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Does Secukinumab Improve Self-reported Quality of Life in Patients with Moderate-to-severe Ankylosing Spondylitis When Taken Regularly?

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Does secukinumab improve self-reported quality of life in patients with moderate-to-severe ankylosing spondylitis when taken regularly?

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ABSTRACT

Objective: The objective of this selective EBM review is to determine whether or not secukinumab improves self-reported quality of life in patients with moderate-to-severe ankylosing spondylitis when taken regularly.

Study design: A systematic review of three randomized placebo-controlled trials (RCTs), published in peer-reviewed journals between 2013 and 2015, all in the English language.

Data sources: All three studies were found and accessed on PubMed.

Outcomes measured: Patient quality of life was assessed in all three studies using the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire and reported as mean change from baseline. ASQoL is scored from 0-18 with a higher score representing a lower quality of life and a greater degree of disability.

Results: With the exception of the smallest dose tested in the initial study conducted by Baeten et al. (2013), all other tested doses of secukinumab were shown to improve self-reported quality of life in patients with moderate-to-severe disease compared to placebo.

Conclusions: The results of these studies indicate that given a sufficient dose, regular administration of secukinumab can lead to improvements in self-reported quality of life. This is especially important given that patients selected for some of these studies already had inadequate responses to max doses of NSAIDs and/or TNF-α inhibitors, which have been the only available therapies.

Keywords: ankylosing spondylitis, secukinumab

INTRODUCTION

Ankylosing spondylitis (AS) is a chronic inflammatory condition affecting the joints of the axial skeleton, which results in pain, new bone formation, and progressive stiffening. AS is in a group of conditions known as seronegative spondyloarthropathies, which is indicative of the fact that they are not currently associated with any specific serum antibodies. Unlike many other causes of back pain, AS is most often seen in patients in their late teens and early 20s. Males are more frequently affected than females, and symptoms are typically more severe in males as well. Pain associated with AS is often worse in the morning and stiffness can last for hours; however, these symptoms improve with activity in contrast to degenerative or acute causes of back pain, which are more commonly exacerbated by movement. The disease usually first affects the sacroiliac (SI) joints, and with progression of the disease, increasingly cephalad portions of the spine are affected eventually resulting in complete spinal fusion.[1] As one might expect, this leads to significant discomfort, loss of mobility, and reduction in quality of life (QoL). While axial disease is the hallmark of AS, patients may also experience changes and acute flares to peripheral joints. Other signs and symptoms of AS include fatigue, SI joint tenderness, sleep disturbance, enthesopathy, and in late disease, loss of lumbar lordosis, kyphosis, and dyspnea.[2]

With an incidence of only 0.2 – 0.5% of the general population of the United States, AS is not a particularly common disease.[3] Incidence is highest at 6.5% in HLA-B27 positive patients, but this gene is only present in 6.1% of the US population.[4,5] That being said, back pain, a primary symptom of AS, is incredibly common. Researchers in 2013 reviewed the medical records of 142, 377 individuals in one Minnesota county across 5 years and found that back pain was the third most common complaint amongst all age groups.[6] So, while AS may be uncommon, it is important to recognize as a potential cause of back pain, especially if presenting

in a younger patient. Additionally, physician assistants frequently work in primary care, which is often where complaints of back pain are first addressed. If PAs and other providers are able to better recognize and differentiate AS from other causes of back pain, then appropriate management can begin leading to better quality of life for patients.

As with many diseases, patients with AS are burdened by significant medical costs. One study calculated the average yearly all-cause cost associated with AS at $17,728 per year.[7] On top of that, many patients with AS take time off of work, and as a result, suffer from lost wages. While some of the time taken off work is undoubtedly due to severity of symptoms and inability to attend work, these patients also spend a significant amount of time obtaining care. On average, a patient with AS has 10.8 office visits, 6.6 hospitalizations, and 2 ER visits per year.[7] In comparison, the Centers for Disease Control & Prevention (CDC) reported that in 2015 the average person within the United States utilized approximately 3.1 office visits, 0.41 hospitalizations, and 0.43 ER visits that year.[8,9]

