Combination therapy of the chimeric monoclonal anti-tumor necrosis factor α antibody (infliximab) with methotrexate in patients with rheumatoid arthritis

C. Antoni, J.R. Kalden

Institute of Immunology and Rheumatology, Department of Medicine III, University of Erlangen-Nürnberg, Germany.

Christian Antoni, MD; Joachim R. Kalden, Prof. Dr. med. Dr. h.c., Professor of Internal Medicine, Head of the Department for Internal Medicine III and the Institute for Clinical Immunology.

Please address correspondence and reprint requests to: Prof. J.R. Kalden, Medizinische Klinik III mit Poliklinik, Friedrich-Alexander-Universität Erlangen-Nürnberg, Postfach 3560, 91023 Erlangen, Germany.

Clin Exp Rheumatol 1999; 17 (Suppl. 18): S73 - S77.

Key words:
Infliximab, methotrexate, tumor necrosis factor, combination treatment, rheumatoid arthritis, efficacy, side effects, immunogenecity.

ABSTRACT

Infliximab, a chimeric anti-TNFα antibody, showed in two double-blind placebo-controlled trials efficacy in combination with methotrexate (MTX) in patients with severe rheumatoid arthritis (RA). Whereas in the first trial low-dose MTX or placebo was compared to infliximab alone and in combination, the second trial compared infliximab to placebo in patients with active RA despite maximal tolerated MTX treatment. Infliximab showed synergistic effects in combination with MTX. The immunogenicity of infliximab was reduced by the combination. Infliximab in combination with high-dose MTX is effective and safe in long-term treatment up to 54 weeks.

Introduction

The chimeric monoclonal anti-tumor necrosis factor α (TNFα) antibody (cA2, infliximab; Remicade®) has been proven efficacious in reducing signs and symptoms in two open-label trials and one double-blind placebo-controlled trial in patients with active rheumatoid arthritis (RA) (1-3). In these trials, no other disease-modifying antirheumatic drugs (DMARDs) were allowed for combination treatment. The results of two recent trials testing the combination of infliximab and methotrexate (MTX) have been published (4, 5), and follow-up data through week 54 from the ATTRACT trial (Anti-TNF Trial in RA with Concomitant Therapy) has been presented at the EULAR (European League Against Rheumatism) 1999 meeting (6).

Patients treated with a single infusion of infliximab showed a significant response 4 weeks after treatment versus placebo according to the Paulus criteria (7), a combination of six clinical, observational, and laboratory variables. The Paulus 20% response rates at week 4 were 8% in the placebo group, 44% in the 1 mg/kg infliximab group, and 79% in the 10 mg/kg infliximab group. The more stringent Paulus 50% criteria were met by 8%, 28%, and 58% of the patients, respectively (3). Together with the open-label re-treatment study (2), these data indicated that blockade of TNFα with infliximab was highly effective, safe, and could be administered for up to 4 cycles.

MTX, an analog of folic acid, has been documented to be an effective and safe DMARD in long-term studies of the management of RA (8-10). In combination studies with cyclosporin (11, 12), and in triple therapy with sulfasalazine and hydroxychloroquine (13), or leflunomide (14), or etanercept (15), synergistic effects have been observed without an increase of toxicity.

Rationale for combination treatment of infliximab and MTX

To investigate whether the combination of infliximab with MTX is superior to one of the monotherapies and whether the addition of MTX influences the immunogenicity of the chimeric antibody, a double-blind trial comparing three different doses of infliximab with low-dose MTX was designed (4). Because of the guidelines for clinical practice in Europe prevailing at the time the protocol was written, and to minimize potential toxicity, a fixed MTX dosage of 7.5 mg/week was chosen.

Study design

A total of 101 patients with active RA who had an incomplete response or flare of disease activity while receiving low-dose MTX were enrolled in a multicenter, double-blind, placebo-controlled, 26-week trial. Patients received an infusion of either placebo or 1, 3 or 10 mg/kg infliximab at weeks 0, 2, 6, 10 and 14, and were monitored through week 26. Patients who received infliximab were randomly assigned to receive MTX tablets 7.5 mg/week or placebo tablets (Fig. 1).

