

A Phase I Study Assessing the Safety, Clinical Response, and Pharmacokinetics of an Experimental Infliximab Formulation for Subcutaneous or Intramuscular Administration in Patients with Rheumatoid Arthritis

RENÉ WESTHOVENS, FRÉDÉRIC HOUSSIAU, JOHAN JOLY, DANIEL E. EVERITT, ESTHER BOUMAN-THIO, YAOWEI ZHU, DEBORAH SISCO, BART van HARTINGSVELDT, MARY ANN MASCELLI, MARTIN A. GRAHAM, and PATRICK DUREZ

ABSTRACT. Objective. To assess safety, clinical response, and pharmacokinetics of subcutaneous (SC) and intramuscular (IM) doses of an experimental formulation of infliximab [including experimental SC doses following administration of commercially-formulated intravenous (IV) infliximab] in patients with rheumatoid arthritis (RA) refractory to methotrexate.

Methods. In this randomized, open-label, 3-stage design, 43 subjects were enrolled in 7 dose groups. In Stage I, 15 subjects received single SC doses of 0.5, 1.5, or 3.0 mg/kg. In Stage II, 21 subjects received one of 3 regimens: 100 mg SC every 2 weeks (3 injections); 3 mg/kg commercially-formulated IV infliximab every 2 weeks (2 infusions) followed by 100 mg SC every 2 weeks (3 injections); or 100 mg IM every 2 weeks (3 injections). In Stage III, 7 subjects received 100 mg SC every 4 weeks (3 injections).

Results. No treatment-related serious adverse events were observed, and there were no serious injection site reactions. A low-titer infliximab antibody response was detected in 27% of subjects receiving single SC doses, 5% receiving multiple SC doses, and 43% receiving IM doses. SC administration yielded roughly dose-proportional increases in C_{max} and AUC. American College of Rheumatology 20% response (ACR20) was achieved 2 weeks after the last injection by 86.7% of subjects receiving single SC doses, 85.7% receiving SC doses every 2 weeks, 85.7% receiving both IV and SC doses, 57.1% receiving multiple IM doses, and 80.0% receiving SC doses every 4 weeks.

Conclusion. SC and IM treatment with this experimental infliximab formulation was well tolerated and was associated with a favorable ACR response. (First Release April 1 2006; J Rheumatol 2006;33:847–53)

Key Indexing Terms:

RHEUMATOID ARTHRITIS SUBCUTANEOUS INTRAMUSCULAR INFlixIMAB

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder of unknown etiology that afflicts roughly 1% of the population¹ and is associated with impaired physical

function, progressive disability, and poor quality of life. Tumor necrosis factor- α (TNF- α) is a key cytokine in the pathogenesis of RA; successful treatment of the signs, symptoms, and radiological progression of RA has been demonstrated with 3 TNF-blocking agents: the monoclonal antibodies infliximab and adalimumab and the soluble receptor fusion protein etanercept²⁻⁴.

The anti-TNF- α agent infliximab (Remicade[®]) is a recombinant immunoglobulin G1- κ (IgG1- κ) human-murine chimeric monoclonal antibody that specifically and potently binds and neutralizes the soluble TNF- α homotrimer and its membrane-bound precursor. This high-affinity binding prevents the interaction of TNF- α with its cellular receptors, attenuating inflammatory and other deleterious effects related to TNF overproduction⁵. Infliximab is approved in combination with methotrexate (MTX) for the treatment of RA, and is commercially formulated for intravenous (IV) administration at a recommended initial dosing regimen of 3 mg/kg given at 8-week intervals.

In addition to physician judgment, factors related to patient

From the Rheumatology Department, University Hospitals KU Leuven, Leuven, Belgium; Rheumatology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium; Johnson & Johnson Pharmaceutical Research and Development, LLC, Springhouse, Pennsylvania, USA; Centocor, Inc., Malvern, Pennsylvania, USA; Centocor, BV, Leiden, The Netherlands; and PKPD Inc., Philadelphia, Pennsylvania, USA.

Supported by Centocor, Inc.

R. Westhovens, MD, PhD, Professor, Rheumatology Department, KU Leuven; F. Houssiau, MD, PhD, Professor, Rheumatology Department, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain; J. Joly, RN, Department of Rheumatology, KU Leuven; D.E. Everitt, MD; E. Bouman-Thio, MD; Y. Zhu, PhD; D. Sisco, BS; B. van Hartingsveldt, MSc; M.A. Mascelli, PhD; M.A. Graham, PhD; P. Durez, MD, Chef de Clinique Adjoint, Service de Rhumatologie, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain.

