

Norms-based assessment of patient-reported outcomes associated with adalimumab monotherapy in patients with ankylosing spondylitis

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Abstract

Objectives

To compare the impact of ankylosing spondylitis (AS) on health-related quality of life (HRQL) and of adalimumab on initial and sustained improvement in HRQL for patients with active AS versus the general US population.

Methods

Data from the 5-year ATLAS trial were analysed. HRQL burden of AS and treatment impact on HRQL were assessed by comparing health status and utility scores from ATLAS (Short Form 36 Health Survey [SF-36] and Health Utilities Index Mark 3 [HUI3]) with population norms.

Results

Baseline scores for all measures were comparable between adalimumab and placebo. All scores for both groups were significantly worse than general population norms (all $p < 0.0001$). Within- and between-group improvements in SF-36 Physical Component Summary and SF-6D scores from baseline to Weeks 12 and 24 were clinically relevant for patients receiving adalimumab. For patients initially randomised to adalimumab, HRQL scores improved from Weeks 25 to 52 and remained relatively stable through 3 years but remained lower than for the general US population at all time points.

Conclusions

Findings demonstrate a significant burden of AS on HRQL. Treatment with adalimumab significantly improved physical functioning and other measures of HRQL compared with placebo. Clinically relevant improvements in HRQL outcomes over 3 years represent a significant benefit of adalimumab. Because of the advanced AS disease, patient health status remained below that of the general population. Treatment earlier in the course of AS may be needed to restore HRQL to the level of the general population.

Key words

adalimumab, ankylosing spondylitis, health-related quality of life, Health Utilities Index Mark 3, patient-reported outcomes, physical functioning, Short Form 36 Health Survey.

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Introduction

Symptoms of pain, joint stiffness, and the loss of spinal mobility are characteristic of ankylosing spondylitis (AS). AS is a chronic, inflammatory, systemic disease primarily affecting the axial skeleton, peripheral joints and entheses (1). The condition is typically diagnosed between 20 and 40 years of age and has a prevalence of 0.1% to 0.8%, with men being disproportionately affected (1). Symptoms of AS often result in reduced health-related quality of life (HRQL) (2), having an impact on pain, physical function, fatigue and psychological well-being and making patient-reported outcomes (PROs) suitable for evaluating the impact of disease and treatment in this population.

Management of AS has changed over the last several years owing to the availability of new imaging techniques and treatments (3-5). The availability of anti-tumour necrosis factor (anti-TNF) agents has resulted in a reduction of the signs and symptoms of disease, leading to improvements in HRQL as measured by instruments such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (6-8). Improvements in signs and symptoms of AS have been persistent, lasting up to 3 years (7, 9), although discontinuation of treatment has led to relapse (6, 9). Measures used to assess treatment efficacy have been recommended by the Assessment of SpondyloArthritis international Society (ASAS) and include the ASAS20, ASAS40, ASAS 5/6, Patient's Global Assessment of disease activity, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Bath Ankylosing Spondylitis Functional Index (BASFI) (10-12).

Currently, several therapies for AS are available, including non-steroidal anti-inflammatory drugs, sulphasalazine, steroid injection and biologics, providing continuous control of inflammatory symptoms and resulting in improvement of daily function (13). Monotherapy with adalimumab, a fully human monoclonal antibody that binds TNF, improves clinical signs and symptoms, physical function and HRQL in patients in both the short term (14, 15) and after

3 years of treatment (16). The impact of adalimumab monotherapy on improvement in work status and work productivity has also been demonstrated (17). Interpretation of changes in HRQL scores has not been well-established, although at least two studies have reported on the HRQL of patients with AS compared with the general population (18, 19). Median SF-36 Physical Component Summary (PCS) scores were assessed by van der Heijde *et al.* (18), who reported that baseline values of PCS scores in patients with AS were below the range of US and European general population values and Mental Component Summary (MCS) scores were within the normal range. Davis *et al.* (19) also reported an improvement in SF-36 PCS scores with treatment. Comparisons of HRQL to general population norms have also been conducted in populations with cancer (20-22), visual impairment (23), dry eye (24), systemic lupus erythematosus (25) and coronary heart disease (26). The statistical problems associated with comparisons of HRQL (specifically the SF-36) with general population norms and potential solutions have been addressed in other publications (27, 28).

