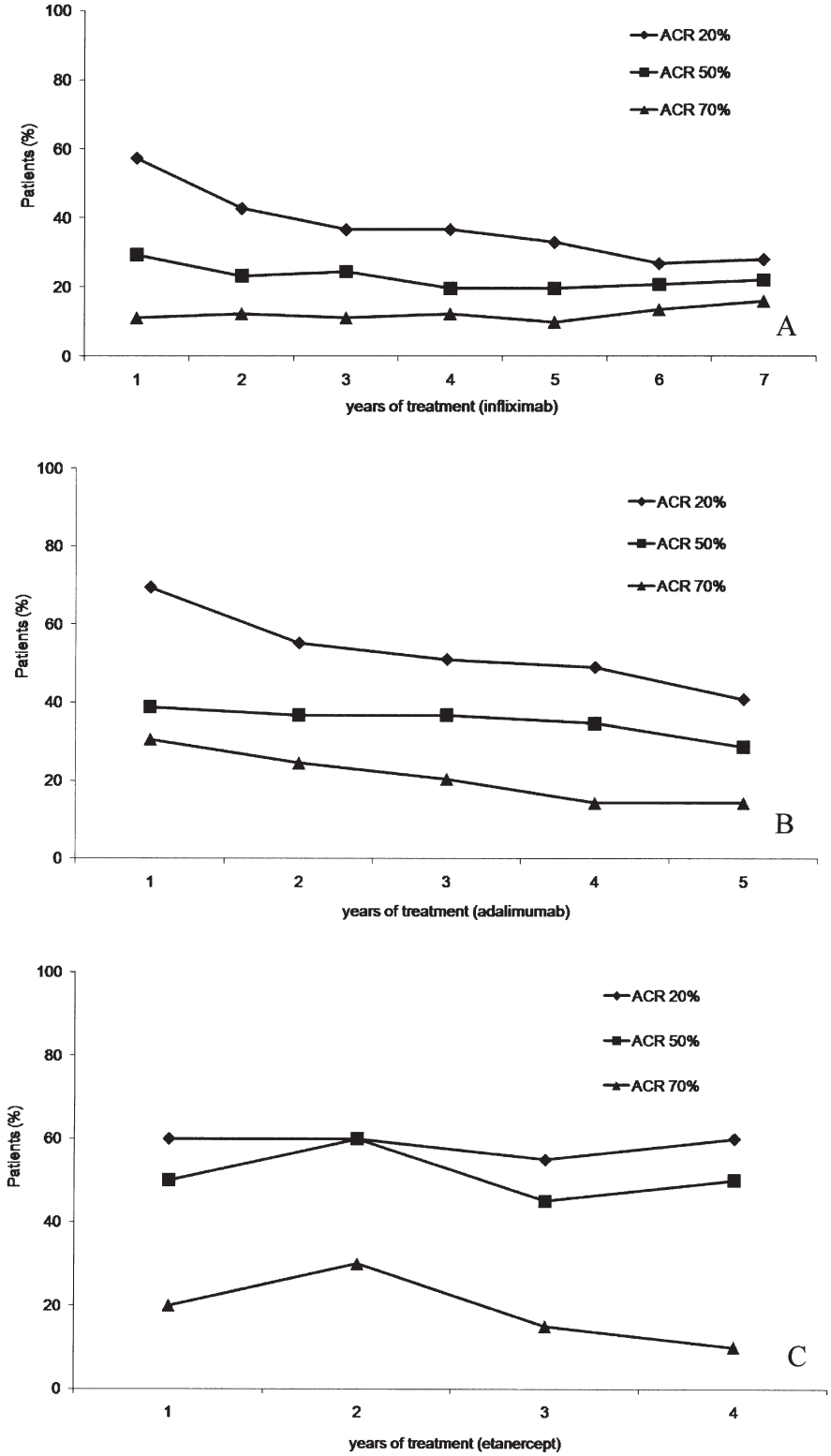

Fig. 2. Response to infliximab (**A**), adalimumab (**B**) and etanercept (**C**) treatment according to ACR criteria.

