Secukinumab: A Review in Psoriatic Arthritis

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Abstract
Secukinumab (Cosentyx®) is a fully human monoclonal antibody that selectively targets interleukin (IL)-17A, a proinflammatory cytokine involved in the pathogenesis of psoriatic arthritis (PsA). Administered subcutaneously, the first-in-class anti-IL-17 agent is approved in numerous countries worldwide for the treatment of adults with active PsA. In the phase III FUTURE trials, secukinumab 150 or 300 mg improved the clinical signs and symptoms of PsA versus placebo in patients with active disease despite previous treatment with NSAIDs, biological disease-modifying anti-rheumatic drugs (bDMARDs) and/or tumour necrosis factor inhibitors (TNFi). The benefits of secukinumab were seen regardless of whether or not patients had received previous TNFi therapy, and were maintained during longer term (up to 5 years) treatment. In FUTURE 1 and 5, secukinumab inhibited structural joint damage and was associated with sustained low rates of radiographic progression through 1–3 years of treatment. Treatment with secukinumab improved physical function and health-related quality of life (HR-QOL) and was generally well tolerated, both in the short- and longer-term. In the head-to-head EXCEED trial, secukinumab did not quite attain statistical significance for superiority versus adalimumab in the joint domain. In conclusion, secukinumab is effective across all key PsA domains and is generally well tolerated, and thus represents a useful treatment alternative to TNFi and other bDMARDs in adult patients with active PsA.

1 Introduction
Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal condition characterized by a wide range of symptoms including arthritis, spondylitis, dactylitis, enthesitis, psoriasis and nail disease [1, 2]. PsA is also associated with several comorbidities [1–3], and can significantly worsen health-related quality of life (HR-QOL) [1]. Traditional pharmacological treatment options for PsA include NSAIDs and conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate [1, 3]. Over recent decades, the development of biological DMARDs (bDMARDs) has considerably changed the PsA treatment landscape [1]. The first bDMARDs to be approved were the tumour necrosis factor inhibitors (TNFi), based on the finding that TNF-α is a key mediator of acute inflammation in PsA [4]. In addition to TNF-α, other proinflammatory cytokines, such as interleukin (IL)-12, IL-17 and IL-23, have been shown to play a key role in the pathogenesis of PsA [1, 4, 5]. IL-17A (a member of the IL-17 family) is up-regulated in psoriatic lesional skin and in the synovial fluid of PsA patients [1, 4, 5], providing a rationale for the development of targeted anti-IL-17 therapies [5].

Secukinumab (Cosentyx®) is a recombinant, high affinity, fully human monoclonal antibody targeted against IL-17A. It is approved in numerous countries, including the USA [6] and those of the EU [7], for the treatment of adult patients with active PsA. The pharmacological properties of secukinumab have been reviewed in detail previously [8] and are summarized in Table 1. This review focuses on the clinical use of secukinumab in patients with PsA. Secukinumab is also approved for the treatment of plaque psoriasis [9], ankylosing spondylitis (AS) [10, 11] and non-radiographic axial spondyloarthritis (nr-axSpA); however, discussion of the use of secukinumab in these indications is beyond the scope of this review.
2 Therapeutic Efficacy of Secukinumab

The efficacy of secukinumab for the treatment of PsA was evaluated in several randomized, double-blind, placebo-controlled, multicentre, phase III trials: FUTURE 1–5 [12–16] (Sect. 2.1.1), MAXIMISE [17] (Sect. 2.1.2) and ULTIMATE [18] (Sect. 2.1.3). These data are supported by a randomized, double-blind, active-controlled, multicentre, phase IIIb trial comparing secukinumab with adalimumab (EXCEED) [19] (Sect. 2.2). The efficacy of secukinumab in the real-world setting is also briefly discussed (Sect. 2.3).

2.1 Versus Placebo

2.1.1 FUTURE Trials

The FUTURE trials enrolled patients aged ≥ 18 years with a diagnosis of PsA that met the Classification of Psoriatic Arthritis criteria [12–16]. All patients had active disease,
defined as ≥ 3 tender joints and ≥ 3 swollen joints, despite previous treatment with NSAIDs, DMARDs and/or TNFi. Patients who had previously received TNFi could enrol if they had had an inadequate response or had discontinued treatment due to safety or tolerability issues. Stable doses of concomitant corticosteroids and methotrexate were allowed. Across all trials, the mean age of patients was 47–50 years, 65–76% of patients were TNFi-naïve and 47–61% were receiving concomitant methotrexate [12–16].