Address reprint requests to Dr. R. Westhovens, Rheumatology Department, UZ Gasthuisberg, Katholieke Universiteit Leuven, Leuven, Belgium.

E-mail: rene.westhovens@uz.kuleuven.ac.be

Accepted for publication December 6, 2005.

preference may play a role in selecting a treatment for RA. IV infliximab treatment is highly effective and generally well tolerated, but the option of one or more alternative routes of administration could be attractive for some patients. While several studies have examined the effect of IV administration of infliximab on serum concentrations, clinical response, and immunogenicity in subjects with RA or Crohn's disease⁶⁻⁸, such analyses have not been reported to date for subcutaneous (SC) or intramuscular (IM) dosing. We evaluated an experimental infliximab formulation developed specifically for SC and IM administration, in a pilot study involving patients whose RA was refractory to MTX therapy.

MATERIALS AND METHODS

Study design. This phase I, open-label, randomized study, conducted at 2 sites in Belgium, evaluated the safety, pharmacokinetics, and clinical effect of single- and multiple-dose regimens of an experimental formulation of infliximab

(Centocor, Inc., Malvern, PA, USA) that was specially created for SC and IM use. This injectable infliximab formulation has not received approval from the US Food and Drug Administration or any other regulatory agency for human therapeutic use. The study protocol was approved by the institutional review boards of both participating centers in accord with the Declaration of Helsinki. All subjects provided written informed consent.

The study was conducted in 3 stages (Figure 1). In Stage I, 15 subjects were randomly assigned to receive a single SC injection of infliximab 0.5 mg/kg, 1.5 mg/kg, or 3.0 mg/kg; 5 subjects received each dose. The pharmacokinetic data from Stage I were analyzed, and a dose of 100 mg was chosen for evaluation in Stage II.

In Stage II, 21 subjects received one of the following 3 infliximab treatment regimens, with 7 subjects randomized to each treatment group: 100 mg SC injections at Weeks 0, 2, and 4 (Group 1); 3 mg/kg IV infusions of commercially-formulated infliximab (Remicade[®], Centocor) at Weeks 0 and 2 followed by 100 mg SC injections of the SC formulation at Weeks 4, 6, and 8 (Group 2); or 100 mg IM injections at Weeks 0, 2, and 4 (Group 3). In Stage III, 7 additional subjects received 100 mg SC infliximab injections at Weeks 0, 4, and 8.

