Janssen Research & Development

**Clinical Study Report Synopsis: 54-Week
Protocol C0168T22**

CNTO312 (Infliximab)

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Summary

Title
A placebo-controlled, double-blinded, randomized clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment (ATTRACT): 54-week report

Objectives
The objectives of this trial were to evaluate the efficacy and safety of chronic treatment with infliximab in combination with methotrexate (MTX) in patients with active rheumatoid arthritis (RA) despite treatment with MTX. The primary objective of the study was to evaluate the efficacy and safety of infliximab treatment in reducing clinical signs and symptoms of RA at 30 weeks following the onset of treatment; the primary objective of the week-54 analyses presented in this report was to evaluate the safety and efficacy of infliximab in preventing structural damage.

Investigators
Multicenter trial (34 sites: 19 US; 3 Canadian; 12 European)

Dates of Studied Period
31 March 1997 to 11 February 1999 (This report presents data and analyses of data through the week-54 evaluation. The additional endpoints at week 102 will be analyzed and reported in future reports.)

Methods

Study Design
This trial was a placebo-controlled, double-blind, randomized study of chronic treatment of RA with infliximab. Four infliximab treatment regimens were evaluated and compared with placebo. All patients continued to receive MTX during the study.

Patient Selection (Main Criteria for Inclusion)
Patients who were eligible for this study were to have been diagnosed with RA according to the American Rheumatism Association (ARA) criteria, and had to have evidence of active disease (6 or more swollen and tender joints plus 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate [ESR] ≥ 28 mm/h, C-reactive protein [CRP] ≥ 20 mg/L) despite treatment with MTX (a stable dose of ≥ 12.5 mg/wk of MTX given orally or parenterally).

Study Agent Administration; Lot Number
Patients in each of the 4 infliximab treatment groups were to receive an infusion at weeks 0, 2, and 6; 2 groups were to receive 3 mg/kg infusions and the other 2 groups were to receive 10 mg/kg infusions. After 6 weeks, treatments were to be continued through 1 year with one of the 3 mg/kg and one of the 10 mg/kg groups receiving infliximab infusions

every 4 weeks (q 4 wks), and the other 3 mg/kg and 10 mg/kg groups receiving infliximab infusions every 8 weeks (q 8 wks), with placebo infusions at the intervening 4-week visits. Patients in the placebo treatment group received placebo infusions at weeks 0, 2, and 6, then every 4 weeks thereafter. Patients were to be offered retreatment during the second year according to the treatment regimen to which they were originally randomly assigned.

Five lots of infliximab (96E06, 97A07, 97A10, 97C07, and 97E08) and 2 lots of placebo (95J14, and 97A05) were used. Only 1 patient was treated with more than 1 lot of study agent (infliximab). In France and, for the latter part of the study in Austria, placebo without human serum albumin (normal saline) was used to comply with their regulations.

Evaluation of Data
Patients' demographic data (age, weight, height, race, and gender), baseline disease characteristics (degree of joint damage [van der Heijde modification of Sharp score], duration of disease, anatomical stage, functional class, history of joint surgery, presence of extra-articular manifestations of RA, rheumatoid factor (RF)-positive status, number of swollen joints, number of tender joints, pain by visual analog scale (VAS), evaluator's and patient's assessment of disease by VAS, health assessment questionnaire (HAQ), CRP, ESR, duration of morning stiffness, fatigue by VAS, and SF-36 Quality of Life Scale), and concomitant medications were summarized and analyzed for treatment group differences.

Evaluation of Efficacy
The primary week-54 endpoint was the prevention of structural damage as measured by the change from baseline in the van der Heijde modification of the Sharp score, which utilizes radiographs of both the hands and feet, at the week-54 follow-up visit. The primary analysis included all patients with complete evaluations at baseline and week 54 in the treatment groups to which they were randomly assigned and compared the change in the van der Heijde modification of the Sharp score from baseline to week 54 among patients in each of the infliximab treatment groups with that of the placebo group (ie, MTX alone). Additional analyses were performed to examine the robustness of the primary analysis for prevention of structural damage at week 54.

