Intravenous Human Recombinant Tumor Necrosis Factor Receptor p55-Fc IgG1 Fusion Protein, Ro 45-2081 (Lenercept): Results of a Dose-Finding Study in Rheumatoid Arthritis

DANIEL E. FURST, MICHAEL WEISMAN, HAROLD E. PAULUS, KENNETH BULPITT, MICHAEL WEINBLATT, RICHARD POLISSON, MICHEL ZAUG, JOHANNES KNEER, PHILIPPE VAN DER AUWERA, RANDALL M. STEVENS, and THE RHEUMATOLOGY STUDY GROUP 825

ABSTRACT. ***Objective.*** To determine the optimal dose regimen of intravenous (IV) Ro 45-2081 (lenercept), a tumor necrosis factor receptor p55-Fc IgG1 fusion protein, in patients with active rheumatoid arthritis (RA)

Methods. In a double-blind, placebo-controlled, parallel-group, multicenter trial, adult patients with long-standing active RA stabilized on conventional therapy were randomly assigned to receive 3 IV infusions, one every 4 weeks, of one of the following: (a) placebo, (b) lenercept 0.01 mg/kg (maximum 1 mg), (c) lenercept 0.05 mg/kg (maximum 5 mg), (d) lenercept 0.2 mg/kg (maximum 20 mg), or (e) lenercept 0.5 mg/kg (maximum 50 mg). The material utilized in the study had a lower relative bioavailability [lower area under the time-concentration curve (AUC) per mg infused] than that used in a recent similar trial. Efficacy variables included change from baseline in number of swollen joints and tender joints, scores on physician and patient assessments of disease activity, and patient assessment of pain.

Results. Patients treated with lenercept exhibited improvement as early as one day after the first IV infusion. The treatment benefit, however, was modest, maximized by 2 weeks and then diminished or vanished as non-neutralizing anti-lenercept antibody concentrations increased. The majority of adverse experiences were mild or moderate and not considered related to study drug.

Conclusion. Our results showed that lenercept administered by IV infusion every 4 weeks is well tolerated, but only transiently effective in patients with long-standing RA, likely due to both the low relative bioavailability of the material used in the study and the formation of non-neutralizing anti-lenercept antibodies. (J Rheumatol 2003;30:2123–6)

Key Indexing Terms:

TUMOR NECROSIS FACTOR-α RECEPTOR
RHEUMATOID ARTHRITIS CONTROLLED TRIAL PHASE II

It is well established that the synovial inflammation of rheumatoid arthritis (RA) can be strongly influenced by proinflammatory cytokines including tumor necrosis factor (TNF)-α[1-3]. Recent clinical trials of monoclonal antibodies against TNF-α[4-8] and of a soluble TNF receptor p75 fusion protein[9-12] have proven such agents to be highly effective with regard to the symptoms, signs, and radiographic progression of RA.

In a single-dose study, intravenous (IV) infusions of Ro 45-2081 (lenercept), a fusion protein combining the human p55 kDa TNF receptor and human IgG1 heavy chain, produced significant pain relief, reduction in swollen and tender joint counts, and improvement in physician- and patient-assessed disease activity scores. Efficacy was apparent within 24 h of dosing and lasted approximately 3 weeks[13]. Conducted in the United States, our study was designed to investigate the magnitude and duration of clinical response following infusions of lenercept or placebo every 4 weeks for 3 months[14]. Although lenercept development has been discontinued, we believe it is worthwhile to present our study in conjunction with a similar trial in

From the Virginia Mason Research Center, Seattle, Washington; University of California, San Diego; University of California, Los Angeles, California; Brigham and Women's Hospital, Boston; Massachusetts General Hospital, Boston, Massachusetts; F. Hoffmann-LaRoche, Nutley, New Jersey, USA; and Basel, Switzerland.

Supported by F. Hoffmann-LaRoche.

D.E. Furst, MD, Virginia Mason Research Center (current address University of California, Los Angeles); M. Weisman, MD, University of California, San Diego (current address Cedars Sinai Medical Center, Los Angeles); H. Paulus, MD; K. Bulpitt, MD, University of California, Los Angeles; M. Weinblatt, MD, Brigham and Women's Hospital; R. Polisson, MD, Massachusetts General Hospital; M. Zaug, Pharm D, MSc; J. Kneer, PhD; P. Van der Auwera, MD, F. Hoffmann-LaRoche, Basel; R. Stevens, MD, F. Hoffmann-LaRoche, Nutley.

