

# The Role of Interleukin 23/17 Axis in Psoriasis Management: A Comprehensive Review of Clinical Trials

Luca Potestio , Fabrizio Martora , Giuseppe Lauletta , Ylenia Vallone, Teresa Battista, Matteo Megna

Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Napoli, Italy

\*These authors contributed equally to this work

Correspondence: Luca Potestio, Section of Dermatology - Department of Clinical Medicine and Surgery, University of Naples Federico II, Via Pansini 5, Napoli, 80131, Italy, Tel +39 - 081 - 7462457, Fax +39 - 081 - 7462442, Email potestioluca@gmail.com

**Abstract:** Psoriasis pathogenesis is influenced by genetic factors and characterized by a complex interplay between genetic predisposition and various environmental triggers. These triggers set off metabolic processes involving inflammation, cell signaling, immune response dysregulation, and antigen presentation. Several types of innate and adaptive immune cells are involved in psoriasis. Among the cytokine cascade which leads to psoriasis development, the interleukin (IL)-23/Th17 axis, especially IL-17 production, emerges as crucial. Recognizing the pivotal role of this axis has facilitated the development of selective and effective biological drugs, such as anti-IL17 and anti-IL23 monoclonal antibodies. These drugs aim to achieve the complete or near-complete disappearance of psoriatic lesions, as indicated by PASI100 and PASI90 responses, respectively. In this context, the aim of our review was to delve into the functioning of the IL-23/Th17 axis, its dysregulation in psoriasis pathogenesis, and the therapeutic potential of its inhibition. Currently, 4 anti-IL17 (secukinumab, ixekizumab, bimekizumab and brodalumab) and 3 anti-IL23 (guselkumab, risankizumab and tildrakizumab) have been approved. All these drugs showed high levels of effectiveness in both clinical trials and real-life experiences, with an excellent profile in terms of safety. Certainly, further studies will allow for better characterization of biologics' profile, in order to administer the right drug for the right patients at the right moment.

**Keywords:** psoriasis, management, clinical trial, IL-17/23 axis

## Introduction

Psoriasis, a chronic-relapsing inflammatory skin condition, affects up to 3% of the general population.<sup>1,2</sup> The prevalence is consistent across genders, displaying a bimodal onset distribution with peaks at 30–39 years and 60–69 years in men, and occurring 10 years earlier in women.<sup>3</sup> Clinically, several phenotypes can be distinguished, with plaque psoriasis as the commonest form (about 90% of cases), characterized by the excessive proliferation and abnormal differentiation of keratinocytes, leading to well-defined erythematous-desquamative plaques covered by whitish or silvery scales, predominantly found on elbows, knees, scalp, and the lumbar area.<sup>1,3</sup> Other phenotypes include guttate, erythrodermic, pustular, inverse, and palmoplantar psoriasis.<sup>1,3,4</sup>

Moreover, psoriasis is now considered as a systemic disease, as it is frequently linked to several comorbidities such as psoriatic arthritis, metabolic syndrome, diabetes mellitus, chronic inflammatory bowel disease (IBD), and other systemic diseases.<sup>5,6</sup> Additionally, individuals with psoriasis exhibit elevated rates of depression, anxiety, and neurological disorders, highlighting the significant negative impact on the quality of life of this disease.<sup>7</sup>

As regards the etiopathogenesis, multiple factors are involved, including environmental (such as infections, drugs, trauma, and obesity), genetic (up to 40% of psoriasis patients have relatives with the disease), and immunologic elements extensively discussed in the literature.<sup>8</sup> In particular, psoriasis pathogenesis is significantly influenced by genetic factors

and characterized by a complex interplay between genetic predisposition and various environmental triggers.<sup>8</sup> These triggers set off metabolic processes involving inflammation, cell signalling, immune response dysregulation, and antigen presentation.<sup>9,10</sup> Genome-wide association studies (GWAS) have identified more than 63 susceptibility regions associated with psoriasis in European populations, along with over 20 other loci in the Chinese population.<sup>11</sup>

