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Patient Burden of Axial Spondyloarthritis

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Abstract: Axial spondyloarthritis (AxSpA) is an inflammatory spondyloarthritis (SpA) that has significant impact on a patient's life. Symptoms, including fatigue, sleep problems, depression, and sexual dysfunction, can profoundly impact health-related quality of life (HRQoL) and limit work, leisure, and daily activities. Available therapies effectively manage pain and inflammation in early-stage disease, but patients often continue to experience impaired HRQoL. Thus, there remains a need for new therapies with novel mechanisms that can stop disease progression, potentially reverse damage caused by AxSpA and improve HRQoL in patients with AxSpA. Newer biologic agents, such as those targeting the interleukin 17–interleukin 23 axis, have promising efficacy and may improve HRQoL for patients with AxSpA. The AxSpA has many negative effects on HRQoL. By targeting disease pathways responsible for the development of AxSpA, approved and emerging therapies potentially reduce disease activity and improve the functional status of patients with AxSpA. This narrative review reflects on the findings of studies evaluating HRQoL of individuals with AxSpA and the role of newer therapies.

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Seronegative spondyloarthritis (SpA) is a group of chronic rheumatic diseases with common clinical and etiologic features, including axial and peripheral inflammatory arthritis, enthesitis, extra-articular manifestations, and strong associations with the major histocompatibility complex class 1 human leukocyte antigen B27 (HLA-B27).[1,2] According to data from the 2009–2010 National Health and Nutrition Examination Survey, SpA, including ankylosing spondylitis (AS), spondylitis associated with inflammatory bowel disease and psoriasis, and reactive SpA due to enteric or urogenital infections, affects an estimated 1% of adults in the United States.[3] Patients with SpA are classified by the location of joint involvement, and axial spondyloarthritis (AxSpA) consists of individuals with AS and nonradiographic axial spondyloarthritis (nr-AxSpA).

A study using newer classification criteria for AxSpA validated by the Assessment of SpondyloArthritis International Society (ASAS) working group reported that AxSpA has a prevalence of 0.7% in adults from the United States that is equally divided between AS and nr-AxSpA.[4] Inflammatory back pain is the most common symptom of SpA, but the sensitivity of inflammatory back pain for a diagnosis of AxSpA is approximately 70%.[5] In addition to spinal inflammation, AxSpA is characterized by a broad clinical spectrum of disease manifestations, including peripheral arthritis, dactylitis, uveitis, psoriasis, inflammatory bowel disease, and aortic insufficiency.[6,7] Comorbidities associated with AxSpA include cardiovascular disease, diabetes mellitus, osteoporosis, and depression.[8–11] Renal, neurologic, and pulmonary disease manifestations also have been reported.[12]

Disease progression varies among individuals, but some general trends have been observed. Younger age (≤40 years) at disease onset is generally associated with a predominance of axial symptoms, whereas patients with later disease onset tend to have more peripheral manifestations.[13] Atypical disease progression is increasingly being recognized, particularly in women, who are less likely than men to have classic biomarkers or radiographic evidence of sacroiliac joint disease (e.g., HLA-B27, C-reactive protein). Of note, women are more likely to develop severe symptoms in shorter periods, and their disease is less likely to respond to standard treatment.[14]

Disease severity and impaired health-related quality of life (HRQoL) in patients with AxSpA are influenced by disease mechanisms that affect the bones, tendons, ligaments, and synovial membranes, as well as secondary organ systems (e.g., eyes, gut, skin). This article provides an overview of the negative effects of manifestations of AxSpA on HRQoL, followed by a discussion of how approved and emerging therapies that target AxSpA disease pathways can potentially reduce disease activity and improve physical function and HRQoL.

