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Effects of Disease-Worsening Following Withdrawal of Etanercept or Methotrexate on Patient-Reported Outcomes in Patients With Rheumatoid Arthritis

Results From the SEAM-RA Trial

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Background/Objective: The effect of treatment withdrawal on patient-reported outcomes (PROs) in patients with rheumatoid arthritis (RA) whose disease is in sustained remission has not been well described. This analysis aimed to compare PRO changes in patients with RA following medication withdrawal and disease worsening.

Methods: SEAM-RA (Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Rheumatoid Arthritis) was a phase 3, multicenter, randomized withdrawal, double-blind controlled study in patients with RA taking methotrexate plus etanercept and in remission (Simple Disease Activity Index ≤3.3). Patient's Global Assessment of Disease Activity, Patient's Assessment of Joint Pain, Health Assessment Questionnaire–Disability Index, and 36-Item Short-Form Health Survey were evaluated for 48 weeks following methotrexate or etanercept withdrawal. Treatment differences for patients with versus without disease worsening were evaluated using a 2-sample *t* test for continuous end points and log-rank test for time-to-event end points.

Results: Of 253 patients, 121 experienced disease worsening and 132 did not. All PRO scores were similar to those of a general population at baseline and deteriorated over time across the study population. The PtGA and Patient's Assessment of Joint Pain values deteriorated less in those on etanercept monotherapy compared with methotrexate monotherapy. More patients with versus without disease worsening experienced deterioration that was greater than the minimal clinically important difference (MCID) for all PROs tested. In patients with disease worsening, PtGA deterioration more than the MCID preceded Simple Disease Activity Index disease worsening.

Conclusions: Etanercept monotherapy showed benefit over methotrexate in maintaining PRO scores. Patients with disease worsening experienced a more rapid worsening of PtGA beyond the MCID versus patients without disease worsening.

Categories: autoinflammatory disease, biological therapy, DMARDs, rheumatoid arthritis

Key Words: etanercept, methotrexate, patient-reported outcomes, rheumatoid arthritis

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Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory autoimmune disease that affects more than 1 million adults in the United States.[1] The condition causes pain, swelling, and stiffness of the synovial joints, leading to functional disability that can negatively impact patients' ability to perform daily activities, including engagement in family, social activities, and occupational activities.[2] The disease also poses a significant health and socioeconomic burden; it is associated with $19.3 billion in direct and indirect costs and an additional $19.9 billion from deterioration of patients' quality of life (QoL) and premature mortality.[3]

Patient-reported outcomes (PROs) are important tools for understanding patients' perspectives on their health status and impact of the disease and its treatment independent from clinician assessment.[4] Patient-reported outcomes provide qualitative information that can complement the physician's evaluation. For these reasons,

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the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), and the Outcome Measures in Rheumatology recommend assessment of PROs in randomized clinical trials.[4–7] The most frequently evaluated PROs in RA include the Health Assessment Questionnaire (HAQ), global assessment, pain, physical function, health-related QoL, fatigue, morning stiffness, coping, sleep disturbances, and work and social activity.[6,8,9]

Improvements in treatment have led to many patients achieving sustained remission with combination therapy.[10] Guidelines published in 2021 by the ACR mention that dose reduction/tapering may be considered in patients who are at target (remission or low disease activity) for at least 6 months and suggest that patients maintain a therapeutic dose of at least 1 disease-modifying antirheumatic drug (DMARD) instead of stopping all DMARDs to avoid the risk of flares and potential irreversible joint damage.[11] Few studies have assessed the effect of treatment withdrawal on PROs in patients with RA who attain sustained remission while receiving a combination of methotrexate and a biological DMARD or targeted synthetic DMARD.[12–14] The Study of Etanercept and Methotrexate in Combination or as Monotherapy in Subjects With Rheumatoid Arthritis (SEAM-RA) was the first study of its kind to investigate the effect of stopping either methotrexate or etanercept on maintenance of remission. SEAM-RA showed that significantly more patients receiving etanercept monotherapy maintained remission defined by the Simple Disease Activity Index (SDAI) than those receiving methotrexate monotherapy at 48 weeks.[15] A number of PROs were assessed in this study to better understand the effects of withdrawal of either etanercept or methotrexate in patients with sustained remission receiving coadministration of etanercept and methotrexate.

