Community-Based Evaluation of Etanercept in Patients with Rheumatoid Arthritis

PENDAR FARAHANI, MITCHELL LEVINE, KATHRYN GAEBEL, EDWARD C.Y. WANG, and NADER KHALIDI

ABSTRACT. ***Objective***. Etanercept is one of a new subgroup of biological disease modifying antirheumatic drugs (DMARD) to treat patients with rheumatoid arthritis (RA) who are non-responsive or intolerant to conventional DMARD. We evaluated the effects of etanercept (Enbrel®) therapy in patients with RA in community-based clinical practice in Canada.

Methods. Using a cohort design, patients requesting etanercept therapy were stratified into treatment and control arms based upon their individual accessibility to obtain the drug. Patients were interviewed serially during a 12-month period of monitoring. The study measured painful or tender joint count, morning stiffness, pain severity, quality of life measures, medication utilization, health services utilization, and presence of adverse events.

Results. The baseline demographic and clinical variables for the treatment group (n = 223) and the control group (n = 208) were similar, except for education, income, and drug plan coverage. In followup, there was greater improvement in most clinical variables in the treatment arm compared to the control arm during the first 6 months, but the magnitude of difference between the 2 groups for some clinical variables decreased or became non-significant during the second 6 months. During the 12 month followup period there were 40 (18%) patient dropouts in the treatment group

Conclusion. In a community based setting for the treatment of RA, etanercept can effectively improve the disease state, functional class, work disability, and quality of life during the first 6 months of use. To determine the longterm sustainability of these effects studies with more than 12 months' duration will be required. (First Release Mar 1, 2006; J Rheumatol 2006;33:665–70)

Key Indexing Terms:
ETANERCEPT RHEUMATOID ARTHRITIS COHORT STUDY

From randomized clinical trial data and observational studies the competitive inhibitor of tumor necrosis factor-α (TNF-α), etanercept (Enbrel®) appears to be effective and safe for use in patients with rheumatoid arthritis (RA)[1-6]. Previously published "real world" studies on etanercept have important design limitations. Some of the studies are extensions of randomized controlled trials[7,8] and some lack an appropriate control group[9,10]. The objective of our study was to compare RA patients in community practice settings who were first-time users of etanercept with a cohort of similar patients who did not receive etanercept.

From the Centre for Evaluation of Medicines, St. Joseph's Healthcare, Hamilton, Ontario, Canada.

Supported by a grant from Wyeth Pharma, Markham, Ontario

P. Farahani, MD, Centre for Evaluation of Medicines, St. Joseph's Healthcare; M. Levine, MD, MSc, FRCPC, FISPE, Centre for Evaluation of Medicines, St. Joseph's Healthcare; and Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton; K. Gaebel, MSc, Centre for Evaluation of Medicines; E.C.Y. Wang, PharmD, MBA, Cephalon, Inc. Frazer, Pennsylvania, USA; N. Khalidi, MD, FRCPC, Division of Rheumatology, Department of Medicine, Faculty of Health Sciences, McMaster University.

Address reprint requests to Dr. M. Levine, Centre for Evaluation of Medicines, 105 Main Street East, Level 1, Hamilton, ON L8N 1G6 Canada. E-mail: LEVINEM@mcmaster.ca

Accepted for publication November 25, 2005.

MATERIALS AND METHODS

Inclusion criteria. Patients with RA across Canada who were at least 18 years of age, had 6 painful or tender joints, and who called the "Enbrel® information line" were eligible to participate in the study. The information line was set up to facilitate patient access to etanercept therapy, which was in limited supply when first marketed in 1999.

Exclusion criteria. Patients who could not speak English, who were hearing impaired, or who did not have their own phone were ineligible to participate.

Design. We conducted a cohort study of patients with RA. Patients were stratified post hoc into 2 groups, a control arm comprising patients who had not yet received etanercept during a 12 month monitoring period, and a treatment arm, representing patients who used etanercept at some time during the 12 month monitoring period. No constraints were placed on any other RA treatments that the patients could receive.

