ORIGINAL PAPER

SECUKINUMAB - AN OVERACHIEVER IN REAL-LIFE CLINICAL SETTING

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ABSTRACT

The treat to target approach aims to attain remission or minimal disease activity in patients with spondyloarthritis (SpA) or psoriatic arthritis (PsA). Secukinumab (SEK), an IL-17A inhibitor is of high use in anti-TNF fails or as first-line therapy when skin involvement is dominant. Primary outcome of the study was to evaluate response to SEK in bDMARD naïve and non-naïve AS and PsA patients in a real-world cohort. Secondary outcomes were SEK mean retention rate, adverse events occurrence. A single-center observational, retrospective study was performed in AS and PsA patients started or switched on SEK, with a minimum follow-up period of six months. Outcome measures (BASDAI, ASDAS, inflammatory markers) were recorded at baseline and at the last follow-up visit. Statistical analysis used SPSS 20.0. Forty patients were included in the study, two discontinued treatment. Out of the 38 remaining patients, 9 had PsA and 29 SpA, mean age 54.6 and 49.75 respectively, with a slight male predominance (57.8% versus 42.1%). Mean disease duration was 108.4 months. 14 patients were started directly on SEK 150mg, while 24 were switched from a previous anti-TNF, ranging from one to five agents (12 non-responders, 12 adverse reactions). Patients with PsA required a more frequent switch on SEK than patients with SpA. A drastic decrease in BASDAI score was observed in patients after they were started on SEK, from a mean value of 6.38 to 1.78, indicating an inactive disease at follow-up ($p<0.0001$). ASDAS-CRP decreased from a mean 4.12 to 1.67, classifying patients as having inactive to moderate disease ($p<0.0001$). In the PsA group the DAPSA score decreased with a mean of 26.1 points ($p<0.0001$) from 35.2 to 9.1 ($p<0.0001$). Likewise, C-reactive protein significantly decreased with a mean of 26 mg/dl at follow-up. While there was no significant difference in BASDAI, the ASDAS-CRP mean difference confirmed benefit in patients who were first started on SEK compared to those with previous bDMARDs (-3.12 vs -2.21) $p=0.08$. Mean retention rate for SpA patients was 23.5 months, while for PsA patients it was 16.2 months ($p=0.019$). SEK survival rate was higher in patients with prior anti-TNF alpha therapy when compared to naïve-patients, with a value of 23.3 months versus 18.9, p 0. 034.There was no difference in SEK drug survival as monotherapy versus combination with csDMARD (p 0.28). SEK was effective in lowering disease activity as proven by a reduction in clinical parameters and inflammatory markers showing prompt effect of the anti-IL17 agent.

KEYWORDS: *spondyloarthritis, psoriatic arthritis, secukinumab, anti-IL17, enthesitis, uveitis, cancer*

INTRODUCTION

Spondyloarthritidis are a group of conditions with similar pathogenic and clinical features as well as therapeutic options [1]. Among others, it encompasses ankylosing spondylitis (AS) that leads to inflammation and structural damage of axial structures such as the spine and the sacroiliac joints and psoriatic arthritis (PsA), usually accompanied by skin involvement and various articular patterns. Both conditions can add enthesitis, dactylitis or eye involvement [2].

Managing patients with spondyloarthritis (SpA) or psoriatic arthritis (PsA) was once an intriguing challenge in times when only non-steroidal (NSAIDs) were within reach [3]. According to latest recommendations, the concept of treatment in SpA has a treat-to-target approach, aiming to attain remission or minimal disease activity [4]. Response to treatment is evaluated using disease activity scores like Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or Ankylosing Spondylitis Disease Activity Score [5] (ASDAS) for SpA and Disease Activity in Psoriatic Arthritis (DAPSA) for PsA [6].

The 2016 Assessment of SpondyloArthritis International Society/ European League Against Rheumatism (ASAS/EULAR) update in the management of SpA patients represents a cornerstone in treatment guidelines, since this was the first time that another class of biologic drug-modifying anti-rheumatic drugs (DMARDs) was included as an option, namely the anti-interleukin17[5] (IL-17). A different mode of action by IL-17 pathway inhibition, with secukinumab being the class representative, proved efficacious and safe in patients with axial SpA and becoming an option in non-responders to anti-tumor necrosis factor (TNFs) [7].

