

Persistent Clinical Response of Infliximab Therapy in Patients with Refractory Rheumatoid Arthritis, over a 3-Year Period

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Abstract: Infliximab, a chimeric monoclonal anti-tumor necrosis factor alpha antibody is approved for the treatment of patients with rheumatoid arthritis (RA) who had an inadequate response to methotrexate (MTX) therapy. This report provides analyses by using infliximab in combination with various disease modifying anti-rheumatic drugs, infliximab "survival" over a period of three years, and its effectiveness on synovial tissue damage using magnetic resonance (MR) imaging. The study was started in 1999 as an open label study using infliximab in combination with cyclosporin A (CsA) in refractory RA patients who were unable to tolerate MTX. A total of 18 RA patients were investigated. After a year of treatment, 80% of patients achieved the 20% American College of Rheumatology Response criteria. Two patients dropped out; one because of an immediate hypersensitivity reaction and the other because of the development of pulmonary tuberculosis. In a subsequent study we investigated infliximab "survival" over a period of 3 years. A total of 84 RA patients were included in the study. After 3 years of therapy, 59% of patients still continued receiving infliximab. The factor that was associated with infliximab "survival" was the concomitant use of MTX. A total of 28 (33%) patients discontinued this study. More specifically, 16 (19%) presented adverse drug reactions, 9 (11%) had drug failure, and 3 (3%) were lost from follow-up. Finally, to evaluate by MR imaging the inflammatory tissue changes in refractory RA patients treated with infliximab, 16 patients were examined with MR imaging of the dominant affected wrist and hand before and one year after therapy. The volume of the enhancing inflammatory tissue (VEIT) was evaluated. A significant decrease of VEIT was observed in 88% of patients after therapy. We conclude that in refractory RA patients infliximab was proved to be efficacious and well tolerated in combination with CsA. The clinical response of infliximab was persistent over a 3-year period and was associated with the concomitant use of MTX. This clinical improvement was also associated with the reduction of inflammatory disease tissue damage.

Keywords: Rheumatoid arthritis, Infliximab, Long-term, Methotrexate, Cyclosporine A, Magnetic resonance imaging.

INTRODUCTION

Rheumatoid arthritis (RA) is a systemic inflammatory disease characterized by chronic synovitis, which leads to cartilage damage and joint destruction. Recent studies on the incidence of RA have rather consistently obtained a prevalence of 0.5-1% and an annual incidence of around 25-50 new cases per 100.000 at risk [1-3]. In the last few years significant advances have been made in our understanding of the molecular mechanisms underlying RA pathogenesis. Activated autoreactive T cells and macrophages, as well as an increased number and activity of synovocytes, have been implicated in the pathogenesis of bone and joint destruction in RA [4,5]. Aberrant overproduction of proinflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF)-alpha by inflammatory cells leads to persistent up-regulation of various molecules responsible for the inflammatory and destructive processes in the joints of patients with RA [4-6].

Pharmacotherapy is the cornerstone of treatment of RA and includes three kinds of drugs [7]. The first comprises non-steroidal anti-inflammatory drugs, which are given for their immediate analgesic and anti-inflammatory effects but

which do not influence the disease process itself. The second comprises so-called disease modifying antirheumatic drugs (DMARDs), which influence the disease process and also slow down joint and bone destruction [8,9]. Finally, small doses of steroids may also modify the RA disease process. Several DMARDs have been proposed for the treatment of RA: gold salts, D-penicillamine, hydroxychloroquine, azathioprine, sulfasalazine, cyclosporin A (CsA) and methotrexate (MTX). Recently leflunomide and mycophenolate mofetil are two newer antirheumatic drugs for the treatment of RA patients. Today, MTX treatment is the drug of choice in early disease or after failure of other DMARDs.

Current treatments for RA with first- and second-line drugs are inadequate in that they only partially control established RA. They also have many adverse effects that limit their use during the disease process and interfere with prolonged administration. Thus, despite optimal use of current DMARDs, the outcome for many patients with RA is a severe functional decline, work disability and premature death. Thus, biological anti-TNF-alpha agents and IL-1 receptor antagonists are now the first generation antirheumatic drugs in clinical practice.

