

ORIGINAL ARTICLE

Treatment of Rheumatoid Arthritis by Selective Inhibition of T-Cell Activation with Fusion Protein CTLA4Ig

Joel M. Kremer, M.D., Rene Westhovens, M.D., Ph.D., Marc Leon, M.D.,
Eduardo Di Giorgio, M.D., Rieke Alten, M.D., Serge Steinfeld, M.D., Ph.D.,
Anthony Russell, M.D., Maxime Dougados, M.D., Paul Emery, M.D., F.R.C.P.,
Isaac F. Nuamah, Ph.D., G. Rhys Williams, Sc.D., Jean-Claude Becker, M.D.,
David T. Hagerty, M.D., and Larry W. Moreland, M.D.

ABSTRACT

BACKGROUND

Effective new therapies are needed for rheumatoid arthritis. Current therapies target the products of activated macrophages; however, T cells also have an important role in rheumatoid arthritis. A fusion protein — cytotoxic T-lymphocyte-associated antigen 4–IgG1 (CTLA4Ig) — is the first in a new class of drugs known as costimulation blockers being evaluated for the treatment of rheumatoid arthritis. CTLA4Ig binds to CD80 and CD86 on antigen-presenting cells, blocking the engagement of CD28 on T cells and preventing T-cell activation. A preliminary study showed that CTLA4Ig may be effective for the treatment of rheumatoid arthritis.

METHODS

We randomly assigned patients with active rheumatoid arthritis despite methotrexate therapy to receive 2 mg of CTLA4Ig per kilogram of body weight (105 patients), 10 mg of CTLA4Ig per kilogram (115 patients), or placebo (119 patients) for six months. All patients also received methotrexate therapy during the study. The clinical response was assessed at six months with use of the criteria of the American College of Rheumatology (ACR), which define the response according to its extent: 20 percent (ACR 20), 50 percent (ACR 50), or 70 percent (ACR 70). Additional end points included measures of the health-related quality of life.

RESULTS

Patients treated with 10 mg of CTLA4Ig per kilogram were more likely to have an ACR 20 than were patients who received placebo (60 percent vs. 35 percent, $P < 0.001$). Significantly higher rates of ACR 50 and ACR 70 responses were seen in both CTLA4Ig groups than in the placebo group. The group given 10 mg of CTLA4Ig per kilogram had clinically meaningful and statistically significant improvements in all eight subscales of the Medical Outcomes 36-Item Short-Form General Health Survey. CTLA4Ig was well tolerated, with an overall safety profile similar to that of placebo.

CONCLUSIONS

In patients with active rheumatoid arthritis who were receiving methotrexate, treatment with CTLA4Ig significantly improved the signs and symptoms of rheumatoid arthritis and the health-related quality of life. CTLA4Ig is a promising new therapy for rheumatoid arthritis.

From the Center for Rheumatology, Albany, N.Y. (J.M.K.); the Department of Rheumatology, Universitaire Ziekenhuizen Leuven, Leuven, Belgium (R.W.); Free University of Brussels, Centre Hospitalier Universitaire Ambroise Paré, Mons, Belgium (M.L.); Centro de Enfermedades Reumáticas, Quilmes, Argentina (E.D.G.); the Department of Rheumatology, Schlosspark-Klinik, Berlin, Germany (R.A.); the Department of Rheumatology, Erasme University Hospital, Brussels, Belgium (S.S.); the University of Alberta Hospital, Edmonton, Alta., Canada (A.R.); Rene Descartes University, Hospital Cochin Assistance Publique — Hôpitaux de Paris, Paris (M.D.); the Department of Rheumatology, Leeds General Infirmary, Leeds, United Kingdom (P.E.); Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, N.J. (I.F.N., G.R.W., J.-C.B., D.T.H.); and the Department of Medicine, University of Alabama at Birmingham School of Medicine, Birmingham (L.W.M.). Address reprint requests to Dr. Kremer at the Center for Rheumatology, 1367 Washington Ave., Suite 1, Albany, NY 12206, or at jkremer@joint-docs.com.

N Engl J Med 2003;349:1907-15.

Copyright © 2003 Massachusetts Medical Society.

RHEUMATOID ARTHRITIS IS A SYSTEMIC disease that causes progressive joint damage and disability.¹ The macrophage is an important pathogenic mediator in rheumatoid arthritis, and cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-1 are therapeutic targets. Drugs that block TNF- α decrease joint inflammation and slow radiographic progression.²⁻⁸ However, since only approximately 40 percent of patients have an improvement of 50 percent, according to the criteria of the American College of Rheumatology (ACR), during treatment with TNF- α inhibitors, effective therapies directed against novel targets are needed.

Class II major-histocompatibility-complex (MHC) phenotype confers susceptibility to rheumatoid arthritis.⁹ HLA-DR1 and DR4 are expressed in over 80 percent of white patients with rheumatoid arthritis.¹⁰ Class II MHC molecules present antigens to CD4+ T cells, suggesting an important role of T cells in the pathogenesis of rheumatoid arthritis.

The rheumatoid synovium contains activated T cells, providing further support for the theory that T cells have an important role in rheumatoid arthritis.^{11,12} Cells resembling monocytes and macrophages and dendritic cells are also present in the rheumatoid synovium. These antigen-presenting cells are activated and express both class II MHC and costimulatory molecules such as CD80 (B7-1) and CD86 (B7-2).¹³⁻¹⁷ These observations suggest that synovial T cells, macrophages, dendritic cells, and B cells may have a direct role in the disease process.

