

Improved Health-related Quality of Life With Effective Disease-modifying Antirheumatic Drugs: Evidence From Randomized Controlled Trials

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Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the articular synovium, resulting in bony erosions, deformity, and, ultimately, joint destruction. With associated comorbid conditions, especially cardiovascular conditions, RA can result in significant morbidity as well as early mortality.^{1,2} Patients with RA report significant decrements in health-related quality of life (HRQOL) in comparison with age- and sex-matched populations without arthritis. These decreases in HRQOL are attributed to the pain, impairment in physical function, and fatigue associated with this disease.³

Since 1996, the American College of Rheumatology (ACR) criteria (ACR 20%/50%/70% responses) have been used to differentiate effective therapies from placebo in randomized controlled trials (RCTs).^{4,5} They are defined as $\geq 20\%/50\%/70\%$ improvement in tender and swollen joint counts and 3 of the following 5 measures: physician global assessment, acute phase reactants (erythrocyte sedimentation rate [ESR] or C-reactive protein [CRP]), patient global assessment of disease activity, patient-reported pain, and patient-reported physical function by the Health Assessment Questionnaire (HAQ). ACR responses, in association with improvements in the Disease Activity Score (DAS), have been utilized to demonstrate the efficacy of 7 new disease-modifying antirheumatic drugs (DMARDs), approved since 1998. In addition, these trials have demonstrated “inhibition of radiographic disease progression” and, importantly, “improvement in physical function and HRQOL”—now established labeling claims. In part, data were collected in response to US Food and Drug Administration (FDA) requirements for “durability of response,” requesting evaluation of physical function and HRQOL during 24 months of treatment. The HAQ Disability Index (HAQ-DI) and its modifications—modified (MHAQ) and multidimensional (MDHAQ)—have become the primary measure of physical function in RA, accompanied by use of generic measures such as Medical Outcomes Study 36-Item Short Form (SF-36), Euro QOL (EQ-5D), and Health Utilities Index-3 (HUI3) to assess HRQOL in RA.⁶ Uhlig et al compared

Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation of the articular synovium, resulting in bony erosions, deformity, and, ultimately, joint destruction. With associated comorbid conditions, especially cardiovascular, it can result in significant morbidity as well as early mortality. Patients with RA report impairments in health-related quality of life (HRQOL) in comparison with age- and sex-matched populations without arthritis. These decreases in HRQOL are attributed to the pain, impairment in physical function, and fatigue associated with this disease. The introduction of new disease-modifying antirheumatic drugs has revolutionized the treatment of RA, particularly the biologic agents: etanercept, infliximab, adalimumab, abatacept, and rituximab. Importantly, administration of these agents has resulted in statistically significant and clinically meaningful improvements in physical function and HRQOL. Many clinical studies confirm that with these therapies, RA patients report improvements in HRQOL, reflected by improved physical function, less fatigue, and better emotional and mental function. Maintenance of physical function is no longer the only treatment goal for RA but also to improve, restore, and preserve HRQOL. Results from pivotal clinical trials are analyzed in this article and the relevance of the data derived from the clinical studies to day-to-day clinical practice are also discussed.

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reported scores using HAQ-DI, MHAQ, SF-36, and the Arthritis Impact Measurement Scale (AIMS).⁷ As expected, HAQ-DI and MHAQ scores correlated well, but HAQ-DI discriminated more precisely in those patients with significant disability.⁷ Although both may be utilized in RCTs, standard effect sizes are larger, and the minimum clinically important difference (MCID) is lower with HAQ-DI (−0.22) than MHAQ (−0.25).⁸

Joint pain and range of motion influence performance of physical activities, including activities of daily living, discretionary activities such as shopping and sports, and participation in family and social events. A study investigated associations between HAQ-DI and clinical variables of disease in 304 patients with RA.⁹ Decreased range of motion and grip strength, higher swollen joint counts, and pain correlated with more impairments in physical function assessed by HAQ-DI. In addition to physical function, age and socioeconomic factors such as education, employment status, race, living setting, and economic status affect patient-reported HRQOL; those older, less educated, not employed, and/or less affluent reported significantly lower HRQOL.^{10,11}

This article reviews patient-reported physical function and HRQOL from RCTs with traditional DMARDs methotrexate and leflunomide, as well as biologic agents, including etanercept, infliximab, adalimumab, abatacept, and rituximab. The relevance of HRQOL data derived from RCTs to day-to-day clinical practice will be discussed in this article. These clinically meaningful interpretations are presented in the tables and figures that follow.

Prior to the introduction of the new DMARDs, longitudinal series reported progressive deterioration in physical function or, at best, stabilization in RA with standard of care (including methotrexate). Summarizing data from 12 studies, Scott et al demonstrated average increases of 0.033 per year in HAQ-DI scores.^{12,13} A J-shaped curve plotting disability measured by HAQ-DI versus disease duration was observed, reflecting that patients with early disease reported more impairments in physical function, which were dramatically improved when treatment with the first DMARD was initiated.¹⁴ West and Jonsson et al compared SF-36 in RA patients at disease onset and after 2 years, with patients with long-term disease of 21 to 25 years' duration.¹⁵ Two years after diagnosis, patients reported significant improvements in role physical and bodily pain domains of SF-36 compared with disease onset. As expected, impairments in physical function were fewer in patients with early versus longer-duration RA. As with physical function, HRQOL is negatively impacted in early RA. Therefore, comparisons of reported improvements in HAQ-DI and SF-36 scores across treatment groups must

account for disease duration as well as baseline characteristics in protocol populations.

Differences in results with active therapy versus placebo are most pronounced in patient-reported outcomes of pain, physical function, and global disease activity and best differentiate active from placebo therapy.^{16,17} When comparing changes from baseline in HAQ-DI scores at 6 and 12 months in RCTs, mean improvements in patients who received active treatment ranged from −0.25 to −0.80, compared with patients receiving placebo, where mean change scores did not meet or exceed the MCID of −0.22.¹⁸ As noted earlier, it is difficult to compare changes across RCTs and treatments; the proportion of patients reporting improvements \geq MCID offers another way to interpret data from RCTs. Recent publications have reported a proportion of patients with improvements in HAQ-DI scores \geq −0.25, \geq −0.50, or \geq −0.80 or attaining final scores of 0 to 0.5, representing non-RA population norms¹⁹ and considered to reflect clinically meaningful improvements.

Values for MCID in domain and SF-36 summary scores (physical component summary [PCS] and mental component summary [MCS]) have been derived in RA, osteoarthritis, psoriatic arthritis, ankylosing spondylitis, systemic lupus erythematosus, and fibromyalgia, based on correlations with patient-reported improvements in global disease activity, on an individual patient basis, as reviewed by Khanna and Tsevat in this supplement. Changes of 5 to 10 points in domain scores and 2.5 to 5.0 points in PCS and MCS are considered to represent MCID.^{8,20-30} Changes that meet or exceed 0.5 standard deviation (SD) of the mean can be considered to reflect “minimally important differences” (MIDs), statistical definitions not specifically anchored to patient-reported outcomes.

Another interpretation of the “clinical meaningfulness” of changes in reported HRQOL is to compare baseline and end point domain and summary scores of SF-36 to age- and sex-matched norms in relevant cultural populations. Baseline scores reported by patients in RA RCTs reflect large decrements in physical function, role physical, pain, vitality, and general health perception domains, as well as PCS scores, often approaching 2 SDs below the expected norm of 50. Changes in SF-36 scores at end point can be evaluated by how closely they approach a “goal” of normative scores. (See **Figure 1** as an example.)