Secondary efficacy assessments included number of new erosions, radiologic progression, and structural damage of the hands only; ACR 20% response at week 54, over time, and at a majority of visits; higher degrees of ACR response (ie, 50%, 70%, and 90%); individual ACR component responses over time (ie, the number of tender and swollen joints, HAQ, morning stiffness, fatigue, patient assessment of pain, patient's and evaluator's global assessments, CRP, and ESR); the average degree of clinical improvement over time in the individual ACR components; RF; major clinical indices (ie, clinical remission and major and complete clinical responses); and functional indices (ie, disability and quality of life).

Evaluation of Pharmacokinetics
The pharmacokinetic samples from all patients for whom samples were available were analyzed through week 54. The concentration of free infliximab in serum was measured by using a monoclonal-based enzyme immunoassay (EIA).

Evaluation of Safety
All adverse experiences (AEs), serious adverse experiences (SAEs; including malignancies and deaths), reasonably related AEs and SAEs, and clinically noteworthy events, including infections, infusion reactions, autoimmune diseases, and AEs that led to discontinuation of treatment were summarized by treatment group and WHOART preferred term. Summary statistics for laboratory and vital signs measurements and for the changes from baseline were tabulated by treatment group at each evaluation time.

Statistical Methodology
The primary efficacy analysis included all patients with complete evaluations at baseline and week 54 in the treatment groups to which they were randomly assigned. The change from baseline to week 54 was compared among the treatment groups by using analyses of variance of van der Waerden normal scores. The chi-square test was used to compare the proportion of patients achieving categorical endpoints. If there was a significant overall treatment effect, then comparisons of each of the infliximab treatment groups with the placebo group were performed by using the same test, except for safety endpoints, where pairwise comparisons versus control were performed by using Fisher's exact test. Secondary continuous response parameters were compared by using an analysis of variance on the van der Waerden normal scores. The consistency of treatment benefit was examined by using plots of differences in mean changes from baseline between treatment groups with 95% confidence intervals.

Study Population

Patient Disposition
A total of 428 patients from 34 study sites were enrolled in this trial. Of the 340 patients who were randomly assigned infliximab treatment, 86 were assigned 3 mg/kg q 8 wks, 86 were assigned 3 mg/kg q 4 wks, 87 were assigned 10 mg/kg q 8 wks, and 81 were assigned 10 mg/kg q 4 wks. A total of 88 patients were assigned placebo. The distribution of patients across the treatment groups was well balanced.

Study Population Characteristics
As expected in this study population, the majority of the patients (77.6%) were women, which reflects the overall distribution of RA in men and women in the general population. Most (90.9%) of the 428 patients were white; their ages ranged between 19 and 80 years (median of 53.5 years). There were no significant differences among the groups with respect to demographic characteristics.

Like the demographic characteristics, the baseline disease characteristics were well balanced across all treatment groups. The median duration of disease in the enrolled patients was 8.4 years, and the median number of swollen joints and tender joints at baseline was 20 and 31, respectively. Nearly one-fourth of the study population had undergone joint replacement surgery and approximately one-half of the patients had extensive anatomical destruction (Stage III and IV) and limited functional capacity (Class III and IV) prior to enrollment in the study, thereby demonstrating the severity of the RA in much of the study population. Approximately one-half of the patients in the study population had been on MTX therapy

for 3 or more years and approximately one-third of the total study population had received an estimated cumulative dose of 3 g or more of MTX. A subpopulation of 82 patients had early RA (ie, RA for $\leq$ 3 years' duration).

Efficacy Results

Primary Endpoint

Each of the 4 infliximab treatment regimens (3 and 10 mg/kg; q 4 and q 8 wks), in combination with MTX, prevented structural damage to a statistically significantly greater degree than patients receiving MTX alone ($p < 0.001$). At week 54, the median changes from baseline to week-54 in the van der Heijde modification of the Sharp score were 0.50, 0.00, 0.50, and -0.50 for the 3 mg/kg q 8 wks, 3 mg/kg q 4 wks, 10 mg/kg q 8 wks, and 10 mg/kg q 4 wks treatment groups, respectively, versus 4.00 for the placebo (MTX only) group. This benefit was also evident at the week-30 evaluation and continued after week 30 through week 54.