THERAPY WITH THE ANTI-TNF ANTIBODY - INFliximab

At the beginning of the 1990s, clinical trials using chimeric human/mouse or humanized anti-TNF-alpha monoclonal antibodies (mAbs) in patients with RA provided the

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first direct evidence that inhibitors of TNF- α might be useful therapeutic agents. Thus, 20 patients with active RA were treated with 20 mg/kg of anti-TNF- α in an open phase I/II trial lasting 8 weeks. The treatment was well tolerated, with no serious adverse events. Significant improvement was seen in the Ritchie Articular Index, and reduction of C-reactive protein (CRP), IL-6 and A-amyloid were noted [10]. In a subsequent double-blind, multicentre European trial, 73 patients were randomly assigned to single infusions of either placebo, low doses of infliximab (1 mg/kg) or high dose infliximab (10 mg/kg). Seventy nine percent of patients treated with the high-dose infliximab showed a 20% Paulus response after 4 weeks of treatment as did 44% of the patients treated with the low dose, which both clearly contrasted with only the 8% of placebo responders [11]. In another trial in a small number of patients with active RA, infliximab in combination with small doses of MTX 7.5 mg/week showed an enhanced degree and duration of efficacy [12]. Recent, short- and long-term studies of infliximab in combination with MTX showed that infliximab is well-tolerated and can be used safely, and may reduce the rate of joint damage in patients with RA [13-15].

Adalimumab, a monoclonal human anti-TNF- α antibody is administered subcutaneously (40 mg every other week). Data reported that adalimumab in combination with MTX significantly reduced the signs and symptoms, improve physical function and inhibit progression of structural damage in RA patients [16,17]. On the other hand, etanercept is a recombinant version of the soluble p75 TNF- α receptor. Is given subcutaneously 25 mg twice per week. The efficacy of etanercept has been evaluated in a number of clinical trials. Administration of etanercept consistently reduced clinical signs and symptoms, improved functional status and quality of life [18,19]. In addition, inhibition of peripheral joint damage was demonstrated [19]. TNF- α inhibitors are generally safe and well tolerated. Rare but important adverse events have been reported for each. These include serious and opportunistic infections, including tuberculosis, malignancies, demyelination disorders, allergic reactions, autoantibody formation and others [20,21].

However, the safety aspects of infliximab therapy need further evaluation in long-term regimens for the following reasons: (i) human antichimeric antibody responses occur in a considerable number of patients which may lead to shortening of clinical response and the development of adverse effects; (ii) >10% of the infliximab recipients developed anti-double stranded DNA antibodies and one of these patients showed symptoms of a drug-induced lupus syndrome; (iii) major chronic infections such as chest tuberculosis may develop [22]; and (iv) some of the treated patients developed malignancy. In this review we try to give answers to the above questions and we report the results of an observational study from a single University Center monitoring immunological agent infliximab in clinical practice. First we wanted to see whether infliximab is effective in combination with CsA, second its effectiveness and safety in a long-term fashion for a period of 3 years and finally if the clinical response of infliximab influences the synovial tissue damage.

PATIENTS AND METHODS

Eighty-four RA patients with established disease, refractory or intolerant to at least two DMARDs were recruited between September 1999 and June 2003, from the Rheumatology Clinic of the University Hospital of Ioannina. All patients fulfilled the American College of Rheumatology (ACR) criteria for RA [23]. Patients were fully informed about the treatment regimen and entered the study after having read and signed an informed consent form. They were followed-up at predefined times according to a standardized protocol. The protocol had been approved by the Institutional Scientific Board of the University Hospital of Ioannina, Greece. Infliximab was given intravenously (infusion time >2 hours) in a loading dose of 3 mg/kg/body weight at weeks 0, 2, 6 and every eight weeks thereafter. If the therapeutic response was insufficient, then the dose of infliximab could be increased to 5 mg/kg/body weight keeping the same dosage interval. If this failed to give an acceptable treatment response, the interval was shortened to six or four weeks. Data concerning infliximab efficacy, tolerability, concomitant therapy, adverse events, and drug discontinuation were all recorded. In addition, the clinical and laboratory variables according to the ACR criteria [24] and disease activity score for the 28 joint indices (DAS-28) [25] were also recorded. All patients had a last follow-up examination in May 2004.