solid malignancy were recorded. In the group of adalimumab, 6 (12.2%) patients discontinued therapy due to lack of efficacy, 6 (12.2%) patients due to drug's side effects, 2 (4.1%) patients due to comorbidities and 13 (26.5%) patients were lost from follow-up. Three (6.1%) immediate hypersensitivity reactions were recorded, while 2 (4.1%) patients presented severe infections. Of these, one patient with negative purified protein derivative skin test developed extra-pulmonary tuberculosis and the other one developed pulmonary aspergillosis. In both cases, the severity was moderate to high, but the outcome was favourable. Finally, one case of solid malignancy was recorded. In the group of etanercept 2 (10%) patients experienced adverse drug reactions and ceased anti-TNF-α therapy, while 6 (30%) patients were lost from follow-up. No terminations due to lack of efficacy or due to comorbidity were recorded. The trial profile and the reasons for discontinuations are presented in Figure 4. From a total of 90 patients who discontinued anti-TNF-α treatment 41 (45.6%) patients changed to other anti-TNF-α agent.

Of note, concomitant use of CsA was well tolerated. Of a total of 65 patients receiving CsA, 5 (7.7%) had reversible increases in serum creatinine levels, while 6 (9.2%) patients had an elevated blood pressure. CsA was used at the lowest effective dose.

Discussion

The present open-label study was conducted in order to evaluate the long-term efficacy, safety and survival of TNF-α inhibitors in RA patients. This study indicate long-term efficacy of TNF-α inhibitors on pain, joint tenderness and swelling as well as inflammation. The efficacy of the three TNF-α inhibitors in the first four years was comparable. To our knowledge, there are no head-to-head randomised controlled trials (RCTs) in the literature that compare the efficacy of TNF-α inhibitors. The results coming from indirect comparisons of RCTs are unconvincing (18-21). Thus, there is no evidence that an individual TNF-α blocking agent is more effective than the others in RA.

With regard to safety, our study demonstrated an acceptable toxicity profile of anti-TNF-α therapy similar to that described by other investigators (11, 22-24). As expected, the infusion and systemic allergic reactions were more often in the group of patients treated with infliximab. Among the serious infections that occurred in our RA patients, there

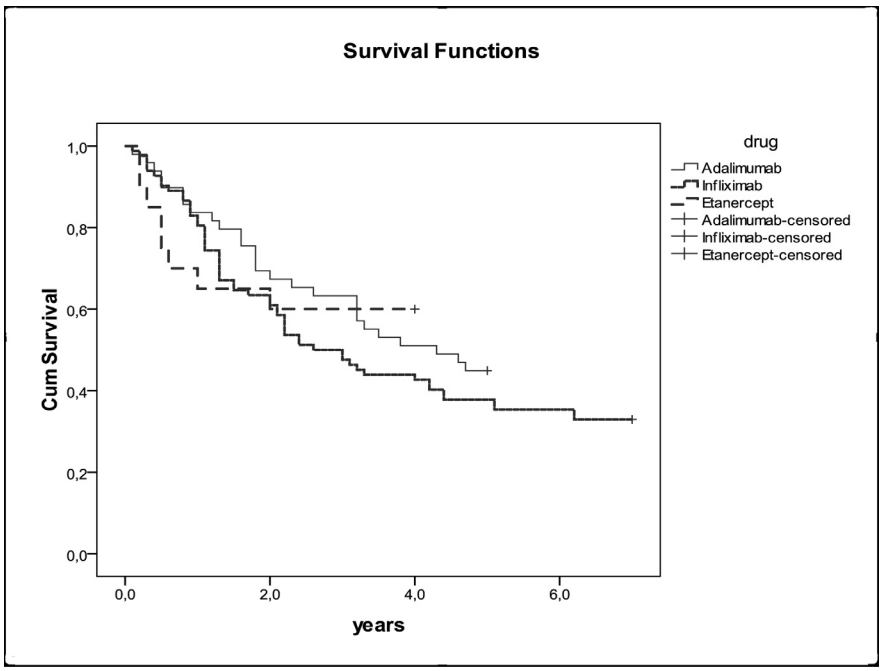

Fig. 3. TNF-α inhibitors' survival in patients with rheumatoid arthritis.

were four cases of tuberculosis (three in the infliximab group and one in the adalimumab group). It is noteworthy that all these four patients had normal chest x-rays and negative purified protein derivative skin tests before anti-TNF-α therapy. Additionally, all cases of tuberculosis apart from one occurred at least one year after initiation of anti-TNF-α therapy. A late manifestation of tuberculosis has also been described and it is indicative of either a *de novo* infection with mycobacterium tuberculosis or a reactivation of a latent disease in anergic RA patients with negative purified protein derivative skin tests (25).