Recruitment. Between 1999 and 2002 supplies of Enbrel were limited, and RA patients who were prescribed etanercept by a specialist had to call the Enbrel information line in order to gain access to etanercept therapy. Health care workers operating the information line at WTP Health (a division of Zurich Canada) read a standard script asking all eligible patients their interest to participate in the research study. The name, address, and telephone number of all consenting patients were faxed to the project coordinator at the Centre for the Evaluation of Medicines (CEM).

Interviews. A baseline telephone interview was scheduled by the research center within 72 h of receiving the patient's name. Patients received followup interviews at 1, 3, 6, 9, and 12 months after their baseline interview. The baseline interview took 30 to 50 minutes on average and each of the followup interviews took 20 to 35 minutes on average. Any patient who was delayed from starting etanercept immediately following the baseline interview had their followup interview schedules adjusted accordingly so that data were collected at 1, 3, 6, 9 and 12 months after the initiation of therapy. The patients

who never received etanercept during the 12 month monitoring period made up the control group in this observational study. These patients failed to receive etanercept despite a prescription from a rheumatologist due to the lack of drug availability (the drug was in short supply) or there was inadequate drug benefit insurance to cover the high cost of the drug.

Outcome measures. The data were collected through a standardized questionnaire, which included patient demographics, RA history, current drug utilization, past RA drug utilization, and co-morbid conditions. The questionnaire was computer-based and contained a minimum of 58 primary questions, with additional questions asked depending upon the responses to the primary questions. The specific clinical outcomes that were measured included patient reported painful or tender joint count, morning stiffness (range 0 to 180 min), pain severity (range 1 to 5, 1 being least pain), fatigue intensity (range 0 to 5, 0 being least fatigue intensity), fatigue effect (range 0 to 5, 0 being least fatigue effect), and overall well being (range 0 to 10, 10 being best overall well being). Health-related quality of life data were collected using the Medical Outcome Study Short Form Survey (SF-36) (score 0-100)[11]. The Health Assessment Questionnaire (HAQ, score 0-3) was used to measure functional disability[12]. The use of patient reported painful or tender joint count can be justified as being reasonably close to that of a physician examination. In our study the patient reported painful or tender joint count that closely approximated the HAQ score, and the HAQ score has been shown to be as effective as any available clinical measure, including laboratory tests and radiographs, to predict a range of factors including work disability and premature mortality[13]. Other recorded variables included adverse events, health care service utilization, work productivity, and economics.

Statistical analyses. Data analyses were conducted using SAS program version 8.0. The t test, chi-squared test, and analysis of variance methods were applied for comparisons. Because of multiple comparisons for clinical outcomes alpha < 0.005 was considered the threshold for statistical significance (Bonferroni correction). Analysis of covariance (ANCOVA) was used to adjust for possible confounding baseline characteristics in the analyses conducted at 6 and 12 months. The data are presented as means (standard deviations) except where otherwise indicated.

Ethics. All patients gave verbal consent for the baseline interview and written informed consent for the followup interviews. The study had been approved by the Research Ethics Committee of St. Joseph's Healthcare, Hamilton.

RESULTS

Baseline data (Table 1) were collected in 223 patients (74% female) in the treatment (T) group and 208 patients (68% female) in the control (C) group. Patients in both groups had a mean age in the early 50s and 12 years duration of RA. Baseline demographic characteristics data were not statistically different between the 2 groups except for education ($p = 0.03$), income ($p < 0.001$) and drug plan reimbursement for etanercept ($p < 0.001$), which were all significantly higher in the treatment group than in the control group.

All clinical and quality of life variables at baseline (Tables 2 and 3) were similarly distributed between the 2 groups except for a slightly higher value in the Mental Component Summary (MCS) score of the SF-36 in the treatment group [T = 50.5 (12) vs C = 48 (12), $p = 0.04$], which would be of minimal clinical significance (i.e., difference less than 5). Differences were noted in the role emotional domain score [T = 71.5 (42) vs C = 61 (45), $p = 0.01$] and mental health domain score [T = 71 (20) vs C = 65 (20), $p = 0.003$]. No difference was observed for the Physical Component Score (PCS).