Definitions

Refractory RA was defined as increasing DMARDs dosage above standard dosage regimen, using combination therapy, and adding or increasing the dosage of corticosteroids [26]. *Lack of efficacy* was defined as patients not fulfilling the ACR 20% criteria [24] or the disease activity score for 28 joint indices improvement >1.2 score [25]. *Failure of drug treatment* was defined as patients who stopped receiving the drug for more than 2 months because of lack of efficacy. Adverse drug reactions were defined as patients who had reactions that required the permanent discontinuation of infliximab due to life-threatening conditions or because of intolerability. Discontinuation was decided when patients presented failure of drug treatment or experienced adverse drug reactions [27].

Infliximab Therapy in Combination with CsA

Firstly we investigated whether infliximab could be used in combination with CsA in patients with refractory RA that could not tolerate MTX. Studies have shown that infliximab is effective and safe in combination with MTX in patients with refractory RA. However, not all patients tolerate MTX and there have been no reports using infliximab with other DMARDs in patients with RA. On the other hand, a study by Maini *et al.* has shown that combined treatment with low dose CsA and anti-TNF- α treatment caused a significant reduction in severity of disease in collagen induced arthritis, suggesting that CsA could be given in combination with anti-TNF- α [28]. Thus, eighteen patients with refractory RA receiving low dose CsA (2 mg/kg/day) and prednisone (5 mg/day) were treated with intravenous infliximab. Fourteen patients (80%) receiving the combination treatment with CsA and infliximab achieved the 20% ACR criteria for response

to treatment, whereas 7 (39%) satisfied the 50% response criteria (Fig. 1). Finally, a reduction in CRP and erythrocyte sedimentation rate (ESR) was maintained throughout the study. In general, treatment was well tolerated, with minimal adverse drug reactions. Two patients dropped out; one because of an immediate hypersensitivity reaction and the other because of the development of pulmonary tuberculosis [29].

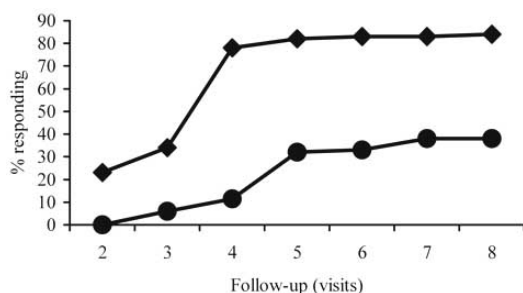


Fig. (1). ACR criteria for response to treatment. Eighty percent of patients receiving the combination treatment of infliximab and CsA achieved the 20% response criteria (line with rhombus), and 39% of patients satisfied the 50% response criteria (line with dots). Visits correspond to infliximab infusions at 0, 2, 6 weeks and every 8 weeks thereafter.