Globally, the formation of psoriatic plaques relies on the intricate interaction between keratinocytes and immune response cells, including T lymphocytes, myeloid and plasmacytoid dendritic cells, macrophages, NK and NK-T cells, granulocytes, mast cells, and innate lymphoid cells. This extensive crosstalk between innate and adaptive immune cells and resident skin cells initiates and sustains a chronic inflammatory state underlying psoriasis.<sup>12</sup> Current pathogenetic models propose that environmental events, such as infection, trauma, or psychological stress, trigger the activation of innate and adaptive immune cells, leading to cytokine production.<sup>12</sup> Dendritic cells (DCs), particularly important in the early stages, play a key role.<sup>12</sup> Their activation depends on the recognition of antimicrobial peptides released by keratinocytes, with LL-37 peptide being emphasized due to its overexpression in psoriatic skin.<sup>13</sup> LL-37's binding to damaged cell DNA activates plasmacytoid dendritic cells, stimulating them to produce Interferon (IFN)-alpha in the psoriatic plaque.<sup>13</sup> This sets off a cascade, involving myeloid dendritic cells and naive T lymphocytes, resulting in the production of cytokines like Tumor Necrosis Factor (TNF)-α, interleukin (IL)-6, IL-12, and IL-23.<sup>14,15</sup> The IL-23/Th17 axis, especially IL-17 production, emerges as crucial in psoriatic lesion development.<sup>14,15</sup> Studies using mouse models show that IL-23 injection induces erythema and hardening similar to psoriatic lesions.<sup>14,15</sup> Additionally, elevated levels of IL-17C, when associated with other proinflammatory factors, lead to psoriatic skin-like symptoms in mice.<sup>16,17</sup> High levels of IL-23 and IL-17 in human psoriatic plaques and patient serum have spurred interest in understanding the IL-23/Th17 axis's role in psoriasis pathogenesis.<sup>16,17</sup> Recognizing the pivotal role of this axis has facilitated the development of selective and effective biological drugs, such as anti-IL17 and anti-IL23 monoclonal antibodies.<sup>18,19</sup> These drugs aim to achieve the complete or near-complete disappearance of psoriatic lesions, as indicated by PASI100 and PASI90 responses, respectively.<sup>16,17</sup> In this context, the aim of our review was to delve into the functioning of the IL-23/Th17 axis, its dysregulation in psoriasis pathogenesis, and the therapeutic potential of its inhibition.

## Materials and Methods

A comprehensive analysis of the current medical literature was performed on the PubMed, Ovid, Scopus, Embase, and Cochrane Library databases until January 26, 2024. In conducting this review, Medical Subject Headings (MeSH) terms and medical terminology related to clinical trials were employed, focusing on the pharmacological agents secukinumab, ixekizumab, brodalumab, bimekizumab, guselkumab, risankizumab, and tildrakizumab. The search strategy incorporated specific research terms such as “IL-17 inhibitors”, “IL-23 inhibitors”, “IL-23/IL-17 axis”, “guselkumab”, “risankizumab”, “tildrakizumab”, “secukinumab”, “ixekizumab”, “brodalumab”, “bimekizumab”, in conjunction with “psoriasis”, and “clinical trial”. All fields including title, abstract, keywords, and full text were involved in the search. Moreover, also references were reviewed to include manuscript which could have missed. The review encompassed clinical and epidemiological studies, as well as reviews and systematic reviews focusing on these biologic agents. Non-English manuscripts were excluded. It is crucial to highlight that the information presented in this article is derived from previously conducted studies.

## Results

Results are divided in two main sections entitled IL-23 inhibition and IL-17 inhibition. At the end of each paragraph, a focus on the safety of the inhibition of each IL has been discussed.

### IL-23 Inhibitors

IL-23 is a cytokine consisting of a heterodimer with a shared p40 subunit with IL-12 and a p19 subunit common to both IL-23 and IL-39.<sup>20</sup> In psoriatic lesions, IL-23 is significantly upregulated compared to non-lesional skin.<sup>21</sup> Dermal CD11c+ immune cells, including macrophages and various subsets of myeloid dendritic cells, are the primary cellular sources of IL-23 in psoriatic lesions.<sup>21</sup> The production of IL-23 is intricately regulated by TLR receptor signalling and is augmented by TNFα, IFN-γ, and specific transcription factors.<sup>22</sup>

IL-23 exerts its effects through a cellular receptor, IL-23R, expressed on memory T cells, NK cells, mast cells, neutrophils, macrophages, and ILCs.<sup>23</sup> In psoriatic lesions, the most notable impact of IL-23 is the stabilization of a Th17-secreting phenotype and the stimulation of IL-17 secretion by effector and memory T cells.<sup>24</sup> The pivotal role of IL-23 in the pathogenesis of psoriasis, particularly in the persistence of psoriatic lesions, has been substantiated by the remarkable reduction, and in some cases, complete disappearance, of skin lesions observed in psoriasis patients treated with IL-23 inhibitors. Currently, three IL-23 inhibitors—guselkumab, tildrakizumab, and risankizumab—have received approval for the treatment of psoriasis.