Patients in each trial were randomized to one of two [12, 14, 15] or three [13, 16] secukinumab groups or a placebo group; randomization was stratified by previous use of TNFi [12–16]. In FUTURE 1, secukinumab recipients received intravenous loading doses of secukinumab 10 mg/kg at weeks 0, 2, and 4, followed by subcutaneous secukinumab 75 or 150 mg every 4 weeks [12]. In FUTURE 2, secukinumab recipients received subcutaneous secukinumab 75, 150 or 300 mg at weeks 0, 1, 2, 3 and 4, then every 4 weeks [13]. In FUTURE 3, subcutaneous secukinumab 150 or 300 mg was self-administered via autoinjector at weeks 0, 1, 2, 3 and 4, then every 4 weeks [14]. In FUTURE 4, subcutaneous secukinumab was self-administered via prefilled syringe with a loading regimen (i.e. 150 mg at weeks 0, 1, 2 and 3, then every 4 weeks) or without a loading regimen (i.e. 150 mg every 4 weeks) [15]. In FUTURE 5, subcutaneous secukinumab was self-administered via prefilled syringe with a loading regimen (i.e. 150 or 300 mg at weeks 0, 1, 2 and 3, then every 4 weeks) or without a loading regimen (i.e. 150 mg every 4 weeks) [16]. Discussion in this section focuses on the approved doses of 150 and 300 mg (Sect. 4), with data for the 75 mg dose presented in Table 2 for completeness.

At week 16 in each trial, patients were classified as responders (i.e. improvement of ≥ 20% from baseline in the number of tender and swollen joints) or non-responders [12–16]. Patients in the placebo groups were then reassigned to receive secukinumab 75 or 150 mg in FUTURE 1 [12], 150 or 300 mg in FUTURE 2, 3 and 5 [13, 14, 16], and 150 mg in FUTURE 4 [15] every 4 weeks from week 16 (non-responders) or week 24 (responders).

The primary endpoint was the proportion of patients achieving ≥ 20% improvement in the American College of Rheumatology response criteria (ACR20) at week 24 in FUTURE 2, 3, and 5 [12–16] analyses. The clinical responses reported with secukinumab at week 16 were significantly (p < 0.05) higher with secukinumab than with placebo among TNFi-naïve patients in all trials [12–16]. Among TNFi-experienced patients, ACR20 response rates were numerically higher with secukinumab than with placebo in all trials [12–16] and significantly (p < 0.05) higher than with placebo in FUTURE 1, 3 and 5 [12, 14, 16]. In prespecified (FUTURE 3) [14] or post hoc (FUTURE 1 and 2) [12, 13] analyses, ACR20 response rates at week 24 were significantly higher with secukinumab than with placebo regardless of concomitant methotrexate use.

With regard to secondary endpoints, secukinumab was associated with improvements in several other clinical domains of PsA at week 16 [15, 16] or 24 [12–14]. The proportions of patients achieving ≥ 50% improvement in the ACR response criteria (ACR50) and ≥ 75 and ≥ 90% improvement in Psoriasis Area-and-Severity Index (PASI) scores (PASI75 and PASI90) were significantly higher with secukinumab than with placebo in all trials, with the exception of ACR50 with secukinumab 150 mg in FUTURE 2 and PASI90 with secukinumab 150 mg in FUTURE 3 (Table 2). Changes from baseline in 28-joint Disease Activity Score using C-reactive protein levels (DAS28-CRP) were significantly greater with secukinumab than with placebo in all trials (Table 2). Secukinumab provided resolution of dactylitis and enthesitis among patients who had these disease characteristics at baseline, although rates of resolution were not always significant versus placebo (Table 2) [12–16].

The clinical responses reported with secukinumab at week 16 or 24 were maintained through 52 weeks [12–15, 20] and 104 weeks [15, 21–23] of treatment. For example, ACR20 response rates (with multiple imputations and as observed data, where reported) ranged from 47 to 73% at week 52 [12–15, 20] and from 64 to 73% at week 104 [15, 21–23]. Over the longer term, secukinumab provided sustained improvements in ACR20 response rates and other key efficacy endpoints for up to 5 years in FUTURE 1 [24, 25] and FUTURE 2 [26, 27]. For example, ACR20 response rates at 5 years remained high (70–74%) [24, 27].

2.1.1.2 Radiological Response Secukinumab was associated with low rates of radiographic structural progression in patients with PsA [12, 16]. In FUTURE 1 and 5, the change from baseline in van der Heijde-modified total Sharp score (vdH-mTSS; higher scores indicate more damage) at week 24 was significantly (p < 0.05) lower among secukinumab than placebo recipients [12, 16]. The inhibition of radiographic progression achieved with secukinumab at week 24 was maintained through 52 weeks [20, 28], 104 weeks [21, 23] and 156 weeks [25] of treatment. Moreover, switching to secukinumab inhibited further radiographic progression in patients initially randomized to placebo [20].
Table 2  Efficacy of secukinumab at week 16 [15, 16] or week 24 [12–14] in patients with psoriatic arthritis in the phase III FUTURE trials