T cells require at least two signals to become fully activated.^{18,19} Signal 1 is antigen-specific and is delivered by engagement of the T-cell receptor with an MHC-peptide complex on an antigen-presenting cell. Signal 2 is delivered by the binding of a costimulatory receptor on T cells to a ligand on the antigen-presenting cell. A key costimulatory signal is provided by the interaction of CD28 on T cells with CD80 or CD86 on antigen-presenting cells.²⁰⁻²² In the presence of optimal T-cell-receptor and CD28 signals, T cells proliferate and produce cytokines that can activate other inflammatory cells, such as macrophages. With only a T-cell-receptor signal and no CD28 signal, T-cell activation is not optimal, and T cells may be rendered poorly responsive to otherwise optimal subsequent stimulation, or they may undergo apoptosis.¹⁹

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) is expressed on the surface of T cells hours or days after they become activated. CTLA4 is the

high-avidity receptor for both CD80 and CD86, binding approximately 500 to 2500 times as avidly to these ligands as to CD28.²³⁻²⁵ CTLA4Ig is constructed by genetically fusing the external domain of human CTLA4 to the heavy-chain constant region of human IgG1. CTLA4Ig binds both CD80 and CD86 on antigen-presenting cells, thereby preventing these molecules from engaging CD28 on T cells. By blocking the engagement of CD28, CTLA4Ig prevents the delivery of the second costimulatory signal that is required for optimal activation of T cells. Blocking the second signal is a novel therapeutic concept. Preclinical studies demonstrated the efficacy of CTLA4Ig in many animal models of autoimmune disease^{26,27} and allograft rejection.²⁸

In a three-month pilot study in which patients with rheumatoid arthritis were given 0.5, 2, or 10 mg of CTLA4Ig per kilogram of body weight as monotherapy on days 1, 15, 29, and 57, 53 percent of patients who received the dose of 10 mg per kilogram had a 20 percent improvement (an ACR 20 response) after 85 days and 16 percent had a 50 percent improvement (an ACR 50 response), according to the ACR criteria.²⁹ Here, we report the results of a six-month, double-blind, randomized, placebo-controlled investigation of the effectiveness of CTLA4Ig therapy in patients with rheumatoid arthritis who had an inadequate response to methotrexate.

METHODS

PATIENTS

The study population consisted of patients 18 to 65 years of age who met the ACR criteria for rheumatoid arthritis and were in functional class I, II, or III.³⁰ Entry requirements included active disease, characterized by 10 or more swollen joints, 12 or more tender joints, and C-reactive protein levels of at least 1 mg per deciliter (upper limit of the normal range, 0.4). Patients had to have been treated with methotrexate (10 to 30 mg weekly) for at least 6 months and to have received a stable dose for 28 days before enrollment. All patients continued to receive methotrexate. All other disease-modifying antirheumatic drugs were discontinued. Leflunomide and infliximab were discontinued at least 60 days before enrollment, and other disease-modifying antirheumatic drugs were discontinued at least 28 days before enrollment. Stable low-dose corticosteroids (≤ 10 mg per day) and nonsteroidal antiinflammatory drugs were permitted. Women who were nursing

or pregnant were excluded. Patients were enrolled in the study between December 11, 2000, and December 11, 2001.

STUDY PROTOCOL

This was a six-month randomized, double-blind, placebo-controlled study to compare the safety, efficacy, and immunogenicity of 2 mg or 10 mg of CTLA4Ig per kilogram with those of placebo in patients with active rheumatoid arthritis. The study sponsor was involved in the design of the study, collection of the data, and analysis of the data. The academic investigators had access to the data and were responsible for interpreting the data. The protocol was approved by the appropriate international regulatory boards and the human-research committees at each participating center. Written informed consent was obtained from all patients before they underwent randomization or any study-related procedures. A central randomization procedure was used. To ensure that the treatment groups were balanced at each site, patients were randomly assigned with use of a permuted-block size of 6. CTLA4Ig or placebo was infused intravenously over a 30-minute period on days 1, 15, and 30 and monthly thereafter for a total of six months.

EFFICACY MEASUREMENTS

The primary efficacy variable was the percentage of patients who had a 20 percent improvement according to ACR criteria (an ACR 20 response) at six months.³¹ The ACR criteria assess 68 joints for tenderness and 66 joints for swelling. An ACR 20 response indicates a decrease of at least 20 percent in both the number of tender joints and the number of swollen joints, as well as a 20 percent improvement in at least three of the following: the patient's global assessment of disease status, the patient's assessment of pain, the patient's assessment of physical function (measured with use of the Modified Stanford Health Assessment Questionnaire), the physician's global assessment of disease status, and the C-reactive protein level. Secondary outcome measures were 50 percent improvement and 70 percent improvement according to ACR criteria (an ACR 50 response and an ACR 70 response, respectively). The ACR response was assessed on days 1, 15, and 30 and then monthly. Assessments were performed by rheumatologists or trained professional staff members who were unaware of patients' treatment assignments and were not involved in the infusion of CTLA4Ig or placebo.

Health-related quality of life was assessed at base line, 90 days, and 180 days with use of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).^{32,33} The SF-36 consists of 36 items, 35 of which are aggregated to evaluate eight dimensions of health: physical function, pain, general and mental health, vitality, social function, and physical and emotional health. Scores on the eight subscales were aggregated to derive the physical-

