Patients with Moderate Rheumatoid Arthritis (RA) Achieve Better Disease Activity States with Etanercept Treatment Than Patients with Severe RA

EDWARD KEYSTONE, BRUCE FREUNDLICH, MICHAEL SCHIFF, JUAN LI, and MICHELE HOOPER

ABSTRACT. ***Objective.*** This analysis examined clinical and radiographic responses to methotrexate (MTX), etanercept (ETN), and combination ETN and MTX in patients with moderate versus severe rheumatoid arthritis (RA) in both early and late disease.

Methods. Data from the Trial of Etanercept and Methotrexate With Radiographic Patient Outcomes (TEMPO) and the Early Rheumatoid Arthritis trials were used. Patients were classified with moderate or severe RA based on Disease Activity Score including 28-joint count (DAS28). Outcomes included DAS28 remission, DAS28 low disease activity, Health Assessment Questionnaire (HAQ), American College of Rheumatology (ACR) scores, Total Sharp Score (TSS) progression, no radiographic progression (annualized change in TSS $\leq$ 0), change from baseline in TSS, and the change in TSS for patients who had radiographic progression (TSS > 0).

Results. Patients with moderate disease generally achieved better clinical outcomes than patients with severe disease, including significant differences in DAS28 remission, low disease activity, and HAQ $\leq$ 0.5 at Month 12. Patients with baseline severe disease had higher ACR and DAS responses than patients with moderate disease.

Conclusion. Patients with severe RA disease activity achieved substantial clinical improvement with high-dose MTX and/or ETN treatment, but patients with moderate disease were more likely to reach a lower disease activity state. These findings were independent of disease duration. The results support the opportunity for excellent clinical outcomes, particularly with combination therapy, in patients with moderate RA. (J Rheumatol First Release Feb 15 2009; doi:10.3899/jrheum.080663)

Key Indexing Terms:
ETANERCEPT RHEUMATOID ARTHRITIS OUTCOMES
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Achieving a low disease activity state or even remission is an important goal in the treatment of rheumatoid arthritis (RA). Disease duration, disease activity, and prior intensity of therapy are important considerations for optimizing the treatment of RA. Tumor necrosis factor (TNF) antagonists and high-dose methotrexate (MTX) reduce synovitis and halt joint destruction in a majority of, but not all, treated patients, providing radiographic evidence of inhibition of disease progression in patients with both early and established RA[1-3]. As a consequence of a rapid onset of action, substantial reduction in signs and symptoms, and marked inhibition of radiographic progression, TNF antagonists have contributed to a new paradigm of therapy for RA.

The efficacy of TNF antagonists has been demonstrated in clinical trials that have almost universally included patient populations mostly with severe RA. Although these patients have yielded important data, they represent only a subset of the entire RA population. Indeed, many patients seen in clinical practice do not have the level of severity seen in a typical clinical trial[4].

It is hypothesized that patients with more moderate disease activity will respond better to treatment than patients with severe disease activity. This hypothesis is based on preliminary data from a subanalysis of patients with moderate disease [defined by the Disease Activity Score including a

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28-joint count (DAS28)] treated with adalimumab who achieved a better outcome than those who began with severe disease activity[5]. Further, in a pooled analysis of clinical trials, a correlation was observed between lower baseline disease activity (by the Simplified Disease Activity Index) and disease remission after 1 year of MTX and/or TNF antagonist treatment[6].

To investigate this concept, we carried out a post hoc analysis of a large dataset of patients from 2 clinical trials of etanercept (ETN). The objective of this analysis was to examine clinical and radiographic responses to MTX, ETN, and ETN and MTX combination therapy in patients with moderate versus severe RA in both early and late disease.

MATERIALS AND METHODS

Patients. Data from the Trial of Etanercept and Methotrexate With Radiographic Patient Outcomes (TEMPO)[3] and the Early Rheumatoid Arthritis (ERA) trial[7] were used for the analysis. The study protocols were approved by the institutional review boards and independent ethics committees at the participating study centers, and patients provided written informed consent. Methodology and study results from TEMPO and ERA have been published[3,7]. Briefly, the TEMPO study included 682 patients with active RA not adequately responding to disease-modifying antirheumatic drug therapy other than MTX (43% had previous MTX use), with mean disease duration of about 6.6 years (patient eligibility requirement range, 6 months to 20 years)[3]. Patients were randomized to receive MTX monotherapy, ETN monotherapy 25 mg twice weekly, or concomitant MTX and ETN 25 mg twice weekly treatment for 12 months. The ERA study included 632 patients who had had RA for not more than 3 years and had not previously been treated with MTX. Patients received MTX or ETN (10 mg or 25 mg twice weekly) for 12 months[7], although the 10-mg ETN group was not included in this analysis. Radiographic data were available at 6 and 12 months in both studies.