CLINICAL MANIFESTATIONS AND HRQoL BURDEN

Unlike rheumatoid arthritis, which causes joint damage primarily through bone and cartilage resorption and destruction, or psoriatic arthritis, in which destruction is caused by cortical bone resorption and formation of bone spurs in entheses, AxSpA

is characterized by new bone formation.[15] This new bone formation results in bone fusion and sclerosis of the sacroiliac joints, lumbar spine, and later the thoracic and cervical spine, as well as proliferative arthritis of the peripheral joints.[15] Many of the adaptive autoimmune features that contribute to synovitis in rheumatoid arthritis are absent in SpA.[16]

Only recently, with the development of validated instruments to measure patient-reported outcomes in AxSpA, have clinicians gained an improved understanding of the profound negative effects that AxSpA can have on HRQoL and of how pharmacologic treatment, physical therapy, and psychosocial interventions can improve HRQoL.[17] In addition, studies using general measures of HRQoL, including the Short Form-36, have identified distinct patterns in different rheumatic diseases as a result of the specific functional limitations and comorbidities associated with each condition.[18,19] A study of disease burden in 1093 patients with rheumatoid arthritis, 365 patients with psoriatic arthritis, and 333 patients with AxSpA found that patients with AxSpA and psoriatic arthritis experienced more pain and fatigue than did those with rheumatoid arthritis, and patients with AxSpA had more overall and nighttime spinal pain than did the other 2 groups.[20] In patients with AS, Short Form-36 domain scores for physical function, physical role, bodily pain, general health, vitality, and mental health are all significantly correlated with functional disability.[21]

The characteristic pathophysiologic changes associated with AxSpA result in persistent inflammation of the sacroiliac joints, causing chronic back pain and skeletal/postural changes.[15] Symptoms of pain, stiffness, and fatigue associated with progressive bony fusion of the spine are major contributors to disease burden and limit physical functioning, including the ability to perform activities of daily living, such as dressing, walking, bathing, and eating.[18,22] Approximately 66% of patients with AxSpA experience fatigue, and sleep quality is a major contributor to fatigue.[23,24] Patients with AxSpA report awakening 1.5 times per night, and 46% have moderate to severe insomnia.[24]

The physical limitations of AxSpA can also affect employment, leisure activities, mood, and interpersonal relationships.[17,22] In a study of men with AxSpA, 45% switched to a less physically demanding job, and 24% retired early at a mean age of 36 years because of the condition.[25] Similarly, an evaluation of patients with SpA (74% AxSpA) showed high or moderate work instability (i.e., mismatch between a person's functional abilities and demands of a job) in 40% of individuals.[26] The economic impact of work limitations related to AxSpA is substantial and is compounded by the typically young age at diagnosis.[26] Treatment resulting in Bath Ankylosing Spondylitis Functional Index responses after 12 weeks resulted in significantly increased work and leisure activity participation in a population with a similar number of patients with AS or nr-AxSpA.[27]

Spinal deformation/curvature and poor posture can result in significant body image disturbances, which are linked to increased rates of anxiety and depression.[28] In a study of patients with AxSpA, Kilic and colleagues[29] found that 45% were at high risk of depression, and 21% were at high risk of anxiety. Notably, rates of diagnosed depression are 80% higher in women and 50% higher in men with AxSpA than in the general population.[11] In addition, sexual dysfunction and dissatisfaction, impaired relationships with intimate partners, and lower urinary tract symptoms are significantly more common in men with AxSpA ($P < 0.05$) than in matched control subjects.[30] Erectile dysfunction is significantly more common in men with AxSpA than in control subjects (42% vs. 18%, $P = 0.0006$), and sexual dysfunction is associated with increased rates of anxiety and depression.[30] A survey of men and women with AxSpA reported that sexual relationships were affected in 38% of respondents.[31]

Various disease and demographic factors are predictive of poorer HRQoL in patients with AxSpA. HLA-B27 is associated with higher disease activity and more extra-articular manifestations, and peripheral joint involvement is associated with significant declines in HRQoL.[23,32] Abnormal spinopelvic parameters (e.g., sagittal vertical axis, sacral slope, lumbar lordosis) in patients with AxSpA are also significant predictors of decreased HRQoL.[33] Furthermore, women are reported to experience greater disease burden and HRQoL impairment compared with men.[14,23,32]