A Long-term Observational Study of Infliximab in RA Patients

Secondly, we investigated the efficacy, toxicity and drug discontinuation rates in an observational study of patients with established RA treated with infliximab. During the recruitment period (September 1999 to June 2003) 95 RA patients were investigated. Of these 3 patients refused treatment and 8 were excluded from the study. More specifically, 4 patients had a positive purified protein derivative skin test, 2 were positive for hepatitis B surface antigen, one had congestive heart failure and another presented with erythema nodosum. Thus, 84 RA patients who had negative purified protein derivative skin test and normal chest x-rays were included in the study (Fig. 2). There were 61 women and 23 men with a mean age of 59 ± 8 years and disease duration 11 ± 6 years. The mean follow-up duration was 25 ± 12 months (range 1-56). Seventy-five percent of patients were positive for IgM rheumatoid factor (RF) and all were refractory or did not tolerate at least two DMARDs. The mean number of DMARDs received by our patients was 3 ± 0.5 . Sixty patients were on MTX, twenty were treated with CsA and four were on leflunomide. All patients were also taking prednisone at a mean dose of 6.5 ± 2.5 mg/day. All patients had active disease with a high DAS-28 score (5.2 ± 1.0), high CRP (17.5 ± 6.3) and high ESR (59.4 ± 10.2). In 30 patients who did not respond to infliximab therapy (3 mg/kg), the dose was increased to 5 mg/kg. In addition, in 25 patients the dosage interval was shortened. After the first year “drug survival” was 86%, while this rate was 73% after the second year and 59% after the third year, according to the Kaplan-Meier methods. The clinical response is shown in Fig. 3, which is calculated on the basis of 84 patients presented at entry. A total of 28

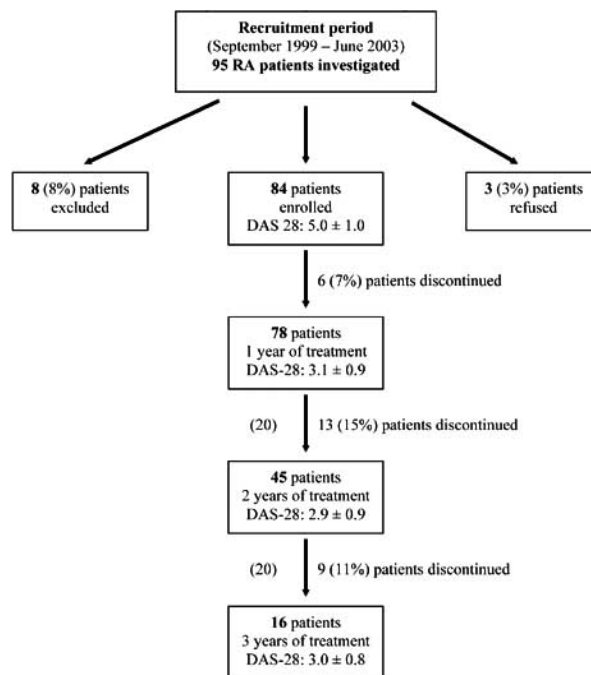


Fig. (2). Trial profile of RA patients in a long-term observational study. Numbers in parenthesis denote patients who continued therapy but were not followed-up for a full 2 or 3 years (modified by the reference 30).

(33%) patients discontinued infliximab therapy. More specifically, 16 (19%) discontinued the study due to adverse drug reactions, 9 (11%) due to lack of efficacy, while 3 (3%) were lost from follow-up. Six dropped out during the first year of treatment, 13 during the second year and 9 during the third year of therapy. The factor related to infliximab treatment in the Cox regression analysis was the concomitant use of MTX. For patients receiving MTX, after the first year 54/60 (90%) were still being treated with infliximab, while 49/60 (82%) were continuing treatment after the second year, and 44/60 (73%) after the third year. The main reasons for drug discontinuation due to side effects were immediate hypersensitivity reactions (9, 11%), followed by infections (6, 7%). Of these, two patients developed pulmonary tuberculosis. Both were on MTX and prednisone. Finally, 24 patients developed antinuclear antibodies at a titer ranging from 1/160 to 1/640 with a fine speckled pattern and 3 patients developed low titers of antibodies to double stranded DNA. None of them developed symptoms or signs of systemic lupus erythematosus (SLE) [30].

