

INFLIXIMAB AND METHOTREXATE IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

Background Neutralization of tumor necrosis factor α (TNF- α) for three to six months reduces the symptoms and signs of rheumatoid arthritis. However, the capacity of this approach to effect a more sustained benefit and its effect on joint damage are not known.

Methods We treated 428 patients who had active rheumatoid arthritis despite methotrexate therapy with placebo or infliximab, a chimeric monoclonal antibody against TNF- α , in intravenous doses of 3 or 10 mg per kilogram of body weight every 4 or 8 weeks in combination with oral methotrexate for 54 weeks. We assessed clinical responses with use of the criteria of the American College of Rheumatology, the quality of life with a health-status questionnaire, and the effect on joint damage radiographically.

Results The combination of infliximab and methotrexate was well tolerated and resulted in a sustained reduction in the symptoms and signs of rheumatoid arthritis that was significantly greater than the reduction associated with methotrexate therapy alone (clinical response, 51.8 percent vs. 17.0 percent; $P < 0.001$). The quality of life was also significantly better with infliximab plus methotrexate than with methotrexate alone. Radiographic evidence of joint damage increased in the group given methotrexate, but not in the groups given infliximab and methotrexate (mean change in radiographic score, 7.0 vs. 0.6; $P < 0.001$). Radiographic evidence of progression of joint damage was absent in infliximab-treated patients whether or not they had a clinical response.

Conclusions In patients with persistently active rheumatoid arthritis despite methotrexate therapy, repeated doses of infliximab in combination with methotrexate provided clinical benefit and halted the progression of joint damage. (N Engl J Med 2000;343:1594-602.)

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TUMOR necrosis factor α (TNF- α) has a central role in the pathogenesis of rheumatoid arthritis,¹⁻³ as demonstrated by the clinical benefit of TNF- α -neutralizing therapy⁴⁻⁹ with either a TNF- α type II receptor-IgG1 fusion protein (etanercept) or a chimeric (human and mouse) monoclonal antibody against TNF- α (infliximab). Sustained clinical benefit occurred when the TNF- α -neutralizing agents were administered alone^{5,8} or concomitantly with methotrexate,^{6,7,9} the current standard disease-modifying therapy for patients with rheumatoid arthritis.^{10,11}

Rheumatoid arthritis is a chronic disease with the potential to cause substantial joint damage and disability.¹² Critical issues concerning the effect of therapy, therefore, are the ability to control symptoms and signs of the disease for prolonged periods as well as the capacity to retard the damaging effect of rheumatoid inflammation on articular cartilage and bone. Although TNF- α -neutralizing therapy reduces the symptoms and signs of rheumatoid arthritis, it has been given for only three to six months,⁵⁻⁹ and no analysis of the effect on the progressive damage to joint structure has been reported. We evaluated the ability of repeated administration of infliximab along with methotrexate to control the clinical manifestations of rheumatoid arthritis over a one-year period, and the effect of this therapy on damage to cartilage and bone as determined by radiographic assessment.

METHODS

Patients

The eligibility criteria and the design of the study have been described in detail elsewhere.⁷ Patients were enrolled from March 31, 1997, to January 22, 1998. Briefly, patients were eligible for the study if they had active rheumatoid arthritis despite treatment with

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at least 12.5 mg of methotrexate per week. Active rheumatoid arthritis was defined by the presence of six or more swollen joints, six or more tender joints, and at least two or more of the following: morning stiffness that lasted at least 45 minutes, an erythrocyte sedimentation rate of at least 28 mm per hour, and a serum C-reactive protein concentration of at least 2.0 mg per deciliter. The effect of 30 weeks of therapy on the symptoms and signs of rheumatoid arthritis in these patients has been reported previously.⁷

Study Protocol

The patients were randomly assigned to receive the same dose of methotrexate they had been receiving weekly before the study plus infusions of placebo or infliximab (Remicade, Centocor, Malvern, Pa.) at a dose of 3 or 10 mg per kilogram of body weight for 54 weeks. No other disease-modifying drugs were permitted. Initially, all patients received intravenous infusions at the initiation of treatment (week 0) and at weeks 2 and 6. Two infliximab groups (one receiving 3 and the other receiving 10 mg per kilogram) and the placebo group received subsequent infusions every four weeks, whereas two other infliximab groups (receiving 3 and 10 mg per kilogram) received infliximab every eight weeks and placebo infusions on the interim four-week visits. Patients were allowed to continue the same dose of nonsteroidal antiinflammatory drug and oral glucocorticoid (prednisone, ≤ 10 mg per day) they had been taking at study entry. The study protocol was approved by the institutional review committee at each participating center, and each study subject gave written informed consent.