TREATMENTS

According to the 2010 ASAS/European League Against Rheumatism guidelines for management of AS, "The primary goal of treating the patient with ankylosing spondylitis is to maximize long-term HRQoL through control of symptoms and inflammation, prevention of progressive structural damage, and preservation/normalization of function and social participation."[34]

Nonpharmacologic Interventions

The ASAS/European League Against Rheumatism guidelines recommend that patients regularly exercise to improve physical function, with physical therapy being noted as particularly effective.[34] Patient advocacy organizations, self-help groups, shared patient experiences, and information about other patient resources can provide disease education to those with AxSpA.[34,35] Patients with AxSpA can also incorporate numerous other behavioral/lifestyle modifications into their daily routines to improve their living and working environments (Table 1).[35]

Pharmacological Interventions: Traditional Therapies

Limited evidence is available on the effect of traditional disease-modifying antirheumatic drugs on HRQoL in patients with AxSpA. For instance, a Cochrane literature review of 3 studies reported that there is not enough evidence to support any benefit of using methotrexate in patients with AS.[36] In another Cochrane literature review of 11 studies, the level of evidence was insufficient to support any benefit of sulfasalazine in reducing pain or improving physical function and spinal mobility in patients with AS.[37] Several studies have shown that nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs can effectively control pain and improve physical function, but have little to no impact on fatigue.[24,38,39]

Pharmacological Interventions: Tumor Necrosis Factor α Inhibitors

The 2015 American College of Rheumatology guidelines (i) strongly recommend treatment with tumor necrosis factor α inhibitors for adults with active AS, despite treatment with NSAIDs and (ii) conditionally recommend treatment with tumor necrosis factor α inhibitors for adults with active nr-AxSpA, despite treatment with NSAIDs.[40] Currently, 5 tumor necrosis factor α inhibitors are available (i.e., etanercept, adalimumab, infliximab, golimumab, and certolizumab pegol), with demonstrated efficacy for reducing signs and symptoms in active AS.[41] With long-term treatment, tumor necrosis factor α inhibitors may have neutral or favorable effects on bone mineralization, bone formation, and disease progression as measured by radiography, magnetic resonance imaging, and bone turnover markers.[42–46] Tumor necrosis factor α inhibitors generally improve symptoms of AxSpA, and limited

TABLE 1. Recommended Behaviors to Improve the Living and Working Environments of Patients With AS[35]

Activity	Recommended Behaviors
General	Maintain proper posture day and night
	Avoid becoming exhausted
	Avoid becoming overweight; maintain a healthy weight
	Do not smoke
	Maintain a positive attitude
Sitting	Sit in chairs with flat, firm surfaces
	Avoid sitting for prolonged periods, especially in low, soft sofas that slope
	Tables with tilted work surfaces facilitate proper reading posture
Walking	Take large-enough steps to prevent limitation of hip joint extension
	Wear shoes with shock-absorbing heels
Sleeping	A firm, flat mattress is best for maintaining proper sleeping posture
	Sleep on your back to prevent bending of the back and hip joints
	Lie on your front before falling asleep and before rising in the morning
	Avoid large pillows that lift shoulders and bend the spine
	Do not sleep with a pillow under your knees
Working	Try to maintain a dry, draft-free work environment
	Maintain good posture
	Avoid prolonged stooping or bending
	Avoid physical activity that strains your back or neck
	Alternate between sitting, standing, and walking throughout the day
	Try to find time during a break to lie flat for a few minutes; alternate lying face up and face down
Exercise	Engage in some form of physical activity every day
	Perform doctor-recommended muscle-strengthening and mobility exercises
	Perform deep-breathing exercises, including thoracic breathing
	Back, leg, and shoulder extension exercises are helpful as long as they do not strain your neck
	Range-of-motion exercises can help reduce pain and stiffness during flares
Sports/recreation	Choose sports based on the state of your disease and known limitations
	Activities that promote good posture and extending and rotating the trunk can be beneficial
	Sports requiring extended periods of spinal flexion (e.g., golf, bowling, long-distance cycling) may not be advisable
	Avoid sports with a high risk of injury (e.g., football, boxing, skiing)
	Singing or playing a musical instrument can improve breathing/lung capacity
Diet	Limit red meat and fish consumption to 2 meals/wk each
	Consider individual nutrient sensitivities or intolerances
	Consume sufficient vitamin D and calcium to prevent osteoporosis
Sexuality	AS generally should not interfere with sexual activity
	Adjust positions, as needed, to reduce stress on hips
Driving	Wide-view mirrors can increase visibility for patients with limited neck mobility
	Always use seatbelts and head restraints
	A back cushion may be helpful
	Take breaks every 1–2 h to stretch and walk around
	Carry emergency information about your diagnosis/special needs
Fall prevention	Wear skid-resistant shoes
	Wear shoes with fold-out spikes in icy conditions
	Use railings when going down stairs
	Consider using a shower stall instead of a bathtub
	Use a bath mat and/or grab bars to avoid slipping
	Avoid slippery surfaces and loose carpet
	Use floor lighting at night