The latest EULAR recommendations for the management of PsA issued in May 2020 have specifically pointed out the role of secukinumab in these patients [8]. Thus, in patients with peripheral arthritis who fail conventional synthetic DMARDs, an IL-17 inhibitor is preferred if skin involvement is relevant. The same recommendation is indicated in patients with active axial disease who add significant skin involvement. Another essential point in PsA guidelines brings into consideration patients with enthesitis that respond insufficiently to NSAIDs or local glucocorticoid injections. The updated protocol allows using all biologic DMARDs (TNF, IL-17 and IL12/23 inhibitors) since they were proven to have the same efficacy for enthesitis [8].

Both genetic and animal models suggested a potential role of IL-23/IL-17 axis in the pathogenesis of SpA, other than its confirmed contribution in Crohn's disease and psoriasis [9]. High serum and synovial fluid levels of IL-17 and IL-23 in SpA patients correlated to a highly active and more severe disease [10]. The presence of predisposing genes like human leukocyte factor (HLA) B27 can play a part in overstimulating the innate immunity leading to IL-23 production and an increased IL-17 production [11].

Secukinumab (SEK) is a human monoclonal antibody that selectively links and neutralizes IL-17A, thus inhibiting its interaction with the IL-17 receptor which is expressed in a variety of cells. As a result, SEK inhibits the action of proinflammatory cytokines and tissue damage mediators with benefits in SpA and PsA [12], [13]. European Medicines Agency (EMA) reviewed and authorized SEK in 2015 and Food and Drug Administration (FDA) approved the use of SEK in AS and PsA in January 2016[14], [15], [16]. SEK is the first IL-17 inhibitor that proved efficacy in both SpA and PsA in multiple randomized controlled trials [17].

The aim of the present study is to evaluate the efficacy and safety of secukinumab in a real-world cohort of AS and PsA patients treated in a secondary-care Rheumatology Department.

MATERIALS AND METHOD

A single-center retrospective study was performed in AS and PsA patients who were either started on or switched on SEK, with a minimum follow-up period of six months. Data

was pooled from local registries and physician charts. Common clinical (history of dactylitis, enthesitis or uveitis, the presence of HLA B27 antigen) and demographic data was analyzed. Previous therapies, concomitant synthetic conventional DMARD, namely sulfasalazine (SSZ) or methotrexate (MTX) was noted and reasons of switch were investigated in non-naïve bDMARD patients with AS and PsA. Patients who were discontinued from SEK were debated as individual cases.

Primary outcome of the study was to evaluate response to SEK in bDMARD naïve and non-naïve patients in both AS and PsA. In order to assess patient response to SEK, outcome measures were recorded at baseline and at the last follow-up visit. Outcome measures included disease activity scores like BASDAI and ASDAS in SpA patients and DAPSA in the PsA group, together with inflammation markers like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Secondary outcomes were SEK mean retention rate, adverse events occurrence.

The statistical analysis was performed using the SPSS statistical software, version 20.0, with a standardized significant p value of less than 0.05 and 0.01. Data was expressed as mean value ± standard deviation (SD). Differences between outcome measures were recorded with the aid of t-test and Chi-test, while Bland-Altman statistics aimed to observe mean score differences as per treatment algorithm by using a case-to-case analysis. Kaplan-Meier curves were used to assess treatment retention rate.

RESULTS

Forty patients were included in the study, out of which two patients were discontinued as further discussed. Out of the 38 remaining patients, 9 had PsA and 29 were diagnosed with SpA with a mean age of 54.6 and 49.75 respectively, with no significant difference between groups. 42.1% patients in the study group were females while 57.8% were males. Mean disease duration was 108.4 months.

From the patient total, 14 were started directly on SEK 150mg (9 with SpA, 5 with PsA), while 24 were switched from a previous anti-TNF (20 SpA and 4 PsA), ranging from one to five agents, as seen in Table 1. One patient was a primary non-responder, 11 were secondary non-responders and 12 suffered from adverse reactions that imposed switching the biologic. Reported adverse events were anti-TNF induced lupus, psoriasis, tuberculosis, allergic reactions and a case of uveitis to etanercept, as seen in Figure 1.

