Continued Inhibition of Radiographic Progression in Patients with Psoriatic Arthritis Following 2 Years of Treatment with Etanercept

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ABSTRACT. ***Objective.*** Clinical and radiographic responses were evaluated in patients with psoriatic arthritis (PsA) treated for up to 2 years with etanercept.

Methods. Patients were previously randomized to receive placebo or etanercept in a double-blind study and chose to participate in the current open-label extension phase. All patients received etanercept 25 mg twice weekly. Radiographic progression was determined at baseline, 1 year, and 2 years using the Sharp method modified to include joints frequently affected in PsA. Arthritis and psoriasis responses were determined using American College of Rheumatology 20% (ACR20) improvement criteria, PsA response criteria (PsARC), and the psoriasis area severity index (PASI).

Results. Of 205 patients randomized, 169 entered open-label, and 141 [71 randomized to receive placebo (placebo/etanercept) and 70 randomized to receive etanercept (etanercept/etanercept)] had radiographic data available for analysis at 2 years. ACR20 criteria, PsARC, and PASI 50 criteria were met by 64%, 84%, and 62%, respectively, of etanercept/etanercept patients at the end of the 48-week open-label period. Placebo/etanercept patients achieved comparable results within 12 weeks that were sustained at 48 weeks (63%, 80%, and 73%). Radiographic progression was inhibited in the etanercept/etanercept patients (mean adjusted change in total Sharp score of –0.38 from baseline to 2 yrs). In placebo/etanercept patients, disease progression was inhibited once patients began receiving etanercept (mean adjusted change of –0.22 from 1 year to 2 years). Adverse event rates were similar to those observed during randomized phase, with only one serious adverse event deemed possibly related to etanercept.

Conclusion. These data demonstrate a sustained benefit of etanercept treatment, including inhibition of radiographic progression, in patients with PsA. (First Release Feb 1, 2006; J Rheumatol 2006;33:712–21)

Key Indexing Terms:
PSORIATIC ARTHRITIS TUMOR NECROSIS FACTOR RECEPTORS RADIOGRAPHS

Psoriatic arthritis (PsA) is a chronic inflammatory condition that occurs in patients with psoriasis, a group consisting of 2% to 3% of the general population[1]. The reported prevalence of PsA varies between 6% and 39% of patients with psoriasis[2-5], depending on the population studied and the criteria used for diagnosis. While PsA shares some features of rheumatoid arthritis (RA), it frequently manifests with distinct features, such as asymmetric involvement limited to a few joints, involvement of distal interphalangeal (DIP) and axial joints, and the presence of dactylitis and enthesitis[6,7]. Further, PsA frequently exhibits specific radiographic features, including the presence of pencil-in-cup deformity, gross osteolysis, joint space widening, ankylosis, juxtaarticular periostitis, shaft periostitis, and tuft resorption[6,7] distinct from that of RA.

Prior to the use of biologic agents, therapies for PsA typically involved nonsteroidal antiinflammatory (NSAID) medications and traditional disease modifying antirheumatic drugs (DMARD), principally methotrexate (MTX), sulfasalazine, and gold. Placebo-controlled trials of these agents, however, have shown only marginal benefit in PsA[8-12]. Leflunomide, an oral pyrimidine synthesis inhibitor, has shown efficacy in PsA and psoriasis, but requires monitoring for elevations in liver enzymes and bone marrow suppression[13]. As most patients with PsA exhibit chronic, progressive disease with early radiographic damage[14] and significant impairment in quality of

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life[15], the need for more effective and early treatment options for PsA is clear.

Recent studies have shown improved efficacy for newer biologic agents directed at inhibition of tumor necrosis factor (TNF) signaling or T cell activation[7], both of which are involved in the inflammatory response in PsA[16-19]. As reported by Mease, *et al*[20], etanercept is the first of these agents to demonstrate not only significant improvement in the clinical symptoms of arthritis and psoriasis, but also inhibition of radiologic progression at 1 year in a placebo-controlled study of patients with PsA. In that study[20], patients randomized to receive etanercept were significantly more likely than patients who received placebo to meet both American College of Rheumatology 20% improvement criteria (ACR20; 59% vs 15%, respectively) and PsA response criteria (PsARC; 72% vs 31%, respectively) and to have improved target lesion scores (32% vs 15%, respectively) after only 12 weeks of treatment. Moreover, at the 1-year timepoint, patients randomized to etanercept had significantly greater inhibition of radiographic disease progression [–0.03 unit change in total Sharp score (TSS)] than patients randomized to placebo (+1.00 unit change in TSS).

We report longer term data with respect to clinical outcome for arthritis and psoriasis and radiographic progression of arthritis following an additional 48 week, open-label treatment period available to patients originally randomized to etanercept or placebo who completed the randomized portion of the study. For patients originally randomized to receive etanercept, these data represent outcome for up to 2 years of treatment.

MATERIALS AND METHODS

This study comprised 3 treatment periods. The initial phase of 24 weeks was a randomized, double-blind comparison of etanercept (25 mg injected subcutaneously twice weekly) and placebo (vehicle) for treatment of patients with PsA[20]. Randomization was stratified according to concomitant use of MTX. Patients who completed the randomized treatment were given the option to continue maintenance therapy, according to the randomized treatment assignment, until all patients had completed the randomized portion of the study. The final period comprised open-label treatment of all eligible patients with etanercept for 48 weeks, and commenced after the last patient enrolled completed the randomized treatment period. All patients who completed at least 12 weeks of treatment and 24 weeks of evaluations in the randomized portion of the study were eligible to participate in the open-label extension, whether they participated in the maintenance phase or not.