Address reprint requests to Dr. D.E. Furst, University of California, Los Angeles, 1000 Veteran Ave, Los Angeles, California, USA, 90095-1670. E-mail: defurst@mednet.ucla.edu

Submitted February 19, 2002; revision accepted March 19, 2003.

Europe[15], as it represents the first clinical experience with a TNF receptor fusion protein in a controlled trial and demonstrates the influence of non-neutralizing antibodies on efficacy.

MATERIALS AND METHODS

The study methodology has been described[15]. Briefly, this was a double-blind, placebo-controlled, parallel-group, multicenter trial, in which adult patients with active RA were randomly assigned to receive 3 slow IV infusions, at 4 week intervals, of either (a) placebo, (b) lenercept 0.01 mg/kg (maximum 1 mg), (c) lenercept 0.05 mg/kg (maximum 5 mg), (d) lenercept 0.2 mg/kg (maximum 20 mg), or (e) lenercept 0.5 mg/kg (maximum 50 mg). Previous disease modifying antirheumatic drugs (DMARD) were stopped at least 4 weeks before the first infusion. Nonsteroidal antiinflammatory drugs (NSAID) and corticosteroids were continued at a stable dose. The primary efficacy variable was the reduction from baseline in the number of swollen joints. A patient was categorized as a responder if more than a 50% reduction from baseline was achieved in swollen joint counts, averaged independently for the first and third dosing intervals, each containing 4 weekly assessments.

Anti-lenercept antibody concentrations were measured, but the pharmacokinetic and pharmacodynamic analyses originally planned were not completed following a decision to stop production of the material and manufacturing process utilized in this study. This process produced a batch of lenercept with a different glycosylation pattern, shorter half-life and a 60% lower area under the time-concentration curve (AUC) than that used in the trial previously reported[15].

RESULTS

A total of 118 adult patients (79% female), ranging in age from 22 to 76 years (mean, 50), were randomized to 5 treatment groups (Table 1). The mean duration of RA was 13 years. Ninety-three percent of the patients were rheumatoid factor positive.

Swollen joint counts among patients treated with 0.05 mg/kg, 0.2 mg/kg, and 0.5 mg/kg doses of lenercept decreased, while those among placebo and 0.01 mg/kg lenercept-treated patients increased (Figure 1). Therapeutic benefit was evident in some patients one day after the initial infusion, peaked by one or 2 weeks, then diminished or vanished by 4 weeks. A response was only sustained after the second and third infusions in the 0.05 mg/kg dose group. This response pattern was even more pronounced among other efficacy measurements. For example, the highest dose group achieved maximum mean improvements in tender joint counts, physician- and patient-assessed disease activity, and patient-assessed pain of 47%, 38%, 46%, and 48%, respectively. However, therapeutic benefit diminished and these same measures were 19%, 3%, 14%, and 0%, respectively, at the fourth week. The percentage of patients qualifying as responders was modest across groups (Table 2). At month 1 there was a significant relationship between lenercept dose and response rates ($p = 0.027$), but there was no such relationship at month 3.

The majority of adverse experiences were mild or moderate and considered unrelated or only remotely related to study medication. The following were reported by greater than 5% of the patients, with no significant differences between the placebo and active treatment groups: headache (28%), upper respiratory tract infection (19%), nausea (17%), irritated pharynx (8%), and dyspepsia (7%). Infections were similar in type, frequency, and severity among treatment and placebo groups. No clinically signifi-

Table 1. Baseline demographic and disease characteristics (mean and range, except where otherwise noted).

