

Janssen Research & Development

Clinical Study Report Protocol C0168T26; Phase 3

CNTO312 (Infliximab)

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Summary

Title of Study

A Randomized, Double-blind, Placebo-controlled Trial of Anti-TNF α Chimeric Monoclonal Antibody (Infliximab, REMICADE®) in the Long-term Treatment of Patients with Fistulizing Crohn's Disease.

Investigators

This was a multicenter study conducted at 45 sites. The co-lead investigators were [REDACTED] MD, [REDACTED], MD, PhD, [REDACTED], The Netherlands.

Study Site(s)

Patients were enrolled in 45 study sites: 34 in North America, 9 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 21 January 2000 and the last completed visit occurred on 17 October 2001.

Objectives

The primary objective of the study was to determine the efficacy and safety of maintenance dosing with infliximab in reducing the number of draining fistulas compared with treatment with a 3-dose induction regimen of infliximab only.

The highest ranked secondary objective of the study was to evaluate the effectiveness of infliximab to induce complete fistula response (no draining fistulas). Additional secondary objectives were to evaluate the effectiveness of infliximab through analyses of, Crohn's Disease Activity Index (CDAI), C-reactive protein (CRP), Inflammatory Bowel Disease Questionnaire (IBDQ), and 36-item short form health survey (SF-36).

Methods

Study Design

This study was a multi-site, randomized, double-blind, placebo-controlled clinical study of maintenance infliximab treatment in patients with fistulizing Crohn's disease. All patients received an initial dose of 5 mg/kg of infliximab at weeks 0, 2, and 6. At week 14, all patients were randomized to 1 of 2 treatment groups to receive blinded study

medication (placebo or 5 mg/kg infliximab). The first blinded infusion was administered at week 14, and additional blinded infusions were administered every 8 weeks through week 46. A fistula response was defined as a $\geq 50\%$ reduction from baseline in the number of draining fistulas. A patient was classified as a responder if fistula response was observed at both weeks 10 and 14. Otherwise, patients were classified as nonresponders. Responders and nonresponders were randomized separately. Patients who responded to treatment and subsequently lost their fistula response were eligible to cross over to treatment with infliximab at 5 mg/kg, if receiving placebo, or to a higher dose of infliximab (10 mg/kg), if receiving infliximab, at either a regularly scheduled visit or an unscheduled visit.

Patient Selection

To be included, patients must have been ≥ 18 years of age with single or multiple draining fistulas, including enterocutaneous and rectovaginal fistulas, of at least 3 months duration (the 3 months immediately prior to screening visit). All fistulas should have been separate and distinctly identifiable. Patients must also have had Crohn's disease of 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 such as strictures, abscesses, or other disease complications for which surgery might be indicated (conditions possibly confounding the evaluation of benefit from infliximab treatment). If an abscess was present, the abscess should have been drained prior to screening, with at least 3 weeks between drainage and screening. Diagnosis of an abscess was determined by physician's clinical examination. 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 lots of infliximab were used in this study.

Evaluation of Data

Evaluation of Pharmacology

Concentrations of infliximab were summarized by treatment group and time. Numbers of patients with undetectable serum concentrations were also summarized by treatment group and time.

Evaluation of Efficacy

Closure of enterocutaneous fistulas was assessed by the absence of drainage despite gentle compression. Closure of rectovaginal fistulas was assessed by physical exam or by history (passage of fecal material, or flatus). At selected sites in the United States (US) and Europe, photographs of fistulas were taken to provide documentation of

healing. The CDAI was also utilized for assessing general fistula response to infliximab therapy. Two quality of life assessments, the 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.

Evaluation of Safety

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

Statistical Methodology

Simple descriptive statistics, such as mean, median, standard deviation, interquartile range, minimum, and maximum for continuous variables, and counts and percentages for categorical variables were used to summarize most data. For endpoints defined by time to an event, Life Table methods were employed and the log-rank test was used for comparisons between treatment groups. Analyses suitable for categorical data (ie, chi-square tests, logistic regression) were used to compare the proportion of patients achieving some endpoint (eg, the proportion of patients responding). Fisher's exact test was used in analyses of safety data. Continuous response parameters were compared by using an analysis of variance on the van der Waerden normal scores. All statistical tests were performed 2-sided. In addition to statistical analyses, graphical data displays (eg, box plots) and patient listings were used to summarize the data. When applicable, nominal 2-sided p-values were reported for secondary and safety analyses.

Patients' demographic data, smoking history, baseline disease characteristics (ie, duration of disease, involved intestinal areas, previous segmental resections, abdominal mass, extra-intestinal manifestation, other Crohn's disease-related gastrointestinal surgery, number of draining fistulas, CDAI, IBDQ, CRP, and SF-36), and concomitant medications at baseline were examined by treatment group. The baseline measurement was defined as the closest measurement taken prior to the week-0 infusion or at the time of the week-0 visit.

Study Population

A total of 306 patients were enrolled in the study. By week 14, 24 patients had discontinued study treatment, and 282 patients were assessed for a fistula response. For both responders and nonresponders, patients were randomly distributed in an approximately 1:1 ratio between the 2 treatment groups: 143 in Group I (placebo maintenance) and 139 in Group II (5 mg/kg infliximab maintenance).