Reported changes in specific queries in SF-36 (eg, decreases in walking limitations; less time lost at work because of health reasons; less inability to work because of pain; less time felt tired or worn out; less interference of health in social activities; and fewer patients reporting feeling downhearted or blue most of the time) offer another method for interpreting clinically meaningful changes attributed to treatment.

Answers to the “transition question” of SF-36 (ie, “compared with a year ago...”) also offer a way to interpret clinically meaningful treatment-associated changes. Importantly, changes from baseline in RCTs may exceed those reported in longitudinal studies, largely attributed to “expectation bias” on the part of patients (as well as treating physicians).

Methotrexate and Leflunomide

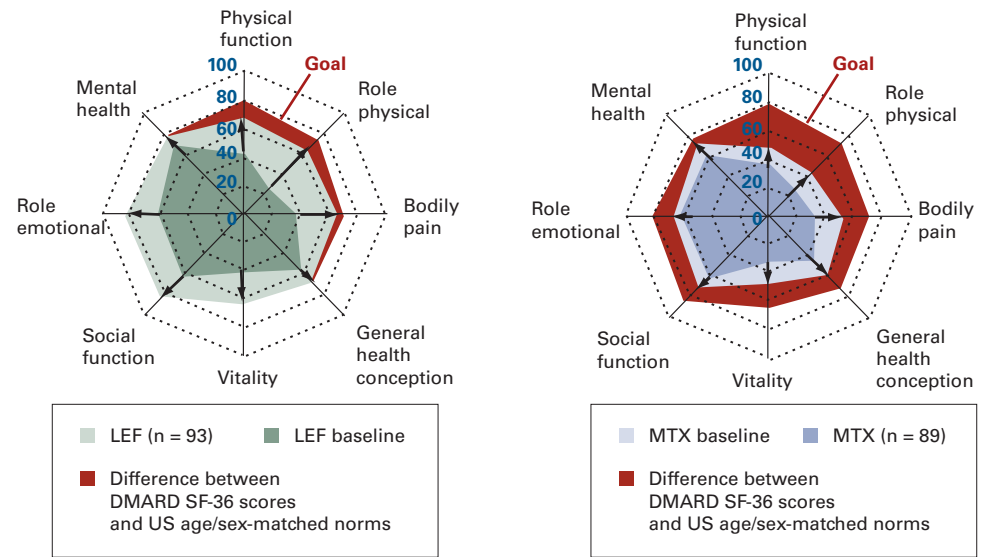
Methotrexate is the most commonly prescribed DMARD in RA, with proven efficacy as monotherapy and in combination with other DMARDs, including biologic agents.³¹

Symptomatic benefit is typically maximal at 6 months.³¹ Leflunomide, a synthetic DMARD approved by the FDA in 1998 for treatment of active RA, has been shown in RCTs to be equivalent to methotrexate and is perceived now as the best alternative to methotrexate, either as monotherapy or in combination with other DMARDs, including biologic agents.³²

A 24-month, placebo-controlled RCT (US 301) was the first to show that SF-36 was a valid and sensitive instrument to measure HRQOL in patients with active RA.^{8,32-34} Subsequently, results from 3 phase 3 RCTs over 2 years of blinded treatment with leflunomide, methotrexate, or sulfasalazine demonstrated that improvements in physical function and HRQOL were sustained and clinically meaningful.³² In the 2 studies that compared methotrexate and leflunomide, US 301 and MN 302/4, patient-reported outcomes included HAQ-DI, MHAQ, and SF-36. After 12 and 24 months of treatment with leflunomide or methotrexate, 71% to 78% of leflunomide-treated and 59% to 73% of methotrexate-treated patients reported improvements in HAQ-DI \geq MCID in these trials.³⁵ Mean disease duration was 6.7 years in US 301 and 3.2 years in MN 302/4, and baseline HAQ-DI scores were 1.2 and 1.5, respectively (Table 1).³² Despite these overall differences, 40% to 45% of patients in each study had disease duration of \leq 2 years.³²

In the year-2 cohorts from both trials,³² improvements from baseline in HAQ-DI evident at 6 months were sustained

Figure 1. “Spider Grams” Depicting Baseline and Final Values at Year 2 for SF-36 Domain Scores in Protocol US 301



Mean baseline and mean SF-36 domain scores at 24 months compared with US normative values (red) for leflunomide (LEF), in blue, and methotrexate (MTX), in green. SF-36 indicates Medical Outcomes Study 36-Item Short Form; DMARD, disease-modifying antirheumatic drug.

over 24 months of treatment and statistically significant ($P = .005$ at 24 months) (Table 1). These values were consistent with HAQ-DI values reported in the intent-to-treat population at 12 months. For SF-36 PCS, mean change scores reported by patients receiving leflunomide or methotrexate were not statistically different and met or exceeded MCID in 80% of leflunomide-treated and 77% of methotrexate-treated patients. Baseline SF-36 MCS scores approached US norms and did not demonstrate statistically or clinically meaningful improvements. Reported improvements in SF-36 domains were equivalent between leflunomide and methotrexate except in bodily pain, vitality, and role emotional; for these domains, patients treated with leflunomide demonstrated statistically significantly greater improvements ($P < .05$ vs methotrexate). At 2 years (or 24 months), with the exception of physical function, role physical, and bodily pain domain scores, reflecting largest decrements at baseline, final mean SF-36 scores approached age- and sex-matched US norms in 5 of 8 domains with leflunomide but none of 8 with methotrexate (Figure 1).

Based on improvements in HAQ-DI and SF-36, the number needed to treat (NNT) to achieve another patient reporting improvements in HAQ-DI \geq MCID and/or normative PCS levels were 3 to 5 for leflunomide versus 6 to 17 with methotrexate versus placebo.³⁵

■ **Table 1.** Clinically Meaningful Changes from Baseline in Physical Function and HRQOL in RA Patients Receiving MTX or LEF*

Protocol	US 301	US 301	MN 302/4	MN 302/4
Rx	LEF	MTX	LEF	MTX
No. of patients [†]	98	101	292	320
Mean disease duration (yr)	5.9	6.7	3.5	3.8
Mean DMARDs failed	0.8	0.9	1.0	1.1
Baseline HAQ-DI	1.2	1.2	1.5	1.5
Mean (median) changes at 12, 24 mo	-0.60 (-0.63) -0.60 [‡] (-0.63)	-0.37 (-0.38) -0.37 (-0.38)	-0.56 (-0.50) -0.48 (-0.38)	-0.61 (-0.56) -0.56 (-0.50)
% with improvements ≥MCID	71	59	67	73
Baseline SF-36 PCS	30.9	30.2		
Mean (median) changes at 12, 24 mo	11.9 (11.3) 10.8 (9.7)	8.0 (4.6) 8.4 (5.4)		
% with improvements ≥MCID	80	77		
Baseline SF-36 MCS	48.5	49.8		
Mean (median) changes at 12, 24 mo	3.6 (2.9) 4.7 (4.2)	2.5 (0.6) 2.7 (0.4)		
% with improvements ≥MCID	10	5		

*Changes of -0.22 point for HAQ-DI, 5 to 10 points in SF-36 domain scores, and 2.5 to 5 points in PCS and MCS were considered to be MCIDs.

[†]Year 2 cohort.

[‡]*P* = .005, LEF vs MTX.

HRQOL indicates health-related quality of life; RA, rheumatoid arthritis; MTX, methotrexate; LEF, leflunomide; DMARDs, disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; MCID, minimum clinically important difference; SF-36, Medical Outcomes Study 36-Item Short Form; PCS, physical component summary; MCS, mental component summary.