The discontinuation rates of the three TNF-α inhibitors did not differ at the predefined time points. Our results are in agreement with those of other investigators (18, 20, 21, 26). However, analyses from other registries show higher discontinuation rate of infliximab than of adalimumab or etanercept (27-31). Reasons for this discrepancy may be the differences in the number of patients included, differences in disease duration, in disease severity or in the length of the follow up time period. In our study, the anti-TNF-α treatment survival ranged between 43.9 and 60% after 4 years of treatment. As we have previously shown (32), after 3 years of therapy, 59% of patients still continue to receive infliximab. However, in the present study it was found that after the 5th year, infliximab survival declines significantly. The survival rate of infliximab after 7 years of treatment was decreased to 32.9%, which is comparable with the 31% rate observed in another longitudinal study of RA patients with severe long-standing refractory disease treated with infliximab (33). Loss of TNF-α inhibitor survival may be due to generation of antibodies against the administered biopharmaceutical agent. It has recently been reported that antibodies against infliximab or adalimumab may be responsible for the loss of the initial response to treatment over time in RA patients (34, 35). Concomitant administration of MTX seems to suppress the formation of anti-drug antibodies and prolong the drug's

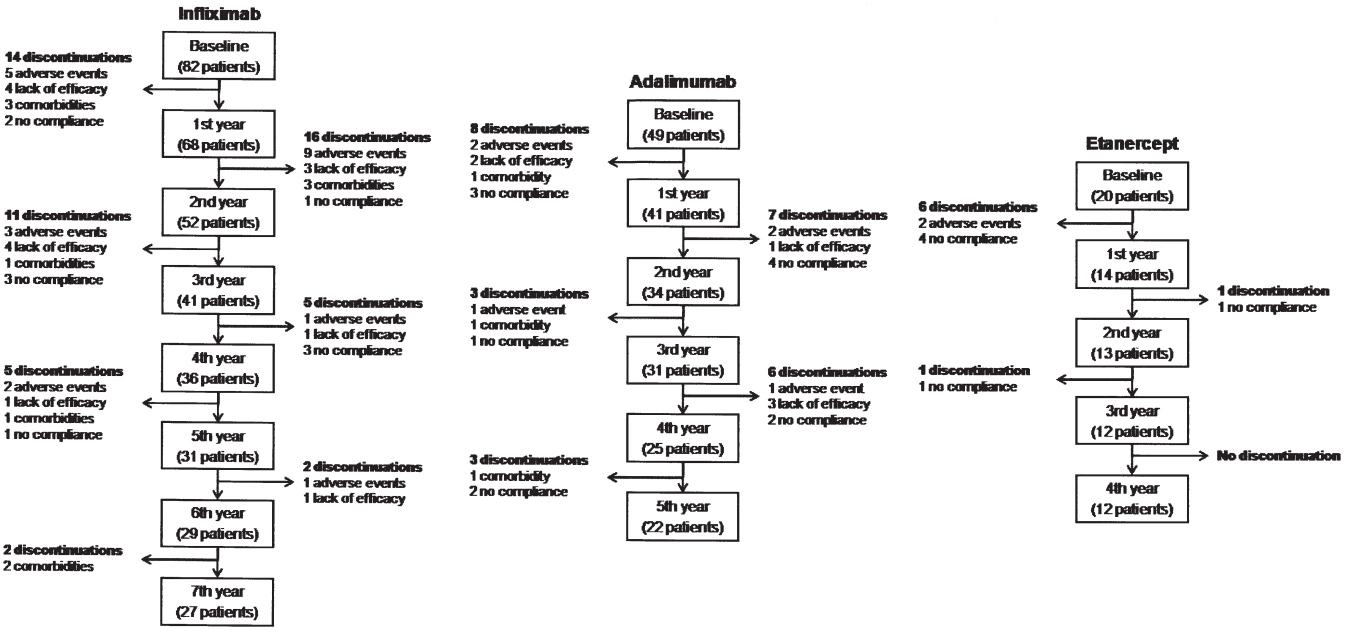

Fig. 4. Trial profile and reasons for discontinuation from infliximab, adalimumab and etanercept therapy in an intention to treat analysis.