1st bDMARD	No. of patients
Adalimumab	4
Etanercept	3
Infliximab	2
Golimumab	3
Certolizumab	0

Table 1 – Previous bDMARDs (original/ biosimilar) received by patients prior to initiation of secukinumab as second-line therapy

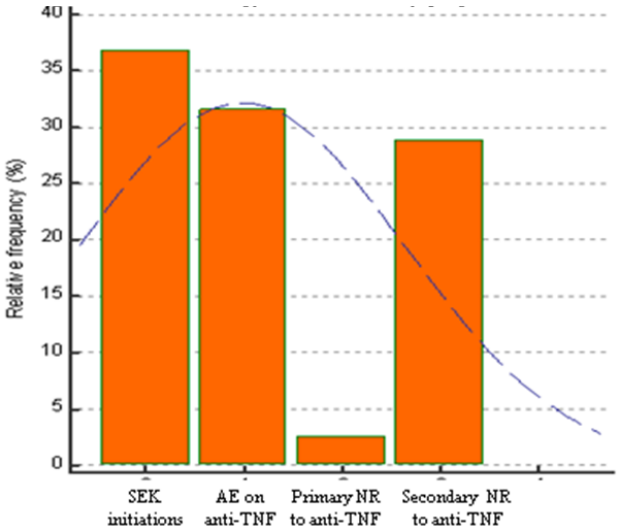

Figure 1 – Distribution of secukinumab initiation and anti-TNF failures in the study cohort

The rest of six patients had more than two anti-TNF agents, ranging from three to five, before switching to the anti-IL17 mechanism (Table 2).

The treatment history in the study group is briefly summarized in Figure 2.

According to the Chi-square test, the reason to switch patients on SEK was not related to the type of disease, either SpA or PsA (p=0.24). However, it seems that patients with PsA required a more frequent switch on SEK than patients with SpA.

1st bDMARD	No. of patients	2nd bDMARD	No. of patients
Adalimumab	1	Adalimumab	2
Etanercept	4	Etanercept	2
Infliximab	0	Infliximab	0
Golimumab	1	Golimumab	1
Certolizumab	0	Certolizumab	1

Table 2 – Previous bDMARDs (original/ biosimilar) received by patients prior to initiation of secukinumab as third-line therapy

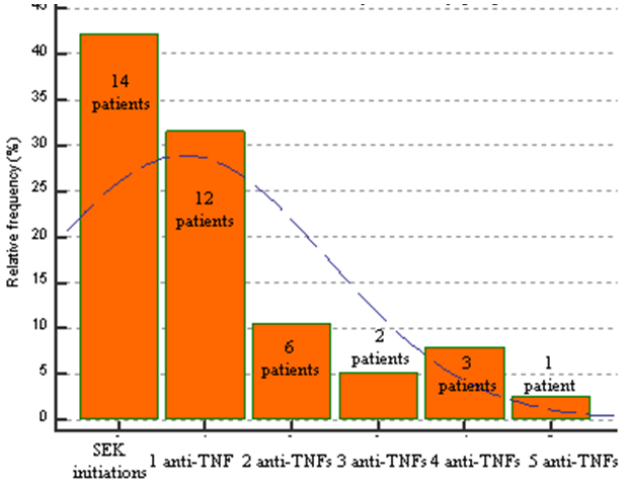

Figure 2 – Biological treatment history in the study cohort

60.5% of patients had confirmed enthesitis with imaging methods like plain x-ray, ultrasound or magnetic resonance imaging (MRI) and 18.4% had dactylitis. Concerning eye involvement, 15.7% had at least one episode of anterior uveitis. The presence of HLA B27 was noted in two-thirds of patients (65.7%). No patient in the study group was reported as having signs or confirmed inflammatory bowel disease.