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Biologic Agents: TNF-alpha Inhibitors

Inhibition of the activity of tumor necrosis factor (TNF)-alpha, a pleiotropic proinflammatory cytokine pathogenic in RA, has revolutionized treatment of this disease.³⁶ Phase 3 RCTs with infliximab, etanercept, and adalimumab have demonstrated a significant and clinically meaningful impact on physical function and HRQOL in patients with active RA, many of whom have failed methotrexate.²⁸ HAQ-DI and SF-36 were studied in the phase 3 RCT Anti-tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy (ATTRACT),³⁷ in the phase 4 Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO),³⁸ and in all phase 3 adalimumab³⁹ RCTs.

Infliximab. In ATTRACT, 428 RA patients with mean disease duration of 9 to 12 years and failing methotrexate received infliximab or placebo in addition to methotrexate over 12 and 24 months of treatment.^{37,40} Baseline HAQ-DI scores and SF-36 PCS scores were more than 2 SDs below US norms, whereas MCS scores were within 1 SD.⁴¹ All active-treatment groups reported statistically significant and clinically

meaningful improvements in physical function and HRQOL that were evident at 6 to 10 weeks, with the greatest changes in role physical and bodily pain domains.

Treatment with infliximab plus methotrexate over 24 months or placebo plus methotrexate in ATTRACT resulted in significant improvements in HAQ-DI (overall median improvement in infliximab groups of 0.4 vs 0.1 in the placebo group; *P* ≤ .006) and SF-36 PCS scores (median changes of 2.8 with placebo vs 6.4 with infliximab; *P* ≤ .011). Changes from baseline in HAQ-DI and SF-36 scores in ATTRACT are presented in **Table 2**.⁴⁰⁻⁴² In patients with improvements in HAQ exceeding MCID (≥0.25), 21% versus 3% with changes <0.25 gained employment during this trial.⁴¹ The impact of RA on MCS was not as marked at baseline, yet median changes in all active-treatment groups reflected statistically significant improvements in all domain and PCS scores over 2 years of treatment versus placebo and exceeded MCID in 5 of 8 domains compared with none receiving methotrexate plus placebo (**Figure 2**).³⁹ In a combined analysis of RA patients from ATTRACT and Safety Trial for Rheumatoid Arthritis with Remicade Therapy (START) trials, more active- than placebo-

Table 2. Changes from Baseline in HAQ-DI and SF-36 Scores in ATTRACT*

Protocol: ATTRACT					
Rx	MTX + Placebo	3 mg/kg INF every 8 weeks + MTX	3 mg/kg INF every 4 weeks + MTX	10 mg/kg INF every 8 weeks + MTX	10 mg/kg INF every 4 weeks + MTX
No. of patients	88	86	86	87	81
Duration of disease (yr)	11 ± 8	10 ± 8	9 ± 8	11 ± 9	12 ± 9
Baseline HAQ-DI	1.7	1.8	1.7	1.7	1.7
Median change in HAQ, 24 mo	0.1	0.4	0.4	0.4	0.3
Baseline SF-36 PCS	25.7	25.2	23.9	25.7	25.8
Median change in SF-36 PCS, 24 mo	2.8	4.6 [†]	6.8 [‡]	6.9 [‡]	6.7 [‡]
Baseline SF-36 MCS	48.5	46.8	49.9	47.6	47.9
Median change in SF-36 MCS, 24 mo	1.9	3.8	2.2	2.9	3.7

*MCID was defined as -0.25 point for SF-36 domain scores and as ≥10 points for PCS and MCS scores.

[†]P = .011 vs MTX.

[‡]P < .001 vs MTX.

HAQ-DI indicates Health Assessment Questionnaire Disability Index; SF-36, Medical Outcomes Study 36-Item Short Form; ATTRACT, Anti-tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy; MTX, methotrexate; INF, infliximab; MCID, minimum clinically important difference; PCS, physical component summary; MCS, mental component summary.

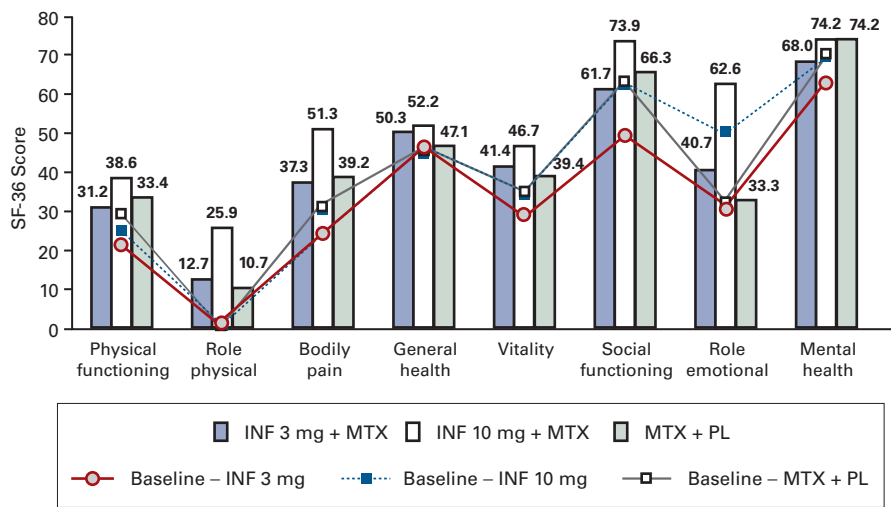
Sources: References 37, 40-42.

treated patients reported changes ≥MCID (5 points) from baseline to first assessment at 6 weeks or 10 in PCS (54% vs 35%; P < .001) and MCS scores (42% vs 35%; P < .01), respectively.⁴¹

In a small, randomized trial of 27 RA patients with active disease despite methotrexate treatment, patients were randomized to pulse intravenous methylprednisolone or intravenous infliximab.⁴³ Physical function, bodily pain, general health, and social functioning domains of SF-36 improved more significantly with infliximab than methylprednisolone treatment (P ≤ .05). Small sample sizes precluded observation of significant changes within each group.

Etanercept. A phase 3 RCT of etanercept versus placebo in 234 patients with active RA demonstrated improvements in physical function according to HAQ-DI scores as early as 2 weeks after initiation.⁴⁴ Baseline HAQ-DI scores in the placebo and etanercept 10- and 25-mg groups were 1.7, 1.8, and 1.6, respec-

Figure 2. SF-36 Changes in ATTRACT: Scores at Baseline and Median Scores at 2 Years*



*Patients received infliximab 3 mg/kg q8 weeks plus methotrexate ([MTX]; baseline [light grey circle]; median at 2 years [blue bar]), infliximab 10 mg/kg q8 weeks plus MTX (baseline [dark blue square]; median at 2 years [white bar]), or placebo plus MTX (baseline [white square]; median at 2 years [green bar]).