Table 1. Base-Line Characteristics of the Patients.*

| Characteristic | Placebo + Methotrexate (N=119) | CTLA4Ig, 2 mg/kg, + Methotrexate (N=105) | CTLA4Ig, 10 mg/kg, + Methotrexate (N=115) |
|--|--------------------------------------|---|--|
| Age (yr) | | | |
| Mean | 54.7 | 54.4 | 55.8 |
| Range | 23–80 | 23–80 | 17–83 |
| Weight (kg) | | | |
| Mean | 79.9 | 78.7 | 77.8 |
| Range | 44–140 | 48–186 | 40–144 |
| Female sex (%) | 66 | 63 | 75 |
| White race (%) | 87 | 87 | 87 |
| Duration of disease (yr) | 8.9±8.3 | 9.7±8.1 | 9.7±9.8 |
| Methotrexate dose (mg/wk) | 15.8±4.1 | 15.8±4.5 | 15.0±4.4 |
| Mean duration of methotrexate therapy (yr) | 2.9±3.5 | 2.6±3.0 | 2.5±2.7 |
| Previous treatment with anti-TNF drug (%) | 2.6 | 5.7 | 2.6 |
| Joints (no.)† | | | |
| Tender | 29.2±13.0 | 28.2±12.0 | 30.8±12.2 |
| Swollen | 21.8±8.8 | 20.2±8.9 | 21.3±8.4 |
| Pain score‡ | 65.2±22.1 | 64.5±22.3 | 62.1±21.4 |
| Physical-function score§ | 1.0±0.6 | 1.0±0.5 | 1.0±0.5 |
| Global assessment score‡ | | | |
| Patient | 62.8±21.6 | 59.4±23.7 | 60.1±20.7 |
| Physician | 63.3±15.5 | 61.0±16.7 | 62.1±14.8 |
| Positive for rheumatoid factor (%) | 90 | 90 | 99 |
| Erosive disease (%) | 100 | 100 | 100 |
| C-reactive protein (mg/dl) | 3.2±3.2 | 3.2±2.6 | 2.9±2.8 |
| SF-36 score¶ | | | |
| Physical component | 32.3±7.7 | 30.8±8.5 | 31.3±8.5 |
| Mental component | 41.9±11.0 | 43.1±11.0 | 44.5±10.5 |

* Plus-minus values are means ±SD. TNF denotes tumor necrosis factor.

† Sixty-eight joints were assessed for tenderness, and 66 were assessed for swelling.

‡ A 100-mm visual-analogue scale was used in which higher values indicated more severe abnormalities.

§ The Modified Stanford Health Assessment Questionnaire was used. Scores can range from 0 to 3, with higher scores indicating greater disease activity.

¶ Scores on the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36) were standardized on the basis of a mean score of 50±10 in the general U.S. population. Higher scores indicate a better quality of life.

component summary score and the mental-component summary score. The eight subscales, physical-component summary, and mental-component summary were scored with use of norm-based methods that standardize the scores to a mean (\pm SD) of 50 ± 10 on the basis of an assessment of the general U.S. population of persons without chronic conditions.³⁴ Scores on each subscale range from 0 to 10, and the summary scores range from 0 to 100, with higher scores indicating better health. Absolute differences of three or more in both the subscale scores and summary scores were considered clinically meaningful.^{35,36}

SAFETY ASSESSMENTS

Patients were asked about adverse events at each visit, and the investigator assessed the severity of any reported event and its relation to the study medication. A data and safety monitoring board supervised the overall safety assessment in an unblinded fashion.

IMMUNOGENICITY TESTING

Serum samples were obtained for the measurement of drug-specific antibodies on days 1, 30, 90, and 180. Formation of specific antibody against the whole molecule (CTLA4Ig) and against the CTLA4 portion alone were evaluated separately according to previously described methods.²⁹ Results were expressed as the end-point titer, defined as the reciprocal of the interpolated dilution with an absorbance value equal to five times the mean absorbance background value. Seroconversion was defined by an increase of at least two serial dilutions (by a factor of nine) relative to the predose value.

STATISTICAL ANALYSIS

A sample of 107 patients per treatment group was determined to yield 94 percent power at the 5 percent level (two-sided) to detect an absolute difference of 25 percent between the group given 10 mg of CTLA4Ig per kilogram and the group given pla-