The experimental formulation of infliximab was specifically developed

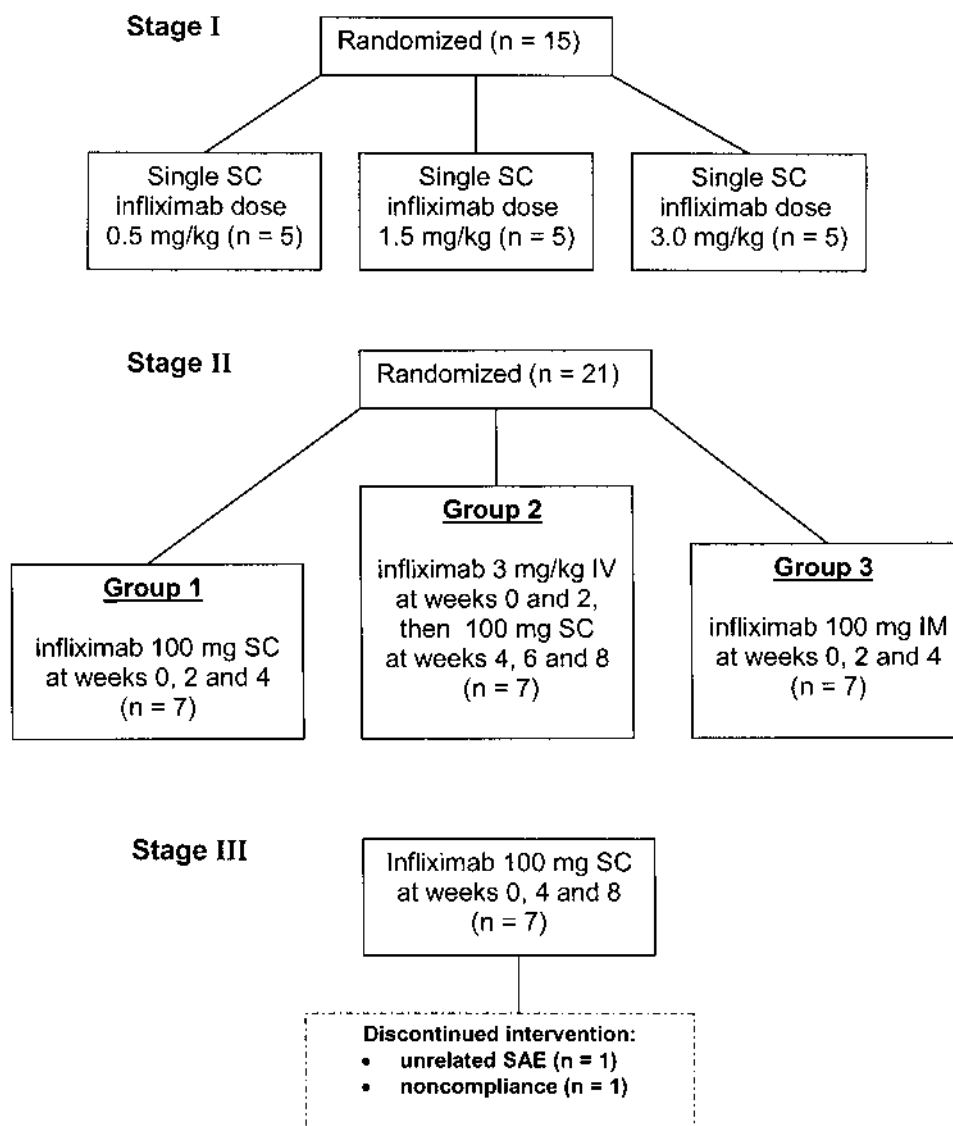


Figure 1. Study design.

for SC and IM use only and was supplied as a single-use, sterile, white, lyophilized powder containing 100 mg infliximab in a 2 ml Type 1 tubing glass vial. Reconstitution with 1 ml sterile water resulted in a solution containing 100 mg/ml infliximab.

Patients. Patients over 18 years of age and weighing ≤ 90 kg were considered eligible if they had a diagnosis of RA according to American College of Rheumatology (ACR) criteria⁹ and duration of active disease > 3 months. At baseline, patients were required to have ≥ 6 swollen joints and ≥ 8 tender joints out of 28 joints examined, plus at least 2 of the following 3 criteria: morning stiffness for at least 45 minutes, 1-hour erythrocyte sedimentation rate (ESR) of at least 28 mm, or serum C-reactive protein (CRP) concentration at least 20% above the laboratory reference range (0 to 0.5 mg/dl). Patients were also required to be naive to therapy with TNF-blocking agents.

Patients were required to have received MTX therapy for at least 3 months, with a stable dose for at least the previous 4 weeks. Therapy with corticosteroids (up to 10 mg/day prednisone or equivalent) and/or nonsteroidal antiinflammatory drugs was permitted if dosages had been stable for at least the 4 weeks prior to enrollment; subsequently, dosages had to remain stable throughout the trial. Intraarticular corticosteroid injections were prohibited.

Subjects underwent screening procedures during the 4 weeks prior to administration of the study agent. All subjects were carefully screened for tuberculosis (TB) with both chest radiography and purified protein derivative tuberculin skin testing. Those with any findings indicating the presence of TB were excluded from participation. After receiving study agent, subjects were monitored on an inpatient basis for at least 8 hours.

A preliminary analysis of Stage I data to determine the appropriate SC dose to be used in Stage II was conducted when pharmacokinetic data from 3 subjects from each Stage I dose group became available about 28 days following treatment.

Assessment. Safety assessments included evaluation of adverse events (AE), including injection site reactions and hypersensitivity reactions, and determination of changes from baseline in vital signs, electrocardiograms, and laboratory measures. AE were monitored during treatment and for up to 16 weeks after administration of the last dose of study agent.

Study agent immunogenicity was assessed by evaluating subjects for the possible development of antibodies to infliximab. Subject immune function was also determined by assessing for the development of antinuclear antibodies (ANA) and antibodies to double-stranded DNA (dsDNA), and by evaluating subject response to immunization with tetanus toxoid and with 23-valent pneumococcal vaccine. Ability to generate a naive antibody response was evaluated in all subjects who had not received pneumococcal vaccine within the preceding 5 years; ability to generate a humoral recall response (i.e., memory B cell antibody response) was assessed in all subjects who had not received tetanus toxoid within the preceding 10 years. Subjects were vaccinated or inoculated 3 days after the last administration of study agent. Immune response titers were measured 25 days later and were compared with baseline values. Subjects with a ≥ 2 -fold increase over baseline titers against more than 6 of the 12 evaluated pneumococcal serotypes, or subjects with ≥ 4 -fold increase in postvaccine tetanus titers over baseline titers, were considered responders.