SF-36 indicates Medical Outcomes Study 36-Item Short Form; ATTRACT, Anti-tumour Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy; INF, infliximab; PL, placebo.

tively.⁴⁵ Both active-treatment groups reported statistically significant improvements in HAQ-DI score and SF-36 PCS scores at months 1, 3, and 6 versus placebo (P ≤ .01, with the exception of 10 mg vs placebo at month 1), 39% in patients

■ **Table 3.** Clinically Meaningful Improvements from Baseline in Physical Function and HRQOL in RA Patients Receiving TNF Inhibitors*

Protocol	ASPIRE ^{48,49}	ASPIRE	ASPIRE	TEMPO ⁴⁷	TEMPO	TEMPO	PREMIER ⁵⁰	PREMIER	PREMIER
Rx	3 mg/kg INF + MTX	6 mg/kg INF + MTX	MTX	ETN	ETN + MTX	MTX	ADA	ADA + MTX	MTX
No. of patients	359	363	282	223	231	228	274	268	257
Mean disease duration	1 ± 1	1 ± 1	1 ± 1	6 ± 5	7 ± 5	7 ± 6	1 ± 1	1 ± 1	1 ± 1
Mean DMARDs failed	71% naive	68% naive	65% naive	2.3 ± 1.4	2.3 ± 1.4	2.3 ± 1.6	67% naive	67% naive	68% naive
Baseline HAQ-DI	1.5	1.5	1.5	1.7	1.8	1.7	1.6	1.5	1.5
Mean Δ at 12, 24 mo	-0.80 [†]	-0.88 [†]	-0.68 [†]	-0.70, -0.70	-1.0, -1.01	-0.60, -0.61	-0.8, -0.9	-1.1, -1.0	-0.8, -0.9
% with Δ ≥ MCID	76	76	65	77	86	77	58	72	63
% with Δ ≥ -0.5	65	69	56	55	72	53	—	—	—
% achieving HAQ-DI ≤ 0.5	48	47	35	34	44	34	19	33	19
Baseline SF-36 PCS	28.8 ± 7.7	29.3 ± 8.2	29.5 ± 7.7	—	—	—	—	—	—
Mean Δ at 12, 24 mo	11.7 ± 11.6	13.2 ± 12.0	10.1 ± 11.4	—	—	—	—	—	—
Baseline SF-36 MCS	45.4 ± 11.5	44.2 ± 11.9	44.7 ± 11.9	—	—	—	—	—	—

*MCID was defined as improvements of ≥0.22 in HAQ score.

[†]12 months.

HRQOL indicates health-related quality of life; RA, rheumatoid arthritis; TNF, tumor necrosis factor; ASPIRE, Active-Controlled Study of Patients Receiving Infliximab for the Treatment of Rheumatoid Arthritis of Early Onset; TEMPO, Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes; INF, infliximab; MTX, methotrexate; ETN, etanercept; ADA, adalimumab; DMARDs, disease-modifying antirheumatic drugs; HAQ-DI, Health Assessment Questionnaire Disability Index; MCID, minimum clinically important difference; SF-36, Medical Outcomes Study 36-Item Short Form; PCS, physical component summary; MCS, mental component summary.

Source: Reference 49.

treated with etanercept 25 mg versus 2% in patients receiving placebo at 6 months. MCS scores in both active groups and placebo groups were comparable at baseline, but by 3 months, those receiving etanercept 25 mg reported statistically significant improvements, also evident in the 10-mg treatment group at 6 months ($P \leq .02$).

In patients with long disease duration failing methotrexate, addition of etanercept resulted in significant improvements in physical function.⁴⁶ Median HAQ-DI scores improved 47% from baseline over 6 months of treatment, from 1.5 to 0.8, in patients receiving etanercept plus methotrexate, versus 27% (from 1.5 to 1.1) with methotrexate plus placebo.

In TEMPO, 682 RA patients with a mean 6.3 to 6.8 years' disease duration, having failed a mean of 2.3 DMARDs, were randomized to receive etanercept, methotrexate, or combination therapy.³⁸ Baseline HAQ-DI scores were 1.7 to 1.8; mean improvements at 12 and 24 months with either monotherapy were exceeded by combination treatment (Table 3),³⁸ sustained from 6 to 48 weeks ($P < .01$).⁴⁷ Patient-reported improvements in HAQ, global assessment of disease activity (visual analog scale [VAS]), general health (VAS), and EQ-5D VAS were highly correlated with DAS. At 12 months,

41% of those receiving combination therapy reported EQ-5D VAS scores comparable to population norms. The improved efficacy of etanercept when combined with methotrexate versus either monotherapy has also been observed with other TNF inhibitors (Table 3).⁴⁷⁻⁵⁰

Adalimumab. The Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab (ARMADA or DE009) RCT was a 6-month comparison of adalimumab 20 or 40 mg versus placebo in 271 patients failing methotrexate.⁵¹ Baseline HAQ-DI scores reflected significant impairment of physical function.^{39,52} Mean improvements at week 1 and months 3 and 6 exceeded MCID in all active-treatment groups compared with placebo plus methotrexate and were statistically significant ($P < .05$). At 6 months, significant improvements in SF-36 PCS scores (Table 4)^{39,51-53} were observed, as well as improvements in 7 of 8 and 8 of 8 domains of SF-36 in patients receiving 20 and 40 mg of adalimumab plus methotrexate, respectively, versus only 4 of 8 domains with placebo plus methotrexate ($P < .05$). Mean increases in 6 of 8 domain scores exceeded MCID (≥10 points) for all active-treatment groups combined compared

Table 4. Clinically Meaningful Improvements in HAQ-DI and SF-36 PCS Scores in Patients Receiving Adalimumab: DE009 (ARMADA)^{38,50,51} and DE019^{52*}

Protocol	DE009	DE009	DE009	DE019	DE019	DE019
Rx	Placebo + MTX	20 mg ADA qow + MTX	40 mg ADA qow + MTX	Placebo + MTX	40 mg ADA qow + MTX	20 mg ADA weekly + MTX
No. of patients	62	69	67	200	207	212
Duration of disease (yr)	11 ± 8	13 ± 8	12 ± 11	11 ± 9	11 ± 9	11 ± 9
Mean no. of previous DMARDs	3.0	3.0	2.9	2.4	2.4	2.4
Baseline HAQ-DI	1.64	1.52	1.55	1.48	1.45	1.44
Mean change in HAQ-DI, wk 1	-0.15	-0.26 ^{†‡}	-0.24 [†]	NR	NR	NR
Mean change in HAQ-DI, mo 3	-0.25	-0.53 ^{†‡}	-0.55 ^{†‡}	NR	NR	NR
Mean change in HAQ-DI, mo 6	-0.27	-0.53 ^{†‡}	-0.62 ^{†‡}	-0.24	-0.56 [§]	-0.60 [§]
Mean change in HAQ-DI, mo 12	NR	NR	NR	-0.25	-0.59 [§]	-0.61 [§]
Baseline SF-36 PCS	28.3	27.9	28.4	NR	NR	NR
Mean change in SF-36 PCS, mo 6	2.6	7.1 ^{†‡}	9.3 ^{†‡}	NR	NR	NR

*MCID was defined as changes ≥ 0.22 for HAQ scores in DE009 and ≥ 10 points for SF-36 domains in both studies.

[†]Statistically significant vs placebo.

[‡] \geq MCID.

[§] $P \leq .001$ vs placebo.