METHODS

Study Design

SEAM-RA (NCT02373813) was a multicenter, randomized withdrawal, double-blind, controlled trial in patients with RA receiving etanercept and methotrexate. The study consisted of a 30-day screening period, 24-week open-label run-in period, and 48-week double-blind period. During the run-in period, patients received etanercept and methotrexate at the same dose they were receiving during screening. Patients were eligible to enter the double-blind period if SDAI ≤3.3 was achieved at visit 3 of the run-in period. For the double-blind period, patients were randomly assigned 2:2:1 to 3 treatment groups: etanercept monotherapy 50 mg once weekly (QW), methotrexate monotherapy 10 to 25 mg QW, or coadministration of etanercept and methotrexate. Following randomization, patients who experienced an SDAI score higher than 11 at any time, an SDAI score higher than 3.3 during 2 consecutive visits at least 2 weeks apart, or an SDAI score higher than 3.3 on 3 or more separate visits were considered to have disease worsening. Patients with disease worsening resumed or continued treatment with etanercept plus methotrexate (rescue therapy) using the same dosages received at study enrollment.

Patient Population

A detailed account of eligibility criteria has been previously reported.[15] Briefly, patients who were at least 18 years of age with a history of RA consistent with ACR/EULAR classification criteria, had good disease control for at least 6 months, were in a state of remission (SDAI score ≤3.3) at the time of screening and at the end of the 6-month run-in period, and received etanercept 50 mg QW and methotrexate 10 to 25 mg QW for at least 6 months were included. Patients diagnosed with Felty syndrome; those with a known history of alcoholic hepatitis, nonalcoholic steatohepatitis, or immunodeficiency syndromes, including HIV infection, or with active or serious infection, or who received a biological DMARD other than etanercept or had used a Janus kinase inhibitor in 6 months or less prior to run-in period were excluded.

Assessment and Schedule of PROs

The PROs evaluated in this analysis were the Patient's Global Assessment of Disease Activity (PtGA), Patient's Assessment of Joint Pain (PtJP), HAQ–Disability Index (HAQ-DI), and the 36-Item Short-Form Health Survey (SF-36), including the physical component summary (PCS), mental component summary (MCS), and 8 domain scores (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health). The PtGA and PtJP were assessed at baseline (ie, at the time of randomization, at the end of the 6-month run-in period) and at weeks 12, 24, 36, and 48. The HAQ-DI and SF-36 component and domain scores were assessed at baseline and at weeks 24 and 48.

Statistical Analysis

Analyses were performed using the primary, disease worsening, and non–disease-worsening sets. The primary analysis set included all randomized patients, irrespective of the actual treatment received during the study. Mean change from baseline in PROs was assessed by treatment arm in the primary analysis set. The disease-worsening analysis set included randomized patients who met the definition of disease worsening at any point after randomization. Mean change from baseline in PROs was assessed by treatment arm in the disease-worsening and non–disease-worsening sets. Furthermore, a post hoc analysis was performed to assess the cumulative proportion of patients with deterioration or improvement greater than the minimal clinically important difference (MCID) for each instrument/domain in patients with versus without disease worsening as well as by treatment arm. The PtGA and PtJP values were assessed at an MCID of a 10- and 20-point change from baseline.[16,17] The MCID for HAQ-DI was set at ≥0.35-point change,[16] and the MCID for SF-36 PCS and MCS was ≤−2.5-point change.[18] Data are reported as observed. Comparisons of treatment differences between groups were performed using a 2-sample *t* test for continuous end points and log-rank test for time-to-event end points. In time-to-event analyses, patients who received rescue therapy prior to deterioration greater than the MCID were censored at the date of first receiving rescue therapy and were considered to not have achieved the event. Patients who never observed disease deterioration on study and were never rescued were censored at their last assessment date on the study. The *p* values presented are nominal; no adjustment for multiplicity was performed. All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).[19]