Clinical Response

The number of tender and swollen joints was evaluated by an independent assessor who had no knowledge of the patient's treatment assignment. A total of 68 joints were assessed for tenderness, and 66 for swelling. A clinical response at week 54 was defined according to the American College of Rheumatology (ACR) definition of a 20 percent improvement (ACR 20), indicating a decrease of at least 20 percent in the number of tender joints and a decrease of at least 20 percent in the number of swollen joints, along with a 20 percent improvement in three of the following: the patient's global assessment of disease status, the patient's assessment of pain, the health assessment questionnaire estimate of disability, and the physician's global assessment of disease status, all of which were assessed with the use of visual-analogue scales (range, 0 to 10 cm, with higher scores indicating poorer status or more severe pain); and the erythrocyte sedimentation rate or serum C-reactive protein concentration.¹³ The percentages of patients with an improvement of 50 percent (ACR 50) and 70 percent (ACR 70), according to the ACR criteria, were assessed in a similar manner.

Arthritis-related functional disability was measured with the Health Assessment Questionnaire, a well-validated, self-administered form that assesses functional ability in a variety of areas, including the ability to dress, arise, eat, walk, maintain personal hygiene, reach, and grip, on a scale ranging from 0 (no difficulty) to 3 (unable to perform the activity).¹⁴ General health status was assessed by the Medical Outcomes Study Short-Form Health Survey (SF-36) as described previously.^{15,16} Eight aspects of health status were assessed: general and mental health, physical function, social function, physical and emotional health, pain, and vitality; the score on each subscale ranges from 0 (worst) to 100 (best). The individual aspects of the survey were grouped into physical-component and mental-component summary scores, each of which was assigned a mean (\pm SD) score of 50 ± 10 on the basis of an assessment of the general U.S. population of persons without chronic conditions.¹⁶ Individual scores were compared with the normalized scores for the general population.

Serologic Studies

Serum antibodies against infliximab were measured as described previously.^{5,17} Serum antinuclear antibodies and antibodies against double-stranded DNA were measured at base line; at weeks 2, 4, 6, and 10; and every eight weeks thereafter.¹⁸⁻²⁰

Radiographic Evaluations

The effect of therapy on articular damage was assessed on the basis of an evaluation of radiographs of the hands and the feet for both erosions and joint-space narrowing, according to the van der Heijde modification of the Sharp scoring system.²¹⁻²⁴ Scores on this scale can range from 0 to 440, with higher scores indicating more articular damage. The reliability of this method has been previously documented.²² Anteroposterior radiographs of the hands and feet were obtained at base line and after 30 and 54 weeks. Two readers scored the films independently without knowledge of the order of the radiographs or the patient's treatment assignment or clinical response. For each set of radiographs, the mean score of the two readers was used for the analyses. Patients with missing radiographs at base line or week 54 and joints that had undergone surgery before enrollment were not included in the analysis; in the case of patients who had undergone surgery on specific joints during the trial the values used in the analyses were the mean changes from base line in the specific joint group. Patients with unequivocal evidence of major progression were defined as those with changes from base line that exceeded the 95 percent confidence intervals of the mean of the scores of the two readers.²⁴

Statistical Analysis

We examined the overall effect of treatment by evaluating the difference in the means or proportions in the five treatment groups. Pairwise comparisons of the infliximab and placebo groups were made when the overall effect of treatment had a significant ($P < 0.025$) effect on the primary end point — a clinical response. We used the chi-square test to evaluate categorical variables and analysis of variance to evaluate continuous variables. The proportion of patients who had a response was analyzed by chi-square test, and we used Fisher's exact tests for pairwise comparisons of adverse effects. For continuous variables, we made pairwise comparisons using linear contrasts. All statistical tests were two-sided.

RESULTS

Characteristics of the Patients

The patients were predominantly white women with considerable disease activity (Table 1). The scores on the physical-component subscales of the SF-36 were more than 2 SD below the score for the general U.S. population of persons without chronic conditions.¹⁶ A considerable degree of joint damage was documented at base line. There were no significant differences in any of these characteristics among the treatment groups (Table 1).

Forty-four patients (50 percent) in the group that received methotrexate alone discontinued treatment, as compared with 71 of the total of 340 patients (21 percent) in the groups that received infliximab plus methotrexate (Fig. 1). Lack of efficacy was the reason for discontinuation in the case of 32 patients (36 percent) in the group that received methotrexate alone and 40 patients (12 percent) in the groups that received infliximab plus methotrexate. Similar numbers of patients in the treatment groups discontinued therapy because of adverse events (Fig. 1).

Efficacy

The symptoms and signs of rheumatoid arthritis decreased in more patients in the groups that received infliximab plus methotrexate than in the group that received methotrexate alone, as judged by the percent-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

