
Quality of life in patients with rheumatoid arthritis: Does abatacept make a difference?

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune disease that, in addition to causing joint damage, is associated with pain, fatigue, disability and functional loss, which can substantially decrease a patient's quality of life (QoL). Along with improvements in signs and symptoms, QoL benefits have become increasingly important in optimizing treatment outcomes in RA. Measurements of QoL have previously been under-used in all areas of medicine and only recently have clinical trials included them as a measure of treatment effectiveness. The existence of a positive relationship between improvements in signs and symptoms and concomitant improvements in QoL provides additional evidence that QoL measures are useful benchmarks for evaluating the effectiveness of treatment for RA. Furthermore, since these outcome measures evaluate the real-life, patient-centered benefits of RA therapies, they are likely to become increasingly central to the assessment of disease impact in clinical trials and practice, and to both drug approval and reimbursement decisions.

This article reviews the impact of abatacept, a selective co-stimulation modulator, on the QoL of patients with active RA across a number of pivotal clinical trials. Firstly, an overview of the key QoL measurements used in abatacept clinical trials is provided, including those such as the Short Form-36, Health Assessment Questionnaire and Visual Analog Scale for pain, sleep and fatigue. We then present QoL data obtained in a wide range of patients with RA, including those with an inadequate response to either methotrexate or anti-tumor necrosis factor therapy, who have been treated with abatacept. Analysis of these data demonstrates that abatacept therapy has the potential to improve QoL across a range of patients with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic, progressive, autoimmune disease that is estimated to affect between 0.5% and 1% of the adult population worldwide, and has increasing prevalence with age (1). Although RA affects a wide range of joints, the most commonly involved are those of the hands, knees and feet, with significant radiographic joint damage occurring in most patients within the first 2 years of the disease (2, 3). In addition to causing joint damage, RA is associated with pain, fatigue, disability and functional loss (4-7), which can substantially decrease a patient's quality of life (QoL). Quality of life refers to an individual's or group's perception of general health over time; the many factors that can affect general health include physical function, social support, employment capability, sleep quality, fatigue and pain. Furthermore, due to the underlying immunopathology of the disease, RA is associated with marked morbidity and increased mortality (8). Patients with RA are reported to have a mortality rate double that of individuals without RA over a 10-year period (9).

The economic and societal burden of RA is considerable, as is the physical and mental impact on the patient and their families (1, 10, 11). Most patients with the disease require continuous treatment to retard or stop progression and to control disease flares; ultimately, they may also require surgery, such as total hip or knee replacement. In addition to these direct costs, work disability leads to reduced productivity, early retirement and, as a result, substantial indirect costs (1, 12). Indeed, work disability has been associated with a 35% reduction in family income over the course of the disease (13); this is detrimental not only to the patients and their families, but also places a burden on society, as patients with RA are less able to contribute through their work

productivity compared with physically unimpaired individuals.

Beyond the impact of RA on the physical aspects of patients' lives, RA has also been shown to influence their mental status. Impaired ability to work or perform everyday tasks may further reduce the patients' emotional well-being, and many RA patients experience increased anxiety and depression (14). A trial assessing QoL measures in a rheumatology clinic population showed that patients with severe RA and a high level of physical impairment also had deterioration in both the psychological and social domains of QoL. This observation was corroborated by a study which demonstrated that increasing severity of disease is associated with a worsening of the QoL status (15).

Patients rate the effect of RA on their physical function and loss of independence as highly important. The Outcome Measures in Rheumatology (OMER-ACT) consensus group and the Arthritis Foundation report that patients regard rapid improvements in fatigue as one of the most important benefits of an effective RA treatment regimen (16, 17). Therefore, improvements in these areas are, or should be, among the main goals of treatment for RA. Since there is no known cure for RA, treatment aims to alleviate symptoms by reducing severity and retarding disease activity, with the ultimate goal being remission. The considerable impact that RA has on these aspects of patients' daily lives and the burden that RA poses on society makes improving patient QoL an imperative factor when evaluating the impact of treatment strategies.

Although the use of traditional disease-modifying antirheumatic drugs (DMARDs, which include methotrexate [MTX]) and the new biologic DMARDs (such as the tumor necrosis factor [TNF] antagonists) have demonstrated efficacy in improving the signs and symptoms of RA in many patients (18-22), the use of DMARDs often provides inadequate QoL benefits (23-27). Abatacept, a selective T-cell co-stimulation modulator, has been shown to alleviate the signs and symptoms of RA and also to improve a wide range of QoL outcomes (11, 28-34).

This review will examine the QoL measurements frequently used in clinical trials and focus on the QoL benefits achieved with abatacept compared to placebo in patients with RA who have had an inadequate response to either MTX or anti-TNF therapy.

Quality of life measures utilized in RA

Quality of life is the result of a complex interaction between physical, social and psychological factors that are patient self-assessed and therefore subjective. Because measurements of functional limitation allow for an improved understanding of the impact of RA on worker productivity, a worker's function in society, and the emotional impact of the disease on the patient, measurements of QoL are now becoming increasingly important. These QoL measurements are relevant not only to the patient, but also to employers, healthcare providers, insurers and policymakers, particularly in relation to the choice of RA treatment.

QoL utility score

A generic quality of life measure that is widely used to compare outcomes of treatments across diseases is the QoL utility score. It provides decision-makers with a common metric for comparisons of health between different populations and disease states and is weighted on a simple scale, with a perfect health state at 1 and a death state at 0 (35). Generic QoL can be measured by direct or indirect instruments. The latter are easier to administer because patients answer set health-related questions and a QoL utility score is ascertained by the preference weights for their health state (35). These preference weights are determined by direct QoL utility instruments, which include the standard gamble (SG), the time trade-off (TTO) and the visual analog scale (VAS). Using a utility score, the health benefits of patients can be expressed in terms of quality-adjusted life-years (QALYs) and the cost-effectiveness of treatments can be compared by estimating the cost per QALY for each of them.

QoL utility scores and QALYs allow multiple disease states and treatments to

be compared directly (36), but disparity exists regarding which utility measures are best for RA treatment comparisons (37). Unfortunately, very few clinical trials for RA treatment have incorporated a QoL utility measure. This could be due to several factors, including the reluctance of investigators to increase the patient and staff burden, and/or the increased cost to conducting a clinical trial that is associated with each additional question (38). Furthermore, a utility measure may not improve sufficiently to justify the cost of a particular treatment as, depending on the utility measure used, results can vary significantly (39).