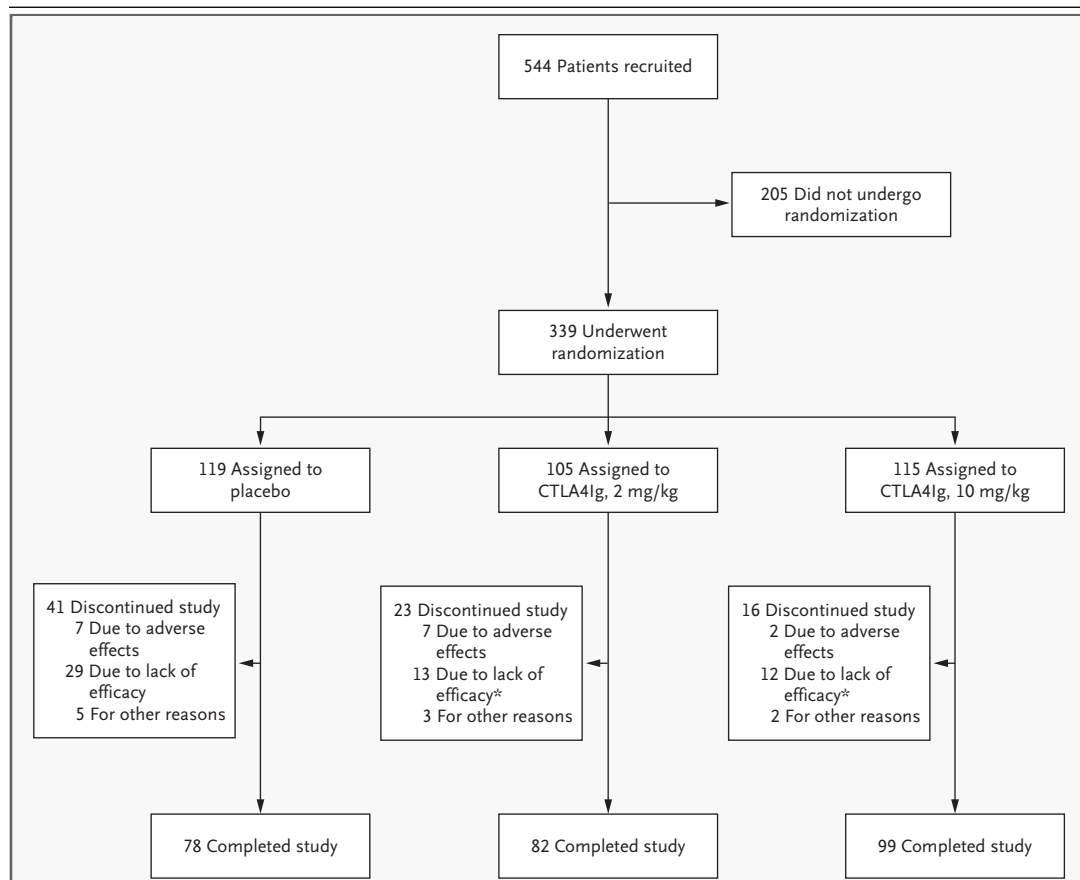


Figure 1. Enrollment and Disposition of the Patients. Asterisks indicate a significant difference ($P < 0.05$) from placebo plus methotrexate.

cebo plus methotrexate, on the basis of an expected ACR 20 response rate at six months of 25 percent in the placebo group and a dropout rate of 15 percent in each treatment group. A closed testing procedure based on an ordered analysis of variance³⁷ was established for hypothesis testing: if there was a significant difference in the rates of ACR 20 responses between the group given 10 mg of CTLA4Ig per kilogram and the placebo group with use of a chi-square test, then we compared the group given 2 mg of CTLA4Ig per kilogram with the placebo group. This testing strategy was also used to identify differences in the rates of ACR 50 and ACR 70 responses.

Descriptive statistics were used to compare the demographic and base-line characteristics of the patients in the three treatment groups. The efficacy analyses included all patients who received at least one dose of study medication. To account for missing data in the assessment of the ACR responses in the primary, prespecified analysis, we considered patients who discontinued the study because of worsening disease not to have had a response, and we carried forward the values obtained at the last assessment for patients who discontinued the study for any other reason. Thus, all patients were assessed for an ACR response. When assessing the change from base line in the health-related quality of life and the individual components of the ACR response in patients who discontinued the study for any reason, we used the values obtained at the last assessment and carried them forward. A secondary analysis was performed in which all patients who discontinued the study for any reason were classified as having had no response.

Fisher's exact tests were used to compare the incidence of adverse events in the CTLA4Ig groups and the placebo group. For other end points, analysis of covariance (adjusted for base-line values) with linear contrasts was used for continuous variables and chi-square tests were used for proportions. All statistical tests were two-sided and conducted at the 5 percent level.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Study medication was administered to 339 patients: 119 patients were randomly assigned to receive placebo plus methotrexate, 105 to receive 2 mg of CTLA4Ig per kilogram plus methotrexate, and 115 patients to receive 10 mg of CTLA4Ig per kilogram plus methotrexate. The demographic and base-line

clinical characteristics were similar among the treatment groups (Table 1). Despite concurrent treatment with methotrexate, patients had a high degree of base-line disease activity on the basis of the numbers of swollen and tender joints.

A total of 259 patients completed six months of treatment (Fig. 1). More patients in the placebo group discontinued the study than in either of the CTLA4Ig groups. The most common reason for discontinuation was lack of efficacy as indicated by worsening arthritis.

CLINICAL EFFICACY

The percentage of patients who had an ACR 20 response at six months was significantly higher in the group given 10 mg of CTLA4Ig per kilogram than in the placebo group (Fig. 2 and Table 2). There was no significant difference in the rate of ACR 20 responses at six months between the group given 2 mg of CTLA4Ig per kilogram and the placebo group ($P=0.31$). ACR 20 responses in the group given 10 mg of CTLA4Ig per kilogram were significantly higher than those in the placebo group from month 2 through month 6 (Fig. 2).

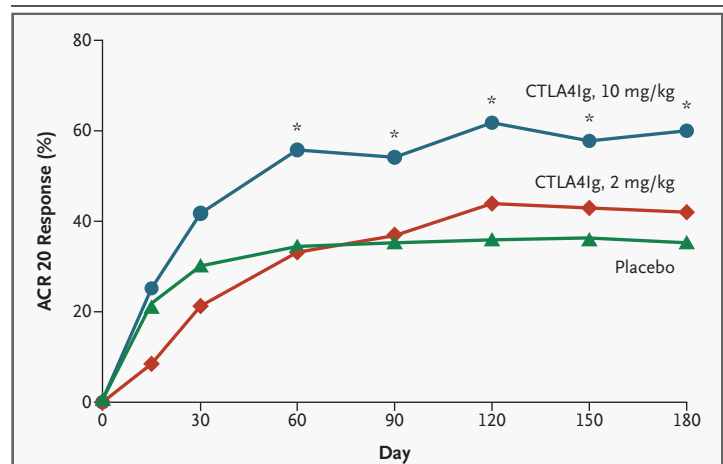


Figure 2. Clinical Efficacy of CTLA4Ig.

A clinical response 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 both tender joints and 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 patient's estimate of physical function (measured with use of the Modified Stanford Health Assessment Questionnaire), the physician's global assessment of disease status, and the serum C-reactive protein level. At each study visit, measurements were obtained before any treatment was administered. Asterisks indicate a significant difference ($P<0.001$) between the group given 10 mg of CTLA4Ig per kilogram and the placebo group.

