Janssen Research & Development

Clinical Study Report Synopsis: 54-Week Protocol C0168T21; Phase 3

CNTO312 (Infliximab)

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Summary

Title of Study

A Randomized Double-blind Placebo-controlled Trial of Anti-TNFα Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in the Long-term Treatment of Patients with Moderately to Severely Active Crohn's Disease

Investigators

This was a multicenter trial at 55 sites. The co-lead investigators were [redacted] MD, [redacted] and [redacted], MD, PhD, [redacted] Gastro-enterologie, [redacted] Belgium.

Study Site(s)

Patients were enrolled in 55 study sites: 40 in North America, 13 in Europe, and 2 in Israel.

Dates of Study Period

For this study report which includes the results through the 54-week period, the first patient was enrolled on 26 February 1999 and the last completed visit occurred on 15 March 2001.

Objectives

The primary objective of the study was to determine the efficacy and safety of maintenance treatment with infliximab in providing reductions in the signs and symptoms of Crohn's disease in patients with moderately to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] ≥ 220 and ≤ 400) compared with treatment with a single dose of infliximab.

Methods

Study Design

This was a multicenter, randomized, double-blind, clinical trial of maintenance infliximab treatment compared with a single dose of infliximab in patients with moderately to severely active Crohn's disease. All patients received an initial dose of 5 mg/kg of infliximab at week 0. At week 2, all patients were randomly assigned to 1 of 3 treatment groups to receive blinded study medication. Patients in Group I received placebo at weeks 2 and 6, and then every 8 weeks thereafter; patients in Group II received 5 mg/kg at weeks 2 and 6, and then every 8 weeks thereafter through week 46; and patients in Group III received 5 mg/kg at weeks 2 and 6 and then 10 mg/kg every 8

weeks thereafter through week 46. Patients who did not respond to the initial infusion were randomized separately from those who responded to the initial infusion. Only the responders were analyzed for the primary endpoint. Patients who responded to treatment and subsequently lost their clinical benefit were eligible to cross over to active episodic retreatment at or after week 14. Patients who crossed over to episodic retreatment had an additional 5 mg/kg of infliximab added to their maintenance dose of study medication.

Patient Selection

To be included, patients must have been ≥ 18 years of age with a CDAI of ≥ 220 and ≤ 400. Patients must also have had Crohn's disease for at least 3 months' duration, with colitis, ileitis, or ileocolitis, confirmed by radiography or endoscopy.

Patients were excluded from this study for local manifestations of Crohn's disease (eg, strictures, abscesses, or other disease complications at screening) for which surgery might have been indicated and would confound interpretation of response to treatment. Patients with draining enterocutaneous fistulas or any internal fistulas were not eligible for this protocol. Patients with previously draining fistulas, which had not drained for at least 8 weeks prior to prescreening, were permitted to enroll in the study. Also excluded were patients who, within 3 months prior to prescreening, had surgery for bowel diversion with placement of a stoma.

Study Agent Administration

All study agent was administered via infusion. Multiple lot numbers of infliximab were used in this study.

Evaluation of Data

Evaluation of Pharmacology

Serum concentrations of infliximab were measured over time. Undetectable serum concentrations of infliximab were also noted.

Evaluation of Efficacy

The CDAI was the primary tool for assessing clinical response to infliximab therapy in this study. Observations during endoscopic examinations were used to determine mucosal healing, and the CDEIS (Crohn's Disease Endoscopic Index of Severity) was a tool used for evaluating the findings during endoscopy. Two quality of life assessments, the Inflammatory Bowel Disease Questionnaire (IBDQ), which is a disease-specific quality-of-life assessment, and the SF-36, which is a nondisease-specific quality-of-life assessment, were performed periodically during the study. C-reactive protein (CRP) was used to assess systemic inflammatory activity.

Evaluation of Safety

Safety evaluations included the incidence, type, and severity of adverse events (AEs), and changes in vital signs and laboratory parameters. Evidence of antibodies to infliximab, and the development of antinuclear antibodies (ANA) or antibodies to double-stranded DNA (dsDNA) were determined from samples collected periodically.

