Prompt Clinical Response to Secukinumab in Patients with Axial Spondyloarthritis: Real Life Observational Data from Three Italian Referral Centers

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ABSTRACT: **Background:** Clinical research is needed to identify patients with axial spondyloarthritis (axSpA) who are more likely to be responsive to interleukin (IL)-17 inhibition.

Objectives: To evaluate short-term efficacy of secukinumab in the management of axSpA.

Method: Twenty-one patients (7 males, 14 females) with axSpA were consecutively treated with secukinumab. Laboratory and clinical assessments were based on erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI). Data were recorded at baseline and at a 3 month follow-up visit.

Results: The study was comprised of 21 patients. Both BASDAI and ASDAS-CRP showed a statistically significant reduction between the baseline and the 3 month visit ($P < 0.0001$ and $P = 0.0005$, respectively). During the laboratory assessment, ESR showed a significant decrease ($P = 0.008$) while CRP improvement did not reach statistical significance ($P = 0.213$). No statistical significance was observed between patients treated with secukinumab 150 mg vs. 300 mg in BASDAI ($P = 0.99$), ASDAS-CRP ($P = 0.69$), ESR ($P = 0.54$), and CRP ($P = 0.56$). No significant differences emerged between the BASDAI ($P = 0.15$), ASDAS-CRP ($P = 0.09$), and CRP ($P = 0.15$) rates in biologic-naïve patients and those previously failing tumor necrosis factor-α inhibition. Conversely, ESR decrease was significantly higher in the biologic-naïve subgroup ($P = 0.01$). No adverse events were reported.

Conclusions: Secukinumab has proven remarkable short-term effectiveness, regardless of the biologic treatment line. A dosage of 150 mg proved to be appropriate in the clinical and laboratory management of axSpA.

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KEY WORDS: axial spondyloarthritis (axSpA), interleukin (IL)-17, secukinumab, seronegative arthritis

Axial spondyloarthritis (axSpA) is an inflammatory rheumatic disease that usually manifests with chronic low back pain and considerable stiffness, which tends to improve with exercise [1]. A complex spectrum of other musculoskeletal and extra-articular manifestations is often associated with axSpA, including inflammatory bowel disease (IBD), psoriasis, anterior uveitis, and increased cardiovascular risk [2,3]. In the past decades, patients with axSpA were exclusively identified and classified according to the radiographic assessment of sacroiliac joints [4]. However, the introduction of magnetic resonance imaging has allowed for early detection of inflammation in the sacroiliac joints, which precedes the radiographic damage. This finding has brought about the distinction between radiographic and non-radiographic axSpA, which is differentiated by the presence or absence of structural changes suggestive of sacroiliitis at conventional radiology [5,6].

Regarding therapeutic aspects, treatment with non-steroidal anti-inflammatory drugs (NSAIDs) are often effective, but not always suitable for long-term management [7]. In this context, the introduction of tumor necrosis factor (TNF)-α inhibitors has radically changed the management and outcome of axSpA during the last 2 decades [8-11]. More recently, new insights on the role of interleukin (IL)-17 as a pathogenic proinflammatory cytokine in patients with axSpA [12-14] have paved the way to IL-17 blockade as a further treatment option that has been approved for this condition [7]. Specifically, in the MEASURE1 (NCT01358175) and MEASURE2 (NCT01649375) trials, the fully human anti-IL-17A monoclonal antibody secukinumab proved to be significantly effective in improving clinical signs of ankylosing spondylitis (AS) both in anti-TNF-α naïve patients and in subjects failing a previous TNF-α inhibition [15,16]. Accordingly, a recent extension of the MEASURE1 trial confirmed the efficacy and safety of secukinumab after one additional year of treatment [17].

*The first and second authors contributed equally to this study

Despite the good clinical results described here, data on secukinumab in axSpA are still scarce, and further studies are required to better establish the impact on co-morbidities and the subgroup of patients more likely responsive to IL-17 inhibition. Therefore, we report our experience from the real-life of patients affected by axSpA, focusing on the short-term effectiveness of secukinumab according to the different clinical features and the dosage prescribed.