RESULTS

Patient Disposition, Demographics, and Baseline Characteristics

Of 253 patients randomized and allocated to the treatment groups, 121 experienced disease worsening over the 48-week treatment period. Demographics and baseline disease characteristics were generally balanced between the 3 treatment groups. Most patients were women (76.3%) and White (87.0%); mean age was 55.6 years. Mean methotrexate dose was 16.3 (SD, 4.69) mg (median, 10 [range, 15–25] mg/wk for all groups) and mean duration of RA was 10.3 (SD, 7.8) years. At baseline, mean PRO scores were similar to the values observed in a general patient population (Table 1).

TABLE 1. Patient Demographics and Clinical Characteristics

Characteristic	MTX (n = 101)	ETN (n = 101)	ETN + MTX (n = 51)	Total Primary Analysis Population (n = 253)
Age, mean (SD), y	56.2 (11.4)	54.8 (12.8)	55.9 (12.6)	55.6 (12.2)
Women, n (%)	76 (75.2)	77 (76.2)	40 (78.4)	193 (76.3)
White, n (%)	92 (91.1)	86 (85.1)	42 (82.4)	220 (87.0)
Duration of RA, mean (SD), y	9.7 (8.0)	11.0 (7.4)	10.3 (8.2)	10.3 (7.8)
MTX dose, mean (SD), mg/wk	16.26 (4.56)	15.97 (4.65)	17.06 (4.99)	16.30 (4.69)
PtGA (0–100 scale), mean (SD)	4.44 (0.58)	4.54 (0.76)	3.45 (0.77)	4.28 (0.41)
PtJP (0–100 mm), mean (SD)	4.91 (0.65)	5.47 (1.13)	3.51 (0.74)	4.85 (0.54)
HAQ-DI (0–3 scale), mean (SD)	0.32 (0.04)	0.26 (0.04)	0.28 (0.06)	0.29 (0.03)
SF-36 PCS, mean (SD)	52.13 (0.73)	52.69 (0.60)	52.27 (0.92)	52.38 (0.42)
SF-36 MCS, mean (SD)	55.46 (0.79)	55.81 (0.71)	57.14 (0.96)	55.94 (0.47)
SF-36 domain (scale 0–100), mean (SD)				
Physical functioning	83.07 ± 1.85	85.89 ± 1.59	84.51 ± 2.88	84.49 ± 1.13
Role-physical	86.14 ± 1.80	86.63 ± 1.56	85.91 ± 2.48	86.29 ± 1.07
Bodily pain	81.05 ± 1.78	84.09 ± 1.50	83.90 ± 2.17	82.84 ± 1.03
General health	73.80 ± 1.62	72.37 ± 1.61	74.20 ± 2.38	73.31 ± 1.03
Vitality	72.83 ± 1.66	74.26 ± 1.59	79.04 ± 2.60	74.65 ± 1.06
Social functioning	90.97 ± 1.40	92.20 ± 1.25	90.69 ± 2.62	91.40 ± 0.91
Role-emotional	92.99 ± 1.28	92.08 ± 1.52	93.95 ± 1.78	92.82 ± 0.87
Mental health	82.33 ± 1.71	84.70 ± 1.35	86.57 ± 1.97	84.13 ± 0.96

Values are presented as mean ± SEM, unless specified.

ETN, etanercept; MTX, methotrexate.

Change in PROs From Baseline in the Primary Analysis Set

In the primary analysis population, PtGA and PtJP scores were very low at baseline and showed some deterioration over the study period in all treatment groups (Table 1). Patients receiving etanercept monotherapy had less deterioration of PtGA and PtJP scores versus those assigned to methotrexate monotherapy, with a nominally significant treatment difference observed at almost all time points for PtGA and PtJP at weeks 12 and 36 ($p < 0.05$; Fig. 1). The HAQ-DI and SF-36 component scores (PCS and MCS) showed slight deterioration from baseline, with nonsignificant differences observed between groups at weeks 24 and 48. All SF-36 domain scores also deteriorated from baseline, with treatment differences not significant between groups (except role-physical, which was nominally significant at week 24 for the etanercept vs. methotrexate groups; Supplemental Table 1, http://links.lww.com/RHU/A490).