| CHARACTERISTIC | METHOTREXATE PLUS PLACEBO (N=88) | 3 mg OF INFlixIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=86) | 3 mg OF INFlixIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=86) | 10 mg OF INFlixIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=87) | 10 mg OF INFlixIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=81) |
|--|--|--|--|---|---|
| | Age (yr) | 51±12 | 54±11 | 52±13 | 54±12 |
| Female sex (%) | 80 | 81 | 77 | 77 | 73 |
| Duration of disease (yr) | 11±8 | 10±8 | 9±8 | 11±9 | 12±9 |
| Positive serum test for rheumatoid factor (%) | 77 | 84 | 80 | 82 | 82 |
| Dose of methotrexate (mg/wk) | 16±4 | 16±4 | 16±4 | 16±3 | 17±4 |
| Glucocorticoid therapy (%) | 64 | 63 | 54 | 58 | 65 |
| NSAID therapy (%) | 72 | 79 | 76 | 77 | 68 |
| No. of swollen joints† | 21±12 | 22±12 | 21±11 | 23±13 | 24±12 |
| No. of tender joints‡ | 31±18 | 32±18 | 31±15 | 32±16 | 34±16 |
| Duration of morning stiff- ness (min) | 199±279 | 164±248 | 186±263 | 226±317 | 181±281 |
| Health Assessment Ques- tionnaire score§ | 1.7±0.6 | 1.8±0.6 | 1.7±0.6 | 1.7±0.6 | 1.7±0.6 |
| SF-36 score¶ | | | | | |
| Physical component | 27±8 | 27±7 | 25±8 | 26±7 | 27±8 |
| Mental component | 47±12 | 46±11 | 48±12 | 48±11 | 47±11 |
| Erythrocyte sedimentation rate (mm/hr) | 49±25 | 49±23 | 52±24 | 50±24 | 49±23 |
| Serum C-reactive protein (mg/dl) | 4.0±4.2 | 3.9±3.4 | 3.5±4.2 | 3.3±3.4 | 4.2±4.3 |
| Total radiographic score | 82±77 | 79±73 | 71±73 | 67±61 | 76±72 |

*Plus-minus values are means ±SD. NSAID denotes nonsteroidal antiinflammatory drug.

†Sixty-six joints were assessed for swelling.

‡Sixty-eight joints were assessed for tenderness.

§Scores can range from 0 (no difficulty) to 3 (unable to perform the activity).

¶Scores for the Medical Outcomes Study Short-Form General Health Survey (SF-36) were compared with normalized scores for the general U.S. population, for which the mean score was 50±10. Higher scores indicate a better quality of life.

||Scores can range from 0 to 440, with higher scores indicating more articular damage on radiographic evaluation.

ages with ACR 20, ACR 50, and ACR 70 responses (Table 2). Although there was a tendency for the lowest dosage of infliximab (3 mg per kilogram every eight weeks) to be less effective than the other doses, this difference was significant only with respect to the ACR 50 responses ($P=0.008$ for the comparison with the group given 10 mg of infliximab per kilogram every eight weeks, and $P=0.02$ for the comparison with the group given 10 mg of infliximab per kilogram every four weeks). The results were similar when the individual components of the ACR criteria were analyzed, including the number of swollen joints, the number of tender joints, the patient's assessment of pain, patient's and physician's global assessments (data not shown), and serum C-reactive protein concentrations: all dosages of infliximab plus methotrexate were superior to methotrexate and placebo ($P<0.001$, except in the case of pain in the group given 3 mg per kilogram every eight weeks, for which $P=0.016$). All dosages of infliximab plus methotrexate also significantly ($P<0.001$) reduced serum rheumatoid factor

values (by approximately 40 percent) at 54 weeks, whereas methotrexate alone had no significant effect. The combination of infliximab and methotrexate also had a significantly greater effect on arthritis-specific function, as assessed by the Health Assessment Questionnaire, than did treatment with methotrexate alone (Fig. 2). Moreover, in general, the combination also had a significantly greater effect on the scores for the physical component of the SF-36 than methotrexate alone (Fig. 2). Although neither methotrexate alone nor infliximab plus methotrexate had a significant effect on the scores for the mental component of the SF-36, all dosages of infliximab plus methotrexate resulted in a significant improvement in the scores for the vitality subscale and the social-functioning subscale of the SF-36, whereas treatment with methotrexate alone did not (data not shown).

Adverse Effects

Adverse events were common in all treatment groups: 94 percent of the patients who received meth-