PATIENTS AND METHODS

We enrolled patients diagnosed with axSpA and with secukinumab in three Italian referral centers (Siena, Bari, Florence). Diagnosis of axSpA was performed according to the Assessment in SpondyloArthritis international Society (ASAS) criteria [18].

At the beginning of the treatment, an induction scheme was started according to the therapeutic schedule. In particular, secukinumab 150 mg weekly for the first five injections and then a maintenance dose of 150 mg monthly were administered subcutaneously. Conversely, secukinumab 300 mg was prescribed in place of secukinumab 150 mg in patients presenting psoriasis as co-morbidity.

Patients underwent secukinumab treatment as a first-line biologic treatment or after a lack or loss of efficacy to previous anti-TNF-α agents. Before starting treatment, a full serological and instrumental screening was performed to rule out active infectious diseases. Patients presenting with latent tuberculosis underwent a complete 6 month prophylaxis regimen with isoniazid (400 mg/day).

Laboratory and clinical evaluation of patients was performed at the start of secukinumab treatment and after 3 months. Laboratory assessment included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Clinical evaluation was performed by using both Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI).

The primary aim of this study was to evaluate short-term efficacy of secukinumab in the management of axSpA. Secondary aims were to identify differences in the clinical and laboratory assessment according to the dosage administered, to report any difference between biologic-naïve patients and subjects previously treated with TNF-α inhibitors, and to describe the rate of adverse events occurred in patients enrolled.

The primary endpoints were represented by a statistically significant reduction of ASDAS and BASDAI indexes and a statistically significant reduction of inflammatory markers (ESR, CRP) at the 3 month follow-up visit compared to baseline. Secondary endpoints were represented by a statistically significant difference in the reduction of clinometric indexes and inflammatory markers between patients undergoing secukinumab 150 mg and those treated with secukinumab 300 mg, a statistically significant difference in the reduction of clinometric indexes and inflammatory markers between biologic-naïve patients and subjects previously treated with TNF-α inhibitors, and the frequency of adverse events occurring during the treatment. The study was approved by the local ethics committee of Azienda Ospedaliera Universitaria Senese, AOUS (Siena, Italy).

Mean ± standard deviation (SD), median, and ranges are reported as descriptive statistics. Paired *t*-test or Wilcoxon matched-pairs signed rank test (as appropriate) were used to evaluate BASDAI and ASDAS decrease between the baseline and the 3 month follow-up visit. Unpaired comparisons were performed using the unpaired *t*-test or the Mann–Whitney U test, as appropriate, after having assessed data distribution with the Anderson-Darling test. Significance was defined as $P < 0.05$. Graphpad Prism 6.0 software (GraphPad Software, Inc., California, USA) was used for statistical computations.

RESULTS

The study comprised 21 consecutive patients (7 males, 14 females) affected by axSpA treated with secukinumab. Their demographic and clinical data are summarized in Table 1.

Six patients (28.6%) were administered with secukinumab as a first-line biologic agent, while the other 15 subjects (71.4%) had previously experienced a failure with one (n=6, 28.6%), two (n=5, 23.8%), or three (n=4, 19.1%) TNF-α inhibitors.