Patients. Eligible patients were 18 to 70 years of age with active arthritis, with at least 3 swollen and 3 tender/painful joints at the time of study entry and an inadequate response to NSAID therapy. Patients had one or more of the following PsA clinical subtypes[21]: DIP joint involvement; polyarticular arthritis; arthritis mutilans; asymmetric peripheral arthritis; and ankylosing spondylitis-like arthritis. Patients also were required to have stable psoriasis that involved a target lesion with a diameter of at least 2 cm at any location other than the scalp, axillae, or groin. The study excluded patients who were pregnant or breastfeeding, as well as those with diabetes mellitus requiring insulin, uncompensated congestive heart failure, angina pectoris, uncontrolled hypertension, severe pulmonary disease requiring therapy, and history of cancer other than resected cutaneous basal and squamous cell carcinoma or *in situ* cervical cancer. All patients provided written informed consent before study entry. The Institutional Review Board of each participating center approved the protocol.

Concomitant therapy. During the blinded treatment period the following concomitant drugs were permitted: MTX at a maximal dose of 25 mg/week, corticosteroid use at a dose ≤ 10 mg/day prednisone equivalent, and NSAID at doses not exceeding the maximal dose recommended on the drug label. Other DMARD were not allowed and were to be discontinued at least 4 weeks before study entry. Phototherapy and oral retinoids were not permitted. Topical vitamin A or D analog preparations and anthralin were permitted only for treatment of the scalp, axillae, and groin (i.e., areas excluded from designation as the target psoriatic lesion).

Dose modifications of MTX, corticosteroids, and NSAID were permitted during the maintenance phase. DMARD could be used after completion of the randomized treatment period by patients not continuing maintenance therapy. Topical therapies were permitted during maintenance. At least 2 weeks before the start of open-label treatment, patients receiving DMARD off-study had to stop DMARD therapy, and stable doses of MTX, NSAID, corticosteroids, and topical therapies had to be achieved. During the open-label treatment period, patients originally randomized to etanercept could receive MTX, NSAID, glucocorticoids, or topical therapies at the discretion of the investigator. Patients originally randomized to placebo were required to remain at the stabilized doses of MTX, NSAID, glucocorticoids, or topical therapies for the first 12 weeks of the open-label period. Thereafter, doses could be modified at the discretion of the investigator.

Study drug. During the open-label period, study medication was supplied as sterile, lyophilized powder in vials containing 25 mg etanercept, 40 mg mannitol, 10 mg sucrose, and 1.2 mg tromethamine or placebo (identical except without etanercept), reconstituted with 1 ml bacteriostatic water for injection. Study medication was self-administered by subcutaneous injection twice weekly.

In the case of grade 3 or 4 toxicity (as defined by the National Cancer Institute common toxicity criteria), interruptions of up to 1 week (i.e., 2 doses) were permitted. Change in dose of study drug was not permitted. Recurrence of the same grade 3 or 4 toxicity necessitated discontinuation of treatment.

Clinical assessments. Efficacy of treatment of arthritis was measured by the percentage of patients meeting ACR20, ACR50, and ACR70[22] improvement criteria and PsA response criteria (PsARC)[8,23] at 12, 24, 36, and 48 weeks of the open-label period, as described[20]. Patients who originally received placebo or discontinued prematurely during the randomized treatment period had an additional assessment at Week 4. Both the ACR and PsARC measures included assessments of 78 joints for pain/tenderness and 76 joints for swelling.

Response to treatment of psoriasis was based on the dermatologist's global assessment of target lesions (clear, almost clear, mild, moderate, severe, very severe). Additionally, patients with psoriasis affecting at least 3% of body surface area at baseline were assessed using the psoriasis area and severity index (PASI)[11].

Radiographic assessments. Assessment of articular damage was based on radiographic images of the hands and wrists taken at 6 and 12 months from baseline and after 48 weeks of open-label treatment (up to 2 years from study entry). For inclusion in this analysis, patients were required to have radiographs taken at the 48-week timepoint or at the time of early withdrawal from the open-label period. Digitized radiographs from all timepoints for each patient were read in random order by 2 site-independent, blinded radiologists selected from a pool of 4 blinded reviewers.

Radiographic images were scored by the Sharp method[24] with the following modifications: 25 hand/wrist joints were scored for erosion; 24 hand/wrist joints were scored for joint space narrowing (JSN), with exclusion of the radio-ulnar and lunate-triquetrum joints of the wrist; DIP joints were included; and the erosion score was modified to allow a change of one integer in the score for each joint if the number of erosions had changed or there was a change of ≥ 20% in the area eroded. The erosion score used a scale of 0 to 5, and the JSN score used a scale of 0 to 4, both as originally described.

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Additionally, radiographs of the hands and wrists were scored for the presence or absence of juxtaarticular periostitis, shaft periostitis, tuft resorption, pencil-in-cup deformity, gross osteolysis, joint space widening, and ankylosis.

Statistical analysis. All analyses were performed using the subset of patients who had radiographs available for inclusion in the 2-year assessment, as described above. Efficacy variables assessed during the open-label treatment period were calculated relative to each patient's original baseline in the double-blind period of the study. Descriptive statistics of efficacy endpoints are presented. Results are based on the observed population at each timepoint, as efficacy evaluations were not available for all patients at all timepoints during the open-label period.

Changes in the erosion score, the JSN score, and the total Sharp score were assessed at target timepoints of 6 months, 1 year, and 2 years from baseline. Each score for each patient was taken as the average of the 2 reviewers' scores. As the actual timing for individual radiographs may have differed from the target timepoints, linear interpolation and extrapolation were used to temporally adjust each observed Sharp score (erosion, JSN, and TSS), as well as mean changes in each score, to the target timepoints.

Exploratory analyses were performed to examine the mean adjusted change in TSS from baseline to 2 years according to baseline disease status [TSS = the median (8.5 units) vs > the median for all randomized patients], baseline duration of PsA [≤ the median (7.1 yrs) vs > median for all randomized patients], sex (male vs female), and baseline weight [≤ median (88.4 kg) vs > median for all randomized patients].

Adverse events, infections, and abnormal laboratory data were graded according to National Cancer Institute common toxicity criteria, and analyzed using summary statistics.