survival (36). MTX intake ranged between 61–79% among the three treatment groups of patients in our study. It is notable that apart from MTX other DMARDs such as CsA were also used by our patients. There are few studies in the literature suggesting that CsA may be an alternative DMARD to be used in combination with infliximab in patients with established RA who are refractory or cannot tolerate MTX (37, 38). However, in Greece, CsA is a drug that is usually used in clinical practice since it has been found to be effective as a combination therapy in RA in previous studies (39-41).

In our study, the fact that an important proportion of our patients under subcutaneous anti-TNF-α therapy were lost from follow-up, has certainly determined the respective drug survival. Since our University centre is the only one in north-western Greece, it is possible that some of our RA patients, who first visited our centre for a second opinion, after the initiation of adalimumab or etanercept therapy and a time period of follow-up that varied among patients, they continued their follow-up somewhere else. It is known that subcutaneous anti-TNF-α therapy does not demand hospitalisation in contrast to infliximab intravenous therapy. This could explain the high percentage of subcutaneous anti-TNF-α treated patients who were lost from follow-ups. Additionally, the fact that in our country etanercept was introduced a few years after adalimumab explains the small proportion of patients using etanercept. The present observational study is one of the longest in the literature to evaluate the survival of anti-TNF-α treatment in RA. This applies mainly to infliximab which was used for a maximum 7-year follow-up in RA patients. Our study reflects usual clinical care; our patients were treated with TNF-α-inhibitors outside of a clinical trial setting. Thus, a limitation is that they were not randomised to receive a specific TNF-α-inhibitor. Patients' willingness/ability to inject her/himself or preference for intravenous infusions was taken into account. Although, the costs of the different biologic agents did not influence this decision (as mentioned in the materials and methods section), this is a parameter that may also count in real life. Another limitation of our study is the fact that it is an open label study based on a limited number of patients especially in the etanercept group. Additionally, the three groups differ in several baseline characteristics (low concomitant DMARDs in etanercept group, different sex ratio, etc.). However, to overwhelm these potential sources of bias COX regression model was used.

In conclusion, anti-TNF-α treatment is effective at improving the signs and symptoms of patients with established RA refractory to conventional therapy with DMARDs. TNF-α inhibitors have an acceptable safety profile. Their survival rate is high in the first years of treatment; however, infliximab survival decreases considerably after the fifth year.