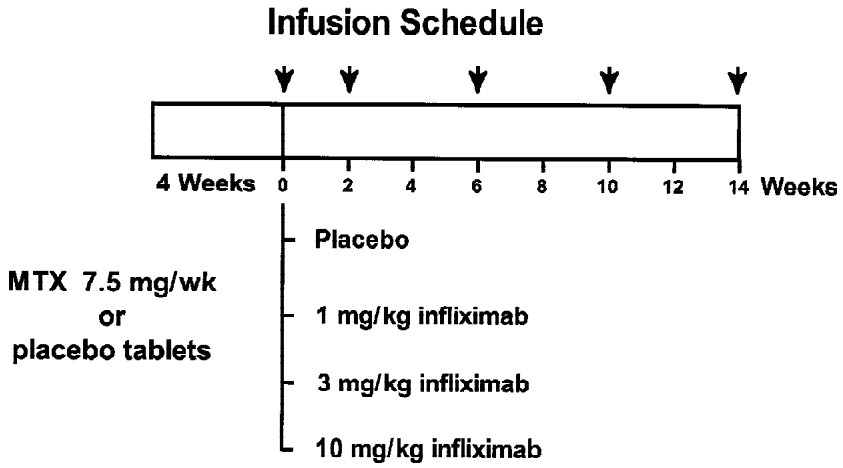

Fig. 1. Multicenter, double-blind, placebo-controlled 26-week trial in 101 rheumatoid arthritis patients not responsive to low-dose (7.5 mg/week) methotrexate (MTX). Patients were randomly assigned to receive either placebo or infliximab infusions at week 0, 2, 6, 10 and 14, in combination with MTX or placebo tablets. Both placebo groups were not combined.

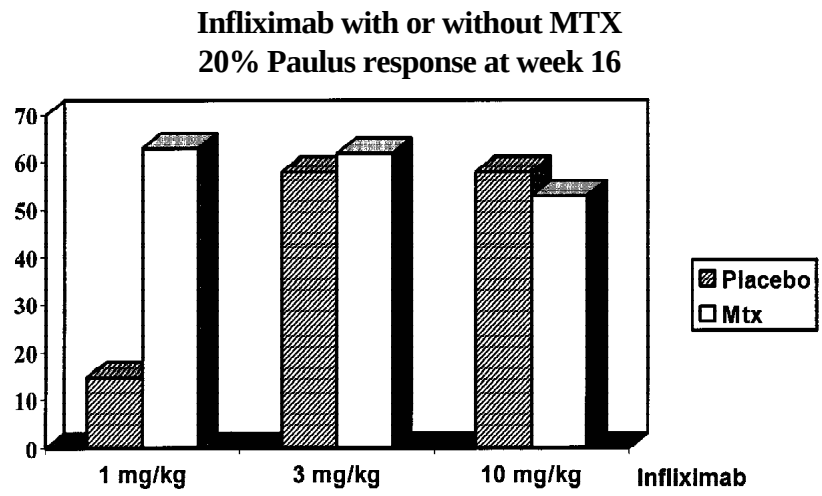

Fig. 2. The 3 and 10 mg/kg infliximab groups showed a good clinical response at week 16 with or without MTX. Only the 1 mg/kg infliximab group showed a better response rate in the combination with 7.5 mg/week MTX.

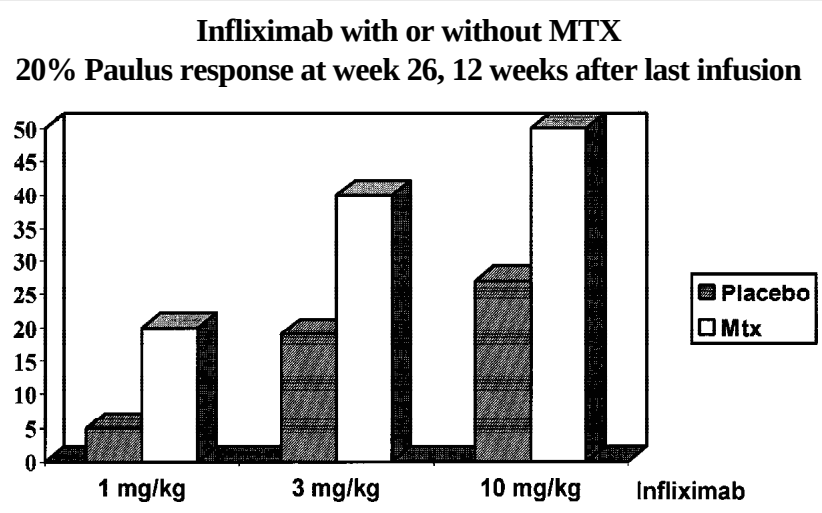

Fig. 3. At week 26 (12 weeks after the last infliximab/placebo infusion) patients with MTX showed synergistic effects prolonging the response. Up to 30% of patients without MTX still showed a clinical response 3 months after the last infliximab infusion.