RESULTS

Patients. Among the 205 patients originally enrolled in the randomized phase of the study, 169 (88 originally randomized to etanercept; 81 originally randomized to placebo) chose to participate in the open-label study, and 141 (71 originally randomized to etanercept and 70 originally randomized to placebo) were evaluable for radiographic progression at 2 years (Figure 1). Most of the 169 patients with PsA participating in the open-label period of the study were Caucasian (n = 152; 90%) and less than 65 years of age (n = 160; 95%). About half were men and half were women. The 169 patients who chose to participate in the open-label study, as well as the subset of 141 patients considered evaluable for radiographic progression at 2 years, had demographic characteristics and disease history similar to those reported[20] for the overall cohort of 205 patients originally enrolled in the randomized portion of the study (Table 1).

Among the 141 patients included in the 2 year radiographic analysis, 6 had final radiographs taken at the time of early withdrawal (one at 5 months, one at 7 months, and 4 after 8 months or more of open-label treatment). Twenty-eight patients could not be included in the radiographic analysis because 15 patients lacked radiographs taken at early withdrawal and 13 lacked radiographs taken at the time of study completion.

Nineteen patients (all originally randomized to receive etanercept) deviated from the protocol by using systemic corticosteroids at doses greater than the equivalent of 10 mg/day prednisone; reasons for use of systemic corticosteroids varied and included reasons other than for treatment of PsA (e.g., rib pain). Twenty-four patients (14 originally randomized to etanercept, 10 originally randomized to placebo) missed 2 consecutive planned doses of etanercept.

Clinical evaluation

Arthritis response. ACR responses to etanercept previously reported for the first half of the open-label period[20] were sustained after 48 weeks of open-label treatment both for patients originally randomized to etanercept and for those originally randomized to placebo, with 64% and 63%, respectively, meeting ACR20 criteria, and 44% and 49%, respectively, meeting ACR50 criteria. As reported[20], comparability between the groups was reached by 12 weeks of treatment. Twenty-three percent of patients initially randomized to etanercept and 13% of patients originally randomized to placebo met ACR70 criteria at the end of the open-label treatment period.

The efficacy of etanercept also was evaluated using the PsARC. Among patients originally randomized to receive etanercept, the percentage of patients deemed responders according to PsARC was at least 80% throughout the open-label treatment period (Figure 2). Among patients originally randomized to receive placebo, the response rate according to PsARC reached parity with that of patients originally randomized to etanercept by 12 weeks, and this effect was maintained at the end of the open-label period.

Psoriasis response. Among patients originally randomized to etanercept therapy, the percentage achieving a target lesion response of clear or almost clear ranged from 45% to 58% over the course of the open-label treatment period. Patients originally randomized to receive placebo showed similar target lesion responses by 12 weeks of open-label therapy with etanercept (Figure 3A).

PASI was evaluated for 102 patients (55 originally randomized to etanercept; 47 originally randomized to placebo) who had psoriasis that involved at least 3% of their body surface area (BSA; mean 16% BSA at baseline). Throughout the open-label period, 56% to 69% of patients originally randomized to etanercept met the PASI 50 improvement criteria (i.e., a 50% improvement from baseline in PASI score; Figure 3B). While only 23% of patients originally randomized to placebo met PASI 50 improvement criteria at the beginning of the open-label period, this proportion reached parity with the group originally randomized to etanercept by 12 weeks, and the effect was maintained for the remainder of the open-label period. Additionally, the PASI 75 improvement criteria (i.e., a 75% improvement from baseline in PASI score) were met by 38% of all patients by 12 weeks, an improvement that was maintained for the remainder of the study (Figure 3C).

Radiographic evaluation. The mean adjusted changes in TSS, erosion, and JSN scores from baseline to 6 months, 1 year, and 2 years are shown in Figure 4. In the group of patients originally randomized to receive etanercept, radiographic disease

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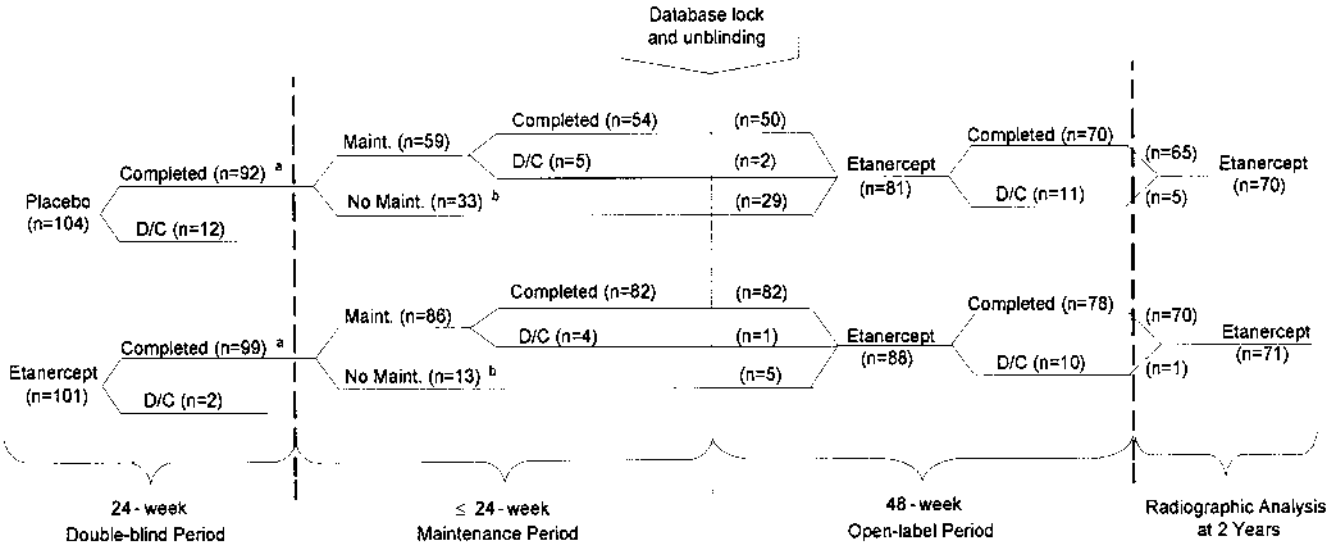

Figure 1. Patient participation during the randomized, maintenance, and open-label phases. Numbers of patients are shown in parentheses. [a]Completed 24 weeks of evaluations and ≥ 12 weeks of investigational product; [b]completed the 24 week double-blind period but did not participate in the maintenance period (these subjects were eligible to enter the open-label period after database lock and unblinding of the study). D/C: discontinued; Maint: maintenance.

