Etanercept (Enbrel®) in Patients with Rheumatoid Arthritis with Recent Onset Versus Established Disease: Improvement in Disability

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ABSTRACT. ***Objective.*** To compare etanercept-induced improvement in disability of patients with recent onset of rheumatoid arthritis (RA) to that of patients with established RA.

Methods. Health Assessment Questionnaire (HAQ) scores were collected over 3 years in 2 groups of patients with RA who were treated with etanercept. The first group consisted of 207 patients with recent onset RA (mean duration of 1 year) who had not previously received methotrexate, and the second group consisted of 464 patients with established RA (mean duration of 12 years) who had failed one or more disease-modifying antirheumatic drugs.

Results. Baseline demographics and disease characteristics were similar in the 2 groups, except for HAQ scores and C-reactive protein levels, which were higher in the established RA group. Patients in both groups showed rapid and sustained clinical responses with etanercept therapy, but patients with recent onset RA showed significantly greater improvement in HAQ scores compared with patients with established RA. The difference in magnitude of HAQ score improvement between groups was observed as early as week 2 after initiation of etanercept and persisted throughout the 3-year time frame. At year 3, significantly more patients with recent onset RA had a HAQ score of zero (26%) versus those with established RA (14%, p = 0.0095).

Conclusion. Although etanercept therapy significantly improved disability scores in both groups, patients with recent onset of RA showed greater benefit in HAQ scores than patients with established RA. These results support prompt treatment of RA at an early stage of disease to minimize patient disability. (J Rheumatol 2004;31:1532–7)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ETANERCEPT
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Most patients with rheumatoid arthritis (RA) face deteriorating physical function as their disease progresses. Thus, prevention of disability is an important goal of antirheumatic therapy. The Health Assessment Questionnaire (HAQ) incorporates patient-centered dimensions such as physical function, disability, and ease of daily activities and is an important outcome assessment of treatment success.

Because half of RA patients develop a moderate loss of functional ability within 2 years of diagnosis[1], early diagnosis and treatment may be vital. Recently, treatment strategies for RA have shifted toward earlier use of combinations of traditional disease-modifying antirheumatic drugs (DMARD) and/or biologics, with the expectation that patient outcomes may improve. Importantly, intervention with traditional DMARD early in the disease course has been shown to be more effective in preventing radiographic progression[2-4], but has been unable to prevent the worsening of disability over time[5].

Etanercept (Enbrel®, Amgen Inc.) is a fully human soluble tumor necrosis factor (TNF)-receptor fusion protein approved to reduce signs and symptoms, inhibit structural damage, and improve physical function in patients with moderately to severely active RA. Our goal was to assess whether early intervention with etanercept in RA patients is more effective in reducing disability, as measured by the HAQ, than when therapy is initiated later in the disease course.

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MATERIALS AND METHODS

This *post hoc* analysis was a comparison of HAQ scores of 2 groups of adult RA patients, distinct in their duration of disease, who received etanercept over a 3-year period.

Patient populations. The first group of adult patients (recent onset RA, n = 207) was obtained from the Enbrel Early Rheumatoid Arthritis (ERA) trial[6]. Patients were required to have RA for no more than 3 years, with no previous methotrexate (MTX) therapy. The recent onset RA patients included those who received blinded etanercept [25 mg administered subcutaneously (SC) twice-weekly (BIW)] and placebo pills (matched to MTX) for at least 12 months and then switched to open-label 25 mg BIW etanercept for the second and third years[7].

The second group of patients (established RA, n = 464) was obtained from a longterm safety study of etanercept monotherapy[8] and included all patients who had a baseline HAQ score prior to the first administration of etanercept. These adult patients previously had a less-than-optimal response to at least one DMARD (including MTX), and had discontinued the DMARD because of lack of effect. The dosages of etanercept in this group were 10 mg BIW or the recommended dose (25 mg BIW); the vast majority of patients in this group (84%) received 25 mg BIW etanercept for all of their time on therapy. Because the mean duration of RA in this group of patients was 12 years, this population represented RA patients with established disease.