When analyzing primary outcome measures, a drastic decrease in BASDAI score was observed in patients after they were started on SEK, from a mean value of 6.38 to 1.78, classifying them as having an inactive disease at follow-up (p<0.0001), Figure 3. A case-by-case analysis was performed in order to obtain a correlation index, showing that BASDAI values before and after treatment do not correlate (p 0.41, r 0.15). This result indicates that a certain subtype of SpA patients in the study group respond better to SEK than others.

Similar evaluation was made for the ASDAS-CRP score, with a marked decrease of mean values, from 4.12 to 1.67, classifying patients as having inactive to moderate disease (p<0.0001). However, when fulfilling the case-to-case analysis we observe there is no correlation between ASDAS-CRP scores at baseline and at follow-up (p 0.52, r 0.12), indicating that for a subset of patients SEK treatment has greater efficacy (Figure 4).

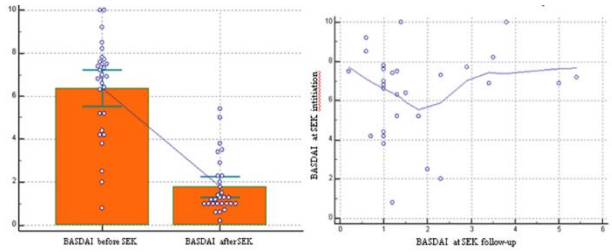

Figure 3 – BASDAI score variation in the study group. Mean BASDAI before and after Secukinumab initiation (a). Variation of BASDAI on case-to-case analysis

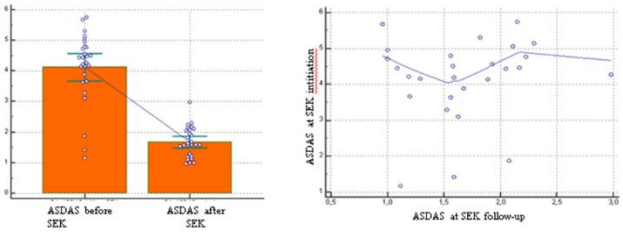

Figure 4 – ASDAS-CRP score variation in the study group. Mean ASDAS-CRP before and after Secukinumab initiation (a). Variation of ASDAS-CRP on case-to-case analysis

In the PsA group the DAPSA score decreased with a mean of 26.1 points (p<0.0001) from 35.2 to 9.1 (p<0.0001), as shown in Figure 5.

Apart from disease activity scores variation, significant differences were noted in inflammatory markers such as ESR and CRP measured at the time of SEK initiation versus moment of last physician evaluation.

Thus, CRP value significantly decreases with a mean of 26 mg/dl at follow-up, almost reaching the normal laboratory reference value (34.46 vs 7.71). Similarly, the ESR value decreases with a mean of 31.94 mm/h, reaching within normal limits (51.34 vs 19.39) (Figure 6).

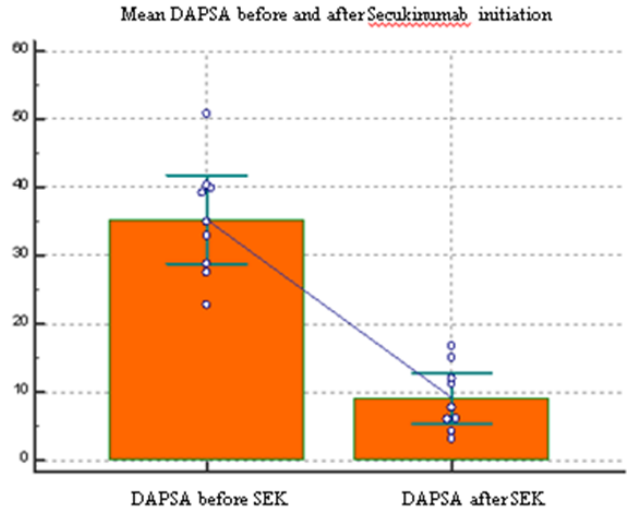

Figure 5 – Mean DAPSA before and after Secukinumab initiation

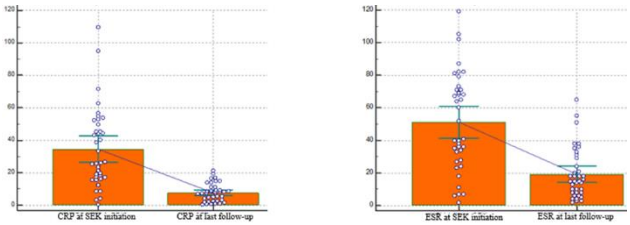

Figure 6 – Inflammatory markers (ESR, CRP) dynamics after SEK initiation in the study group