Table 1. Baseline demographics and disease characteristics of all patients in the original double-blind period, compared with patients in the open-label period.

	Double-Blind: All Patients			Open-Label: All Patients Received Etanercept 25 mg BIW	
	Placebo, N = 104	Etanercept, n = 101	Total, n = 205	All Patients, Total, N = 169	Patients with 2-yr Radiographs, Total, n = 141
Age, mean yrs	47.3	47.6	47.4	47.0	47.2
Women, no. (%)	57 (55)	43 (43)	100 (49)	82 (49)	77 (55)
Caucasian, no. (%)	95 (91)	91 (90)	186 (91)	152 (90)	125 (89)
Duration of PsA, mean yrs	9.2	9.0	9.1	9.3	9.2
Duration of psoriasis, mean yrs	19.7	18.3	19.0	19.2	19.0
Psoriasis BSA, mean percentage	10.2	10.9	10.6	10.7	10.3
Evaluable for PASI, no. (%)	62 (60)	66 (65)	128 (62)	113 (67)	89 (63)
Radiographic scores at baseline, mean					
Total Sharp score	18.30	25.89	NA	NA	22.48
Erosion score	8.57	12.88	NA	NA	11.19
Joint space narrowing	9.73	13.01	NA	NA	11.29
No. of prior DMARD, mean	1.6	1.7	1.6	1.7	1.7
Randomized to MTX strata, no. (%)	43 (41)	42 (42)	85 (41)	74 (44)	64 (45)
Subtype of PsA, no. (%)					
DIP joints of hand and feet	52 (50)	52 (51)	104 (51)	86 (51)	68 (48)
Arthritis mutilans	2 (2)	1 (1)	3 (1)	3 (2)	2 (1)
Polyarticular arthritis	86 (83)	87 (86)	173 (84)	141 (83)	119 (84)
Asymmetric peripheral arthritis	40 (38)	41 (41)	81 (40)	67 (40)	57 (40)
Ankylosing spondylitis-like	4 (4)	3 (3)	7 (3)	7 (4)	5 (4)

BSA: body suface area; DIP: distal interphalangeal; DMARD: disease modifying antirheumatic drug; MTX: methotrexate, NA: not available; PASI: psoriasis area and severity index; PsA: psoriatic arthritis.

progression continued to be suppressed after 2 years of treatment. Mean (SE) adjusted change in TSS from baseline to 2 years for this group was –0.38, a result comparable to that observed at the 6 month and 1 year timepoints[20]. In the group of patients originally randomized to receive placebo, disease progression was inhibited once patients began receiving etanercept, as evidenced by a decreased positive mean adjusted change in TSS (0.72 from baseline to 1 year and 0.50 from baseline to 2 years). The decrease in TSS from 1 year to 2 years of treatment for patients who switched from placebo to

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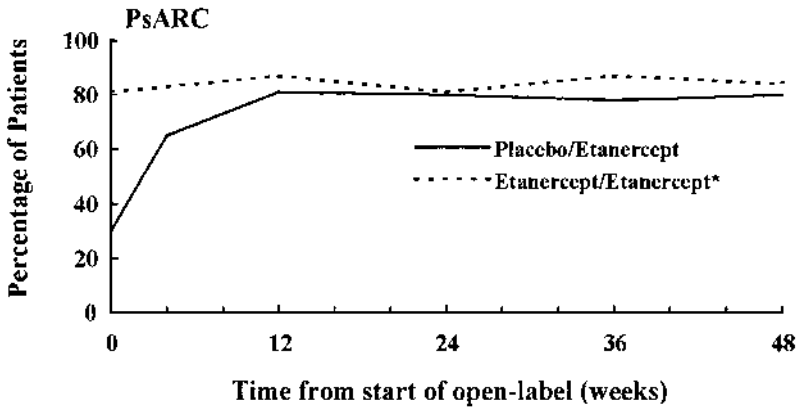

Figure 2. PsARC responses during the open-label treatment period. Percentage of patients meeting PsARC criteria from 0 to 48 weeks of open-label treatment. *Evaluation at 4 weeks for the etanercept/etanercept group was excluded as it involved only 6 patients who had discontinued treatment during the maintenance phase of the protocol.

etanercept (mean adjusted change of –0.22) was comparable to the response shown after the first year of therapy (mean adjusted change of –0.28) by patients originally randomized to etanercept. The decreases in TSS for both groups of patients reflected changes in the mean erosion score at both the 1 year and 2 year assessments. JSN scores remained essentially unchanged for both the placebo/etanercept group and the etanercept/etanercept group throughout the open-label phase.

The percentage of patients within each of the original randomized treatment groups who showed no radiographic progression (change in adjusted TSS = 0) was higher for patients originally randomized to etanercept and remained relatively constant over the entire course of the study (Table 2). Thirty patients (24 originally randomized to etanercept; 6 originally randomized to placebo) had a change in TSS from baseline to 1 year that was < 0. In 27 (90%) of these patients, the change remained < 0 at 2 years. Similarly, among patients with changes in adjusted TSS ≤ –1 and ≤ –2 at 1 year, 15/17 (88%) and 5/7 (71%), respectively, had changes ≤ –1 and ≤ –2 at 2 years.

Cumulative probability plots of radiographic progression (TSS, erosion, and JSN scores) illustrate these results in a continuous manner, where all individual patient data are plotted in Figure 5; the x axis shows the cumulative percentage and the y axis shows the actual change from baseline. The graphs show that a lower number of patients had structural progression (upper right quadrant of each graph) and a higher number had negative scores (lower left quadrant of each graph) in the original etanercept group, compared with the group originally assigned to placebo and crossed-over to etanercept.