Although QoL utilities are valuable tools for analyses and comparisons of cost effectiveness, both clinicians and patients have understandable difficulty in interpreting their findings. For example, if a patient starts treatment with a utility of 0.78 and after 1 year ends with a utility of 0.72, should the rheumatologist consider changing his treatment? Furthermore, a change in utility could arise from other causes, such as a fall and consequent fracturing of bones, and not necessarily reflect a change in RA disease activity. As a single value, therefore, the utility measure is ineffective for clinical practice whereas a specific QoL factor such as morning stiffness is much more meaningful. Nonetheless, the assessment of disease burden using QoL utilities is crucial for priority setting by decision makers in order to maximize health benefits at minimal cost (40). RA inflicts a considerable burden on both patients and society as a whole, and consequently society would prefer to prioritize treatments with low costs per QALY in order to maximize cost-effectiveness (41).

Instruments to assess QoL

Over the last three decades, several instruments to assess QoL have been developed that focus on physical function and the patients' ability to carry out certain activities. Standard assessments of QoL established for use in multiple diseases include the Stanford Health Assessment Questionnaire (HAQ) (42, 43) and the Medical Outcomes Study Short Form-36 (SF-36) (44-46). Since

the primary symptoms of RA are physical in nature, generic QoL instruments have become the mainstay in clinical studies on RA patients. For example, the HAQ (which measures disability) and the pain 100 mm VAS have both become standard tools in RA clinical trials owing to their demonstrated ability to predict important health outcomes (11, 28-34). Table I presents a summary of commonly used QoL assessment tools that have been employed in abatacept clinical trials, as discussed in the next section.

The HAQ is a validated self-assessment measure and includes items that evaluate fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both the upper and lower extremities. The instrument consists of 20 questions and can be self-administered in 5 minutes and scored in less than 1 minute (43). The questionnaire is divided into eight subscales focusing on physical functions: dressing and grooming, arising, eating, walking, hygiene, reaching, gripping and other daily

activities (43). When the HAQ is administered to a patient, scores for each component are recorded on a four-tier difficulty scale (0-3), with 0 indicating normal (no difficulty) and 3 indicating that the patient is unable to perform the task. A modified version of the HAQ (mHAQ), consisting of eight questions encompassing eight subscales designed to evaluate a patient's perceived satisfaction and changes in the level of difficulty associated with each component, is also used extensively (47).

The SF-36 is a generic, multi-purpose, self-reporting questionnaire consisting of 36 items designed to evaluate QoL. It has eight subscales that include both physical and mental aspects (physical function, physical health, pain, general health, vitality, social function, emotional and mental health) and two component summaries – the physical component summary (PCS) and the mental component summary (MCS). Low scores indicate extreme pain and problems, while high scores indicate no limitations (44-46). The PCS and MCS are then normalized to a scale

from 0 to 100, with higher scores indicating better health and well-being (the mean for the US population as a whole being set at 50 with a standard deviation [SD] of 10 (48)). The SF-36 is a valuable tool as it compares the relative burden of a disease and can differentiate the health benefits achieved using different treatments (45). A tool employed in conjunction with the SF-36 is the SF-6D, an algorithm that will calculate a single QoL index score based on 11 items from the SF-36. The SF-6D index can range from 0 (worst health state) to 1 (best health state) (45). Such scores provide useful input for assessments of cost-effectiveness related to QALYs (11, 49). As health is a function of QoL over time, the QALY combines these domains of health into a single measure (11).

In addition to these established measures, several other validated measures are utilized in RA clinical trials. In the trials on abatacept these include: 100 mm VAS which can be used to assess pain and fatigue (32, 34); the Medical Outcomes Study Sleep Scale (MOS-Sleep)

Table I. Commonly used tools for assessing quality of life in rheumatoid arthritis.

Generic measurement	Time to complete	Categories	Scoring	Clinically meaningful improvement	Advantages	Disadvantages
HAQ	5 minutes	Dressing/grooming, arising, eating, walking, hygiene, reaching, gripping, other daily activities	0 to 3 (3 being the worst)	Change of ≥ 0.22	Self-administered, easy, highly reliable, high validity, highly sensitive, useful in early RA	No evaluation of psychological status
SF-36	5-8 minutes	Physical function, physical health, pain, general health, vitality, social function, emotional health, mental health	0 to 100 (100 being the best)	Change of ≥ 3	Self-administered, acceptable validity, evaluates some aspects of function and well-being not utilized in the HAQ	Complex
Fatigue/pain VAS	1 minute	Single-item scale measuring severity of fatigue/pain over the past week with one specific question	0 to 100 (100 being the worst)	Change of ≥ 10	Can be used in routine clinical care, very rapid	No evaluation of psychological status; is a single question
MOS-Sleep VAS	3-5 minutes	12 questions related to sleep quantity and quality, sleep habits, waking and daytime symptoms for the past 4 weeks	0 to 100 (100 being the worst) Items within each scale are averaged together to create the 7-scale scores	Change of ≥ 6	Pools the information that items have in common, good validity, sensitive	No evaluation of psychological status

HAQ: Health Assessment Questionnaire; RA: rheumatoid arthritis; SF-36: Short Form-36; VAS: visual analog scale; MOS-Sleep: Medical Outcomes Study Sleep Scale.

(50) (Table I), and the patient-reported activity limitation over a given number of days (51).

It should be noted that QoL measures often overlap, so that an improvement in one component, such as vitality, will likely be associated with reduced pain and, consequently, improved overall health (52). Thus, the most effective treatment for RA will improve overall health by treating both the physical signs and symptoms, and as a consequence improve the QoL. Indeed, it has been suggested that HAQ, pain and SF-36 measurements have more long-term relevance than standard laboratory and physician-measured clinical outcome measures (53).

