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The role of secukinumab in the treatment of psoriatic arthritis and ankylosing spondylitis

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Abstract: Psoriatic arthritis and ankylosing spondylitis are chronic inflammatory diseases that can cause significant disability. The commercialization of the first tumour necrosis factor (TNF) inhibitors led to a radical improvement of the quality of life of people affected by these conditions; however, response was not universal, highlighting the need for alternative therapeutic targets. Secukinumab is a monoclonal interleukin (IL)-17A inhibitor which has been proven efficacious for psoriatic arthritis and ankylosing spondylitis in recent clinical trials. Dactylitis, enthesitis, skin and nails are some of the domains in which the inhibition of IL-17 has shown significant improvements apart from the joints. Its safety profile and satisfactory medium-to long-term outcome data are some of the aspects suggesting its potential impact in treatment protocols in the short term.

Keywords: ankylosing spondylitis, anti-IL-17, cosentyx, IL-17, monoclonal antibody, psoriatic arthritis, secukinumab, spondyloarthropathies, treatment

Introduction

The spondyloarthropathies (SpA) are a family of chronic rheumatic conditions that can produce inflammation in and outside the joints [1]. Ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA) and the arthropathy related to inflammatory bowel are the main disorders included in this group, whose collective prevalence is similar to that of rheumatoid arthritis [2]. Recently developed criteria allow for the classification of these subgroups into axial and peripheral forms. Both forms may associate with enthesitis, dactylitis and extra-articular manifestations such as uveitis, psoriasis and inflammatory bowel disease. The burden associated with these pathologies can lead to significant disability for affected individuals [3]. There is a strong genetic component and familial heritability in SpA which is still not fully understood. Whereas HLA-B27 is strongly linked with severity and persistence of axial forms in SpA, particularly AS and a subset of axial PsA,[4] there is ample evidence suggesting that these are highly heterogeneous, polygenic disorders. Treatment of SpA is largely dictated by the clinical phenotype [5,6]. The advent of biologics over the last 20 years has led to important insights into the pathogenesis of these diseases and has in part reaffirmed the understanding of them being part of the same family group. This review will focus on the role of secukinumab, a newly licensed anti-interleukin (IL)-17A compound on the treatment of PsA and AS, the better characterized SpA phenotypes.

Pathophysiology

IL-17 is a family of cytokines consisting of six members (IL-17A, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F), of which IL-17A is known to play an important role in SpA. T helper (Th)- 17 cells are a subset of lymphocytes different from Th1 and Th2, characterized by the production of this interleukin (IL-17); however IL-17A can also be produced by other cells such as neutrophils, natural killer (NK) cells, fibroblast-like synoviocytes, endothelial cells, osteoblasts and chondrocytes. IL-17A can either be a homodimer (two chains of IL-17A) or a heterodimer (IL-17A and IL-17F) binding with different affinity to the five IL-17 receptors, which are expressed by hematopoietic cells, monocytes, macrophages, epithelial cells, endothelial cells, keratinocytes and osteoblasts. Once the binding takes place, the nuclear factor κB (NF-κB) inflammatory pathway is triggered leading to the release of many cytokines [tumour necrosis factor (TNF)-α, IL-6, IL-8, IL-1B] [7-10]. IL-17A is also able to act synergically with TNF- α by stimulating the expression of the adhesion molecules in the endothelial cells; and crucially it has been found to be involved in bone remodelling together with TNF-α by inducing the expression of the receptor activator of nuclear factor kappa-B ligand (RANKL) *via* NF-κB ligand [11] *(see Figure 1).* However, the origin of the pathogenesis of the disease may not lay in the bones: *Ciccia* and colleagues found that in patients with AS, type 3 innate lymphoid cells producing IL-17 are increased not only in peripheral blood, synovial fluid and bone marrow, but also in the gut [12]. This would support the theory that there is a link between the bowel and joint disease.

Why is IL-17/IL-23 important in SpA?

IL-23 is a heterodimeric cytokine mainly produced by dendritic cells and formed by two subunits: IL-23p19 and IL-12p40. The misfolding of HLA-B27 is responsible for an increase in IL-23 production;