References

1. BRENNAN FM, MAINI RN, FELDMANN M: TNF-α pivotal role in rheumatoid arthritis? *Br J Rheumatol* 1992; 31: 293-8.
2. FELDMANN M, BRENNAN FM, MALNL RN: Role of cytokines in rheumatoid arthritis. *Annu Rev Immunol* 1996; 14: 397-440.
3. VAN DER HEIDE A, JACOBS JW, BIJLSMA JW *et al*.: The effectiveness of early treatment with "second-line" antirheumatic drugs. A randomized, controlled trial. *Ann Intern Med* 1996; 124: 699-707.
4. VAN JAARSVELD CH, JACOBS JW, VAN DER VEEN MJ *et al*.: Aggressive treatment in early rheumatoid arthritis: a randomised controlled trial. On behalf of the Rheumatic Research Foundation Utrecht, the Netherlands. *Ann Rheum Dis* 2000; 59: 468-77.
5. NEWSOME G: for the American College of Rheumatology. Guidelines for the management of rheumatoid arthritis: 2002 Update. *Am Acad Nurse Pract* 2002; 14: 432-7.
6. MAKINEN H, KAUTIAINEN H, HANNONEN P *et al*.: Sustained remission and reduced radiographic progression with combination disease modifying antirheumatic drugs in early rheumatoid arthritis. *J Rheumatol* 2007; 34: 316-21.
7. RANTALAIHO V, KORPELA M, LAASONEN L *et al*.: Early combination disease-modifying antirheumatic drug therapy and tight disease control improve long-term radiologic outcome in patients with early rheumatoid arthritis: the 11-year results of the Finnish Rheumatoid Arthritis Combination Therapy trial. *Arthritis Res Ther* 2010; 12: R122.
8. FURST DE, BREEDVELD FC, KALDEN JR *et al*.: Updated consensus statement on biological agents for the treatment of rheumatoid arthritis and other immune mediated inflammatory diseases (May 2003). *Ann Rheum Dis* 2003; 62 (Suppl. 2): ii2-9.
9. VAN DER HEIJDE D, KLARESKOG L, LANDEWÉ R *et al*.: Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 3928-39.
10. EMERY P, BREEDVELD FC, HALL S *et al*.: Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008; 372: 375-82.
11. WESTHOVENS R, YOCUM D, HAN J *et al*.: The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities. A large, randomized, placebo controlled trial. *Arthritis Rheum* 2006; 54: 1075-86.
12. BREEDVELD FC, WEISMAN MH, KAVANAUGH AF *et al*.: The PREMIER study: a multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006; 54: 26-37.
13. VOULGARI PV, ALAMANOS Y, NIKAS SN, BOUGIAS DV, TEMEKONIDIS TI, DROSOS AA: Infliximab therapy in established rheumatoid arthritis: An observational study. *Am J Med* 2005; 118: 515-20.
14. LIN J, ZIRING D, DESAI S *et al*.: TNF alpha blockade in human diseases: an overview of efficacy and safety. *Clin Immunol* 2008; 126: 13-30.
15. EXARCHOU SA, VOULGARI PV, MARKATSELI TE, ZIOGA A, DROSOS AA: Immune-mediated skin lesions in patients treated with anti-tumour necrosis factor alpha inhibitors. *Scand J Rheumatol* 2009; 38: 328-31.
16. ARNETT FC, EDWORTHY SM, BLOCH DA *et al*.: The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 315-24.
17. PREVOO ML, VAN 'T HOF MA, KUPER HH *et al*.: Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 44-8.
18. GARTLEHNER G, HANSEN RA, JONAS BL, THIEDA P, LOHR KN: The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: a systematic review and metaanalysis. *J Rheumatol* 2006; 33: 2398-408.
19. ALONSO-RUIZ A, PIJOAN JI, ANSUATEGUI E, URKAREGI A, CALABOZO M, QUINTANA A: Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. *BMC Musculoskeletal Disorders* 2008; 9: 52.
20. LEE YH, WOO JH, RHO YH, CHOI SJ, JI JD, SONG GG: Meta-analysis of the combination of TNF inhibitors plus MTX compared to MTX monotherapy, and the adjusted indirect comparison of TNF inhibitors in patients suffering from active rheumatoid arthritis. *Rheumatol Int* 2008; 28: 553-9.