The conclusions, as well as the statistical significance of the primary endpoint analysis, were not affected by missing x-ray data; potential bias between the 2 radiograph readers; or level of baseline radiographic scores or CRP; and were considered robust according to 7 different sensitivity analyses. Furthermore, each of the 4 infliximab treatment regimens, in combination with MTX, provides a statistically significant prevention of structural joint damage, regardless of whether improvement in signs and symptoms as determined by ACR criteria is observed.

Infliximab-treated patients consistently achieved greater prevention of structural damage at week 54 than patients who received placebo, regardless of treatment regimen, demographic characteristics, geographical location, baseline disease characteristics, or concomitant medication use. Moreover, statistically significant prevention of structural damage was also seen in the subset of patients with early RA (ie, $\leq$ 3 years of disease).

Secondary Endpoints

Each of the 4 infliximab treatment regimens, in combination with MTX, prevented new erosions or reduced erosive damage, prevented or reduced radiologic progression, and reduced disability to a significantly greater degree than placebo.

Moreover, each of the infliximab treatment regimens, in combination with MTX, provided continued reductions in the signs and symptoms of disease activity, as measured by ACR 20% criteria, that were statistically significantly greater than the reductions achieved by patients receiving MTX alone ($p < 0.001$). At week 54, the response rates were 41.9% and 47.7% for the 3 mg/kg dose groups (ie, every 8 and 4 weeks), 58.6% and 59.3% for the 10 mg/kg dose groups (ie, every 8 and 4 weeks), versus 17.0% for the placebo group. Following 54 weeks of treatment, there appeared to be a treatment-dependent effect of infliximab on the clinical response, at least among the lowest treatment regimens.

At week 54, 33.2% of the infliximab-treated patients overall achieved $\geq$ 50% ACR improvement, which was significantly better than placebo (8.6%). This pattern of response

was also seen for the other ACR response categories (ie, $\geq 70\%$ and $\geq 90\%$), but with lower response rates. At the week-54 visit, there were significantly more patients in each of the infliximab treatment groups achieving a $\geq 50\%$ or $\geq 70\%$ responses than in the placebo group ($p < 0.001$).

A greater proportion of patients in the 4 infliximab treatment groups (45.9%) achieved clinical responses at a majority of visits (8 or more of the 14 follow-up visits) than patients who received placebo (12.5%). Furthermore, 51.1% of the patients who received placebo failed to achieve an ACR 20% response even once, compared with only 19.4% for infliximab-treated patients. No (0%) patients in the placebo group achieved an ACR 20% response at all 14 visits, compared with 8.2% of infliximab-treated patients. Compared with those who received placebo alone, patients in each of the infliximab treatment groups attained significantly greater percent improvements from baseline through week 54 for each of the individual ACR components, with the exception of the HAQ in the 3 mg/kg q 8 wks group.

Through week 54, 1.2% to 4.6% of infliximab-treated patients achieved clinical remission, according to the Pinals criteria, compared with 0% of patients in the placebo group. A major clinical response (ie, a 70% ACR improvement for 6 consecutive months) was achieved in 3.5% to 8% of infliximab-treated patients compared with 0% of patients in the placebo group. This difference approached but did not reach statistical significance ($p = 0.094$). Finally, patients treated with infliximab over 54 weeks achieved significant improvements in the ability to reach and grip, as well as in their quality of life according to each of the physical component scores of the SF-36 and, to some extent, mental functioning (ie, vitality and social functioning) scores.

In 82 patients with early RA (less than 3 years), all 4 infliximab treatment regimens, in combination with MTX, prevented structural damage to a statistically significantly greater degree than patients receiving MTX alone ($p \leq 0.020$). At week 54, the median changes from baseline to week-54 in the van der Heijde modification of the Sharp score were -0.50, -0.25, 0.00, and 1.51 for the 3 mg/kg q 8 wks, 3 mg/kg q 4 wks, 10 mg/kg q 8 wks, and 10 mg/kg q 4 wks treatment groups, respectively, versus 7.75 for the placebo group. Moreover, results of the signs and symptoms (ACR 20% response) and disability (HAQ) endpoints for these patients, while not statistically significant because of the small numbers of patients, mirrored those seen in the overall study population.