HAQ-DI indicates Health Assessment Questionnaire Disability Index; SF-36, Medical Outcomes Study 36-Item Short Form; PCS, physical component summary; ARMADA, Anti-TNF Research Study Program of the Monoclonal Antibody Adalimumab; MTX, methotrexate; ADA, adalimumab; DMARDs, disease-modifying antirheumatic drugs; NR, not reported; MCID, minimum clinically important difference.

with 2 of 8 domains with placebo plus methotrexate. At 6 months, mean improvement in scores in the fatigue scale of the Functional Assessment of Chronic Illness Therapy (FACIT) in the 40-mg active-treatment group (8.5) was statistically significant versus placebo plus methotrexate (3.0).⁵¹

In DE019, a 12-month phase 3 RCT, 619 patients with active RA and inadequate responses to methotrexate were randomized to receive adalimumab (40 mg biweekly or 20 mg weekly) plus methotrexate compared with placebo plus methotrexate; primary and secondary end points included changes in HAQ-DI and SF-36.^{52,53} At approximately 1 year, reported improvements in physical function by HAQ-DI were statistically significant with adalimumab 40 mg biweekly and 20 mg weekly compared with placebo (Table 4).^{52,53} As shown in **Figure 3**, patients receiving adalimumab reported significant improvements in 7 of 8 domains (40 mg biweekly) and 8 of 8 domains (20 mg weekly) of SF-36.⁵³ Improvements exceeded MCID (≥ 10 points) in 5 of 8 domains with adalimumab 40 mg biweekly plus methotrexate and in 7 of 8 domains with weekly adalimumab 20 mg plus methotrexate, compared with only 1 of 8 domains with placebo plus methotrexate treatment.⁵³

In RA patients completing 1 of 6 phase 1 to 3 RCTs, including DE026, 505 received long-term adalimumab treatment over a mean of 19.2 months. Mean disease duration in

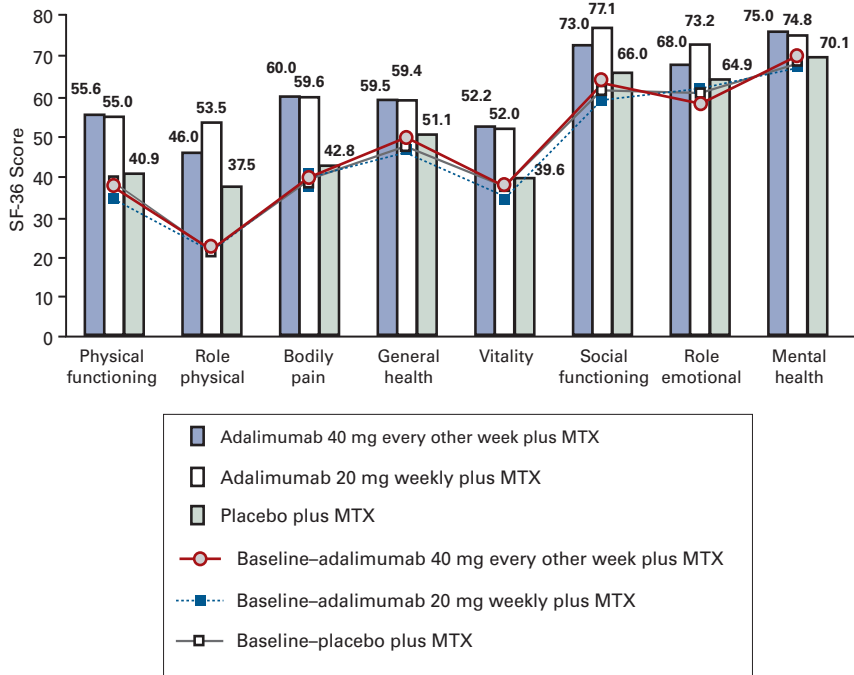
this population was 12.4 years, having failed approximately 4 prior DMARDs. Baseline SF-36 scores in those enrolled in this continuation protocol overall were ≥ 10 points lower than in DE026; nonetheless, treatment-associated improvements in SF-36 scores confirmed rapid and sustained improvements in HRQOL over 6.5 months in the entire population, from 25.4 to 34.4 and 43.7 to 50.0 in PCS and MCS scores, respectively.⁵⁴ Mean baseline PCS scores in the entire population were similar to MCS, indicating patients with longer disease duration report more decrements in physical functioning, role physical, bodily pain, general health, and vitality. After long-term treatment, mean area under the curve of SF-36 scores demonstrated sustained and clinically meaningful improvements in HRQOL.

T-cell Costimulation Modulator

Abatacept, a T-cell costimulation modulator, has been demonstrated to improve signs and symptoms of RA, to inhibit progression of structural damage, and to improve physical function and HRQOL over 24 months of treatment in adult patients with active RA with inadequate responses to methotrexate or TNF-alpha antagonists.⁵⁵⁻⁵⁹

In the Abatacept in Inadequate Responders to Methotrexate (AIM) trial, HAQ-DI and SF-36 scores were compared in 652 patients with inadequate responses to methotrexate,

■ **Figure 3.** SF-36 Changes in DE019: Scores at Baseline and Mean Scores at 12 Months*



*Patients received adalimumab 40 mg every other week plus methotrexate ([MTX]; baseline [light grey square]; mean at 12 months [dark blue bar]), adalimumab 20 mg weekly (baseline [blue square]; mean at 12 months [white bar]), or placebo plus MTX (baseline [white square]; mean at 12 months [green bar]). SF-36 indicates Medical Outcomes Study 36-Item Short Form. Reprinted with permission from Reference 53.

randomized 2:1 to receive abatacept plus methotrexate or placebo plus methotrexate over 12 months.⁵⁸ Mean baseline HAQ-DI scores were 1.7, and SF-36 domain scores were ≥ 1 SD below US norms (Table 5).^{55,58-60} Mean PCS and MCS scores approximated 2 and 1 SDs, respectively, below US norms of 50.⁵⁹ A responder analysis determined the percentage of patients from each treatment group who reported improvements ≥ 0.5 SD at 12 months, representing MID.

Statistically significant differences between abatacept and placebo groups in reported improvements in all 8 SF-36 domains were evident as early as 3 months and sustained over 12 months of treatment ($P < .01$) (Figure 4).⁵⁹ Responder analyses demonstrated that a significantly greater percentage of patients receiving abatacept reported improvements in HRQOL approximating US age- and sex-matched norms at 6 months for PCS and MCS ($P < .01$ for both; data for months 12 and 24 are presented in Table 5). Based on this differential effect, the NNT to achieve another patient reporting normative levels in PCS was 6, and in MCS, 10. The percentage of patients reporting improvements in HRQOL scores of ≥ 0.5 SD—reflecting MIDs—was significantly higher with abata-

cept treatment versus placebo over 12 months ($P < .001$ for HAQ, FACIT, and SF-36 PCS comparisons).

In the Abatacept Trial in Treatment of Anti-TNF Inadequate Responders (ATTAIN), an RCT, 391 patients with an average of 11.4 to 12.2 years of disease duration, having failed predominantly etanercept and/or infliximab due to inadequate responses or adverse effects, were randomized to receive abatacept ($n = 258$) or placebo ($n = 133$) plus DMARDs over 6 months.⁵⁵ Significantly more abatacept-treated versus placebo-treated patients reported improvements from baseline ≥ 0.30 (exceeding MCID) in HAQ ($P < .001$), and clinically meaningful differences (defined as ≥ 3 points) in PCS and MCS scores ($P < .01$) (Table 5). HAQ-DI and 7 of 8 SF-36 domains (all but role emotional) were significantly improved with abatacept treatment in those with lower 28 joint-count DAS scores at baseline. The percentage of patients reporting improvements \geq MID at 6 months was significantly higher with

abatacept treatment ($P < .0001$).