### Guselkumab

Guselkumab is an IL-23 p19 subunit antagonist approved in July 2017 for the management of adult patients with moderate-to-severe plaque psoriasis at the dosage of 100 mg administered subcutaneously at weeks 0 and 4, followed by a maintenance dose given every 8 weeks (Q8W).<sup>25</sup> The antagonism of IL-23 p19 subunit, led to the obstruction of the binding of IL-23 to its receptor.<sup>25</sup> Two double-blind, placebo-controlled Phase III trials, VOYAGE 1 (NCT02207231) and VOYAGE 2 (NCT02207244), assessed the efficacy and safety of guselkumab compared to placebo in patients with moderate-to-severe psoriasis.<sup>26,27</sup> In both studies, guselkumab demonstrated superiority over adalimumab through week 48.<sup>28,29</sup> VOYAGE 1 showed that, at week 16, 85.1% of guselkumab-treated patients achieved clear or minimally psoriatic lesions, with 73.3% achieving PASI 90, while adalimumab percentages were lower (65.9% and 49.7%, respectively) and placebo even more so (6.9% and 2.9%, respectively).<sup>28</sup> In VOYAGE 2, at week 16, 84.1% of guselkumab-treated patients achieved clear or minimally psoriatic lesions, with 70% achieving PASI 90, compared to lower percentages for adalimumab (67.7% and 46.8%, respectively) and placebo (8.5% and 2.4%, respectively).<sup>29</sup> Long-term efficacy and consistent safety of guselkumab were demonstrated in a trial extension, with 84.1% and 82.0% achieving  $\geq 90\%$  improvement in PASI at week 252 in VOYAGE 1 and VOYAGE 2, respectively.<sup>30</sup> The NAVIGATE study (NCT02203032) evaluated guselkumab efficacy in patients with moderate-to-severe plaque psoriasis who did not adequately respond to 16 weeks of ustekinumab treatment.<sup>31</sup> Guselkumab demonstrated superior efficacy over ustekinumab in terms of achieving an investigator global assessment (IGA) score of 0/1 with an improvement  $\geq 2$ .<sup>32</sup> Moreover, in a Phase 3, double-blind, randomized study (ECLIPSE, NCT03090100), guselkumab was compared to secukinumab. Guselkumab was found to be superior, with a higher percentage achieving PASI 90 at Week 48 (84.5% vs 70.0%,  $p < 0.001$ ).<sup>33</sup>

In the Phase IV IXORA-R trial, ixekizumab showed a faster response than guselkumab at week 24, although efficacy at 24 weeks was comparable.<sup>34</sup> Guselkumab also demonstrated superiority over fumaric acid esters (FAEs), with 82% of guselkumab-treated patients achieving PASI90 versus 27% of FAEs-treated.<sup>34</sup> Finally, the effectiveness of guselkumab has been confirmed by real-life studies.<sup>35–39</sup>

### Risankizumab

Risankizumab, a humanized IgG1 monoclonal antibody targeting the p19 subunit of IL-23, received the approval from the European Medicines Agency in April 2019 for the management of moderate-to-severe plaque psoriasis at the dosage of 150 mg at week 0, week 4, and then every 12 weeks (Q12W) thereafter, administered as subcutaneous injection.<sup>40</sup> Its efficacy and safety in treating moderate-to-severe plaque psoriasis were assessed in both clinical trials and several real-life experiences.<sup>41–45</sup> In particular, two double-blind, randomized, placebo-controlled, and ustekinumab-controlled phase 3 trials—UltIMMa-1 and UltIMMa-2.<sup>46</sup> These trials demonstrated higher efficacy in achieving PASI90 and static Physician Global Assessment (sPGA) scores at week 16 compared to ustekinumab.<sup>46</sup> UltIMMa-1 showed PASI90 rates of 75.3% vs 42%, and sPGA 0/1 rates of 87.7% vs 63% for risankizumab and ustekinumab, respectively.<sup>46</sup> UltIMMa-2 reported PASI90 rates of 74.8% vs 47.5%, and sPGA 0/1 rates of 83.7% vs 61.6% for risankizumab and ustekinumab, respectively.<sup>46</sup> The IMMhance trial, was a placebo-controlled phase III trial which confirmed the long-term efficacy of risankizumab.<sup>47</sup> Moreover, a five-year follow-up from a phase 3 open-label extension study, LIMMitless, showed sustained efficacy of risankizumab (150 mg every 12 weeks) for adults with moderate-to-severe plaque psoriasis.<sup>48</sup> At week 256, 85.1% achieved PASI90, 52.3% achieved PASI100, 85.8% achieved sPGA 0/1, and 76.4% achieved Dermatology Life Quality Index (DLQI) 0/1. The safety profile remained consistent with no emerging safety signals.<sup>48</sup>

In the IMMvent trial, a phase 3 randomized double-blind clinical trial comparing risankizumab to adalimumab, risankizumab exhibited significantly greater efficacy than adalimumab in achieving skin clearance for moderate-to-severe plaque psoriasis.<sup>49</sup> Indeed, more than 72% of patients achieved PASI90, and over 83% reached an sPGA of 0/1 at week 16.<sup>49</sup>

The IMMerge study comparing risankizumab to secukinumab found risankizumab to be non-inferior to secukinumab at week 16 regarding PASI90 and superior to secukinumab at week 52 (86.6% vs 57.1%,  $p < 0.001$ ). Secondary endpoints also demonstrated risankizumab's superiority at week 52.<sup>50</sup> Thaçi et al conducted a comparison between risankizumab and FAEs and found a substantial difference in efficacy at week 24: 83.3% of risankizumab-treated patients achieved PASI90 compared to 10% with FAEs.<sup>51</sup> In the IMPulse study, a 52-week phase IV multicentre study, the efficacy and safety of risankizumab versus apremilast in adults with moderate plaque psoriasis were compared. Risankizumab was more effective than apremilast at week 16 and exhibited clear clinical benefits even at 52 weeks for patients who had switched from apremilast to risankizumab.<sup>52</sup>