Of interest, exploratory analyses of the data by concomitant MTX and corticosteroid use showed no significant differences in radiographic outcome.

Although etanercept inhibited overall progression as measured by TSS, the percentages of patients with PsA-specific radiographic features (ankylosis, joint space widening, pencil-in-cup deformity, gross osteolysis, shaft periostitis, juxtaarticular periostitis, and tuft resorption) were essentially unchanged in both treatment groups from baseline to Year 2.

Subgroup analyses. Exploratory analyses of the prognostic effects of baseline disease status, PsA duration, and sex indicated that these characteristics could not be used as predictors of responsiveness to etanercept. Statistically comparable responses were observed in men and women and in patients above and below the baseline study medians for TSS, duration of disease, height, and weight; however, there was a trend toward greater improvement in men, in those with a TSS > 8.5 at baseline, and in those diagnosed more than 6.58 years before study entry.

Safety and tolerability. Etanercept continued to be well tolerated during the open-label portion of the study. There were no deaths. Three patients withdrew from the open-label period because of adverse events (severe transient elevated alanine transaminase, moderate left shoulder fracture/dislocation, and mild numbness in fingers); none of these events was judged by the investigator to be related to the study drug. The patient who experienced elevated liver enzymes received concomitant MTX treatment, which provides a plausible cause for the adverse event. Nineteen severe adverse events were reported in 19 patients during the open-label period. All but one (suspected bacterial pneumonia in a 60-year-old woman) were deemed unrelated to etanercept. Three grade 3 infections (2 cases of pneumonia, one case of pharyngitis) were reported in 3 patients. Rates per patient-year of upper respiratory infection, sinusitis, urinary tract infection, flu syndrome, pharyngitis, and bronchitis were similar to those observed during the randomized phase of the study. Injection site reactions occurred in 10% of patients in the original etanercept group, compared with 27% of patients in the original placebo group.

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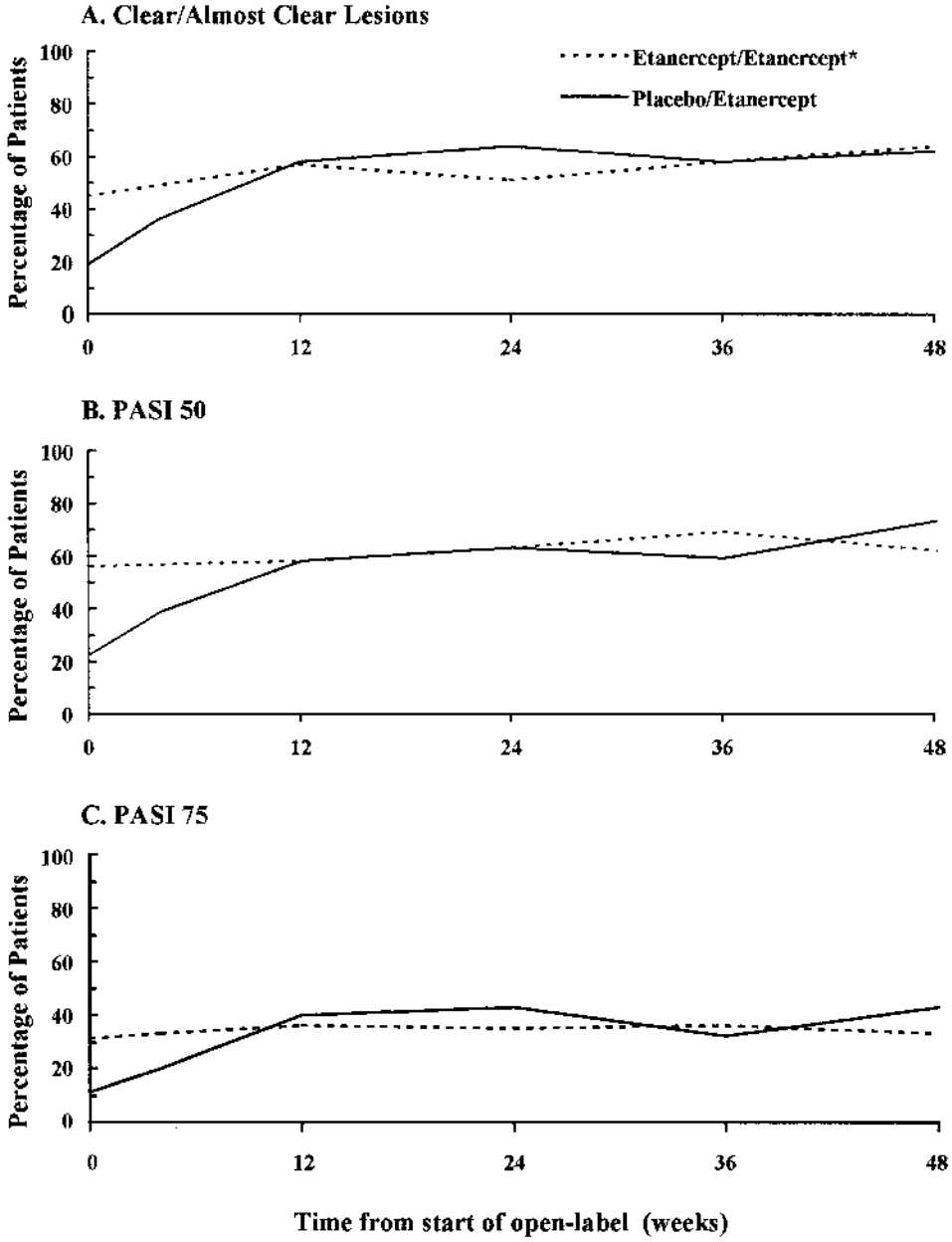

Figure 3. Responses to treatment of psoriasis in the open-label treatment period. A. Percentage of patients with clear or almost clear target lesion responses. B. Percentage of patients achieving PASI 50. C. Percentage of patients achieving PASI 75. *Evaluation at 4 weeks for the etanercept/etanercept group was excluded as it involved only 6 patients who had discontinued treatment during the maintenance phase of the protocol.