which results in the release of IL-17 not only by Th17 cells, but also by NK, ILC3 and γδ T cells [13]. The heavy chain of HLA-B27 can also make KIRDL2-positive T cells and NK cells produce IL-17 by the formation of aberrant homodimers on the surface of the cells. IL-17 induces the production of IL-12 by dendritic cells [14]. The polarization of naïve T cells towards Th17 cells is complex: transforming growth factor (TGF)-β, IL-6 and IL-2 commence it by inducing the expression of RORγt in naïve T cells and it is continued by IL-6 and IL- β, which intensify this process. The role of IL-23 is to aid the stabilization and the expansion of Th17 cells, which at the same time secrete IL-21 and IL-22, also able to act as boosts for Th17 cells [15-16]. Data have shown that in PsA, IL-17 is found in high levels in serum, synovial fluid and psoriatic plaques.[9] Experiments with mice have evidenced the key role of the axis IL-23/IL-17 in the skin as keratinocytes express receptors for IL-17, making them more vulnerable to its effect [17]. A study carried out by *Nakae* and colleagues [18] evidenced the importance of IL-17 in joint involvement in AS and PsA, showing that IL-17-deficient mice did not develop experimental arthritis. This cytokine promotes bone resorption and osteoclastogenesis through RANKL. It works synergically with TNF and other mediators, perpetuating the cascade of inflammation. This leads to damage in the cartilage and synovial neoangiogenesis [19]. In AS, the macrophage production of IL-23 is also increased [10]. A study by *Sherlock* and colleagues concluded that IL-23 overexpression in mice leads to spondyloarthritis-like disease [20] whereas the lack of this interleukin protects from the development of inflammatory arthritis [21]. Interestingly, another study suggested that there are different mechanisms of disease in males and females which can explain why the first tend to develop a more severe phenotype [22]. Although these inflammation pathways are unknown, IL-17A and Th17 cell frequency appeared to be increased in men but not in women [23].

Bone involvement

SpA diseases lead to complex bone pathology that in many cases will include simultaneous bone destruction, that is, erosions and excessive bone formation. IL-17 is able to stimulate osteoblasts, osteoclasts and chondrocytes. Osteoclastogenesis is activated directly by IL-17A and also indirectly by the increased expression of RANKL and Macrophage colony stimulating factor (M-CSF) by stromal cells. RANKL is produced by Th17 lymphocytes and its expression is also potentiated by IL-17. TNF-α together with IL-17 also promote osteoclastogenesis and osteoblast differentiation from the mesenchymal stem cells [11,23].

Unmet need

For the last few years, nonsteroidal anti-inflammatory drugs (NSAIDs) have constituted the first-line therapy for SpA, with TNF inhibitors (TNFi) being considered in those cases with persistent disease activity or insufficient response to the standard treatment [24]. Although they have proven their efficacy, there is a substantial proportion of affected individuals who may not achieve clinical remission with TNFi [25,26] prompting the need to look for alternative mechanisms of action. Secukinumab (Cosentyx) is a human immunoglobulin (Ig)-G1-κ monoclonal antibody which inhibits the action of IL-17A, interrupting the inflammatory cascade [27] and has recently been licensed for the treatment of skin psoriasis, PsA and AS.

Literature search methods

To inform this review, we performed a search in Medline (through PubMed) using the terms: ‘spondyloarthropathies’, ‘ankylosing spondylitis’ and ‘psoriatic arthritis’, each one of them combined with ‘secukinumab’, ‘anti-IL-17’, ‘treatment’ or ‘biologic’. In addition, we searched for articles that included the terms ‘secukinumab’, ‘IL-17’ and ‘anti-IL-17’. We restricted the search to articles published between 1 January of 2012 and 31 March of 2018.

Efficacy of clinical trials in PsA

The efficacy and safety of secukinumab in PsA were assessed for the first time in a 24-week, randomized, double-blind, placebo-controlled phase II clinical trial [28] carried out in Germany, the Netherlands and the UK. A total of 42 patients who met the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria for PsA participated. Thirty-nine percent of those receiving secukinumab achieved ACR20 response at week 6 *versus* 23% of patients treated with placebo. ACR20 is a composite measure defined as both improvement of 20% in the number of tender and number of swollen joints, and a 20% improvement in three of the following five criteria: patient global assessment, physician global assessment, functional ability, visual analogue pain scale, and erythrocyte sedimentation rate or C-reactive protein. Even though the primary endpoint was not met, other parameters such as the lowering of acute phase reactants and the clinical response led to the design of the larger, confirmatory FUTURE trials.