### Tildrakizumab

Tildrakizumab is a high-affinity IgG1  $\kappa$  antibody which targets IL-23 p19 blocking its activity, approved in March 2018 for the treatment of moderate-to-severe plaque psoriasis at the dosage of 100 mg administered subcutaneously at weeks 0 and 4 followed by a maintenance dose given Q12W.<sup>53</sup> The efficacy and safety of tildrakizumab in adults with moderate-to-severe chronic plaque psoriasis were evaluated in two Phase III, parallel-group, double-blind, randomized trials: reSURFACE 1 (NCT01722331) and reSURFACE 2 (NCT01729754).<sup>54,55</sup> In reSURFACE 1, 772 patients were randomized to receive tildrakizumab 200 mg, tildrakizumab 100 mg, or placebo, while in reSURFACE 2, 1090 patients were randomized to receive tildrakizumab 200 mg, tildrakizumab 100 mg, placebo, or etanercept 50 mg.<sup>56</sup> Tildrakizumab was administered subcutaneously at weeks 0 and 4 (part 1) and every 12 weeks thereafter (part 2), while placebo was administered at weeks 0 and 4 (part 1), and participants initially receiving placebo were re-randomized to receive tildrakizumab 200 or 100 mg at weeks 12 and 16.<sup>57</sup> In reSURFACE 2, etanercept was administered twice a week in part 1 and once a week in part 2.<sup>57</sup> Primary endpoints showed that after 12 weeks of treatment, both tildrakizumab doses achieved significantly higher PASI 75 and PGA response rates compared to placebo in both studies. At week 28, tildrakizumab continued to demonstrate efficacy with high PASI 75, PASI 90, and PGA response rates.<sup>57</sup> In the extension period of reSURFACE 1 and reSURFACE 2 studies, the efficacy and safety of tildrakizumab were demonstrated up to 5 years of treatment. Responders to tildrakizumab 100 mg and 200 mg, as well as partial responders/non-responders to etanercept switched to tildrakizumab 200 mg at week 28, showed sustained efficacy over the 244-week period. The safety profile of tildrakizumab remained consistent and reassuring throughout the 5-year extension period.<sup>58</sup> Notably, the discontinuation rate for tildrakizumab due to adverse events was only 1% in both trials, indicating a favorable safety profile.<sup>57</sup> In conclusion, tildrakizumab demonstrated superior efficacy compared to both placebo and etanercept at week 12, and its effectiveness continued to increase until week 28, with no significant difference observed between the two dosage groups. The long-term extension studies further supported the sustained efficacy and safety of tildrakizumab over a 5-year period.<sup>58</sup> Finally, real-life experiences confirmed the effectiveness of this drug.<sup>59–67</sup>

### IL-23 Inhibitors Safety Profile

The Phase III trials with IL-23 inhibitors reported common adverse events, including non-serious upper respiratory infections, nasopharyngitis, headache, neutropenia, arthralgias, and mild injection site reactions. Rare adverse events included skin or soft tissues abscesses and non-melanoma skin cancers. Unlike IL-17 inhibitors, drugs inhibiting IL-23 are not associated with worsening or the onset of chronic IBD. Additionally, a Phase 2 study of risankizumab demonstrated the occurrence of clinical remission of chronic IBD.<sup>68</sup>

A recent disproportionality analysis of drug-event pairs in the FDA Adverse Event Reporting System (FAERS) conducted by Woods highlighted a potential cerebrovascular accident (CVA) signal in psoriasis patients treated with risankizumab. Woods found that risankizumab was associated with significantly disproportionate CVA reporting compared to all other drugs in FAERS (ROR 2.48; 95% CI 2.14–2.88).<sup>69</sup> However, these results were criticized by Sinvhal et al, who pointed out numerous limitations in the analysis conducted by Woods and concluded that CVA is not a safety concern in patients treated with risankizumab.<sup>70</sup> Further long-term safety studies will be necessary to clarify the significance of this unconfirmed security signal in real life.

## IL-17 Inhibitors

IL-17 plays a pivotal role in the pathogenesis of psoriatic disease, as evidenced by the critical impact of biologic drugs targeting this cytokine (in particular IL-17A, IL-17F, and IL-17 receptor A).<sup>16</sup> Specifically, IL-17A, released by CD8+ T cells, neutrophils, mast cells,  $\gamma\delta$  and  $\alpha\beta$  T cells in individuals with psoriatic lesions, induces the proliferation of keratinocytes, leading to the production of proinflammatory cytokines and antimicrobial peptides, thereby promoting tissue inflammation.<sup>71,72</sup> Furthermore, IL-17A downregulates the production of essential substances like filaggrin, crucial for the physiological differentiation of keratinocytes, contributing to alterations in the skin barrier, leading to manifestations such as erythema, hyperkeratosis, and desquamation.<sup>73</sup> Currently, 4 IL-17 inhibitors have received approval for the treatment of psoriasis. In particular, there are 2 IL-17A inhibitors (secukinumab and ixekizumab), 1 dual IL-17A and F inhibitor (bimekizumab), and 1 anti-IL17 receptor antagonist (brodalumab). Phase III clinical trials have demonstrated the high efficacy and safety of these inhibitors in managing psoriasis.