Change in PROs From Baseline (Disease-Worsening Analysis Set)

Similar to the results in the primary analysis population, patients receiving etanercept monotherapy who experienced disease worsening during the study period showed less PtGA and PtJP deterioration from baseline than those receiving methotrexate at weeks 12, 36, and 48. In patients with disease worsening, a greater proportion had worse PtGA scores that were higher than a 10-point change and at least a 20-point change from baseline versus those patients without disease worsening (PtGA >10: 74.4% vs. 27.5%; PtGA ≥20: 62.8% vs. 16.0%; Table 2). Similar results were also observed for PtJP, wherein greater proportions of patients with versus without disease worsening had worse PtJP scores that were higher than a 10-point change from baseline (73.6% vs. 32.1%) and at least a 20-point change from baseline (57.9% vs. 13.7%). Furthermore, there were more patients with disease worsening and PtGA and PtJP changes greater than 10 and 20 points from baseline than those without disease worsening across treatment groups (Table 3). In patients whose PtGA or PtJP changed greater than either the 10- or 20-point MCID threshold, approximately 20% to 30% did not meet the definition for disease worsening based on the SDAI. The proportion of patients who experienced a change greater than the MCID and did not experience disease worsening was even higher for the HAQ-DI, SF-36 PCS, and SF-36 MCS (approximately 40%).

Patient-reported outcome deterioration seemed to precede disease worsening. In patients with disease worsening, most experienced PtGA deterioration prior to worsening by SDAI (58.3% [MCID >10] and 50.0% [MCID ≥20] vs. 74.4% [MCID >10] and 62.8% [MCID ≥20] of patients with disease worsening who experienced PtGA deterioration at any time). For PtJP, 59.2% (MCID >10) and 46.7% (MCID ≥20) experienced PRO deterioration prior to SDAI disease worsening versus 73.6% (MCID >10) and 57.9% (MCID ≥20) of patients with SDAI disease worsening who experienced PRO deterioration at any time. Similarly, of the patients who experienced PtGA deterioration, 66.0% (70/106, MCID >10) and 74.1% (60/81, MCID ≥20) later experienced SDAI worsening. Patient's Global Assessment of Disease Activity deterioration greater than MCID (>10) occurred at a median of 168 days in patients with disease worsening and 346 days in patients without disease worsening (Fig. 2). Median time to PtGA deterioration in those with disease worsening (168 days) was shorter than the median time to disease worsening (198 days in the methotrexate group; not evaluable in the etanercept and combination groups, as the cumulative probability of disease worsening was always <50%). Similar results were found for time to deterioration on PtJP (Fig. 2). Among patients with disease worsening with at least a 20-point change from baseline in PtGA and PtJP, those who received rescue therapy had greater improvement