Within each treatment group, patients with moderate disease activity at baseline were compared with patients with severe disease activity using the DAS28 as the measure for distinguishing moderate RA and severe RA. [DAS28 = 0.56*square root (tender28) + 0.28*square root (swollen28) + 0.70*ln (ESR) + 0.014*general health (measured on a visual analog scale of 100 mm); in which ESR is erythrocyte sedimentation rate[8].] The calculation of DAS28 for assignment into moderate or severe disease activity groups was post hoc and not prespecified in either the TEMPO or ERA study protocols. Moderate RA was defined as DAS28 between > 3.2 and ≤ 5.1, and severe RA as DAS28 > 5.1[9,10]. Five TEMPO and 10 ERA patients with low disease activity (DAS28 ≤ 3.2) at baseline or missing baseline DAS28 were excluded from the analysis.

Outcomes evaluated. This was a post hoc analysis of clinical and radiographic outcomes. Clinical outcomes included DAS28 remission and DAS28 low disease activity. Remission was defined as DAS28 < 2.6[11]. Low disease activity was defined as a DAS28 score ≤ 3.2. Other clinical endpoints included the change in Health Assessment Questionnaire (HAQ) and American College of Rheumatology (ACR) 20, 50, and 70 scores. A number of radiographic outcomes were evaluated: mean annualized Total Sharp Score (TSS) progression, no radiographic progression defined as an annualized change in TSS ≤ 0, and change from baseline in TSS and change in TSS for patients who had radiographic progression (defined as an annualized change in TSS > 0) over a 6- to 12-month period. Radiographic progression was evaluated by annualized rates. Radiographs were evaluated using the van der Heijde-modified Sharp method[12].

Statistical methods. Descriptive statistics were used to describe disease severity for the 3 different treatment groups by HAQ, Physician Global Assessment (PGA), Patient Global Assessment, patient pain assessment (0–100), tender joint count (TJC), swollen joint count (SJC), C-reactive protein (CRP), and ESR. A generalized linear model or Mann-Whitney U test was used to compare the moderate and severe groups on these measurements as well as radiographic outcomes. Logistic regressions and chi-square tests were used to examine the differences in categorical outcomes, such as DAS remission and DAS low disease activity, between baseline severity groups and between treatment groups, with interaction terms. Fisher exact tests were used instead of chi-square tests when the expected count in any frequency table cell was less than 5.

Cumulative probability plots were used to illustrate radiographic progression in a continuous manner. The probability plots are useful because they are not subject to a prespecified cutoff point for defining "no progression," and they enable observers to easily visualize all of the data in either the positive (annualized change in TSS > 0) or negative (annualized change in TSS ≤ 0) direction. Probability plots for the change from baseline in TSS at 1 year were created for the different treatment groups in the TEMPO and ERA studies. Within each probability plot, each dot represents an individual patient. The y-axis is the patient's change from baseline in TSS at Year 1, and the x-axis is the percentile of that value within each treatment group and severity group based on baseline DAS28. All analyses were performed using SAS/STAT® Version 9.1 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographics and baseline characteristics. Baseline demographic characteristics for the TEMPO and ERA study populations have been published[3,7]. Baseline demographic data were similar between treatment groups within each study, but were not similar between the 2 studies. A number of patient characteristics were different between the TEMPO and ERA study populations, including mean disease duration (6.6 yrs vs 1 yr), prior MTX use (43% vs 0%), percentage of patients who were rheumatoid factor-positive (74% vs 88%), and mean age (53 yrs vs 50 yrs). About three-quarters were women in each study. In the analysis of TEMPO, 16, 8, and 17 patients in the MTX, ETN, and combination therapy groups, respectively, were categorized as having moderate disease activity by DAS28; 211, 214, and 211 patients had severe disease activity. In the ERA MTX and ETN groups (disease duration no more than 3 yrs), there were 33 and 32 patients, respectively, with moderate disease activity and 178 and 171 patients with severe disease activity defined by DAS28. The mean duration of RA in patients with moderate and severe disease activity, respectively, in TEMPO was 3.2 and 7.1 years in the MTX group, 5.1 and 6.4 years in the ETN group, and 6.1 and 6.8 years in the combination therapy group. Tables 1 and 2 summarize other baseline disease characteristics for TEMPO and ERA by disease severity. As expected, differences between severity groups in HAQ, TJC, SJC, CRP, and ESR were observed across all treatment groups and studies.

Clinical outcomes. In general, patients with moderate disease activity achieved better final outcomes on most measures at 6 months (data not shown) and 12 months than patients with severe disease activity (Table 3). In particular, significant differences in the rates of DAS28 remission

Table 1. Baseline disease characteristics in patients with moderate and severe rheumatoid arthritis in TEMPO. Values are mean (SD).