Measuring QoL improvement

Regarding the importance of QoL improvements in the clinical setting, in addition to standard statistical analyses to test the significance of any improvements, minimum clinically important differences (MCIDs) define the change in score required to mark an improvement that can be considered of clinical benefit to the patient. The standard MCID for the HAQ is considered to be a change from baseline of ≥ 0.22 units (54), while the MCID for SF-36 scores is ≥ 3 units (55). In a recent analysis conducted by Wells *et al.* (33), the MCID for activity limitation, fatigue and sleep quality were determined to be improvements of 4, 10 and 6 units, respectively (33). Patients who improve their scores by at least the MCID are most likely to achieve a noticeable improvement in their QoL and overall health, even if there remains room for improvement. Although MCIDs are an important statistical tool for interpreting data from randomized controlled clinical trials, they do not reflect the degree of improvement consistent with a 'really important difference' (RID). The RID percentage values [(actual improvement/RID) 100%] are three to four times greater than MCID values, and offer a simplified means to interpret RCT data in a broader perspective in terms of the additional treatment effect required (56).

The multi-faceted nature of most QoL assessment tools often means that,

while useful in assessing the response to treatment in clinical trials, they are rarely used in clinical practice. Indeed, their complexity is often considered as a barrier by practicing physicians who face time-constrained clinic visits. Many studies have also disregarded the mental outcomes of QoL measurements, which describe the direct effects of functional loss on patients' lives and their emotional well-being (34). Given the importance of QoL measurements, there is a need for the medical community to have a continued awareness of the value and also an understanding of QoL assessments, and to highlight the importance of including these measurements of response in clinical trials.

Impact of abatacept on quality of life: clinical studies

This section will focus on the data obtained from three key studies in which the impact of abatacept therapy on QoL was examined in patients with RA.

In a multi-center, double-blind, Phase IIb study, 339 patients with active RA and an inadequate response to MTX therapy were treated with abatacept (10 mg/kg data only are reviewed here) plus MTX or placebo plus MTX for 12 months. The patients had a mean age of 55 years, a mean disease duration of 9–10 years and, despite long-term treatment with MTX, a high level of disease activity at baseline (tender joint count [TJC]: 28–31; swollen joint count [SJC]: 20–22) (30).

The Phase III AIM trial (Abatacept in Inadequate responders to MTX) was a multi-center, randomized, double-blind study in which 652 patients with active RA despite MTX treatment received either abatacept (approx. 10 mg/kg) plus MTX or placebo plus MTX for 12 months. Patients had a mean duration of disease of 9 years and high disease activity at baseline (TJC: 31–32; SJC: 21–22) (29).

In the 6-month, randomized, Phase III ATTAIN trial (Abatacept Trial in Treatment of Anti-TNF INadequate responders), 391 patients with active RA who had an inadequate response to ≥ 3 months of TNF antagonist therapy received either abatacept and ≥ 1 DMARD, or placebo with ≥ 1 DMARD

for 6 months. Patients had a mean duration of disease of 11–12 years and, despite DMARD therapy, high disease activity at baseline (TJC: 31–33; SJC: 22) (28).

QoL with abatacept in patients with an inadequate response to MTX

Phase IIb

In the Phase IIb trial at baseline, patients treated with abatacept (10 mg/kg) had mean PCS and MCS scores that were comparable with the scores of an average RA patient population (PCS 30.7 and 32.2; MCS 45.6 and 44.6 for abatacept-treated patients and the average RA patient population, respectively) (57). Mean improvements from baseline to 12 months for abatacept-treated patients ranged from 5.3 to 9.3 points across the eight SF-36 scales (Fig. 1A) and were 8.0 and 5.7 points for the PCS and MCS, respectively (11). Abatacept treatment in combination with MTX resulted in significant improvements in all eight subscales of the SF-36 at 1 year compared with patients who received placebo plus MTX (Fig. 1A) (11). The greatest improvements (difference in mean change scores) for the abatacept-versus placebo-treated patients were in the physical function (5.1; $p < 0.0001$), bodily pain (5.8; $p < 0.0001$), vitality (5.8; $p < 0.0001$), and social function (4.0; $p < 0.01$) subscales of the SF-36. In addition, treatment with abatacept plus MTX was associated with significant improvements in both the PCS and the MCS of the SF-36 over 12 months (Fig. 2 A–B) (11).

It is perhaps worth noting that improvements in QoL have been found to be closely related to clinical response assessed using American College of Rheumatology (ACR) response rates. For each subscale of the SF-36, as well as the PCS and MCS, the magnitude of the mean score for improvement was shown to improve incrementally with increasing ACR response (11).

At baseline, the SF-6D was similar between the abatacept and placebo treatment groups (0.57 and 0.55, respectively); whereas after 12 months improvements were significantly greater in the abatacept-treated patients compared with the placebo-treated group (mean