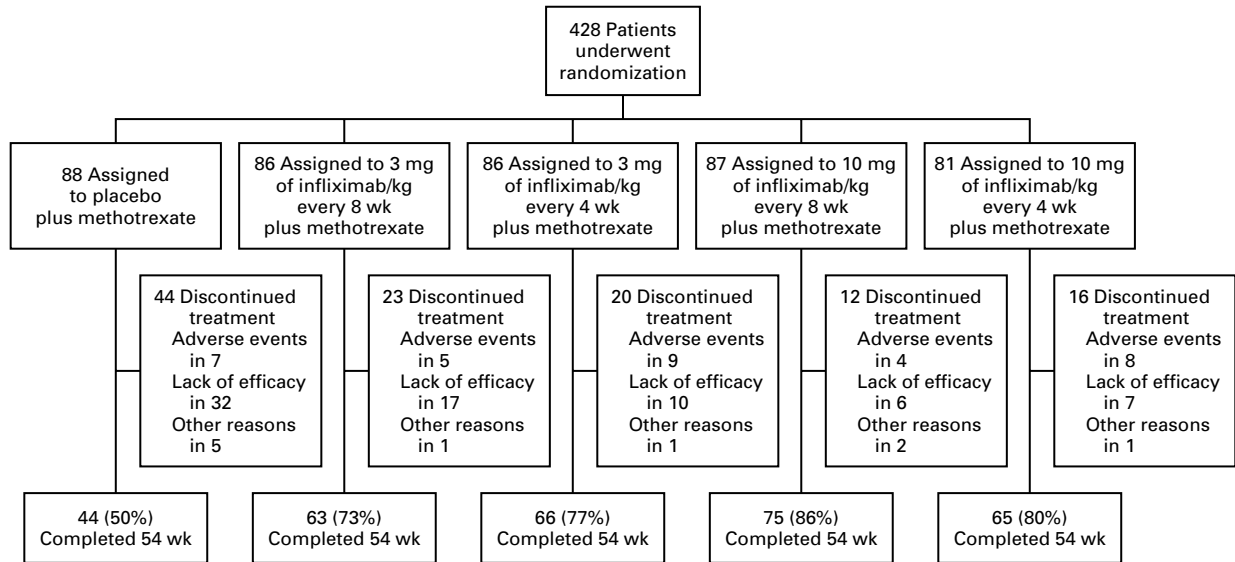


Figure 1. Randomization, Reasons for Discontinuing Treatment, and the Numbers of Patients Who Completed the Trial. Other reasons for discontinuing treatment included withdrawal of consent and withdrawal because of noncompliance.

TABLE 2. CLINICAL AND LABORATORY RESPONSES AT 54 WEEKS.*

| RESPONSE | METHOTREXATE PLUS PLACEBO (N=88) | 3 mg OF INFLIXIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=86) | 3 mg OF INFLIXIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=86) | 10 mg OF INFLIXIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=87) | 10 mg OF INFLIXIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=81) |
|---------------------------------------|----------------------------------|---|---|--|--|
| ACR criteria | | | | | |
| 20% improvement (%) | 17 | 42 | 48 | 59 | 59 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| 50% improvement (%) | 8 | 21 | 34 | 39 | 38 |
| P value | | 0.027 | <0.001 | <0.001 | <0.001 |
| 70% improvement (%) | 2 | 10 | 17 | 25 | 19 |
| P value | | 0.04 | 0.001 | <0.001 | <0.001 |
| Decrease in no. of swollen joints (%) | 13±61 | 37±62 | 50±54 | 60±38 | 63±34 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Decrease in no. of tender joints (%) | 23±63 | 49±52 | 55±48 | 56±52 | 65±33 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Serum C-reactive protein (mg/dl) | 2.8±3.1 | 1.6±1.9 | 1.5±2.5 | 1.2±1.7 | 1.1±1.4 |
| P value | | 0.006 | <0.001 | <0.001 | <0.001 |

*Plus-minus values are means ±SD. P values are for the comparison with the group given methotrexate and placebo. ACR denotes American College of Rheumatology.

otrexate alone and 95 percent of those who received infliximab plus methotrexate had at least one adverse event, but most were minor. Serious adverse events were less common, but again the overall frequencies in the group that received methotrexate alone (21 percent) and the groups that received infliximab plus methotrexate (17 percent) were similar (Table 3). The numbers of patients with infections that required an-

timicrobial-drug therapy were also similar in the group that received methotrexate alone (35 percent) and the groups that received infliximab plus methotrexate (44 percent). Moreover, the frequency of serious infections was similar (8 percent and 6 percent, respectively).

Although the difference was not significant, certain adverse events tended to occur more frequently in the

groups that received infliximab plus methotrexate than in the group that received methotrexate alone, including upper respiratory tract infections (34 percent vs. 22 percent), sinusitis (17 percent vs. 6 percent), pharyngitis (11 percent vs. 6 percent), and headache (26 percent vs. 16 percent). Cancer developed in five infliximab-treated patients during the trial (two were recurrences and three were new cases); three of these cases were reported previously, because the cancers were diagnosed during the first 30 weeks of the trial.⁷ One patient had two basal-cell carcinomas, one at two months and one at five months after treatment with 10 mg of infliximab per kilogram every eight weeks was begun, and one patient who was receiving 10 mg of infliximab per kilogram every eight weeks had a moderately differentiated rectal carcinoma.

There were eight deaths in the trial, three (3 percent) in the group given methotrexate alone and five (1 percent) in the groups given infliximab plus methotrexate. During this trial, the percentages in whom antinuclear antibodies and antibodies against double-stranded DNA developed were significantly higher in the groups given infliximab plus methotrexate than in the group given methotrexate alone (Table 3). However, symptoms (cutaneous rash) developed in only one patient who received infliximab (at a dosage of 10 mg per kilogram every eight weeks), as described previously.⁷ Because of the presence of infliximab in many of the serum samples, the development of antibodies against infliximab could not be assessed in most patients. However, among 60 patients who had discontinued treatment before 30 weeks or after 54 weeks, 5 (8 percent) had serum antibodies against infliximab, all at a low titer.

Radiographic Evaluation of Joint Damage

There was significantly more progression of joint damage from base line in the group given methotrexate alone as compared with the groups given infliximab plus methotrexate ($P < 0.001$, by Wilcoxon's signed-rank test) (Table 4). In this group, there was a 9 to 10 percent increase in the total radiographic score, a finding similar to those previously reported for patients

Figure 2. Mean Percent Improvement from Base Line in the Scores for the Health Assessment Questionnaire (HAQ) (Panel A) and the Mental Component (Panel B) and the Physical Component (Panel C) of the Medical Outcomes Study Short-Form General Health Survey (SF-36).