Patients who took MTX with placebo infusion showed no significant additional clinical response at any time. In contrast, 60% of the patients who took 3 mg/kg or 10 mg/kg infliximab showed a rapid Paulus 20% response lasting through week 16 (Fig. 2). No statistically significant difference was seen between those who received or did not receive MTX. Twelve weeks after the last infusion (at week 26), the response rate in the combination group was similar to that at week 16.

In the patients who received 3 mg/kg infliximab without MTX the response rate at week 26 dropped to 20%, and in the 10 mg/kg group the rate dropped to approximately 30% (Fig. 3). Unlike the 3 mg/kg and 10 mg/kg groups, the 1 mg/kg group showed a 60% Paulus 20% response after 2 weeks, which dropped rapidly to placebo levels despite the subsequent infusions.

The co-administration of MTX showed a synergistic effect in the 1 mg/kg infliximab group which consisted of: (i) prolonging the duration of the response in > 60% of the patients to a median of 16.5 weeks ($P < 0.001$ versus placebo, $P < 0.006$ versus no MTX); and (ii) prolonging the Paulus 50% response to 12.6 weeks ($P < 0.001$ versus placebo $P < 0.002$ versus MTX). In all of the groups except the MTX/placebo and the 1 mg/kg infliximab/placebo groups, C-reactive protein levels dropped within one week to normal values. The dropout rate due to lack of efficacy was higher in the MTX /placebo group (57%) and in the 1 mg/kg infliximab/placebo group (33%) than for those receiving 1 mg/kg (0%), 3 mg/kg (0%), or 10 mg/kg (7%) combination treatment.

Synergistic effect of infliximab and MTX

There was no response at any time in patients who took the combination MTX and placebo. In contrast, the median response time in the group receiving 1 mg/kg infliximab and placebo tablets was 2.6 weeks, and 16.5 weeks in those who received the combination. In the higher-dose groups, the difference between MTX and non-MTX treatment became apparent only after the last infusions in the follow-up period. In this trial, the

combination of MTX and infliximab showed a synergistic effect in the low-dose infliximab group, and a prolonged Paulus response rate after the last infusion using the combination therapy.

Conclusions

In this first trial of low-dose MTX and infliximab, the combination of both had greater efficacy in the low-dose infliximab group, and resulted in longer responses in all dosage groups versus monotherapy with infliximab. Low doses of MTX alone resulted in no significantly increased response in comparison to previous MTX therapy. The data suggest that the observed synergistic effect could be due partially to a reduction in the immunogenicity of the chimeric antibody. This raises the possibility of using similar combinations of MTX with other biologicals such as the anti-CD4 monoclonal antibodies to reduce immunogenicity. However, the relatively short duration of this trial of MTX plus infliximab leaves open the question as to whether long-term combination therapy may lead to sustained immunosuppression with an increased risk of infection. In addition, two points open to criticism in this trial were the low dose of MTX used and the small sample size (14 - 15 patients) of each group. Therefore a larger combination trial was initiated, the ATTRACT study (Anti-TNF Trial in RA with Concomitant Therapy).

ATTRACT Phase III combination trial

In a phase III ATTRACT combination trial, 428 patients with active RA who were being treated with MTX at the highest tolerated level (12.5 - 25 mg/week oral and parenteral) were randomly assigned to 5 treatment groups (81 - 88 patients per group), each of which received one of the following: placebo infusions, 3 mg/kg infliximab every 4 weeks, 3 mg/kg infliximab every 8 weeks, 10 mg/kg infliximab every 4 weeks, or 10 mg/kg infliximab every 8 weeks. Co-medication with stable doses of corticosteroids and non-steroidal antiinflammatory drugs was allowed. The double-blind trial is still ongoing; an interim analysis of the data from weeks 30 and 54 has been published (5, 6). The patients included in this trial had longstanding severe disease with a mean MTX dosage of 15 mg/week. The primary endpoint was the ACR 20% criteria of improvement (16).

