Janssen Research & Development

Clinical Study Report Synopsis
Protocol C0168T20; Phase 3

CNTO312 (Infliximab)

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Summary

Title
A Placebo-Controlled, Repeated-Dose Study of Anti-TNF Chimeric Monoclonal Antibody (cA2) in the Treatment of Patients with Enterocutaneous Fistulae as a Complication of Crohn's Disease.

Investigator/Sites
A total of 12 study sites, 7 study sites in the United States and 5 study sites in Europe, enrolled patients in this clinical trial.

Dates of Study
Patients were enrolled in the study from 30 May 1996 until 1 October 1996. The last clinical evaluation (week 26) took place on 31 March 1997.

Clinical Phase
Phase III

Objectives
To evaluate in a double-blind study the efficacy and safety of cA2 compared with placebo in closure of enterocutaneous fistulae in patients with Crohn's disease.

Methodology
Patients who met the inclusion/exclusion criteria and gave written informed consent were randomized to 1 of 3 treatment groups using an adaptive stratified design with investigational site and number of fistulae (1 or >1) as the strata. Patients received 3 infusions of 10 mg/kg cA2, 5 mg/kg cA2 or placebo at weeks 0, 2 and 6.

Following the week 0 infusion of study medication, clinical and/or laboratory evaluations were performed at 2, 6, 10, 14 and 18 weeks. Patients who responded to treatment at weeks 14 and 18 returned for efficacy evaluations at weeks 22 and 26 (or earlier in case of worsening of disease). At weeks 26 and 34, all patients returned for a blood draw to measure human antichimeric antibody (HACA) responses.

Number of Patients
94 patients (50 women and 44 men)

Diagnosis and Eligibility Criteria
The study population consisted of men and women 18 to 63 years of age. Patients in the study were to have Crohn's disease with, as a complication, a single or multiple draining enterocutaneous (including perianal) fistula(e) of at least 3 months' duration.

Dosage and Administration

A total of 94 patients was randomized to 1 of 3 treatment groups:

10 mg/kg	32 patients	Infusion of 10 mg/kg cA2 at weeks 0, 2 and 6
5 mg/kg	31 patients	Infusion of 5 mg/kg cA2 at weeks 0, 2 and 6
placebo	31 patients	Infusion of placebo at weeks 0, 2 and 6

A single placebo lot (95L14) and a single cA2 lot (95K06) were used.

Duration of Treatment

A total of 6 patients (6.4%; 4 placebo patients, one 5 mg/kg patient and one 10 mg/kg patient) did not receive their last (third) infusion. The reasons for discontinuation of treatment were lack of efficacy (3 placebo patients), administrative (1 placebo patient), withdrawal of consent (5 mg/kg patient) and an adverse experience (10 mg/kg patient). None of the cA2 infusions given were interrupted or discontinued early. The duration of cA2 infusions ranged from 1.0 hours to 2.6 hours, with the exception of one 5 mg/kg infusion of 0.5 hour.

Criteria for Evaluation

Serum cA2 Concentration (Pharmacokinetics)

Serum concentration of cA2 was determined by a monoclonal antibody based enzyme immunoassay (EIA) method. This assay was capable of detecting a serum cA2 concentration of at least 0.10 μg/mL.

Efficacy Data

The primary efficacy response was a $\geq$50% reduction from baseline in the number of draining fistulae for at least 2 consecutive evaluation visits (i.e., at least 1 month). This response could not be accompanied by an initiation and/or increase in antibiotics, aminosalicylates, corticosteroids or immunomodulatory agents or a surgery related to Crohn's disease. If a patient had only one draining fistula at baseline, response occurred when that fistula was closed for at least 2 consecutive evaluations. A fistula was considered to be closed when it no longer drained with gentle compression.

Secondary efficacy parameters included: complete response (all fistulae closed); onset of response; duration of response; response over time; fistulae closure over time; patient's global disease assessment; Crohn's disease activity index (CDAI); components of the CDAI; and perianal disease activity index (PDAI).