| Study       | Treatment [mg] (no. of pts) | Response (% pts) | Mean change from BL | Resolution (% pts) |
|-------------|-----------------------------|-------------------|---------------------|--------------------|
|             |                             | ACR20             | ACR50         | PASI75            | PASI90          | DAS28-CRP   | SF-36 PCS   | HAQ-DI   | Dactylitis | Enthesitis |
| FUTURE 1    | SEC 75 (202)                | 51****            | 31***         | 65****           | 49****          | − 1.67****  | + 5.41****  | − 0.41*** | 52*       | 48*        |
|             | SEC 150 (202)               | 50***             | 35***         | 61****           | 45****          | − 1.62***  | + 5.91****  | − 0.40**  |           |            |
|             | PL (202)                    | 17                | 7             | 8                | 4               | 0.77       | + 1.82      | − 0.17   | 16         | 13         |
| FUTURE 2    | SEC 75 (99)                 | 29*               | 18            | 28               | 12              | − 1.12     | + 4.38      | − 0.32   | 47**       | 40**       |
|             | SEC 150 (100)               | 51****            | 35            | 48**             | 33**            | − 1.58**   | + 6.39**    | − 0.48   |           |            |
|             | SEC 300 (100)               | 54****            | 35**          | 63****           | 49****          | − 1.61**   | + 7.25**    | − 0.56** |           |            |
|             | PL (98)                     | 15                | 7             | 16               | 9               | 0.96       | + 1.95      | − 0.31   | 15         | 22         |
| FUTURE 3    | SEC 150 (138)               | 42****            | 19*           | 50**             | 37              | − 1.24*    | + 3.42      | − 0.27   | 39         | 37         |
|             | SEC 300 (139)               | 48****            | 35****        | 47****           | 34**            | − 1.56**** | + 6.46**    | − 0.38** | 48**       | 40**       |
|             | PL (137)                    | 16                | 9             | 10               | 7               | − 0.64     | + 2.94      | − 0.17   | 14         | 15         |
| FUTURE 4    | SEC 150 LD³ (114)           | 41***             | 23**          | 53***            | 36***           | − 0.98***  | + 3.42**    | 33      | 32         |            |
|             | SEC 150 NLD (113)           | 40**              | 17*           | 50***            | 20**            | − 0.84**   | + 3.44**    | 42      | 39*        |            |
|             | PL (114)                    | 18                | 6             | 8                | 2               | 0.21       | + 0.63      | 32      | 21         |            |
| FUTURE 5    | SEC 150 LD³ (220)           | 56****            | 36*           | 60*              | 37*             | − 1.29*    | − 0.44*     | 58*     | 55*        |            |
|             | SEC 150 NLD (222)           | 60****            | 32*           | 58*              | 32*             | − 1.29*    | − 0.45*     | 56      | 42         |            |
|             | SEC 300 LD³ (222)           | 63****            | 40*           | 70*              | 54*             | − 1.49*    | − 0.55*     | 66*     | 56*        |            |
|             | PL (332)                    | 27                | 8             | 12               | 9               | − 0.63     | − 0.21      | 32      | 35         |            |

For the primary endpoint and other binary endpoints, missing values were imputed as non-responses.

All endpoints (except PASI90 and resolution of dactylitis/enthesitis in FUTURE 4, which were assessed as prespecified exploratory endpoints) were analysed using a sequential hierarchical testing method, with p-values adjusted for multiplicity; testing order differed between trials.

ACR-$x$ improvement of ≥ $x$% from BL in American College of Rheumatology response criteria, BL baseline, DAS28-CRP 28-joint Disease Activity Score including levels of C-reactive protein, HAQ-DI Health Assessment Questionnaire Disability Index, IV intravenous, LD loading dose, NLD no loading dose, PASI $x$ improvement of ≥ $x$% from BL in Psoriasis Area and Severity Index score, PL placebo, pts patients, SC subcutaneous, SEC secukinumab, SF-36 PCS Medical Outcomes Study 36-item Short-Form Health Survey physical component summary.

*p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001 vs PL

aPrimary endpoint

bScores range from 2 to 10, with > 5.1 indicating active disease, ≤ 3.2 indicating low disease activity and < 2.6 indicating remission. BL scores ranged from 4.5 to 4.9 across all groups in all trials.

cScores range from 0 (maximum disability) to 100 (no disability). BL scores ranged from 36.2 to 39.2 across all groups in FUTURE 1–3.

dScores range from 0 to 3, with higher scores indicating greater disability. BL scores ranged from 1.1 to 1.3 across all groups in all trials.

In FUTURE 1, 4-weekly SC dosing of SEC was preceded by an IV loading regimen of 10 mg/kg at weeks 0, 2 and 4.

fData for all SEC groups were pooled.

hStatistical significance could not be tested under the hierarchical strategy since not all other endpoints higher in the hierarchy had reached significance for all doses; exploratory post hoc analyses showed significance for all doses of SEC vs PL (p-values not adjusted for multiplicity).

In the SEC LD groups, 4-weekly SC dosing of SEC was preceded by a SC loading regimen at weeks 0, 1, 2 and 3.
In subgroup analyses, low rates of radiographic progression were observed with secukinumab regardless of prior exposure to TNFi [20, 28] and whether patients were receiving concomitant methotrexate [28]. At week 52, the majority (85–92%) of patients receiving secukinumab had no radiographic progression, defined as ≤ 0.5 change from baseline in vdh-mTSS [20, 28].