Pharmacokinetics Results
The pharmacokinetic analyses of the patients in this trial indicated that intravenous weight-adjusted administrations of infliximab yield predictable serum concentrations that are proportional to the dose and are consistent with a primarily intravascular distribution. The consistent prevention of structural damage with the different infliximab treatment regimens was evident despite differences in the serum concentrations of infliximab across the treatment groups. However, there was a relationship between higher infliximab levels and higher degrees of improvement in signs and symptoms as assessed by ACR components.

Safety Results

Overall, 54 weeks of infliximab administration (up to 15 infusions) was well tolerated by the patients in this study; relatively few patients discontinued treatment because of an AE and SAEs were reported at rates no higher than with placebo. Similar to the week-30 results, the most frequent AE for infliximab-treated patients were upper respiratory tract infections. While not expected to be serious, these may require treatment. Infections were more common with infliximab treatment than with placebo, and occurred in more patients at the higher doses (10 mg/kg). Similar results were noted for treated infections; however, very few patients had serious infections. Thus, while infliximab administration might be expected to be associated with an increased incidence of infection, and in particular, with upper respiratory tract infection, such infections are in most cases not serious and resolve either spontaneously or with treatment.

The frequency of infusion reactions was low and such reactions were rarely severe and none were serious. Generally, over 54 weeks, 3.8% of infusions were associated with an infusion reaction. Importantly, infusion reactions were unrelated to cumulative dose received or infusion schedule, and delayed hypersensitivity reactions were not observed. Application site reactions were also notably infrequent (1 of every 329 infliximab infusions).

Malignancies occurred in very few patients; only one additional malignancy, a basal cell carcinoma was observed through week 54. After week 54 through the cut-off date of this report, one additional rectal adenocarcinoma was reported. Repeated infliximab administration does not appear to play a role in enhancing susceptibility to malignancy. The production of autoantibodies was more frequent for infliximab-treated patients than for placebo-treated patients; however, through 54 weeks of treatment, only 1 patient was noted to have an autoimmune (lupus-like) syndrome.

Effects on hepatic and renal function were minimal; mild elevations in AST and ALT were noted in some infliximab-treated patients and, conversely, decreases in WBC and neutrophil counts were also noted, with a trend toward larger changes at the higher doses of infliximab. However, because the changes were generally not sustained or associated with other symptoms, they did not appear to be clinically significant.

Conclusions

In summary, this report presents data through 54 weeks of this Phase III trial of multiple infusions of infliximab in patients with RA who were receiving concomitant MTX. Treatment with infliximab at a regimen as low as 3 mg/kg given at weeks 0, 2, 6, and then every 8 weeks in patients with active RA and an inadequate response to MTX prevented the progression of structural damage and sustained the improvements in the signs and symptoms of the disease. Indeed, patients who were considered nonresponders with respect to achievement of 20% improvement in the ACR criteria had equal benefit from infliximab treatment with respect to the prevention of structural damage compared with those patients who did meet the ACR 20% response criteria. Moreover, treatment at all doses, but especially at 10 mg/kg given at weeks 0, 2, 6, and then every 4 or 8 weeks thereafter was shown to reverse structural damage in some patients, as well as provide additional

reductions in the signs and symptoms of the disease. Furthermore, patients treated with infliximab achieved significant improvement in disability after only 54 weeks of treatment.