Statistical Methodology

After receiving an initial infusion of 5 mg/kg, patients were randomly assigned to one of 3 treatment groups at week 2. The randomization was carried out separately in responders and nonresponders. In patients randomized as responders, the time to loss of response, the primary endpoint at week 54, was compared between patients in Group I (placebo maintenance) and patients in Group II (5 mg/kg infliximab maintenance) and Group III (10 mg/kg infliximab maintenance) combined using a 2-sided log-rank test. Pairwise comparisons were between Groups II and III combined and Group I, between Group II and Group I, and between Group III and Group I.

This study was designed to maintain an overall type I error of 0.05 or less. Because there were 2 coprimary endpoints, the time to loss of response based on the data collected through week 54 was analyzed using an α of 0.04 (2-sided). Nominal 2-sided p-values were reported for secondary analyses.

Study Population

Approximately 170 patients were planned to be enrolled into each of the 3 treatment groups. A total of 580 patients were enrolled. By week 2, 7 patients had discontinued study treatment, and 573 patients were assessed for whether they had achieved a clinical response. For both responders and nonresponders, patients were randomly distributed in an approximately 1:1:1 ratio among 1 of 3 treatment groups: 188 in Group I (placebo maintenance), 192 in Group II (5 mg/kg infliximab maintenance), and 193 in Group III (10 mg/kg infliximab maintenance).

As reported at week 30, for all patients randomized as responders, no significant differences were observed among treatment groups in categories of sex, race, age, or height. A difference in weight, however, was observed among the treatment groups ($p = 0.017$). It appeared that patients in the 5 mg/kg maintenance group had fewer heavier patients than in the other maintenance groups. Within each treatment group, women outnumbered men; overall 61.2% were women and 38.8% men. A majority (94.0%) of the patients were Caucasian, the median age of patients was 35, and the median height was approximately 169 cm.

The demographic characteristics of all randomized patients were comparable to those observed among the responders. Among the demographic characteristics evaluated, again only weight showed a significant difference ($p = 0.011$) among treatment groups. Just as in the responders, it appeared that patients in the 5 mg/kg maintenance group had fewer heavier patients than in the other maintenance groups.

Pharmacology Results

Pharmacokinetic (PK) data showed that the observed serum infliximab concentration is directly proportional to the administered infliximab dose in both maintenance and episodic retreatment. The pre- and postinfusion median serum infliximab concentrations were stable during maintenance treatment at each of the treatment regimens tested from week 22 to week 54. During maintenance use of infliximab at or following week 30, the proportion of patients with preinfusion serum infliximab concentrations < 0.1 μg/mL ranged from approximately 20% to 26% and 11% to 13% in the 5 mg/kg and 10 mg/kg infliximab maintenance groups, respectively. The median serum infliximab concentrations were comparable for patients randomized at week 2 as responders and nonresponders. Patients who were receiving 5 mg/kg of infliximab every 8 weeks and who were administered immunomodulators (with or without corticosteroids) had higher preinfusion (trough) serum infliximab concentrations than patients who were not receiving immunomodulators. Higher serum infliximab concentrations were associated with a greater clinical benefit as measured by reduction in CDAI.

Results from the Biopsy Substudy showed that pharmacodynamic data are consistent with infliximab's ability to distribute to the inflamed mucosal tissue of Crohn's disease patients in amounts sufficient to reduce local levels of the proinflammatory cytokine, TNFα. In addition, the reduction in TNFα levels was associated with a decrease in the macrophage component of the inflammatory cell infiltrate mediated, in part, by the downregulation of ICAM-1 expression on both mononuclear and endothelial cells.