Other than the distinguishing criteria outlined above, inclusion criteria were similar in the trials from which patient data were aggregated. All patients satisfied the 1987 American Rheumatology Association criteria for RA, had at least 10 swollen joints and at least 12 painful/tender joints, and satisfied at least one of the following criteria: erythrocyte sedimentation rate (ESR) > 28 mm/h, C-reactive protein (CRP) > 2.0 mg/dl, or duration of morning stiffness of at least 45 minutes.

Data collection and statistical analyses. Data were initially collected at least monthly and then every 3 or 4 months in the longterm study (from 6 months to 3 years), including numbers of tender joints (0–71 scale) and swollen joints (0–68 scale), HAQ scores (0–3 scale), and American College of Rheumatology (ACR) 20, 50, and 70% responses. Summaries and statistical analyses were based on a completers dataset for all endpoints. Differences between the recent onset and established RA groups for categorical variables were compared using the chi-square test. Differences in continuous variables were compared using the Wilcoxon rank-sum test. The effects of baseline variables on the observed differences were assessed with logistic regression and analyses of variance or covariance. All statistical tests were performed at the 2-sided, 0.05 level.

RESULTS

The recent onset RA group comprised 207 patients who were randomized at ERA study entry to receive 25 mg BIW etanercept in a double-blind fashion. Of these patients, 162 (78%) initiated the open-label (25 mg BIW etanercept) extension study, and 148 (71%) had HAQ assessed at year 3. For the majority of recent onset RA patients (53%), the reason for missing HAQ data at year 3 was administrative in nature (e.g., patients lost to followup, HAQ score not assessed at year 3 visit) with smaller numbers due to discontinuations because of adverse events (29%) or inefficacy (19%).

The established RA group comprised 464 patients; 393 had received etanercept (10 mg or 25 mg BIW) as monotherapy in one of 2 clinical trials where baseline HAQ was obtained, and 71 patients had enrolled in the open-label (25 mg BIW etanercept) continuation study after receiving placebo in one of the 2 initial clinical trials. Of the 393 originally receiving etanercept, 336 (85%) enrolled in the open-label (25 mg BIW etanercept) continuation study. Of the total 464 established RA patients, 288 (62%) had HAQ assessed at year 3. For the majority of established RA patients, the reason for missing HAQ data at year 3 was administrative in nature (52%) with smaller numbers due to discontinuations because of adverse events (24%) or inefficacy (24%).

Patients with recent onset disease had shorter duration of RA (mean duration of 1 year) than those with established RA (mean duration of 12 years) and had been treated with fewer numbers of DMARD (Table 1). In addition, patients with established RA had significantly higher baseline HAQ scores (p = 0.0004) and CRP levels (p = 0.0005) than did recent onset RA patients. Otherwise, baseline demographics and disease characteristics, including numbers of tender and swollen joints, were similar between groups. Whereas baseline CRP was not a significant predictor of percentage change in HAQ at any timepoint, baseline HAQ score was a significant predictor of percentage change in HAQ, particularly at the earlier timepoints. Therefore, baseline HAQ score was controlled for in all analyses.

Patients in both the recent onset RA and established RA groups achieved rapid and sustained clinical responses with etanercept therapy, as shown by similar decreases in number of tender and swollen joints. In the recent onset RA group, the mean number of tender joints was 31 at baseline and decreased by a mean of 69% at year 3, compared with the established RA group's baseline tender joint count of 32 and mean reduction of 75% at year 3 (Figure 1, Panel A). Swollen joint counts responded to etanercept therapy in a similar manner (Figure 1, Panel B). Improvements in duration of morning stiffness and in patient and physician assessments of disease activity were also comparable between groups (data not shown). Overall, the percentages of patients achieving ACR 20, 50, and 70% responses at year 3 were 76%, 56%, and 33% respectively in the recent onset

Table 1. Baseline demographics and disease characteristics. Values are expressed as mean (standard deviation) unless otherwise noted.

Characteristic	Recent Onset RA (n = 207)	Established RA (n = 464)
Female, %	74	80
White, %	86	91
Rheumatoid factor positive, %	87	82
Age, yrs	51.1 (13.4)	53.0 (12.3)
Duration of RA, yrs	1.0 (0.9)	12.2 (9.3)
Number of prior DMARDs	0.5 (0.7)	3.4 (1.7)
HAQ score	1.45 (0.6)	1.64 (0.7)
No. of tender joints	30.6 (15.8)	32.0 (14.7)
No. of swollen joints	23.5 (11.9)	25.1 (11.2)
CRP (mg/dl)	3.3 (4.0)	4.5 (5.2)

RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; HAQ: health assessment questionnaire; CRP: C-reactive protein.