This paper reports the HRQL impact of AS compared with general US population norms and the impact of adalimumab on initial and sustained improvement in HRQL using comparisons to the general US population.

Methods

AS sample

Secondary data analysis was conducted on the AS study population using data collected from the Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis (ATLAS; ClinicalTrials.gov, NCT00085644) and on the general population normative data collected from the Medical Expenditure Panel Survey (MEPS), the US Valuation of the EuroQol 5D Health States Survey (USVEQ) and the National Health Measurement Study (NHMS) (29-31). Further details regarding ATLAS have been published elsewhere (8, 14-17). Briefly, ATLAS was designed to demonstrate the safety and efficacy of

adalimumab in patients with active AS. The study enrolled 315 patients and included an initial 24-week, randomised, placebo-controlled, double-blind period comparing adalimumab 40 mg or placebo given subcutaneously every other week. Patients who failed to meet ASAS20 response criteria at the Week-12, Week-16 or Week-20 visits were to have three options: 1) remain on blinded study medication through Week 24 at the discretion of the investigator and if agreeable to the patient, 2) initiate early escape open-label therapy with adalimumab (40 mg every other week) or 3) discontinue study medication and withdraw from the trial. Patients in the trial completed PRO measures such as the SF-36 and Health Utilities Index Mark 3 (HUI3) at baseline and at Weeks 12 (SF-36 only) and 24.

Sample of US general population

General population normative data came from three sources: 1) the 2005 wave of the MEPS, a nationally representative sample of the non-institutionalised US civilian population (n=33,961) (29); 2) the 2002 USVEQ, a nationally representative sample (n=4048) of non-institutionalised adults (18 years and older) living in the United States (32); and 3) the 2005 NHMS, a nationally representative sample (n=3844; 1641 men and 2203 women) of adults (35–89 years old) living in the community in the contiguous United States (31).

Demographics, clinical characteristics, and HRQL measures

Demographic characteristics were collected at baseline (Week 0) of ATLAS. Clinical characteristics and HRQL were collected at prespecified time points throughout the trial. Clinical measures of disease activity included the BASDAI (33), the BASFI (34), and visual analogue scales for back pain and morning stiffness. General health status was assessed using the SF-36 (35), which has extensive evidence of reliability and validity (36–38) and has been used in trials to assess patients with AS (14, 18, 39–41). SF-36 Version 1 (self-administered) was used in ATLAS and Version 2 (interviewer-administered) was used in the NHMS; available guidelines and

norms were used to compare the two versions (38, 42). The Short Form 12 Health Survey (SF-12) (Version 2, self-administered) was used in the MEPS sample (42). A preference-based score, the Short Form-6 Dimensions (SF-6D), was estimated when the 11 SF-36 items that it comprises were completed (43, 44). Utility scores reflecting HRQL were obtained from the HUI3, which is part of a family of generic health profiles and preference-based systems (45, 46). The interviewer-administered HUI3 was used in the NHMS, whereas the self-administered HUI was used in the USVEQ.

Statistical analyses and data interpretation

Norm-based analyses were conducted in an intent-to-treat population, defined as all patients randomised to treatment who received at least one injection of study medication. All analyses were based on data obtained within the treatment window for each visit (visit windows were defined as ± 7 days). All statistical tests were two-sided and used an alpha level of 0.05. Results were adjusted for multiple comparisons using the Bonferroni adjustment.

Descriptive statistics were reported for demographic and clinical characteristics such as age and duration of AS. Means and standard deviations were used to describe continuous variables, whereas frequency distributions were used to describe categorical variables.

To assess the impact of disease and treatment in active AS, analysis of covariance models were used to compare mean scores (SF-36, SF-6D and HUI3) for adalimumab *vs.* US norms and placebo *vs.* US norms at baseline and Weeks 12 and 24. A matched-case analysis was conducted, in which US general population data (based on MEPS and USVEQ) were matched 1:1 by age, sex and race of the ATLAS trial sample. F-tests were used to assess the overall model fit [*e.g.* PCS = treatment/general population + age + sex + race], whereas Bonferroni adjustments for multiple comparisons were used to assess mean differences between general population norms and treatment means. A last observation carried forward approach was

used to handle missing data in the randomised controlled phase of the study (baseline to Weeks 24).