data indicate improvement in peripheral disease manifestations.[41] However, the therapeutic potential of tumor necrosis factor α inhibitors for extra-articular manifestations (e.g., uveitis) is limited,[41] and up to approximately 40% of patients with AxSpA fail to respond to initial tumor necrosis factor α inhibitor therapy.[41,47–50]

Tumor necrosis factor α inhibitors are associated with a global improvement in HRQoL in patients with AxSpA. In the studies summarized in Table 2,[52–57] improvements seen in both physical and mental measures of HRQoL usually met or exceeded clinically meaningful thresholds used in HRQoL analyses.[18,57]

In addition, in a study designed to evaluate patient-reported outcomes for 12 weeks, a significant proportion of patients receiving etanercept achieved minimal clinically important difference (MCID) for the EuroQoL Group Health State Assessment utility score and most Short Form-36 subscales compared with placebo.[58] In another study of patient-reported outcomes, certolizumab pegol showed significantly greater improvement in the Short Form-36 physical component score, Short Form-36 mental component score, and Ankylosing Spondylitis Quality of Life (ASQoL) measure compared with placebo; most differences exceeded the MCID.[57] A recent retrospective study by Wu and colleagues[59] found that only 22% of patients receiving tumor necrosis factor α inhibitors had significant improvements in both pain and fatigue after an average of 59 weeks of treatment. In this study, fatigue severity was reduced on average by 20%, and most patients reported residual fatigue while on treatment.[59] Whereas Keat and colleagues[60] found that tumor necrosis factor α inhibitor therapy improved patients' capacity for work, other studies have failed to show improvements in employment status and work disability.[61,62] Despite reported functional improvements with tumor necrosis factor α inhibitor therapy, many patients continue to experience burdensome symptoms and difficulties with activity.[62]

Pharmacological Interventions: Newer Therapeutic Targets

Interleukin 17A

The T_H17 pathway, which is involved in the pathogenesis of psoriasis and psoriatic arthritis, is also active in AxSpA.[63,64] Compared with patients with rheumatoid arthritis, patients with SpA have elevated levels of T_H17 effector cells, suggesting a strong therapeutic potential for targeting T_H17-derived cytokines, such as interleukin 17A, in SpA.[63,64] Mast cells in inflamed synovial joints also produce interleukin 17 in patients with SpA,[64,65] and interleukin 17 contributes to bone erosion and inflammation through up-regulation of receptor activator of nuclear factor κB ligand.[66]

Studies of anti–interleukin 17–targeted agents in AxSpA are outlined in Table 3.[64–74] In a phase 2 study, the interleukin 17a inhibitor secukinumab demonstrated rapid, meaningful clinical improvement in symptoms of AxSpA and clinically relevant improvement in ASQoL measures compared with placebo.[67] In an open-label extension of this study, clinical response and regression of spinal inflammation by magnetic resonance imaging were maintained for up to 2 years.[75] Similarly, in 2 phase 3 studies, treatment with secukinumab provided rapid and sustained improvement in signs and symptoms of AxSpA and was associated with improvements in physical functioning and HRQoL compared with placebo (Fig.).[76] In addition, the efficacy of secukinumab and improvements in HRQoL measures were sustained to 2 years of treatment.[68]

Improvements in Short Form-36 physical component scores and ASQoL measures with secukinumab exceeded thresholds for MCID used in other analyses.[18,57] Based on these findings, secukinumab was recently approved in the United States for the treatment of active AS. Other agents that target interleukin 17 (i.e., ixekizumab, brodalumab) have not yet been investigated in AxSpA.