FUTURE 1

This was a 2-year, double-blind, placebo controlled phase III clinical trial [29] with 606 patients with PsA according to CASPAR criteria, randomized 1:1:1 into different treatment groups: 10 mg/kg of intravenous secukinumab at weeks 0, 2 and 4, continuing with either 150 or 75 mg of subcutaneous secukinumab every 4 weeks *versus* placebo. After evaluation at week 16, the non-responders from the placebo group were randomized to 150/75 mg of subcutaneous secukinumab, with responders (those who achieved ACR20) randomized at week 24. A total of 553 patients remained in the study until week 24. Evaluation at week 52 was done on 515 patients with 476 (78.5%) remaining until the end of week 104 [30]. The primary endpoint was ACR20 at week 24, achieved by 50.0%, 50.5% and 17.3% of patients receiving secukinumab 150 mg, 75 mg or placebo respectively. This similarity in the response rate between both secukinumab groups was attributed to the effect of the initial intravenous doses. There was a remarkable improvement in the secondary endpoints for the patients treated with secukinumab: Psoriasis Area and Severity Index (PASI)75, PASI90, Disease Activity Score Calculator for Rheumatoid Arthritis (DAS28-CRP), 36-Item Short Form Health Survey (SF-36), Health assessment questionnaire disability index (HAD-DI) scores, global disease activity, physical function and some peripheral manifestations [30]. By week 52 of therapy, 59.9% (121) of patients receiving secukinumab 150 mg and 56.9% (115) of patients on secukinumab 75 mg maintained ACR20 response. This good clinical outcome was sustained by week 104, with 66.8% of patients on secukinumab 150 mg and 58.6% of patients on secukinumab 75 mg meeting ACR20 response [30]. It is important to highlight that a higher number of TNFi-naïve patients achieved an ACR20 response in comparison with those who had been treated with TNFi previously. This pattern was seen over time: at week 24, the response rates for ACR20 in TNFi-naïve patients were 54.5% for the 150 mg dose, 55.6% for the 75 mg dose and 17.5% for placebo. At week 104, the ARC20 response rates for patients on 150 mg secukinumab were 75.2% for TNFi-naïve patients and 48.0% for TNF-IR patients (patients with previous inadequate response to TNFi). For the 75 mg group, the rates were 63.7% and 46.9% for TNFi-naïve patients and TNF-IR patients respectively.

FUTURE 2

This was a multicentre, double-blind, placebo controlled phase III trial [31] recruiting 397 patients with PsA from Asia, Oceania, Europe and North America. Subjects were randomized 1:1:1:1 to subcutaneous secukinumab 300 mg, secukinumab 150 mg, secukinumab 75 mg or placebo every week for 4 weeks, and after that, monthly. At week 16, placebo patients were randomized again to subcutaneous secukinumab 150 mg or 300 mg. The non-responders would start immediately with secukinumab but the initiation of the treatment would be put off until week 24 for the placebo responders.

The primary endpoint was ACR20 at week 24, which was achieved by 54% of patients receiving 300 mg of subcutaneous secukinumab, 51% of those receiving 150 mg, 29% of the 75 mg dose group and 15% of patients taking placebo. The main secondary endpoints were PASI75, PASI90, variations in the DAS28-CRP, SF36- PCS, HAQ-DI and ACR50. All these parameters had better outcomes with the 300 mg and 150 mg doses of secukinumab compared with placebo. However, the 75 mg dose did not improve PASI75 in a statistically significant way. A total of 20% of patients receiving secukinumab 300 mg achieved ACR70. The rates for patients on 150 mg, 75 mg and placebo were 21%, 6% and 1% respectively. The difference between the response rates of patients in the secukinumab 300 mg *versus* 150 mg group became smaller over time. At week 52, ACR20 was achieved in 64%, 64% and 51% of patients receiving 300 mg, 150 mg and 75 mg of secukinumab respectively. The percentage of patients who achieved ACR50 were 44%, 39% and 30% in patients treated with 300 mg, 150 mg and 75 mg secukinumab respectively and ACR70 response rates were 24%, 20% and 16%.ACR20 response rates were maintained by week 104 in 69.4%, 64.4% and 50.3% of patients receiving 300 mg, 150 mg and 75 mg of secukinumab respectively [32] ACR50 was achieved in 50.6%, 36% and 28.2% and ACR70 in 33.1%, 23.1% and 14.9% for the 300 mg, 150 mg and 75 mg doses respectively. Similar to FUTURE 1 [29] a sub analysis showed that TNF-naïve patients had better response rates to secukinumab than TNFi-IR patients: at week 104, ACR20 was met in 74.8% *versus* 58.4% of patients on the 300 mg secukinumab dose, 79.3% *versus* 38.9% on the 150 mg dose and 62.7% *versus* 26.3% on the 75 mg dose. The resolution of dactylitis, enthesitis and the improvement of other secondary endpoints such as the HAQ-DI or SF-36 physical component score (SD-36 PCS) was sustained throughout the trial until week 104 [32].

Prospective

There are other phase III clinical trials currently ongoing in patients with PsA. In the same line as previous studies, FUTURE 3 is a phase III clinical trial [33] assessing the safety and efficacy of different