To assess the impact of the US normative populations used on outcomes, sensitivity analyses were conducted evaluating the previously described analysis of covariance models using US norms data from the NHMS. Similar models evaluating treatment outcomes from the open-label extension portion of ATLAS (from Weeks 25 to 156) were used to assess the long-term impact of adalimumab treatment over time; an observed data approach was used to assess data from this phase.

A difference of 2.5 to 3.0 points in SF-36 PCS or MCS scores is considered clinically important in patients with rheumatoid arthritis (47, 48). There is evidence for the comparability of the SF-12 and SF-36 summary scores (42). The minimum clinically important difference (MCID) of the SF-6D utility scores has been estimated to be 0.03 based on an analysis of seven longitudinal studies (44). The MCID for the HUI3 has been estimated to be 0.03 (49, 50).

Ethics

Each patient provided written informed consent, and each participating site received ethics approval. The study was conducted according to International Conference on Harmonization guidelines and the Declaration of Helsinki.

Results

Demographics and clinical characteristics

A total of 315 patients from ATLAS were included in this analysis, of which 208 received adalimumab and 107 received placebo. Baseline characteristics were similar between the two treatment groups (Table I). The majority of patients were men (approximately 75%) and experienced AS for 11 years. Approximately 80% were HLA-B27-positive and the mean BASDAI score of >4 suggested active disease (51).

Impact of AS and treatment on HRQL at baseline

Significantly lower scores on all measures of HRQL were observed for patients in each ATLAS treatment

Table I. Baseline characteristics of ATLAS groups.

Characteristic	Treatment group	
	Adalimumab (n=208)	Placebo (n=107)
Age (years), mean (SD)	41.7 (11.69)	43.4 (11.32)
Male sex, n (%)	157 (75.5)	79 (73.8)
White race, n (%)	202 (97.1)	99 (92.5)
HLA-B27-positive, n (%)	163 (78.4)	85 (79.4)
Duration of AS (years), mean (SD)	11.3 (9.99)	10.0 (8.34)
Patient's Global Assessment, mean (SD)*	6.3 (2.2)	6.5 (2.0)
Total back pain, mean (SD)*	6.4 (2.1)	6.7 (2.2)
Inflammation (cm), mean (SD)*	6.7 (2.0)	6.7 (1.9)
BASFI score, mean (SD)*	5.2 (2.2)	5.6 (2.2)
BASDAI score, mean (SD)*	6.3 (1.7)	6.3 (1.7)
CRP (mg/dL), mean (SD)	1.8 (2.2)	2.2 (2.9)

AS: ankylosing spondylitis; ATLAS: Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BASFI: Bath Ankylosing Spondylitis Functional Index; CRP: C-reactive protein.

*Visual analogue scale from 0 to 10.

group compared with the general US population (based on MEPS and USVEQ; Table II). Mean SF-36 summary scores were significantly lower in patients receiving adalimumab or placebo compared with the general US population for both the PCS (31.4, 30.4 and 49.1 points, respectively) and MCS (42.8, 44.0 and 49.8 points, respectively). SF-6D scores were also lower for patients receiving adalimu-

mab or placebo (0.54 and 0.56, respectively) compared with the general US population (0.76). Similarly, HUI3 scores were lower for patients receiving adalimumab or placebo compared with the general US population (0.45, 0.46 and 0.80, respectively). For both treatment groups compared with the general US population, all differences were statistically significant at the $p < 0.0001$ level.

Impact of treatment on HRQL in the randomised controlled trial

As early as Week 12, the impact of treatment with adalimumab was seen through improvements in HRQL scores, but improved scores were still below those of the general US population (Table II). Mean PCS and SF-6D scores for patients receiving adalimumab improved by 6.3 and 0.08 points, respectively, which were greater than the MCID. Mean PCS and SF-6D scores for adalimumab were significantly lower compared with the general US population (differences of 11.7 and 0.15 points, respectively; both $p < 0.0001$). Of note, the HUI3 was not administered at Week 12. For patients receiving placebo, PCS and SF-6D scores improved slightly compared to baseline but did not reach the MCID. Mean PCS and SF-6D scores for placebo were significantly lower than the general US population (differences of 16.5 and 0.19 points, respectively; both $p < 0.0001$). MCS scores remained consistent for patients in both treatment groups.