The primary pathologic processes in the development of ankylosing spondylitis are inflammation, cartilage erosion, and importantly, ossification. Early in disease, MRI may detect bilateral and symmetric sacroiliitis. With more time, inflammation and sclerosis at the edges of the annulus fibrosus result in a characteristic “shiny corner” sign, which progresses to ossification and formation of bridging syndesmophytes. While this occurs, anterior and lateral ligaments of the spine become calcified. The result is spinal fusion and the appearance of a “bamboo spine” on plain radiographs.[1] Two factors that have been limiting research into more precise pathophysiology are the slow progression of the disease and the technically difficult task of obtaining samples of affected tisue.[4]

As noted above, there is a well-recognized link between HLA-B27 (B27) and AS. The

presence of B27 not only increases the risk of disease but is also associated with increased severity, and while 90% of individuals with AS are B27-positive, it is not a requirement for disease. As part of the major histocompatibility complex (MHC), B27 is responsible for presenting proteins to T-cells for recognition of intracellular pathogens and activating natural killer (NK) cells. B27 exhibits preferential binding for the NK receptors, which may explain part of its role in pathogenesis. Recent genetic studies have identified other gene products that may influence the activity of B27. Inflammation is initially dominated by the presence of mononuclear cells and osteoclasts, which degrade trabecular bone. Accordingly, bone resorption markers, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) are elevated in patients with active AS. Other consistent findings within SI joints of affected individuals are high levels of T-cells, TNF-α protein, macrophages, mRNA, and other pro-inflammatory cytokines such as IL-10, IL-15, IL-17 and IL-23.[4,10] It is currently hypothesized that inflammation is paradoxically prerequisite and inhibitory in the process of new bone growth, which may explain why syndesmophytes continue to form despite treatment with potent anti-inflammatories like TNF-α inhibitors.[4]

Currently, no therapies have shown efficacy in slowing the progression of disease or inducing remission.[11] Until such a discovery is made, the focus remains on minimizing symptoms and improving quality of life. Anti-inflammatories such as non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, physical therapy, and opiate analgesics are commonly employed for this purpose. Physical therapy, including hydrotherapy, and daily stretching are important for prolonging better posture, flexibility, and mobility.[11] Corticosteroids are somewhat controversial as they have little efficacy in axial disease and regular use leads to osteopenia, among other problems.[1] TNF-α inhibitors have been essentially the only option for

patients with refractory disease. Although disease-modifying antirheumatic drugs (DMARDs) like methotrexate and sulfasalazine are sometimes prescribed, they have not proven to be effective in axial disease and are generally reserved for cases of concomitant and/or transient peripheral disease. Firstline treatment involves high dose NSAIDs with education about nonpharmacologic therapy and the use of TNF-α inhibitors, if refractory. Adjuncts include DMARDs and corticosteroids for peripheral arthritis. Smoking has also been linked to progression of axial disease, so cessation should be encouraged.[11]

Secukinumab is a fully human biologic agent that targets the cytokine IL-17A (IL-17) instead of the longtime target of TNF-α. This alone is potentially important because patients with symptoms refractory to TNF-α inhibitors have been largely without alternatives. Research has shown that IL-17 is normally involved in the elimination of bacterial and fungal pathogens, but dysregulation of this cytokine results in overactivation of the inflammatory process and subsequent disease. This process has been linked to rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, psoriasis, uveitis, and ankylosing spondylitis making IL-17 a prime target of therapy for reducing inflammation and improving symptoms.[12]

OBJECTIVE

The objective of this selective evidence-based medicine (EBM) review is to determine whether or not secukinumab improves self-reported QoL in patients with moderate-to-severe ankylosing spondylitis when taken regularly.

METHODS

This systematic review takes into account the results of three double-blind, randomized, placebo-controlled trials (RCTs). Two of the studies continued past their primary endpoints and safety windows to a total of 5 years. All three trials were found and accessed personally via

PubMed using the search terms 'ankylosing spondylitis' and 'secukinumab.' The articles were published in peer-reviewed journals in the English language between 2013 and 2015. These articles were chosen because of their relevance to the objective and their inclusion of self-reported QoL as a measured outcome. Inclusion criteria for studies in this review were: double-blind RCTs, studies published within the last 10 years, use of secukinumab on patients with AS, and ASQoL as a reported measure. Exclusion criteria were: studies with published systematic reviews and studies not assessing POEMs.