### Secukinumab

Secukinumab is a fully human monoclonal antibody which targets and neutralizes IL-17A, inhibiting its interaction with the IL-17 receptor.<sup>74</sup> It was the first anti-IL17A inhibiting drug ever approved for the treatment of adults with moderate-to-severe plaque psoriasis in January 2015.<sup>74</sup> It is administered subcutaneously, at a dose of 300 mg at weeks 0, 1, 2 and 3, followed by a maintenance dose of 300 mg every 4 weeks (Q4W). Its effectiveness has been widely reported by clinical trials and real-life experiences.<sup>75–80</sup> In particular, to confirm the crucial role of IL-17A in psoriasis, two double-blind, 52-week clinical, randomized, phase 3 trials which evaluated the efficacy and safety of secukinumab in patients with moderate-to-severe plaque psoriasis were conducted.<sup>81</sup>

The ERASURE (NCT01365455) (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) study included 738 adults with moderate-to-severe plaque psoriasis who were randomized 1:1:1 to receive subcutaneous secukinumab at a dose of 300 mg or 150 mg (once a week for 5 weeks, later Q4W), or placebo.<sup>82</sup>

In the FIXTURE (NCT01358578) (Full Year Investigative Examination of Secukinumab vs Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) study 1306 patients were randomized 1:1:1:1 to receive subcutaneous secukinumab at a dose of 300 mg or 150 mg (once a week for 5 weeks, later Q4W), etanercept at a dose of 50 mg (twice a week for 12 weeks, later once a week) or placebo.<sup>83</sup> Of note, in this second study, secukinumab was compared with etanercept.

Both studies had a screening period of 1 to 4 weeks, a 12 weeks induction period, a 40 weeks maintenance period and a 8 weeks follow-up period. Primary endpoints were a reduction of 75% or more from baseline in the psoriasis area-and-severity index score (PASI 75) and a score of 0 (clear) or 1 (almost clear) on a 5-point modified IGA (coprimary endpoints).<sup>81</sup>

At the end of the induction period (12 weeks) in the ERASURE study, 81.6% of patients who received secukinumab 300 mg achieved PASI 75 compared to 71.6% of patients who received secukinumab 150 mg and 4.5% of patients treated with placebo ( $P<0.001$  for secukinumab groups vs placebo one).<sup>84</sup> Furthermore, 65.3% of patients treated with secukinumab 300 mg achieved IGA 0 or 1 compared to 51.2% treated with secukinumab 150 mg and 2.4% of patients treated with placebo ( $P<0.001$  for secukinumab groups vs placebo one).<sup>84</sup> At the end of the induction period (12 weeks) in the FIXTURE study, instead, 77.1% of patients who received secukinumab 300 mg achieved PASI 75 compared to 67.0% of patients who received secukinumab 150 mg, 44% of patients who received etanercept and 4.9% of patients from the placebo group ( $P<0.001$  for secukinumab groups vs comparators).<sup>84</sup> Furthermore 63% of patients treated with secukinumab 300 mg achieved IGA 0 or 1 compared to 51.1% of patients treated with secukinumab 150 mg, and 2.8% of patients treated with placebo ( $P<0.001$  for each secukinumab group vs comparators).<sup>84</sup> About secondary endpoints, the percentage of patients who achieved DLQI of 0 or 1 after induction time was much more important in secukinumab groups in comparison with etanercept or placebo arms ( $P<0.001$  for all comparisons).<sup>84</sup> Besides, the median time to a 50-percent reduction in PASI from baseline was much shorter in both secukinumab groups (3 weeks for 300mg secukinumab and 4 weeks for 150mg secukinumab) in comparison with etanercept group (7 weeks) ( $P<0.001$  for both comparisons).<sup>84</sup> During both studies, Secukinumab, in particular at the dose of 300 mg, appeared superior to placebo in all of the endpoints and to etanercept in all of the secondary endpoints.