HRQL scores remained stable from Week 12 to Week 24 (Table II). Compared with baseline, mean PCS, SF-6D and HUI3 scores for patients

Table II. HRQL impact of disease and treatment in active AS by treatment group: randomised controlled trial phase.

	Adalimumab		Placebo		General US population**		F statistic	p-value ^{‡§}	p-value ^{‡§}
	n	LS mean (standard error)	n	LS mean (standard error)	n	LS mean (standard error)			
Baseline**									
PCS	207	31.38 (1.01)	104	30.41 (1.12)	315	49.13 (0.92)	154.4	<0.0001	<0.0001
MCS	207	42.81 (1.29)	104	43.98 (1.44)	315	49.77 (1.18)	13.3	<0.0001	<0.0001
SF-6D	192	0.54 (0.02)	96	0.56 (0.02)	308	0.76 (0.01)	102.5	<0.0001	<0.0001
HUI3	208	0.45 (0.03)	107	0.46 (0.03)	315	0.80 (0.03)	73.9	<0.0001	<0.0001
Week 12***									
PCS	206	37.67 (1.11)	103	32.30 (1.24)	315	48.84 (1.01)	82.4	<0.0001	<0.0001
MCS	206	44.38 (1.33)	103	44.57 (1.49)	315	48.36 (1.22)	6.0	0.0002	0.0079
SF-6D	179	0.62 (0.02)	86	0.58 (0.02)	308	0.77 (0.02)	47.0	<0.0001	<0.0001
Week 24**									
PCS	206	38.16 (1.12)	103	32.57 (1.25)	315	48.78 (1.02)	77.5	<0.0001	<0.0001
MCS	206	44.92 (1.31)	103	44.18 (1.47)	315	48.06 (1.20)	5.7	0.0042	0.0054
SF-6D	182	0.62 (0.02)	86	0.58 (0.02)	308	0.76 (0.02)	46.0	<0.0001	<0.0001
HUI3	202	0.56 (0.03)	104	0.48 (0.03)	315	0.78 (0.03)	40.2	<0.0001	<0.0001

AS: ankylosing spondylitis; HRQL: health-related quality of life; HUI3: Health Utilities Index Mark 3; LS: least squares; MCS: Mental Component Summary; MEPS: Medical Expenditure Panel Survey; PCS: Physical Component Summary; SF-36: Short Form 36 Health Survey; SF-6D: Short Form-6 Dimensions; USVEQ: US Valuation of the EuroQol 5D Health States Survey.

*SF-36 and SF-6D derived from MEPS and HUI3 derived from USVEQ databases; †Matched-case analysis, matching by age, sex and race (1:1 match); ‡Bonferroni adjustment for multiple comparisons; §Adalimumab vs. general US population; ¶Placebo vs. general US population; **Last observation carried forward approach; §HUI3 was not collected at Week 12.

Table III. HRQL impact of disease and treatment in active AS by treatment group: extension phase.

	Adalimumab		Placebo		General US population*†		F statistic	p-value‡§	p-value‡§
	n	LS mean (standard error)	n	LS mean (standard error)	n	LS mean (standard error)			
Week 52**§									
PCS	179	41.40 (1.25)	89	39.83 (1.39)	288	49.37 (1.14)	35.8	<0.0001	<0.0001
MCS	179	48.31 (1.32)	89	50.44 (1.47)	288	49.70 (1.21)	1.7	0.4694	1.0000
SF-6D	168	0.66 (0.02)	86	0.67 (0.02)	278	0.77 (0.02)	22.2	<0.0001	<0.0001
HUI3	188	0.67 (0.03)	94	0.70 (0.03)	288	0.82 (0.03)	17.6	<0.0001	<0.0001
Week 104**§									
PCS	166	42.69 (1.30)	93	40.95 (1.43)	288	49.83 (1.18)	30.3	<0.0001	<0.0001
MCS	166	48.75 (1.36)	93	49.23 (1.49)	288	49.53 (1.23)	0.8	1.0000	1.0000
SF-6D	155	0.68 (0.02)	83	0.67 (0.02)	278	0.77 (0.02)	18.5	<0.0001	<0.0001
HUI3	170	0.71 (0.03)	94	0.68 (0.03)	288	0.83 (0.03)	14.6	<0.0001	<0.0001
Week 156**§									
PCS	146	44.00 (1.28)	85	39.80 (1.38)	288	49.68 (1.13)	29.7	<0.0001	<0.0001
MCS	146	48.97 (1.39)	85	48.41 (1.51)	288	49.30 (1.23)	0.8	1.0000	1.0000
SF-6D	141	0.70 (0.02)	82	0.66 (0.02)	278	0.77 (0.02)	16.4	<0.0001	<0.0001
HUI3	148	0.74 (0.03)	87	0.66 (0.03)	288	0.82 (0.03)	12.8	0.0031	<0.0001