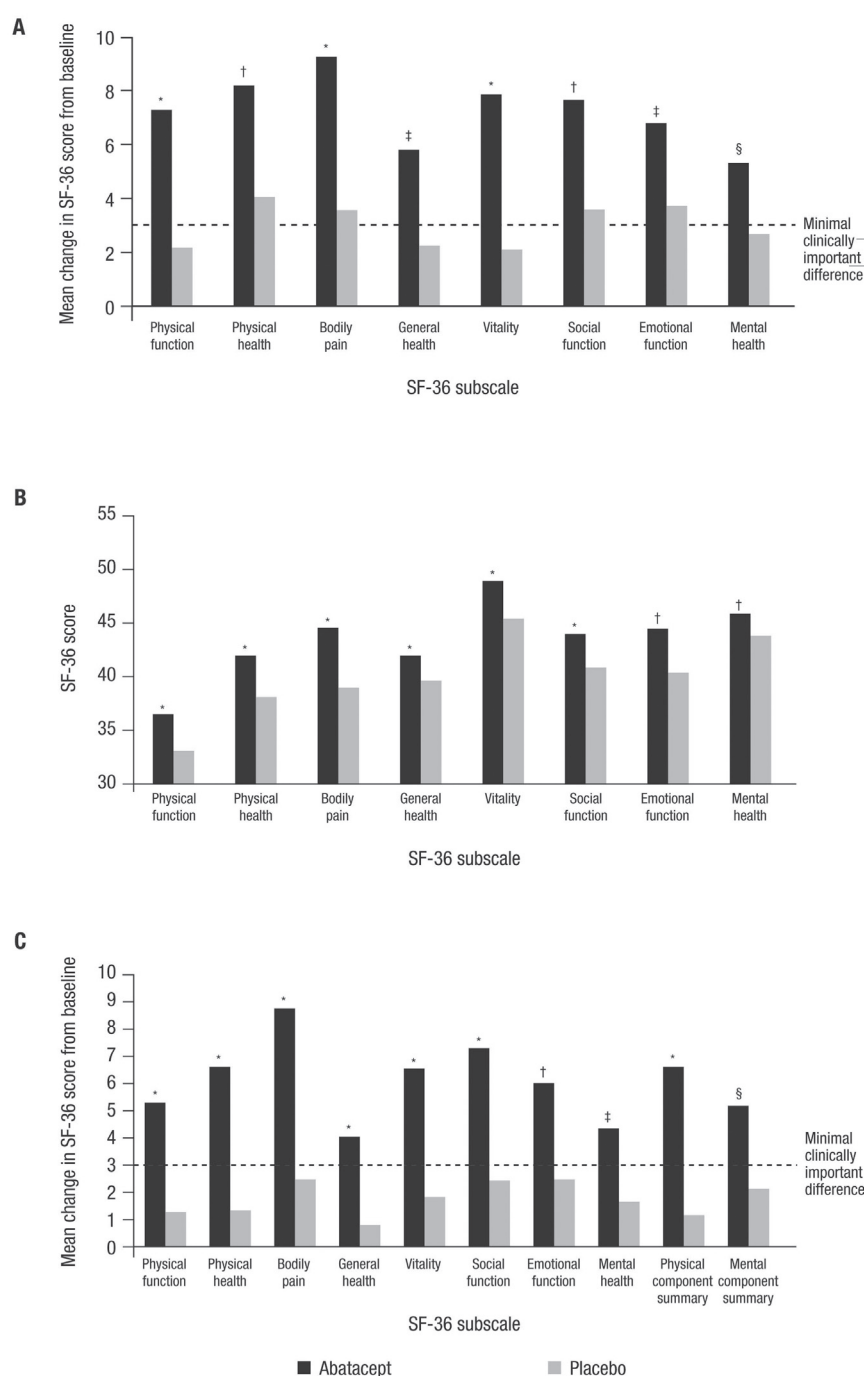


Fig. 1. SF-36 scores for all eight subscales in abatacept- and placebo-treated patients in (A) Phase IIb trial showing mean changes in SF-36 scores from baseline to Year 1: patients were treated with abatacept plus MTX or placebo plus MTX (* $p < 0.0001$; † $p < 0.01$; ‡ $p < 0.001$; § $p < 0.05$ versus placebo) (11); (B) AIM trial showing mean SF-36 domain scores at Year 1: patients were treated with abatacept plus MTX or placebo plus MTX (* $p < 0.01$; † $p < 0.001$) (32); (C) ATTAIN trial showing mean changes in SF-36 scores from baseline to 6 months: patients were treated with abatacept plus DMARDs or placebo plus DMARDs (* $p < 0.001$; † $p < 0.05$; ‡ $p < 0.01$; § $p = 0.005$) (28). SF-36: Short Form-36; MTX: methotrexate; AIM: Abatacept in Inadequate responders to MTX; ATTAIN: Abatacept Trial in Treatment of Anti-TNF INadequate responders; DMARD: disease-modifying antirheumatic drug.

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change from baseline: 0.11 vs. 0.06, respectively; $p < 0.001$) (11). Expressing the results in another way, 100 patients receiving abatacept plus MTX over 1 year would have an additional 5 full QALYs compared with a similar group of 100 taking placebo plus MTX.

At the start of this trial, physical function (as measured by the mHAQ) was poor, with scores of 1.0 (standard deviation [SD] 0.6) for both treatment groups; after 1 year mHAQ had significantly improved in the abatacept- (by 42.3%) compared with placebo- (by 10.3%) treated patients ($p < 0.001$). These clinically meaningful improvements in physical function were observed by Day 30 in abatacept-treated patients. Further improvements were observed at 6 months, when 58.3% versus 33.6% of abatacept- versus placebo-treated patients had achieved clinically meaningful improvements in mHAQ ($p < 0.001$); these results were sustained through 12 months of abatacept treatment (49.6% vs. 27.7%; $p < 0.001$) (30).

Phase III AIM trial

Quality of life assessments in the Phase III AIM trial, in a similar patient population of inadequate responders to MTX, further demonstrated the effects of abatacept plus MTX on a wide range of QoL subscales, including physical and mental well-being, physical function and fatigue. Patient QoL (SF-36, HAQ and fatigue) improved significantly more with abatacept compared to placebo regardless of disease duration (32).

In the AIM trial, at baseline the mean SF-36 scores for most subscales were approximately 1 SD or more below the US population norm of 50 (1 SD = 10 points). The mean PCS score was 30.6, which is roughly 2 SDs below the US population norm and lower than the average RA population (32.2). The mean MCS score was 41.8, which is approximately 1 SD below the US population norm and similar to an average RA population (44.6).

Statistically significant improvements in the SF-36 were observed for abatacept-treated patients compared with placebo-treated patients as early as Day 29 on five of the eight subscales (self-reported bodily pain, role-physical, general