Statistical tests comparing each infliximab group with the group given methotrexate (MTX) and placebo were performed at weeks 30 and 54, and the results were as follows: in Panel A, the differences were significant at week 30 ($P < 0.001$) and week 54 ($P \leq 0.001$) for all infliximab groups but the one receiving 3 mg per kilogram every eight weeks; in Panel B, there were no significant differences at either time; and in Panel C, the differences were significant for all infliximab groups at week 30 ($P < 0.05$) and for all infliximab groups but the one receiving 3 mg per kilogram every eight weeks at week 54 ($P \leq 0.015$).

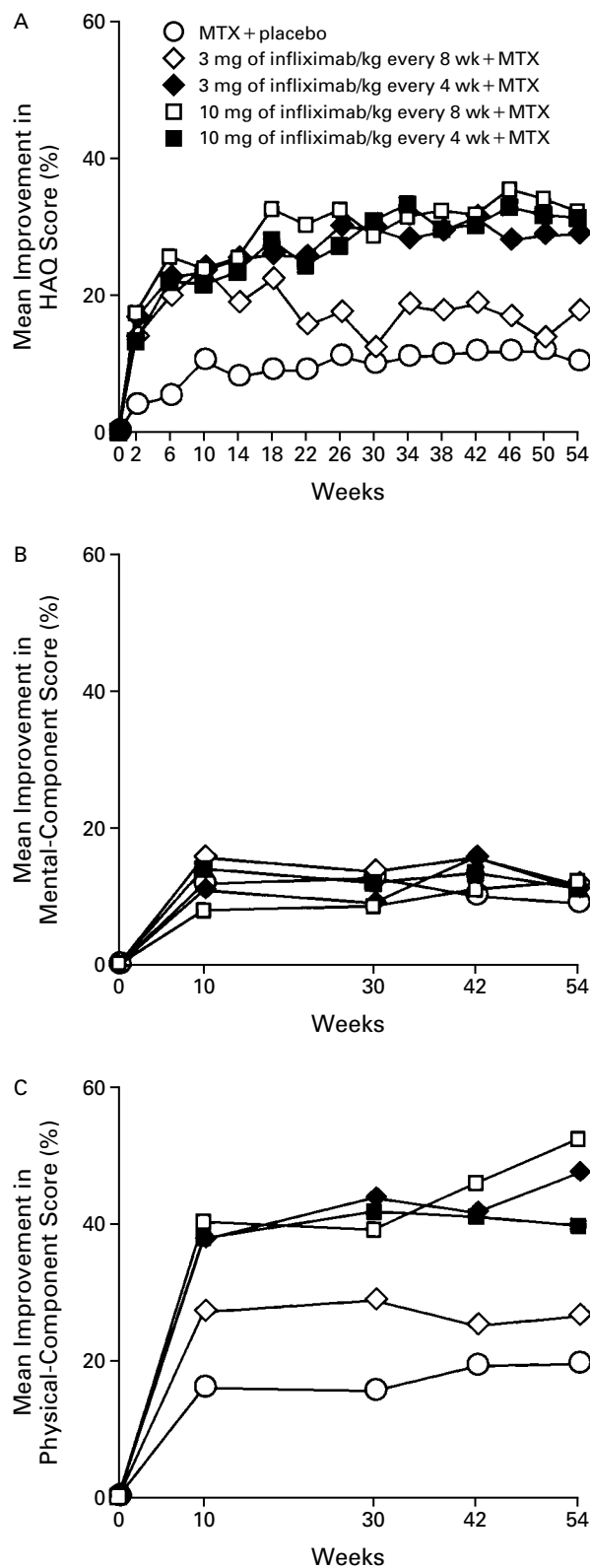


TABLE 3. INCIDENCE OF ADVERSE EVENTS.

| ADVERSE EVENT | METHOTREXATE PLUS PLACEBO (N=86)* | 3 mg OF INFLIXIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=88)* | 3 mg OF INFLIXIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=86) | 10 mg OF INFLIXIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=87) | 10 mg OF INFLIXIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=81) |
|--|-----------------------------------|--|---|--|--|
| Serious adverse events — no. (%)† | 18 (21) | 10 (11) | 14 (16) | 17 (20) | 16 (20) |
| Serious infections — no. (%)‡ | 7 (8) | 2 (2) | 6 (7) | 7 (8) | 6 (7) |
| Serious infusion reactions — no. | 0 | 0 | 0 | 0 | 0 |
| Antinuclear antibodies — no./total no. (%)§ | 18/69 (26) | 50/74 (68) | 40/64 (62) | 44/71 (62) | 34/64 (53) |
| P value¶ | | <0.001 | <0.001 | <0.001 | 0.002 |
| Antibodies against double-stranded DNA — no./total no. (%) | 0/84 | 9/88 (10) | 9/85 (11) | 9/87 (10) | 6/81 (7) |
| P value¶ | | 0.003 | 0.003 | 0.003 | 0.013 |

*Two patients who were supposed to receive placebo inadvertently received a partial dose of infliximab and thus were included in an infliximab group (3 mg per kilogram every eight weeks) for the analysis of adverse events.