AS: ankylosing spondylitis; HRQL: health-related quality of life; HUI3: Health Utilities Index Mark 3; LS: least squares; MCS: Mental Component Summary; MEPS: Medical Expenditure Panel Survey; PCS: Physical Component Summary; SF-36: Short Form 36 Health Survey; SF-6D: Short Form-6 Dimensions; USVEQ: US Valuation of the EuroQol 5D Health States Survey.

*SF-36 and SF-6D derived from MEPS and HUI3 derived from USVEQ databases; †Matched-case analysis, matching by age, sex and race (1:1 match);

‡Bonferroni adjustment for multiple comparisons; §Adalimumab vs. general US population; ¶Placebo vs. general US population; **Observed-data approach;

§For patients randomised to adalimumab at baseline who agreed to participate in the extension study or patients randomised to placebo at baseline who agreed to participate in the extension study.

receiving adalimumab improved by 6.8, 0.08 and 0.11 points, respectively, which were greater than the MCID. Mean PCS, SF-6D and HUI3 scores for adalimumab were significantly lower compared with the general US population (differences of 10.6, 0.14 and 0.22 points, respectively; all $p < 0.0001$). For patients receiving placebo, mean PCS, SF-6D and HUI3 scores remained relatively unchanged compared with baseline and did not reach the MCID. Mean PCS, SF-6D and HUI3 scores for placebo were significantly lower than the general US population (differences of 16.2, 0.18 and 0.3 points, respectively; all $p < 0.0001$).

Impact of treatment on HRQL in the extension study

After Week 24, all patients who remained in the study were treated with adalimumab (ie, patients initially randomised to adalimumab remained on adalimumab and those randomised to placebo switched to adalimumab). For patients initially randomised to adalimumab, mean PCS and SF-6D scores were still significantly lower than for the general population (all $p < 0.001$) but improved by 3.2 and 0.04 points,

respectively, from Weeks 25 to 52. The scores remained relatively stable over time from Weeks 53 to 156 (Table III; Fig. 1A-1B). Mean PCS scores were within 8 points of the normative values. HUI3 scores for these patients improved throughout the extension phase (Table III; Fig. 1C) but remained significantly lower than for the general US population. After switching to adalimumab, PCS, MCS, SF-6D and HUI3 scores for patients initially randomised to placebo improved by 7.3, 6.3, 0.09 and 0.22 points, respectively, from Weeks 24 to 52. Scores remained stable over time from Weeks 53 to 156 (Table III; Figs. 1A-D) but were significantly lower than the general US population (all $p < 0.01$).

Sensitivity analyses

Additional analyses were conducted to assess the impact of population norm selection on findings. Sensitivity analysis using NHMS data revealed similar findings to those using the MEPS and USVEQ data. However, scores (for both treatment groups, for all HRQL scales and at all time points) were somewhat lower when using NHMS data compared with scores obtained

when the MEPS and USVEQ data were used (data not shown). These findings may be due to differences in demographic characteristics, such as age and sex, between the NHMS and ATLAS populations. In addition, the magnitude of treatment impact based on differences between treatment groups and general US population means were somewhat larger for analyses using the NHMS data.

Discussion

A review by Kiltz and van der Heijde (52) described the decrements in HRQL for patients with rheumatoid arthritis and AS on a variety of domains, including pain, functional disability, fatigue, mental health, and socioeconomic status. Our study examined the burden of AS on patient functioning and well-being compared with two US population samples (MEPS and NHMS). Regardless of the data source defining the general US population, patients with AS reported significantly impaired functioning and well-being compared with population norms, even after adjusting for age, sex and race. The negative influence of AS was primarily observed on the physical components