Efficacy Results

Primary Endpoint

For patients receiving infliximab maintenance treatment, the median time to loss of response was greater through week 54 than for patients receiving placebo maintenance. The median time to loss of response through week 54 (ie, the primary endpoint) was 38 weeks and greater than 54 weeks for the 5 mg/kg and 10 mg/kg infliximab maintenance groups, respectively, versus 19 weeks for the placebo maintenance group ($p = 0.002$ and $p < 0.001$ in pairwise comparisons, respectively). Sensitivity analyses indicated these results were robust.

Secondary Endpoints

At weeks 10, 30, and 54, a significantly greater proportion of patients in the infliximab maintenance groups were in clinical response than were patients in the placebo maintenance group ($p = 0.008$, $p < 0.001$, and $p < 0.001$, respectively). At week 54, almost 3 times as many patients were in clinical response in the infliximab maintenance groups compared with the placebo maintenance group (ie, 42.9% versus 15.5%, respectively).

At weeks 10 and 54, a significantly greater proportion of patients in the infliximab maintenance groups ($p = 0.003$ and $p < 0.001$, respectively) were in clinical remission

than were patients in the placebo maintenance group. At week 54, approximately 2.5 times as many patients were in clinical remission in the infliximab maintenance groups compared with the placebo maintenance group (ie, 33.3% versus 13.6%, respectively). Approximately 3 times as many patients in the infliximab maintenance groups were in sustained clinical remission than in the placebo maintenance group. From week 14 to week 54, 21% of patients in the combined infliximab maintenance group were in remission versus 7% in the placebo maintenance group.

Changes in CDAI and CRP all showed rapid and significant improvement in patients receiving infliximab maintenance therapy compared with placebo maintenance. Median CDAI scores were at or near the remission levels for all treatment groups at week 2. Through week 54, median CDAI scores worsened for patients in the placebo maintenance group, but stayed at or near remission levels for the infliximab maintenance groups.

Initial improvement in IBDQ scores was observed in all treatment groups. By week 10, the change from baseline was lower in the placebo maintenance group compared with the combined infliximab maintenance group. This difference was maintained through week 54.

Both the physical and mental components of the SF-36 improved from baseline. The change from baseline in the SF-36 physical component summary scores at weeks 10, 30, and 54 were significantly greater for the combined infliximab maintenance groups than for the placebo maintenance group ($p \leq 0.001$ for all comparisons). Additionally, significant differences in the changes from baseline SF-36 in the mental component summary scores were observed between placebo and infliximab maintenance groups at week 54 ($p = 0.023$).

A greater number of patients, randomized as responders during maintenance treatment, in the combined infliximab maintenance group achieved mucosal healing at weeks 10 and 54 than in the placebo maintenance group (at week 10, 31.1% versus 0.0% and at week 54, 63.2% versus 0.0%).

Among patients randomized as responders and receiving corticosteroids at baseline, a significantly greater proportion of patients in both infliximab maintenance treatment groups received ≤ 10 mg/day (prednisone equivalent) for ≥ 3 months than patients in the placebo maintenance group; approximately 45.5% of the combined infliximab maintenance treatment group versus approximately 17% of the placebo maintenance group were receiving this dose. The median number of weeks that ≤ 10 mg/day (prednisone equivalent) was received for patients in the placebo maintenance group was 5.5 weeks versus 35.5 and 41.0 weeks for patients in the 5 and 10 mg/kg infliximab maintenance groups, respectively.

Among patients randomized as responders and receiving corticosteroids at baseline, approximately 3 times as many patients in the combined infliximab maintenance group had discontinued all corticosteroids and were in clinical remission at week 54 than in the placebo maintenance group (28.1% versus 8.9%, respectively, $p = 0.004$). For the 5 and 10 mg/kg infliximab maintenance groups, these values were 24.1% and 32.1%,

respectively ($p = 0.029$, and $p = 0.002$ for pairwise comparisons with the placebo maintenance group).

In all patients randomized to the placebo maintenance group, after receiving a single infusion of infliximab at week 0, 81.4% of the patients responded at or after week 2. In the infliximab maintenance groups, in which patients received a 3-dose induction regimen followed by maintenance therapy every 8 weeks, 86.1% of the patients responded.