†Serious adverse events were classified according to the World Health Organization adverse-reaction terminology.

‡Serious infections included bacterial infection, bronchitis, cellulitis, fungal infection, herpes zoster infection, peritonitis, pneumonia, pyelonephritis and urinary tract infection, sepsis, and tuberculosis.

§The values are the numbers of patients who were initially negative for antinuclear antibodies and who had a positive test (a serum titer of at least 1:320) at any time during the trial.

¶P values are for the comparison with the group given methotrexate plus placebo.

||The values are the numbers of patients who were initially negative for serum antibodies against double-stranded DNA and who had both a positive crithidia immunofluorescence assay and a positive Farr assay (a level of more than 25 IU per milliliter) at any time during the trial.

with rheumatoid arthritis who were treated with disease-modifying drugs.²⁵⁻²⁷ In contrast, there was no significant change in the mean radiographic score when base-line scores were compared with those at 54 weeks in the groups given infliximab plus methotrexate and there were no significant differences among these four groups ($P=0.43$).

Infliximab was also found to have a significant benefit when erosions and joint-space narrowing were examined independently and when the hands and feet were examined separately (Table 4). The rate of progression of joint damage was reduced in the patients who had a clinical response to infliximab plus methotrexate at 54 weeks as well as in those who did not have a clinical response (Table 4). In contrast, in the group given methotrexate alone, the small number of patients who had a clinical response had a rate of progressive joint damage that was similar to that in patients who did not have a clinical response. The results were similar whether a clinical response was defined as a decrease of more than 20 percent in the number of swollen joints, the number of tender joints, or the serum C-reactive protein concentration. The effect of infliximab plus methotrexate on joint damage was similar in a subgroup of patients who had had

rheumatoid arthritis for no more than three years, as well as in subgroups of patients with a small degree of joint damage at base line as assessed by the modified Sharp scoring system (a score of less than 30), those with a moderate degree of damage (30 to 90), and those with a high degree of joint damage (>90) (data not shown).

The percentage of patients with unequivocal radiographic evidence of major progression was analyzed as previously described²⁴ to assess the effect of therapy in individual patients. As shown in Table 4, 31 percent of the patients in the group given methotrexate alone had radiographic evidence of major progression, as compared with 0 to 13 percent of the patients in the groups given infliximab plus methotrexate ($P<0.001$). Finally, a significantly higher percentage of the patients in the groups given infliximab plus methotrexate than in the group given methotrexate alone had an improvement in radiographic scores after 54 weeks of treatment (39 to 55 percent vs. 14 percent).

Progressive joint damage occurred in a minority of patients despite treatment with infliximab and methotrexate. However, this damage was not correlated with base-line characteristics, including the duration of disease, the duration of methotrexate therapy, the

TABLE 4. EFFECT OF 54 WEEKS OF TREATMENT ON JOINT DAMAGE IN PATIENTS WITH RHEUMATOID ARTHRITIS.*

| VARIABLE | METHOTREXATE PLUS PLACEBO (N=64) | 3 mg OF INFlixIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=71) | 3 mg OF INFlixIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=71) | 10 mg OF INFlixIMAB/kg EVERY 8 WK PLUS METHOTREXATE (N=77) | 10 mg OF INFlixIMAB/kg EVERY 4 WK PLUS METHOTREXATE (N=66) |
|--|----------------------------------|---|---|--|--|
| Radiographic score | | | | | |
| Total score (increase or decrease from base line) | 7.0±10.3 | 1.3±6.0 | 1.6±8.5 | 0.2±3.6 | -0.7±3.8 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Erosion score (increase or decrease from base line) | 4.0±7.9 | 0.2±2.9 | 0.3±4.7 | 0.2±2.9 | -0.7±3.0 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Joint-space-narrowing score (increase from base line) | 2.9±4.2 | 1.1±4.4 | 0.7±4.3 | 0.0±3.1 | 0.0±2.5 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Major progression (% of patients) | 31 | 8 | 13 | 1 | 0 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Improvement (% of patients) | 14 | 44 | 48 | 39 | 55 |
| P value | | <0.001 | <0.001 | <0.001 | <0.001 |
| Clinical response† | | | | | |
| No. of patients | 14 | 35 | 36 | 48 | 44 |
| Total radiographic score (increase from base line) | 6.0±8.7 | 1.5±7.2 | 0.7±5.5 | 0.1±3.8 | 1.4±4.0 |
| P value | | 0.017 | 0.009 | 0.006 | <0.001 |
| No clinical response† | | | | | |
| No. of patients | 50 | 36 | 35 | 29 | 22 |
| Total radiographic score (increase from base line) | 7.2±10.8 | 1.1±4.7 | 2.6±10.7 | 0.2±3.4 | 0.7±3.2 |
| P value | | <0.001 | <0.001 | <0.001 | 0.002 |
| Duration of disease ≤3 yr | | | | | |
| No. of patients | 14 | 15 | 16 | 17 | 4 |
| Total radiographic score (increase or decrease from base line) | 9.1±7.7 | 0.4±4.5 | -1.1±6.4 | 0.6±2.7 | 0.3±3.3 |
| P value | | <0.001 | <0.001 | <0.001 | 0.007 |

*Plus-minus values are means ±SD. Joint damage was assessed radiographically with use of the van der Heijde modification of the Sharp scoring system. Total scores can range from 0 to 440. Scores on the erosion subscale used can range from 0 to 280, and scores on the joint-space-narrowing subscale can range from 0 to 160. Higher scores indicate more articular damage. P values are for the comparison with the group given methotrexate and placebo.