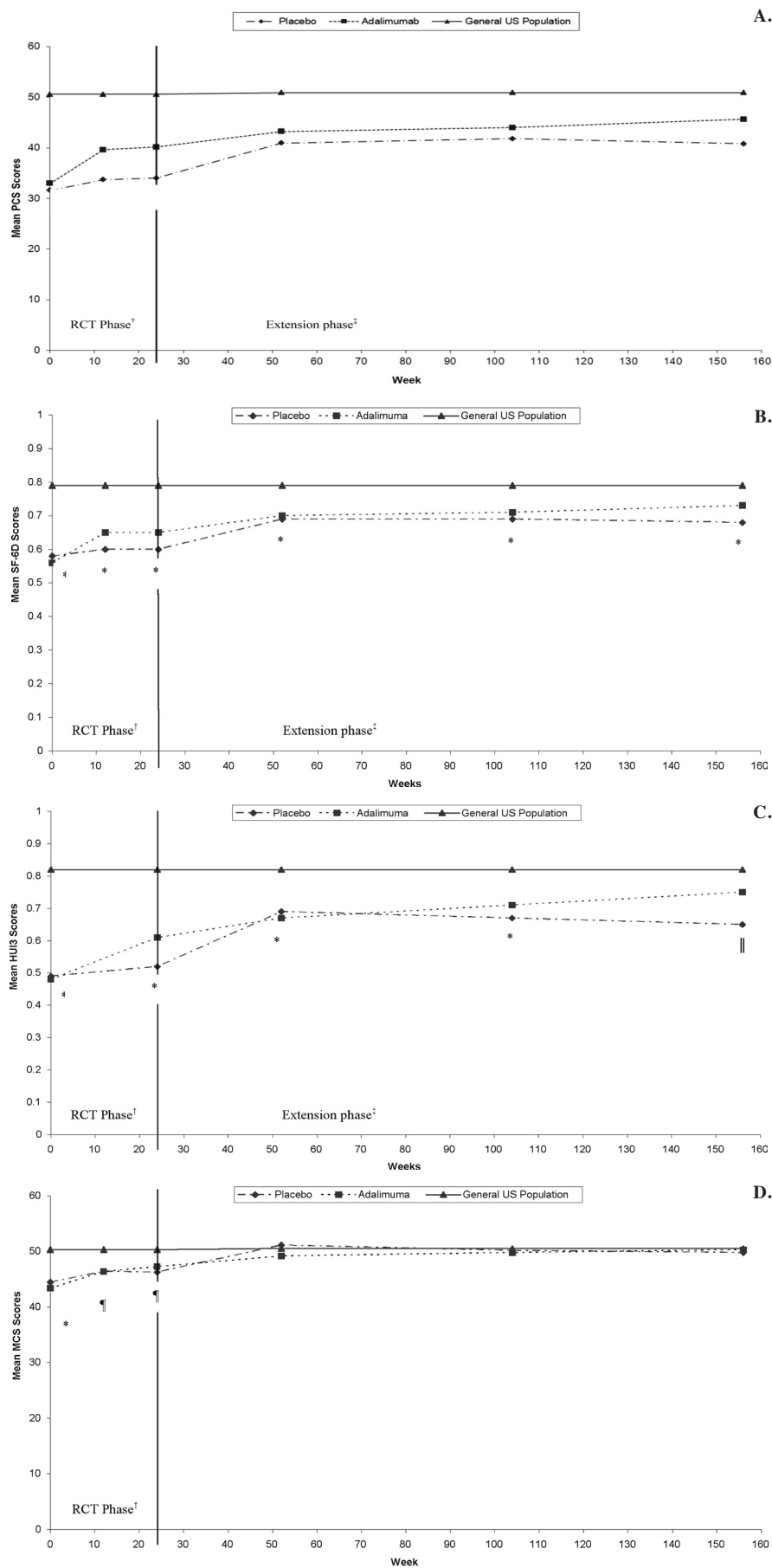


Fig. 1. Unadjusted mean HRQL scores over 16 weeks for ATLAS patients compared with population norms. **A.** PCS: ATLAS vs. MEPS. **B.** SF-6D: ATLAS vs. MEPS. **C.** HUI3: ATLAS vs. USVEQ. **D.** MCS: ATLAS vs. MEPS. * $p < 0.001$ for adalimumab and placebo compared with general US population. †During the 24-week, randomised, double-blind phase, patients received adalimumab or placebo. ‡During the extension phase, patients initially receiving placebo were switched to adalimumab and those initially receiving adalimumab continued receiving adalimumab. § $p < 0.01$ for adalimumab and $p < 0.001$ for placebo compared with general US population. ¶ $p < 0.01$ for adalimumab and placebo compared with general US population. ATLAS: Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis; HRQL: health-related quality of life; HUI3: Health Utilities Index Mark 3; MCS: Mental Component Summary; MEPS: Medical Expenditure Panel Survey; PCS: Physical Component Summary; RCT: randomised controlled trial; SF-6D: Short Form-6 Dimensions; USVEQ: US Valuation of the EuroQol 5D Health States Survey.