Magnetic Resonance (MR) Imaging Quantification in RA Patients Treated with Infliximab

Finally, the clinical response was investigated and we evaluated by MR imaging the inflammatory tissue changes in refractory RA patients. Sixteen refractory RA patients who were treated with intravenous infliximab were examined with MR imaging of the dominant affected wrist and hand before treatment and 1 year after therapy. The volume of the enhancing inflammatory tissue (VEIT) was evaluated in fat suppressed contrast enhanced T1-weighted images by using

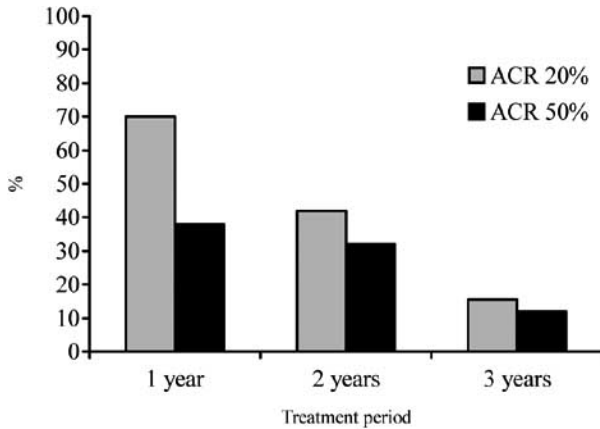


Fig. (3). Response to treatment according to ACR response criteria. Percentage of response are calculated on the basis of 84 patients presented at entry.

the Analyse 4.0 software (Biomedical Imaging Resource, Mayo Clinic, Minn). There were 13 females and 3 males with mean age 49.5 ± 17.0 years and mean disease duration 10.5 ± 8.0 years. Ten patients had positive IgM RF. One year after treatment, a significant reduction of the ESR, CRP, DAS-28 and VEIT was observed. All but two of the RA patients achieved the ACR 20% response criteria, while 9 (56.3%) and 5 (31.3%) patients achieved the 50% and 70% ACR response criteria respectively. A positive correlation between the VEIT, swollen joint count, tender joint count, as well as DAS-28 ($r = 0.66$, $r = 0.79$, $r = 0.57$ respectively) was found before treatment [31].

CONCLUSIONS AND COMMENTS

The results of our studies show that (i) infliximab was effective and had a relatively acceptable toxicity profile. After the third year of treatment, 59% of patients continued to be treated with infliximab and this was associated with the concomitant use of MTX; (ii) in RA patients that cannot tolerate MTX, infliximab may be used in combination with CsA; (iii) it seems that the clinical improvement of infliximab was associated with decrease of inflammatory tissue damage. A limitation of our study is the fact that it

lacks a control group for comparison. However, in long-term observational studies, this is very difficult to be achieved. Among the undesired effects of infliximab therapy infections have been a primary concern. Studies have shown that infections occurred in about 53% of patients treated with infliximab, while serious life threatening infections in about 18% [32]. The results from our study concerning infections did not differ from those reported by others [13-15]. The background risk of serious infection is approximately twice as high among patients with RA as among those without this condition [33], therefore, it is difficult to interpret sporadic reports of infection in patients receiving infliximab therapy. However, the risk of tuberculosis is increased. Such observations are congruent with animal studies showing that TNF-alpha is important for granuloma formation [34] and preventing the reactivation of latent tuberculosis [35]. The rate of tuberculosis among patients with RA who had been treated with infliximab was 24.4 cases per 100,000 as compared with the background rate of 6.2 cases per 100,000 patients with this illness [22]. Tuberculosis in patients who are receiving infliximab most often arises from reactivation of latent infection and usually occurs within the first two to five months of treatment. However, in some cases a late manifestation may occur [22]. Three of our patients developed pulmonary tuberculosis. These 3 patients had normal chest x-rays and negative purified protein derivative skin tests before infliximab therapy. Therefore, it is possible that they developed a de novo infection with mycobacterium tuberculosis or a reactivation of a latent disease since a number of RA patients are anergic and may have negative purified protein derivative skin tests [22]. Infliximab therapy may induce antinuclear antibodies and other autoantibodies and some patients may develop SLE [36]. In our study 25 patients developed antinuclear antibodies and 3 had double stranded DNA. However, none developed symptoms or signs of SLE. Another issue with repeat administration of TNF-alpha inhibitors is immunogenicity. In the case of infliximab, the indicated dosing regimen for RA (3 mg/kg) was optimized to achieve a low rate of immunogenicity [37]. One unexpected serious adverse event that has been reported after treatment with anti-TNF-alpha agents, is demyelinating disease. A publication in December 2001 reported 20 cases of neurological diseases: 18 after etanercept and 2 after