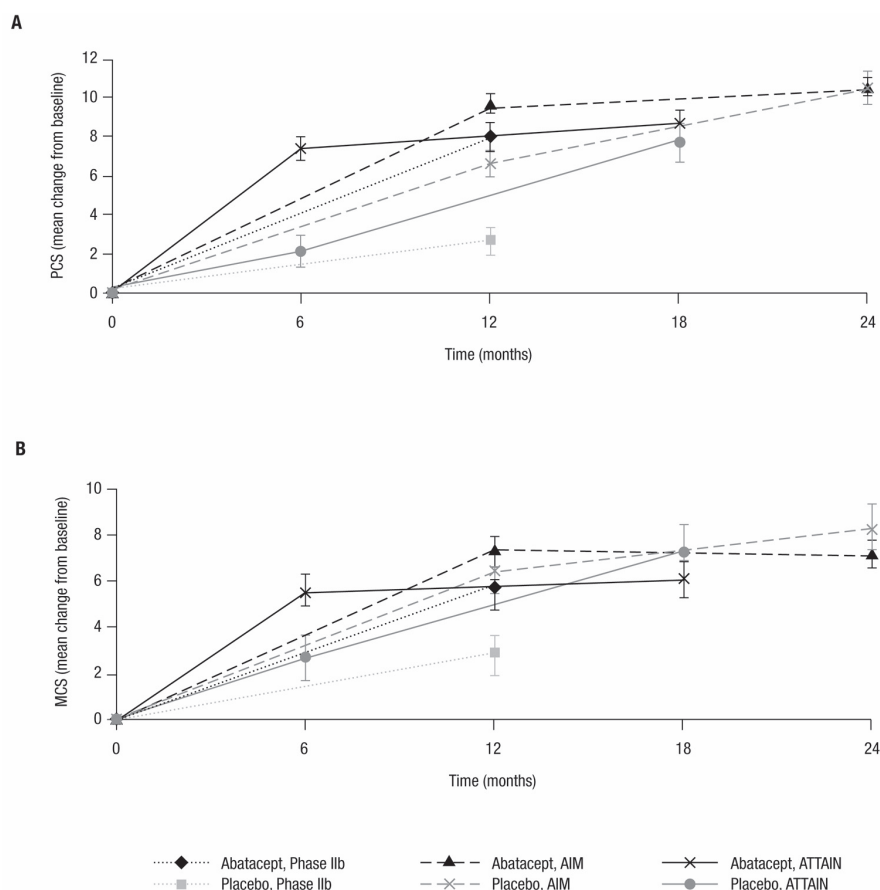


Fig. 2. SF-36 summary scores for (A) physical (PCS) and (B) mental (MCS) components in abatacept plus MTX- and placebo plus MTX-treated patients (Phase IIB and AIM trials) and abatacept plus DMARD- and placebo plus DMARD-treated patients (ATTAIN trial). The double-blind Phase IIB study trial was 12 months. Data shown for the AIM and ATTAIN trials include all patients entering the open-label LTE. In the AIM trial, the double-blind period was 12 months and the LTE was 12 months; for the ATTAIN trial, the double-blind period was 6 months with an LTE of 12 months. Data are expressed as the mean $\pm$ standard error of the mean (11, 58, 61). SF-36: Short Form-36; PCS: physical component summary; MCS: mental component summary; MTX: methotrexate; AIM: Abatacept in Inadequate responders to MTX; ATTAIN: Abatacept Trial in Treatment of Anti-TNF INadequate responders; LTE: long-term extension.

health, vitality and social function). For the abatacept-treated patients, both the PCS and MCS significantly improved from baseline when compared with placebo-treated patients at 6 months (29), and these improvements were sustained over 1 year (Fig. 2 A–B) (29, 32), when SF-36 scores for all eight subscales were significantly higher in the abatacept- versus the placebo-treated patients ($p < 0.01$) (Fig. 1B) (32). Furthermore, during an open-label extension period of the AIM trial in which all patients received abatacept plus MTX, these improvements were maintained after 1 year regardless of the original randomization group (Fig. 2 A–B) (58).

At baseline, physical function (as measured by the HAQ) was consider-

ably impaired in both groups (1.7 for both). However, significant improvements from baseline for abatacept-compared with placebo-treated patients were observed at 1 year (0.66 vs. 0.37; $p < 0.001$ at Year 1) (32), with more abatacept- than placebo-treated patients demonstrating a clinically significant improvement of at least 0.3 units (exceeding the MCID of ≥ 0.22) in physical function (Fig. 3) (32). Furthermore, these benefits were maintained through 2 years of abatacept treatment in the open-label extension period of the AIM study (58). In patients originally randomized to abatacept who entered the extension period, 67% achieved a HAQ response ≥ 0.3 units at Year 2, while among those originally receiving

placebo 63% achieved a HAQ response after switching to abatacept therapy for 1 year (Fig. 3) (58).

Baseline mean fatigue, as measured by the 100 mm VAS, was 64 for the abatacept group (33) in the AIM trial, indicating a greater level of fatigue problems compared with a general RA population (mean 100 mm VAS score = 47) (56). At Year 1, greater improvements from baseline in fatigue scores were observed for the abatacept- versus the placebo-treated patients (Fig. 4A) (32). Furthermore, in the open-label extension period of the trial these improvements were maintained through 2 years of abatacept treatment, when improvements were clinically meaningful (MCID defined as a change from baseline of ≥ 10 points) regardless of original randomization group (Fig. 4A) (59). These statistically significant improvements from baseline for abatacept compared with placebo treatment were seen as early as Day 29 ($p < 0.01$), which concurs with the improvements observed in the SF-36 scores. In the AIM trial, patients achieving the MCID were classified as fatigue responders (33). At the end of Year 1, there was a higher proportion of abatacept-treated patients who were considered responders compared with placebo-treated patients (69% vs. 51%, respectively; $p < 0.0001$) (33). At the start of the AIM study, 44% of patients had fatigue scores of 70–100; after 2 years of abatacept treatment, the number of patients reporting this level of fatigue had decreased to 10% (60).

Similarly, improvements in sleep quality assessed using the Sleep Problems Index (SPI) of the MOS-Sleep were maintained through 2 years of abatacept treatment. For patients in the original abatacept group, mean reductions from baseline for the SPI were 10.8 at Year 1 and 10.9 at Year 2 (both deemed to be clinically meaningful, exceeding the MCID of 6 points) (Fig. 4B) (33, 59). In patients originally receiving placebo during the double-blind period, sleep problems were reduced by 8.0 at Year 1 and by 11.8 at Year 2 after switching to abatacept therapy (Fig. 4B) (59). At the end of the double-blind period, a higher number of abatacept-treated patients were considered to be sleep responders

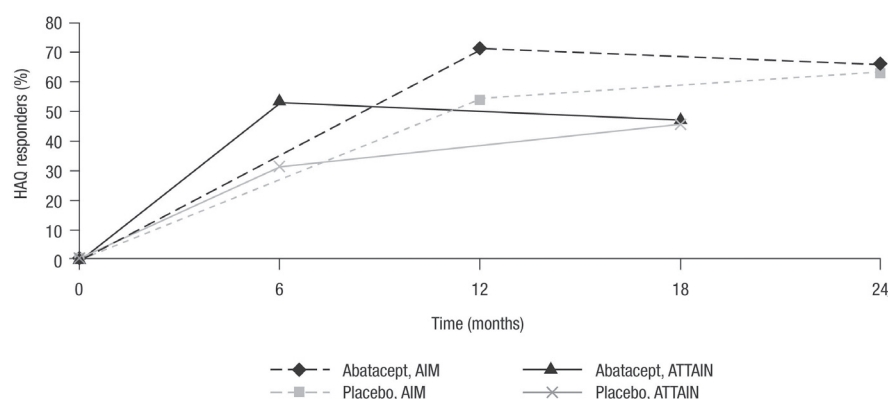


Fig. 3. The proportion of patients achieving HAQ responses (≥ 0.3 unit improvement from baseline in HAQ) in abatacept plus MTX- versus placebo plus MTX-treated patients (AIM trial) (58) and in abatacept plus DMARD- versus placebo plus DMARD-treated patients (ATTAIN trial) (61). Data shown include all patients entering the open-label LTE. In the AIM trial, the double-blind period was 12 months and the LTE was 12 months; for the ATTAIN trial, the double-blind period was 6 months with an LTE of 12 months. HAQ: Health Assessment Questionnaire; MTX: methotrexate; AIM: Abatacept in Inadequate responders to MTX; DMARD: disease-modifying antirheumatic drug; ATTAIN: Abatacept Trial in Treatment of Anti-TNF INadequate responders; LTE: long-term extension.