In each of the three studies being reviewed, patients must have been ≥18-years-old and be men or non-pregnant women. In Baeten et al. (2013), patients must also have been ≤65-years-old. In all three studies, the patients must have been diagnosed with AS as defined by the Modified New York Criteria, have a score of ≥4 on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) indicating moderate-to-severe disease, and be experiencing spinal pain ≥4/10cm on the visual analog pain scale.[13,14] Subjects in each study were randomized into groups that would either receive doses of secukinumab or matched placebo. Apart from ASQoL, a number of other outcomes were reported in each study, but will not be discussed, including ASAS20, ASAS40, ASAS5/6, hsCRP, BASDAI, BASFI, SF-36, and MRI Berlin score. Statistics used in these studies include p-value and mean change from baseline. Additional details about the demographics of the reviewed studies can be found below in **Table 1**.

OUTCOMES MEASURED

While many outcomes were reported, the sole focus of this review is on patient-reported QoL. This metric was assessed in each study using the Ankylosing Spondylitis Quality of Life (ASQoL) questionnaire. The questionnaire is comprised of 18 'yes' or 'no' questions pertaining to the patient's degree of symptoms and aspects of life that are affected by AS. Questions ask

Table 1: Demographics & Characteristics of included studies

Study	*Type*	*# Pts*	*Age (yrs)*	*Inclusion criteria*	*Exclusion criteria*	*W/D*	*Interventions*
Baeten, 2013[13]	RCT	60	42.8 ±9.9	• 18-65 y/o with moderate-to-severe AS defined by Modified New York Criteria and BASDAI score of ≥4, and spinal pain ≥4/10cm on the visual analog pain scale • Taking ≥ 1 NSAID for ≥ 3 months at max dose with inadequate response • No evidence of liver disease or injuries on LFTs	• Patients on prior TNF-α blockers or immunosuppressants other than MTX, SSZ, and systemic corticosteroids must have a 1-month washout period prior to baseline • MTX, SSZ, and/or NSAIDs must be at a stable dose ≥4 weeks prior to baseline and throughout the study and cannot exceed 10mg/day for steroids or 25mg/day for MTX • Positive HIV, HBV, or HCV test results • Any evidence of active systemic infection within the past 2 weeks including positive chest X-ray • Current S/Sx of other specified diseases	5	Secukinumab 10 or 1 or 0.1 mg/kg IV given on days 2 and 22
Baeten, 2015[14]	RCT	371	41.8 ±12.4	• ≥18 y/o with moderate-to-severe AS defined by Modified New York Criteria and BASDAI score of ≥4, spinal pain ≥4/10cm on the visual analog pain scale • ≤ 1 TNF-α inhibitor or NSAIDs with inadequate response • Must be at a stable dose of NSAID	• Pregnant or lactating females • Total ankylosis of the spine • CXR demonstrating infection or malignancy • Prior treatment with any biologic immune modulating agent except those that target TNF-α • Prior treatment with cell-depleting therapies	13	Secukinumab 10 mg/kg IV q2weeks x3 followed by either 75mg or 150mg SC q4weeks
Baeten, 2015[14]	RCT	219	43.3 ±12.9			11	Secukinumab 75 mg or 150 mg SC weekly for 4 weeks, then every 4 weeks thereafter

about pain, stiffness, fatigue, depression, and functionality in simple ways that allow the questionnaire to quickly assess the patient's perceived QoL. Each affirmative response is given a value of 1, and the assessment is scored on a scale of 0 to 18 with higher scores indicating a lower QoL. The ASQoL has previously proven to have high test-retest reliability and congruence with more complex assessments.[15]