All of these findings are particularly important considering the advanced nature of the disease, as indicated by the severity of the anatomical and functional disease present in much of the patient population at the beginning of the study. While a treatment-dependent response, which correlated well with serum infliximab concentrations, was evident for endpoints measuring signs and symptoms of RA, such a relationship associated with radiologic endpoints was less apparent. Moreover, patients with early RA also were equally likely to benefit from infliximab treatment as those patients with more advanced disease. Treatment with infliximab was well tolerated at doses up to 10 mg/kg every 4 weeks, although the incidences of infections were lower in patients who received the 3 mg/kg doses, thereby suggesting that the lower doses may be better tolerated in some patients without substantially affecting efficacy. Given that the lowest incidence of infections was observed with the lower dose groups, clinical therapy should begin with administration of 3 mg/kg every 8 weeks; this dose may be increased up to 10 mg/kg every 8 weeks if the patient has an inadequate response to the initial dose. Thus, infliximab, administered in all 4 treatment regimens, was safe and effective in preventing the structural damage, reducing the signs and symptoms, and improving the disability of patients with active RA despite MTX treatment.

Summary

Title of Study

A placebo-controlled, double-blinded, randomized clinical trial of anti-TNF chimeric monoclonal antibody (cA2; infliximab) in patients with active rheumatoid arthritis despite methotrexate treatment (ATTRACT)

Investigators

This was a multicenter trial at 34 sites. The two independent rheumatologist representatives of the Executive Committee were considered to be the lead investigators: Peter E Lipsky, MD, Southwestern Medical School, ███████, and Professor RN Maini, Kennedy Institute of Rheumatology, █████ England.

Study Site(s)

34 sites: 19 US; 3 Canadian; 12 European

Dates of Study Period

The first patient was enrolled on 31 March 1997; the last patient's last evaluation (excluding long-term safety follow-up evaluations) was performed on 09 March 2000.

Objectives

The purpose of this trial was to evaluate the efficacy and safety of chronic treatment with infliximab in combination with methotrexate (MTX) in patients with active rheumatoid arthritis (RA) despite treatment with MTX. The 3 coprimary objectives of the study were to evaluate the efficacy and safety of infliximab treatment in reducing clinical signs and symptoms of RA at 30 weeks, preventing structural damage at 54 weeks, and improving physical function at 102 weeks following the onset of treatment.

Methods

Study Design

This trial was a placebo-controlled, double-blind, randomized study of chronic treatment of RA with infliximab. Four infliximab treatment regimens were evaluated and compared with placebo. All patients continued to receive MTX during the study.

Patient Selection

Patients who were eligible for this study were to have been diagnosed with RA according to the American Rheumatism Association (ARA) criteria, and had to have evidence of

active disease (6 or more swollen and tender joints plus 2 of the following: morning stiffness ≥ 45 min, erythrocyte sedimentation rate [ESR] ≥ 28 mm/h, C-reactive protein [CRP] ≥ 20 mg/L) despite treatment with MTX (a stable dose of ≥ 12.5 mg/wk of MTX given orally or parenterally).

Study Agent Administration

Patients in each of the 4 infliximab treatment groups were to receive an infusion at weeks 0, 2, and 6; 2 groups were to receive 3 mg/kg infusions and the other 2 groups were to receive 10 mg/kg infusions. After 6 weeks, treatments were to be continued through 1 year with one of the 3 mg/kg and one of the 10 mg/kg groups receiving infliximab infusions every 4 weeks (q 4 wks), and the other 3 mg/kg and 10 mg/kg groups receiving infliximab infusions every 8 weeks (q 8 wks), with placebo infusions at the intervening 4-week visits. Patients in the placebo treatment group received placebo infusions at weeks 0, 2, and 6, then every 4 weeks thereafter. Patients who completed 54 weeks of treatment were offered retreatment during the second year according to the treatment regimen to which they were originally assigned. Following the evaluation of 54-week results, per the recommendation of the Safety Monitoring Committee (07 September 1999), the study was unblinded with regard to placebo versus infliximab treatment (infliximab treatment regimens were not unblinded) and patients in the placebo treatment group were given the opportunity to discontinue study treatment and receive infliximab off study. A total of 89 patients were unblinded at or before the time of the week-102 HAQ evaluation, but 38 of these patients were unblinded during the week-102 visit and it is not known whether the unblinding occurred before or after the week-102 HAQ evaluation. No patients had more than 4 HAQ evaluations performed after the time of unblinding. Thus, the unblinding of patients for ethical reasons was not likely to have substantively impacted the primary analysis at week 102, which was an AUC analysis of HAQ through 102 weeks of treatment.

