Anti-tumor necrosis factor (TNF) therapy in rheumatoid arthritis: Correlation of TNF-alpha serum level with clinical response and benefit from changing dose or frequency of infliximab infusions

A.F. Edrees, S.N. Misra, N.I. Abdou

The Center for Rheumatic Disease & The Center for Allergy Immunology, St. Luke's Hospital of Kansas City and University of Missouri, Kansas City, Missouri, USA

Abstract

Objective

To determine the relationship between serum TNF-α level and clinical response in rheumatoid arthritis patients treated by infliximab. This could be of value to predict clinical response to infliximab and to determine the optimal dose and interval between dosing of infliximab. RA patients who did not respond adequately to conventional doses (3 mg/kg) of infliximab were studied to see if increasing the dose or frequency of infliximab infusions would be more effective.

Methods

Fifty-five RA patients who fulfilled the American College of Rheumatology criteria and were receiving treatment by anti-TNF-α (infliximab 3 mg/kg body weight every 8 weeks) were evaluated by: clinical disease activity using the Richie score index before receiving their scheduled infliximab infusion. Serum level of TNF-α, as measured by competitive ELISA assay, was determined immediately before and 9–11 days after receiving infliximab. RApatients who did not respond adequately to treatment with infliximab were given either a larger dose of infliximab or given the infusion at six-week intervals. Their clinical response was then evaluated sixteen months later.

Results

Patients were divided into 2 groups according to Richie score, active group with score >10 (score 20.3 ± 7.7 mean ± standard deviation, n = 25) and inactive group with scores ≤10 (score 4.1 ± 3.2, n = 30). TNF-α serum levels pre-infliximab infusion were significantly higher in the active group 76.1 pg/ml than the inactive group 38.0 pg/ml (P < 0.02). Whereas TNF serum level significantly dropped post infliximab in the inactive group (P < 0.05), it did not drop in the active group. The mean level of the post-infusion TNF-α serum level was higher (76.6 ± 93.4 ng/ml) in the active than the mean level of the post-infusion serum TNF-α levels in the inactive group (26.4 ng/ml ± 7.9) P< 0.01 using the t-test. Increasing the frequency was superior in RApatients' clinical outcome than increasing the dose of infliximab infusions.

Conclusion

RA patients who responded well to infliximab and had inactive disease at the time of the study have lower levels of serum TNF-α which could be further suppressed by the recommended doses of infliximab. RApatients with active disease have higher serum levels of TNF-α which could not be suppressed after the recommended doses of infliximab infusion. Changing the frequency of infliximab infusions in the active group was more effective than increasing the dose of infliximab in inducing improved clinical outcome. We suggest that the lack of suppression of TNF-α in the active group could be due to inadequate dosing of infliximab or to the presence of a neutralizing antibody directed against infliximab. It remains to be seen if serum TNF-α levels could be used as a guide in determining the dose and intervals between dosing of anti-TNF therapy in RA in order to achieve the desired clinical response.

Key words

Rheumatoid arthritis, tumor necrosis factor, infliximab.

Amr F. Edrees, MD, Sounak N. Misra, MD and Nabih I. Abdou, MD, PhD.

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Address correspondence and reprint request to: N.I. Abdou, MD, PhD, The Center for Rheumatic Disease & The Center for Allergy Immunology, 4330 Wornall Road, Suite 40-II, Kansas City, Missouri 64111, USA.
E-mail address: niabdou@centerforrheumatic.com

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Introduction

Tumor necrosis-α (TNF-α) is an inducible cytokine produced primarily by monocytes and macrophages (1). Many biologic activities of TNF-α appear to be involved in the pathogenesis of chronic inflammation and arthritis (1, 2). TNF-α can induce resorption of cartilage and bone (3), endothelial adherence and activation of granulocytes (4), stimulation of fibroblast growth via platelet derived growth factor (5, 6) and stimulation of synovial cell prostaglandin E_2 and collagenase production (7).