Again, all occurrences were mild or moderate (grade 1 or 2) in severity. All laboratory abnormalities were mild (grade 1 or 2) with the exception of the aforementioned grade 3 transiently elevated alanine transaminase. Overall, rates (per patient-year) of adverse events that occurred in at least 5% of all patients treated with etanercept during the maintenance and open-label periods were similar to or lower than those observed during the 24 week double-blind treatment (data not shown).

DISCUSSION

We previously reported that etanercept demonstrated clinical efficacy, inhibited structural progression, and was well tolerated in patients with PsA after up to 1 year of treatment[20]. Our current report shows that etanercept continues to be efficacious and well tolerated, and importantly, that it continues to inhibit structural progression in patients with PsA after 2 years of treatment. The initial favorable clinical responses, measured by ACR20, PsARC, PASI 50 criteria, and target lesion

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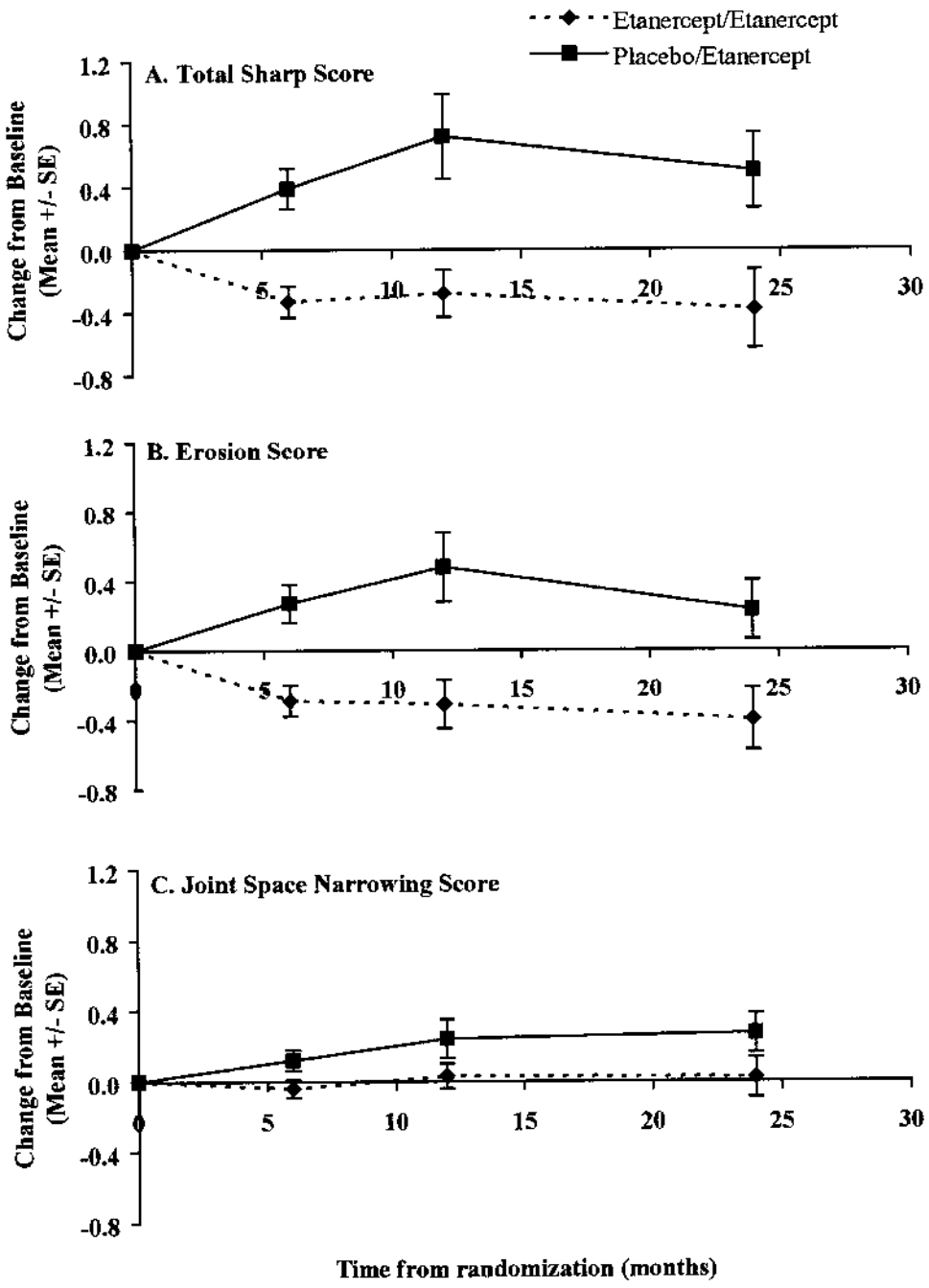

Figure 4. Mean adjusted changes in Sharp scores from baseline to 2 years. A. Total Sharp scores. B. Erosion scores. C. Joint space narrowing scores. Each data point represents the mean (± standard error of the mean) change from baseline.

responses, were maintained in patients who continued to receive etanercept for longer term treatment: 64% of patients met ACR20, 80% met PsARC, 62% met PASI 50, and 49% had clear or almost clear target lesions after 48 weeks of open-label treatment compared with 50%, 70%, 47%, and 40%, respectively, at Week 24 of the randomized portion of the study. Patients who switched from placebo to etanercept rapidly reached parity in all clinical responses with their etanercept/etanercept treated counterparts after roughly 12 weeks of treatment, with 63% meeting ACR20 criteria, 80% meeting PsARC, 73% meeting PASI 50, and 62% achieving clear or almost clear target lesions at 48 weeks.

Radiographic disease progression in this study was quantified using a modification of the Sharp method[24]. As previous-

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Table 2. Number (%) of patients with no radiographic progression, defined as a change ≤ 0 in adjusted total Sharp score, erosions, and joint space narrowing over time.