The pharmacokinetic profile was evaluated by determining the maximum observed serum concentration (C_{\max}), area under the curve (AUC), and terminal half-life ($T_{1/2}$) of single SC doses of infliximab (Stage I). Half-life values for the Stage II and Stage III dose groups (multiple SC doses given at 2 or 4-week intervals, multiple IM doses, and multiple SC doses following 2 IV doses) were also determined.

The effect of infliximab on clinical disease indicators was evaluated through the 16-week post-administration monitoring period by determining the proportion of subjects whose clinical response met ACR 20% (ACR20) criteria, defined as 20% improvement from baseline in the number of tender and swollen joints and 20% improvement of at least 3 of the 5 remaining ACR core set measures (patient global assessment, physician global assessment, pain, disability, and results of an acute-phase reactant)¹⁰. The proportions of subjects who achieved 50% and 70% improvements (ACR50 and ACR70) were also determined.

Statistics. This was a phase I, open-label study, with no formal hypothesis testing. Simple descriptive statistics, such as mean, median, and range for continuous variables and percentages for categorical variables were used to summarize the data. With the exception of the immunogenicity analysis, which is of special interest, treatment groups defined by routes of administration were combined for the analysis of safety due to the small sample sizes.

RESULTS

Patient characteristics at baseline. Baseline demographic characteristics are summarized in Table 1. A total of 43 patients were enrolled in the study, of whom 34 (79%) were women. Median age was 55 years (range 28–75 yrs). Median disease duration at baseline was 6.5 years, with a median number of 15 swollen joints and median CRP of 1.4 mg/dl; 88.1% of subjects had a positive rheumatoid factor screen, and roughly the same percentage had a history of disease modifying antirheumatic drug use > 1 year.

Safety and tolerability. Because preliminary analyses revealed no substantial differences in the hematology, clinical chemistry, vital signs, or electrocardiographic measurements among the treatment groups, and because of the small overall sample size, AE data for the various treatment regimens were pooled.

Of the 43 subjects, 34 (79.1%) experienced one or more AE during the study through Week 16, which were generally transient and mild to moderate in intensity. The events most commonly observed were respiratory infection, pain after vaccination, and headache, each occurring in 14.0% of subjects. The only 2 serious AE were experienced by a single subject. An intraventricular cerebral hemorrhage and a subarachnoid hemorrhage occurred in a 74-year-old hypertensive woman in the Stage III treatment group (infliximab 100 mg SC at Weeks 0, 4, and 8); these events were not considered by the investigator to be related to infliximab. She recovered following surgical intervention with minimal neurological sequelae. Study medication was permanently discontinued by 2 subjects (6.7%), both in the Stage III treatment group, before the completion of the trial; this was due in one case to the serious AE noted above, and in the other case to noncompliance.

One or more infections were experienced by a total of 10 subjects (23.3%) during the study. The infections were generally transient and mild to moderate in intensity, and responsive to appropriate antimicrobial therapy if indicated. No serious or opportunistic infections were observed. Bronchitis was the most common infection, occurring in 5 subjects (11.6%). Injection site reactions of at least 5 mm occurred in 9 subjects (20.9%), and these were mild and transient. There were no reported serious injection site reactions, cases of anaphylaxis, severe allergic reactions, or delayed hypersensitivity reactions.

Immune response and immunogenicity. Thirteen of 27 subjects with evaluable samples had a response to tetanus toxoid; 11 of 35 subjects with evaluable samples had a response to pneumococcal vaccine. The rates of response to both tetanus and pneumococcal vaccine were variable across the treatment

Table 1. Baseline characteristics of subjects.