Measure	MTX Moderate, n = 16	ETN 25 mg Severe, n = 211	ETN + MTX Moderate, n = 8	Severe, n = 214	Moderate, n = 17	Severe, n = 211
HAQ, 0–3	0.92 (0.67)	1.77 (0.66)	1.02 (0.64)	1.78 (0.65)	1.10 (0.74)	1.81 (0.56)
Tender joint count, 0–28	9.44 (4.43)	18.25 (6.22)	9.13 (3.44)	18.80 (6.32)	8.53 (5.49)	19.22 (6.17)
Swollen joint count, 0–28	10.0 (2.92)	15.41 (5.54)	7.38 (2.50)	15.72 (5.66)	9.24 (4.22)	15.44 (5.78)
CRP, mg/l	0.75 (0.54)	2.73 (2.89)	1.38 (2.66)	3.28 (3.78)	1.77 (2.28)	3.0 (3.23)
ESR, mm/h	10.31 (8.54)	43.08 (25.74)	17.25 (11.76)	41.52 (22.68)	14.94 (13.22)	41.51 (24.69)

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ETN: etanercept; HAQ: Health Assessment Questionnaire; MTX: methotrexate.

Table 2. Baseline disease characteristics in patients with moderate and severe rheumatoid arthritis in ERA. Values are mean (SD).

Measure	MTX		ETN 25 mg	
	Moderate, n = 33	Severe, n = 178	Moderate, n = 32	Severe, n = 171
HAQ, 0–3	1.00 (0.51)	1.52 (0.58)	0.87 (0.65)	1.55 (0.57)
Tender joint count, 0–28	6.30 (3.96)	16.41 (6.56)	7.65 (4.62)	16.61 (6.76)
Swollen joint count, 0–28	8.70 (6.33)	15.26 (5.80)	8.27 (3.36)	15.61 (6.12)
CRP, mg/l	1.12 (1.09)	4.23 (4.70)	1.09 (1.08)	3.63 (4.06)
ESR, mm/h	15.15 (11.72)	44.67 (26.38)	14.31 (9.61)	42.69 (25.87)

Definitions as in Table 1.

(< 2.6) in moderate patients versus severe patients were observed in all treatment groups in the TEMPO study at Month 6 ($p = 0.004$ for MTX; $p = 0.0147$ for ETN, and $p < 0.0001$ for ETN + MTX). At Month 12, significant differences were observed in the MTX ($p = 0.0035$) and combination ETN and MTX groups ($p = 0.0006$), and a numerical trend was observed in the ETN group ($p = 0.1487$). In the ERA study, both ETN and MTX treatment resulted in significantly greater percentages of patients in DAS28 remission in the moderate disease activity compared with the severe disease activity groups at 6 months ($p = 0.0003$ for ETN and $p = 0.0058$ for MTX) and 12 months ($p < 0.0001$ for ETN, $p = 0.0094$ for MTX). A greater percentage of patients with moderate disease activity also achieved DAS28 low disease activity at 6 and 12 months, with significant differences between these groups observed with MTX alone ($p = 0.0454$ at 6 mo and $p = 0.0172$ at 12 mo) and combination ETN and MTX treatment in TEMPO ($p = 0.0002$ at 6 mo and $p = 0.0097$ at 12 mo); and ETN monotherapy ($p < 0.0001$ at 6 mo and $p = 0.0006$ at 12 mo) and MTX monotherapy ($p < 0.0001$ at 6 mo and $p = 0.0022$ at 12 mo) in ERA.

Mean DAS28 scores over time showed a rapid decline by Week 4, continued to improve through Week 24, and were sustained over the second 24 weeks across treatment groups in both studies, with the moderate disease activity group demonstrating consistently lower disease activity than the severe group (Figure 1). In the MTX and ETN monotherapy groups in ERA and TEMPO, the changes in DAS28 were greater in the severe than in the moderate disease activity group. In the ERA study, the 12-month changes in DAS28 from baseline in the moderate and severe disease activity groups, respectively, were 1.2 and 2.4 ($p < 0.0001$) in the MTX monotherapy group and 1.7 and 2.4 ($p = 0.0110$) in the ETN monotherapy group (Figure 1 and Table 3). The corresponding 12-month changes in DAS28 from baseline in the TEMPO study were 1.6 and 2.6 ($p = 0.0076$) in the MTX monotherapy group, 1.5 and 2.7 ($p = 0.0268$) in the ETN monotherapy group, and 2.5 and 3.5 ($p = 0.0069$) in the combination ETN and MTX group (Figure 1 and Table 3).

Similar trends were observed in HAQ scores over time (Figure 2 and Table 3). In the ERA study, the 12-month changes in HAQ scores from baseline in the moderate and severe disease activity groups, respectively, were 0.44 and 0.77 ($p = 0.0107$) in the MTX monotherapy group and 0.45 and 0.75 ($p = 0.0070$) in the ETN group. In the TEMPO study, the 12-month changes in HAQ scores from baseline in the moderate and severe disease activity groups, respectively, were 0.29 and 0.68 ($p = 0.0138$) in the MTX monotherapy group, 0.42 and 0.74 ($p = 0.1329$) in the ETN monotherapy group, and 0.74 and 1.00 ($p = 0.0895$) in the combination ETN and MTX group. Although not all treatment groups showed statistically significant differences at 12 months (ETN + MTX group in TEMPO, $p = 0.0009$; and ETN group in ERA, $p = 0.0005$),

Table 3. Differences in clinical outcomes between patients with moderate and severe disease activity based on DAS28 at Month 12. Values are mean (SD).