At week 30, all groups in which patients were randomly assigned to infliximab showed statistically significant ACR 20% responses versus placebo (5). The response rate was 20% for the placebo and MTX group, versus between 50% and 58% for all of the infliximab and MTX combination groups ($P < 0.001$ for all treatment groups versus placebo). A rapid ACR 20% response within 6 weeks was seen in more than 40% of infliximab-treated patients; the number of responder patients continued to rise until week 30. At week 30, all infliximab-treated patient groups showed a significant improvement in each of the response parameters ($P < 0.001$).

The response rate was maintained at week 54 in all of the infliximab groups (6). Most intriguing compared with other long-term studies was the fact that the overall efficacy increased from 50% up to approximately 60% for ACR 20% responses in all treatment groups.

Immunogenicity

In earlier trials, immune responses to human anti-chimeric A2 antibody (HACA) were reported in up to 50% of treated patients (2). However, the development of HACA, the clinical response, and the duration of the response were not correlated significantly (2). In the combination trial, the HACA response was clearly dose-related, with 53%, 21%, and 7% of the patients in the cohorts receiving 1 mg/kg, 3 mg/kg, or 10 mg/kg, respectively, of infliximab. Concomitant MTX therapy reduced the rate of HACA formation to 15%, 7%, and 0%, respectively. The finding that most patients who received high dose infliximab did not develop HACA suggests the induction of a phenomenon resembling tolerance. The actual mechanism underlying this phenomenon, however, remains unknown.

The HACA response and the clinical response are reflected in the pharmacokinetic data from this trial. In the 1 mg/kg infliximab group without MTX, plasma levels of infliximab dropped below the detection limit of 0.1 µg/ml after the second and following infusions. By contrast, plasma levels in patients receiving concomitant MTX remained around 10 µg/ml. In the 3 mg/kg group, plasma levels of infliximab rose from 10 µg/ml pre-infusion to 100 µg/ml after infusion. In the 10 mg/kg group, levels remained approximately 40-300 µg/ml. In all groups, repeated infusions did not result in any change in the pharmacokinetic pattern. The addition of MTX to 3 mg/kg or 10 mg/kg infliximab did not change the pharmacokinetics during the infusion period. After week 14, the decline in plasma levels was slower in the combination groups (4).

The ATTRACT trial is still ongoing. A complete evaluation of the HACA response is not yet available. Only one patient among 32 who discontinued treatment was found to be HACA positive. The infusion reaction rate was constant - approximately 5% in all groups including those receiving placebo infusions. The infusion reaction rate and the response rate showed no significant change with increasing treatment cycles. The absent HACA levels in the patient who discontinued treatment and the constant low level of infusion reactions with constant efficacy in the treatment groups, may provide indirect evidence that there is no clinically significant HACA response during combination treatment with infliximab and methotrexate (17).

Adverse events

The first reports from open-label and double-blind infliximab trials showed that repeated infusion with the antibody did not lead to significant infusion reactions or severe infections (1-3). Infections were the most commonly reported adverse events, with 1 in the placebo group, 5 in the 1 mg/kg group, and 1 in the 10 mg/kg group.

In the first trial with the combination of infliximab and MTX, 32.2% of patients who received infliximab with or without MTX were reported to develop infections, compared with 21.4% in the MTX /placebo group ($P = 0.541$) (4). In this trial involving 101 patients, one patient who received five infusions of 3 mg/kg infliximab plus 7.5 MTX developed a bacterial enopthalmitis following a cataract surgery 9 weeks after the last infu-

sion. One patient withdrew from the study after the third infusion of 10 mg/kg infliximab plus MTX because of lack of efficacy. Fifteen weeks later, this patient developed septicemic shock with blood culture positive for Staphylococcus and died within 24 hours of hospitalization. A relationship between the infliximab dose and the co-medication with MTX could not be shown for the adverse events (4).