Through week 102, 2 lots of placebo (95J14, and 97A05) were used. In France, and for the latter part of the study in Austria, placebo without human serum albumin was used to comply with local regulations. Through week 54, 5 lots of infliximab (96E06, 97A07, 97A10, 97C07, and 97E08) were used. In the second year of treatment, each infliximab-treated patient's first infusion was to use the same lot as that used previously. Subsequent infusions in the second year were to use lots 97E08 and 97E09.

Evaluation of Data

For patients who entered the second year of treatment, patients' demographic data (age, weight, height, race, and gender) and baseline disease characteristics (degree of joint damage [van der Heijde modified Sharp score], duration of disease, anatomical stage, functional class, history of joint surgery, presence of extra-articular manifestations of RA, rheumatoid factor [RF]-positive status, number of swollen joints, number of tender joints, pain by visual analog scale [VAS], evaluator's and patient's assessment of disease by VAS, HAQ, CRP, ESR, duration of morning stiffness, fatigue by VAS, and SF-36 Quality of Life Scale), and concomitant medications, were summarized.

Evaluation of Pharmacology

The pharmacokinetic samples from all patients for whom samples were available were analyzed through week 102. The concentration of free infliximab in serum was measured by using a monoclonal-based enzyme immunoassay (EIA) and were summarized over time.

Evaluation of Efficacy

Improvement in physical function was measured as improvement in HAQ averaged over time. In addition, no concurrent worsening in weighted mean SF-36 mental component summary score over the same period (compared with the placebo group) should be observed.

Secondary efficacy assessments included the following endpoints: the change from baseline in the van der Heijde modified Sharp (vdH-S) score at the week-102 follow-up visit; the number of new erosions, radiographic progression, and structural damage of the hands only; American College of Rheumatology (ACR) 20%, 50%, 70%, and 90% responses at week 102 and over time; the average degree of clinical improvement over time in the individual ACR components; RF; and major clinical indices (ie, clinical remission and major and complete clinical responses).

Evaluation of Safety

All adverse experiences (AEs), serious adverse experiences (SAEs; including malignancies and deaths), reasonably related AEs and SAEs, and clinically noteworthy events, including infections, infusion reactions, autoimmune diseases, and AEs leading to discontinuation of treatment were summarized by treatment group and World Health Organization adverse reaction terminology (WHOART) preferred term. Summary statistics for laboratory and vital signs measurements and for the changes from baseline were tabulated by treatment group at each evaluation visit. For patients who had not entered the second year of treatment but continued to have safety follow-up evaluations, information on autoimmune diseases, malignancies, serious infections, and deaths was collected after week 78.

Statistical Methodology

The weighted mean changes from baseline in HAQ scores through week 102 (the primary endpoint) were compared among treatment groups. The primary efficacy analysis included all patients in the treatment groups to which they were randomly assigned. To assess improvement in physical function, the weighted mean changes from baseline through week 102 (ie, improvement averaged over time) for the HAQ and the SF-36 mental component summary score were calculated for each patient as the area under the summary scale versus time curve, adjusted for the duration of observation. The change from baseline in continuous endpoints, such as the HAQ, SF-36, and the vdH-S score at week 102, were compared among the treatment groups using an analysis of variance on van der Waerden normal scores and contrast statements for pairwise comparisons of infliximab treatment versus placebo if the overall test showed a difference among

treatment groups. The chi-square test was used to compare the proportions of patients achieving categorical endpoints. If there was a significant overall treatment effect, then comparisons of each of the infliximab treatment groups with the placebo group were performed by using the same test, except for safety endpoints, where pairwise comparisons versus control were performed by using Fisher's exact test. The consistency of treatment benefit was examined for the primary endpoint in various subgroups by using plots of differences in mean changes from baseline between treatment groups with 95% confidence intervals.

Study Population

A total of 428 patients from 34 study sites were enrolled in this trial between 31 March 1997 and 22 January 1998. Of the 340 patients who were randomly assigned infliximab treatment, 86 were assigned 3 mg/kg q 8 wks, 86 were assigned 3 mg/kg q 4 wks, 87 were assigned 10 mg/kg q 8 wks, and 81 were assigned 10 mg/kg q 4 wks. A total of 88 patients were assigned placebo. Study treatment was initiated in all patients who were randomly assigned a study treatment. The distribution of patients across the treatment groups was well balanced.