†A clinical response was defined as an improvement of at least 20 percent according to the criteria of the American College of Rheumatology (ACR 20).

number of clinically involved joints, or the serum C-reactive protein concentration.

DISCUSSION

This multicenter, placebo-controlled trial demonstrated that therapy with infliximab plus methotrexate for one year provided sustained clinical benefit in patients with active rheumatoid arthritis despite previous therapy with methotrexate. This combined therapy not only controlled the symptoms and signs of rheumatoid arthritis effectively, but also improved the quality of life and caused a significant improvement in biochemical measurements of inflammation. Therapy with infliximab plus methotrexate prevented the progressive joint damage characteristic of rheumatoid inflammation and resulted in improvement in radiographic scores of joint damage in a significant percentage of patients. The combination of infliximab and methotrexate halted the progression of joint damage not only in patients with limited joint damage, but also in those with extensive damage. Prevention of progressive joint damage during the year of treatment was

observed in patients who had a clinical response as well as in those who did not have a clinical response. These results imply that TNF- α has a critical role in the clinical manifestations of rheumatoid arthritis as well as in the progressive bone and cartilage damage. Even in patients in whom the clinical manifestations are not apparently mediated by TNF- α , this cytokine appears to have a critical role in the progressive bone and cartilage damage.

Therapy with infliximab plus methotrexate resulted in a sustained reduction in symptoms and signs of rheumatoid arthritis and increased the function of patients, as measured by the Health Assessment Questionnaire or by the SF-36. Even though it is generally accepted that two years of treatment is required to demonstrate prevention of disability,²⁸ our results suggest that infliximab plus methotrexate reduced disability. The reduction of disability coupled with prevention of damage to articular structures suggests a potent effect of the combination of infliximab plus methotrexate in patients with rheumatoid arthritis.

The combination of infliximab and methotrexate

was well tolerated and safe. Although the frequency of serious infections was no greater than with methotrexate alone, the frequency of infectious complications will have to be carefully monitored when a larger number of patients are treated with infliximab and methotrexate. Cancers did occur in patients treated with infliximab and methotrexate, all in those receiving the dose of infliximab of 10 mg per kilogram. However, the overall frequency of cancers was similar to that predicted from the Surveillance, Epidemiology, and End Results data base.²⁹ Finally, the administration of TNF- α -neutralizing agents is clearly associated with the development of autoantibodies. This finding has been reported with both infliximab and etanercept and in patients with Crohn's disease as well as in those with rheumatoid arthritis.^{5,7,9,30} The mechanisms of this phenomenon are uncertain, but the development of these autoantibodies was only rarely associated with symptoms suggestive of an autoimmune disease.

Current therapies for rheumatoid arthritis have only a moderate effect on the radiographic progression of the disease.^{21,26,31-35} Our finding that the addition of infliximab to methotrexate therapy arrested the progression of joint damage is therefore noteworthy. Not only did the combination of infliximab and methotrexate prevent progressive joint damage during the one year of therapy, but in 40 to 55 percent of the patients, the radiographic evidence of joint damage decreased, implying that some damage had been repaired. Our results are consistent with the conclusions that in patients with aggressive rheumatoid arthritis that is not responsive to methotrexate therapy, the combination of infliximab plus methotrexate can prevent progressive joint damage over a one-year period. This observation follows from the known capacity of TNF- α to stimulate resorption of bone³⁶ and inhibit the synthesis of proteoglycans by cartilage.³⁷

In summary, the combination of infliximab and methotrexate improves the symptoms and signs of inflammation, physical function, and the quality of life and prevents radiographic evidence of progressive joint damage in a majority of patients with rheumatoid arthritis who have no response to methotrexate alone.