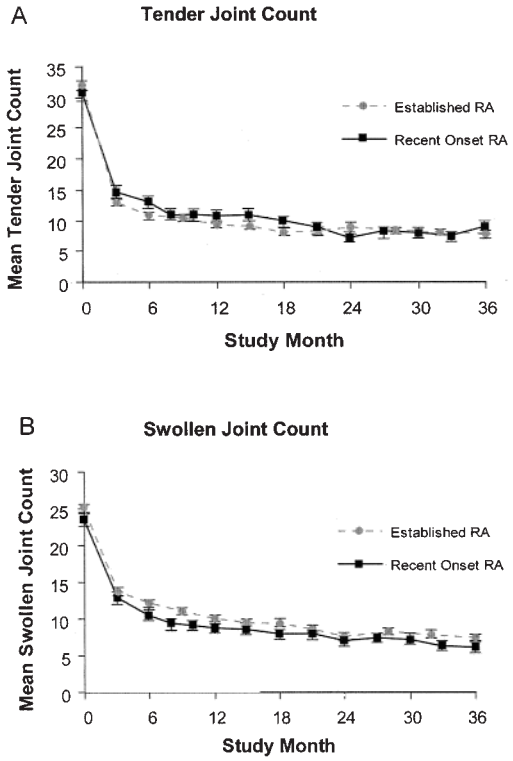

Figure 1. Tender and swollen joint counts throughout 3 years of observation in patients with RA treated with etanercept. Established RA refers to the group of patients with long-standing disease (n = 464, mean duration of 12 years), while recent onset RA refers to those with early disease (n = 207, mean duration of 1 year). Error bars represent standard errors. Tender and swollen joint counts decreased rapidly with etanercept therapy and low counts were maintained for 3 years; there were no significant differences between groups.

RA group compared with 77%, 50%, and 28%, respectively, in the established RA group.

Although improvements in HAQ scores were rapid in both groups, the magnitude of improvement in disability with etanercept therapy was greater in patients with early disease compared with the established RA group (Figure 2). Table 2 lists the mean percentage improvements of HAQ scores from baseline for both groups at week 2, month 1, month 3, and year 3. The difference in mean percentage improvement in HAQ score between groups reached statistical significance as early as week 2 ($p = 0.0074$) and was sustained throughout the 3 years of observation. For example, the HAQ scores of the recent onset RA group improved by 36% at 1 month, compared with 26% in the established RA group ($p = 0.0046$). At year 3, patients with early RA had improved by 56% compared with 39% in those with long-standing disease ($p = 0.0016$).

The Outcome Measures in RA Clinical Trials (OMERACT) guidelines suggest that a reduction in HAQ score of at least 36% from baseline constitutes clinical benefit for an individual patient[9]. In other terms, a reduction of at least 0.22 units in HAQ score is clinically meaningful

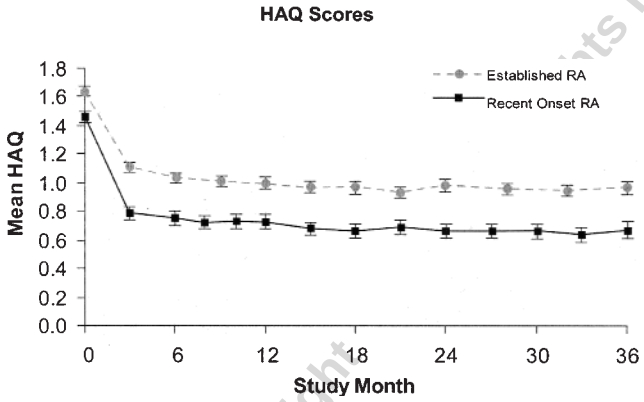

Figure 2. HAQ scores throughout 3 years of observation in patients with RA treated with etanercept. Error bars represent standard errors. HAQ scores decreased rapidly in all RA patients treated with etanercept, but the magnitude of the reduction was significantly greater in the recent onset RA group compared with the established RA group at all time points.