2.1.1.3 Patient-Reported Outcomes Secukinumab improved physical function in patients with PsA, as indicated by significantly greater changes from baseline in Health Assessment Questionnaire Disability Index (HAQ-DI) scores at week 16 [15, 16] or 24 [12–14] with secukinumab 150 mg versus placebo in FUTURE 1 and 5 [12, 16] and with secukinumab 300 mg versus placebo in FUTURE 2, 3 and 5 [13, 14, 16] (Table 2). In FUTURE 4, the HAQ-DI response rate at week 16 was 34% in the secukinumab load group, 43% in the secukinumab no-load group (p < 0.01 vs placebo) and 29% in the placebo group [15]. Improvements in physical function seen with secukinumab at week 16 or 24 were maintained for up to 5 years in FUTURE 1 [23–25, 29] and FUTURE 2 [22, 26, 27].

Secukinumab improved HR-QOL, as assessed by the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [12–16] and the Functional Assessment of Chronic Illness Therapy (FACIT) measurement system [14, 15, 22, 29]. At week 16 [15] or 24 [12–14], secukinumab was associated with significantly greater improvements from baseline than placebo in SF-36 physical component summary scores (Table 2) [12–15] as well as FACIT-Fatigue scores [14, 15, 22, 29]. At week 24 in FUTURE 1 and 2, secukinumab was also associated with improvements from baseline in visual analogue scale (VAS) pain scores, PsA QOL, Work Productivity and Activity Impairment-General Health, Dermatology Life Quality Index and EuroQol 5-Dimension Health Status Questionnaire scores compared with placebo, with continued or additional improvements in these scores at week 52 [29] and week 104 [22, 30]. Improvements in HR-QOL were sustained over the longer term (up to 5 years) in FUTURE 1 [23–25] and FUTURE 2 [27].

In FUTURE 3, > 99% of patients reported successful self-administration of secukinumab using the autoinjector at week 1 [14]. Self-Injection Assessment Questionnaire scores for feelings about injections, self-confidence and satisfaction with self-injection were high. At week 2, ≥ 88% of patients were satisfied or very satisfied with the use of the autoinjector and found the device easy or very easy to use [14].

2.1.1.4 Disease Activity Endpoints Minimal disease activity (MDA), a composite measure including multiple PsA domains, was assessed in FUTURE 2 [31] and as a pre-specified exploratory endpoint in FUTURE 4 and 5 [15, 16]. Significantly (p < 0.05) more secukinumab than placebo recipients achieved an MDA response (i.e. fulfilling ≥ 5/7 criteria) at week 16 [15, 16, 31], with response rates sustained through 52 weeks in FUTURE 4 [15] and 5 years in FUTURE 2 [27]. In FUTURE 2, 40–49% of MDA responders met the more stringent criteria for very low disease activity (VLDA; fulfilling 7/7 criteria) at 2 years [31].

Post hoc analyses assessed the ability of secukinumab to achieve remission or low disease activity (LDA) using Disease Activity Index for Psoriatic Arthritis (DAPSA) and Psoriatic Arthritis Disease Activity Score (PASDAS) scores [16, 32, 33]. In FUTURE 2 and 5, more secukinumab than placebo recipients achieved DAPSA remission (score of ≤ 4) or LDA (score of > 4 to ≤ 14) at week 16 [16, 33], with responses maintained through 2 years [33]. In FUTURE 2, more patients achieved DAPSA remission (score of ≤ 4) compared with VLDA, and DAPSA remission + LDA (score of ≤ 14) compared with MDA [33]. More secukinumab than placebo recipients achieved PASDAS remission (score of ≤ 1.9) or LDA (score of > 1.9 to < 3.2) at week 16, with responses sustained through 2 years [32].

2.1.2 MAXIMISE Trial

The MAXIMISE trial enrolled patients aged ≥ 18 years with PsA and active spinal disease with a spinal pain VAS score of ≥ 40/100 and a Bath Ankylosing Spondylitis Disease Activity Index score of ≥ 4 despite the use of at least two NSAIDs [17]. Patients were randomized to receive subcutaneous secukinumab 150 mg (n = 165), secukinumab 300 mg (n = 167) or placebo (n = 166) weekly for 4 weeks and then every 4 weeks. At week 12, patients in the placebo group were re-randomized to secukinumab 150 or 300 mg. The primary endpoint was the proportion of patients achieving ≥ 20% improvement in the Assessment of Spondyloarthritis International Society response criteria (ASAS20) at week 12 [17].

Secukinumab improved axial manifestations in patients with PsA [17]. An ASAS20 response at week 12 was achieved by 66 and 63% of secukinumab 150 and 300 mg recipients, compared with 31% of placebo recipients; the odds ratios (ORs) for secukinumab 150 and 300 mg versus placebo were 4.4 (95% CI 2.7–7.0) and 3.8 (95% CI 2.4–6.1; both p < 0.0001). Similar ASAS20 response rates were seen in the subgroup of patients with positive MRI for spine and/or sacroiliac joints at baseline (66 and 70% vs 27%). ASAS20 response rates continued to increase through 52 weeks of treatment. The observed ASAS20 response rates at week 52 were 80% in the secukinumab 150 mg group, 81% in the secukinumab 300 mg group, 80% in patients who switched from placebo to secukinumab 150 mg at week 12 and 75% in patients who switched from placebo to secukinumab 300 mg at week 12. Secukinumab also reduced inflammation in the spine and sacroiliac joints (exploratory endpoint). Both doses of secukinumab significantly improved Berlin MRI
scores for the entire spine \((p < 0.05)\) and the sacroiliac joint \((p < 0.01)\) versus placebo at week 12, providing evidence of response in the objective signs of inflammation; these responses were sustained through week 52 [17].