Timepoint	Placebo/ Etanercept Group, n = 70 (%)	Etanercept/ Etanercept Group, n = 71 (%)
Total Sharp score		
6 mo	48 (69)	64 (90)
1 yr	45 (64)	59 (83)
2 yrs	44 (63)	61 (86)
Erosions		
6 mo	54 (77)	68 (96)
1 yr	51 (73)	62 (87)
2 yrs	52 (74)	62 (87)
Joint space narrowing		
6 mo	60 (86)	63 (89)
1 yr	53 (76)	60 (85)
2 yrs	56 (80)	62 (87)

ly described, the modifications for this trial were aimed at improving the applicability of the method to quantifying unique features of PsA, such as shaft periostitis, juxtaarticular periostitis, and tuft resorption, and to include the distal interphalangeal regions of digits that are frequently affected in PsA. Our analysis shows that etanercept continued to be effective in inhibiting radiographic progression through up to 2 years of treatment. Mean adjusted change in TSS were equal to –0.28 units at 1 year and –0.38 units at 2 years, suggesting durable efficacy. Moreover, whereas radiographic progression was observed for patients treated with placebo during the randomized phase of the study, further radiographic progression was inhibited once these patients began receiving etanercept. For patients originally randomized to placebo, the mean adjusted changes in TSS were 0.72 units from baseline to 1 year and 0.50 units from baseline to 2 years, and the mean adjusted change from 1 year to 2 years was –0.22, a decrease similar in magnitude to that observed from baseline to 1 year (–0.28) in their counterparts who were originally randomized to etanercept. The changes in TSS in both patient groups primarily reflected changes in the erosion score, but not the JSN score.

The percentage of patients who showed no radiographic progression remained relatively constant over the entire course of the study, and was higher for patients originally randomized to etanercept. Notably, most patients in whom radiographic progression was inhibited at 1 year continued to show inhibition of progression at 2 years, indicating that etanercept maintained its inhibitory effect on radiographic disease progression during longterm treatment in individual patients.

The percentage of patients with PsA specific features did not change over the course of this study. This observation may be due to the need for longer treatment and followup or the need for a scoring system with greater sensitivity to changes in periostitis, tuft resorption, pencil-in-cup deformity, gross osteolysis, and ankylosis.

The observation of negative changes in TSS observed with etanercept suggests that inhibition of TNF signaling may contribute not only to halting of radiographic disease progression, but also to repair in PsA[25]. The ability of etanercept to halt disease progression implies a benefit for early treatment, as previous investigation has shown that most patients with PsA have already sustained some joint damage by the time they present for treatment, and nearly half have sustained damage within 2 years of diagnosis[14].

During extended exposure, etanercept continued to be well tolerated in patients with PsA and psoriasis. Overall rates of adverse events and infections were similar to those observed during the 24 week randomized phase of the study. One serious adverse event was deemed possibly related to etanercept by the investigator. No clinically relevant abnormal laboratory results were observed during the open-label period.

The efficacy and safety data presented here demonstrate a sustained benefit for use of etanercept in the treatment of both arthritis and psoriasis in patients with PsA, and importantly, show lasting inhibition of radiographic disease progression with minimal adverse side effects. In addition, the data suggest that early and longterm treatment may provide the most benefit to patients with PsA. Further studies are warranted to address the longer-term effects of etanercept on disease progression in patients with PsA.

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REFERENCES

1. Koo J. Population-based epidemiologic study of psoriasis with emphasis on quality of life assessment. Dermatol Clin 1996;14:485-96.
2. Biondi Oriente C, Scarpa R, Pucino A, Oriente P. Psoriasis and psoriatic arthritis. Dermatological and rheumatological co-operative clinical report. Acta Derm Venereol Suppl Stockh 1989;146:69-71.
3. Leonard DG, O'Duffy JD, Rogers RS. Prospective analysis of psoriatic arthritis in patients hospitalized for psoriasis. Mayo Clin Proc 1978;53:511-8.
4. Scarpa R, Oriente P, Pucino A, et al. Psoriatic arthritis in psoriatic patients. Br J Rheumatol 1984;23:246-50.
5. Shbeeb M, Uramoto KM, Gibson LE, O'Fallon WM, Gabriel SE. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. J Rheumatol 2000;27:1247-50.
6. Anandarajah AP, Ritchlin CT. Etanercept in psoriatic arthritis. Expert Opin Biol Ther 2003;3:169-77.
7. Gladman DD. Psoriatic arthritis. Dermatol Ther 2004;17:350-63.
8. Clegg DO, Reda DJ, Mejias E, et al. Comparison of sulfasalazine and placebo in the treatment of psoriatic arthritis. A Department of Veterans Affairs Cooperative Study. Arthritis Rheum 1996;39:2013-20.
9. Cuellar ML, Espinoza LR. Methotrexate use in psoriasis and psoriatic arthritis. Rheum Dis Clin North Am 1997;23:797-809.
10. Farr M, Kitas GD, Waterhouse L, Jubb R, Felix-Davies D, Bacon PA. Sulphasalazine in psoriatic arthritis: a double-blind placebo-controlled study. Br J Rheumatol 1990;29:46-9.
11. Fredriksson T, Pettersson U. Severe psoriasis — oral therapy with a