Table 1. Baseline demographics variables. Values are percentages unless otherwise indicated.

Variable	Treatment Group	Control Group	p
No. of patients	223	208	—
Age, yrs, mean (SD)	53.5 (22.5)	52.7 (11.3)	0.65
Female	74	68	0.35
Duration of RA, yrs, mean (SD)	12.5 (9.2)	12.3 (9.7)	0.85
Employment status			
Full-time	23.1	21.9	
Part-time	6.6	5.9	
Self employed	6.1	5.3	
Unemployed due to RA	15.1	15.5	
Unemployed other	1.4	1.6	0.77
Retired	19.8	21.9	
Student	0.9	0	
Disability pension	18.9	21.4	
Homemaker	5.2	5.9	
Income			
< $20,000	4.7	18.7	
20,000–30,000	12.7	18.7	
30,000–40,000	11.3	13.9	
40,000–50,000	13.2	5.9	
50,000–60,000	10.4	11.2	0.001
> 60,000	42.9	24.1	
Don't know/refused	4.1	7.4	
Education			
Higher education	59	47	
High school diploma	23	26	0.03
Less than high school diploma	18	27	
Drug plan	98	89	< 0.001

Clinical and quality of life variables including painful or tender joint count, pain severity, overall well being, fatigue effect, HAQ score, and the SF-36 PCS score in the treatment group showed significant improvement compared to the control group during the 12 months (Tables 2 and 3). On the other hand, morning stiffness and fatigue intensity showed less sustained improvement, and the differences between the treatment group and the control group for these variables were insignificant during most of the 12 months of treatment. There was no difference between the 2 groups during the 12 months in the MCS score of the SF-36. The differences for most of the clinical and quality of life variables between the 2 groups became insignificant by the 12th month of the monitoring period.

In the treatment group a lack of efficacy (6%) and the occurrence of adverse events (9%) led to patient withdrawals (Table 4). Two percent of patients in the treatment group (5 cases) withdrew from the study because they could not afford the cost to purchase etanercept.

The accumulated number of missed days from work at 6 months was significantly less for the treatment group compared to the control group [T = 2.5 (7) vs C = 7.8 (19), p = 0.03], but the difference was no longer significant by 12 months (p = 0.6) (Table 5). The total number of "down" days (the days that the patient did not feel well and needed rest due to RA) in the treatment group was significantly less than the control group at 6 months [T = 32.9 (5) vs C = 45.8 (44), p = 0.02] and 12 months [T = 60.7 (8) vs C = 86.5 (86), p = 0.02]. Among employed patients there were fewer mean down days for etanercept users (11.8 days) than non-users (28.0 days) over the initial 6 month period (p < 0.002), but at 12 months the significant difference was only demonstrated for the unemployed patients (p = 0.02). Drug utilization was measured during the 12 months of the study. Data for disease mod-

Table 2. Clinical outcomes.

Variables	Groups	Baseline	Mean Δ over the 12 mo	Δ at Month 6	Δ at Month 12
Painful or tender joint count	Treatment	23.6 (15)	–11.0	–11.0	–10.5
	Control	26.0 (15)	–4.0	–4.5	–4.5
	p	0.1	< 0.001	< 0.001	0.005
Pain severity	Treatment	3.5 (0.9)	–0.8	–0.9	–0.7
	Control	3.5 (0.9)	–0.3	–0.5	–0.5
	p	0.9	< 0.001	0.002	0.15
Morning stiffness, min	Treatment	102 (65)	–40.5	–45.0	–38.5
	Control	110 (64)	–15.5	–17.5	–15.5
	p	0.2	0.01	< 0.001	0.02
Fatigue intensity	Treatment	3.4 (1)	–0.7	–0.9	–0.6
	Control	3.5 (1)	–0.4	–0.5	–0.5
	p	0.7	0.02	0.01	0.60
Fatigue effect	Treatment	6.6 (2)	–2.1	–2.4	–2.1
	Control	6.7 (3)	–0.9	–1.1	–1.1
	p	0.9	0.001	< 0.001	0.008
Overall well being	Treatment	4.9 (2)	1.5	1.6	1.5
	Control	5.1 (2)	0.3	0.6	0.3
	p	0.375	< 0.001	0.001	< 0.001

Δ: change from from baseline; p values are for differences between treatment and control groups.