Interleukin 12/23

Interleukins 12 and 23 both serve as important agents in the pathophysiology of AxSpA, and these cytokines share the interleukin 12p40 subunit.[77] Both cytokines are secreted by inflammatory myeloid cells and promote differentiation of T_H17 cells, which produce interleukin 17.[77] While both interleukin 12– and interleukin 23–positive cells have been observed in subchondral bone marrow from the joints of patients with AxSpA, interleukin 23–containing cells were more frequently observed.[78]

Misfolding of HLA-B27 can trigger interleukin 23 production, and increased levels of interleukin 23 have been detected in macrophages from patients with AxSpA.[64,66] In addition, the *interleukin 23r* R381Q gene variant has been shown to protect against AxSpA through selective impairment of interleukin 17A production.[64]

Ustekinumab, an interleukin 12/23 inhibitor that targets the interleukin 12p40 subunit, is the only anti–interleukin 12/23 agent currently under development in AxSpA. In an open-label phase 2 study,[69] ustekinumab showed meaningful clinical improvement in symptoms of AxSpA and statistically significant improvement in HRQoL measures compared with placebo, which exceed clinically meaningful thresholds used in other analyses (Table 3).[57,73]

Other Therapeutic Targets

Unfortunately, biologic agents targeting interleukin 1, interleukin 6, B cells, and costimulatory molecules (i.e., anakinra, tocilizumab, sarilumab, rituximab, and abatacept) have failed to provide significant improvement in patients with AxSpA (Table 3).[79] However, a phase 2 pilot study of the small-molecule phosphodiesterase 4 inhibitor, apremilast, demonstrated observable but statistically insignificant improvements in Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale scores compared with placebo.[72] To date, MCID thresholds have not been established in AxSpA for FACIT-F measurements. Early-stage development of the oral Janus kinase inhibitor tofacitinib is ongoing in AxSpA, but clinical data regarding its therapeutic potential are not yet available.[80]

DISCUSSION AND CONCLUSIONS

The AxSpA can have a profound negative impact on HRQoL. As such, rheumatologists need to screen patients for signs of fatigue, sleep problems, and depression, along with social, occupational, and sexual dysfunction. Furthermore, rheumatologists can recommend numerous lifestyle modifications to improve patients' quality of life.

Effective biologic therapies targeting tumor necrosis factor α are available for the management of pain and inflammation in early-stage disease. However, some patients continue to experience impaired HRQoL despite treatment with these agents, and the effects of tumor necrosis factor α inhibitors on radiographic progression are only beginning to be understood. New therapies are needed with novel mechanisms that can stop disease progression, and clinical research is needed that evaluates these agents based on outcomes that are important to patients. In addition, cost-utility analyses should be performed to determine the economic benefit of these agents. Targeting novel pathways may uncover new disease manifestations and improve our understanding of how AxSpA affects patients. Biologic agents targeting interleukin 17A or interleukin 12/23 may provide insights into the underlying disease mechanisms of AxSpA and change perceptions about the level of improvement that can be achieved in both physical and psychosocial manifestations of AxSpA.