doses of subcutaneous secukinumab *versus* placebo in patients with PsA. ACR20 response rate at week 24 was significantly higher in the secukinumab groups: 300 mg, 48.2% ($p < 0.0001$); 150 mg, 42% ($p < 0.0001$); placebo, 16.1% and this response was sustained for 52 weeks. FUTURE 4 [34] is investigating the safety and efficacy of subcutaneous secukinumab 150 mg with and without a loading dose (LD) *versus* placebo. The 16-week results showed that ACR20 response was achieved by 41.2% of patients with secukinumab 150 mg with a LD, 39.8% of those without a LD and 18.4% of patients on placebo. At week 52, ACR20 was achieved by 60.5% of patients with secukinumab and a LD and 57.5% of those without a LD. The results for ACR50 at 16 weeks showed that it was achieved by 22.8% of patients with a LD, 16.8% of those without a LD and 6.1% of patients on placebo. At 52 weeks 40.4% of patients on secukinumab and a LD achievedACR50 *versus* 32.7% of those without a LD. FUTURE 5 [35] aimed to test the progression of structural damage in patients with PsA taking subcutaneous secukinumab 300 mg and 150 mg with and without a LD for 2 years. It is still ongoing, but the primary results (until week 24) showed that radiographic progression measured by Van der Heijde-modified total Sharp score was significantly inhibited in all secukinumab arms *versus* placebo. Regarding disease activity, ACR20 response at week 16 was achieved by 62.6% of patients on secukinumab 300 mg with a LD, 55.5% of patients on 150 mg with a LD, 59.5% of patients on 150 mg without a LD and 27.4% of patients on placebo. ACR50 response at week 16 was achieved by 39.6% of patients on secukinumab 300 mg with a LD, 35.9% of those on 150 mg with a LD, 32.0% of patients on 150 mg without a LD and 8.1% of patients on placebo.

Efficacy of clinical trials in AS

Baeten and colleagues [36] published the first study that demonstrated the efficacy of a non-TNF blocker for the treatment of AS. It was a double blind, placebo-controlled, proof-of-concept study carried out in eight centres in Germany, the Netherlands and the UK. Thirty patients with AS were randomized 4:1 to placebo or secukinumab 10 mg/kg at days 1 and 22 and were followed up for 28 weeks. The primary endpoint was Assessment of Spondyloarthritis international Society (ASAS)20 at week 6, which was achieved by 61% of patients on secukinumab *versus* 17% of patients receiving placebo. However, the response had decreased progressively by week 28. Eligible subjects on MEASURE trials were 18 years of age or older and met the modified New York criteria for AS with active disease as evidenced by a Bath Ankylosing Spondylitis Functional Index (BASDAI) of at least 4 and spinal pain of at least 4. Previous treatment with prior TNFi was permitted only if suspended because of an inadequate response or intolerance (TNFi-IR) [37].

MEASURE 1

This was a double-blind, placebo-controlled phase III study [38] with 371 subjects recruited, of which 290 remained until the end of the 2-year study period with 260 completing the voluntary 3-year extension. Patients with AS were randomized 1:1:1 to intravenous secukinumab 10 mg/ kg at weeks 0, 2 and 4, continuing with subcutaneous secukinumab 150 mg or 75 mg very 4 weeks *versus* placebo. Subjects in this last group were evaluated at week 16 and randomly reassigned to one of the secukinumab arms. Non-responders started immediately with responders switched at week 24. At week 16, 61% and 60% of patients in the secukinumab 150 mg and 75 mg groups achieved ASAS20 respectively. ASAS40 was meet by 42% and 33% respectively *versus* 13% of placebo patients. Patient reported outcomes were also favourable. There were significant improvements in BASDAI, SF-36 PCS, BASFI and EQ-5D in the secukinumab patients compared with placebo [39]. At week 104, the response rates for ASAS20 were 73.7% and 68% in the 150 mg and 75 mg groups respectively and ASAS40 was achieved in 55.7% and 48.5% of the 150 mg and 75 mg groups [40]. At week 156, 80.2% and 61.6% of patients on secukinumab 150 mg achieved ASAS20 and ASAS40 respectively. There were no differences in the response rates at week 156 for TNFi-naïve and TNFi-IR patients [38].

MEASURE 2

This is an ongoing 5-year, double-blind, placebo controlled phase III trial that started in October 2012 [41]. A total of 219 patients with active AS disease were randomized 1:1:1 to subcutaneous placebo, secukinumab 75 mg or secukinumab 150 mg weekly for a month, and then one monthly dose. Sixty-one percent of patients treated with 150 mg secukinumab and 41% of those treated with 75 mg secukinumab met ACR20 at week 16. At that point, patients in the placebo group were randomized to the 150 mg or 75 mg secukinumab arms. The response rates for ASAS40 at week 16 were 36%, 26% and 11% for 150 mg secukinumab, 75 mg secukinumab and placebo respectively. Focusing only on the TNFi-naïve patients, ASAS20 was achieved by 68.2%, 51.1% and 31.1% of patients treated with 150 mg secukinumab, 75 mg secukinumab and placebo respectively. For TNFi-IR patients, the response rates were 50.0%, 25.0% and 24.1% respectively. At week 52, 74% of patients on the 150

mg dose achieved ASAS20. In a further sub analysis comparing TNFi-naïve and TNFi-IR patients, ASAS20 response rates were 72.7% *versus* 46.4% respectively for the 150 mg secukinumab group and 66.7% *versus* 32.1% respectively for the 75 mg group. Long-term efficacy was assessed at week 104: ASAS20 and ASAS40 response rates were 71.5% and 47.5% for both secukinumab groups. Concerning other endpoints, a good outcome was maintained from week 16. In a TNFi-naïve *versus* TNF-IR sub analysis, ASAS20/ASAS40 response rates were 76.9%/56.6% and 85.0/50.0% respectively for the 150 mg group. For the 75 mg dose the response rates were 80.0%/60.0% and 68.8%/43.8% respectively [42].