for an individual patient[10], and this benchmark is often cited as the minimal clinically important difference (MCID). In our analysis, most patients achieved the MCID by week 2 of etanercept therapy (66.3% of the recent onset RA group and 51.9% of the established RA group), and the proportions achieving the MCID continuously increased over the observation period (84.8% of the recent onset RA group and 75.3% of the established RA group at year 3; Table 2). This benchmark also illustrates the more rapid HAQ improvement in patients with early RA compared with those having established disease; in the recent onset RA group, 72.5% achieved the MCID by month 1 of etanercept therapy, whereas in the established RA group, 70.1% achieved the MCID by month 3.

More patients with recent onset than with established disease achieved HAQ scores of less than 1.0 (considered mild disability[11]) (Figure 3). Specifically, at year 3, HAQ scores less than 1.0 were achieved in 62% of patients with early disease compared with 52% of patients with established disease, but when adjusted for baseline HAQ score this difference was not statistically significant ($p = 0.22$). Importantly, a significantly greater proportion of patients with recent onset RA (26%) achieved a HAQ score of zero at year 3 than did patients with established RA (14%), even when controlling for baseline HAQ score ($p = 0.0095$).

DISCUSSION

Our objective was to compare the magnitude and sustainability of etanercept-induced improvement in disability between RA patient groups differing in the duration of their disease. Etanercept improved the disability profile of patients with recent onset RA and patients with established RA, but those with early disease were afforded greater and more rapid improvement. A significant difference in magnitude of HAQ improvement persisted between the recent

Table 2. Improvement in HAQ scores from baseline, including patients with HAQ evaluations receiving etanercept 25 mg BIW and excluding those with a HAQ score of 0 at baseline (recent onset RA, n = 6; established RA, n = 2).

Time	Recent Onset RA	Established RA	p
Week 2			
n	196	77	
Mean percent improvement (SE)	29.8 (2.2)	17.6 (3.6)	0.00074*
Number achieving MCID (%)	130 (66.3)	40 (51.9)	0.0094**
Month 1			
n	200	297	
Mean percent improvement (SE)	36.4 (2.3)	26.3 (1.9)	0.0046*
Number achieving MCID (%)	145 (72.5)	176 (59.3)	0.0008**
Month 3			
n	194	374	
Mean percent improvement (SE)	49.9 (2.6)	34.5 (2.1)	< 0.0001*
Number achieving MCID (%)	161 (83.0)	262 (70.1)	0.0004**
Year 3			
n	145	287	
Mean percent improvement (SE)	55.7 (3.4)	39.3 (3.2)	0.0016*
Number achieving MCID (%)	123 (84.8)	216 (75.3)	0.0125**

HAQ: health assessment questionnaire; RA: rheumatoid arthritis; SE: standard error; MCID: minimal clinically important difference, defined as ≥ 0.22 unit improvement in HAQ score from baseline[10]. * Values are from analysis of variance controlling for baseline HAQ score. ** Values are from logistic regression controlling for baseline HAQ score.

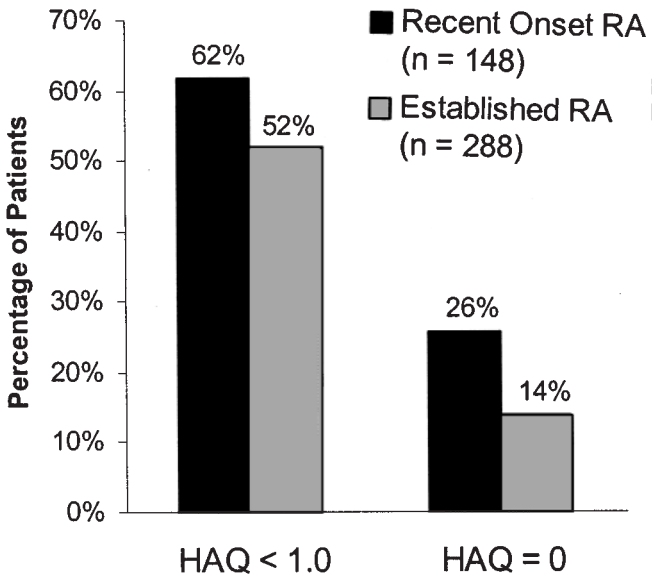

Figure 3. Percentages of patients in the recent onset RA (mean duration of 1 year) and established RA (mean duration of 12 years) groups with a HAQ score of less than one at year 3 and equal to zero at year 3. Analysis controlling for differences in baseline HAQ scores showed no statistical difference of percentages of patients with HAQ < 1.0 between groups (p = 0.22), but significantly more patients with recent onset RA achieved a HAQ of 0 than those with established RA (p = 0.0095).

onset RA group and established RA group from week 2 through year 3.