– rather than the mental health components – of health status. Although adalimumab significantly improved HRQL outcomes, physical functioning in patients with AS remained below those of the general population samples. Patients in this study had long-standing AS for more than 10 years, so improvements in HRQL equivalent to the general population may not be expected even after extended treatment. Baseline PCS scores for ATLAS treatment groups were 17.8 to 19.7 points lower compared with two US population samples. These findings are consistent with the Ankylosing Spondylitis Study for the Evaluation of Recombinant Infliximab Therapy population, in which baseline PCS scores for the treatment groups were approximately 20 points lower (two population standard deviations) than for mean population norms of 50, indicating substantial impairment in physical functioning (18). In addition, baseline physical function scores from ATLAS (data not shown) were similar to physical function scores from other AS trials for etanercept (53, 54) and infliximab (55), all of which were approximately 40 points below US population norm of 78 points. For both treatment groups, mean MCS scores in ATLAS were approximately 10 points lower than for the general US population at baseline, suggesting less impair-

ment in mental health compared with physical health. These mental health findings were consistent with those seen in other trials evaluating the impact of mental health (MCS and the individual mental health scale) in AS populations (18, 53-55). Mean HUI3 scores at baseline for the adalimumab and placebo groups in this were approximately 0.35 points lower than the general US population (USVEQ) evaluated in this study and 0.45 points lower than a Canadian general population (50).

The impact of adalimumab treatment was seen as early as Week 12, when clinically relevant within-group improvements were seen for PCS (6.8 points) and SF-6D (0.08 points) scores, based on MCIDs of 3 points and 0.03 points, respectively. In addition, clinically relevant and favourable between-group differences in PCS (5.4 points) and SF-6D (0.04 points) scores were observed for patients receiving adalimumab compared with placebo. These clinically significant improvements and between-group differences were maintained at Week 24 for those treated with adalimumab monotherapy. Additionally at Week 24, clinically relevant improvements and between-group differences were observed for adalimumab-treated patients based on HUI3 scores (improvement of 0.11 and difference of 0.08), based on an MCID of 0.03 points (49). These improvements and differences were maintained over the 3-year treatment period for all measures (PCS, SF-6D and HUI3).

Placebo-treated patients who were switched to adalimumab during the extension phase of the trial experienced clinically relevant improvements in all PROs, including mental health. From Week 24 to Week 52, scores improved by 7.3, 6.3, 0.09 and 0.22 points, respectively, for the PCS, MCS, SF-6D and HUI3. Similar to patients initially treated with adalimumab, improvements in functioning were gained after patients switched to adalimumab and were maintained for the remaining 2 years of the trial. These findings are consistent with a 72-week, open-label extension study (56) that examined the impact of switching from placebo to etanercept, in which improvements