RESULTS

Baeten et al. (2013) was a proof-of-concept RCT conducted in two parts that included a small number of subjects (n=60). The article itself only discusses the results of the first half of the study, which included 30 subjects, but the results of their complete study are available in the supplement allowing analysis of the complete study. The study was conducted over a period of 28 weeks and subjects were randomized into 4 groups placing 30 subjects in the 10 mg/kg group, 12 subjects in each of the 1.0 mg/kg and 0.1 mg/kg groups, and 6 subjects in the placebo group. The study recorded ASQoL at four separate time points, once at baseline and again at day 29, week 12, and week 28. The results showed that the 10 mg/kg and 1.0 mg/kg groups experienced clinically relevant improvements in QoL, which will be defined as a reduction in ASQoL of ≥2, at day 29 and week 12. This is an important result because the final dose of secukinumab was given on day 22, which indicates that the medication has a lasting effect, and as it wears off, symptoms once again worsen and QoL declines. In comparison, the 0.1 mg/kg dose and placebo did not produce a clinically relevant improvement in QoL at any point in the study.[16] **(Table 2)** Adverse events were common and occurred in 87% of subjects on secukinumab and 100% of subjects on placebo. The most common complaints among secukinumab users were headache (20.4%), diarrhea (16.7%), and nasopharyngitis (16.7%). Serious events occurred in 3 subjects and included a subcutaneous abscess and anaphylactic reaction in patients on secukinumab, and

elevated blood pressure in a patient on placebo.[17]

Table 2: Average ASQoL at baseline and mean change from baseline at different time points for each dose of secukinumab with (standard deviation). Clinically relevant reductions presented in bold.

	10 mg/kg	*1.0 mg/kg*	*0.1 mg/kg*	*Placebo*
Baseline	12.1 (3.49)	14.8 (3.33)	8.3 (3.32)	10.3 (5.57)
Day 29	**-3.2 (3.78)**	**-3.1 (2.63)**	-0.7 (2.26)	-0.7 (2.58)
Week 12	**-2.7 (2.91)**	**-2.7 (4.71)**	-1.3 (3.16)	0.0 (1.00)
Week 28	-1.4 (3.37)	-1.3 (3.66)	-0.9 (2.15)	-1.3 (2.06)

The Measure 1 study was much larger in scale (n=371) and assessed the efficacy of 150 mg and 75 mg subcutaneous secukinumab after receiving IV loading doses. The study ran for 16 weeks to its primary endpoint, at which time the placebo group was divided into two groups by prior response to TNF-α inhibitor treatment. Non-responders started one of the two subcutaneous doses of secukinumab, while responders continued placebo until week 24, at which point they too began secukinumab therapy. Mean change from baseline of ASQoL was reported at weeks 16 and 52; however, no baseline ASQoL values were provided. The study ran for two years with a three-year extension study. At both assessments, subjects being treated with secukinumab experienced clinically relevant improvements in self-reported QoL, while subjects on placebo did not. Based on mean change from baseline in ASQoL, there was little difference in efficacy between the two dosing regimens. **(Table 3)** No p-value was noted for week 52 due to absence of a placebo group. During the 16-week placebo-controlled phase, 68% of patients taking secukinumab experienced adverse events compared to 56% on placebo. The most common adverse events were nasopharyngitis (12%), dyslipidemia (10%), and headache (8%). Incidence of infection was also higher in the secukinumab group (30%) compared to placebo (12).[14,18]

Table 3: Mean change from baseline in ASQoL. Clinically relevant reductions presented in bold. († = $p < 0.001$)

	150 mg	*75 mg*	*Placebo*
Week 16	**-3.58†**	**-3.61†**	-1.04
Week 52	**-4.68**	**-4.49**	N/A

The Measure 2 study was conducted alongside Measure 1 and was of similar scale (n=219). The purpose of this study was to evaluate the efficacy of secukinumab 150 mg or 75 mg subcutaneously with weekly SC loading doses instead of IV. Measure 2 also ran for 16 weeks to its primary endpoint, and as with Measure 1, the placebo group was then divided into the two treatment arms. The treatment groups then continued to receive secukinumab at the assigned dose every 4 weeks up to the end of the 5-year study; however, data was only available for review up to week 52. Results from the study showed that both doses were capable of producing a significant improvement in the ASQoL compared to placebo with the 150 mg dose appearing to be consistently more effective. The incidence of adverse events was nearly equal in the treatment (61%) and placebo groups (64%); however, the incidence of infection was again higher in the treatment arm (32% vs. 27%). Nasopharyngitis (10%), headache (8%), and nausea (3%) were among the most common complaints.[14,18] **(Table 4)**