(their scores exceeding the MCID of 6 points on the 100 mm VAS), compared with placebo-treated patients (58% vs. 47%, respectively; $p \leq 0.01$) (33). At baseline 9% of patients had sleep problem scores of 70–100; after 2 years of abatacept treatment, this number had decreased to 2% (60).

Mean reductions in pain (assessed using the 100 mm VAS) were also observed with abatacept compared with placebo through Year 1 (35.5 vs. 24.1; Fig. 4C) (59). These benefits were maintained through Year 2 of the open-label period, such that at Year 2 patients who received abatacept for 1 year in the long-term extension (LTE) experienced virtually identical reductions in pain to those who had received abatacept for 2 years (Fig. 4C) (59). At the start of the AIM study, 44% of patients had pain problem scores of 70–100; after 2 years of abatacept treatment, this number had decreased to 4% (60).

At the start of the AIM trial, the abatacept group had limitations in their daily activities for an average of 14 out of 30 days (33). Through 1 year, abatacept-treated patients showed a greater mean improvement from baseline and were able to participate in their daily activities for an additional 8 out of 30 days compared with 5 out of 30 days in the placebo group ($p = 0.0002$). These improvements in activity were clinically significant for the abatacept-treated pa-

tients (the MCID for activity limitation was defined as an additional 4 out of 30 days of activity). At the end of the trial, a higher proportion of abatacept-treated patients were considered responders in terms of activity limitation (with scores exceeding the MCID) compared with placebo-treated patients (59% vs. 45%, respectively; $p = 0.0007$) (33).

QoL with abatacept in patients with an inadequate response to TNF antagonists

Phase III ATTAIN trial

Improvements in QoL were also observed in abatacept-treated patients who previously had an inadequate response to TNF antagonist therapy in the 6-month Phase III ATTAIN trial (28).

At the start of the ATTAIN trial, the abatacept-treated patients had a PCS and MCS of 27.6 and 41.2, respectively, indicating a high degree of physical and mental limitation compared with both the US population norm (50 for both PCS and MCS) (48) and with an average RA patient population (32.2 and 44.6 for PCS and MCS, respectively) (57). Therefore, patients in the ATTAIN trial were functioning between 1 to 2 SDs (10 to 20 points) below QoL norms (34). Significant improvements in all eight subscales of the SF-36 were observed at 6 months for the abatacept-treated patients compared with the placebo-treated patients (Fig. 1C) (28).

A similar trend was observed for both the PCS and MCS scores, which significantly improved from baseline in abatacept-treated patients compared to placebo-treated patients at 6 months (Fig. 2 A–B) (28). These improvements were sustained over the first year of the open-label extension period of the ATTAIN trial, in which all patients received abatacept plus DMARDs after the 6-month double-blind period (61). Furthermore, those patients who had originally received placebo achieved improvements after 1 year on abatacept similar to those who had been treated with abatacept for 18 months (Fig. 2 A–B) (61).

At baseline, physical function (measured by the HAQ) was considerably impaired in both groups (1.8 for both). However, after 6 months patients receiving abatacept had significantly greater improvements in their HAQ scores (-0.5) than placebo-treated patients (-0.1 ; $p < 0.001$). At 6 months, the proportion of HAQ responders (≥ 0.3 unit decrease) was higher in abatacept-treated patients compared with those receiving placebo (47% vs. 23%, respectively, $p < 0.001$), with clinical improvement between the groups seen at Day 15 (28). Results from the first year of the open-label period demonstrated that these improvements were maintained through 18 months, irrespective of the original randomization group (Fig. 3) (61).

At baseline, fatigue (as measured by the 100 mm VAS) was 73 for the abatacept group (33), a score that indicated a greater level of fatigue compared to the general RA population (mean 100 mm VAS = 47) (32). By the end of the trial, abatacept-treated patients experienced greater improvements from baseline in fatigue scores compared with placebo-treated patients (33), changes that were sustained through 2 years during the open-label period. Patients who were switched to abatacept after 6 months of placebo showed similar improvement (Fig. 4A) (59). The improvement in the abatacept group exceeded the MCID of 10 at 6 months, with a higher number of responders than among placebo-treated patients (59% vs. 37%, respectively; $p < 0.0001$) (33). At the start of the ATTAIN trial, 68% of patients had