In the Abatacept Study of Safety in Use with Other RA Therapies (ASSURE), 1441 patients received placebo or treatment with abatacept, added to background DMARD therapy; 1231 completed 12 months of protocol treatment.⁶¹ Baseline HAQ-DI scores ranged from 1.5 to 1.6; improvements of 30% and 22% were observed in those receiving abatacept plus background DMARDs, compared with 9% and 15% with placebo plus background DMARDs, respectively. Overall, mean improvements of -0.46 in HAQ-DI were reported with abatacept plus background DMARDs versus -0.25 with placebo plus DMARDs. In an RCT of 121 patients receiving etanercept randomized to receive abatacept or placebo in addition for 12 months, those receiving combination therapy reported clinically meaningful changes of ≥ 3 points in PCS and MCS scores compared with baseline. Statistically significant improvements versus placebo were evident in PCS and 5 of 8 SF-36 domains.⁶²

Selective Depletion of B Cells

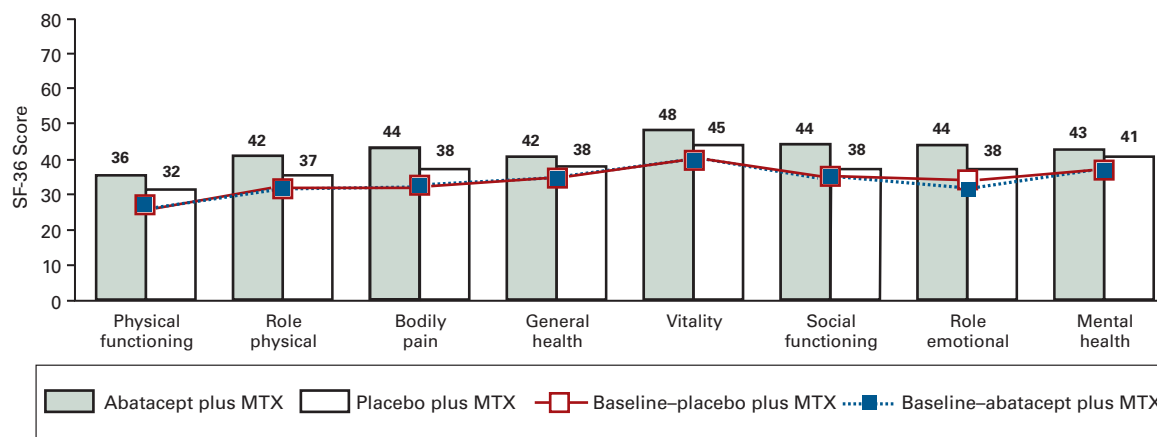
Rituximab, a monoclonal antibody directed against the CD20 antigen on the surface of circulating B lymphocytes, is

Table 5. Clinically Meaningful Improvements from Baseline in Physical Function and HRQOL in RA Patients Receiving Abatacept*

Protocol	AIM ^{58,59}	AIM	ATTAIN ⁶⁰	ATTAIN
Rx	ABA + MTX	Placebo + MTX	ABA + MTX	Placebo + MTX
No. of patients	433	219	258	133
Mean disease duration	9 ± 7	9 ± 7	12 ± 9	11 ± 9
Baseline HAQ-DI	1.7 ± 0.7	1.7 ± 0.6	1.8 ± 0.6	1.8 ± 0.6
Mean changes at 6 (ATTAIN) or 12 (AIM) mo	-0.68 ± 0.03	-0.5 ± 0.05	-0.5 ± 0.6	-0.1 ± 0.4
% with improvements ≥MCID	67.3	39.3	47.3	23.3
% achieving Δ >0.5 SD	72.4	55.2	—	—
Baseline SF-36 PCS	30.6 ± 7.3	30.7 ± 7.5	27.6 ± 7.0	27.7 ± 6.4
Mean changes at 6 (ATTAIN) or 12 (AIM) mo	8.82 ± 0.4	4.8 ± 0.59	6.5 ± 9.6	1.0 ± 7.7
% achieving norm = 50	47.1	30.7	23	10
% achieving Δ >0.5 SD	67.2	51.1	—	—
Baseline SF-36 MCS	41.8 ± 11.4	40.8 ± 11.2	41.2 ± 12.4	42.9 ± 11.9
Mean changes at 6 (ATTAIN) or 12 (AIM) mo	6.22 ± 0.49	3.83 ± 0.7	5.4 ± 11.7	1.7 ± 10.2
% achieving norm = 50	60.4	50.5	—	—

*MCID was defined as changes ≥0.25 in the AIM study,⁵⁸ and ≥0.3 in the ATTAIN study.⁵⁵ HRQOL indicates health-related quality of life; RA, rheumatoid arthritis; ABA, abatacept; AIM, Abatacept in Inadequate Responders to Methotrexate; ATTAIN, Abatacept Trial in Treatment of Anti-TNF Inadequate Responders; MTX, methotrexate; HAQ-DI, Health Assessment Questionnaire Disability Index; MCID, minimum clinically important difference; SD, standard deviation; SF-36, Medical Outcomes Study 36-Item Short Form; PCS, physical component summary; MCS, mental component summary.

Figure 4. SF-36 Changes in AIM: Scores at Baseline and Mean Scores at 12 Months*



*Patients received abatacept plus methotrexate ([MTX]; baseline [blue square]; mean score at 12 months [green bar]) or placebo plus MTX (baseline [white square]; mean score at 12 months [white bar]). SF-36 indicates Medical Outcomes Study 36-Item Short Form; AIM, Abatacept in Inadequate Responders to Methotrexate. Reprinted with permission from Reference 59.

indicated in combination with methotrexate for treatment of patients with active RA who have had inadequate responses to ≥1 TNF inhibitor. In an initial phase 2 RCT, 161 patients with active RA failing methotrexate were randomized to receive 1 of 4 treatments for 6 months: rituximab alone,

rituximab plus methotrexate, rituximab plus cyclophosphamide, or methotrexate plus placebo.⁶³ Patients remained in follow-up until re-treatment was required. A higher proportion of patients in active-treatment arms had continuing ACR responses and did not require re-treatment at 6, 12, and 18

■ **Table 6.** Clinically Meaningful Improvements in HAQ Score in Patients Receiving Rituximab^{64,65*}

Protocol	Phase II	Phase II	Phase II	Phase II	DANCER	DANCER	DANCER
Rx	Placebo + MTX	RTX 1000 mg × 2	RTX 1000 mg × 2 + CTX	RTX 1000 mg × 2 + MTX	Placebo + MTX	RTX 500 mg × 2 + MTX	RTX 1000 mg × 2 + MTX
No. of patients	40	40	41	40	149	124	192
Baseline HAQ-DI	2.0	2.0	1.8	1.8	1.7	1.8	1.7
% of patients ≥MCID at 3 mo	38	63	61	55	NR	NR	NR
% of patients ≥MCID at 6 mo	45	68	59	63	34	63	67
% of patients ≥MCID at 12 mo	28	43	39	68	NR	NR	NR
% of patients ≥MCID at 18 mo	18	18	22	48	—	—	—

*MCID is defined as changes of ≥ 0.25 .⁶⁴

HAQ indicates Health Assessment Questionnaire; DANCER, Dose-ranging Assessment: International Clinical Evaluation of Rituximab in RA; MTX, methotrexate; RTX, rituximab; CTX, cyclophosphamide; HAQ-DI, HAQ Disability Index; MCID, minimum clinically important difference; NR, not reported.

months. Proportions of patients with clinically meaningful improvements in HAQ-DI (MCID ≥ 0.25 reduction) are shown in **Table 6**.^{64,65} Differences favoring rituximab plus methotrexate persisted up to 24 months, with high dropout rates in the other treatment groups.

In the Dose-ranging Assessment: International Clinical Evaluation of Rituximab in RA (DANCER) trial, 465 patients received 1 of 3 treatments—2 infusions of rituximab 500 mg, 2 infusions of rituximab 1000 mg (days 1 and 15), or placebo—plus methotrexate, with intravenous (IV) glucocorticoids, both oral and IV glucocorticoids, or none at all.⁶⁵ Baseline HAQ-DI score and proportions of patients with changes \geq MCID (defined as 0.22 reduction in score) are shown in **Table 6**. Similar improvements were seen in fatigue measured by FACIT, with mean changes \geq MCID in rituximab-treated patients.