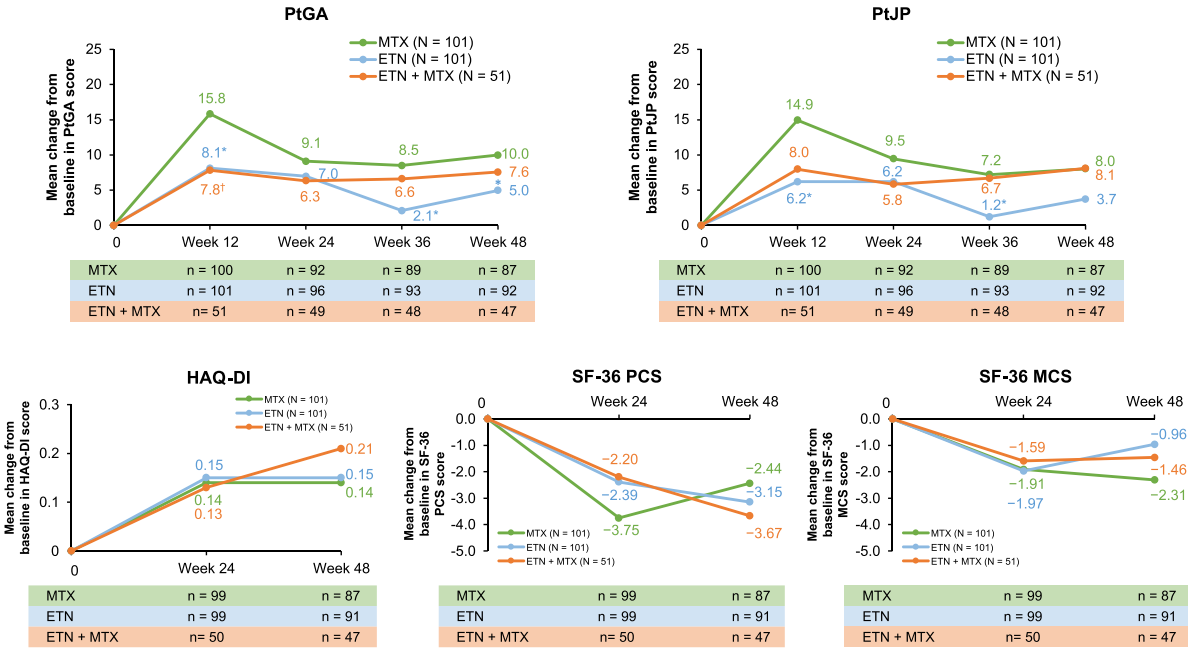

FIGURE 1. Mean change from baseline in PROs in the primary analysis set. *p* Values were calculated using a 2-sample *t* test; no adjustment for multiplicity was performed. n Represents the number of patients who had nonmissing observation for the specified week. The PRO scores at baseline were as follows: PtGA—MTX: 4.4, ETN: 4.5, ETN + MTX: 3.5; PtJP—MTX: 4.9, ETN: 5.5, ETN + MTX: 3.5; HAQ-DI—MTX: 0.32, ETN: 0.26, ETN + MTX: 0.28; SF-36 PCS—MTX: 52.1, ETN: 52.7, ETN + MTX: 52.3; SF-36 MCS—MTX: 55.5, ETN: 55.8, ETN + MTX: 57.1. Primary analysis set included all randomized patients irrespective of the actual treatment received during the study. ETN, etanercept; MTX, methotrexate. *$p < 0.05$ between ETN versus MTX group. †$p < 0.05$ between ETN + MTX versus MTX group.

in their scores compared with those who did not receive rescue therapy (72.6% vs. 7.1% and 82.5 vs. 0.0%, respectively; Supplemental Table 2, http://links.lww.com/RHU/A490).

Similar to the findings observed in the primary analysis set, HAQ-DI and SF-36 component scores showed minimal deterioration from baseline in the disease-worsening analysis set. Those who did deteriorate experienced a gradual reversal of scores close to baseline values by the end of the treatment period (ie, week 48). A higher proportion of patients in the disease-worsening subset experienced HAQ-DI, SF-36 MCS, and SF-36 PCS deterioration greater than MCID compared with those without disease worsening (HAQ-DI ≥0.35: 45.0% vs. 23.8%; SF-36 MCS ≤−2.5: 57.5% vs. 44.6%; SF-36 PCS ≤−2.5: 68.3% vs. 47.7%; Table 2). A similar pattern was observed across all treatment groups, wherein the proportion of patients with HAQ-DI, SF-36 MCS, and SF-36 PCS deterioration greater than MCID was higher in the subset with disease worsening versus those without disease worsening (Table 3). Median time to HAQ-DI deterioration of at least 0.35 was 172 days (95% confidence interval, 169 to not evaluable) in patients with disease worsening (not evaluable in those without disease worsening). Of patients who experienced HAQ-DI, SF-36 MCS, and SF-36 PCS change greater than MCID, 44.2%, 31.0%, and 41.8%, respectively, showed improvement in these measures following rescue therapy (Supplemental Table 2, http://links.lww.com/RHU/A490).