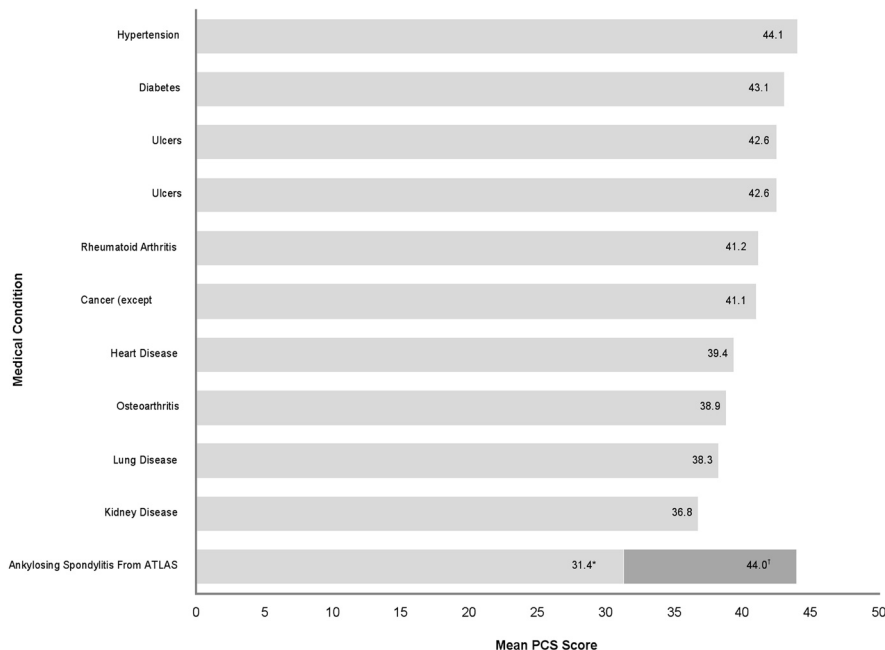


Fig. 2. Comparison of ATLAS PCS scores to other medical conditions; normative data from Ware *et al.* (38). *At baseline for patients randomised to adalimumab. †At Week 156 for patients randomised to adalimumab. ATLAS: Adalimumab Trial Evaluating Long-Term Safety and Efficacy for Ankylosing Spondylitis; PCS: Physical Component Summary.

in HRQL (based on PCS, SF-6D and EuroQol 5D scores) gained during the initial 12-week period after switching were maintained for the remainder of the 72-week trial.

Although treatment with adalimumab did not improve functioning to levels of the general US population, scores improved significantly over 156 weeks, particularly with regard to physical functioning – the domain most impacted by AS. At baseline, mean PCS scores for patients in ATLAS were lower than those reported for patients in the general population reporting medical conditions such as kidney disease, lung disease, osteoarthritis, heart disease, cancer and rheumatoid arthritis (Fig. 2) (38). Similarly, mean baseline HUI3 scores were lower than those reported for patients in the general population reporting medical conditions such as congestive heart failure, emphysema, stroke, angina, myocardial infarction, diabetes and arthritis (range 0.48 to 0.66) (57). However, at Week 156, patients with AS receiving adalimumab reported mean PCS scores greater than or similar to those for patients reporting the previously mentioned medical conditions; these scores were most comparable to patients with hyper-

tension (Fig. 2) (38). Similarly, mean HUI3 scores at Week 156 (0.74) were greater than scores for patients with other medical conditions and again were most comparable to patients with hypertension (0.73) (57). Further, the change in mean overall HUI3 score in the period from baseline to Week 156 (0.29) compares favourably to the gain of 0.23 in overall HUI3 score observed in a study of elective total hip arthroplasty (58). Comparisons of baseline HRQL scores to population norms for other diseases highlight the negative impact of long-standing AS. Moreover, findings regarding treatment show that treatment with adalimumab improves physical functioning and HRQL in patients with advanced AS.

Early treatment in the course of the disease may be needed to improve HRQL to the level of general population. A previous report by Kimel *et al.* (59) noted that patients with early rheumatoid arthritis from the PREMIER study had PCS scores after 1 year of treatment with adalimumab plus methotrexate similar to those of the US population. HRQL for patients with early rheumatoid arthritis treated with adalimumab plus methotrexate improved to US norms.

Several limitations should be considered when interpreting the findings of this study. First, differences in sex and age distributions between the AS group and the general population sample may have had an impact on these comparisons. For example, the NHMS sample includes individuals aged 35 to 89 years and equal distributions of men and women, whereas the AS sample consisted mostly of men (75%) and age ranged from 18 to 71 years. Even with statistical adjustment for demographic characteristics, these differences may have impacted the group comparisons. Second, we determined that there were differences in modes of administration of SF-36 scores and that these differences may also have an effect on the group comparisons.

In conclusion, these secondary analyses of ATLAS demonstrate a significant burden of AS on HRQL. Treatment with adalimumab significantly improved physical functioning and other measures of HRQL. Clinically relevant improvements in HRQL outcomes over 3 years of treatment represent a significant benefit of treatment with adalimumab. Because of the advanced AS disease, the patient health status remained below the health status of the general population. Treatment earlier in the course of AS may be needed to restore HRQL to the level of the general population.

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