The mean ± SD BASDAI score was 5.59 ± 1.62 at the start of treatment and 3.72 ± 1.86 at the 3 month follow-up visit. The

Table 1. Demographic and clinical data combined with therapeutic features of patients with axial spondyloarthritis enrolled in our evaluation

Demographic features	Mean ± SD
Age, years	56.57 ± 9.62
Disease duration, years	12.47 ± 11.53
Gender, female/male	14/7
Clinical features	
HLA B27 +	3/6* (50%)
Radiographic SpA	14/21 (66.7%)
Peripheral involvement	16/21 (76.2%)
Psoriasis	12/21 (57.1%)
Gastrointestinal tract involvement	0/21 (0%)
Ocular involvement	2/21 (9.5%)
PPD Test +	4/21 (19.1%)
QFT +	3/21 (14.3%)
Therapeutic features	
Previous anti-TNF failure	15/21 (71.4%)
Use of concomitant glucocorticoids	6/21 (28.6%)
Use of concomitant DMARDs	9/21 (42.9%)
Secukinumab 150/mg/injection	10/21 (47.6%)
Secukinumab 300/mg/injection	11/21 (52.4%)

*HLA B27 testing was referred only to patients affected by ankylosing spondylitis (n=9); in 3 out of 9 cases HLA B testing had not been performed

HLA = human leukocyte antigen, PPD = purified protein derivative, QFT = quantiFERON-TB, SD = standard deviation, SpA = spondyloarthritis, TNF = tumor necrosis factor

mean ± SD ASDAS-CRP values were 3.24 ± 0.99 at the start of treatment and 2.17 ± 0.90 at the 3 month follow-up visit. Both BASDAI and ASDAS-CRP values showed a statistically significant reduction between the start of secukinumab and at the 3 month follow-up visit ($P < 0.0001$ and $P = 0.0005$, respectively).

The mean ± SD ESR levels were 32.95 ± 32.04 mm/h at the start of treatment and 21.29 ± 18.82 mm/h at the 3 month follow-up visit, thus showing a statistically significant difference ($P = 0.008$). The mean ± SD CRP values were 2.42 ± 3.53 mg/dl at the start of treatment and 1.32 ± 1.98 mg/dl at the 3 month follow-up visit, with no significant reduction ($P = 0.213$).

Eleven of 21 patients (52.38%) underwent secukinumab at the dosage of 300 mg per administration because of the concomitant presence of psoriasis. Ten of 21 patients (47.62%) underwent the standard secukinumab dosage used for axSpA (150 mg per administration). No statistically significant differences were observed in BASDAI and ASDAS-CRP variations between the subgroup undergoing the standard secukinumab dosage and subjects administered with secukinumab 300 mg ($P = 0.99$ and $P = 0.69$, respectively). Similarly, no differences were observed for ESR and CRP variations in the same subgroups analysis ($P = 0.54$ and $P = 0.56$, respectively).

Regarding the line of treatment, no significant differences emerged when comparing BASDAI, ASDAS, and CRP variations between biologic-naïve patients and subjects previously treated with TNF-α inhibitors ($P = 0.15$, $P = 0.09$, and $P = 0.15$, respectively). Conversely, ESR decrease was significantly higher in the biologic-naïve subgroup ($P = 0.01$).

With regard to safety, no adverse events were reported during the period of observation. No infectious disease or tuberculosis reactivations were observed in our cohort, which included three patients with latent tuberculosis who were receiving isoniazid prophylaxis.

DISCUSSION

Currently, TNF-α and IL-17 inhibitors are the only biologic agents approved for treatment of axSpA. However, while plenty of data are available on the efficacy, safety, and long-term management of TNF-α inhibition, information about IL-17 blockade is still fairly limited [15-17,19]. In this regard, the present study has been conducted to provide more information on the therapeutic role of the anti-IL-17 agent secukinumab in patients with active axSpA. In particular, we assessed the short-term effectiveness of secukinumab in a real-life context and specifically investigated differences in the clinical or laboratory response according to dosages used and distinguishing between biologic-naïve and biologic-exposed patients.

According to our results, secukinumab led to a significant decrease of both ASDAS-CRP and BASDAI indexes within 3 months of therapy. Similarly, among laboratory markers, ESR average levels were significantly reduced at the 3 month follow-up compared to baseline, while CRP values were almost halved without reaching a statistical significance. All together, these findings highlight a prompt efficacy of secukinumab on both clinical and laboratory manifestations of axSpA. In addition, the statistically significant reduction of ASDAS-CRP, despite the inferior results obtained with CRP, underline a remarkable effect of secukinumab on axSpA symptoms.