Table 2. Efficacy at Six Months.*

| Variable | Placebo + Methotrexate (N=119) | CTLA4Ig, 2 mg/kg, + Methotrexate (N=105) | CTLA4Ig, 10 mg/kg, + Methotrexate (N=115) |
|--|--------------------------------------|---|--|
| | <i>percent</i> | | |
| ACR response rate† | | | |
| ACR 20 | 35.3 | 41.9 | 60.0‡ |
| ACR 50 | 11.8 | 22.9§ | 36.5‡ |
| ACR 70 | 1.7 | 10.5§ | 16.5‡ |
| Mean change from base line in individual ACR components¶ | | | |
| Tender joints | 32.1 | 43.3 | 59.9§ |
| Swollen joints | 33.4 | 45.1§ | 54.9§ |
| Pain | 8.4 | 22.7§ | 46.4§ |
| Physical function | 14.1 | 17.3 | 41.5§ |
| Patient's global assessment | 17.6 | 9.6 | 40.8§ |
| Physician's global assessment | 25.6 | 38.6§ | 52.0§ |
| C-reactive protein level | -23.6 | 16.2§ | 31.5§ |

* A clinical response 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 both tender joints and swollen joints, along with a 20 percent improvement in at least three of the following: the patient's global assessment of disease status, the patient's assessment of pain, the patient's estimate of function (measured with use of the Modified Stanford Health Assessment Questionnaire), the physician's global assessment of disease status, and the serum C-reactive protein level. 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.

† Patients who discontinued the study because of worsening disease were considered to have had no response; for those who discontinued the study for other reasons the values for the last efficacy observation were carried forward.

‡ P<0.001 for the comparison with the group given placebo plus methotrexate.

§ P<0.05 for the comparison with the group given placebo plus methotrexate.

¶ Values were carried forward from the last efficacy observation.

The rates of ACR 50 and ACR 70 responses at six months were significantly higher in both CTLA4Ig groups than in the placebo group (Table 2). As compared with the patients in the placebo group, patients who received 10 mg of CTLA4Ig per kilogram also had significant improvements in all clinical components of the ACR response criteria (Table 2).

In a secondary analysis, patients who discontinued the study for any reason were classified as having had no response. In this analysis, the rate of ACR 20 responses at six months was significantly higher in the group given 10 mg of CTLA4Ig per kilogram than in the placebo group (57.4 percent vs. 31.1 percent, P<0.001). The rate of ACR 20 responses in the

group given 2 mg of CTLA4Ig per kilogram was 39 percent and did not differ significantly from that in the placebo group (P=0.21). The rates of ACR 50 responses were 35.7 percent in the group given 10 mg of CTLA4Ig per kilogram and 22.9 percent in the group given 2 mg of CTLA4Ig per kilogram, as compared with 10.1 percent in the placebo group (P<0.001 and P=0.009, respectively). The rates of ACR 70 responses were the same as those in the primary analysis.

Patients in the group given 10 mg of CTLA4Ig per kilogram had clinically meaningful and significant improvements from base-line scores in the scores on all eight subscales and both summary scores of the SF-36, with the greatest effect in the physical-health, pain, vitality, and social-function domains (Fig. 3). All improvements were significantly greater than those in the placebo group (P<0.05). For patients treated with 2 mg of CTLA4Ig per kilogram, improvements from base-line values were significant for all domains except mental health but did not differ significantly from those in the placebo group.

SAFETY

CTLA4Ig was well tolerated, and no deaths, cancers, or opportunistic infections were reported by CTLA4Ig-treated patients after six months of treatment. In general, adverse events were reported at a similar or lower rate in the CTLA4Ig groups than in the placebo group. The most frequently reported adverse event was headache, followed in decreasing order by upper respiratory tract infection, musculoskeletal pain, and nausea and vomiting (Table 3).

Fewer serious adverse events were reported in the group given 10 mg of CTLA4Ig per kilogram than in the group given 2 mg of CTLA4Ig per kilogram or the placebo group (Table 3). None of the serious adverse events in the group given 10 mg of CTLA4Ig per kilogram were considered to be related to the study drug. One patient in the group given 2 mg of CTLA4Ig per kilogram was hospitalized for cellulitis of the left foot. No other serious infections were reported. The rate of discontinuation because of adverse events was lower in the group given 10 mg of CTLA4Ig per kilogram (1.7 percent) than in the group given 2 mg of CTLA4Ig per kilogram (6.7 percent) or the placebo group (5.9 percent).

IMMUNOGENICITY TESTING

Most patients had preexisting antibodies against CTLA4Ig. No patient in either of the CTLA4Ig