Specific outcomes

Radiographic progression

Psoriatic arthritis.

The results of FUTURE 1 showed that the group exposed to secukinumab therapy had reduced radiographic progression as assessed by the modified total Sharp/Van der Heijde score (mTSS)[43]. There were no variations at week 52 and only minimal changes at week 104, suggesting inhibition of radiographic progression in 84.3% of patients on 150 mg secukinumab and 83.8% of those on the 75 mg dose [29,30,44]. This is consistent with the primary results of FUTURE 5, which also support that all doses of secukinumab (300 mg and 150 mg) can inhibit radiographic structural progression [35].

Ankylosing spondylitis.

A 94-week extension of a randomized, double-blind trial [45] showed improvement or resolution of inflammatory lesions on spinal magnetic resonance imaging in subjects treated with secukinumab, and this regression was associated with an improvement in clinical parameters. *Baraliakos* and colleagues reported that this effect was sustained for 2 years [46]. In MEASURE 1, *Braun* and colleagues [47] found less changes in modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS) in comparison with previous TNFi studies [48]. No differences were seen between the 75 and 150 mg doses and 80% of the patients showed no radiographic progression after 104 weeks. Male sex, elevated acute phase reactants and syndesmophytes were associated with radiographic progression [40].

Dactylitis and enthesitis

In FUTURE 1, 52.4% and 47.5% of patients receiving secukinumab had resolution of dactylitis and enthesitis by week 24, in contrast to the 15.5% and 12.8% respectively in the placebo group. After 104 weeks, the secukinumab resolution rates of dactylitis increased to 82.6% and 84.6% with the 150 mg and 75 mg doses respectively. Enthesitis was resolved in 73.7% and 76.8% of patients taking 150 mg and 75 mg secukinumab respectively [29]. FUTURE 2 had similar results. By week 24, dactylitis and enthesitis had resolved in 47% and 40% of patients on secukinumab respectively *versus* 15% and 22% of patients receiving placebo respectively [31]. By week 104, the resolution rates for dactylitis increased to 79.9%, 78.0% and 88.6% for the secukinumab 300 mg, 150 mg and 75 mg doses respectively. Enthesitis resolution rates also improved to 71.5%, 61.8% and 68.4% for the 300 mg, 150 mg and 75 mg doses respectively [32]. Baseline rates of dactylitis and enthesitis were so low in patients with AS that it was not possible to assess the efficacy of secukinumab either in the phase II or phase III trials [36].

Antidrug antibodies

Anti-secukinumab antibodies have been detected in a very small percentage (<1%) of subjects taking part in the MEASURE 1, FUTURE 1 and FUTURE 2 studies, with no loss of efficacy or adverse events (AEs) reported as a result [31,38,49].

Dosage administration

Psoriatic arthritis

In the European Union (EU), the recommended dosage is 150 mg subcutaneous secukinumab every 4 weeks preceded by a LD of 150 mg subcutaneously at weeks 0, 1, 2, 3 and 4 [50]. In the United States (US) it can also be administered without a LD (150 mg subcutaneously every 4 weeks) [51]. Dose can be increased to 300 mg in the event of partial response. In TNF-inadequate responders and patients with concomitant moderate to severe cutaneous psoriasis, the recommended dose is 300 mg subcutaneously every 4 weeks for both the EU and the US.

Ankylosing spondylitis

In the EU, the approved dosage is 150 mg subcutaneous secukinumab at weeks 0, 1, 2,3 and 4, followed by monthly doses of 150 mg [52]. In the US, the LD is optional [53,54]. For both indications, response should be assessed within 16 weeks of treatment, with the suggestion for treatment to be discontinued in the event of nonresponse.

Safety and adverse effects

Discontinuation rates were low in all trials across all indications.