In previous reports, etanercept has been shown to reduce disease activity and decrease disability in patients with either early or established RA, both as monotherapy and in combination with MTX[6,7,12,13]. In patients with established disease, these benefits have been sustained with continued etanercept monotherapy for more than 4 years[8]. The shift in treatment paradigm to initiate DMARD and/or biologic therapy early in the disease course is an effort to improve patient outcome, but the effect of early intervention on disability has not been reported.

The HAQ score is a measure of disability and has been shown to be a good predictor of patient outcome in RA[1,6,14-16]. The primary effectors of HAQ scores are inflammatory disease activity (in both early and established RA) and joint damage (in established RA). Most observational studies show that HAQ scores, along with joint damage, increase with disease duration[1,17,18]. Accordingly, in our analysis, the mean baseline HAQ score of patients with established RA was significantly higher than that of patients with recent onset RA (1.64 vs 1.45, p = 0.0004). The relatively high baseline HAQ score of the recent onset RA group is most likely related to pain and inflammatory synovitis causing disability in the absence of joint damage, whereas existing joint damage is a key contributor to the even higher baseline HAQ score of the established RA group.

We found that etanercept significantly decreased disability in both early and later stages of RA, most likely by reducing inflammatory disease activity. However, patients with recent onset RA responded with a greater magnitude of HAQ improvement than did those with established RA. This finding is almost certainly attributable to the existing joint damage in patients with established RA, which prevented them from responding to the same degree as patients

receiving etanercept before significant joint damage developed.

In addition to decreasing inflammatory disease activity, etanercept and other biologics have been shown to retard radiographic progression of RA[6,7,19-22] and etanercept is approved for this indication. Thus, whereas treatment with etanercept later in the course of RA may benefit disability by reducing inflammation (and inhibiting further joint damage), treatment early in the course of RA may maximize improvement of the disability profile by decreasing disease activity and minimize future disability by preventing joint damage.

Greater benefit on disability being afforded to those with early disease is not likely to be an exclusive finding of etanercept, as traditional DMARD and other biologics may provide the same results. However, joint damage is an important contributor to disability, and the newer biologics are superior to MTX, the gold standard DMARD, in their ability to inhibit radiographic progression[7,23]. Starting appropriate therapy early in the course of RA is the best overall strategy. The decision to treat patients with recent onset RA with biologics should be made in consideration not only of proven efficacy, but also of the associated safety profile and cost[24].

Our report is based on a *post hoc* aggregate analysis, which has limitations. One confounder of such an analysis is the lack of randomization, but given the nature of the current comparison (intervention early vs late in the course of RA) randomization would not be feasible or ethical. The completers dataset utilized in our analysis excludes data for patients after they discontinue the study. However, dropout rates were similar between the 2 groups, and the majority of patients who discontinued did so for reasons other than inefficacy. Although prospectively defined analyses are optimal, the strength of our report is the examination of all patients with recent onset and established RA for whom HAQ data were available to address the important, patient-centered issue of disability in patients treated with etanercept for up to 3 years.

A limitation of this report is that the groups of patients analyzed were obtained from separate studies. However, inclusion criteria for the studies were similar, patients received similar dosages of etanercept over 3 years of a roughly comparable calendar time period, and most baseline characteristics of disease were similar between groups. The primary difference in the groups, besides the duration of RA, was that recent onset RA patients had not been previously treated with MTX while the established RA patients had previously had a less than optimal response to one or more DMARD. While it may be argued that these differences may bias the established RA group to include patients with more severe disease, it should be noted that any group with long-standing disease is inherently likely to have tried a larger number of DMARD (as reflected in the baseline characteristics) and had an inadequate response to at least one. Moreover, the fact that the established RA group had a higher HAQ at baseline was adjusted for in all statistical analyses.