In order to better analyze patients who are started on SEK versus patients switched to SEK from an anti-TNF, a "before" and "after" difference in mean scores was made. While there was no significant difference in the BASDAI score in SpA patients according to treatment strategy - start on SEK or switch to SEK (-5.38 vs -4.32, p=0.24), as seen in Figure 7, the ASDAS-CRP mean difference confirmed a real benefit in patients who were first started on SEK. ASDAS-CRP score had a more prominent decrease in patients directly initiated on SEK than those with previous bDMARDs (-3.12 vs -2.21, p=0.08).

Nine patients (7 SpA, 2 PsA) in the study group were on combination therapy, having either sulfasalazine or methotrexate added to SEK.

Mean SEK persistence in the entire study group was 21.9 months with the longest treatment interval of 35 months. Mean retention rate for SpA patients was 23.5 months, while for PsA patients it was 16.2 months (p value 0.019). Mean SEK survival rate was higher in patients with prior anti-TNF alpha therapy when compared to naïve-patients, with a value of 23.3 months versus 18.9, p=0.034, as shown in Figure 8.

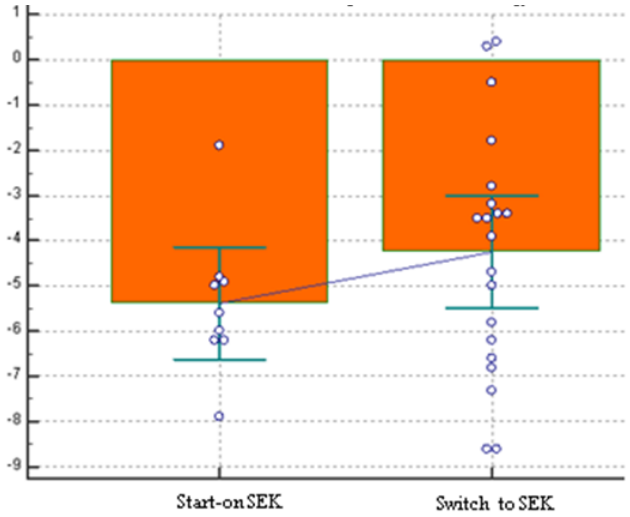

Figure 7 – Mean BASDAI according to treatment strategy (start-on SEK or switch-to SEK)

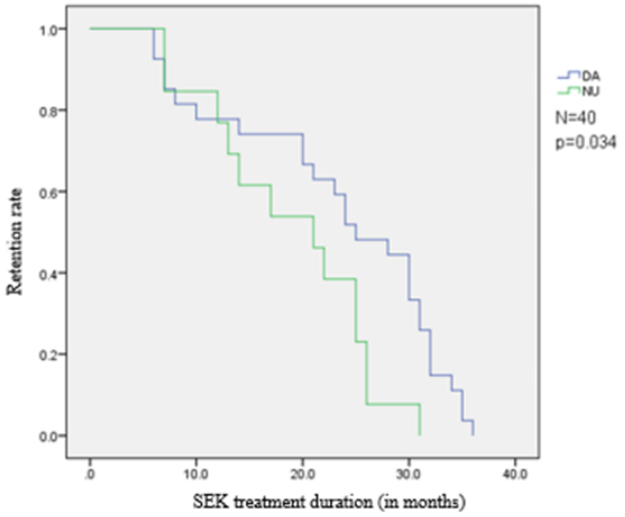

Figure 8 – Secukinumab retention rate in biologic-naive patients versus prior anti-TNF therapy

Statistical analysis showed no difference in SEK drug survival in patients having SEK as monotherapy versus patients having a csDMARD combined with the biologic agent (p 0.28).