Infliximab (Remicade) is a chimeric mouse/human anti-TNF-α monoclonal antibody generated to selectively target TNF-α and binds to soluble as well as membrane-bound TNF-α (8). Infliximab was shown to be effective in combination with methotrexate for the treatment of patients with rheumatoid arthritis who have had an inadequate response to methotrexate as a monotherapy (9,10). Infliximab was shown to delay joint damage in patients with moderate to severe rheumatoid arthritis (10). TNF-α was found to be a marker of RA activity (11). The lack of adequate response to TNF-α antagonists in some RApatients raises important clinical-therapeutic questions about the reasons for the lack of adequate response (8). Recent clinical experience in RA patients who are being treated with intermittent (every 8 weeks) pulse Remicade IV therapy indicates that in some patients the disease flares a few days or weeks before their next pulse therapy. This was recently found to correlate with the serum levels of infliximab (12).

We hypothesize that inadequate treatment responses can result from incomplete suppression of tumor necrosis factor α (TNF-α) activity. To test this hypothesis we investigated 55 prospective RA patients who were already under treatment by anti-TNF-α (infliximab 3 mg/kg body weight every 8 weeks). Patients were evaluated by: clinical disease activity using the Richie score index before receiving their scheduled infliximab. Serum level of TNF-α, as measured by competitive ELISA assay, was determined immediately before and 9–11 days after receiving infliximab. In the ATTRACT study 428 patients were studied in a randomized control fashion on varying infliximab regimens. Based on the findings a standard starting dose of infliximab 3 mg/kg every 8 weeks was recommended (10). It was, however, noted that higher trough concentrations of infliximab correlated with greater clinical response than low or absent trough levels (12). This suggests that increasing patients' dose or frequency of infliximab could in turn improve their clinical response. Whether this theory holds true in clinical practice and whether to increase the infusion dose or the frequency of their infusions are questions that remain unanswered. These studies (12), however, did provide some insight through pharmacokinetic models that predicted that decreasing the interval between infusions by two weeks would yield higher trough levels of infliximab than raising the infusion dose by 100 mg (12). A recent study by Vollenhoven *et al*., demonstrated no significant improvement in patients who had their infliximab dose increased when compared to controls (13). These findings suggest that a reduction of the time between infusions may be of greater therapeutic benefit, but this remains to be proven.

Patients and methods

Patients

Fifty-five RA patients (mean age: 63 yr., male n = 21, females n = 34) who were followed at The Center for Rheumatic Disease and fulfilled the American College of Rheumatology criteria for the diagnosis of RA and were already receiving therapy with anti-TNF-α (infliximab 3 mg/kg body weight every 8 weeks) were evaluated for clinical disease activity using the Richie score index before receiving their scheduled infliximab (14). All patients have been receiving infliximab at the time of the study for periods of 3 to 48 months. The duration of therapy with infliximab between the two groups was not significantly different. The study was approved by the Institutional Review Board.

To determine the clinical response of RA patients while under treatment by

Table I. Differences between the active and inactive rheumatoid arthritis groups in the study.

Parameters*	Active RA[X] n = 25	Inactive RA[X] n = 30	P** value
Richie score (mean ± standard deviation)	20.3 ± 7.7	4.1 ± 3.2	< 0.01
Age in years; mean ± standard deviation	66.6 ± 9.9	59.6 ± 5.1	NS[XX]
Erythrocyte sedimentation rate mm/hr. Mean (range)	47.95 (13–130)	25.30 (5–54)	< 0.05
Rheumatoid factor IU, mean (range)	141.29 (0–700)	83.46 (0–354)	NS[XX]
Prednisone dose mg/d mean (range)	3.2 (0–15)	1.45 (0–10)	NS[XX]
Methotrexate dose mg/week mean (range)	11.56 (0–20)	12.08 (0–25)	NS[XX]
Duration of RAprior to study years, mean (range)	17.12 (1–40)	13.23 (1–40)	NS[XX]
Number of infliximab infusions prior to study mean (range)	13.33 (2–26)	10.56 (1–20)	NS[XX]
Duration in years of infliximab infusions prior to study mean (range)	1.9 (0.3–4)	1.8 (0.24–3.4)	NS[XX]