Safety

The safety of cA2 treatment was examined by evaluation of adverse events and by evaluating serial measurements of laboratory parameters and vital signs. Serial serum samples were collected for detection of HACA against cA2 and to determine the incidence of antinuclear antibodies (ANA)/anti double-stranded DNA antibodies (anti-dsDNA). HACA was measured using a double-antigen EIA, ANA was tested using immunofluorescence techniques (IFT) on Hep2 cells, and anti-dsDNA was tested using IFT on *Crithidia luciliae* and the Farr method.

Statistical Methods

The primary endpoint analysis was performed using the intention to treat principle. The primary analysis was performed in 2 stages. The Mantel-Haenszel chi-square test for a linear association in the proportion of patients achieving the primary endpoint was performed. If this test was significant at an alpha level of 0.05 (two-sided), Fisher's exact test was used to compare the proportion of patients achieving the primary endpoint in each of the cA2 treatment groups with the placebo group at an alpha level of 0.05 (two-sided).

Summary of Results and Conclusions

Clinical Pharmacology

The cA2 serum concentration was dose-proportional with detectable concentrations of cA2 ($\geq$0.1μg/mL) observed through 18 weeks in the majority of the patients.

Efficacy Results

In summary, the observations were as follows:

- Thirty-nine of the 63 cA2-treated patients (61.9%) achieved the primary endpoint (a $\geq$50% reduction in draining fistulae for at least 2 consecutive visits [i.e., 1 month]) compared to 8 of the 31 placebo treated patients (25.8%, p = 0.002). Patients treated with 5 mg/kg cA2 tended to show a greater response rate (67.7%, p = 0.002 vs placebo) compared with patients treated with 10 mg/kg cA2 (56.3%, p = 0.021 vs placebo).

- A complete response (absence of any draining fistulae) over 2 consecutive visits was demonstrated in 46.0% of the cA2-treated patients (almost 75% of the patients achieving the primary endpoint) compared to 12.9% of the placebo-treated patients (p = 0.001).

- The median time to onset of response for both the 5 mg/kg and 10 mg/kg dose groups was 14 days compared to 42 days for the placebo group.

- The duration of response as measured by the maximum number of consecutive visits at which the patient achieved a $\geq$50% reduction from baseline in the number of draining fistulae was significantly more for the cA2-treated patients (a higher proportion of patients with a higher number of consecutive visits) than for the placebo-treated patients (p = 0.019).

- For the other efficacy parameters, including global disease assessment, CDAI and PDAI, a consistent clinical benefit following cA2 treatment was observed.

Safety Results

Treatment with 3 infusions of 5 mg/kg cA2 or 10 mg/kg cA2 was well tolerated. The incidence of patients with 1 or more adverse experiences in the 5 mg/kg cA2 dose group did not differ from that in the placebo group (64.5% in both groups) but was higher in the 10 mg/kg cA2 patients (84.4%). Most adverse experiences were mild or moderate in

intensity. Ten patients (3 each in the placebo and 5 mg/kg dose groups and 4 in the 10 mg/kg dose group) developed one or more infections that required antibiotic therapy. The incidence of reasonably-related adverse experiences did not differ substantially among the 3 treatment groups (placebo, 45.2%; 5 mg/kg cA2, 48.4%; 10 mg/kg cA2, 53.1%).

No deaths were reported during the trial period. Serious adverse experiences were reported in 5 (7.9%) of the 63 cA2-treated patients and none (0.0%) of the 31 placebo-treated patients. Only 3 of these adverse experiences, all in 10 mg/kg cA2-treated patients, were considered by the investigator to be possibly related to treatment (pneumonia, furunculosis, and an abscess). No clinically significant abnormalities occurred in routine blood chemistries, urinalysis or hematologic parameters. In general, the changes in routine laboratory measurements were mild and transient, with most values returning to within the normal range. Double-stranded DNA antibodies were observed following cA2 treatment in 12.7% of the patients, with only one patient (1.6%) testing positive at the last evaluation. No clinical symptoms suggestive of lupus were observed. Of the 50 cA2-treated patients who could be evaluated for HACA, 3 (6.0%) were positive for HACA.