TABLE 2. Cumulative Proportion of Patients Whose PRO Scores Ever Deteriorated More Than MCID Over 48 Weeks

Change From Baseline in Outcome Score, n/N (%)	Disease Worsening (n = 121)	Non–Disease-Worsening (n = 132)
PtGA		
≥20	76/121 (62.8)	21/131 (16.0)
>10	90/121 (74.4)	36/131 (27.5)
PtJP		
≥20	70/121 (57.9)	18/131 (13.7)
>10	89/121 (73.6)	42/131 (32.1)
HAQ-DI		
≥0.35	54/120 (45.0)	31/130 (23.8)
SF-36 MCS		
≤−2.5	69/120 (57.5)	58/130 (44.6)
SF-36 PCS		
≤−2.5	82/120 (68.3)	62/130 (47.7)

PtGA and PtJP are measured on a 0- to 100-point scale.

n, Number of patients reporting deterioration reaching MCID; N, number of patients with nonmissing data.

DISCUSSION

SEAM-RA evaluated the effect of withdrawal for etanercept or methotrexate in patients with sustained remission who were receiving coadministration of these drugs. A significantly higher proportion of patients on etanercept did not experience disease worsening, and time to disease worsening was significantly prolonged in patients receiving etanercept compared with those receiving methotrexate monotherapy.[15] Similarly, in this exploratory analysis, patients on etanercept monotherapy had less deterioration of PROs (especially PtGA and PtJP) versus those on methotrexate monotherapy. In both the primary and disease-worsening analysis sets, PtGA and PtJP scores deteriorated less and recovered to near baseline levels for patients receiving etanercept monotherapy compared with methotrexate monotherapy. Patients who experienced

TABLE 3. Cumulative Proportion of Patients Whose PRO Scores Deteriorated More Than MCID Over 48 Weeks in the MTX, ETN, and ETN + MTX Groups

Change From Baseline in Outcome Score, n/N (%)	MTX		ETN		ETN + MTX	
	DW	Non-DW	DW	Non-DW	DW	Non-DW
PtGA						
≥20	40/63 (63.5)	5/37 (13.5)	23/40 (57.5)	9/61 (14.8)	13/18 (72.2)	7/33 (21.2)
>10	47/63 (74.6)	8/37 (21.6)	29/40 (72.5)	17/61 (27.9)	14/18 (77.8)	11/33 (33.3)
PtJP						
≥20	38/63 (60.3)	3/37 (8.1)	21/40 (52.5)	10/61 (16.4)	11/18 (61.1)	5/33 (15.2)
>10	47/63 (74.6)	9/37 (24.3)	28/40 (70.0)	21/61 (34.4)	14/18 (77.8)	12/33 (36.4)
HAQ-DI						
≥0.35	26/63 (41.3)	8/36 (22.2)	17/39 (43.6)	17/61 (27.9)	11/18 (61.1)	6/33 (18.2)
SF-36 MCS						
≤−2.5	36/63 (57.1)	17/36 (47.2)	24/39 (61.5)	26/61 (42.6)	9/18 (50.0)	15/33 (45.5)
SF-36 PCS						
≤−2.5	39/63 (61.9)	15/36 (41.7)	32/39 (82.1)	29/61 (47.5)	11/18 (61.1)	18/33 (54.6)

PtGA and PtJP are measured on a 0- to 100-point scale.

DW, disease worsening; ETN, etanercept; MTX, methotrexate; n, the number of patients reporting deterioration reaching MCID; N, number of patients with nonmissing data; REM, remission.

disease worsening had a higher proportion of PRO deterioration greater than MCID than those who did not experience disease worsening. This indicates agreement between the SDAI and patient perception of disease activity. However, the decline in PROs occurred before SDAI worsening, suggesting that patients can identify disease worsening sooner than a clinician would using