	Placebo	Intravenous Ro 45-2081 (lenercept)				All Treatments
		0.01 mg/kg	0.05 mg/kg	0.2 mg/kg	0.5 mg/kg	
n	24	23	23	24	24	118
Sex, m/f	9/15	6/17	4/19	2/22	4/20	25/93
Age, yrs	48 (22-70)	54 (35-73)	52 (34-76)	45 (22-72)	51 (27-72)	50 (22-76)
Weight, kg	77 (45-100)	76 (46-109)	69 (44-114)	68 (45-135)	70 (48-141)	72 (44-141)
Height, cm	170 (156-187)	171 (151-190)	167 (156-185)	167 (154-188)	166 (147-192)	168 (147-192)
RA duration, yrs	11 (1-30)	14 (3-30)	13 (4-42)	14 (3-36)	13 (1-22)	13 (1-42)
Clinical measures						
Swollen joints, /48	24 (9-36)	25 (12-43)	23 (11-34)	24 (11-36)	23 (6-46)	24 (6-46)
Tender joints, /50	31 (11-50)	36 (9-50)	29 (14-40)	32 (20-46)	32 (13-49)	32 (9-50)
Physician appraisal, /100*	69 (37-89)	70 (35-95)	62 (46-83)	69 (48-94)	66 (49-89)	67 (35-95)
Patient appraisal, /100*	71 (22-100)	71 (16-99)	64 (16-100)	73 (41-100)	72 (34-95)	70 (16-100)
Patient pain appraisal, /100*	65 (19-100)	71 (23-99)	61 (16-100)	68 (21-98)	66 (22-89)	66 (16-100)
Laboratory measures						
ESR, mm/h	47 (5-116)	41 (5-110)	34 (8-110)	41 (5-120)	40 (1-99)	40 (1-120)
CRP, g/l	60 (5-148)	36 (1-125)	33 (1-100)	27 (1-73)	36 (1-87)	38 (1-148)
Rheumatoid factor, pos/neg**	24/0	19/3†	23/0	23/0	21/3	110/6†
RA Treatments						
NSAID	19/21	18/18	19/19	17/17	16/17	89/92
DMARD	16/30	14/17	14/21	11/17	19/29	74/114
Corticosteroids, oral	16/17	18/18	15/16	21/23	20/21	90/95

* Physician/patient appraisals used 100 mm visual analog scales; ** < 8 IU/ml; †one patient value missing. NSAID: nonsteroidal antiinflammatory drugs. DMARD: disease modifying antirheumatic drugs.

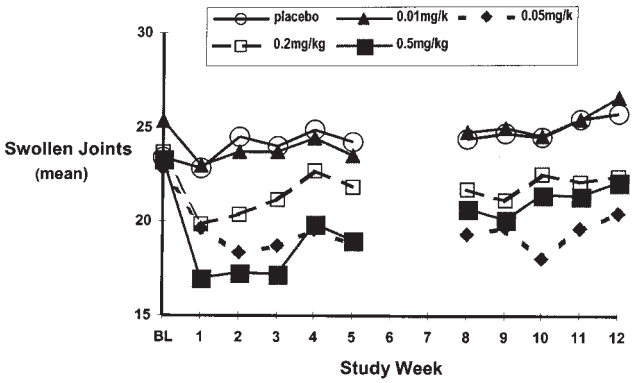

Figure 1. Swollen joint count.

cant changes in mean laboratory values were reported. Median anti-Ro 45-2081 antibody concentrations increased with time in all treatment groups receiving active drug. Antibody concentrations at the 0, 4, and 12 week time points were as follows: 0, 0, and 19 ng/ml for placebo; 0, 1, and 1 ng/ml for the 0.01 mg/kg dose; 0, 4, and 6 ng/ml for the 0.05 mg/kg dose; 0, 285, and 288 ng/ml for the 0.2 mg/kg dose; 0, 423, and 5,520 ng/ml for the 0.5 mg/kg dose.