Of note, in our study no significant differences emerged in the clinical and laboratory response to secukinumab between patients who were previously prescribed with TNF-α inhibitors and biologic-naïve subjects. These findings match the results obtained from the MEASURE1 and MEASURE2 trials in patients with axSpA, in whom secukinumab was effective in both biologic-naïve subjects and in patients formerly exposed to anti-TNF-α agents [15,16]. This issue is interesting because up to 40% of axSpA patients treated with TNF-α inhibitors may experience primary or secondary inefficacy or intolerance, or may present contraindications requiring a different treatment approach [20]. In this context, IL-17 inhibition with secukinumab proved to be effective in axSpA regardless of the biologic treatment line.

Concerning the most useful secukinumab dosage, the results shown in the MEASURE2 trial with 75 and 150 mg every 4 weeks confirmed the latter posology as appropriate in patients with axSpA [16]. This finding was later confirmed in the MEASURE1 extension after one additional year of treatment [17]. We have also statistically assessed all laboratory and clinical differences between patients undergoing secukinumab 150 mg and those treated with 300 mg according to the therapeutic schedule, but no significant differences were identified. This result suggests that no additional benefit is obtained by doubling the standard secukinumab dosage in patients treated for axSpA.

Regarding the safety profile, no adverse events or infectious diseases have been recorded during the study period. In particular, no episodes of candidiasis have been observed in spite of the relatively frequent description of *Candida* infections after secukinumab treatment, due to the protective role of IL-17 on the mucosae [21,22]. This result is probably due to the short period of observation and to the small sample size. However, in previous studies, secukinumab has generally proven to have a good safety profile, with diarrhea, headache, nasopharyngitis, and other upper respiratory tract infections being the most common adverse events reported [15,21].

This study has some limitations including the absence of a control group, the small sample size, and the lack of data on the evolution of psoriasis after secukinumab treatment. However, to the best of our knowledge, this is the first study based on real-life data assessing the short-term efficacy of secukinumab in axSpA along with the role of previously administered biologic treatments and different secukinumab dosages on clinical and laboratory outcomes.

CONCLUSIONS

Secukinumab has shown remarkable short-term efficacy with no safety concerns in both biologic-naïve subjects and patients previously treated with TNF-α blockers. In addition, secukinumab 150 mg administered according to the current therapeutic schedule has been found to be appropriate in axSpA.

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Capsule

Changes in physical activity after total hip or knee arthroplasty: a systematic review and meta-analysis of 6- and 12-month outcomes

Little is known about the extent to which physical activity levels change following total knee or hip joint replacement relative to pain, physical function, and quality of life. **Hammett** and co-authors aimed to conduct a systematic review and meta-analysis on changes in physical activity relative to pain, quality of life, and physical function after total knee or hip joint replacement. Seven studies (336 participants) met the eligibility criteria. No significant increase in physical activity was found at 6 months (SMD 0.14, 95% confidence interval [95%CI] 0.05–0.34; I^2 = 0%) and a small to moderately significant effect was found for increasing physical activity at 12 months (SMD 0.43, 95%CI 0.22–0.64, I^2 = 0%). Large improvements were found at 6 months in physical function (SMD 0.97, 95%CI 0.12–1.82, I^2 = 92.3%), pain (SMD -1.47, 95%CI -2.28 to -0.65, I^2 = 91.6%), and quality of life (SMD 1.02, 95%CI 0.30–1.74, I^2 = 83.2%). The authors concluded that physical activity did not change at 6 months, and a small to moderate improvement was found at 12 months post-surgery, despite large improvements in quality of life, pain, and physical function. The reasons for the lack of increased physical activity are unknown but may be behavioral in nature, as a sedentary lifestyle is difficult to change. Changing sedentary behavior should be a future focus of research in this subgroup.

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