Table 3. Quality of life and disability outcomes.

Variables	Groups	Baseline	Mean Δ over the 12 mo	Δ at Month 6	Δ at Month 12
Physical component summary score of SF-36	Treatment	25.5 (9)	5.0	5.8	4.5
	Control	26.5 (9)	0.6	1.1	0.6
	p	0.25	< 0.001	< 0.001	0.005
Mental component summary score of SF-36	Treatment	50.5 (12)	3.15	2.5	2.2
	Control	48 (12)	2.85	2.1	2.0
	p	0.04	0.80	0.80	0.90
Health Assessment Questionnaire	Treatment	1.7 (0.7)	–0.42	–0.5	–0.4
	Control	1.8 (0.7)	–0.15	–0.2	–0.2
	p	0.40	< 0.001	0.002	0.04

Δ: change from baseline; p values are for differences between treatment and control groups.

Table 4. Withdrawal from active treatment, to 12 months.

Reason for Withdrawal	No. of Patients (%)
Adverse events	21 (9)
Lack of effectiveness	14 (6)
Costs	5 (2)

ifying antirheumatic drugs (DMARD) (including methotrexate, sulfasalazine, and hydroxychloroquine, but excluding TNF-α competitive inhibitors), selective cyclooxygenase-2 inhibitors, nonselective nonsteroidal antiinflammatory drugs, analgesics with codeine or morphine (opiates), simple analgesics, oral corticosteroids (prednisone), and intraarticular cortisone are presented in Tables 6A and 6B. An analysis of drug utilization demonstrated a significant reduction in the use of DMARD in the treatment group compared to the control group ($p < 0.001$), Table 7. There were no significant differences for other therapies between treatment and control groups.

Health care services utilization data (Table 8) demonstrated more frequent appointments with family physicians, social workers, and visiting nurses in the control group than in the treatment group ($p < 0.001$). Conversely, patients in the treatment group visited specialists and physical/exercise therapists more frequently than patients in the control group ($p < 0.001$).

DISCUSSION

This cohort study was designed to assess the effects of etanercept in a community based setting where the patient characteristics and the manner of use would not be dictated by a research protocol. Observational studies have been conducted previously but have had important design limitations that were avoided in the current study. Two previous studies were designed as followup studies from randomized clinical trials[7,8]. This feature can introduce a selection bias, where patients with positive experiences during the trial are more likely to be in the followup study than either non-responders or patients who experienced an adverse effect while on therapy. The present study did not recruit patients who had been previously exposed to etanercept.

A third followup study was not a comparative design as it lacked a control group[9]. As such, it was limited to being a

Table 5. Missed work days and down days. Values are mean (SD).

Variable	Treatment	Control	p value
Missed days in employed patients			
At 6 mo	2.5 (7)	7.8 (19)	0.03
At 12 mo	6.0 (14)	7.6 (18)	0.60
Down days at 6 mo			
In all patients	32.9 (5)	45.8 (44)	0.02
In employed patients	11.8 (18)	28.0 (33)	0.002
In unemployed patients	45.2 (53)	55.5 (46)	0.20
Down days at 12 mo			
In all patients	60.7 (8)	86.5 (86)	0.02
In employed patients	29.4 (35)	34.8 (38)	0.50
In unemployed patients	78.7 (90)	114.8 (92)	0.02

Table 6A. Baseline drug utilization for all patients. Values are percentage of patients.

Drug Group	No. of drugs	Treatment	Control	p
DMARD	0	18.8	18.3	
	1	38.6	38.5	0.99
	≥ 2	42.6	43.3	
COX-2	No	58.3	57.2	0.23
	Yes	41.7	42.8	
NSAID	No	65.9	71.6	0.32
	Yes	34.0	28.4	
Opioids	No	66.8	67.8	0.90
	Yes	33.2	32.2	
Prednisone	No	44.8	54.3	0.10
	Yes	55.3	45.7	
Cortisone	No	96.9	97.6	0.43
	Yes	3.1	2.4	
Analgesics	No	94.6	93.3	0.46
	Yes	5.3	6.7	

Table 6B. Baseline DMARD drug utilization for all patients.