In the ATTRACT trial data at 54 weeks, a relatively constant dropout rate of about 8% was seen for adverse events in the placebo group and in all infliximab groups (17). Serious infections were distributed equally with 7 (8%) in the placebo group and 21 (6%) in the infliximab groups. The rate of infusion reactions remained less than 5% and was not different from placebo. After 54 weeks, four patients have been reported to have malignancies in the ATTRACT trial (17), including one with a B-cell lymphoma, one with recurrent breast cancer, one with both squamous cell cancer and melanoma, and one with recurrent basal cell cancer. At week 30, the expected tumor rate from the NIH SEER database was 0.6 for the placebo group; observed 0 and 2.8 for infliximab groups; observed at that time point 3 (17). The data do not address whether the combination of MTX in low or high doses with infliximab increases the risk of a malignancy compared with monotherapy with MTX or infliximab. From databases by Wolfe and Klareskog it is known that the risk of lymphoproliferative diseases is 8 times higher in patients with RA, and that the incidence of lymphoma is correlated with disease activity rather than with the immunosuppressive medication (17).

Laboratory monitoring of the patients did not indicate any significant abnormalities in the groups treated with combinations. In the first trials, up to 8% of the patients developed anti-dsDNA antibodies (4) and one patient developed anti-cardiolipin antibodies during treatment with infliximab (2). When 100 randomly and blindly selected patients equally distributed between treatment groups were evaluated (19), anti-dsDNA antibodies were detected in 5% of infliximab-treated patients and in 1 of 20 patients in the placebo group. Ten percent of infliximab-treated patients had become seropositive for anti-nuclear antibodies (ANA) at the conclusion of the study compared with study entry. In the group treated with MTX and placebo, the ANA status did not change; 33% of placebo-treated patients and 35% of infliximab-treated patients were ANA negative at study entry and positive at some time during the study.

Conclusion

There is no doubt that anti-TNF blocking treatment provides a major advance in the therapy of RA. However, some rheumatologists are asking that - instead of the 20% ACR response, which was developed to distinguish between drugs with efficacy and non-efficacy (20), and which is already hard to achieve - an ACR 50% or 70% response be established as a more appropriate goal. Double-blind trials using infliximab in RA patients have shown anti-TNF blocking agents to be effective and safe in the treatment of active RA. In addition, a rapid change in the gadolinium uptake in magnetic resonance imaging studies was demonstrated in the synovium of treated RA patients, a change which was correlated with 20% Paulus response criteria (21). A phase II trial combining different dosages of infliximab with MTX showed that this combination therapy is effective and safe and might reduce immunogenicity of the chimeric antibody (4). However, whether the appearance of HACA interferes with the function of infliximab by neutralizing the monoclonal antibody activity has not yet been established beyond doubt. The ATTRACT trial demonstrated the capacity of repeated infusion of infliximab to reduce active disease in patients with severe RA of at least one year's duration (22). This combination therapy prolongs the response rate, suggesting that it may be the treatment of choice for RA. However, longer observation periods appear necessary. Also of interest is the fact that the reported incidence of adverse events in the ATTRACT study was no higher than that expected for single drugs.

Infliximab in combination with MTX may be an optimal therapeutic regimen for patients with severe RA. Data addressing the question of when to begin this combination therapy in RA, and concerning the effect of infliximab on bone and cartilage destruction, are urgently needed. If it can be demonstrated that bone and cartilage destruction may also be prevented or significantly slowed down by the monoclonal antibody, then early combination therapy using infliximab and MTX would appear to be appropriate. Furthermore, additional information is needed to help guide physicians regarding consideration of a decision to start as early as possible with this combination, and more information, preferably accumulated over a sustained treatment period, must be obtained on possible side effects.