TABLE 2. Effects of Tumor Necrosis Factor α Inhibitors on HRQoL in Patients With AxSpA

Study	Agent (Dose)	n	Assessment	Short Form-36 Change From Baseline to End Point	ASQoL Change From Baseline to End Point
Van der Heijde et al.,[48] 2005	Infliximab (5 mg/kg IV)	201	Median change from baseline to week 24 (interquartile range)	ΔPCS = 10.2 (3.9, 17.1),[a] ΔMCS = 2.7 (−2.9, 8.8)	NA
Inman et al.,[50] 2008	Golimumab (50 and 100 mg SC combined)	278	Median change from baseline to week 24 (interquartile range)	ΔPCS: 8.1 (2.0, 16.6),[a] ΔMCS: 2.9 (−2.8, 9.7)[b]	NA
Sieper et al.,[51] 2013	Adalimumab (40 mg SC)	192	Mean change from baseline to week 12	ΔPCS: 5.5[a]	NA
Sieper et al.,[52] 2014	Infliximab (5 mg/kg IV and naproxen 1 g for 28 wk)	158	Mean change from baseline to week 28 vs. placebo and naproxen (SD)	ΔPCS: 12.6 (10.31),[c] ΔMCS: 9.0 (10.96)	NA
Wang et al.,[53] 2014	Adalimumab (40 mg SC)	(Meta-analysis)	Standardized mean differences vs. placebo (95% CI)	ΔPCS: 5.27 (−0.40 to 10.94),[d] ΔMCS: 0.39 (0.23 to 0.56)[d]	ΔASQoL: −6.92 (−7.75 to −6.09)[d]
Van der Heijde et al.,[54] 2015	Adalimumab (40 mg SC for 24 wk then open label)	122 for PCS, 125 for ASQoL	Mean change from baseline to 5 y[e]	ΔPCS: 11.5	ΔASQoL: −5.5
Sieper et al.,[55] 2015	Golimumab (50 mg SC for 16 wk)	198	Mean differences vs. placebo at week 16 (95% CI)	ΔPCS: 6.56 (4.28 to 8.83),[a] ΔMCS: 4.24 (1.42 to 7.07)[f]	ΔASQoL: −3.5 (−4.7 to −2.2)[a]
Van den Bosch et al.,[56] 2015	Etanercept (50 mg SC for 12 wk then open label to 104 wk)	215	Mean difference from baseline to weeks 12 and 104 (SE)	Week 12 ΔPCS: 6.2 (1.0)[b] ΔMCS: 2.4 (1.3) Week 104 ΔPCS: 10.0 (1.0) ΔMCS: 4.9 (1.3)	Week 12 ΔASQoL: −1.9 (0.5) Week 104 ΔASQoL: −4.7 (0.5)

Note: For Short Form-36 summary component scores, an increase of 2.5 to 5.0 points has been used as the MCID in SpA.[18] Short Form-36 summary component scores are transformed into a 100-point scale for which 0 is maximum disability and 100 is no disability. For ASQoL, a decrease of 2.0 or more points has been used as the MCID in AxSpA.[57] Scores on the ASQoL scale range from 0 (best quality) to 18 (poorest quality).

[a] $P \leq 0.001$ vs. placebo.

[b] $P < 0.05$ vs. placebo.

[c] $P = 0.003$ vs. placebo and naproxen.

[d] Changes were significant vs. placebo.

[e] No comparator during open-label phase (24 weeks through 5 years).

[f] $P = 0.0034$ vs. placebo.

CI indicates confidence interval; IV, intravenous; MCS, mental component score; NA, not applicable; PCS, physical component score; SC, subcutaneous; SE, standard error.

TABLE 3. Studies of Newer Targeted Emerging Agents in Patients With AxSpA Reporting HRQoL Data