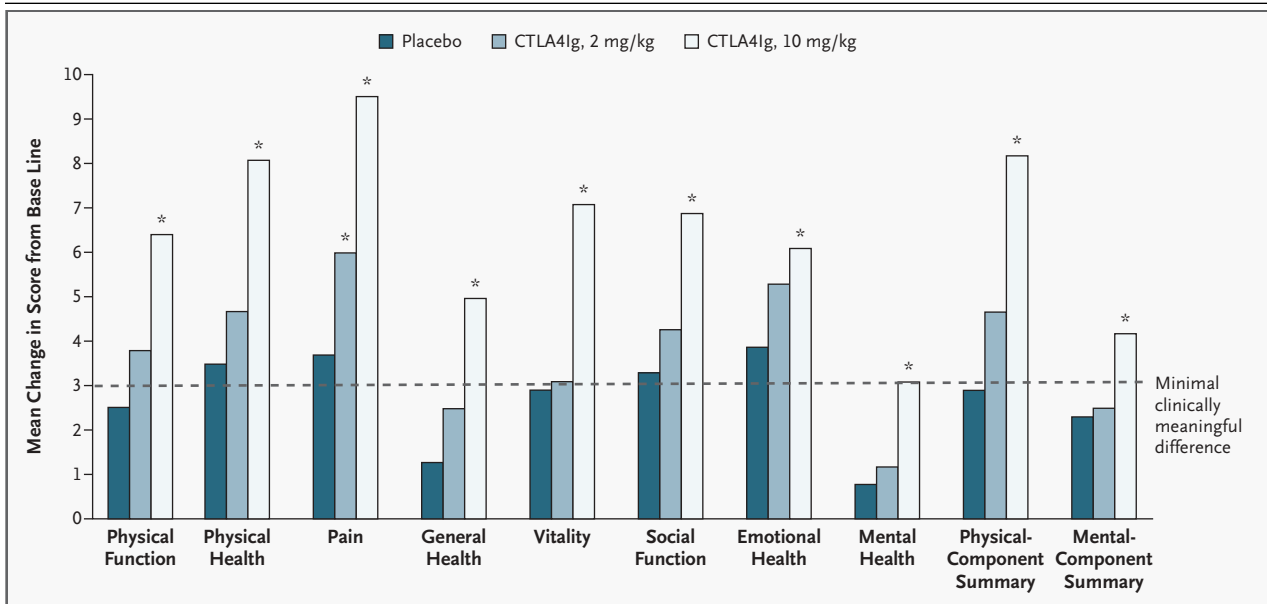


Figure 3. Effect of CTLA4Ig on the Health-Related Quality of Life.

Health-related quality of life was assessed with use of the Medical Outcomes Study 36-Item Short-Form General Health Survey (SF-36).^{32,33} Scores on the eight subscales of the SF-36 were aggregated to derive the physical-component summary score and the mental-component summary score. The eight subscales, physical-component summary, and mental-component summary were scored with use of norm-based methods that standardize the scores to a mean (\pm SD) of 50 ± 10 on the basis of an assessment of the general U.S. population of persons without chronic conditions.³⁴ Scores on each subscale range from 0 to 10, and the summary scores range from 0 to 100, with higher scores indicating better health. Asterisks indicate a significant difference ($P < 0.05$) for the comparison with the placebo group with use of an analysis of covariance model with the base-line value as a covariate. Values were carried forward from the last efficacy observation. Changes from base line were also significant for each subscale score and for the summary scores in the 10-mg CTLA4Ig group.

groups had evidence of seroconversion for CTLA4Ig-specific antibodies during the six-month study period. Seroconversion for CTLA4-specific antibodies was detected in one patient in the group given 10 mg of CTLA4Ig per kilogram (the end-point titer increased from less than 10 at base line to 92 at one month [the last sample collected]) and in one patient in the group given 2 mg of CTLA4Ig per kilogram (the end-point titer increased from less than 10 at base line to 148 at six months).

DISCUSSION

The goal of clinical management of rheumatoid arthritis has been to avert disease progression through treatment with disease-modifying antirheumatic drugs such as methotrexate, sulfasalazine, leflunomide, and hydroxychloroquine. More recently, biologic agents targeting specific inflammatory cytokines such as TNF- α and interleukin-1 have been prescribed for patients with an inadequate response to methotrexate. Even with the use of these newer

therapies, many patients do not have a satisfactory response.

CTLA4Ig is the first in a new class of drugs for the treatment of rheumatoid arthritis known as costimulation blockers. Current biologic agents specifically block the activity of single cytokines produced predominantly by macrophages. CTLA4Ig acts earlier in the inflammatory cascade and directly inhibits the activation of T cells and the secondary activation of other important cells, such as macrophages and B cells. Recently, Grohmann et al.³⁸ demonstrated that CTLA4Ig has a direct inhibitory effect on dendritic cells and macrophages. The binding of CTLA4Ig to CD80 and CD86 appears to lead to the production of indoleamine-2,3-dioxygenase by antigen-presenting cells, which is associated with down-regulation of the inflammatory responses of T cells, dendritic cells, and macrophages.^{39,40}

In this six-month trial, CTLA4Ig therapy induced dose-related improvements in the signs and symptoms of rheumatoid arthritis and in physical function. The magnitude of the ACR 20, ACR 50, and

Table 3. Adverse Events.

| Adverse Event | Placebo + Methotrexate (N=119) | CTLA4Ig, 2 mg/kg, + Methotrexate (N=105) | CTLA4Ig, 10 mg/kg, + Methotrexate (N=115) |
|--------------------------------------|--------------------------------------|---|--|
| | number (percent) | | |
| Death | 0 | 0 | 0 |
| Serious adverse events | | | |
| Total | 12 (10.1) | 12 (11.4) | 3 (2.6)* |
| Related to study drug | 1 (0.8) | 4 (3.8) | 0 |
| Most frequent adverse events† | | | |
| Headache | 15 (12.6) | 15 (14.3) | 12 (10.4) |
| Upper respiratory tract infection | 12 (10.1) | 13 (12.4) | 15 (13.0) |
| Musculoskeletal pain | 15 (12.6) | 15 (14.3) | 8 (7.0) |
| Nausea and vomiting | 14 (11.8) | 7 (6.7) | 16 (13.9) |
| Fatigue | 13 (10.9) | 10 (9.5) | 6 (5.2) |
| Cough | 10 (8.4) | 6 (5.7) | 12 (10.4) |
| Diarrhea | 7 (5.9) | 7 (6.7) | 11 (9.6) |
| Pharyngitis | 7 (5.9) | 5 (4.8) | 12 (10.4) |

* P=0.03 for the comparison with the group given placebo plus methotrexate.

† Rheumatoid arthritis was not included.

ACR 70 responses after treatment with 10 mg of CTLA4Ig per kilogram (60.0 percent, 36.5 percent, and 16.5 percent, respectively) was similar to that in patients who received methotrexate after treatment with 10 mg of infliximab per kilogram every four weeks (ACR 20, 58 percent; ACR 50, 26 percent; and ACR 70, 11 percent).⁴¹ Furthermore, the combination of 10 mg of CTLA4Ig per kilogram and methotrexate resulted in clinically meaningful and significant improvements over base-line scores on all eight subscales of the SF-36.