References

1. ELLIOTT MJ, MAINI RN, FELDMANN M *et al.*: Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α. *Arthritis Rheum* 1993;36:1681-90.
2. ELLIOTT MJ, MAINI RN, FELDMANN M, LONG-FOX A, CHARLES P, BIJL H, WOODY JN: Repeated therapy with monoclonal antibody to tumor necrosis factor α. (cA2) in patients with rheumatoid arthritis. *Lancet* 1994; 344: 1125-7.
3. ELLIOTT MJ, MAINI RN, FELDMANN M *et al.*: Randomised double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor α. (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994; 344: 1105-10.
4. MAINI RN, BREEDVELD FC, KALDEN JR *et al.*: Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1552-63.
5. LIPSKY PE, ST CLAIR W, KAVANAUGH A *et al.*: Long-term control of signs and symptoms of rheumatoid arthritis with chimeric monoclonal anti-TNF α antibody (infliximab) in patients with active disease on methotrexate. *Arthritis Rheum* 1998; 41 (Suppl.).
6. MAINI RN, SMOLEN JS, BREEDVELD F *et al.*: Long-term (1 year) results of a placebo-controlled, randomized phase III trial of infliximab (cA2, Remicade) combined with methotrexate in rheumatoid arthritis. *Ann Rheum Dis* 1999; Abstract book of EULAR 1999: p. 216.
7. PAULUS HE, EGGER MJ, WARD JR *et al.*: Analysis of improvement in individual rheumatoid arthritis patients treated with disease modifying drugs, based on the findings in patients treated with placebo. *Arthritis Rheum* 1990; 33: 477-484.
8. KLIPPEL JH (Ed.): *Primer on the Rheumatic Diseases*, 11th ed. 1997: 171-2.
9. CASH JM, KLIPPEL JR: Second-line drug therapy for rheumatoid arthritis. *N Engl J Med* 1994; 330: 1368-75.
10. WEINBLATT ME, POLISSON R, BLOTNER SD *et al.*: The effects of drug therapy on radio-

graphic progression of rheumatoid arthritis: Results of a 36-week randomized trial comparing methotrexate and auranofin. *Arthritis Rheum* 1993; 36: 613-9.

11. TUGWELL P, PINCUS T, YOCUM D *et al*.: Combination therapy with cyclosporine and methotrexate in severe rheumatoid arthritis. *N Engl J Med* 1995; 333: 137-41.
12. STEIN MC, PINCUS T, YOCUM D *et al*.: Combination treatment of severe rheumatoid arthritis with cyclosporine and methotrexate for forty-eight weeks. *Arthritis Rheum* 1997; 40: 1843-51.
13. O'DELL JR, HAIRE CE, ERIKSON N *et al*.: Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996; 334: 1287-91.
14. WEINBLATT ME, KREMER JM, COBLYN JS *et al*.: Pharmacokinetics, safety, and efficacy of combination treatment with methotrexate and leflunomide in patients with active rheumatoid arthritis. *Arthritis Rheum* 1999; 42: 1322-8.
15. WEINBLATT ME, KREMER JM, BANKHURST AD *et al*.: A trial of etanercept, a recombinant tumor necrosis factor receptor: Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.
16. FELSON DT, ANDERSON J, BOERS M *et al*.: American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
17. BREEDVELD F, LIPSKY P, ST. CLAIR W *et al*.: A phase III randomized, double-blind, placebo-controlled study of infliximab (Remicade) in active RA despite methotrexate therapy: Safety of the ATTRACT trial. *Ann Rheum Dis* 1999; Abstract book of EULAR 1999: p. 216.
18. WOLFE F, MITCHELL DM, SIBLEY JT *et al*.: The mortality of RA. *Arthritis Rheum* 1994; 37: 481-94.
19. SMOLEN J, STEINER G, BREEDVELD F *et al*.: Anti-TNFα therapy and drug induced lupus-like syndrome. *Ann Rheum Dis* 1999; Abstract book of EULAR 1999: p. 217.
20. FELSON DT, ANDERSON JJ, LANGE MLM *et al*.: Should improvement in rheumatoid arthritis trials be defined as 50% or 70% improvement in core set measures, rather than 20%? *Arthritis Rheum* 1997; 39 (Suppl.).
21. KALDEN-NEMETH D, GREBMEIER J, ANTONI C, MANGER B, WOLF F, KALDEN JR: NMR monitoring of rheumatoid arthritis patients receiving anti-TNFα monoclonal antibody therapy. *Rheumatol Int* 1997; 16: 249-55.
22. ANTONI C, MAINI RN, BREEDVELD F *et al*.: Subgroup analyses show consistent clinical benefit in a 30-week, double-blind trial (ATTRACT) with an anti-TNFα monoclonal antibody (infliximab) in rheumatoid arthritis patients on methotrexate. *Ann Rheum Dis* 1999; Abstract book of EULAR 1999: p. 217.