### 2.1.3 ULTIMATE Trial

The ULTIMATE trial enrolled patients with PsA who had joint synovitis on power doppler ultrasonography and at least one clinical enthesitis site [18]. All patients were biological-naïve with active PsA and had an inadequate response to csDMARDs. They were randomized to receive subcutaneous secukinumab 150 or 300 mg \((n = 83)\) or placebo \((n = 83)\) weekly for 4 weeks and then every 4 weeks. The primary endpoint was the difference between secukinumab and placebo in mean change from baseline to week 12 in the global OMERACT-EULAR synovitis score (GLOESS) [18].

Secukinumab significantly reduced joint synovitis in patients with PsA [18]. The least squares mean change in GLOESS at week 12 was significantly \((p = 0.004)\) greater with secukinumab than with placebo \((−9.0 \text{ vs } −5.8)\); improvement was seen as early as week 1. Secukinumab was also associated with significantly \((p < 0.0001)\) higher ACR20 \((68 \text{ vs } 34\%)\) and ACR50 \((46 \text{ vs } 9\%)\) response rates than placebo. The least squares mean change from baseline in Spondyloarthritis Research Consortium of Canada enthesitis index was −2.35 with secukinumab versus −1.65 with placebo \((p = 0.02)\) [18].

### 2.2 Versus Adalimumab

The head-to-head EXCEED trial enrolled patients aged \(≥ 18\) years with active PsA, defined as \(≥ 3\) tender joints and \(≥ 3\) swollen joints [19]. They also had active plaque psoriasis with \(≥ 1\) plaque of \(≥ 2\) cm diameter or nail changes consistent with psoriasis or documented history of plaque psoriasis. All patients were biological-naïve, had an inadequate response or were intolerant to csDMARDs (including, but not limited to, methotrexate) and had an inadequate response to NSAIDs for \(≥ 4\) weeks prior to randomization. Stable dosages of concomitant NSAIDs and corticosteroids were permitted. Following a washout period of 4 weeks for all csDMARDs or 8 weeks for leflunomide, patients were randomized to receive subcutaneous secukinumab 300 mg via prefilled syringe at weeks 0, 1, 2, 3, and 4, then every 4 weeks until week 48 \((n = 426)\) or subcutaneous adalimumab 40 mg every 2 weeks until week 50 \((n = 427)\) [19].

Secukinumab was not more effective than adalimumab in the joint domain in patients with PsA [19]. The ACR20 response rate at week 52 (primary endpoint) was 67% with secukinumab and 62% with adalimumab (Table 3). In a pre-specified sensitivity analysis using non-responder imputation, respective ACR20 response rates were 67 and 59% \((\text{OR } 1.38; 95\% \text{ CI } 1.04–1.83; \ p = 0.0239)\). Because the superiority of secukinumab versus adalimumab for the primary endpoint was not met, statistical significance could not be formally tested for the key secondary endpoints in the hierarchy: PASI90, ACR50, change from baseline in HAQ-DI and resolution of enthesitis (Table 3). Of note, the PASI90 response rate was numerically higher with secukinumab than with adalimumab (Table 3). Overall, 14% of secukinumab recipients and 24% of adalimumab recipients discontinued treatment by week 52 [19].

### 2.3 Real-World Setting

Real-world experience has confirmed the efficacy of secukinumab for the treatment of PsA. In several real-world studies \((n ≥ 100)\) conducted mainly in Europe and the USA, secukinumab improved clinical outcomes (e.g. PsA symptoms,
In observational studies comparing adherence, retention and persistence rates with various bDMARDs in patients with PsA, results were mixed. In a retrospective cohort study using US pharmacy claims data (n = 1558), the 12-month discontinuation rate was lowest with secukinumab (37%), followed by adalimumab (43%), golimumab (45%), etanercept (48%) and certolizumab pegol (52%) [45]. Mean persistence ranged from 241 days with certolizumab pegol to 283 days with secukinumab. The proportion of patients who remained adherent to treatment was highest with secukinumab (46%), followed by adalimumab (44%), golimumab (39%), etanercept (37%) and certolizumab pegol (18%) [45]. In a French cohort study (n = 406), the persistence of secukinumab at 2 years was higher than that of ustekinumab [46]. In an observational study using data from a Nordic collaboration (n = 6062), 1-year treatment retention rates with secukinumab (63–72%) were comparable to those with adalimumab (67–73%), certolizumab pegol (49–66%), etanercept (62–73%), golimumab (56–69%) and infliximab (57–65%) [47].