In the Randomized Evaluation of Long-term Efficacy of Rituximab in RA trial (REFLEX), 520 patients with active RA on methotrexate following inadequate responses to TNF inhibitors received rituximab or placebo for 6 months.⁶⁶ Baseline HAQ-DI scores were 1.9, with changes of -0.4 with rituximab versus -0.1 with placebo; 6% versus 0.5% (1 patient) achieved HAQ-DI scores of 0 at 6 months despite long disease duration of 11.7 to 12.1 years. Improvements in SF-36 PCS and MCS scores of 4.7 and 5.8, respectively, were reported with rituximab versus 1.3 and 0.9, respectively, with placebo; between-group differences were statistically significant and clinically meaningful, as they differed by >3 points.⁶⁶ Changes from baseline in SF-36 scores at week 24 in the REFLEX trial are represented in **Figure 5**.⁶⁷

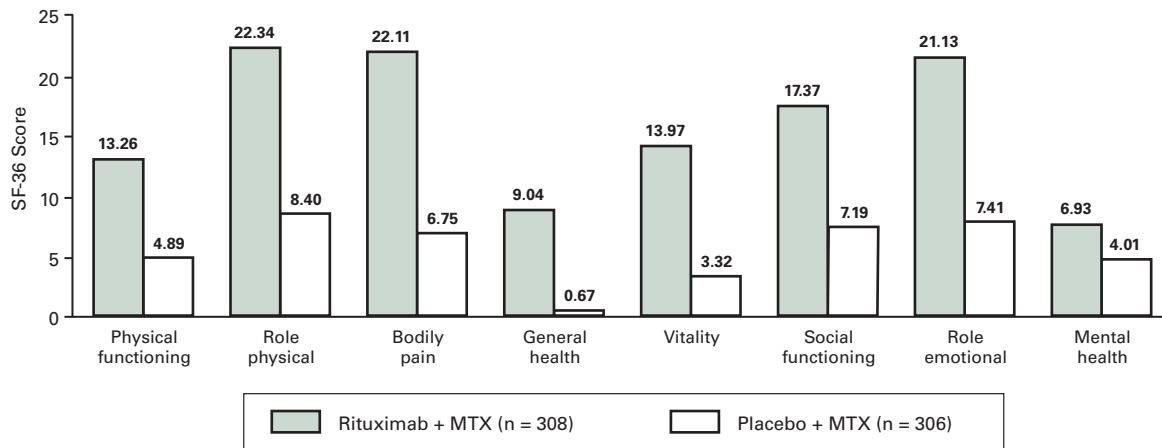
Duration of RA Influences Outcomes

In patients with established disease, baseline PCS scores

were low across trials: 30.2 to 30.9 in US 301; 23.9 to 25.8 in ATTRACT; 27.9 to 29.0 in ARMADA; 28.5 to 29.1 in protocol DE019; 30.6 to 30.7 in AIM; and 27.6 to 27.7 in ATTAIN. (Baseline PCS scores were not reported in etanercept or rituximab RCTs.) Mean and median improvements with active treatment over 12 and 24 months resulted in meaningful increases in PCS scores: Baseline scores were >2 SDs below normative values of 50, while results reached within 1 SD of the norm, and changes well exceeded MCID (2.5-5.0 points) in all trials. These improvements were reflected by reductions in the percentage of patients reporting limitations in performance of common activities. Changes in PCS scores alone do not reflect the full range of improvement in HRQOL, which occurs when treatments positively impact physical function, but also pain and “vitality” in patients with active RA. All studies have demonstrated that treatment-related changes in HAQ-DI scores are closely reflected not only in improvements in physical domains of SF-36 but also social functioning, role emotional, and general health profile. As with HAQ, reported improvements are maximal within 6 months and sustained over 12 to 24 months of continuing therapy.

It is important to understand that a measure of physical function in RA such as HAQ-DI is an assessment of “state” as well as “change.” Development of joint damage, manifested by bony erosions and joint space narrowing, leads to irreversible structural changes that impact physical functioning and lead to irreversible impairments and ultimately inability to work or engage in desired activities, and thus disability. Baseline levels of physical functioning reported in RCTs are clearly influenced by disease activity, severity, and duration. To better understand the impact of disease duration on physical function, Aletaha and Ward conducted a combined

■ **Figure 5.** SF-36 Mean Changes in REFLEX*



*Patients received rituximab plus methotrexate (MTX) or placebo plus MTX. The mean changes from baseline in SF-36 domains were obtained at 6 months. Baseline data were not available for this study.

SF-36 indicates Medical Outcomes Study 36-Item Short Form; REFLEX, Randomized Evaluation of Long-term Efficacy of Rituximab.

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analysis based on reports from 36 RCTs including 64 active-treatment arms and 7628 patients. In these trials, disease duration ranged from 2.5 months to 12.2 years and, as expected, less improvement in HAQ-DI was reported by patients with long-standing RA compared with early RA.⁶⁸ In subsequent analyses, Aletaha et al demonstrated that HAQ-DI has both reversible and irreversible components. Scores were less likely to improve with longer disease duration, indicating irreversible impairments in physical function secondary to joint damage and deformities.⁶⁹ After adjusting for pain scores and tender joint counts in separate regression analyses, baseline HAQ-DI scores were significantly associated with RA disease duration. Effect sizes for HAQ-DI decreased by 0.02 and 0.03, and there was an absolute increase in HAQ-DI scores of 0.01 and 0.02 for each additional year of RA disease duration, in 3- and 6-month assessments, respectively.

Subsequently, data from all RCTs published between 1980 and 2005 that reported changes from baseline in HAQ-DI at 6 and/or 12 months were analyzed.⁷⁰ Treatments were grouped as “biologic” or “traditional” DMARDs compared with placebo, and patients were stratified by disease duration at baseline. A weighted generalized linear model estimated effect sizes of HAQ-DI in treatment groups and marginal means of this effect across different disease durations. Both analyses indicated that discrimination of improvement in physical function between biologics or traditional DMARDs and placebo is reduced in patients with a longer duration of

RA. The effects of treatment on improvement in HAQ-DI scores were striking in early RA, but decreased significantly with increasing duration of RA.

In the Early Rheumatoid Arthritis (ERA) trial, 632 patients with mean disease duration of 11 to 12 months, 50% to 60% of whom were DMARD-naive, were randomized to receive etanercept 10 and 25 mg or methotrexate.⁷¹ Reported improvements in SF-36 scores in all 8 domains and summary scores were significant in all treatment groups but remained below US population norms.⁷² Both etanercept treatment groups reported earlier and greater improvements in HAQ-DI and physical domain scores of SF-36 than the methotrexate group. Over 24 months of treatment in ERA, 55% of patients receiving etanercept 25 mg reported improvements in HAQ-DI ≥ 0.5 versus 37% with methotrexate ($P \leq .001$).⁷³ Despite low PCS scores at baseline (28.0 to 29.2), improvements at 12 and 24 months approached US norms of 50, resulting in fewer patients reporting limitations in physical activities (Table 7).⁷¹⁻⁷³ Mean changes in SF-36 from baseline to month 12 in ERA are represented in Figure 6.⁷²