	Treatment Group, No. of Patients(%)	Control Group, No. of Patients (%)	p
Methotrexate	127 (57.0)	127 (61.1)	0.38
Leflunomide	37 (16.6)	28 (13.4)	0.36
Gold salts	17 (7.5)	15 (7.2)	0.87
Azathioprine	8 (3.8)	6 (2.9)	0.68
Sulfasalazine	28 (12.5)	25 (12.1)	0.86
Cyclosporine	8 (3.9)	7 (3.4)	0.73
Hydrochloroquine	71 (31.9)	58 (27.9)	0.37
Minocycline	4 (1.7)	6 (3.0)	0.20
Penicillamine	0 (0.0)	1 (0.5)	0.47

Gold salts include sodium aurothiomalate, aurothioglucose, and auranofin. The sum of percentages for each group is more than 100% because some patients used more than one DMARD at baseline.

Table 7. Changes in drug utilization at 12 months. Values are percentage of patients.

Drug Group	Drug Use in Individual Patients	Treatment (%)	Control (%)	p
DMARD	Decreased	62.0	6.5	
	Same	37.3	75.3	< 0.001
	Increased	0.7	18.3	
COX-2	Decreased	12.7	10.8	
	Same	79.7	81.7	0.90
	Increased	7.5	7.5	
NSAID	Decreased	11.9	6.5	
(excluding COX-2)	Same	79.9	90.3	0.10
	Increased	8.2	3.2	
Opiates	Decreased	10.5	15.1	
	Same	84.3	72.0	0.10
	Increased	5.2	12.9	
Prednisone	Decreased	15.7	9.7	
(systemic)	Same	80.6	86.0	0.40
	Increased	3.7	4.3	
Cortisone	Decreased	1.5	1.1	
(intraarticular)	Same	93.3	94.6	0.90
	Increased	5.2	4.3	
Simple analgesics	Decreased	3.0	3.2	
	Same	91.8	88.2	0.50
	increased	5.2	8.6	

Table 8. Health services utilization during study period.

Health Care Service	Treatment Group Visits (mean per patient mo)	Control Group Visits (mean per patient mo)	p
Family physician	0.34	0.43	< 0.001
Specialist	0.64	0.58	< 0.001
Outpatient clinic physician or nurse	0.75	0.77	0.15
Chiropractor	0.12	0.11	0.14
Social worker	0.01	0.02	0.006
Physical/exercise therapist	0.39	0.19	< 0.001
Homeopath	0.05	0.05	0.93
Acupuncturist	0.03	0.03	0.75
Visiting nurse	0.16	0.31	< 0.001

descriptive study with no potential for providing valid inferences regarding efficacy or effectiveness.

The Kobelt, *et al* study, which assessed the effectiveness of etanercept in RA patients in the community setting, also lacked an appropriate control group, limiting the validity of the incremental benefits observed from baseline[10]. Because the HAQ score for individual patients can be labile and may fluctuate over time, it is essential that HAQ score changes in patients receiving the treatment of interest be compared to a control group. At 12 months our study showed an improvement in the HAQ of 0.40 from baseline in the treated patients. The Kobelt study demonstrated similar results with a HAQ increase of 0.39. What is not apparent from the Kobelt study but can be observed in our study is that the non-etanercept treated patients improved by 0.20. Therefore the true incremental benefit with etanercept is not necessarily as large as the uncontrolled study would indicate.

DMARD therapy can have several goals, including to reduce the dose or eliminate the use of prednisone. Even though our results demonstrated that DMARD use decreased in the treatment group (but not in the control group), prednisone usage remained the same (Table 7). The ERA trial indicated that etanercept used as monotherapy was superior to methotrexate alone in the first 6 months with respect to the American College of Rheumatology core data set, which by definition means that less prednisone would have been used[2]. However a more recent trial revealed that combination of methotrexate and etanercept was superior to using either drug

alone[6]. The results of the study indicate, however, that instead of lowering the prednisone dose, the practicing physician chose to reduce the DMARD.