Etanercept therapy improves disability, as measured by the HAQ, in patients with early and long-standing RA, with greater benefit conferred on patients with early disease. Early intervention provides an opportunity to achieve and maintain greater physical function in patients with RA. Results from this *post hoc* analysis support prompt treatment of RA at an early stage of disease to minimize patient disability.

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REFERENCES

1. Wolfe F. A reappraisal of HAQ disability in rheumatoid arthritis. Arthritis Rheum 2000;43:2751-61.
2. Pincus T, Callahan LF, Fuchs HA, Larsen A, Kaye J. Quantitative analysis of hand radiographs in rheumatoid arthritis: time course of radiographic changes, relation to joint examination measures, and comparison of different scoring methods. J Rheumatol 1995;22:1983-9.
3. Stenger AA, Van Leeuwen MA, Houtman PM, et al. Early effective suppression of inflammation in rheumatoid arthritis reduces radiographic progression. Br J Rheumatol 1998;37:1157-63.
4. Rich E, Moreland LW, Alarcon GS. Paucity of radiographic progression in rheumatoid arthritis treated with methotrexate as the first disease modifying antirheumatic drug [comment]. J Rheumatol 1999;26:259-61.
5. Gordon P, West J, Jones H, Gibson T. A 10 year prospective followup of patients with rheumatoid arthritis 1986-96. J Rheumatol 2001;28:2409-15.
6. 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.
7. 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.
8. Moreland LW, Cohen SB, Baumgartner SW, et al. Long-term safety and efficacy of etanercept in patients with rheumatoid arthritis. J Rheumatol 2001;28:1238-44.
9. Goldsmith CH, Boers M, Bombardier C, Tugwell P. Criteria for clinically important changes in outcomes: development, scoring and evaluation of rheumatoid arthritis patient and trial profiles. OMERACT Committee. J Rheumatol 1993;20:561-5.
10. Wells GA, Tugwell P, Kraag GR, Baker PR, Groh J, Redelmeier DA. Minimum important difference between patients with rheumatoid arthritis: the patient's perspective. J Rheumatol 1993;20:557-60.
11. Wolfe F, Kleinheksel SM, Cathey MA, Hawley DJ, Spitz PW, Fries JF. The clinical value of the Stanford Health Assessment Questionnaire Functional Disability Index in patients with rheumatoid arthritis. J Rheumatol 1988;15:1480-8.
12. Moreland LW, Schiff MH, Baumgartner SW, et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med 1999;130:478-86.
13. 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.
14. Pincus T, Callahan LF. Taking mortality in rheumatoid arthritis seriously — predictive markers, socioeconomic status and comorbidity. J Rheumatol 1986;13:841-5.
15. Young A, van der Heijde DM. Can we predict aggressive disease? Baillieres Clin Rheumatol 1997;11:27-48.
16. Young A, Dixey J, Cox N, et al. How does functional disability in early rheumatoid arthritis (RA) affect patients and their lives? Results of 5 years of follow-up in 732 patients from the Early RA Study (ERAS). Rheumatology Oxford 2000;39:603-11.
17. Welsing PM, van Gestel AM, Swinkels HL, Kiemeney LA, van Riel PL. The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis. Arthritis Rheum 2001;44:2009-17.
18. Scott DL, Pugner K, Kaarela K, et al. The links between joint damage and disability in rheumatoid arthritis. Rheumatology Oxford 2000;39:122-32.
19. Bresnihan B, Alvaro-Gracia JM, Cobby M, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41:2196-204.
20. Lipsky PE, Van der Heijde DMFM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. N Engl J Med 2000;343:1594-602.
21. Strand V. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159:2542-50.
22. Emery PBF, Breedfeld FC, Lemmel EM, et al. A comparison of the efficacy and safety of leflunomide and methotrexate for the treatment of rheumatoid arthritis. Rheumatology Oxford 2000;39:655-65.
23. Ory PA. Interpreting radiographic data in rheumatoid arthritis. Ann Rheum Dis 2003;62:597-604.
24. Lovinger SP. Use of biologics for rheumatoid arthritis tempered by concerns over safety, cost. JAMA 2003;289:3229-30.