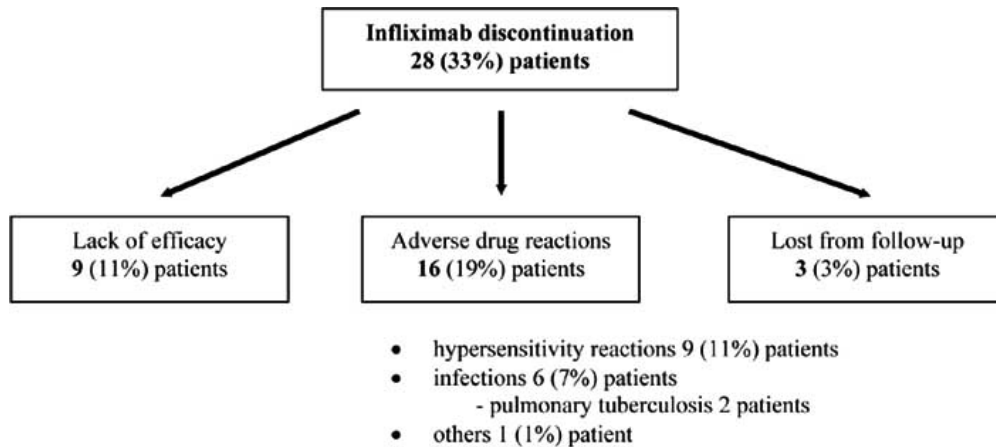


Fig. (4). Infliximab discontinuation due to lack of efficacy, adverse drug reactions and follow-up lost.

infliximab [38]. All cases were temporally associated with treatment and all cases had a partial or complete response when the treatment was stopped. Sixteen had changes on MR imaging consisting with demyelination. These reported numbers are no greater than the expected number in the general population based on the estimated number of patients treated with etanercept [20,21]. Another major event of concern has been in relation to cardiac disease, particularly the possibility that anti-TNF-alpha therapy may lead to worsening of congestive heart failure. Post-marketing reports of congestive heart failure with etanercept and infliximab revealed 51 reports (30 etanercept, 21 infliximab). One-half of the cases had a documented history of risk factors for congestive heart failure, including myocardial infarction, coronary heart disease, hypertension, diabetes mellitus, or pulmonary disease. The median interval from the first dose of TNF-alpha inhibitor to congestive heart failure diagnosis or worsening was 3.5 months [20,21]. For patients who are being considered for therapy with a TNF-alpha inhibitor, therapy should not be initiated in patients with heart diseases or associated risk factors. A rare manifestation of infliximab therapy is the immune reconstitution inflammatory syndrome (IRIS), which represents paradoxical reactions due to withdrawal of infliximab following the diagnosis of tuberculosis. IRIS, typically presents as hectic fevers, lymphadenopathy, worsened pulmonary infiltrates, effusions, hypoxia, and occasionally, the evolution of new lesions not clinically apparent prior starting treatment [39,40]. Another emerging concern with TNF-alpha inhibitors is the risk of lymphoma. It is believed that high inflammatory activity increases the risk of lymphoma. In patients with RA, odds ratios for developing lymphomas range from 2 to 26. Greater odds are associated with active disease, advanced age, immunomodulatory therapy, poor functional class and widespread joint involvement. The cumulative exposure rate of lymphoma with infliximab is 0.14 per 1,000 patients [20,21], and in some reports may be more [41]. No lymphoma or other tumor development was observed in this long-term study. However, seeking causal relationships between infliximab therapy and malignancy is complicated by the higher risk of malignancy in patients with RA compared with the general population. Thus, to assess the risk of major infections or malignancy following infliximab therapy, a long-term, world-wide registry might be required.

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