Among the patients who did not respond at week 2, 46.2% of the placebo maintenance group and 62.3% of the combined infliximab maintenance groups subsequently responded after week 2 through week 54.

Subgroup Analyses

Consistency in the 54-week primary endpoint outcome across various subgroups was assessed by looking at treatment comparisons within each subgroup, using odds ratios and 95% confidence intervals. Treatment benefit was observed when patients treated with infliximab maintenance were compared with patients treated with placebo maintenance. Consistent treatment benefit for infliximab maintenance treatment versus placebo maintenance treatment was observed across all subgroups defined by demographic characteristics, geographic location, baseline disease characteristics, and concomitant medication.

Safety Results

Through the end of the study including episodic retreatment, the majority of patients received 8 infusions, with a mean cumulative dose in the placebo maintenance group of 10.7 mg/kg; in the 5 mg/kg infliximab maintenance group, 36.0 mg/kg; and in the 10 mg/kg infliximab maintenance group, 55.5 mg/kg. The average duration of follow-up was slightly longer for the infliximab maintenance groups at 36.4 and 37.6 weeks versus the 35.4 weeks for patients in the placebo maintenance group; this time includes time receiving placebo for the placebo maintenance group.

In general, the safety data through the end of the study were consistent with the trends seen through week 30. The proportion of patients with each AE was only slightly higher despite the longer period of treatment and length of follow-up. For all randomized patients, the body system with the most frequently reported AEs was the gastrointestinal system, with abdominal pain, nausea, (worsening of) Crohn's disease, and vomiting reported most frequently. Gastrointestinal events were reported at similar frequencies across the 3 treatment groups. The individual AEs that were reported in the highest proportions of all randomized patients were headache (28.6%), upper respiratory tract infection (28.3%), abdominal pain (27.6%), nausea (22.5%), arthralgia (17.1%), (worsening of) Crohn's disease (16.6%), pain (16.2%), pharyngitis (15.4%), rash (14.0%), vomiting (13.6%), dizziness and fever (12.9% each), fatigue (12.6%), sinusitis (10.6%), and diarrhea and insomnia (10.1% each). All other AEs were reported in less than 10% of all randomized patients.

The incidence of serious adverse events (SAEs) was 26.5% of all randomized patients, and the most frequent SAEs were in the gastrointestinal system. Further, the incidence of SAEs was similar across the 3 treatment groups and was consistent with that seen through 30 weeks. The most frequent SAE was (worsening of) Crohn's disease, in 8.7% of all patients. Forty-three patients had events of bowel obstruction, stricture, bowel perforation, peritonitis, or abscess: 19 in the placebo maintenance group, 12 in the 5 mg/kg infliximab maintenance group, and 12 in the 10 mg/kg infliximab maintenance group. Three patients died during the study, and 1 patient died after study completion of a SAE diagnosed during the study. Six (1%) patients had a malignancy. The events were distributed across treatment groups with no signs of a dose effect.

Discontinuation of study treatment because of AEs occurred at a rate of 8.7% in patients overall. The rate of discontinuation due to an AE was notably higher in the infliximab maintenance groups (15.0% and 8.3% versus 2.7% for the placebo maintenance group), and was highest in the 5 mg/kg infliximab maintenance group. The events resulting in discontinuation showed a pattern suggesting infusion-related reactions although the overall incidences were low.

Overall, approximately 53.1% of patients had an infection and this incidence was distributed evenly across the treatment groups. Infections in the respiratory system were the most common, reported in 33.2% of all patients, and the most frequently reported infection was upper respiratory tract infection. These were also the only infections that appeared to occur in a clearly dose-responsive manner.