	Stage I 0.5, 1.5, or 3.0 mg/kg SC (single-dose), n = 15	Stage II Group 1 100 mg SC (wks 0, 2, 4), n = 7	Stage II Group 2 3 mg/kg IV (wks 0, 2) and 100 mg SC (wks 4, 6, 8), n = 7	Stage II Group 3 100 mg IM (wks 0, 2, 4), n = 7	Stage III 100 mg SC (wks 0, 4, 8), n = 7	Totals
Age, yrs, median (range)	54 (28–75)	51 (37–74)	62 (46–70)	55 (40–68)	54 (43–74)	55 (28–75)
Sex, n (%)						
Female	12 (80.0)	5 (71.4)	6 (85.7)	5 (71.4)	6 (85.7)	34 (79.1)
Male	3 (20.0)	2 (28.6)	1 (14.3)	2 (28.6)	1 (14.3)	9 (20.9)
Disease duration, yrs, median (range)	10.4 (2.8–21.4)	4.2 (0.8–12.8)	6 (2.3–34.1)	6 (2.7–22.1)	3.4 (1.2–13.4)	6.5 (0.8–34.1)
DMARD use, yrs, n (%)						
≤ 1	1 (6.7)	2 (28.6)	0 (0.0)	2 (28.6)	0 (0.0)	5 (11.6)
> 1, ≤ 3	2 (13.3)	0 (0.0)	2 (28.6)	2 (28.6)	3 (42.8)	9 (20.9)
> 3, ≤ 5	12 (80.0)	5 (71.4)	5 (71.4)	3 (42.8)	4 (57.2)	29 (67.4)
Corticosteroid use, yrs, n (%)						
None	4 (26.7)	3 (42.8)	3 (42.8)	2 (28.6)	4 (57.2)	16 (37.2)
≤ 1	3 (20.0)	2 (28.6)	1 (14.3)	1 (14.3)	0 (0.0)	7 (16.3)
> 1, ≤ 3	1 (6.7)	0 (0.0)	1 (14.3)	2 (28.6)	2 (28.6)	6 (14.0)
> 3, ≤ 5	7 (46.6)	2 (28.6)	2 (28.6)	2 (28.6)	1 (14.3)	14 (32.6)
Subjects with positive baseline RF, %	100 (15/15)	57.1 (4/7)	100 (7/7)	85.7 (6/7)	83.3 (5/6)	88.1 (37/42)
No. of swollen joints, median (range)	14 (7–30)	17 (9–29)	21 (12–22)	14 (11–29)	17 (9–25)	15 (7–30)
Serum CRP level, mg/dl, median (range)	1.8 (0.4–4.6)	2.0 (0.4–3.5)	1.9 (0.9–8.0)	0.8 (0.4–6.7)	0.9 (0.5–3.0)	1.4 (0.4–8.0)

DMARD: disease modifying antirheumatic drug; CRP: C-reactive protein; RF: rheumatoid factor.

groups. Humoral immune response to tetanus toxoid was not suppressed in a majority of the evaluable subjects who received SC or IM administration of infliximab; pneumococcal response and tetanus toxoid responses, however, were suppressed in all 7 subjects treated with IV infliximab. Overall, 7 of 40 subjects (17.5%) and one of 40 subjects (2.5%) were found to have sera newly positive for the presence of ANA and dsDNA antibodies, respectively, during the course of the study. Four of 15 subjects (26.7%) who received a single SC dose of infliximab developed low-titer antibodies to infliximab, but only one of the 20 subjects (5.0%) who received repeated SC doses developed infliximab antibodies. In contrast, 3 of 7 subjects (42.8%) who received repeated doses of IM infliximab developed antibodies to infliximab.

Pharmacokinetics. After single SC administration at the doses ranging from 0.5 to 3.0 mg/kg, the median $T_{1/2}$ ranged from 8.0 to 8.4 days and the C_{max} and AUC increased in a roughly dose-proportional manner across these dose groups. A 6.0-fold increase in dose resulted in roughly a 6.7-fold increase in median C_{max} and a roughly 6.3-fold increase in median AUC (Figure 2). Median $T_{1/2}$ values ranged from 7.3 to 16.7 days for each treatment arm in Stages II and III. Trough infliximab serum concentrations were observed to be $\geq 1 \mu\text{g/ml}$ throughout the 12-week treatment period for subjects receiving repeated 100 mg SC doses every 4 weeks for a total of 3 doses (Stage III; Figure 3).

Clinical response. Regardless of the route of administration or dosage of infliximab, clinical response as assessed by ACR20 criteria was achieved by over 80% of subjects treated in this study.

Of subjects who received single SC infliximab doses in Stage I, 13 of 15 (86.7%) achieved an ACR20 clinical response when evaluated 2 weeks after receiving treatment. In addition, $\geq 80\%$ of subjects assigned to receive multiple 100 mg SC doses (6 of 7 in Stage II Group 1, 6 of 7 in Stage II Group 2, and 4 of 5 in Stage III) also achieved ACR20 when evaluated 2 weeks after the last dose of infliximab, irrespective of the dosing regimen (Figure 4A). In contrast, the clinical response at the same 2-week posttreatment interval in Stage II Group 3 subjects, who received only IM infliximab administration, was less robust, with 4 of 7 (57.1%) achieving ACR20; by 4 weeks' posttreatment, however, the ratio increased to 5 of 6* (83.3%). The percentage of evaluated subjects who at any time achieved an ACR20 clinical response during the study was also high in all treatment groups in which subjects received repeated SC infliximab injections. Subjects in the treatment group in which SC administration followed IV administration experienced the longest duration of clinical effect, with 5 subjects maintaining an ACR20 response through the 16-week post-administration period.