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APPENDIX

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REFERENCES

- Brennan FM, Feldmann M. Cytokines in autoimmunity. *Curr Opin Immunol* 1992;4:754-9.
- Beckham JC, Caldwell DS, Peterson BL, et al. Disease severity in rheumatoid arthritis: relationships of plasma tumor necrosis factor- α , soluble interleukin 2-receptor, soluble CD4/CD8 ratio, neopterin, and fibrin D-dimer to traditional severity and functional measures. *J Clin Immunol* 1992;12:353-61.
- Charles P, Elliott MJ, Davis D, et al. Regulation of cytokines, cytokine inhibitors, and acute-phase proteins following anti-TNF- α therapy in rheumatoid arthritis. *J Immunol* 1999;163:1521-8.
- Elliott MJ, Maini RN, Feldmann M, et al. Randomised double-blind comparison of chimeric monoclonal antibody to tumour necrosis factor α (cA2) versus placebo in rheumatoid arthritis. *Lancet* 1994;344:1105-10.
- Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998;41:1552-63.
- Kavanaugh A, St Clair EW, McCune WJ, Braakman T, Lipsky P. Chimeric anti-tumor necrosis factor- α monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. *J Rheumatol* 2000;27:841-50.
- Maini R, St Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor α monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. *Lancet* 1999;354:1932-9.
- Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-7.
- 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.
- Weinblatt ME, Coblyn JS, Fox DA, et al. Efficacy of low-dose methotrexate in rheumatoid arthritis. *N Engl J Med* 1985;312:818-22.
- Kremer JM, Lee JK. The safety and efficacy of the use of methotrexate in long-term therapy for rheumatoid arthritis. *Arthritis Rheum* 1986;29:822-31.
- Lipsky PE. Rheumatoid arthritis. In: Fauci AS, Braunwald E, Isselbacher KJ, et al., eds. *Harrison's principles of internal medicine*. 14th ed. Vol. 2. New York: McGraw-Hill, 1998:1880-8.
- Felson DT, Anderson JJ, Boers M, et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.
- Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137-45.
- Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-83.
- Ware JE Jr, Kosinski M, Keller SK. SF-36 physical and mental health summary scales: a user's manual. Boston: Health Institute, 1994.
- LoBuglio AF, Wheeler RH, Trang J, et al. Mouse/human chimeric monoclonal antibody in man: kinetics and immune response. *Proc Natl Acad Sci U S A* 1989;86:4220-4.
- McCarty GA, Rice JR. Characterization and comparison of commercially available antinuclear antibody kits using single pattern index sera. *J Rheumatol* 1980;7:339-47.
- Crowe W, Kushner I. An immunofluorescent method using Crithidia luciliae to detect antibodies to double-stranded DNA. *Arthritis Rheum* 1977;20:811-4.
- Wold RT, Young FE, Tan EM, Farr RS. Deoxyribonucleic acid antibody: a method to detect its primary interaction with deoxyribonucleic acid. *Science* 1968;161:806-7.
- van der Heijde D, van Riel P, Nuver-Zwat IH, Gribnau FW, van de Putte LB. Effects of hydroxychloroquine and sulphasalazine on progression of joint damage in rheumatoid arthritis. *Lancet* 1989;1:1036-8.
- van der Heijde D. Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability. *Baillieres Clin Rheumatol* 1996;10:435-53.
- van der Heijde DM, van Leeuwen MA, van Riel PLCM, et al. Biantal radiographic assessments of hands and feet in a three-year prospective

followup of patients with early rheumatoid arthritis. *Arthritis Rheum* 1991;35:26-34.

24. Lassere M, Boers M, van der Heijde D, et al. Smallest detectable difference in radiological progression. *J Rheumatol* 1999;26:731-9.

25. Kaarela K, Kautiainen H. Continuous progression of radiological destruction in seropositive rheumatoid arthritis. *J Rheumatol* 1997;24:1285-7.

26. Wolfe F, Sharp JT. Radiographic outcome of recent-onset rheumatoid arthritis: a 19-year study of radiographic progression. *Arthritis Rheum* 1998;41:1571-82.

27. Graudal NA, Jurik AG, de Carvalho A, Graudal HK. Radiographic progression in rheumatoid arthritis: a long-term prospective study of 109 patients. *Arthritis Rheum* 1998;41:1470-80.

28. Fries JF, Williams CA, Morfeld D, Singh G, Sibley J. Reduction in long-term disability in patients with rheumatoid arthritis by disease-modifying antirheumatic drug-based treatment strategies. *Arthritis Rheum* 1996;39:616-22.

29. Parker SL, Tong T, Bolder S, Wingo P. Cancer statistics, 1997. *CA Cancer J Clin* 1997;47:5-27. [Erratum, *CA Cancer J Clin* 1997;47:68.]

30. Targan SR, Hanaauer SB, van Deventer SJH, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor α for Crohn's disease. *N Engl J Med* 1997;337:1029-35.

31. Sharp JT, Wolfe F, Mitchell DM, Bloch DA. The progression of erosion and joint space narrowing scores in rheumatoid arthritis during the first twenty-five years of disease. *Arthritis Rheum* 1991;34:660-8.

32. 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.

33. Plant MJ, Jones PW, Saklatvala J, Ollier WE, Dawes PT. Patterns of radiological progression in early rheumatoid arthritis: results of an 8 year prospective study. *J Rheumatol* 1998;25:417-26.

34. Smolen JS, Kalden JR, Scott DL, et al. Efficacy and safety of leflunomide compared with placebo and sulphasalazine in active rheumatoid arthritis: a double-blind, randomised, multicentre trial. *Lancet* 1999;353:259-66.

35. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. *Arch Intern Med* 1999;159:2542-50.

36. Bertolini DR, Nedwin GE, Bringman TS, Smith DD, Mundy GR. Stimulation of bone resorption and inhibition of bone formation in vitro by human tumour necrosis factors. *Nature* 1986;319:516-8.

37. Saklatvala J. Tumor necrosis factor alpha stimulates resorption and inhibits synthesis of proteoglycan in cartilage. *Nature* 1986;322:547-9.

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