*All parameters were recorded at the time of study; [X]active group had Richie score >10 and inactive group had score < 10; **p values by Student's t-test; [XX]NS: not significant.

infliximab, patients were divided into 2 groups according to the Richie score; active group with score >10 and inactive group with score < 10. Table I shows the various parameters of the 2 groups in the study. Significant differences were only seen in the Richie score, and the erythrocyte sedimentation rate (Table I). We elected to use the Richie score index since we did not have—at the time of the study—all the information, including radiological criteria, for using the ACR scoring system. The Ritchie scoring index is a 26-joint tenderness evaluation where each joint is given a score of 0–3 depending on level of pain/tenderness and then the scores for all joints are tallied.

Serum TNF-α assay

Serum TNF-α level was measured by competitive ELISA assay immediately before and 9–11 days after receiving infliximab. ELISA kits were purchased from Pierce-Endogen (Product #EH3-TNFA5, Lot #DG56518C, Rockford, IL). The ELISA assay was performed on all samples at the same time using frozen samples collected from all patients with adequate positive and negative controls. Lyophilized recombinant human TNF-α provided by Pierce Endogen were used as standards. On each ELISA plate a standard curve was constructed. The standard curve was used to determine the amount of human TNF-α in the serum samples and was generated by plotting the sample absorbance (450-550 nm) obtained for each of the standard concentrations on the vertical (Y) axis vs the corresponding human TNF-α concentration on the horizontal (X) axis. A curve fitting statistical software package was used. All samples were run in triplicate. Optical density values obtained from triplicate wells were accepted only if they were within 10% of the mean values. Triplicate values that differed from the mean by greater than 10% were repeated. The ELISA assay for TNF cannot differentiate between free and bound TNF. Statistical analysis: The student's t test was used for statistical analysis and was reviewed by the Biostatics department at Kansas University Medical Center.

Results

Comparison of TNF-α serum levels in active vs inactive RA patients

As can be seen from Table II, active RA patients had higher TNF-α serum levels 76.1 pg/ml ± 103.2 when compared to values of the inactive group 38 ± 19.4 ($p < 0.02$).

Efficacy of infliximab in suppressing TNF-α levels

As can be seen from Table II, infliximab suppressed TNF-α levels in the inactive group but not in the active group, post-infliximab serum TNF-α levels were 26.4 ± 7.9 in the inactive group vs 76.6 ± 93.4 in the active groups. Statistical analysis of serum TNF levels in the inactive group; post versus pre-infliximab $P < 0.05$ and in the active group P = not significant. The values of TNF serum levels post-infliximab were significantly lower in the inactive group when compared to similar values of the active group $P < 0.01$ (Table II).

Benefit from changing the dose or frequency of infliximab

The 25 patients who did not respond adequately to the standard 3 mg/kg q.8 weeks infliximab infusions were divided into three groups. Thirteen of these patients had no change in their infliximab dose (Group S = standard dose).

Table II. Serum TNF-α levels pre- and post-infliximab in RA patients with inactive or active disease.

Group studied (number of patients)	TNF-α serum levels (pg/ml) Mean ± SD	
	Pre-infliximab	Post-infliximab
Inactive[X] (30)	38.0 ± 19.4	26.4 ± 7.9*
Active[X] (25)	76.1 ±103.2**	76.6 ± 93.4[XX]

[X]Inactive group = Richie score < 10; active group = Richie score > 10.
*$p < 0.05$ when compared to pre-infliximab values of same group; **$p < 0.02$ when compared to pre-infliximab value of the inactive group; [XX]$p < 0.01$ when compared to post-infliximab values of the inactive group.

Table III. Rheumatoid arthritis study patients: profile and therapy.