There were two reported non-severe adverse events due to SEK in the study group that had no impact on treatment continuation, namely mild infection of the upper respiratory tract in one patient and urinary tract infection in another SpA patient.

Out of the study group, only two patients discontinued treatment, either due to side effects or to lack of response. One case was recorded as a 71-year old male patient with AS, with a history

of recurrent uveitis. Because of uveitis relapse under the first TNF inhibitor he was switched to a second anti-TNF to which the patient had insufficient benefit, maintaining high disease activity scores and developed a basal cell carcinoma. He was switched to Secukinumab to which the patient responded with a 50% decrease in BASDAI and ASDAS scores at three months. Eight months later, while having satisfactory disease activity markers (BASDAI=0.8, ASDAS=2.08) the patient develops an episode of severe panuveitis assigned as side effect to anti-IL17 treatment. Consequently, he was switched to a novel TNF inhibitor.

The second patient who discontinued Secukinumab is a 62-year old male known with AS and cardiac comorbidities. He was first started on infliximab that was withdrawn after three infusions because of psoriatic lesion occurrence. Secukinumab was the second biologic with good response after the first three months, namely a decrease in inflammatory markers and scores. Nine months later, due to a disease flare with BASDAI 7 and ASDAS-CRP 4.71 he was classified as a secondary non-responder and further switched to etanercept.

One of the patients included in the study cohort is a 61-year old female patient with a history of renal cell carcinoma that required nephrectomy who was later diagnosed with AS due to changes in her body scintigraphy while having an Oncology check-up (intense uptake in the spine and sacroiliac joints). With an overlooked diagnosis the patient used to self-administer NSAIDs that caused her a gastric ulcer. Considering the patient's recent cancer history, she was started on Secukinumab a year after remission was confirmed by the oncologists and is currently in her third year of treatment with an inactive AS and no signs of tumor relapse.

DISCUSSION

In this retrospective, observational, single-center study in SpA and PsA patients, SEK was effective in lowering disease activity as proven by a reduction in all clinical parameters analyzed and inflammatory markers.

The results in the study group, the inflammatory markers, both ESR and CRP had a marked fall after SEK initiation, reaching normal ranges. Despite not having the same follow-up interval in the study group, this reduction in systemic inflammation shows the prompt effect of the anti-IL17 agent and the sustained response over time. Benefits of SEK has previously been demonstrated in large studies in PsA and SpA [18], [19].

A post-hoc pooled analysis conducted by Dougados et al. from the MEASURE 2, 3 and 4 studies in AS patients stated that SEK was associated with a clinically significant NSAID-sparing effect when evaluated at 4 years of treatment [20].

Moreover, Baraliakos et al showed that SEK improves clinical and imaging outcomes in patients with PsA who have axial involvement non-responsive to NSAID intake. The 52-week MAXIMISE trial confirmed that patients achieved ASAS20 and ASAS40 as well as a significant reduction in the Berlin MRI score for the spine and sacroiliac joints [21].

Beside the confirmed axial symptom-releasing, SEK was proved to be beneficial in peripheral manifestations of AS patients in the study of Mease et al. [22]. Data from the four MEASURE trials in 560 patients showed a reduction in both tender and swollen joints in SEK-treated patients versus placebo, some of them attaining resolution at week 16 of evaluation [22].

The recently-released phase 3 ULTIMATE study that evaluated efficacy of secukinumab vs placebo on joint synovitis through ultrasonography at 12 weeks confirmed results as early as week 1 in reducing synovitis and enthesitis scores.

Data from the phase 3 PREVENT study, a multicentric, randomized, double-blind research, aimed to assess the efficacy of SEK in bio-naive patients with active non-radiographic SpA. The ASAS40 response was achieved in patients on SEK versus placebo both at week 16 and at week 52, regardless of the loading dose [23].

60.5% of patients in the study group had enthesitis confirmed through plain x-ray, ultrasound or MRI. Enthesitis is a main characteristic of the spondyloarthritidis group and the production of IL-17 has an essential role in amplifying the inflammatory response at the entheseal site by helping the neutrophil migration and the activation through cytokines and mediators in the mesenchymal cells [24], [25].