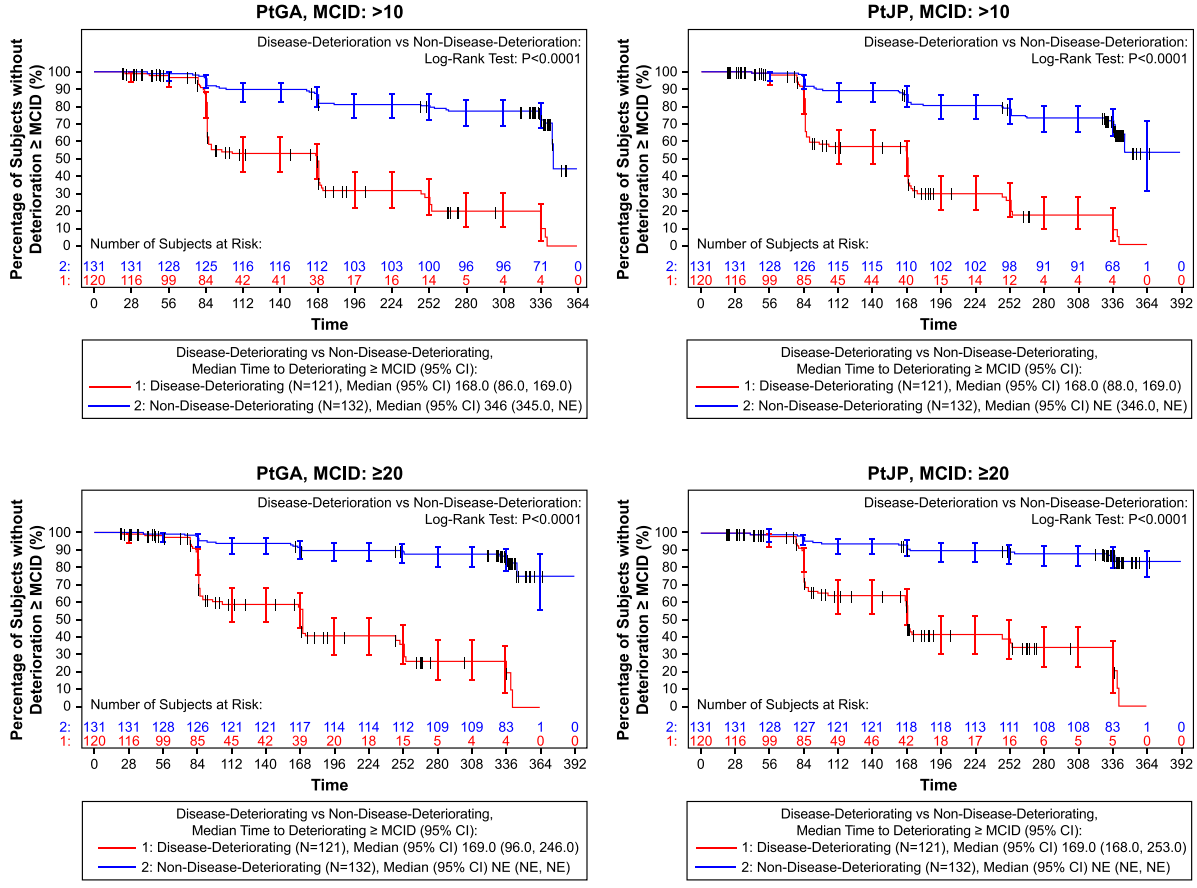

FIGURE 2. Kaplan-Meier curves of time to deterioration reaching MCID. Patients were censored at the earlier of their rescue date and their last available assessment date. Censor indicated by vertical bar. Error bars represent a 95% point-wise confidence interval for the survival function.

the SDAI. Patients who received rescue therapy following disease worsening saw improvement in their PROs.