	S Group[X] (n = 13)	D Group[XX] (n = 7)	F Group[XXX] (n = 11)
Age (years) ❖	57 ±11.8	60.57 ± 16.32	70.18 ± 8.91
RAduration (years) ❖	14 ± 9.59	17.7 ± 10.58	12.64 ± 12.64
Prednisone ✱*	1.8 ± 2.65	2.86 ± 3.67	1.32 ± 1.69
Prednisone ❖*	1.7 ± 1.85	1.79 ± 2.8	1.82 ± 2.72
MTX ✱^	10.8 ± 6.16	11.79 ± 3.45	10.91 ± 5.84
MTX ❖^	10.8 ± 5.81	11.43 ± 3.78	7.27 ± 5.18
Number of prior infliximab infusions ❖	20.4 ± 5.68	25.43 ± 8.7	25.91 ± 7.97

[X]S Group: No change in infliximab regimen;[XX]D Group: increase in infliximab infusion dose;[XXX]F Group: increase in infliximab dosing frequency.
❖Mean values ± standard deviation from 1/04 evaluation; ✱Mean values ± standard deviation from 9/02 evaluation; *milligrams given daily mean values ± standard deviation; ^milligrams given weekly mean values ± standard deviation.

Seven patients had an increase in their infliximab dose with an average increase of 114 mg per infusion (Group D = dose increase). Eleven patients had a decrease in their infliximab infusion interval with an average decrease of 1.9 weeks (Group F = frequency increase). Patients' duration of RA, prednisone dose, methotrexate dose and number of prior infliximab infusions were recorded (see Table III). Mean values obtained for the three infliximab groups were compared to each other as well as to the patients previous scores using the Student's t test. There was no statistical significant difference between the three groups with respect to the parameters shown in Table III.

In Table IV, we compared laboratory and clinical responses to infliximab between the three groups, using the Student's t test. Patients'improvement was defined by outcome measures just before receiving their scheduled infliximab infusion, using the Ritchie scoring index as well as by the American College of Rheumatology (ACR) guidelines (14). All three groups demonstrated reductions in their number of painful and swollen joints. When compared to their previous scores on 3 mg/kg q.8 wks of infliximab, the ACR 20 criteria were met by 18% of the S group, 29% of the D group, and 36% of the F group. Reduction in the mean Ritchie scores for S, D, and F groups were 6, 4.86, and 8 respectively. Only the F group was found to have a statistically significant reduction in the Ritchie score with a P value of 0.0349 (Table IV).

Breaking down the three groups into their previously active (Ritchie score > 10) and inactive (Ritchie score <10) subgroups, we found that none of the previously inactive patients in any of the groups had statistically significant improvement. Previously active patients in the S group had no statistically significant improvement. Previously active patients in the D and F groups however, had a statistically significant improvement with a P value of 0.019 and 0.006 respectively.

Discussion

Infliximab is a chimeric anti-TNF-α monoclonal antibody that binds to soluble and transmembrane TNF-α with high affinity, forming a stable complex that blocks the association of this cytokine with its receptor (15). Infliximab is distributed primarily into the intravascular space and has a half-life of 9.5 days (12, 16). That was the rational for studying serum TNF levels in our pa-

Table IV. Efficacy of changing dose or frequency of infliximab on laboratory and various clinical parameters.

	S Group[X]		D Group[XX]		F Group[XXX]	
	Pre[+]	Post[++]	Pre[+]	Post[++]	Pre[+]	Post[++]
Erythrocyte sedimentation rate (mm/hr.)	39.9 ±29.42	31.6 ± 26.7	29.14 ± 22.87	31.71± 19.27	39.73 ±34.01	44.73 ± 32.35
Number of painful joints	5.7 ± 6.58	2.1 ± 2.22	6.71 ± 6.58	3.71± 4.85	8.18 ± 8.85	4.36 ± 5.57
Number of swollen joints	3.7 ± 4.8	0.7 ± 0.95	4.57 ± 5.14	3.0 ± 5.32	5.09 ± 5.61	1.18 ± 2.68
Functional score	3.9 ± 3.48	2.46 ± 2.52	5.07 ± 2.77	2.8 ± 1.91	4.52 ± 2.85	3.42 ± 2.38
Pain score	3.04± 3.09	2.8 ± 2.31	3.73 ± 2.55	4.9 ± 2.12	4.4 ± 2.74	3.83 ± 2.79
Patient global assessment	2.3 ± 1.81	2.3 ± 1.51	2.79 ± 1.44	2.94± 1.08	3.74 ± 2.26	3.31 ± 2.18
Physician global assessment	2.08± 2.03	2.16 ± 1.77	2.39 ± 1.92	2.53± 0.76	3.2 ± 2.33	2.92 ± 2.02
ACR 20 Improvement [†]	18%		29%		36%	
Ritchie score	10.46± 11.37	4.46 ± 5.58	12.86 ± 10.16	8.0 ± 5.63	12.91 ± 9.98	4.91± 5.75*