The two studies confirmed that IL-17A has an important role in the pathogenesis of psoriasis and, as most of patients treated with secukinumab (in particular at the dose of 300 mg) sustained results obtained during the induction period through to week 52, this cytokine can be considered a good therapeutic target over the long term.<sup>84</sup> Moreover, during FIXTURE study, secukinumab proved to be more effective than the TNF inhibitor etanercept not only at the term of the induction period but also through to week 52.<sup>84</sup>

Thaci et al conducted a double-blind study (CLEAR, NCT02074982) to compare the efficacy and safety of secukinumab versus ustekinumab. Secukinumab was more effective than ustekinumab in terms of PASI90 response at week 16 (79% vs 57.6%, respectively).<sup>85</sup>

The core SCULPTURE study aimed to assess the efficacy and safety of secukinumab through 5 years of treatment in moderate-to-severe psoriasis. Results from this extension study showing how PASI 75/90/100 responses at 1 year of treatment with secukinumab (88.9%, 68.5% and 43.8%, respectively) were sustained to Year 5 (88.5%, 66.4% and 41%). Moreover, DLQI (dermatology life quality index) 0/1 response also sustained through 5 years (72.7% at Year 1 and 65.5% at Year 5). During the study period, no additional or cumulative safety concerns were identified.<sup>86</sup>

Another study (NCT01544595) evaluated the long-term efficacy and safety in psoriasis through to year 5 of treatment such as an extension of the phase III ERASURE and FIXTURE trials and it demonstrated that PASI and DLQI achieved were preserved with secukinumab through to year 5.<sup>87</sup>

### Ixekizumab

Ixekizumab, an IgG4 monoclonal antibody targeting interleukin-17A, was approved for the management of adult patients with moderate-to-severe plaque psoriasis in March 2016, at the labelled dosage of 160 mg initial dose at week 0, followed by an 80 mg dose at weeks 2, 4, 6, 8, 10, and 12. Subsequently, a maintenance dose of 80 mg is administered Q4W.<sup>88</sup> Three pivotal trials, UNCOVER-1 (NCT01474512), UNCOVER-2 (NCT01597245), and UNCOVER-3 (NCT01646177), assessed ixekizumab's efficacy and safety compared to placebo (in all trials) and etanercept (in UNCOVER-2 and UNCOVER-3).<sup>89–91</sup> Patients were randomized to receive placebo, 2-week dosing of ixekizumab, or 4-week dosing of ixekizumab. Additionally, UNCOVER-2 and UNCOVER-3 included patients receiving etanercept.<sup>89–91</sup>

In UNCOVER-1, ixekizumab demonstrated superior efficacy over placebo at week 12, with significant proportions achieving sPGA scores of 0 or 1 (81.8% and 76.4% for 2-week and 4-week dosing, respectively, compared to 3.2% for placebo) and PASI 75 (89.1% and 82.6% for 2-week and 4-week dosing, respectively, compared to 3.9% for placebo).<sup>92</sup> In the UNCOVER-1 and UNCOVER-2 extension, re-randomized patients maintained favorable sPGA scores (73.8%, 39.0%, and 7.0% for 4-week dosing, 12-week dosing, and placebo, respectively).<sup>92</sup> UNCOVER-3 showed sustained efficacy with continuous ixekizumab treatment.<sup>92</sup>

Ixekizumab outperformed placebo in achieving PASI 75 or sPGA scores of 0 or 1 at week 12, a trend observed through 60 weeks in UNCOVER-1. In UNCOVER-2 and UNCOVER-3, ixekizumab showed superiority over etanercept.<sup>93–95</sup> The long-term extension (LTE) of the UNCOVER trials demonstrated sustained efficacy and consistent safety of ixekizumab over 5 years.<sup>93–95</sup>

Comparative studies, such as IXORA-S and IXORA-R, showcased ixekizumab's superiority over ustekinumab and non-inferiority to guselkumab in terms of skin and nail lesion clearance.<sup>93–95</sup> Overall, ixekizumab emerged as an effective and well-tolerated treatment option for moderate-to-severe plaque psoriasis, demonstrating its efficacy and safety over extended periods. Finally, real-life data on the use of ixekizumab in psoriasis management are promising.<sup>96–100</sup>

### Brodalumab

Brodalumab, an entirely human immunoglobulin G2 IL-17RA antagonist, received approval in February 2017 for the treatment of adult patients with moderate-to-severe plaque psoriasis.<sup>101</sup> By binding to IL-17RA, a component of various receptor complexes, brodalumab not only counteracts the effects of IL-17A but also those of IL-17C, IL-17E, and IL-17F.<sup>101</sup> The recommended dosage entails a 210-mg subcutaneous injection at weeks 0, 1, and 2, followed by injections every 2 weeks thereafter.<sup>101</sup> Results from three phase III trials (AMAGINE-1, AMAGINE-2, and AMAGINE-3) underscored the safety and

efficacy of brodalumab in treating moderate-to-severe plaque psoriasis.<sup>102</sup> In the primary endpoints of the AMAGINE trials, over 80% of psoriasis patients treated with brodalumab achieved a PASI75, and in the AMAGINE-2 and AMAGINE-3 studies, brodalumab demonstrated superiority over ustekinumab at week 12, with PASI 100 ranging from 37% to 44%, compared to 19% to 22%.<sup>103</sup> The AMAGINE-1 study also affirmed the long-term efficacy and safety of brodalumab over 120 weeks in the treatment of moderate-to-severe plaque psoriasis.<sup>104</sup> Finally, the effectiveness of brodalumab has been confirmed by real-world evidences.<sup>105–109</sup>