Much higher levels of clinical response were attained by some subjects in all treatment groups during the course of the study. Among subjects receiving single SC infliximab doses, 3 who received 0.5 mg, 2 who received 1.5 mg, and 3 who received 3.0 mg achieved an ACR50 response, and one who received 3 mg achieved an ACR70 response. Among subjects

*Complete clinical response data were not available for one subject at this visit.

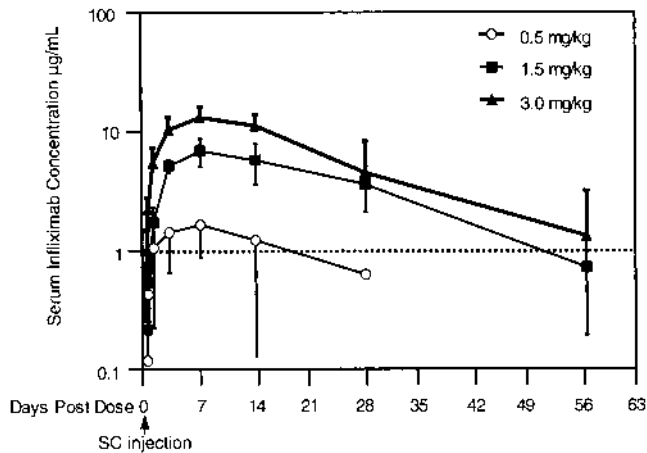


Figure 2. Mean (\pm SD) serum infliximab concentrations per time after single subcutaneous (SC) administrations.

receiving multiple SC infliximab administrations, irrespective of dose regimen, a majority attained ACR50 at some point during the study period, as did close to one-third of those who received IM infliximab (Figure 4B); ACR70 was attained by smaller proportions of subjects in all these treatment groups (Figure 4C).

DISCUSSION

In this early-phase, small-scale exploratory study we looked at the safety, efficacy, and pharmacokinetics of SC and IM dosing for an experimental formulation of infliximab in patients with RA refractory to MTX. Both the single and multiple-dose SC infliximab regimens and the multiple-dose IM regimen were generally well tolerated in this relatively small sample. Only one subject experienced serious adverse events, and

these 2 events were not considered treatment-related. No problems were encountered with respect to the volume of SC study drug administered, and reported skin reactions were mild and, transient, and appeared similar to those previously reported for adalimumab and etanercept^{11,12}.

Marked suppression of humoral-recall immune response was not seen in this study with either SC or IM administration of infliximab, while both pneumococcal and tetanus toxoid responses were suppressed in all subjects who received IV infliximab. In contrast, in a subset of subjects from the ASPIRE study (an active-controlled, double-blind, randomized clinical trial of IV infliximab in patients with early-onset RA), a similar proportion of subjects in each treatment group mounted an effective 2-fold increase in titers to polyvalent pneumococcal vaccine, indicating that IV infliximab did not interfere with B cell-dependent humoral responses¹³. In our study, no meaningful conclusions can be drawn concerning differences found in humoral immune response between SC/IM and IV-treated subjects due to the small number of subjects in each dose group.

Only one of 20 subjects who received repeated doses of SC infliximab developed antibodies to infliximab at any time during the study, comparable with the roughly 5% incidence of antibody formation reported in association with both adalimumab and etanercept¹⁴, and the development of these antibodies did not correlate with any clinical adverse event. The limited subject numbers and short duration of treatment in this study, however, do not permit a truly valid comparison with other agents.

The clinical response to SC infliximab in this small study was impressive, with very high proportions (80%–100%) of subjects in all treatment groups receiving SC doses of infliximab achieving ACR20 criteria, and some in each group attaining much higher levels of clinical response. However,

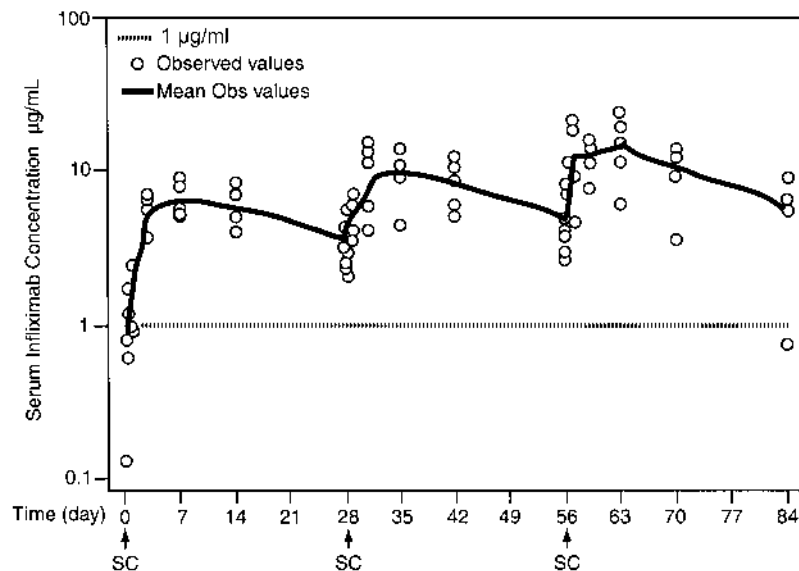


Figure 3. Serum infliximab concentrations per time after 100 mg SC q4w times 3 doses.