The majority of the patients (78%) in this study were women, which reflects the overall distribution of RA in men and women in the general population. In addition, most patients (91%) were white; their ages ranged between 19 and 80 years. There were no significant differences among the treatment groups with respect to demographic characteristics. The baseline disease characteristics of the study population were also well balanced across all treatment groups. The median duration of disease at baseline was 8.4 years and the median numbers of swollen and tender joints at baseline were 20 and 31, respectively. Approximately half of the patients had extensive anatomical destruction (Stage III and IV) and limited functional capacity (Class III and IV) prior to enrollment in the study. Likewise, approximately half of the patients in the study population had been on MTX therapy for 3 or more years and approximately one third of the total study population had received an estimated cumulative dose of 3 g or more of MTX. Conversely, the remaining study population had less advanced RA, with approximately one fifth with RA of ≤ 3 years' duration. Thus, the study population generally mirrored the general patient population by including patients with a broad range of RA severity and disease duration. The subpopulation of patients who completed the first 54 weeks and entered the second year of treatment had baseline characteristics similar to those of the overall patient population, and were as equally well balanced across all treatment groups.

Clinical Pharmacology Results

Pharmacokinetic analyses demonstrated predictable, consistent, and dose-proportional serum concentrations following multiple infusions of 3 or 10 mg/kg of infliximab at 4- or 8-week intervals following the induction regimen at weeks 0, 2, and 6. The postinfusion serum concentrations indicated that infliximab is distributed primarily into the vascular space. Moreover, treatment through 102 weeks provided stable trough serum infliximab concentrations, indicating that any potential effects of antibodies to infliximab were not

interfering with continued therapy. As expected, higher median infliximab concentrations were observed following administration of higher and/or more frequent doses, although there was a range of serum concentrations demonstrated for any given dose group.

Efficacy Results

Primary Week-102 Endpoint

The median improvement in HAQ averaged over time through week 102 was 0.4, 0.4, 0.4, and 0.3 for the 3 mg/kg q 8 wks, 3 mg/kg q 4 wks, 10 mg/kg q 8 wks, and 10 mg/kg q 4 wks treatment groups, respectively, versus 0.1 for the placebo group ($p \leq 0.006$ in pairwise comparisons). The results demonstrated similarly significant improvement in SF-36 physical component summary scores and no worsening through 102 weeks in the mental component summary scores of infliximab-treated patients compared with patients receiving placebo. Thus, improvement in physical function, as defined in regulatory guidances and as prespecified for this study, was demonstrated in patients treated with 3 or 10 mg/kg infliximab every 4 or 8 weeks.

Secondary Endpoints

The results of analyses of radiographic endpoints through week 102 indicated that the median changes from baseline in the total vdH-S score at week 102 were 0.43, 0.50, 1.00, and 0.00 for the 3 mg/kg q 8 wks, 3 mg/kg q 4 wks, 10 mg/kg q 8 wks, and 10 mg/kg q 4 wks treatment groups, respectively, versus 4.25 for the placebo group ($p < 0.001$). Significant benefits were seen in both the erosion and joint space narrowing (JSN) scores, which comprise the total vdH-S score. Patient-level analyses further indicated that significantly more patients in each of the 4 infliximab treatment groups had no major radiographic progression or no worsening in total vdH-S score compared with patients receiving placebo ($p < 0.001$).

As was seen at weeks 30 and 54, all 4 infliximab treatment regimens (3 and 10 mg/kg; q 4 and q 8 wks) in combination with MTX continued to have reductions in the signs and symptoms of disease activity, as measured by ACR 20% criteria, and these were statistically significantly greater than the reductions achieved by patients receiving placebo ($p < 0.001$). At week 102, the ACR 20% response rates were 41.9% and 39.5% for the 3 mg/kg dose groups (ie, every 8 and 4 weeks), 48.3% and 39.5% for the 10 mg/kg dose groups (ie, every 8 and 4 weeks), versus 15.9% for the placebo group ($p < 0.001$). At the week-102 visit, there were significantly more patients in each of the infliximab treatment groups achieving $\geq 50\%$ or $\geq 70\%$ responses than in the placebo group ($p \leq 0.011$).