Measure	TEMPO		ERA	
	Moderate	Severe	Moderate	Severe
DAS28 remission (based on DAS28 < 2.6), n (%)				
MTX	7 (44)	32 (15)*	11 (33)	26 (15)*
ETN	3 (38)	36 (17)	15 (47)	24 (14)**
ETN + MTX	13 (77)	73 (35)**		
DAS28 low disease activity (DAS28 ≤ 3.2), n (%)				
MTX	9 (56)	59 (28)*	18 (55)	49 (28)*
ETN	5 (63)	67 (31)	18 (56)	44 (26)**
ETN + MTX	14 (82)	105 (50)*		
DAS28 change in mean scores (SD) from baseline				
MTX	1.6 (0.3)	2.6 (0.1)*	1.2 (0.2)	2.4 (0.1)**
ETN	1.5 (0.4)	2.7 (0.1)*	1.7 (0.2)	2.4 (0.1)*
ETN + MTX	2.5 (0.3)	3.5 (0.1)*		
ACR20 response, n (%)				
MTX	12 (75)	158 (75)	18 (55)	116 (65)
ETN	6 (75)	163 (76)	21 (66)	119 (70)
ETN + MTX	14 (82)	179 (85)		
ACR50 response, n (%)				
MTX	5 (31)	91 (43)	13 (39)	72 (40)
ETN	2 (25)	106 (50)	17 (53)	81 (47)
ETN + MTX	12 (71)	145 (69)		
ACR70 response, n (%)				
MTX	2 (13)	40 (19)	6 (18)	38 (21)
ETN	1 (13)	53 (25)	7 (22)	41 (24)
ETN + MTX	11 (65)	85 (40)*		
HAQ score, mean (SD)				
MTX	0.6 (0.1)	1.1 (0.1)*	0.6 (0.1)	0.8 (0.0)
ETN	0.6 (0.2)	1.0 (0.1)	0.4 (0.1)	0.8 (0.1)*
ETN + MTX	0.4 (0.2)	0.8 (0.0)*		
HAQ ≤ 0.5, n (%)				
MTX	8 (50)	69 (33)	19 (58)	78 (44)
ETN	4 (50)	72 (34)	24 (75)	71 (42)**
ETN + MTX	14 (82)	86 (41)**		
HAQ change in mean scores (SD) from baseline				
MTX	0.29 (0.12)	0.68 (0.05)*	0.44 (0.09)	0.77 (0.05)*
ETN	0.42 (0.21)	0.74 (0.05)	0.45 (0.09)	0.75 (0.05)*
ETN + MTX	0.74 (0.18)	1.00 (0.05)		

If the patient numbers were < 5 in any treatment group per visit, the Fisher exact test 2-sided p value was used; if the expected count in both moderate and severe frequencies was ≥ 5 in any frequency table cell, then chi-square p value was used. * $p < 0.05$; ** $p < 0.001$. ACR: American College of Rheumatology; DAS28: Disease Activity Score including 28-joint count; ERA: Early Rheumatoid Arthritis; ETN: etanercept; HAQ: Health Assessment Questionnaire; MTX: methotrexate; TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes.

greater percentages of patients with moderate than with severe disease consistently achieved a HAQ score ≤ 0.5 (Table 3).

Radiographic outcomes. Data from the probability plots indicated that although similar proportions of patients did not progress radiographically in the moderate and severe disease activity groups in both trials (Figures 3 and 4), the high end of the TSS curve appears generally to have more severe than moderate patients with progression among all treatment arms in the TEMPO and in the ETN arm in the ERA. Change from baseline in TSS was calculated for patients who had radiographic progression (annualized change in TSS > 0; the right tails of Figures 2 and 3). In patients with radiographic progression, the median change in TSS at 1 year was statistically significant in the moderate versus severe populations only for MTX in the TEMPO study (median 1.00 vs 2.57; $p = 0.014$). Mean changes in TSS for the MTX group were 1.03 vs 6.28 for the moderate and severe groups, respectively. The proportions of patients with a negative change in TSS (improvement; the left tails of Figures 2 and 3) were similar in both groups in both TEMPO and ERA studies.

Table 4. Differences in radiographic outcomes between patients with moderate and severe disease activity based on DAS28 at Month 12.