This community-based study demonstrated that etanercept treatment improved disease status and quality of life in RA patients. Etanercept's effect was primarily related to physical improvement rather than mental or emotional status. Although the clinical and quality of life improvements were superior in the etanercept group compared to the control group in the first 6 months of treatment, the magnitude of the differences between the 2 groups became less or even non-significant for some variables (such as pain severity and fatigue intensity) at 12 months. This finding is consistent with the results of a study by Kosinski, *et al*[14]. In contrast to our results, a multicenter cohort study by Geborek, *et al* demonstrated that clinical response did not decline from the 6 month to the 12 month assessment[9]. It is possible that the loss of the patients between 6 and 12 months and the "on treatment" analysis that was used in the Geborek study resulted in a survivor bias and led to a difference in sustainability between the Geborek study and our study.

In conclusion, it is essential to evaluate the effectiveness of the therapeutics in the real world with the appropriate comparators and for an adequate time-span. In the case of etanercept, the longterm effectiveness of this drug will be determined when appropriate enduring data from clinical practice studies or registries become available[15-17].

REFERENCES

1. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
2. Bathon JM, Martin RW, Fleischmann RM, et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med 2000;343:1586-93.
3. 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;6:1443-50.
4. 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.
5. Yazici Y, Erkan D, Kulman I, Belostocki K, Harrison MJ. Decreased flares of rheumatoid arthritis during the first year of etanercept treatment: further evidence of clinical effectiveness in the "real world". Ann Rheum Dis 2002;61:638-40.
6. 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.
7. Kremer JM, Weinblatt ME, Bankhurst AD, et al. Etanercept added to background methotrexate therapy in patients with rheumatoid arthritis - Continued observations. Arthritis Rheum 2003;48:1493-9.
8. Moreland LM, Cohen SB, Baumgartner SW, et al. Long-term use of Enbrel (R) in patients with DMARD-refractory rheumatoid arthritis [abstract]. Arthritis Rheum 2000;43 Suppl:S270.
9. Geborek P, Crnkic M, Petersson IF, Saxne T. Etanercept, infliximab, and leflunomide in established rheumatoid arthritis: clinical experience using a structured follow up programme in southern Sweden. Ann Rheum Dis 2002;61:793-8.
10. Kobelt G, Eberhardt K, Geborek P. TNF inhibitors in the treatment of rheumatoid arthritis in clinical practice: costs and outcomes in a follow up study of patients with RA treated with etanercept or infliximab in southern Sweden. Ann Rheum Dis 2004;63:4-10.
11. Ware J. SF-36 Health Survey. Manual and interpretation guide. Boston: The Health Institute, New England Medical Centre; 1993.
12. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. Arthritis Rheum 1980;23:137-45.
13. Pincus T, Swearingen C, Wolfe F. Toward a multidimensional Health Assessment Questionnaire (MDHAQ): assessment of advanced activities of daily living and psychological status in the patient-friendly health assessment questionnaire format. Arthritis Rheum 1999;42:2220-30.
14. Kosinski M, Kujawski SC, Martin R, et al. Health-related quality of life in early rheumatoid arthritis: impact of disease and treatment response. Am J Manag Care 2002;8:231-40.
15. Registry of etanercept (Enbrel®) in children with juvenile rheumatoid arthritis. www clinicaltrials gov/ct/gui/show/NCT00078793 2005.
16. The British Society for Rheumatology Biologics Register. [Internet.] Available from: http://www.arc.man.ac.uk/webbiologicsreg.htm. Accessed December 11, 2005.
17. van Vollenhoven RF, Ernestam S, Harju A, Bratt J, Klareskog L. Etanercept versus etanercept plus methotrexate: a registry-based study suggesting that the combination is clinically more efficacious. Arthritis Res Ther 2003;5:R347-R351.