Despite the low number of patients in the PsA group, SEK has proven great efficacy, with a drastic decrease in the DAPSA score. The 2019 EULAR update on pharmacological therapies in PsA emphasize the importance of initiating an IL17 inhibitor if skin involvement is significant or if enthesitis is present [8].

In both SpA and PsA study groups, results have shown better improvement in patients who were first initiated on SEK. The American Columbus Repository aimed to describe patients' characteristics and biologic treatment patterns in a SpA cohort [26].

SEK retention rate in our study had a mean of almost 22 months, with a slightly higher rate in SpA patients that in the PsA group, probably due to the inequality of group. In this study, a somewhat higher drug survival was obtained in patients with prior anti-TNF therapy, emphasizing the benefits of SEK even as second-line class of choice. Regarding the subgroup having combo-therapy with csDMARD, no difference was noted when compared to the monotherapy group.

The EuroSpA initiative evaluated SEK retention rates and treatment outcomes in 1860 axial SpA patients in 13 European countries and identified an adherence rate of around 80% and higher in bio-naive patients [27]. The latter had better results in achieving inactive disease or a low disease activity status.

In line with these results, the German AQUILA study released partial on 311 AS patients showing that SEK improved disease activity, physical functioning and quality of life in both anti-TNF-naïve and pretreated AS patients in a clinical setting. SEK appeared to have more benefits in anti-TNF-naïve patients with a higher retention rate [28].

Moreover, the Turkish HUR-BIO Registry found that since the approval of SEK in SpA patients, it is preferred as alternative in patients who failed more than one anti-TNF agent, with almost half still reaching BASDAI50 response [29].

Uveitis occurrence was around 16% in the study group, recorded as past episodes or during biologic therapy and only one patient had a severe panuveitis while on anti-IL17. A Swedish study whose data was partially published at EULAR 2020 enclosed 2684 SpA patients from the national Registry in order to compare anterior uveitis rates between biological agents [30]. Researchers noted that SEK and ETN were associated with a higher incidence of eye involvement than ADA and INF in clinical practice, mostly in patients with previous episodes (uveitis before any treatment) [30].

However, another extensive study published by Deodhar et al. on the incidence of uveitis in SEK-treated AS patients found that the exposure-adjusted incidence rate (EAIR) was 1.4 per 100 patient-years during treatment. This data does not suggest an increased risk of uveitis in SEK-treated patients included in the MEASURE studies [31].

The study group included two patients with history of neoplasia who received SEK after oncologist's approval, with no evidence of tumoral relapse. The long-term safety of SEK was assessed through clinical trials and post-marketing surveillance data in psoriasis, PsA and SpA and published in May 2019 by Deodhar et al. Out of 7355 patients, with 162269 patient-year, there were 81 cases of cancer. The exposure-adjusted reporting rates (EARRs) for malignancies and MACE were both 0.2 per 100 patient-years, most having additional risk factors or causes for the events [31].

The limitations of this study include the relatively low number of patients, especially in the PsA study group which might have impacted the results of the analysis as well as the variability of the follow-up interval since the data was collected at SEK initiation and the last check-up visit (biannual recorded patient data, study range for SEK 6 to 32 months). Another setback is the lack of imaging monitoring besides the baseline use of x-ray or MRI as diagnostic tool or enthesitis confirmation. A broader time interval would be of use to observe SEK safety profile and uveitis occurrence in this population. Moreover, the small number of PsA patients in the study group limited data analysis on SEK effects on axial or peripheral manifestations.

CONCLUSION

In conclusion, secukinumab, an IL-17A inhibitor is approved for treating SpA and PsA patients. Since it is a more novel biological agent, clinical practice data is needed to enforce phase 3 trials. This clinical review places SEK in a real-life setting and confirms beneficial effects on

lowering disease activity and inflammatory markers in both biological naïve patients and those who previously received anti-TNFs. SEK safety profile is in accordance with published data, since no severe adverse events were reported. There were only two drop-out cases, showing a satisfactory treatment retention rate. SEK is of high use in patients with anti-TNF fails or as first-line therapy when skin involvement is dominant, as reiterated by EULAR updated recommendations.

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