For all patients randomized as responders, no significant differences were observed between treatment groups in sex, race, age, or height. A majority (95.4%) of the patients were Caucasian, the median age of patients was 37, and the median height was 171 cm.

The demographic characteristics of all randomized patients were comparable to those observed among the responders.

Pharmacology Results

Pharmacokinetic (PK) data showed that the observed serum infliximab concentration was directly proportional to the administered infliximab dose for patients receiving maintenance infusions. The preinfusion concentrations for both treatment groups were similar through week 14. In general, the median preinfusion serum infliximab concentration was stable in each treatment group from week 30 to week 46. From week 30 onward, the median pre- and postinfusion concentrations of infliximab remained stable in the 5 mg/kg maintenance group but remained below the detection limit in the placebo maintenance group (ie, < 0.6 µg/mL), reflecting that no additional infliximab infusions were given after the week-6 infusion. During maintenance use of infliximab at or following week 30, the proportion of patients with preinfusion serum infliximab concentrations < 0.6 µg/mL ranged from approximately 12% to 23% in the 5 mg/kg infliximab maintenance group. The preinfusion infliximab concentration was reproducibly observed (1.3 to 1.8 µg/mL) with subsequent 5 mg/kg infliximab maintenance infusions from week 30 through week 54.

Efficacy Results

Primary Endpoint

In patients with fistulizing Crohn's disease, 5 mg/kg infliximab infusions administered at weeks 0, 2, 6 and every 8 weeks thereafter provided substantially greater benefit than the 3-dose induction regimen alone. The time to loss of response for patients receiving 5 mg/kg infliximab maintenance treatment was significantly longer than for patients receiving placebo maintenance ($p < 0.001$). The median time from randomization at week 14 to loss of response was 14 weeks for the placebo maintenance group, and was greater than 40 weeks for the 5 mg/kg infliximab maintenance group (never reached by the end of the study).

Secondary Endpoints

Secondary endpoints based on number of draining fistulas included fistula response by visit, complete fistula response (ie, absence of draining fistulas), fistula response confirmed over a period of at least 4 weeks, delayed fistula response, fistula response at weeks 22 and 54 and every week from week 22 to 54, fistula response to treatment with increased infliximab dose, reduction from baseline in the number of draining fistulas, duration of closure for fistulas draining at baseline, and number of draining fistulas newly developed during the study.

The percentage of patients who achieved a fistula response in the 5 mg/kg infliximab maintenance group was nearly twice that in the placebo group at week 30 (63.5% versus 32.7%; $p < 0.001$) and week 54 (46.2% versus 23.5%; $p = 0.001$). The percentage of patients who attained complete fistula response was greater in the 5 mg/kg infliximab

maintenance group compared with the placebo maintenance group beginning at week 22, after patients in the placebo maintenance group had their first placebo infusion. A difference was observed between the groups both at week 30 (47.9% of patients in the 5 mg/kg infliximab maintenance group versus 26.5% in the placebo maintenance group achieved complete fistula response; $p = 0.002$) and at week 54 (36.3% of patients in 5 mg/kg infliximab maintenance group versus 19.4% in the placebo maintenance group achieved complete fistula response; $p = 0.009$).

Of the patients who were not in fistula response at week 10 or 14, 18.4% in the 5 mg/kg infliximab maintenance group subsequently achieved fistula response compared with 10.0% in the placebo maintenance group.

The percentages of patients in fistula response and complete fistula response both at weeks 22 and 54 and at every visit from week 22 through week 54 were higher in the 5 mg/kg infliximab maintenance group compared with the placebo maintenance group. The majority of patients in fistula response at every visit from week 22 through week 54 were in complete fistula response over that period. More patients in the placebo maintenance group as in the 5 mg/kg infliximab maintenance group crossed over to treatment with increased dose. Similar percentages of patients who crossed over then attained fistula response in the 2 treatment groups (57.1% in 5 mg/kg infliximab maintenance group and 61.0% in placebo maintenance group). Therefore, in patients who lost response, treatment with increased dose tended to re-establish fistula response.

The median duration of fistula closure in the 5 mg/kg infliximab maintenance group (40 weeks with an average of 46 weeks follow-up) was almost twice that in the placebo maintenance group (23 weeks with an average of 40 weeks follow-up). The number of patients who developed newly draining fistulas was smaller in the 5 mg/kg infliximab maintenance group than in the placebo maintenance group, as were the number of newly draining fistulas; 14 patients had 17 new fistulas in the 5 mg/kg infliximab maintenance group and 19 patients had 24 new fistulas in the placebo maintenance group.

Among other secondary endpoints, CDAI improved from baseline to week 14 in both treatment groups (-54 points; $p = 0.768$). However, at week 30, the 5 mg/kg maintenance group showed greater improvement from baseline compared with the placebo maintenance group ($p = 0.004$). This difference between the groups was maintained at every visit through week 54 ($p = 0.038$).