CTLA4Ig was safe and well tolerated, and the rate of discontinuation because of adverse events was no higher than that in the placebo group. In addition, no clinically significant antibody response to CTLA4Ig was detected in either active-treatment group.

In the analysis in which all patients who discontinued the study were considered not to have had a response, the ACR responses remained significant. The low rates of serious adverse effects and discontinuation owing to adverse events, especially with the dose of CTLA4Ig of 10 mg per kilogram, provides further support for its use in the treatment of rheumatoid arthritis. However, longer-term observation of the safety and efficacy of CTLA4Ig in combination with methotrexate, especially with regard to infection, is needed to confirm and extend these encouraging findings.

We found that the combination of CTLA4Ig and methotrexate improved the signs and symptoms of disease, physical function, and quality of life in patients who had active rheumatoid arthritis despite ongoing methotrexate therapy. Clinical responses were dose-dependent. Both the 2 mg per kilogram dose and the 10 mg per kilogram dose of CTLA4Ig were well tolerated, with no antibody response to the fusion protein detected. These data underscore the value of costimulation blockade in the treatment of rheumatoid arthritis. The potential use of CTLA4Ig in the treatment of rheumatoid arthritis and other autoimmune disorders requires further investigation.

Drs. Kremer and Emery report having received grant support from Bristol-Myers Squibb and having served as paid consultants to the company. Drs. Alten, Leon, Dougados, and Moreland report having served as paid consultants to Bristol-Myers Squibb. Drs. Numa, Williams, Becker, and Hagerty are employees of Bristol-Myers Squibb.

APPENDIX

In addition to the authors, the following investigators also participated in the study: A. Bankhurst (Albuquerque, N.M.), A. Beaulieu (Sainte-Foy, Que., Canada), R. Bernstein (Manchester, United Kingdom), C. Birbara (Worcester, Mass.), B. Bockow (Seattle), L. Bridges, Jr. (Birmingham, Ala.), S. Brighton (Pretoria, South Africa), W. Chase (Austin, Tex.), B. Combe (Montpellier, France), B. Diamond (Bronx, N.Y.), G.S. Dolan (Long Beach, Calif.), P. Dura (Endwell, N.Y.), P. Durez (Brussels, Belgium), R. Fleishmann (Dallas), S. Hall (Malvern, Victoria, Australia), A. Hammond (Maidstone, Kent, United Kingdom), P. Hanrahan (South Perth, Western Australia, Australia), B. Haraoui (Montreal), B. Hazleman (Cambridge, United Kingdom), G. Hein (Jena, Germany), R. Honsinger (Los Alamos, N.M.), R. Katz (Chicago), E. Keystone (Toronto), M. Khraishi (St. Johns, Newf., Canada), A. Kivitz (Duncansville, Pa.), S. Klein (Cumberland, Md.), R. Leff (Duluth, Minn.), P. Liang (Sherbrooke, Que., Canada), R. Lies (Wichita, Kans.), J.M. Cocco (Buenos Aires, Argentina), R. McKendry (Ottawa, Ont., Canada), B. Miskin (West Palm Beach, Fla.), R. Moidel (Sellersville, Pa.), M. Molloy (Wilton, Ireland), J. Peller (Rome, Ga.), H. Peter (Freiburg, Germany), D. Pierangelo (Springfield, Mass.), K. Pile (Woodville, South Australia, Australia), A. Rosen (Largo, Fla.), C. Saadeh (Amarillo, Tex.), R. Salach (Titusville, Fla.), J. Sany (Montpellier, France), W. Shergy (Huntsville, Ala.), J. Sibia (Strasbourg, France), W. St. Clair (Durham, N.C.), E. Tindall (Portland, Oreg.), P.L.C.M. Van Riel (Nijmegen, the Netherlands), F. van den Bosch (Ghent, Belgium), A. Weaver (Lincoln, Neb.), and L. Willame (Antwerp, Belgium).