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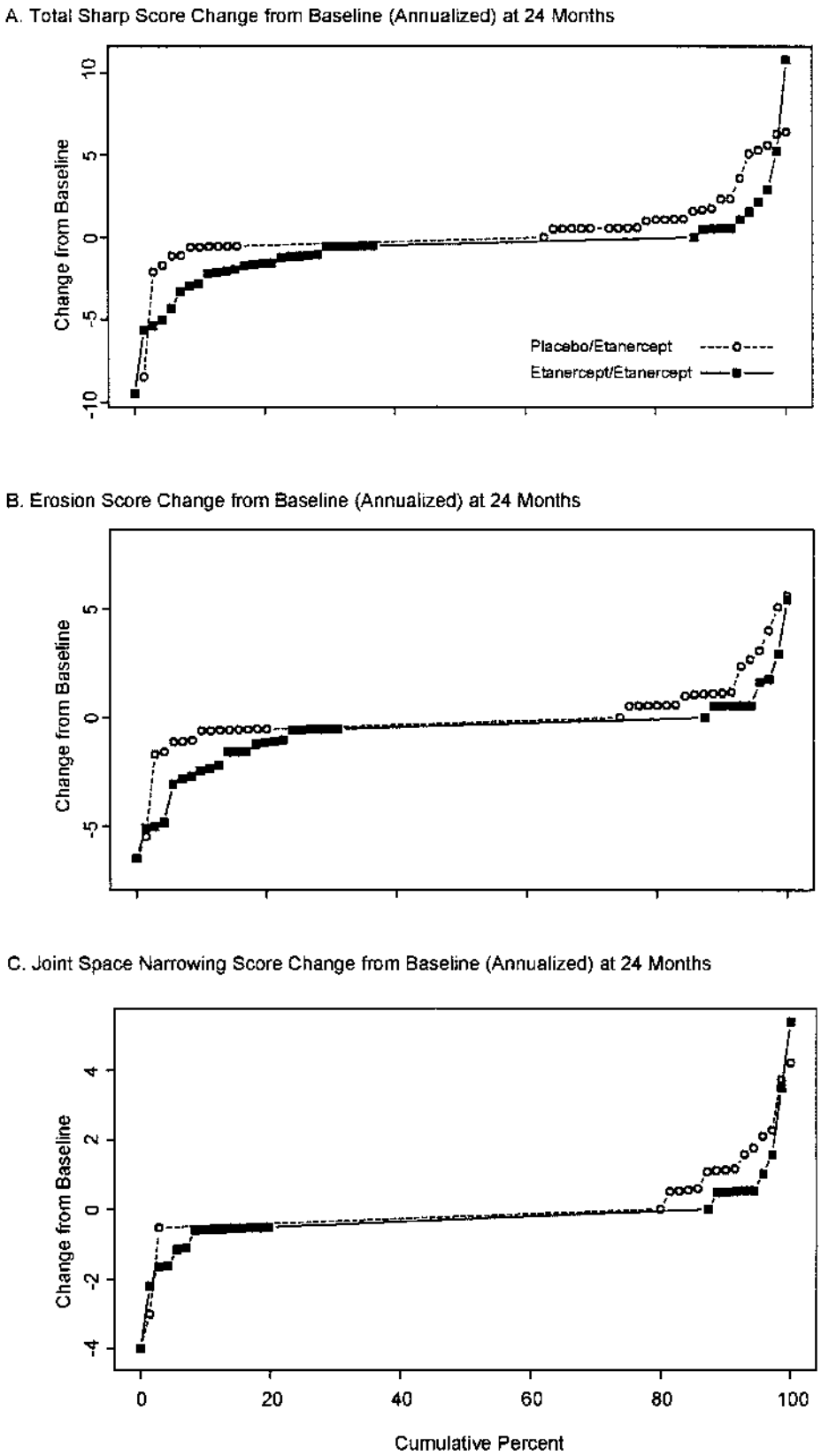

Figure 5. Cumulative probability plots of radiographic progression (TSS, erosion, and JSN scores). All individual patient data are plotted; x axis shows the cumulative percentage, and y axis shows the actual change from baseline. Patients with structural progression are displayed in the upper right quadrant of each graph, patients with negative scores in the lower left quadrant.

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new retinoid. Dermatologica 1978;157:238-44.
12. Willkens RF, Williams HJ, Ward JR, et al. Randomized, double-blind, placebo controlled trial of low-dose pulse methotrexate in psoriatic arthritis. Arthritis Rheum 1984;27:376-81.
13. Kaltwasser JP, Nash P, Gladman D, et al. Efficacy and safety of leflunomide in the treatment of psoriatic arthritis and psoriasis: a multinational, double-blind, randomized, placebo-controlled clinical trial. Arthritis Rheum 2004;50:1939-50.
14. Kane D, Stafford L, Bresnihan B, FitzGerald O. A prospective, clinical and radiological study of early psoriatic arthritis: an early synovitis clinic experience. Rheumatology Oxford 2003;42:1460-8.
15. Zachariae H, Zachariae R, Blomqvist K, et al. Quality of life and prevalence of arthritis reported by 5,795 members of the Nordic Psoriasis Associations. Data from the Nordic Quality of Life Study. Acta Derm Venereol 2002;82:108-13.
16. Ettehadi P, Greaves MW, Wallach D, Aderka D, Camp RD. Elevated tumour necrosis factor-alpha (TNF-alpha) biological activity in psoriatic skin lesions. Clin Exp Immunol 1994;96:146-51.
17. Krueger GG. Selective targeting of T cell subsets: focus on alefacept — a remittive therapy for psoriasis. Expert Opin Biol Ther 2002;2:431-41.
18. Partsch G, Steiner G, Leeb BF, Dunky A, Broll H, Smolen JS. Highly increased levels of tumor necrosis factor-alpha and other proinflammatory cytokines in psoriatic arthritis synovial fluid. J Rheumatol 1997;24:518-23.
19. Ritchlin C, Haas-Smith SA, Hicks D, Cappuccio J, Osterland CK, Looney RJ. Patterns of cytokine production in psoriatic synovium. J Rheumatol 1998;25:1544-52.
20. Mease PJ, Kivitz AJ, Burch FX, et al. Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. Arthritis Rheum 2004;50:2264-72.
21. Moll JM, Wright V. Psoriatic arthritis. Semin Arthritis Rheum 1973;3:55-78.
22. 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.
23. Mease PJ, Goffe BS, Metz J, VanderStoep A, Finck B, Burge DJ. Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. Lancet 2000;356:385-90.
24. Sharp JT, Lidsky MD, Collins LC, Moreland J. Methods of scoring the progression of radiologic changes in rheumatoid arthritis. Correlation of radiologic, clinical and laboratory abnormalities. Arthritis Rheum 1971;14:706-20.
25. van der Heijde DM, Landewe R. Imaging: do erosions heal? Ann Rheum Dis 2003;62 Suppl 2:ii10-2.

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