Other studies in patients with RA in remission have shown similar effects on PROs when treatment is withdrawn. An analysis of the PRIZE (Productivity and Remission in a RandomIZed Controlled Trial of Etanercept versus Standard of Care in Early Rheumatoid Arthritis) study evaluated the effect of dose reduction or treatment withdrawal (etanercept or methotrexate) in patients with early or moderate to severe RA who achieved remission on Disease Activity Score in 28 joints or low disease activity with a combination of etanercept and methotrexate.[12] The study showed that patients continuing combination therapy at a lower dose (etanercept 25 mg QW/methotrexate) maintained their PRO response, whereas withdrawal of etanercept (ie, switching to methotrexate alone) led to a significant ($p \leq 0.05$) decline in health-related QoL measures, including the SF-36, EuroQol 5-Dimension instrument, Functional Assessment of Chronic Illness Therapy–Fatigue scale, Rheumatoid Arthritis–Work Instability Scale, and Work Productivity and Activity Impairment–Rheumatoid Arthritis questionnaire.[12] The PRESERVE study (Study Comparing Etanercept in Combination With Methotrexate in Subjects With Rheumatoid Arthritis), which was a randomized controlled trial that assessed the effect of withdrawing etanercept in patients who achieved sustained low disease activity following treatment with combination etanercept and methotrexate, reported that combination therapy resulted in lower (ie, better) PtGA, pain visual analog scale, and HAQ-DI scores at the end of double-blind treatment period (week 88) compared with those receiving methotrexate monotherapy.[13] Furthermore, the proportion of patients with normal HAQ-DI scores of no higher than 0.5 and those who achieved improvement in HAQ-DI score of at least 0.22 (MCID) was statistically significantly higher in the combination group compared with the group receiving methotrexate monotherapy (normal HAQ-DI: 59.7% vs. 41.6%, $p = 0.0002$; MCID: 72.4% vs. 51.0%, $p < 0.0001$).[13] The CAMEO (Canadian Methotrexate and Etanercept Outcome) study assessed the effect of withdrawing methotrexate after 6 months of combination therapy with etanercept and methotrexate in patients with an inadequate response to methotrexate.[14] The study showed that the mean HAQ-DI, PtGA and pain visual analog scale scores worsened in the etanercept monotherapy group compared with combination group over 6 to 12 months, whereas mean scores were similar between the 2 groups at 12 months.[14]

In the current study, PROs deteriorated following withdrawal of treatment in accordance with earlier studies,[12–14] but the magnitude of deterioration, especially of PtGA and PtJP, was less in the etanercept group compared with the methotrexate group. The SF-36 component and domain scores at baseline were similar to normative values for the general population,[20] and they deteriorated slightly following withdrawal of etanercept or methotrexate with a slight difference observed between treatment groups. The HAQ-DI scores at baseline were also close to normative values in the general population of patients without RA[21] and within normal scores of no higher than 0.5,[5] indicating that patients had low functional disability at baseline. Following withdrawal, the HAQ-DI scores deteriorated in all treatment groups with small differences observed between groups.

Strengths and Limitations

This analysis used well-established PROs, including PtGA, PtJP, and HAQ-DI, as recommended by the ACR, EULAR, and Outcome Measures in Rheumatology.[4–7] The randomized design reduces bias and ensured that patients were followed during the study period and that their PROs were consistently measured at regular intervals.

Some limitations should be considered when interpreting these findings. The external validity or the generalizability of these results may be limited, because the studied population in a controlled environment may differ from the general population encountered in clinical practice. The HAQ-DI and SF-36 were evaluated at weeks 24 and 48 only, whereas other measures were evaluated every 12 weeks; more frequent PRO assessments may have yielded a more sensitive, specific, and rapid ability of changes in the PROs to predict clinical disease worsening by the SDAI.

CONCLUSIONS

This analysis demonstrated that after achievement of remission on combination therapy, etanercept monotherapy has a greater effect on maintaining overall patient benefit than methotrexate monotherapy. Patients who experienced disease worsening following treatment withdrawal also experienced deterioration in their PROs and more patients with disease worsening than those without reported changes in these outcome measures. Patients who received rescue therapy following disease worsening might be able to regain their outcomes but to a lesser extent than those remaining in remission.

KEY POINTS

- Patients who transitioned from combination therapy to etanercept monotherapy maintained better disease control as measured by PtGA and PtJP versus patients who transitioned from combination therapy to methotrexate monotherapy.
- There was agreement between the SDAI and PROs; patients with disease worsening also reported greater PRO deterioration versus those without disease worsening.
- Patient-reported outcome deterioration tended to occur before SDAI disease worsening, suggesting that patients may recognize disease worsening sooner than a clinician would using the SDAI.

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