21. DONAHUE KE, GARTLEHNER G, JONAS DE *et al*.: Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. *Ann Intern Med* 2008; 148: 124-34.
22. FURST DE, SCHIFF MH, FLEISCHMANN RM *et al*.: Adalimumab, a fully human anti-tumor necrosis factor-α monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003; 30: 2563-71.
23. VAN DE PUTTE LB, ATKINS C, MALAISE M *et al*.: Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. *Ann Rheum Dis* 2004; 63: 508-16.
24. VAN DER HEIJDE D, KLARESKOG L, LANDEWÉ R *et al*.: Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum* 2007; 56: 3928-39.
25. KEANE J, GERSHON S, WISE RP *et al*.: Tuberculosis associated with infliximab, a tumor necrosis factor alpha - neutralizing agent. *N Engl J Med* 2001; 345: 1098-104.
26. HOCHBERG MC, TRACY JK, HAWKINS-HOLT M, FLORES RH: Comparison of the efficacy of the tumor necrosis factor α blocking agents adalimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2003; 62 (Suppl. 2): ii13-6.
27. KRISTENSEN LE, SAXNE T, GEBOREK P: The LUNDEX, a new index of drug efficacy in clinical practice: results of a five-year observational study of treatment with infliximab and etanercept among rheumatoid arthritis patients in southern Sweden. *Arthritis Rheum* 2006; 54: 600-6.
28. GEBOREK P, CRNKIC M, PETERSSON IF, SAXNE T: Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. *Ann Rheum Dis* 2002; 61: 793-8.
29. KIEVIT W, ADANG EM, FRANSEN J *et al*.: The effectiveness and medication costs of three anti-tumor necrosis factor α agents in the treatment of rheumatoid arthritis from prospective clinical practice data. *Ann Rheum Dis* 2008; 67: 1229–34.
30. DU PAN SM, DEHLER S, CIUREA A, ZISWILER HR, GABAY C, FINCKH A; SWISS CLINICAL QUALITY MANAGEMENT PHYSICIANS: Swiss Clinical Quality Management Physicians. Comparison of drug retention rates and causes of drug discontinuation between anti–tumor necrosis factor agents in rheumatoid arthritis. *Arthritis Rheum* 2009; 61: 560-8.
31. HETLAND ML, CHRISTENSEN IJ, TARP U *et al*.: Direct comparison of treatment responses, remission rates, and drug adherence in patients with rheumatoid arthritis treated with adalimumab, etanercept, or infliximab: Results from eight years of surveillance of clinical practice in the nationwide danish DANBIO registry. *Arthritis Rheum* 2010; 62: 22-32.
32. VOULGARI PV, ALAMANOS Y, DROSOS AA: Persistent clinical response of infliximab therapy in patients with refractory rheumatoid arthritis, over a 3-year period. *Cur Clin Pharmacol* 2006; 1: 103-8.
33. CRUYSSEN BV, DUREZ P, WESTHOVENS R, DE KEYSER F: Seven-year follow-up of infliximab therapy in rheumatoid arthritis patients with severe long-standing refractory disease: attrition rate and evolution of disease activity. *Arthritis Res Ther* 2010; 12: R77.
34. WOLBINK GJ, VIS M, LEMS W *et al*.: Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006; 54: 711-5.
35. BARTELDS GM, WIJBRANDTS CA, NURMOHAMED MT *et al*.: Clinical response to adalimumab: relationship to anti-adalimumab antibodies and serum adalimumab concentrations in rheumatoid arthritis. *Ann Rheum Dis* 2007; 66: 921-6.
36. KRISTENSEN LE, SAXNE T, NILSSON JA, GEBOREK P: Impact of concomitant DMARD therapy on adherence to treatment with etanercept and infliximab in rheumatoid arthritis: results from a six-year observational study in southern Sweden. *Arthritis Res Ther* 2006; 8: R174.
37. TEMEKONIDIS TI, GEORGIADIS AN, ALAMANOS Y, BOUGIAS DV, VOULGARI PV, DROSOS AA: Infliximab treatment in combination with cyclosporin A in patients with severe refractory rheumatoid arthritis. *Ann Rheum Dis* 2002; 61: 822-5.
38. FERRACCIOLI GF, ASSALONI R, DI POI E, GREMESE E, DE MARCHI G, FABRIS M: Rescue of combination therapy failures using infliximab, while maintaining the combination or monotherapy with methotrexate: results of an open trial. *Rheumatology* 2002; 41: 1109-12.
39. VERSTAPPEN SMM, JACOBS JWG, VAN DER VEEN MJ *et al*.: Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Ann Rheum Dis* 2007; 66: 1443-9.
40. HETLAND ML, STENGAARD-PEDERSEN K, JUNKER P *et al*.: Combination treatment with methotrexate, cyclosporine, and intraarticular betamethasone compared with methotrexate and intraarticular betamethasone in early active rheumatoid arthritis; An investigator-initiated, multicenter, randomized, double-blind, parallel-group, placebo-controlled study. *Arthritis Rheum* 2006; 54: 1401-9.
41. CHOY EH, SMITH CM, FAREWELL V *et al*.; FOR THE CARDERA (COMBINATION ANTI-RHEUMATIC DRUGS IN EARLY RHEUMATOID ARHRITIS) TRIAL GROUP: Factorial randomised controlled trial of glucocorticoids and combination disease modifying drugs in early rheumatoid arthritis. *Ann Rheum Dis* 2008; 67: 656-63.