REFERENCES

1. Grassi W, De Angelis R, Lamanna G, Cervini C. The clinical features of rheumatoid arthritis. *Eur J Radiol* 1998;27:Suppl 1: S18-S24.
2. Moreland LW, Heck LW Jr, Sullivan W, Pratt PW, Koopman WJ. New approaches to the therapy of autoimmune diseases: rheumatoid arthritis as a paradigm. *Am J Med Sci* 1993;305:40-51.
3. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. *N Engl J Med* 2000;343:1586-93. [Errata, *N Engl J Med* 2001;344:76, 240.]
4. Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000;343:1594-602.
5. Moreland LW, Baumgartner SW, Schiff MH, et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N Engl J Med* 1997;337:141-7.
6. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998;41: 2196-204.
7. 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.
8. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. *Ann Intern Med* 1999;130:478-86.
9. Stastny P. Association of the B-cell alloantigen DRw4 with rheumatoid arthritis. *N Engl J Med* 1978;298:869-71.
10. Gregersen PK, Silver J, Winchester RJ. The shared epitope hypothesis: an approach to understanding the molecular genetics of susceptibility to rheumatoid arthritis. *Arthritis Rheum* 1987;30:1205-13.
11. van Boxel JA, Paget SA. Predominantly T-cell infiltrate in rheumatoid synovial membranes. *N Engl J Med* 1975;293:517-20.
12. Cush JJ, Lipsky PE. Phenotypic analysis of synovial tissue and peripheral blood lymphocytes isolated from patients with rheumatoid arthritis. *Arthritis Rheum* 1988;31: 1230-8.
13. Balsa A, Dixey J, Sansom DM, Maddison PJ, Hall ND. Differential expression of the costimulatory molecules B7.1 (CD80) and B7.2 (CD86) in rheumatoid synovial tissue. *Br J Rheumatol* 1996;35:33-7.
14. Liu MF, Kohsaka H, Sakurai H, et al. The presence of costimulatory molecules CD86 and CD28 in rheumatoid arthritis synovium. *Arthritis Rheum* 1996;39:110-4.
15. Ranheim EA, Kipps TJ. Elevated expression of CD80 (B7/BB1) and other accessory molecules on synovial fluid mononuclear cell subsets in rheumatoid arthritis. *Arthritis Rheum* 1994;37:1637-46.
16. Sfikakis PP, Via CS. Expression of CD28, CTLA4, CD80, and CD86 molecules in patients with autoimmune rheumatic diseases: implications for immunotherapy. *Clin Immunol Immunopathol* 1997;83:195-8.
17. Thomas R, Quinn C. Functional differentiation of dendritic cells in rheumatoid arthritis: role of CD86 in the synovium. *J Immunol* 1996;156:3074-86.
18. Lafferty KJ, Prowse SJ, Simeonovic CJ, Warren HS. Immunobiology of tissue transplantation: a return to the passenger leukocyte concept. *Annu Rev Immunol* 1983;1: 143-73.
19. Mueller DL, Jenkins MK, Schwartz RH. Clonal expansion versus functional clonal inactivation: a costimulatory signalling pathway determines the outcome of T cell antigen receptor occupancy. *Annu Rev Immunol* 1989;7:445-80.
20. Linsley PS, Brady W, Grosmaire L, Aruffo A, Damle NK, Ledbetter JA. Binding of the B cell activation antigen B7 to CD28 costimulates T cell proliferation and interleukin 2 mRNA accumulation. *J Exp Med* 1991;173:721-30.
21. Koulouva L, Clark EA, Shu G, Dupont B. The CD28 ligand B7/BB1 provides costimulatory signal for alloactivation of CD4+ T cells. *J Exp Med* 1991;173:759-62.
22. Young JW, Koulouva L, Soergel SA, Clark EA, Steinman RM, Dupont B. The B7/BB1 antigen provides one of several costimulatory signals for the activation of CD4+ T lymphocytes by human blood dendritic cells *in vitro*. *J Clin Invest* 1992;90:229-37. [Erratum, *J Clin Invest* 1993;91:1853.]
23. Peach RJ, Bajorath J, Brady W, et al. Complementarity determining region 1 (CDR1)- and CDR3-analogous regions in CTLA-4 and CD28 determine the binding to B7-1. *J Exp Med* 1994;180:2049-58.
24. Linsley PS, Greene JL, Brady W, Bajorath J, Ledbetter JA, Peach R. Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kinetics to CD28 and CTLA-4 receptors. *Immunity* 1994;1:793-801. [Erratum, *Immunity* 1995;2:203a.]
25. Greene JL, Leytze GM, Emswiler J, et al. Covalent dimerization of CD28/CTLA-4 and oligomerization of CD80/CD86 regulates T cell costimulatory interactions. *J Biol Chem* 1996;271:26762-71.
26. Finck B, Linsley PS, Wofsy D. Treatment of murine lupus with CTLA4Ig. *Science* 1994; 256:1225-7.
27. Webb LMC, Walmsley MJ, Feldmann M. Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2. *Eur J Immunol* 1996; 26:2320-8.
28. Lin H, Bolling SF, Linsley PS, et al. Long-term acceptance of major histocompatibility complex mismatched cardiac allografts induced by CTLA4Ig plus donor-specific transfusion. *J Exp Med* 1993;178:1801-6.
29. Moreland LW, Alten R, Van den Bosch F, et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. *Arthritis Rheum* 2002;46:1470-9.
30. Hochberg MC, Chang RW, Dwosh I, Lindsey S, Pincus T, Wolfe F. The American College of Rheumatology 1991 revised criteria for the classification of global functional status in rheumatoid arthritis. *Arthritis Rheum* 1992;35:498-502.
31. Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis: results of two metaanalyses. *Arthritis Rheum* 1990;33:1449-61.
32. 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.
33. Ware JE Jr, Kosinski M, Keller SD. SF-36 physical and mental health summary scales: a user's manual. Boston: Health Assessment Lab, 1994.
34. Ware JE, Kosinski M. SF-36 physical & mental health summary scales: a manual for users of version 1. 2nd ed. Lincoln, R.I.: QualityMetric, 2001.
35. Strand V, Weinblatt M, Keystone E, Teoh L, Firschkoff S, Chartash E. Treatment with adalimumab (D2E7), a fully human anti-TNF monoclonal antibody, improves physical function and health related quality of life (HRQOL) in patients with active rheumatoid arthritis (RA). *Ann Rheum Dis* 2002;61: Suppl I:175. abstract.
36. Samsa G, Edelman D, Rothman ML, Williams GR, Lipscomb J, Matchar D. Determining clinically important differences in health status measures: a general approach with illustration to the Health Utilities Index Mark II. *Pharmacoeconomics* 1999;15:141-55.
37. Marcus R, Peritz E, Gabriel KR. On closed testing procedures with special reference to ordered analysis of variance. *Biometrika* 1976;63:655-60.
38. Grohmann U, Orabona C, Fallarino F, et al. CTLA-4-Ig regulates tryptophan catabolism *in vivo*. *Nat Immunol* 2002;3:1097-101.
39. Mellor AL, Munn DH. Tryptophan catabolism and T-cell tolerance: immunosuppression by starvation? *Immunol Today* 1999;20:469-73.
40. Tian C, Bagley J, Iacomini J. Expression of antigen on mature lymphocytes is required to induce T cell tolerance by gene therapy. *J Immunol* 2002;169:3771-6.
41. 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.

Copyright © 2003 Massachusetts Medical Society.