3 Tolerability of Secukinumab

Subcutaneous secukinumab 150 or 300 mg was generally well tolerated in clinical trials, including in patients with PsA, plaque psoriasis, AS and other autoimmune conditions [7]. The tolerability profile was consistent across all indications. The most common adverse events (AEs) with secukinumab in clinical trials and post-marketing reports were upper respiratory tract infections (URTIs), most commonly nasopharyngitis and rhinitis [7].

During the 16- or 24-week placebo-controlled periods of FUTURE 1–3 and 5, AEs occurred in 55–65% of secukinumab recipients and 56–62% of placebo recipients, with serious AEs reported in 1–5% of secukinumab and 2–7% of placebo recipients, and discontinuations due to AEs reported in 0–4% of secukinumab and 2–4% of placebo recipients [12–14, 16]. During this period, the most common (incidence ≥ 5%) AEs with secukinumab were URTI, nasopharyngitis and headache [12–14, 16]. In the head-to-head EXCEED trial, the safety profiles of secukinumab and adalimumab were consistent with previous reports [19]. During the 52-week treatment period, AEs were reported in 77% of secukinumab recipients and 79% of adalimumab recipients. The most common (incidence ≥ 10%) AEs were nasopharyngitis (19% with secukinumab vs 19% with adalimumab) and URTI (10 vs 11%). Injection-site reactions occurred in 4% of secukinumab recipients and 11% of adalimumab recipients. Four percent of patients in the secukinumab group and 7% of patients in the adalimumab group discontinued treatment due to AEs [19].

Over the entire safety periods of FUTURE 1–5 (52 weeks in FUTURE 3 and 5 [14, 20], 104 weeks in FUTURE 4 [15], and 260 weeks in FUTURE 1 and 2 [24, 27]), the long-term tolerability profile of secukinumab was generally consistent with that reported previously, with no new or unexpected safety signals. The exposure-adjusted incidence rate (EAIR) of any AE during 5 years of secukinumab treatment was 126.7 per 100 patient-years (PY) in FUTURE 1 [24] and 140.5 per 100 PY in FUTURE 2 [27]. In a pooled analysis of FUTURE 1–3 (n = 1380; total exposure 3866.9 PY), the EAIR of any AE with secukinumab across the entire safety period was 147.0 per 100 PY [48]. Post-marketing safety surveillance data based on cumulative secukinumab exposure of ≈ 285,811 PY across three indications (PsA, plaque psoriasis and AS) confirmed that secukinumab was generally well tolerated over the longer-term [49].

3.1 Adverse Events of Special Interest

Treatment with secukinumab may increase the risk of infections [6, 7], with the incidence of some types of infections appearing to be dose-dependent [6]. In placebo-controlled trials in patients with PsA, plaque psoriasis, AS or nr-axSpA, higher rates of common infections such as URTI, nasopharyngitis and mucocutaneous Candida infections were observed with secukinumab relative to placebo [6, 7]. However, these infections were of mild to moderate severity and did not require discontinuation of secukinumab [7]. In a pooled analysis of FUTURE 1–5 (n = 2678; total exposure 5984.6 PY), serious infections and Candida infections occurred at EAIRs of 1.8 and 1.5 per 100 PY of exposure to secukinumab during the entire safety period [49]. Caution is advised when considering the use of secukinumab in patients with chronic infections or a history of recurrent infection [6, 7]. If signs or symptoms of an infection occur, patients should seek medical advice. Patients who develop a serious infection while receiving secukinumab should be closely monitored and secukinumab should be discontinued until the infection resolves [6, 7].

No cases of active tuberculosis (TB) or latent TB infection reactivation were reported in the secukinumab clinical trial programme [50]. However, patients should be evaluated for TB infection prior to initiating secukinumab, and should be closely monitored for signs and symptoms of active TB during and after treatment [6]. Secukinumab should not be given to patients with active TB, and anti-TB therapy should be considered prior to initiation of secukinumab in patients with latent TB [6, 7].
There have been reports of new-onset or exacerbations of inflammatory bowel disease (IBD), including some serious cases, in patients receiving secukinumab [6, 7]. In the pooled analysis of FUTURE 1–5, the EAIRs of IBD, Crohn’s disease and ulcerative colitis with secukinumab during the entire safety period were 0.03, 0.1 and 0.1 per 100 PY, respectively [49]. Data on a year-on-year basis showed no increase in the EAIR of IBD with secukinumab treatment over time [49]. Data on a year-on-year basis showed no increase in the EAIR of IBD with secukinumab treatment over time [49].

Serious allergic reactions to secukinumab should be treated with appropriate therapy, and the drug should be discontinued immediately [6, 7].

In the pooled analysis of FUTURE 1–5, the EAIRs for a number of other AEs of special interest were low and stable during the entire safety period, namely malignancy (1.0 per 100 PY), major adverse cardiovascular events (MACE; 0.4 per 100 PY) and uveitis (0.1 per 100 PY) [49]. Similar results were seen in post-marketing surveillance. Across five consecutive periodic safety update reporting periods between December 2014 and December 2018, the rates of serious infections, malignancy, total IBD and MACE were 1.4, 0.3, 0.2 and 0.2 per 100 PY, respectively [49].