PsA trials

In the clinical trials FUTURE 1, FUTURE 2 and their 104-week extension periods [30,32,55]. AEs were similar across all secukinumab treatment groups, ranging from mild to moderate. The most commonly reported side effects were nasopharyngitis (in 13.4% and 13.6% of secukinumab patients in FUTURE 1 and 2 respectively) and upper respiratory tract infections (in 12.6% in both FUTURE trials). They were followed by diarrhoea (in 5.5% and 5.0% of patients respectively) and headache. Another less frequent, but especially interesting AE was candidiasis in over 2% of patients where infection appeared localized and did not lead to treatment withdrawal. Nevertheless, this effect was expected considering the role that IL-17 plays in the mucocutaneous defence against fungal infections. In FUTURE 1, four strokes and three myocardial infarctions were reported. Two of those patients died (one due to a stroke and the other due to myocardial infarction). However, they both had underlying cardiovascular disease and their deaths were not related to the treatment. Neutropenia was reported in 12 patients in FUTURE 1 and in 5 patients in FUTURE 2. Concerning inflammatory bowel disease, Crohn's disease was seen in one patient in FUTURE 1 but in none of the patients in FUTURE 2. However, there were two cases of ulcerative colitis, one of haemorrhagic diarrhoea and a fistula in this last trial. Malignancies or unspecified tumours were seen in 6 and 10 patients of FUTURE 1 and 2 respectively and basal cell carcinoma was the most frequent. No cases of tuberculosis or reactivation were reported. There were no cases of suicide or suicidal thoughts.

AS trials

The results of MEASURE 1 and MEASURE 2 [40,41] after 52 weeks were consistent with previous studies [30,32,37,55]. AEs were mainly mild–moderate and nasopharyngitis remained the most common AE in both trials. However, upper respiratory tract infection, headache and diarrhoea had similar incidence rates. There were six cases of candidiasis (in MEASURE 1 and 2 together), but they resolved completely and there was no need to stop the treatment. Other infections reported were herpes simplex and herpes zoster. Four patients presented with neutropenia in MEASURE 1 and one in MEASURE 2, but it was only in one visit. Crohn's disease was reported in four and two patients in MEASURE 1 and MEASURE 2 respectively. There were 13 cases of uveitis, 1 in MEASURE 2; however, 7 of those patients had a previous clinical history of the disease. Two patients died in MEASURE 1 and 2, one due to respiratory failure secondary to cardiac failure at week 100 and the other due to fatal myocardial infarction. None of them were treatment related. There were some serious events in MEASURE 1: one patient had a stroke and another two suffered a myocardial infarction. Concerning malignancies, four cancers were reported in MEASURE 1 and one in MEASURE 2. There were no suicides or suicidal thoughts among patients on secukinumab and no cases of tuberculosis.

Guidelines for treatment of PsA

The latest updates of both European League Against Rheumatism (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for the management of PsA were developed as the data on IL-17 blockade were emerging *(See figures 2–4).*

EULAR recommendations 2015 [57]

NSAIDs are the first-line treatment for PsA except for patients with peripheral arthritis and signs of bad prognosis. In that case, DMARDs should be initiated early. Methotrexate is specially recommended in the presence of cutaneous psoriasis. If there is no improvement in spite of adding glucocorticoid injections, TNFi can be started; however, other bDMARDs targeting IL-12/IL-23 or IL-17 can be an option. For patients with dactylitis or enthesitis who do not show an adequate response to NSAIDs or local steroid injections, bDMARDs (TNFi) can be initiated. In patients with axial disease and insufficient response to NSAIDs, bDMARDs (TNFi) must be considered.

GRAPPA recommendations 2015 [56,58]

The management that GRAPPA suggests is oriented to the dominant manifestations of the disease. It is similar to EULAR guidelines, however due to the emerging results from the secukinumab clinical

trials, there is a conditional recommendation (waiting for regulatory approval) that secukinumab may be used as a second-line therapy, at the same level as TNFi, if the clinician thinks it is appropriate.

Guidelines for treatment of AS

ASAS/EULAR recommendations 2016 [24]

NSAIDs are considered the first-line therapy, with a role for local glucocorticoids which can be used for peripheral symptoms. The next step would be bDMARDs, except for patients with peripheral disease; in those cases, sulfasalazine may be an option. ASAS/EULAR recommendations suggest TNFi as first-line treatment due primarily to the extensive body of evidence for these drugs, the lack of data concerning the efficacy of IL-17 blockade in patients with non-radiographic SpA to date, and the fact that anti-IL-17 should be avoided in patients with IBD. To date, there are no data regarding TNFi effectiveness in patients previously treated with anti-IL-17 therapy, although these are expected to emerge with repeated use of these agents.

Conclusion

Secukinumab is an anti-IL-17A monoclonal antibody that has demonstrated efficacy in the treatment of PsA and AS. Enthesitis, dactylitis, skin and nails are some of the domains in which secukinumab has shown significant response in clinical trials. Considering the good safety profile and medium-term drug survival, secukinumab is likely to play a relevant role in the management of these diseases. Real-life, long-term exposure will help elucidate the positioning of this drug within treatment algorithms in PsA and AS.

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Conflict of interest statement

HMO has received grants from Janssen, Pfizer and UCB, and honoraria/speaker fees from Abbvie, Celgene, Janssen, MSD, Novartis, Pfizer and UCB.