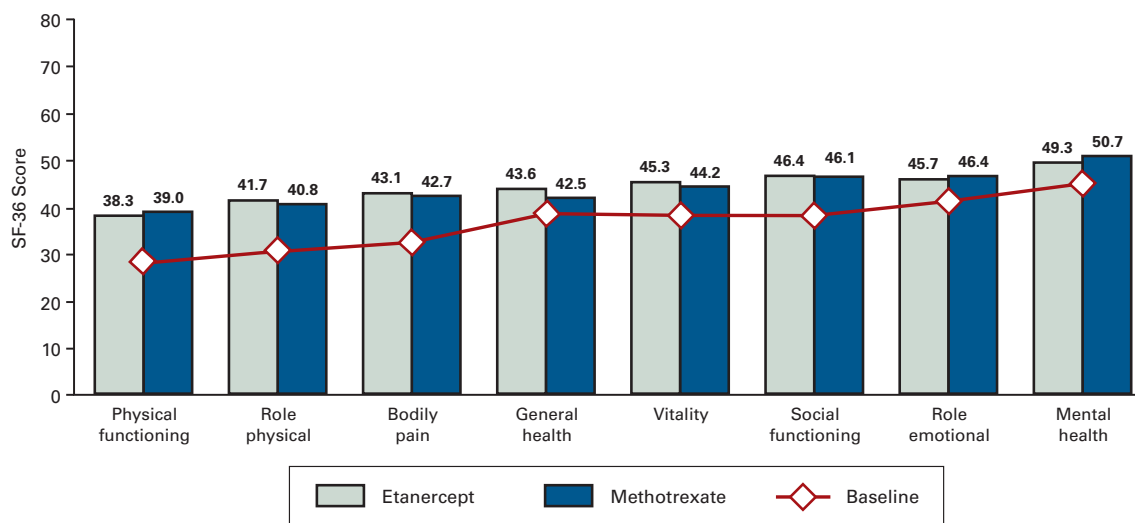
The Active Controlled Study of Patients Receiving Infliximab for RA of Early Onset (ASPIRE) enrolled 1049 patients with a mean disease duration of 7 months. The majority of patients in each group (65% to 71%) were DMARD-naive, and baseline HAQ-DI scores were 1.5.⁴⁹ Seventy-six percent of patients reported improvements \geq MCID in infliximab-plus-methotrexate groups compared with 65% receiving methotrexate alone (Table 3).⁴⁸ Baseline

■ **Table 7.** Percentage of RA Patients Reporting Clinically Meaningful Changes in Limitations in Physical Function by SF-36

	ERA ⁷¹⁻⁷³		US 301 ³²⁻³⁴				Phase IIB ⁷⁴	
	Rx w/MTX or ETN		Rx w/MTX		Rx w/LEF		Rx w/ Abatacept+MTX	
	BL (%)	12 mo (%)	BL (%)	24 mo (%)	BL (%)	24 mo (%)	BL (%)	12 mo (%)
Limitations walking 1 block	65	36	45	38	45	17	72	42
Limitations climbing 1 flight of stairs	75	43	67	43	67	28	—	—
Difficulty performing at work	90	53	89	68	89	47	—	—
Less time lost at work due to health reasons	—	—	—	—	—	—	70	32
Less interference with work due to pain	—	—	—	—	—	—	51	11
Less reported fair or poor general health	—	—	—	—	—	—	64	26
Less time feeling tired or worn out	—	—	—	—	—	—	38	14
Less interference of health on social activities	—	—	—	—	—	—	32	9
Reporting feeling downhearted or blue most of the time	—	—	—	—	—	—	18	4

RA indicates rheumatoid arthritis; SF-36, Medical Outcomes Study 36-Item Short Form; ERA, early rheumatoid arthritis; MTX, methotrexate; ETN, etanercept; LEF, leflunomide; BL, baseline.

■ **Figure 6.** SF-36 Changes in ERA: Scores at Baseline (Diamonds) and Mean Scores at 12 Months*



*Patients received etanercept or methotrexate.

SF-36 indicates Medical Outcomes Study 36-Item Short Form; ERA, early rheumatoid arthritis.

Source: Reference 72.

HAQ-DI scores and use of infliximab, as well as age, baseline joint damage, and fatigue predicted improvement in physical function in RA patients in multivariable regression analyses.

In an RCT of 20 patients with early active RA comparing infliximab plus methotrexate to placebo plus methotrexate,

Quinn et al reported more significant improvements in HAQ-DI and RA quality-of-life questionnaire scores with combination therapy at 3.5, 13.5, and 26 months.⁷⁵

The PREMIER trial was a 2-year RCT comparing the efficacy and safety of adalimumab or methotrexate monotherapy versus adalimumab plus methotrexate in patients with early

RA (8 to 10 months' duration), 67% to 68% of whom were DMARD-naïve (Table 3).⁵⁰ Secondary end points included changes from baseline in HAQ, SF-36, and FACIT.^{50,76} After 12 months of treatment, patients receiving combination therapy reported significantly greater improvements in HAQ-DI (-1.1) versus those receiving adalimumab (-0.8; $P \leq .002$) or methotrexate monotherapy (-0.8; $P \leq .001$) (Table 3). Mean improvements in HAQ-DI after 24 months of treatment with combination therapy (-1.0) were statistically superior to methotrexate (-0.9; $P \leq .05$) but not adalimumab monotherapy (-0.9; $P \leq .058$). At 24 months, significantly more patients receiving combination therapy (72%) reported improvements from baseline \geq MCID compared with the adalimumab (58%) or methotrexate monotherapy (63%) treatment groups (both, $P < .05$), and 33% of patients receiving combination therapy versus 19% in each monotherapy arm achieved HAQ-DI scores of ≤ 0.5 ($P < .001$).

Long-term HAQ-DI data reported for RA patients stratified by age (<65 and ≥ 65 years) were compared in early disease, late disease, and TEMPO RCTs of etanercept therapy that included open-label extension phases of up to 4 years' duration.⁷⁷ The greatest improvements in HAQ-DI scores were reported in the first 3 months of treatment in both early and later RA and were maintained throughout the blinded and open-label extension phases of the RCTs. Improvements ranged from -0.39 to -0.92 in older and -0.57 to -1.00 in younger RA patients, although a similar proportion of patients (60%-88%) in both groups reported changes \geq MCID. As expected, fewer older than younger patients—4% to 27% versus 10% to 33%, respectively—achieved HAQ-DI scores of 0; and 15% to 46% versus 27% to 53%, respectively, reported HAQ-DI scores ≤ 0.5 .

Findings confirm that both HAQ-DI and SF-36 are sensitive to change and accurately reflect treatment-associated improvements in patients with longer duration as well as early disease. Data reflected by SF-36 are “nice but not necessary,” yet offer a means to measure the impact of RA on other aspects of HRQOL and to compare with other chronic diseases, as well as facilitating economic analyses. While improvements in physical function reported by HAQ, MHAQ, and MDHAQ are impacted by disease duration and “damage” with reversible and nonreversible components, SF-36, as a generic measure, can be compared with relevant age- and sex-matched normative populations. These comparisons then offer additional “goals” of treatment: scores that approximate or achieve age- and sex-matched normative data in populations without arthritis—or significant cardiovascular disease, diabetes, or other chronic medical conditions that significantly impact physical function and/or HRQOL.

Conclusions

Over the past decade, the introduction of 7 new DMARDs has revolutionized the treatment of RA. Importantly, administration of these agents has resulted in statistically significant and clinically meaningful improvements in physical function and HRQOL. Many clinical studies confirm that patients report improvements in HRQOL, reflected by improved physical function, less fatigue, and better emotional and mental health for RA patients. Work productivity studies are confirming that fewer patients stop working and that more patients report less impact of their disease on work within and outside of the home, as well as on family and social activities.

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