Measure	TEMPO		ERA	
	Moderate	Severe	Moderate	Severe
TSS progression (annualized change), * mean (SD)				
MTX	0.62 (1.94)	2.95 (13.08)	2.15 (6.27)	1.71 (3.99)
ETN	–0.51 (1.04)	0.55 (4.70)	–0.04 (1.36)	0.89 (2.70)
ETN + MTX	–0.74 (1.43)	–0.53 (3.64)		
No radiographic progression (annualized change in TSS ≤ 0),†** n (%)				
MTX	7 (44)	108 (51)	15 (47)	85 (49)
ETN	6 (75)	127 (59)	22 (69)	109 (65)
ETN + MTX	14 (82)	150 (71)		

ERA: Early Rheumatoid Arthritis; ETN: etanercept; MTX: methotrexate; TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; TSS: Total Sharp Score. * p values not determined using Mann-Whitney U test. Data not normally distributed. Mean (SD) shown here for descriptive purposes. † If the expected number of patients was less than 5 in any treatment group per visit, then the 2-sided Fisher exact test was used; if the expected count in both moderate and severe was ≥ 5 per treatment group per visit, 2-sided chi-square test was used. ** Annualized change in TSS from baseline < 0.05 was categorized as no radiographic progression in the primary analysis.

No statistically significant differences in the annualized rates of change in TSS were observed between patients with moderate and those with severe disease activity (Table 4) in TEMPO or ERA. However, there was a clear numerical trend in the mean annualized TSS change favoring patients with moderate disease in TEMPO with MTX and ETN monotherapy, but not combination therapy.

DISCUSSION

Our post hoc analysis compares responses and outcomes in patients with moderate versus severe disease activity as defined by DAS28. The results demonstrated that regardless of disease duration, patients with moderate RA who were initiating high-dose MTX and/or the TNF antagonist ETN were more likely to achieve a lower disease activity state than patients with severe RA.

Although more patients with moderate disease achieved low disease activity with treatment, changes in clinical outcomes were generally greater in those with severe disease. Changes in DAS and HAQ scores were more pronounced in the severe disease activity groups. These findings were not unexpected, due to a potential "floor effect" in patients who are closer to a better disease activity state. Conversely, patients with severe disease have more opportunity for clinical improvement than patients with moderate disease. Despite the greater change in clinical outcomes in patients with severe disease, the ultimate disease activity state achieved also influences therapeutic decision-making. Thus, patients with persistence of moderate/high disease activity are more likely to be considered for further changes in therapy than those achieving a low disease activity state.

While there was a trend for patients with moderate disease to have better radiographic outcomes, the results were not statistically significant for annualized change in TSS and percentage of patients with no radiographic progression, possibly reflecting the small sample size of patients with moderate disease activity. The results might also reflect that treatment had a significant effect on radiographic progression that was dissociated from the clinical response, as has been previously reported with ETN treatment (especially ETN plus MTX combination therapy) in an analysis of TEMPO data[13]. However, the appearances of the probability plots (which show every individual radiographic score per treatment group plotted against its cumulative probability from lowest to highest observation) showed that for patients who developed radiographic progression in TEMPO, those with severe disease appeared to have greater progression than patients with moderate disease. The greater baseline TSS in the severe versus moderate groups may account for the increased radiographic progression observed in the severe disease groups. The exception was the MTX group in the ERA trial, which did not follow this pattern, showing similar radiographic progression in both the moderate and severe disease activity groups of patients (Figure 3A). This may be of interest and could reflect a greater susceptibility of patients with moderate early RA to radiographic progression.

Our study has several limitations. First, this was a post hoc analysis of studies that were not designed to compare outcomes in patients with moderate disease activity versus those with severe disease activity. In addition, there were small patient numbers in the moderate disease activity groups compared with the severe groups, especially in TEMPO; therefore, statistical comparisons should be interpreted with caution. However, the clinical findings in the moderate disease group are in general consistent between TEMPO and ERA. Moreover, many of the analyses were