Phase (Study Name) Citation	Agent and Dose	n	Key Efficacy Results	HRQoL Results
Interleukin 17–targeting therapies				
Phase 2 proof of concept study (Baeten et al.,[67] 2013)	• Secukinumab IV 2 × 10 mg/kg • Placebo	30	ASAS20 response rate estimate[a] at week 6 • Placebo 24.5% • Secukinumab 59.2% (99.8% probability of superiority to placebo)	ASQoL change ≥2 points at day 29 • Secukinumab: 52% • Placebo: 33%
2-y Extension of MEASURE 2[68]	• Secukinumab 150 mg • Secukinumab 75 mg	219	ASAS20 response at week 104 • Secukinumab 150 mg: 71.5% • Secukinumab 75 mg: 71.5% ASAS40 response at week 104 • Secukinumab 150 mg: 47.5% • Secukinumab 75 mg: 47.5%	SF-36 PCS mean change from baseline to week 104 (SE) • Secukinumab 150 mg: 7.3 (1.0) • Secukinumab 75 mg: 6.6 (1.0) EQ-5D mean change from baseline to week 104 (SD) • Secukinumab 150 mg: 21.2 (26.0) • Secukinumab 75 mg: 14.1 (21.0) FACIT-F mean change from baseline to week 104 (SD) • Secukinumab 150 mg: 11.2 (10.0) • Secukinumab 75 mg: 9.8 (8.2)
Interleukin 12/23–targeting therapies				
Open-label proof of concept study (TOPAS) Poddubnyy et al.,[69] 2014	• Ustekinumab 90 mg SC	20	ASAS40 response at week 24 • 65% (95% CI, 41%–85%) ASAS20 response at week 24 • 75% (95% CI, 53%–90%)	EQ-5D (SD) • Baseline: 0.6 (0.2) • Week 24: 0.8 (0.1; $P < 0.001$) ASQoL (SD) • Baseline: 9.4 (3.1) • Week 24: 5.1 (4.0; $P < 0.001$)
Other targeting therapies (interleukin 1R, CD20, PDE4)				
Open-label proof-of-concept study (Tan et al.,[70] 2004)	• Anakinra 100 mg SC	9	ASAS20 response at week 12 • 67%	ASQoL median score (range) • Baseline: 12 (5–16) • Week 12: 8 (0–15; $P = 0.011$)
Open-label phase 2 (Song et al.,[71] 2010)	• Rituximab 1000 mg IV	20	ASAS20 response at week 24 • 40% (95% CI 20.9%–64.0%)	ASQoL mean change (SD) from screening to week 24 • −3.4 (4.5)
Phase 2 (Pathan et al.,[72] 2013)	• Apremilast 30 mg, BID oral • Placebo	38	Mean change (SD) in BASDAI at week 12 • Placebo: −0.77 (1.47) • Apremilast: −1.59 (1.48; NS) ASAS20 response • Placebo: 15.8% • Apremilast: 35.3% (NS)	FACIT-F mean change (SD) from baseline to week 12 • Placebo: 5.07 (13.44) • Apremilast: 9.38 (12.79; NS)

Note: For ASQoL, a decrease of 2.0 or more points has been used as the MCID in AxSpA.[57] Scores on the ASQoL scale range from 0 (best quality) to 18 (poorest quality). For Short Form-36 summary component scores, an increase of 2.5 to 5.0 points has been used as the MCID in SpA.[18] Short Form-36 summary component scores are transformed into a 100-point scale for which 0 is maximum disability and 100 is no disability. The MCID for EQ-5D has not been reported. The smallest detectable difference has been calculated at 0.36.[73] Scores on the EQ-5D scales range from 0 (best) to 100 (worst). The MCID for FACIT-F for rheumatoid arthritis is 15.9.[74] Scores on the FACIT-F scale range from 0 (maximum fatigue) to 52 (no fatigue).

[a]As assessed by Bayesian analysis.

ASAS20/40 indicates 20%/40% response according to the ASAS criteria for improvement; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BID, twice daily; CD, cluster of differentiation; CI, confidence interval; EQ-5D, EuroQoL Five-Dimension Questionnaire; IV, intravenous; NS, non-significant; PDE, phosphodiesterase; SC, subcutaneous; SF-36 PCS, Short Form-36 Health Survey Physical Component Summary.

KEY POINTS

- The AxSpA is an inflammatory condition associated with progressive bony fusion of the spine and symptoms of pain, stiffness, fatigue, sleep problems, depression, and sexual dysfunction, which impair HRQoL.
- Use of TNF inhibitor biologic agents is associated with an improvement of physical and mental HRQoL in patients with axial SpA.
- New therapies are needed that can improve HRQoL in patients with AxSpA.
- Biologic agents targeting interleukin 17A or interleukin 12/23 may improve HRQoL in patients with AxSpA.