Like all therapeutic proteins, secukinumab has the potential for immunogenicity [6]. Over 52 weeks of treatment in FUTURE 1–3, five (0.4%) secukinumab recipients developed anti-drug antibodies (ADAs) [51]. In four of these cases, the antibodies were non-neutralizing. The emergence of ADAs was not associated with immunogenicity-related AEs, loss of clinical response or deviations in the expected pharmacokinetics of secukinumab [51].

### 4 Dosage and Administration of Secukinumab

Subcutaneous secukinumab is approved in the USA [6] and the EU [7] for the treatment of adult patients with active PsA (when the response to previous DMARD therapy has been inadequate [7]), and may be administered with or without concomitant methotrexate [6, 7]. Secukinumab is available as a lyophilized powder (150 mg) in a vial for reconstitution, or as a 150 mg/mL solution for injection in a prefilled syringe or Sensoready® pen. The lyophilized powder for reconstitution is to be administered by healthcare providers only, while secukinumab in a prefilled syringe or pen may be self-injected after proper training in subcutaneous injection technique [6, 7]. Each injection should be administered at a different site (e.g. upper arm, thigh or abdomen) than the previous injection [6], avoiding areas of skin affected by psoriasis (if possible) [6, 7].

The recommended dose of secukinumab in patients with PsA and concomitant moderate to severe plaque psoriasis (or an inadequate response to TNFi [7]) is 300 mg administered at weeks 0, 1, 2, 3 and 4, followed by 4-weekly (USA) or monthly (EU) maintenance dosing [6, 7]. For other patients with PsA, the recommended dose of secukinumab is 150 mg administered at weeks 0, 1, 2, 3 and 4 (i.e. loading doses), followed by 4-weekly (USA) or monthly (EU) maintenance dosing [6, 7]; or alternatively, in the USA [6], 150 mg administered every 4 weeks without loading doses. The dose of secukinumab can be increased to 300 mg based on clinical response [7] or if active disease persists [6]. Consult local prescribing information for further detailed information regarding contraindications, warnings and precautions, drug interactions and use in special populations.

### 5 Place of Secukinumab in the Management of Psoriatic Arthritis

The main goals in the treatment of PsA are to control symptoms, prevent structural damage, optimize physical function and improve HR-QOL [52]. The choice of treatment is dependent on the clinical presentation of the disease. Consideration should be given to each musculoskeletal manifestation, as well as to non-musculoskeletal manifestations and comorbidities [52]. Treatment guidelines from the Group for Research and Assessment of Psoriasis and PsA (GRAPPA) [53] and EULAR [52] recommend a csDMARD (preferably methotrexate [52]) as first-line therapy for peripheral arthritis, followed by a bDMARD [i.e. TNFi, interkeukin-12/23 inhibitor (IL-12/23i) or interleukin-17 inhibitor (IL-17i)] if treatment targets are not achieved. In patients with predominantly axial disease, EULAR guidelines recommend the use of an IL-17i over a TNFi when there is relevant skin involvement [52]. Joint ACR and National Psoriasis Foundation (NPF) guidelines conditionally recommend a TNFi over an oral small molecule (i.e. csDMARD or apremilast) for treatment-naïve PsA, with IL-12/23i and IL-17i conditionally recommended after TNFi or in patients with contraindications to TNFi [54].

Secukinumab is a fully human monoclonal antibody that inhibits the proinflammatory effects of IL-17A (Table 1), and was the first IL-17i to be approved for the treatment of active PsA (Sect. 4). Subcutaneous secukinumab 150 or 300 mg was effective in the treatment of PsA in phase III clinical trials (Sect. 2). In the FUTURE trials, which included patients with different subtypes of PsA [6, 7], secukinumab improved clinical signs and symptoms compared with placebo, with these benefits maintained over the longer term.
The efficacy of secukinumab was seen across all key clinical domains of PsA, including ACR and PASI response rates, DAS28-CRP, and resolution of dactylitis and enthesitis. Of note, secukinumab was associated with clinically relevant improvements in some of the more stringent endpoints, such as ACR50, PASI90 (Sect. 2.1.1.1), MDA, VLDA and DAPSA remission (Sect. 2.1.1.4).

The clinical benefits of secukinumab were seen regardless of whether patients had or had not received previous TNFi and irrespective of concomitant methotrexate use (Sect. 2.1.1.1). The finding that secukinumab may be effective in both TNFi-naïve and –experienced patients is important, given that GRAPPA and EULAR treatment guidelines recommend switching to either another TNFi or to a different bDMARD class (i.e. IL-17i or IL-12/23i) if treatment targets are not met with the first TNFi [52, 53]. Current ACR/NPF guidelines conditionally recommend switching to a different TNFi after failure of the first TNFi [54].

PsA is a chronic and multifaceted disease which has a significant impact on HR-QOL in terms of physical dysfunction, pain, fatigue, work disability and emotional/social impairment [4]. In clinical trials, secukinumab was associated with clinically meaningful improvements in patient-reported measures of physical function and HR-QOL (including pain, fatigue and work productivity) compared with placebo, with these improvements sustained over the longer term (Sect. 2.1.1.3).