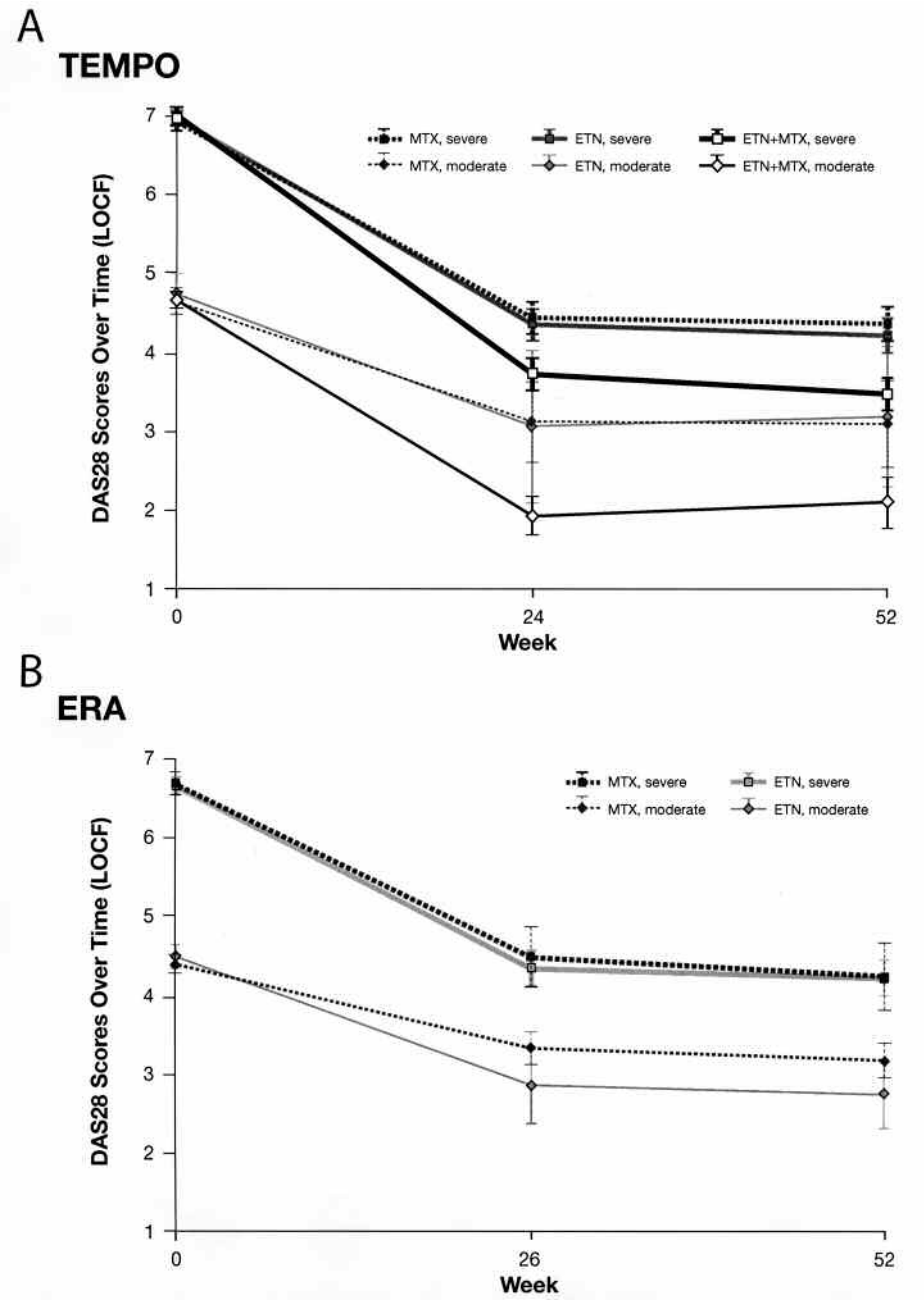

Figure 1. DAS28 scores over time, mean ± SE in (A) TEMPO and (B) ERA. DAS28: Disease Activity Score including 28-joint count; ERA: Early Rheumatoid Arthritis; ETN: etanercept; LOCF: last observation carried forward; MTX: methotrexate; TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes.

statistically significant even with the low patient numbers in the moderate disease activity groups.

Although these limitations of the study cannot be disregarded, the consistency of the results between the 2 trials and the statistically significant comparisons despite such small numbers provide strong preliminary evidence that patients with moderate disease receiving high-dose MTX and/or ETN are more likely to achieve a lower disease activity state compared with patients with severe disease. Even though patients with severe disease are less likely to achieve