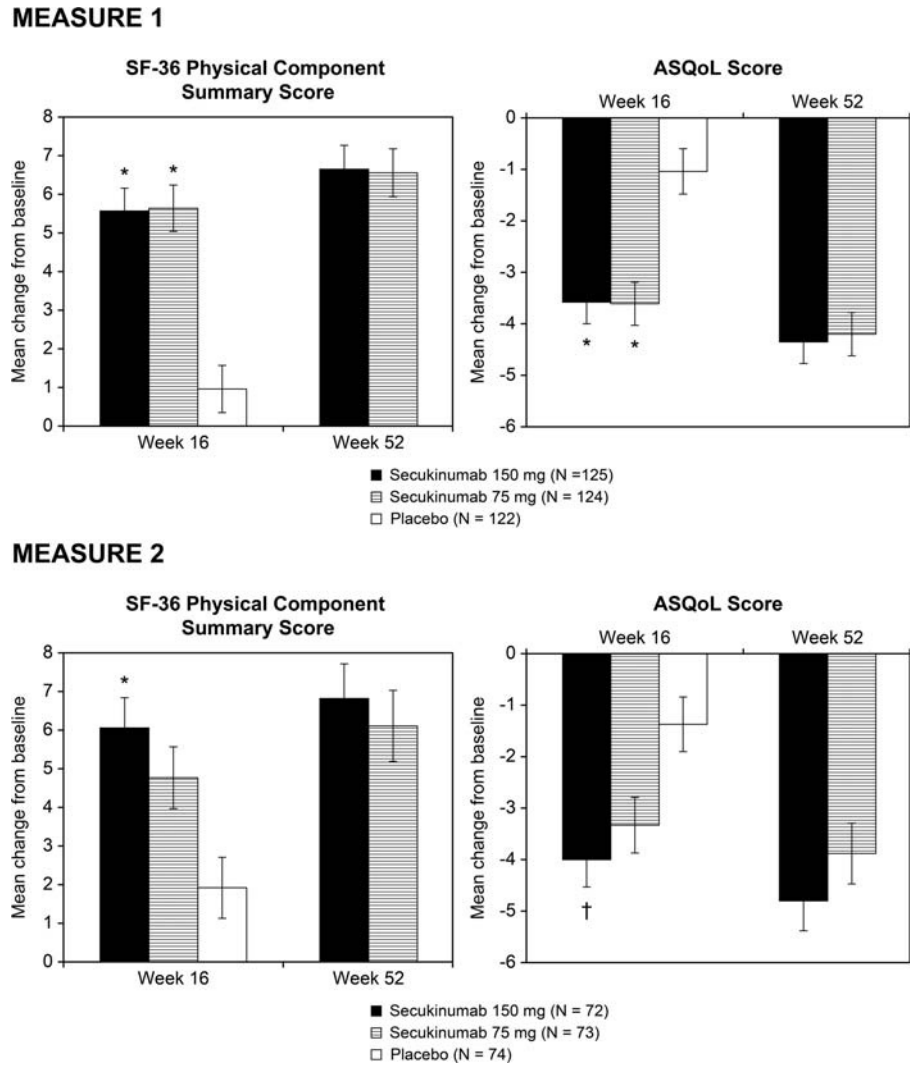

FIGURE. Health-related quality-of-life outcomes from phase 3 trials of newer targeted agents for treatment of AxSpA. Patients receiving placebo were randomized to secukinumab at week 16. Intravenous secukinumab (10 mg/kg) or placebo was given at weeks 0, 2, and 4 followed by subcutaneous secukinumab (150 or 75 mg) or placebo every 4 weeks starting at week 8. Note: For Short Form-36 summary component scores, an increase of 2.5 to 5.0 points has been used as the MCID in SpA.[18] Short Form-36 summary component scores are transformed into a 100-point scale for which 0 is maximum disability and 100 is no disability. For ASQoL, a decrease of 2.0 or more points has been used as the MCID in AxSpA.[57] Scores on the ASQoL scale range from 0 (best quality) to 18 (poorest quality). *$P < 0.001$ versus placebo. †$P < 0.01$ versus placebo. Error bars are +/- standard error.

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