Through 102 weeks of treatment, significantly greater proportions of patients in each of the infliximab treatment groups (6.2% to 14.9%) than in the placebo group (0%) achieved a major clinical response (ie, a $\geq 70\%$ ACR response for 6 consecutive months; $p \leq 0.018$).

Subgroup Analyses

Analyses of the consistency of benefit across subgroups indicated that there were extremely consistent similarities across all subgroups based on demographic features, geographic location, baseline disease characteristics, and concomitant medications in the differences in improvement in HAQ averaged over time.

Safety Results

Infliximab treatment for up to 102 weeks was safe and well tolerated. Increasing duration of treatment through 102 weeks did not result in increased rates of AEs. Overall, the patterns of AEs seen with increased follow-up were similar to those noted through week 54. The most frequently reported AEs for infliximab-treated patients were upper respiratory tract infection (45.3%), headache (31.6%), nausea (26.3%), sinusitis (22.2%), and rash (20.8%). Despite the average 96.7 weeks of follow-up for all infliximab-treated patients (and 74.9 weeks for patients who received placebo), the incidence of SAEs was similar across all treatment groups (including the placebo group). Overall, more infliximab-treated patients than patients in the placebo group, and more patients treated with 10 mg/kg than 3 mg/kg, had infections that were treated. The incidence of infusion reactions did not increase with repeated infusions or as a result of the potentially long interval in some patients between week 54 and the second year of treatment. Despite gaps in treatment of up to 40 weeks for some patients during the second year, delayed hypersensitivity reactions were not a factor. The actual occurrence rates of overall malignancies, with the possible exception of 1 lymphoma (which is not unexpected given the known increased risk in the RA population), were not different from the expected rates based on the surveillance, epidemiology, and end results (SEER) data in a normal population. While infliximab-treated patients developed more autoantibodies than patients who received placebo, clinical manifestations of autoimmune disease were observed in only 2 infliximab-treated patients. The development of antibodies to infliximab did not appear to substantively affect the benefits or increase the risks associated with infliximab treatment. Finally, clinically noteworthy SAEs relating to hematology (eg, anemia, pancytopenia, and thrombocytopenia) were infrequent in all treatment groups.

Conclusions

The ATTRACT 102-week primary endpoint (ie, improvement in HAQ averaged over time) demonstrated statistically significant and clinically meaningful improvements in each of the 4 infliximab treatment groups compared with the placebo group. No concurrent worsening in the mental component summary score of the SF-36 was also observed. The results were similar to those seen at week 54, indicating that the benefit of infliximab treatment with respect to these endpoints was observable after only 54 weeks of treatment, and that the response was durable and sustained through at least 102 weeks of treatment. Moreover, sensitivity analyses indicated the results were robust. Thus, improvement in physical function, as defined in regulatory guidances and as prespecified in the Operational and Analytical Plan (OAP), was demonstrated in patients treated with

3 or 10 mg/kg infliximab every 4 or 8 weeks, with no notable differences among infliximab treatment groups.

Key analyses of the 102-week data from ATTRACT demonstrated the durability of the responses observed as early as 2 weeks after the first infusion and were consistent with the results observed at both the week-30 and week-54 evaluations. The 102-week results were supportive of previous results and further indicate that infliximab, administered with concomitant MTX therapy, in 3 or 10 mg/kg infusions at weeks 0, 2, 6, and then every 8 weeks thereafter, provides substantial benefits to patients by reducing the signs and symptoms of the disease and inhibiting structural damage, in addition to improving physical function. Moreover, treatment with infliximab was safe and well tolerated through 102 weeks, with no changes in the overall patterns, incidences, and types of AEs observed after 30 or 54 weeks of treatment. Thus, these results demonstrate a favorable benefit/risk profile for improving physical function in patients with active RA despite treatment with MTX.