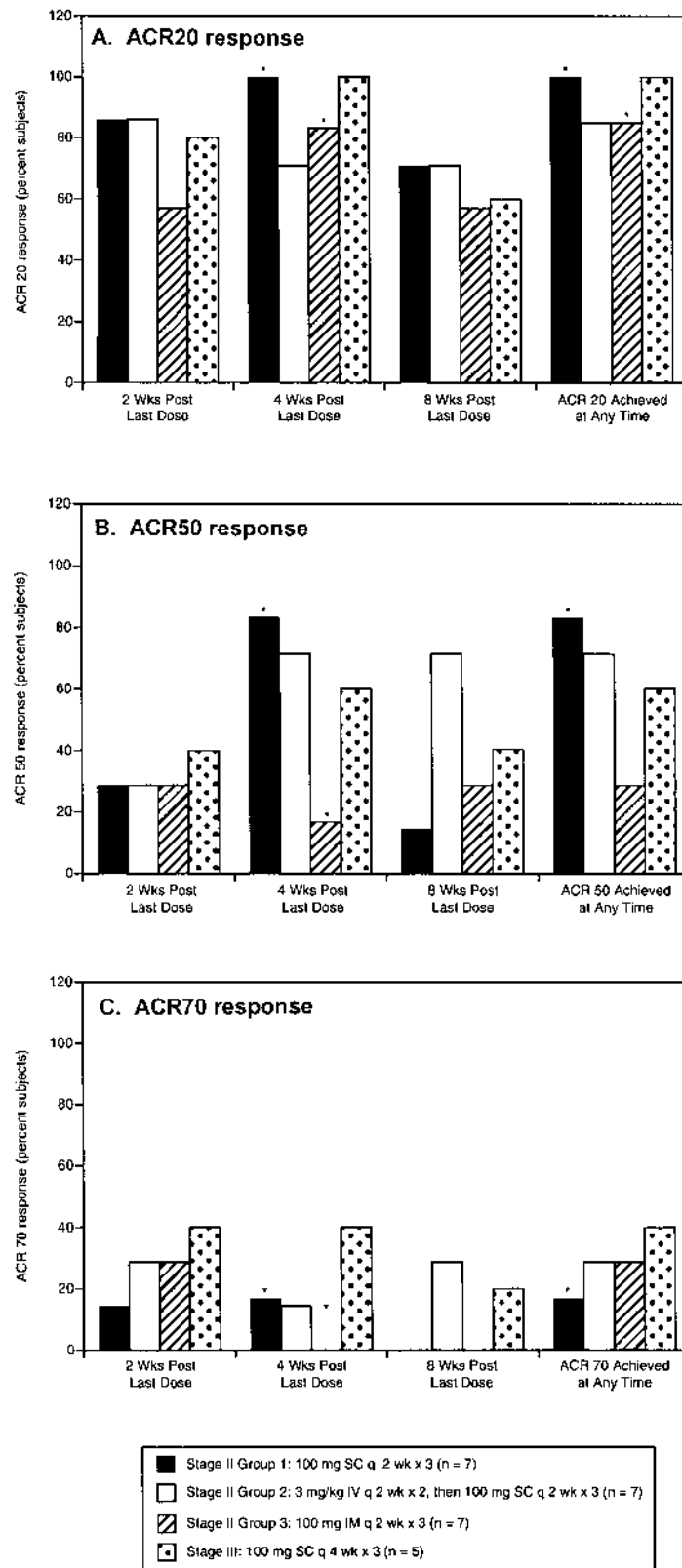


Figure 4. Clinical response by visit for multiple-dose infliximab regimens. A. ACR20 response. B. ACR50 response. C. ACR70 response. *For the "4 weeks post-last dose" visit complete clinical response data were available for only 6 of 7 subjects in Stage II Group 1 and in Stage II Group 3.

the small number of subjects in each dose group, the heterogeneity of the subject population with regard to age, baseline disease characteristics and concomitant medications, and the lack of a placebo control arm all serve to limit the conclusions that can be drawn from the study concerning the effectiveness of either SC or IM treatment with this experimental infliximab formulation in patients with RA.