Table 4: Mean change from baseline in ASQoL. Clinically relevant reductions presented in bold. (‡ = p <0.01)

	150 mg	*75 mg*	*Placebo*
Week 16	**-4.00‡**	**-3.33**	-1.37
Week 52	**-5.23**	**-4.13**	N/A

DISCUSSION

The most significant result is that every tested regimen of secukinumab, except 0.1 mg/kg IV, was effective in improving patient QoL compared to placebo. Another important finding was that the incidence of infection was higher in subjects treated with secukinumab compared to placebo in all three RCTs. One important difference between Baeten et al. (2013) and Measure 1 and 2 was that in the latter two studies, the researchers sought out patients that had an inadequate response to TNF-α inhibitors. Comparing these two studies and secukinumab against phase 3 trials of TNF-α inhibitors showed similar response rates; however, because 30-

40% of the patients in Measure 1 and Measure 2 had previously been on TNF-α inhibitors, secukinumab may have an indication in AS patients that have failed prior TNF-α therapy.[14]

Secukinumab was initially approved by the FDA in 2015 with the indication of moderate-to-severe plaque psoriasis and the tradename Cosentyx®. In 2016, after the results of these studies had been published, the FDA added AS as an indication for use. At that same time, the medication was also approved for use in psoriatic arthritis. The two approved regimens for treating AS only vary by the presence of a 4-week loading dose period as in Measure 2. If giving the loading dose, patients receive 150 mg SC weekly for the first 4 weeks and one dose every 4 weeks thereafter. If no loading dose is being given, patients only receive 150 mg SC every 4 weeks.[19]

Secukinumab currently does not have any black box warnings, and the only absolute contraindication is in patients that have experienced a hypersensitivity reaction to secukinumab or one of its components. However, several other precautions must be taken when prescribing this medication. As observed in the trials, secukinumab increases the risk of infection and should be used with caution in patients with recurrent or chronic infections. If patients do develop a serious infection while being treated, secukinumab should be discontinued until resolution of the infection. As is standard with many immunosuppressant agents, patients should be tested for TB prior to initiation of treatment and treatment should not be started in active cases of TB. Due to the immunosuppressive mechanism, candidates for secukinumab should be updated on all vaccines prior to treatment. If vaccinating during treatment, non-live vaccines may not be effective, and live vaccines should be avoided. There is also some concern that secukinumab may induce or exacerbate IBD, and patients should be made aware that they may develop this condition or have worsening of their flares.[20]

Except for the Baeten et al. (2013), the RCTs evaluated in this review were of good quality in that they were conducted over long periods of time with a large number of subjects. A significant limitation of this review is that patient QoL was not assessed as a primary endpoint in any study and was inadequately reported given the overall length of these studies. Measure 1 and 2 were each conducted for a total of 260 weeks, but the last reported value for change in baseline ASQoL was at week 52. Additionally, statistics to indicate the significance of the change in ASQoL, such as p-value, NNT, and NNH, were either reported inconsistently or not at all.

CONCLUSION

The question posed by this review has been answered in the affirmative, and secukinumab when taken regularly has proven to increase self-reported QoL in AS patients with moderate-to-severe disease. These studies assessed a number of metrics, but changes in ASQoL could have been better reported to give a more precise understanding of the findings. More frequent reporting of change from baseline in ASQoL throughout the duration of the study along with statistics to support the data should be a goal of future studies. An important result from Measure 1 and Measure 2 was that secukinumab may be effective in improving QoL in patients that had previously failed TNF-α therapy. A study directly comparing secukinumab and TNF-α inhibitors would be helpful in determining which is more effective, and a study doing so has recently started. Novartis Pharmaceuticals announced the SURPASS study in January of 2018, which is a 1-year RCT comparing two doses of secukinumab against adalimumab in AS patients. However, the endpoints of this study are related to radiographic evidence of spinal disease progression, inflammation, and syndesmophyte formation. Unfortunately, they will not be evaluating patient-reported QoL in this study.[21] Hopefully a future study will assess this metric.

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