### Bimekizumab

Bimekizumab, an IgG1 antagonist that specifically targets IL-17A and IL-17F, gained approval in June 2023 for treating adult patients with moderate-to-severe plaque psoriasis.<sup>110</sup> This approval represents the latest addition to the array of IL-17-targeted therapies available for managing this condition.<sup>110</sup> The recommended dosage for psoriasis patients involves administering 320 mg (given as two subcutaneous injections of 160 mg each) at weeks 0, 4, 8, 12, and 16, followed by subsequent injections Q8W.<sup>110</sup> Despite its recent approval, emerging real-life data are promising.<sup>111–116</sup>

Extensive trials, including BE ABLE 1, BE ABLE 2, and BE READY, meticulously assessed the efficacy and safety of bimekizumab compared to placebo.<sup>110</sup>

In the BE ABLE 1 study, 250 patients were randomly assigned to various doses of bimekizumab or placebo.<sup>117</sup> All bimekizumab-treated groups exhibited significant PASI90 response rates compared to the placebo at week 12 (ranging from 46.2% to 79.1%,  $p < 0.0001$ ).<sup>117</sup> Extending the research, BE ABLE 2, an extension study up to week 60, revealed sustained response rates with a substantial proportion of patients achieving complete skin clearance.<sup>118</sup> Meanwhile, the BE READY phase III trial investigated bimekizumab's effectiveness and safety in a larger cohort of adults with moderate-to-severe plaque psoriasis over at least 6 months.<sup>119</sup> A total of 435 subjects were enrolled and randomized to receive bimekizumab 320 mg Q4W or a placebo Q4W.<sup>119</sup> Patients treated with bimekizumab who achieved PASI90 at week 16 were reassigned in a 1:1:1 ratio to receive bimekizumab 320 mg every 4 weeks, every 8 weeks, or a placebo for weeks 16 to 56.<sup>119</sup> Conversely, individuals receiving a placebo and achieving a PASI90 response at week 16 continued on placebo every 4 weeks until week 56. Patients who did not attain PASI90 at week 16 were included in a 12-week open-label escape group and treated with bimekizumab 320 mg every 4 weeks.<sup>119</sup> At week 16, PASI90 and PASI100 were achieved by 317 (91%) and 238 (68%) patients in the bimekizumab group, respectively, while only 1 (1%) patient in the placebo group achieved PASI90 and PASI100 ( $p < 0.0001$ ).<sup>119</sup> Similarly, 323 (93%) patients receiving bimekizumab attained an IGA score of 0/1 compared to one (1%) in the placebo group ( $p < 0.0001$ ).<sup>119</sup> These responses were sustained through week 56 with bimekizumab dosing at both Q8W and Q4W.<sup>119</sup>

The efficacy and safety of bimekizumab were also compared to adalimumab, ustekinumab, and secukinumab in separate trials. BE SURE, a 56-week Phase 3 trial, compared bimekizumab to adalimumab, enrolling 478 patients randomized to different bimekizumab or adalimumab dosing regimens.<sup>120</sup> At week 4, a significant improvement in psoriasis was observed in the bimekizumab cohort compared to the adalimumab group, with 244 (76.5%) and 50 (31.4%) patients reaching PASI 75 ( $p < 0.001$ ).<sup>120</sup> At week 16, 275 (86.2%) subjects treated with bimekizumab achieved a PASI 90 response compared to 75 (47.2%) patients in the adalimumab cohort ( $p < 0.001$ ).<sup>120</sup> Finally, a PASI 90 response was observed in 134 (84.8%) patients receiving bimekizumab every 4 weeks, 133 (82.6%) receiving bimekizumab transitioning to Q8W, and 82 (81.8%) who switched from adalimumab to bimekizumab at week 56.<sup>120</sup>

BE VIVID, a 52-week multicenter placebo-controlled study, compared bimekizumab 320 mg Q4W to ustekinumab and placebo.<sup>121</sup> At week 16, the proportion of patients achieving PASI90 was significantly higher in the bimekizumab-treated group compared to the ustekinumab and placebo groups (85% vs 50% vs 5%, respectively,  $p < 0.0001$ ).<sup>121</sup> Similar trends were observed for PASI100 and IGA response rates.<sup>121</sup> Furthermore, patients on bimekizumab demonstrated a rapid response compared to ustekinumab and placebo as early as week 4 ( $p < 0.0001$ ).<sup>121</sup> Clinical efficacy was maintained up to week 52 in the bimekizumab group, and patients switched to bimekizumab at week 16 reported similar responses at week 52 to those receiving bimekizumab since baseline.<sup>121</sup> BE RADIANT, a 48-week phase 3b trial, compared the efficacy and safety of bimekizumab with secukinumab.<sup>122</sup> A total of 743 patients were enrolled and randomized to receive bimekizumab 320 mg every 4 weeks or secukinumab 300 mg weekly up to week 4 and every 4 weeks thereafter.<sup>122</sup> From week 16, patients receiving bimekizumab were split into two groups for maintenance dosing,

every 4 weeks or every 8 weeks (147 and 215 patients, respectively).<sup>122</sup> At week 16, a PASI 90 response was observed in 319 (85.5%) patients treated with bimekizumab compared to 275 (74.3%) receiving secukinumab.<sup>50</sup> By week 48, 83.6% and 70.5% of patients in the bimekizumab and secukinumab cohorts, respectively, achieved a PASI90 response.<sup>122</sup>