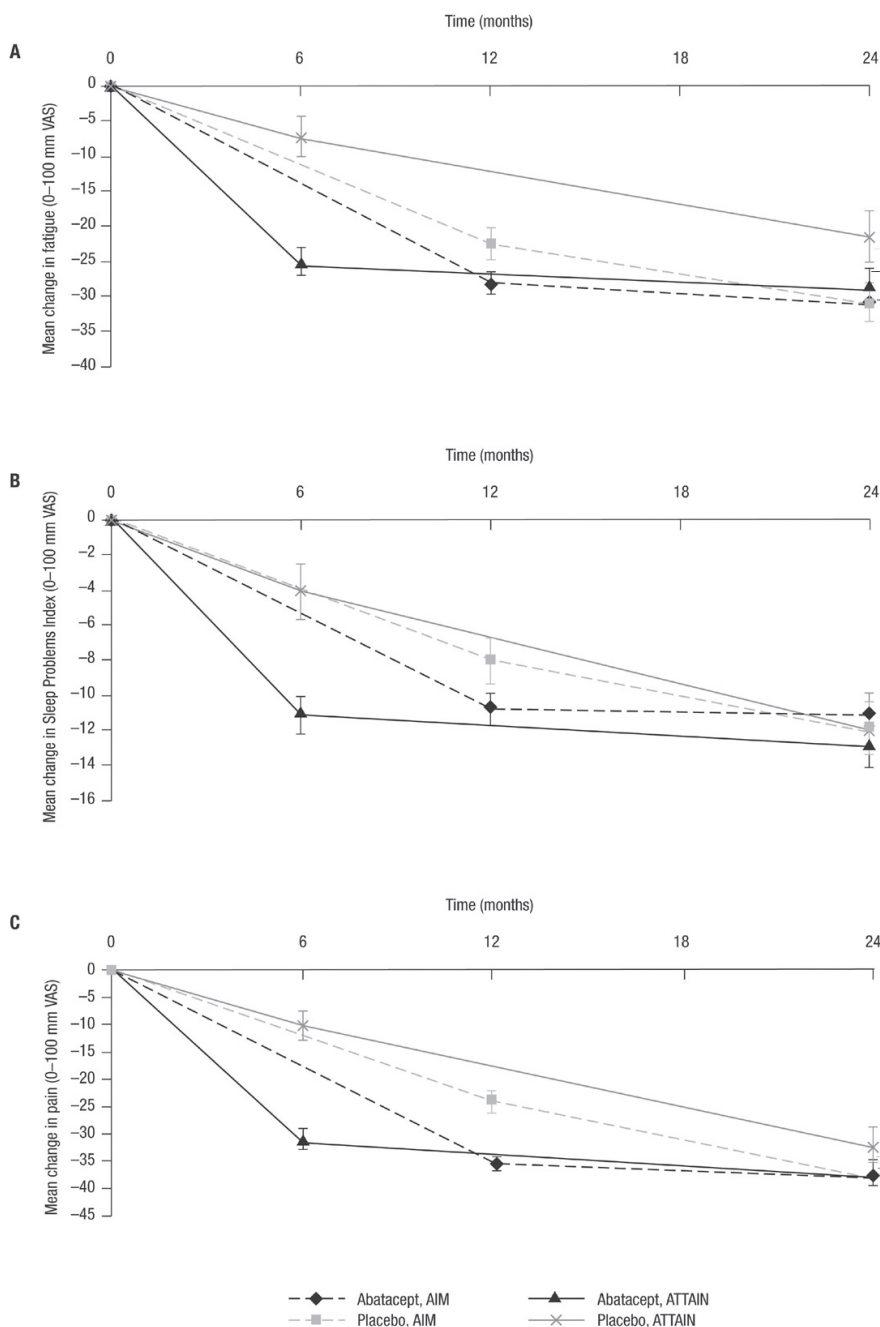


Fig. 4. Mean change from baseline in (A) fatigue (assessed using 0–100 mm VAS); (B) sleep (assessed using MOS-sleep SPI); and (C) pain (assessed using 0–100 mm VAS) in abatacept plus MTX- versus placebo plus MTX-treated patients (AIM trial) and in abatacept plus DMARD- versus placebo plus DMARD-treated patients (ATTAIN trial). Data shown include all patients entering the open-label LTE. In the AIM trial, the double-blind period was 12 months and LTE was 12 months; for the ATTAIN trial, the double-blind period was 6 months with an LTE of 18 months. Data are mean $\pm$ standard error of the mean (59). VAS: visual analog scale; MOS-Sleep: Medical Outcomes Study Sleep Scale; SPI: Sleep Problems Index; MTX: methotrexate; AIM: Abatacept in Inadequate responders to MTX; DMARD: disease-modifying antirheumatic drugs; ATTAIN: Abatacept Trial in Treatment of Anti-TNF Inadequate responders; LTE: long-term extension.

fatigue problem scores of 70–100; after 2 years of abatacept treatment the proportion of patients with severe fatigue had decreased to 24% (60).

In this trial, the mean SPI score at baseline was 47.9 for the abatacept group,

indicating substantial problems with sleep. At the end of the 6-month trial, abatacept-treated patients showed reductions in their SPI scores, which indicates an improvement in sleep quality (–9.8 compared with –2.1 in the placebo

group; $p < 0.0001$) (33). With an MCID for sleep improvement being defined as a reduction of 6 points on the SPI, the improvements were clinically significant for the abatacept-treated patients (33). Improvements, as measured by MOS-Sleep, were maintained through 2 years of therapy, irrespective of the original treatment during the double-blind period (Fig. 4B) (59). At the end of the double-blind period, a higher number of abatacept-treated patients were responders compared with placebo-treated patients (59% vs. 38%; $p < 0.0001$) (33). At the start of the ATTAIN study, 13% of patients had sleep problem scores of 70–100; after 2 years of abatacept treatment this proportion had decreased to 4% (60).

Mean reductions in pain (on 100 mm VAS) were also observed with abatacept compared to placebo through 6 months (30.8 vs. 10.2; Fig. 4C) (59). These benefits were maintained through the open-label period such that, at Year 2, patients in the original placebo group who received abatacept for 18 months during the LTE experienced similar improvements in pain to those who had received abatacept for 2 years (Fig. 4C) (59). At baseline in the ATTAIN trial, 58% of patients had pain scores of 70–100; after 2 years of abatacept treatment, the proportion of patients with this level of pain had decreased to 9% (60).

At the start of the ATTAIN trial, patients had baseline limitations in their daily activities for an average of 17 out of 30 days (33). At 6 months, abatacept-treated patients reported improvements amounting to an additional 7 days of normal activity per month compared with an additional 1 day for the patients on placebo ($p < 0.0001$) (33). The MCID for activity limitation is defined as 4 days, and therefore the improvements were clinically significant in the abatacept-treated patients. At the end of the trial, a higher number of abatacept-treated patients compared with placebo-treated patients were responders (*i.e.*, exceeded the MCID) (53% vs. 31%, respectively; $p < 0.0001$) (33).

In the ATTAIN trial, the improvement in fatigue, HAQ score, and all but two of the SF-36 scales (role-emotional and MCS) were found to be faster

for abatacept-treated patients compared with placebo-treated patients (34). Treatment benefits were seen at 12 weeks in terms of nearly all the QoL measurements. This is crucial as early response to treatment increases the likelihood of patients adhering to their treatment regimen (34). Even in the role-emotional and MCS, patients receiving abatacept were nearly three times more likely to improve than deteriorate compared with the placebo group. These findings are of particular significance as this patient population had been without effective treatment before receiving abatacept (as illustrated by the severe impairment in physical function and SF-36 parameters at baseline).