Systemic exposure of SC infliximab was generally dose-proportional over the dose range of 0.3 to 3.0 mg/kg, and a median $T_{1/2}$ of 7.3 to 16.7 days was observed following multiple SC administrations; this is slightly less than the $T_{1/2}$ of 14 to 19 days reported for SC adalimumab with dosing every 2 weeks¹⁴. Etanercept, a fusion protein, has a much shorter $T_{1/2}$ (4.8 days) than either of the anti-TNF Mab biologics and requires twice-weekly SC dosing^{14,15}.

The different $T_{1/2}$ values obtained for each treatment arm in our study could be due to the limited number of subjects enrolled in each treatment group ($n = 5$ to 7 per group) and the moderate to large interindividual variability in pharmacokinetics of infliximab. Analysis of data from ATTRACT, a placebo-controlled double-blind, randomized clinical trial of infliximab in patients with active RA refractory to MTX treatment, showed that clinical improvement of RA is dose-related and that higher trough levels of infliximab may be beneficial for patients with RA¹⁶. In addition, patients who maintained trough serum concentrations $> 1 \mu\text{g/ml}$ had a greater chance of achieving an ACR20 response. The persistence of detectable serum infliximab concentration well above the $1 \mu\text{g/ml}$ trough level over time after SC administration was demonstrated by the serial infliximab concentration values obtained when fixed 100 mg SC doses were administered every 4 weeks (Figure 3); it is interesting to speculate whether further study might have supported the feasibility of a monthly dosing regimen using this route of administration.

Both SC and IM administration of this experimental infliximab formulation in this small-scale exploratory study were generally well tolerated and were associated with high levels of clinical response in patients with RA refractory to MTX. Subjects receiving repeated SC infliximab doses experienced more rapid clinical response than those receiving repeated IM doses, as well as a lower incidence of antibody formation to infliximab. Pharmacokinetics of SC dosing were dose-proportionate, and detectable serum concentrations of infliximab appeared to be maintained with monthly 100 mg SC administrations. Definitive conclusions concerning safety and efficacy of this investigative infliximab formulation in the treatment of RA, however, cannot be drawn in the absence of placebo-controlled studies of adequate sample size.

ACKNOWLEDGMENT

The authors acknowledge Kathryn E. Krantz, MD, for assistance in preparing the manuscript.

REFERENCES

1. Albani S, Carson DA. Etiology and pathogenesis of rheumatoid arthritis. In: Koopman WJ, editor. Arthritis and allied conditions. 13th ed. Baltimore: Williams and Wilkins; 1997:979-92.
2. Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354:1932-9.
3. Klareskog L, van der Heijde D, de Jager JP, et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675-81.
4. Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50:1400-11.
5. Knight DM, Trinh H, Le J, et al. Construction and initial characterization of a mouse-human chimeric anti-TNF antibody. *Mol Immunol* 1993;30:1443-53.
6. Baert F, Noman M, Vermeire S, et al. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;348:601-8.
7. Durez P, van den Bosch F, Corluy L, et al. A dose adjustment in patients with rheumatoid arthritis not optimally responding to a standard dose of infliximab of 3 mg/kg every 8 weeks can be effective: a Belgian prospective study. *Rheumatology Oxford* 2005;44:465-8.
8. Wolbink GJ, Vis M, Lems WF, et al. Development of antiinfliximab antibodies and relationship to clinical response in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:711-5.
9. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315-24.
10. Felson DT, Anderson JJ, Boers M, et al. American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727-35.
11. Beuthien W, Mellinghoff HU, von Kempis J. Skin reaction to adalimumab. *Arthritis Rheum* 2004;50:1690-2.
12. Zeltser R, Valle L, Tanck C, Holyst MM, Ritchlin C, Gaspari AA. Clinical, histological, and immunophenotypic characteristics of injection site reactions associated with etanercept: a recombinant tumor necrosis factor alpha receptor:Fc fusion protein. *Arch Dermatol* 2001;137:893-9.
13. Visvanathan S, Weiss R, Keenan G, Baker D, Wagner C. Response to the pneumococcal vaccine in patients with early rheumatoid arthritis [abstract]. *Arthritis Rheum* 2004;50 Suppl:S379.
14. Fleischmann R, Shealy D. Developing a new generation of TNF-alpha antagonists for the treatment of rheumatoid arthritis. *Mol Interv* 2003;3:310-8.
15. Enbrel® (Etanercept). Physician's desk reference. Montvale, NJ: Medical Economics Company; 2005.
16. St. Clair EW, Wagner C, Fasanmade AA, et al. The relationship of serum infliximab concentrations to clinical improvement in rheumatoid arthritis: results from ATTRACT, a multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2002;46:1451-9.