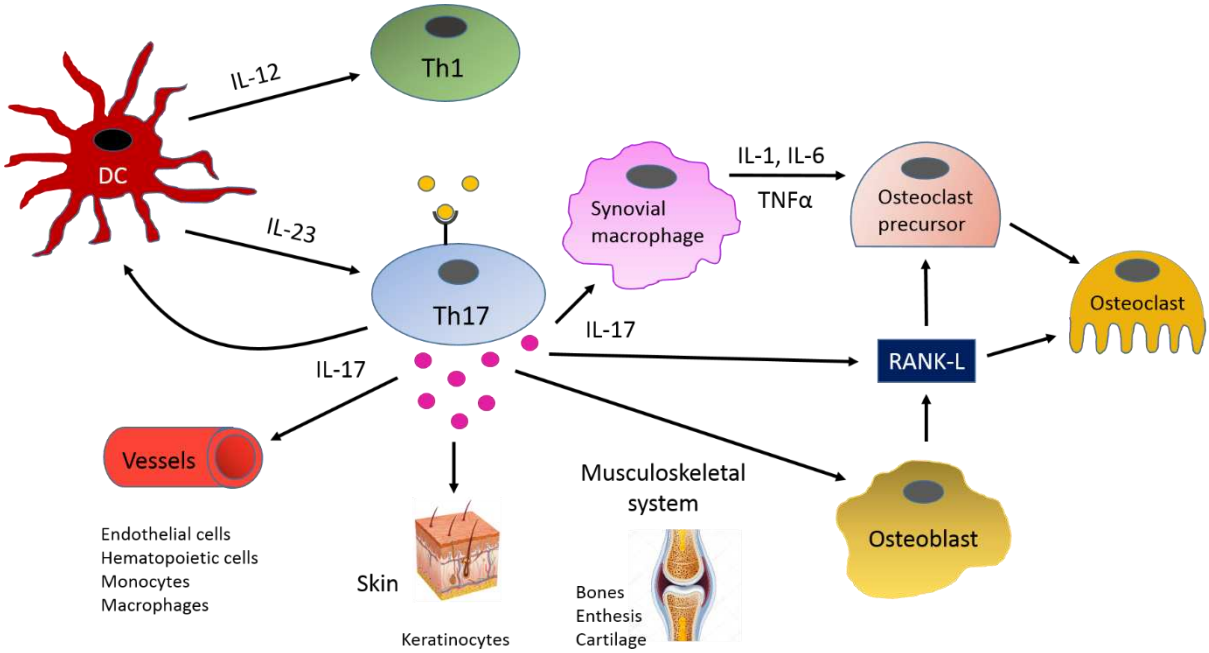

Figure 1. Pathophysiology. DC, dendritic cell; IL, interleukin; TNF, tumour necrosis factor; Th, T helper; RANKL, Receptor activator of nuclear factor kappa-B ligand.

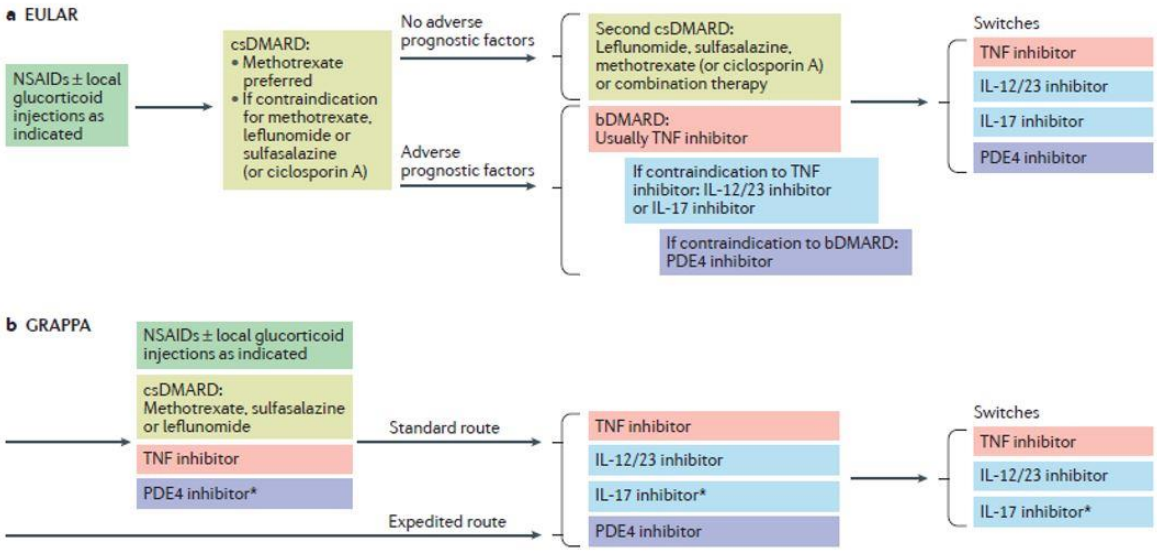

Figure 2. Simplified EULAR (a) and GRAPPA (b) treatment algorithms for predominant peripheral psoriatic Arthritis [56]. *Conditional recommendation in the GRAPPA guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only. bDMARD, biologic disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; PDE4, phosphodiesterase 4; TNF, tumour necrosis factor.