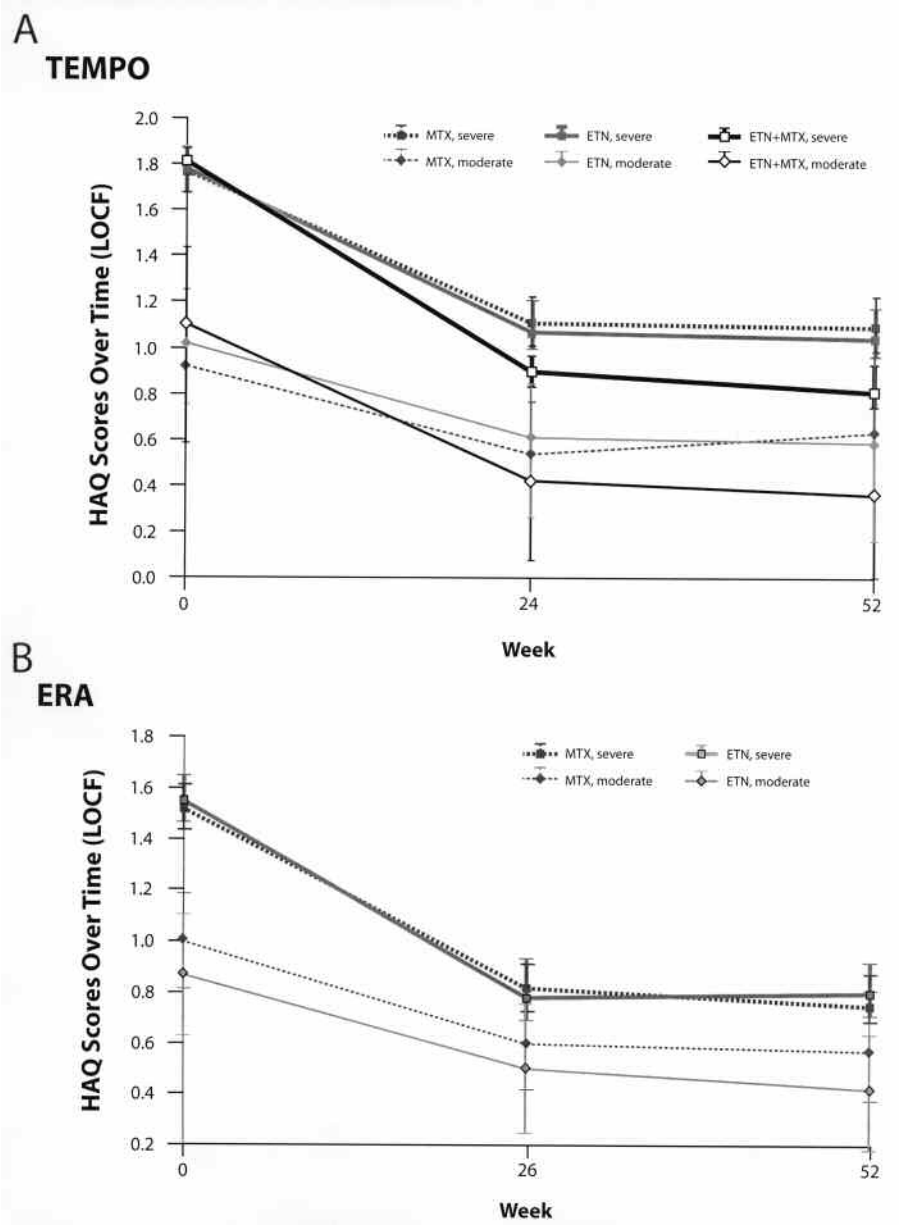

Figure 2. HAQ scores over time, mean ± SE in (A) TEMPO and (B) ERA. ERA: Early Rheumatoid Arthritis; ETN: etanercept; LOCF: last observation carried forward; MTX: methotrexate; TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; HAQ: Health Assessment Questionnaire.

remission, aggressive therapy demonstrated a significant clinical effect on function and on radiographic progression. These data also suggest that aggressive management of moderate disease may prevent development of severe disease, and that patients with moderate disease activity deserve greater attention and adequate representation in future clinical trials.

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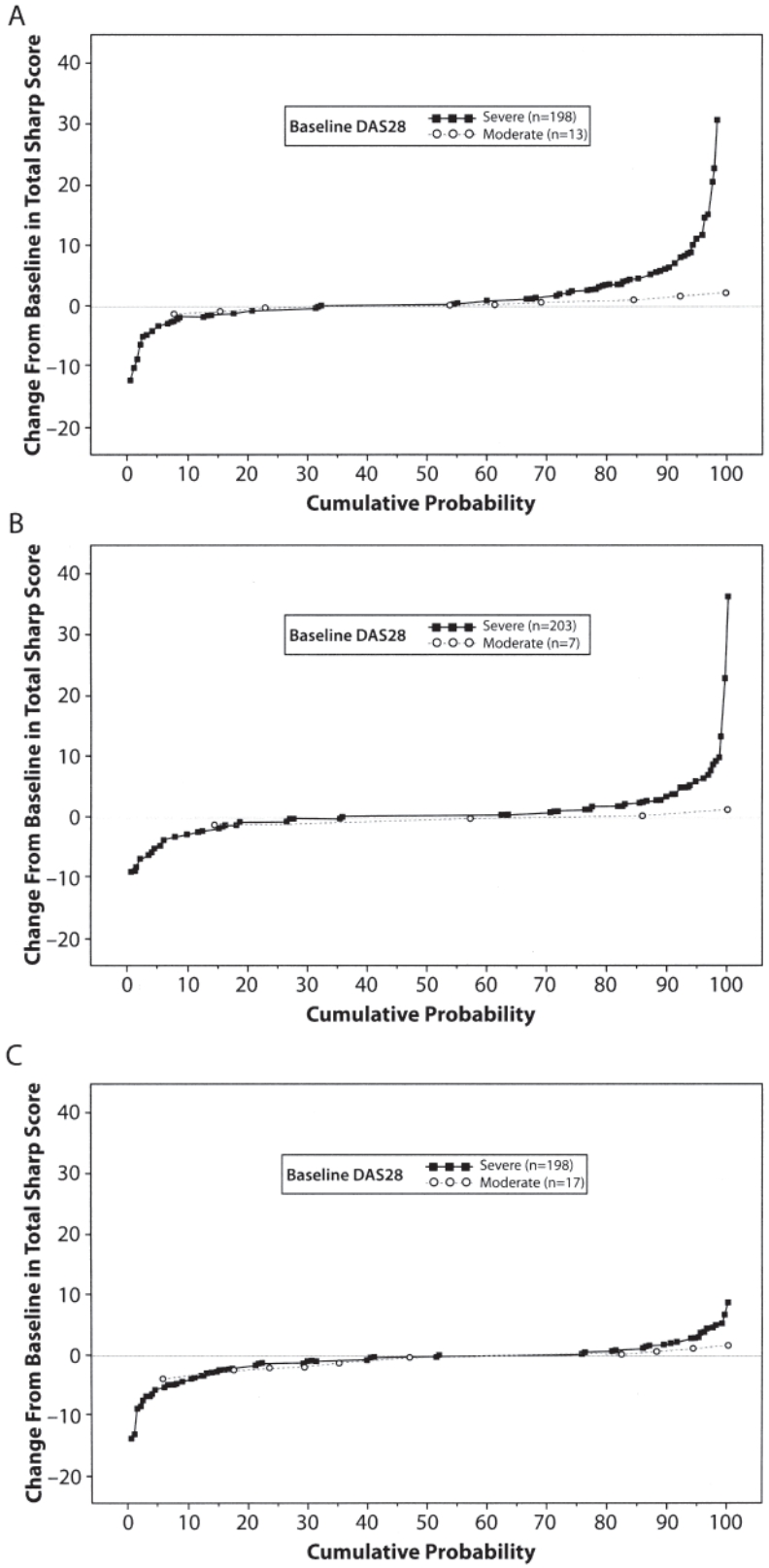