Approximately two thirds of the AEs reported as infections were treated (in 32.5% of all randomized patients) and the most frequent treated infection was upper respiratory tract infection (in 6.5% of all randomized patients). All other AEs recorded as a treated infection occurred in very small numbers of patients and with no discernible pattern. Infections that were serious did not occur with any particular pattern and the only serious infection reported in more than 2 patients overall was abscess, reported in 8 patients (4 in the placebo maintenance group, 3 in the 5 mg/kg maintenance group and 1 in the 10 mg/kg maintenance group). As reported through 30 weeks, 1 patient with a medical history pertinent for a positive PPD upon study entry and who lived with a person who had TB had a diagnosis of TB during the study. No other opportunistic infections for this population were identified through the end of the study.

Overall, less than 5% of infusions had a corresponding infusion reaction and 16.9% of all of the patients had an infusion reaction. The incidence of infusion reactions did not increase in patients given episodic treatment, who had longer intervals between infusions. Six patients had infusion reactions that were serious and 16 patients had infusion reactions that resulted in study agent discontinuation.

Through the end of the study, 14 patients had a cluster of events that could have been a delayed hypersensitivity reaction or serum sickness. However, less than half of the events appeared characteristic of true delayed hypersensitivity reactions. Only 3 of the delayed hypersensitivity reactions were associated with a crossover infusion. No clear risk factor for delayed hypersensitivity reactions can be identified in the timing (eg,

8-week intervals), duration of treatment, or antibody to infliximab production. All patients with delayed hypersensitivity reactions had no detectable antibodies to infliximab through week 54.

A total of 10.8% of randomized patients had neutrophil counts < 1500; the proportions were comparable across all 3 treatment groups. No instances of neutropenia coincident with a serious infection were identified, and no patients discontinued study treatment because of neutropenia or infection. Four (0.7%) patients, all in the 10 mg/kg maintenance group, had markedly abnormal platelet counts ($\leq 75 \times 10^9$/L).

For markedly abnormal clinical chemistry measurements, only those for transaminases occurred in substantial proportions of patients. For patients with ALT ≥ 3X upper limit of normal, there appeared to be a dose effect, with 8.3% of patients in the 10 mg/kg infliximab maintenance group having a markedly abnormal result. No consistent dose effect was observed for markedly abnormal AST results, which were less frequent than the respective ALT results.

Of the patients who were newly positive for ANA and anti-dsDNA antibodies, there were a total of 55.7% and 32.8%, respectively, in the 5 mg/kg infliximab maintenance group and 57.2% and 35.0%, respectively, in the 10 mg/kg infliximab maintenance group compared with 34.8% and 10.6%, respectively, in the placebo maintenance group. As reported through week 30, 1 patient was reported by the investigator as having LE syndrome; there was 1 additional patient that was considered by the Sponsor to have a possible lupus-like syndrome. Thus, the occurrence of autoimmune disorders was infrequent despite a fairly high proportion of patients developing positive ANA and anti-dsDNA.

Across all treatment groups, there were 64 (14.5%) of 442 patients evaluated with antibodies to infliximab, as assessed through week 54. Although there appeared to be a higher incidence of antibodies to infliximab in the placebo maintenance group, the study design and assay characteristics created a bias toward detection of antibodies to infliximab in the treatment group that received only a single infliximab infusion followed by placebo maintenance treatment. The 3-dose induction regimen followed by maintenance therapy resulted in a significantly lower frequency of antibodies to infliximab than a single dose induction regimen followed by episodic retreatment.

Conclusions

In patients with moderately to severely active Crohn's disease, infliximab, given as a 5 mg/kg or 10 mg/kg maintenance treatment regimen every 8 weeks, when compared with a single dose regimen of 5 mg/kg:

- Increases the time to loss of response.
- Maintains a greater proportion of patients in remission for a longer period of time.

- Enables a greater proportion of patients to reduce or even discontinue corticosteroids administered for the treatment of Crohn's disease.
- Heals intestinal mucosa in a greater proportion of patients.
- Provides a more sustained improvement in quality of life.
- Is safe and well tolerated for up to 54 weeks in patients with moderately to severely active Crohn's disease.