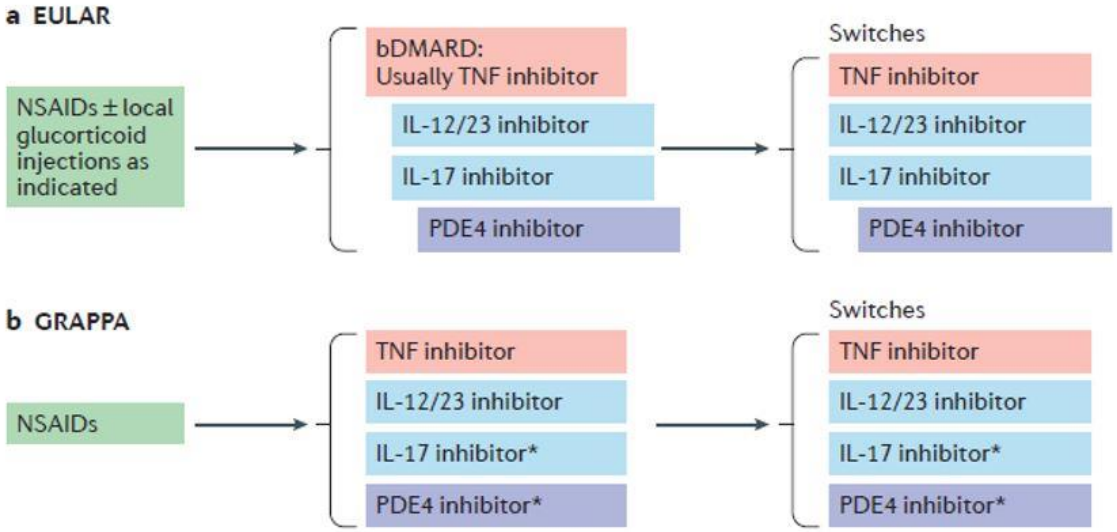

Figure 3. Simplified EULAR (a) and GRAPPA (b) treatment algorithms for predominant entheseal psoriatic Arthritis [56]. *Conditional recommendation in the GRAPPA guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only. bDMARD, biologic disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; PDE4, phosphodiesterase 4; TNF, tumour necrosis factor.

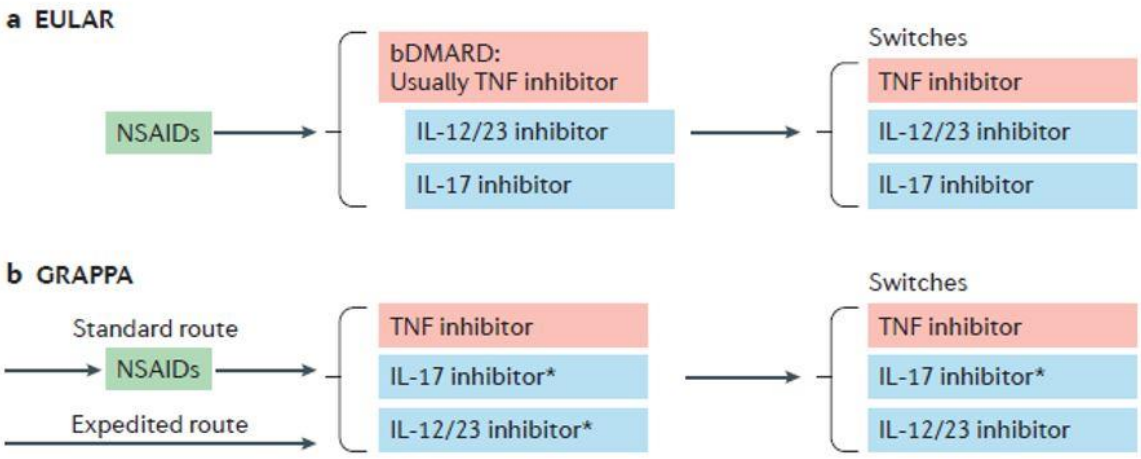

Figure 4. Simplified EULAR (a) and GRAPPA (b) treatment algorithms for predominant axial psoriatic arthritis (PsA) [56]. The order of drug use proposed for patients with PsA and predominant axial involvement, with a step up approach (indicated by staggered boxes) in case of inefficacy or toxicity. *Conditional recommendation in the GRAPPA guidelines for drugs without current regulatory approval or where recommendations are based on abstract data only. bDMARD, biologic disease-modifying antirheumatic drug; EULAR, European League Against Rheumatism; GRAPPA, Group for Research and Assessment of Psoriasis and Psoriatic Arthritis; IL, interleukin; NSAID, nonsteroidal anti-inflammatory drug; TNF, tumour necrosis factor.

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