[X] S Group: No change in infliximab regimen; 3 mg/kg every 8 weeks, n = 13;
[XX] D Group: Increase in infliximab infusion dose. Average increase of 114 mg every 8 weeks, n = 7;
[XXX] F Group: Increase in infliximab dosing frequency. Average decrease of intervals between infusions of 1.9 weeks, n = 11;
[+] Pre = Patients studied in September 2002 while on infliximab 3 mg/kg every 8 weeks. Mean values ± standard deviation;
[++] Post = Patients studied in January 2004. Mean values ± standard deviation;
[†] % of Patients who met the criteria for improvement;.
* p value statistically significant (P= 0.0349) when compared to the pre value of the same group.

tients 9–11 days post-infliximab infusion.

Our study demonstrated inadequate suppression of serum TNF-α level after infliximab infusion in RApatients with active disease. RA patients with active disease had significantly higher levels of serum TNF-α which could not be suppressed by infliximab. When compared to the post-infusion serum TNF-α levels in RA patients with active disease, the serum levels in the inactive group were significantly lower than the active group. The lack of suppression of TNF-α in the active group could be due to inadequate dosing of infliximab. St. Clair *et al.*, (12) suggested that some patients with RA may benefit from infliximab given at higher dose than 3 mg/kg or more frequently than every 8 weeks. They found that in RA patients there was a relationship of serum infliximab concentrations to the clinical improvement (12).

The lack of suppression of serum TNF-α level in the active group in our study could also be due to the presence of antibodies to infliximab. It has been reported that patients with RA who were treated with infliximab without methotrexate developed a high incidence of antibodies to infliximab (17). This group of patients also cleared infliximab more rapidly from the circulation than did other treatment groups with a lower incidence of antibodies to infliximab (17). Moreover in Crohn's disease immunogenicity to infliximab influenced the long term efficacy of the drug (18). Patients who developed antibodies against infliximab had a reduced response to therapy and an increased incidence of infusion reactions.

In our study the lack of response in the active RAgroup despite treatment with infliximab could be due to higher serum levels of TNF-α requiring higher doses of infliximab or due to the presence of other cytokines responsible for the disease persistent activity. Both IL-1 and TNF-α are important in the pathogenesis of RA, and interaction between the two cytokines may produce synergistic effects (19). Experimental evidence suggests that TNF-α may be more important in promoting mechanisms leading to inflammation, whereas IL-1 may be more important in cartilage and bone destruction and in limiting mechanisms involved in cartilage repair (19). It remains to be determined, whether patients with poor therapeutic responses to either an IL-1 or TNF-α blockers will have better responses when inhibitors of both cytokines or other cytokines are used (20).

Our study suggests that serum TNF-α levels could be used as a guide in determining the dose and intervals between dosing anti-TNF-α blockers in RA in order to achieve the desired clinical response. Larger studies are needed to clarify the clinical implications of our findings. Our findings also indicate that increasing either the frequency or dose of infliximab infusions is beneficial in achieving a greater clinical response for RA patients whose disease remains active on the standard infliximab dose of 3 mg/kg q.8 weeks. Increasing the frequency, however, as per the ATTRACT pharmacokinetic model prediction appears to be superior to increasing the dose of infliximab. In addition, the greatest clinical improvements are seen in patients who while on standard 3 mg/kg q.8 weeks infliximab, continue to have active disease. Further investigation into more objective measures such as serum TNF-α levels may provide even greater precision in determining the efficacy of infliximab in suppressing TNF levels. We admit that the number of patients in our study is relatively small, however, we believe that these findings are highly suggestive and warrant further large scale investigations in the future.

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