During the 5 mg/kg infliximab induction phase, median IBDQ scores improved from baseline ($p < 0.001$ at weeks 2, 10, and 14). At week 30 and week 54, the change from baseline in IBDQ score was higher in the 5 mg/kg infliximab maintenance group than in the placebo maintenance group. The mean numbers of hospitalizations, surgeries/procedures, and physician visits were lower in the 5 mg/kg infliximab maintenance group compared with the placebo maintenance group.

Subgroup Analyses

Consistent benefits of infliximab maintenance treatment in the proportion of patients in fistula response at week 54 were observed across all subgroups.

Safety Results

Through the end of the study, the average number of infusions per patient was 7.4, with a median cumulative dose of 40.0 mg/kg of infliximab in the 5 mg/kg infliximab maintenance group, and 15.1 mg/kg of infliximab in the placebo maintenance group. The average weeks of treatment was slightly longer for the 5 mg/kg infliximab maintenance group at 42.1 weeks compared with 39.3 weeks for patients in the placebo maintenance group.

No patients died nor were any malignancies reported in patients during this study.

For all randomized patients, 89.1% of patients in the 5 mg/kg infliximab maintenance group and 92.4% of patients in the placebo maintenance group reported an AE. The body system with the most frequently reported AEs was the gastrointestinal system. The incidence of (worsening of) Crohn's disease was notably lower in the 5 mg/kg infliximab maintenance group than in the placebo maintenance group. The majority of the remaining notable AEs were associated with allergic or infusion reactions. Overall, no difference in the incidence of events was observed between the 2 groups.

During maintenance treatment, the distribution of AEs was similar to that observed for all randomized patients during the entire trial. For all randomized patients, events in the system-organ class of skin and appendages disorders were the events most often judged to be related to study agent, and rash was the AE most often reported as reasonably related. No notable difference between treatment groups was observed in the proportions of patients with any particular type of reasonably related events.

The incidence of serious adverse events (SAEs) for all randomized patients was generally low and the most frequent SAEs were in the gastrointestinal system. The incidence of SAEs was lower in the 5 mg/kg infliximab maintenance group (13.8%) compared with the placebo treatment group (22.9%). The most frequent SAE was (worsening of) Crohn's disease, in 6.4% of all patients. Discontinuation due to AEs occurred at a low rate. A total of 3.6% of patients in the 5 mg/kg infliximab maintenance and 8.3% of patients in the placebo maintenance groups discontinued study infusions because of an AE.

Overall, 49.3% of all randomized patients had an infection. The most frequently reported infection was upper respiratory tract infection, reported in 14.9% of all patients. Among all randomized patients, 4.6% (4 patients in the 5 mg/kg infliximab maintenance group and 9 patients in the placebo maintenance group) had a serious infection.

No difference was observed between the 5 mg/kg maintenance and placebo maintenance groups in the development of 1 or more newly developed fistula-related abscesses, either

during maintenance treatment or following treatment with increased dose. Of the 42 newly developed abscesses observed during the study, 7 were evaluated as serious infections.

During maintenance treatment, > 3 times as many patients receiving infliximab infusions had an infusion reaction compared with patients receiving placebo infusions. The incidence of infusion reactions following crossover to treatment with an increased dose was highest in the placebo maintenance group. A total of 10 infusion reactions were serious, severe, or resulted in discontinuation of study agent. Infusion reactions that resulted in the discontinuation of study agent occurred in patients in both the 5 mg/kg infliximab maintenance and in the placebo maintenance groups.

Through the end of the study, 5 patients had a cluster of events that could have been a delayed hypersensitivity reaction or serum sickness; only 4, however, seemed to qualify as possible true delayed hypersensitivity reactions. The fifth patient had a reaction following the second placebo infusion. Only 1 of the patients had events associated with a crossover infusion in the placebo maintenance group. Three of the events led to discontinuation of study treatment.

The occurrence of autoimmune disorders was infrequent despite a fairly high proportion of patients developing positive ANA and anti-dsDNA. Across both treatment groups, the incidence of antibodies to infliximab was 17.1% of patients. The 3-dose induction regimen followed by maintenance therapy resulted in a lower frequency of antibodies to infliximab than the 3-dose induction regimen followed by placebo maintenance with or without crossover infusions to an increased dose of infliximab. Antibodies to infliximab were associated with a 2- to 3-fold higher risk of infusion reactions. The induction of antibodies to infliximab did not appear to affect the proportion of patients that achieved a fistula response or complete fistula response.

Conclusions

In patients with fistulizing Crohn's disease, infliximab, given as a 5 mg/kg maintenance treatment regimen every 8 weeks, when compared with a 3-dose induction regimen of 5 mg/kg:

- Increased the time to loss of fistula response.
- Enabled a greater proportion of patients to achieve and maintain fistula closure.
- Enabled more than half of the patients with a sustained fistula response to maintain complete fistula response.
- Provided a greater improvement from baseline in both CDAI and IBDQ.
- Was associated with substantially fewer hospitalizations and surgeries/procedures.

Regardless of treatment group, of those patients who responded and subsequently lost fistula response, the majority re-established fistula response following treatment with increased dose.

In patients with fistulizing Crohn's disease, maintenance treatment with infliximab was well tolerated.