DISCUSSION

Our findings in this study performed in North America support those performed in Europe[15]. Lenercept administered by IV infusion was initially effective in patients with severe RA and this effect was rapid in onset. Treatment effect peaked one to 2 weeks after the initial infusion, then deteriorated rapidly, without substantial improvement following the second and third infusions. The pattern of diminishing efficacy with time observed in this trial was consistent across all efficacy variables. The initial efficacy observed was less than that observed in the European trial[15], likely due to the reduced AUC per mg of the batch of lenercept used for the this trial

In the study reported by Rau, *et al*[15], anti-lenercept antibody concentrations generally increased with dose and time, concomitant with an increase in lenercept clearance rates. It was hypothesized that the erosion of clinical efficacy that occurred was attributable to the formation of antibody-drug complexes leading to accelerated drug clearance, likely the most appropriate explanation for the observations in this trial as well. In order for efficacy to be maintained and to provide substantial benefit to patients, stable concentrations of lenercept over time would be required. This might be achieved by alterations in the dosing regimen, and/or by combining lenercept with agents that reduce the anti-drug antibody response.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Virginia Holcombe for her expert advice and helpful recommendations and would like to acknowledge the valuable contributions of the following F. Hoffmann-LaRoche Rheumatology Study Group 825 personnel: S. Dickinson, Welwyn Garden City, United Kingdom; M.R. Kaehny, E. Luedin, T. McAuliffe, Basel, Switzerland; P. Rumpelt, P. St Clair, Nutley, New Jersey, USA.

REFERENCES

1. Choy EHS, Panai GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907-16.
2. Feldmann M, Brennan FM, Maini RN. Role of cytokines in rheumatoid arthritis. Annu Rev Immunol 1996;14:397-440.
3. Feldmann M, Maini RN. Anti-TNF alpha therapy of rheumatoid arthritis: what have we learned? Annu Rev Immunol 2001;19:163-96.
4. Maini RN, Breedveld FC, Kalden JR, et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998;41:1552-63.
5. Lipsky PE, van der Heijde D, St Clair W, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
6. den Broeder A, van de Putte L, Rau R, et al. A single dose, placebo controlled study of the fully human anti-tumor necrosis factor-alpha antibody adalimumab (D2E7) in patients with rheumatoid arthritis. J Rheumatol 2002;29:2288-98.
7. van de Putte LBA, Atkins C, Malaise M, et al. Adalimumab (D2E7) monotherapy in the treatment of patients with severely active rheumatoid arthritis [abstract]. Arthritis Rheum 2002;46 Suppl:S205.
8. Keystone E, Kavanaugh AF, Sharp J, et al. Adalimumab (D2E7), a fully human anti-TNF-alpha monoclonal antibody, inhibits the progression of structural joint damage in patients with active RA despite concomitant methotrexate therapy [abstract]. Arthritis Rheum 2002;46 Suppl:S205.
9. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
10. Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. N Engl J Med 1999;340:253-9.
11. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of

Table 2. Patients achieving greater than 50% reduction in mean swollen joint count (averaged over 4 visits of each interval) during months 1 and 3. Intent to treat analysis.

	IV Placebo	IV Ro 45-2081 (Lenercept)				
	n = 24 (%)	0.01 mg/kg n = 23 (%)	0.05 mg/kg n = 23 (%)	0.2 mg/kg n = 24 (%)	0.5 mg/kg n = 24 (%)	Cochrane-Armitage Trend Test
Month 1	0 (0)	2 (9)	3 (13)	2 (8)	5 (21)	p = 0.027
Month 3	0 (0)	1 (4)	3 (13)	2 (8)	4 (17)	NS

etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
12. Genovese MC, Bathon JM, Martin RW, et al. Etanercept versus methotrexate in patients with early rheumatoid arthritis: Two-year radiographic and clinical outcomes. Arthritis Rheum 2002;46:1443-50.
13. Hasler F, van de Putte L, Dumont E, et al. Safety and efficacy of TNF neutralization by lenercept in patients with rheumatoid arthritis exposed to a single dose [abstract]. Arthritis Rheum 1996;39 Suppl:S243.
14. Furst D, Weisman M, Paulus H, et al. Neutralization of TNF by lenercept (TNFR 55 TgGt, Ro 45-2081) in patients with rheumatoid arthritis treated for 3 months: Results of a phase II trial [abstract]. Arthritis Rheum 1996;39 Suppl:S243.
15. Rau R, Sander O, van Riel P, et al. Intravenous human recombinant TNF receptor p55-Fc IgG1 fusion protein, Ro 45-2081: Double-blind, placebo-controlled dose finding study in long-standing, active rheumatoid arthritis. J Rheumatol 2003;30:680-90.