These data suggest that in patients who have failed TNF antagonist therapy there could be a marked benefit to treatment with abatacept before clinical symptoms become irreversible. However, the relationship between disease therapy and the impact of abatacept treatment on improvements in QoL is still not fully understood (34).

Impact of abatacept on QoL: comparison of benefit across patient populations

In presenting the results of two different trials of abatacept side by side, it might be anticipated that similar responses in terms of the QoL measures would be observed.

In fact, while improvements in the SF-36 subscale scores and in the fatigue, sleep and pain measures were similar across the two trials in the patients treated with abatacept, improvements in other measures such as MCS were more marked in the AIM trial than the ATTAIN trial during the open-label period of treatment with abatacept. However, there were major differences in study design and study population between the two trials that could account for the different responses observed. In addition, the placebo response was much greater in the AIM than in the ATTAIN trial. Boers suggested that this could be due to the shorter time (3 months) required for MTX treatment or to non-response before enrollment that might have created a trial of partial-re-

sponders (62). However, the patients in the AIM trial had been on MTX for an average of 2.3 years (SD 3.2) and a median of 1.0 year before their enrollment (average MTX dose 15.9 mg at baseline [data on file; Bristol-Myers Squibb]), which diminishes the likelihood of this explanation. Another possible reason for the large placebo effect may be the psychosomatic effect of a monthly office infusion visit in the case of trial patients in less affluent countries, where healthcare may be suboptimal and routine visits to a doctor are less common.

In both the AIM and ATTAIN trials, during the double-blind periods a significantly higher proportion of patients receiving abatacept were responders (*i.e.*, exceeded the MCID) as measured by the HAQ, fatigue 100 mm VAS, and MOS-Sleep scores, than those receiving placebo. However, in both studies when patients originally randomized to placebo were switched to abatacept during the open-label period, they achieved similar responses to those who had received abatacept throughout the entire study period. Improvements in activity were also clinically significant (exceeding the MCID) in a higher proportion of abatacept- versus placebo-treated patients in both trials during the double-blind periods. Thus, in both the AIM and ATTAIN trials, improvements in QoL measures were statistically significant and clinically meaningful in abatacept-treated patients compared with those receiving placebo.

In addition to the MCID improvements achieved, some of the improvements observed with abatacept treatment were so substantial that they also met the RID QoL parameter (56). For example, the mean changes in PCS in the AIM and ATTAIN trials were 11 (from baseline to 24 months) and 9 (from baseline to 18 months), respectively, differences which are similar to those of patients with RA claiming work disability compared to non-claimants.

In a long-term study conducted in the United States by the National Data Bank for Rheumatic Diseases (NDB) (63), patients with RA showed the same mean difference in improvement in QoL measures as seen in abatacept

clinical trials, also improved dramatically in other QoL areas not measured by these randomized controlled trials. For example, in the AIM trial HAQ scores improved from 1.70 to 1.04 over 12 months; in the NDB study 197 patients showed a similar improvement in their HAQ scores after 1 year (from 1.75 to 1.125 or 1.625 to 1.00), and also improved in their EQ-5D utility score by 0.15 (from 0.50 to 0.65) and in their patient-global assessment on the 100 mm VAS by 1.1 (4.4 to 3.3).

To illustrate the seriousness of RA, other disease states with similar utility scores include incurable colon cancer or those who have had major stroke (utility 0.5), and the improvement of 0.15 may be more analogous to that seen in a patient in the second year of hyperthyroidism without any treatment (utility 0.65) (64). Although they have the same utility values, we are not suggesting that these health states are equivalent; we merely present them in order to demonstrate how utilities can be used to compare independent diseases and provide perspective on the dramatic improvement a difference of 0.15 can reflect.

Conclusions

The evolution in RA treatments has raised expectations for patients and physicians alike. Along with improvements in signs and symptoms, QoL benefits have become increasingly important in optimizing treatment outcomes in RA. In addition to causing joint damage, RA is associated with pain, fatigue, disability and functional loss, which can substantially decrease a patient's QoL. Measurements of QoL have been previously under-used in all areas of medicine and only recently have clinical trials included them as a measure of treatment effectiveness. The existence of a positive relationship between improvements in signs and symptoms and the level of improvement in QoL provides additional evidence that QoL measures are useful benchmarks for evaluating the effectiveness of RA treatment.

Here we have described how the selective T-cell co-stimulation modulator abatacept is not only associated with improvements in signs, symptoms and function in RA, but also improvements

in all parameters of QoL, including fatigue and sleep quality. Great advances in the treatment of RA have been seen over the last decade, predominantly due to the increased use of traditional DMARDs and the introduction of targeted biologic therapies such as anti-TNF agents. However, not all patients respond or are tolerant to these therapies and therefore there is a real need for novel biologic agents with alternative mechanisms of action. Abatacept represents one such agent that, along with others currently in development, holds promise in improving not only the signs and symptoms but also the QoL in a range of patients with RA.

Key points box

- Beyond the clinical signs and symptoms of disease, rheumatoid arthritis (RA) is associated with pain, fatigue, disability and functional loss, which can substantially decrease a patient's mental and physical quality of life (QoL)
- Quality of life refers to an individual's or group's perception of general health over time; the many factors that can affect general health include physical function, social support, employment capability, fatigue and pain
- Commonly used QoL assessment tools for RA include the Health Assessment Questionnaire, which is a generic measure of disability, the pain 100 mm Visual Analog Scale, and the Short Form-36 (a 36-item questionnaire evaluating eight subscales of QoL including both physical and mental aspects)
- Although the use of traditional disease-modifying antirheumatic drugs (DMARDs), which include methotrexate, and the biologic DMARDs, such as the TNF antagonists have demonstrated efficacy in improving the signs and symptoms of RA in many patients, the use of DMARDs can provide inadequate QoL benefits

- Due to the multidimensional effects of RA on a patient's QoL, assessment tools often evaluate multiple physical, social and psychological factors, which are patient self-assessed
- Across multiple clinical trials in patients with RA, abatacept, a selective T-cell co-stimulation modulator, has been shown to provide clinically meaningful and statistically significant improvements in multiple aspects of QoL and physical function, in addition to improvements in measures such as fatigue, sleep quality and activity limitation

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