Figure 3. Probability plots from TEMPO for the change from baseline in Total Sharp Score at 1 year for (A) MTX, (B) ETN, and (C) ETN + MTX. DAS28: Disease Activity Score including 28-joint count; TEMPO: Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes.

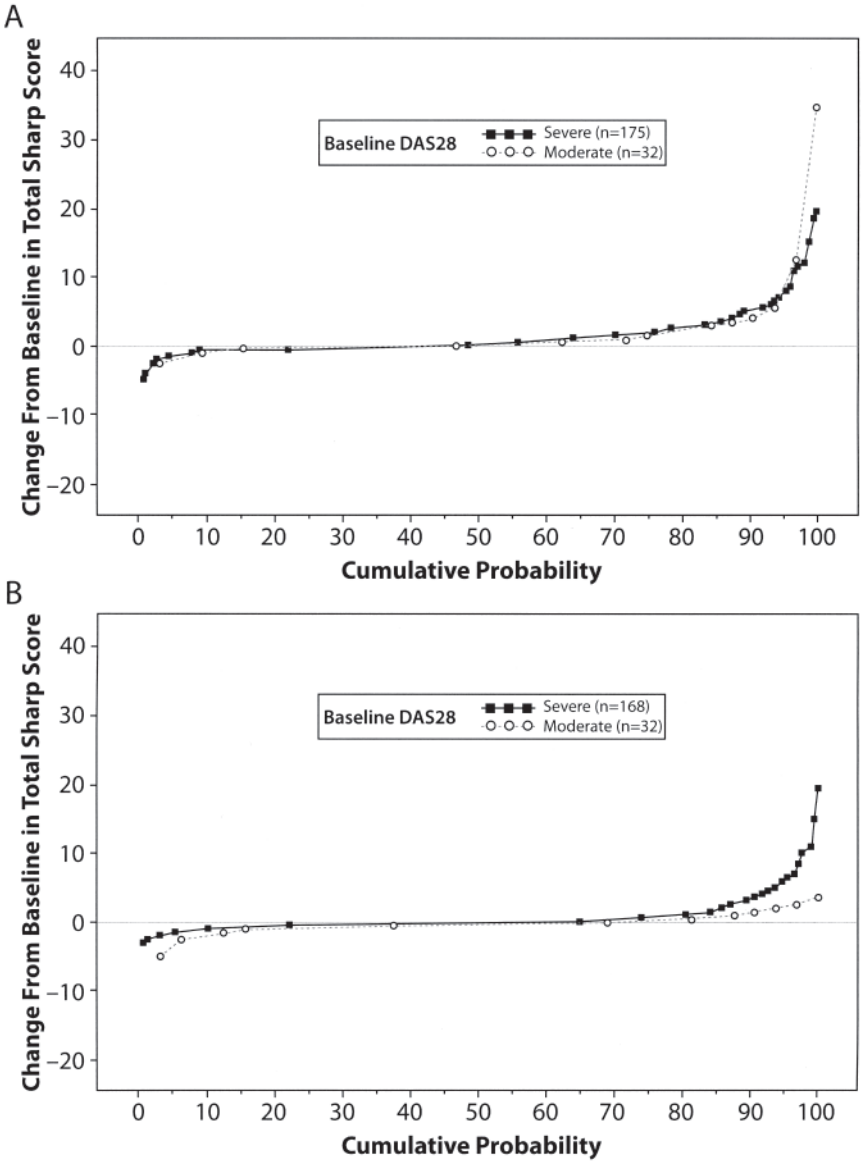

Figure 4. Probability plots from ERA for the change from baseline in Total Sharp Score at 1 year for (A) MTX, and (B) ETN. DAS28: Disease Activity Score including 28-joint count; ERA: Early Rheumatoid Arthritis.

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