Bone erosions are evident in approximately half of patients with PsA within 2 years of diagnosis, and many patients experience irreversible joint damage and disability [16]. Therefore, the prevention of structural damage is a fundamental goal in the management of PsA [52]. In FUTURE 1 and 5, secukinumab inhibited structural joint damage, with sustained low rates of radiographic progression seen over the longer term (Sect. 2.1.1.2). Notably, switching to secukinumab inhibited further radiographic progression in patients initially randomized to placebo (Sect. 2.1.1.2).

Axial disease is reported to affect 25–70% of patients with longstanding PsA [17]. Its burden of disease is underestimated, and it is distinct from axial spondyloarthritis [17]. The effect of secukinumab on axial disease was not assessed in the FUTURE trials, which was specifically noted as a potential limitation of FUTURE 1 and 2 [12, 13]. MAXIMISE was the first randomized controlled trial to evaluate the efficacy of a biological agent in the management of axial manifestations of PsA [17]. Final 52-week results demonstrated that secukinumab improved ASAS responses and reduced inflammatory MRI lesions in the spine and sacroiliac joints in PsA patients with axial involvement (Sect. 2.1.2). Further clinical trials with other bDMARDs would be of interest.

In the head-to-head EXCEED trial, secukinumab did not quite attain statistical significance for superiority versus the TNFi adalimumab in the joint domain (Sect. 2.2). Nevertheless, the trial provides new information regarding the comparative efficacy of two bDMARDs with differing mechanisms of action [55], and may help guide clinical decision-making regarding treatment choices for PsA after csDMARD failure or intolerance [19]. Additional well-designed clinical trials directly comparing secukinumab with other pharmacological agents in patients with PsA are needed. A phase III head-to-head trial comparing the efficacy of secukinumab and the IL-12/23i ustekinumab in patients with PsA and TNFi failure (AGAIN; NCT04632927) is currently underway. In addition, a number of systematic reviews and meta-analyses have indirectly compared the efficacy of bDMARDs (e.g. TNFi, ustekinumab, the IL-17i ixekizumab, secukinumab) and targeted synthetic DMARDs (e.g. apremilast) in patients with psA [56–61]. However, the findings of these analyses require cautious interpretation due to the indirect nature of the comparisons and the heterogeneity of the studies and patient populations assessed.

Secukinumab was generally well tolerated in clinical trials (Sect. 3). The tolerability profile of secukinumab in patients with PsA was consistent with the profile of the drug used in other approved indications, including plaque psoriasis and AS. Secukinumab remained generally well tolerated over the longer term (up to 5 years), with no new or unexpected safety signals. Post-marketing safety surveillance data based on cumulative secukinumab exposure of > 285,000 PY were consistent with data from clinical trials (Sect. 3).

Treatment retention is a composite measure of a drug’s efficacy and tolerability [47], and low adherence rates and/or high discontinuation rates may indicate suboptimal treatment [45]. In real-world studies, rates of adherence, retention and persistence with secukinumab were better than or similar to those with other bDMARDs (Sect. 2.3). Additional studies would help to further elucidate the position of secukinumab in the real-world setting. The ongoing, longitudinal, observational SERENA study (n = 2932) will assess the long-term (up to 5 years) retention of secukinumab in routine clinical practice across three indications (plaque psoriasis, AS and PsA) [62].

The choice of treatment for PsA is individualized and should take into account factors such as comorbidities and patient preferences (e.g. route of administration, ease of use) [53, 54]. Like all newer bDMARDs, secukinumab is administered subcutaneously. After appropriate training, secukinumab can be self-administered via a prefilled syringe or pen (Sect. 4). Such devices offer patients convenience and ease of administration, both of which may improve...
their adherence to treatment. In the FUTURE 3 trial, most patients were satisfied or very satisfied with the autoinjector and found it easy or very easy to use (Sect. 2.1.1.3). In real-world clinical practice, secukinumab was associated with high levels of patient and physician satisfaction (Sect. 2.3).

Cost is another factor that can influence the choice of therapy in PsA. Current National Institute for Health and Care Excellence guidance indicates that secukinumab is cost effective in some clinical settings [63]. Semi-Markov models were used to evaluate the cost effectiveness of secukinumab in patients with PsA from the perspectives of the German statutory health insurance system [64] and the Argentinean social security healthcare system [65]. Results suggest that, over a lifetime horizon, secukinumab is cost effective compared with other bDMARDs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab and ustekinumab) in both biological-experienced patients and biological-naïve patients (without or without concomitant moderate to severe psoriasis) [64, 65]. Additional pharmacoeconomic data relevant to the EU and the USA would be useful.

In conclusion, subcutaneous secukinumab is effective across all key PsA domains and is generally well tolerated, with efficacy and tolerability sustained over the longer term. Thus, secukinumab represents a useful treatment alternative to TNFi and other bDMARDs in adult patients with active PsA.

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