### IL-17 Inhibitors Safety Profile

The safety profiles of secukinumab, ixekizumab, brodalumab, and bimekizumab are generally reassuring, with common adverse effects noted in clinical trials, including nasopharyngitis, upper respiratory infections, injection-site reactions, headache, mild neutropenia, *Candida albicans* mucocutaneous infections, and diarrhea. Uncommon cases of neutropenia could be attributed to the reported role of IL-17A in promoting granulopoiesis and neutrophil migration. *Candida albicans* mucocutaneous infections appear to be a specific risk associated with IL-17 inhibitors, as IL-17A plays a crucial role in mucocutaneous microbial defense against extracellular pathogens.

During the FIXTURE phase 3 study,<sup>81</sup> at week 52, *Candida* infections were documented in 4.7% of patients in the 300 mg secukinumab group and in 2.3% of patients in the 150 mg secukinumab group. In the phase 3 trials of ixekizumab (UNCOVER-1, UNCOVER-2, and UNCOVER-3), the percentage of patients experiencing a *Candida* infection was 1.4% for those taking ixekizumab Q2W and 0.6% for those taking ixekizumab Q4W, compared to 0.5% in the placebo group.<sup>123</sup> Brodalumab (AMAGINE-1) reported *Candida* infections in 0.5% of patients in the 140 mg dose group, 2.3% in the 210 mg dose group, and 1.4% in the placebo group during the induction phase (12 weeks).<sup>104</sup> In the BE-RADIANT study, a 48-week phase 3b trial comparing the efficacy and safety of bimekizumab with secukinumab, oral candidiasis was more likely observed in bimekizumab-treated patients (19.3% vs 3.0%).<sup>122</sup> Of the 72 cases of oral candidiasis occurring with bimekizumab, 36 were classified as mild, 34 as moderate, and none led to treatment discontinuation.<sup>122</sup> The higher frequency of oral candidiasis in bimekizumab-treated patients could be explained by its additional inhibitory role on IL-17F.

All cases of *Candida* infections related to IL-17 inhibitor treatment were mild or moderate, with none being systemic. Additionally, the inhibition of IL-17 or its receptor has been associated, less frequently, with worsening or new-onset outbreaks of chronic IBD. A meta-analysis by Burisch et al involving over 19,000 patients treated with secukinumab, ixekizumab, and brodalumab for over six years found no significant increase in the risk of IBD in these patients.<sup>124</sup> However, a database analysis by Deng et al, using the US FDA Adverse Event Reporting System database from 2015 to 2022, identified a significant reporting rate of IBD events among patients treated with secukinumab (ROR = 2.13, 95% CI [1.96–2.30]) and ixekizumab (ROR = 2.79, 95% CI [2.39–3.27]), while brodalumab did not trigger a safety signal (ROR = 1.48, 95% CI [0.48–4.6]).<sup>125</sup> In clinical trials for Crohn's disease (CD), both secukinumab and brodalumab failed to demonstrate clinical benefits and were associated with an increased number of cases of worsening CD in patients with active CD compared with placebo.<sup>126,127</sup> Although a low incidence rate of developing new-onset IBD has been reported with anti-IL17 drugs, exacerbating pre-existing IBD is more common. Hence, IL-17 inhibitors should be avoided in patients with IBD or at risk of developing it.<sup>128</sup> Furthermore, four suicides were reported in the AMAGINE trials for brodalumab, raising some concerns regarding the safety of this agent. Subsequently, Lebwohl et al demonstrated a lack of evidence for a causal relationship between brodalumab and suicidal ideation.<sup>129</sup>

## Discussion

Several factors are involved in psoriasis etiopathogenesis, triggering metabolic processes involving inflammation, cell signalling, immune response dysregulation, and antigen presentation.<sup>130</sup> In particular, the extensive crosstalk between innate and adaptive immune cells, initiates and sustains a chronic inflammatory state underlying psoriasis.<sup>12</sup> New knowledge on psoriasis pathogenesis led to the recognition of the IL-23/Th17 axis as crucial in psoriatic lesion development.<sup>14,15</sup> Recognizing the pivotal role of this axis, has led to the development of selective and effective biological drugs, such as anti-IL17 and anti-IL23 monoclonal antibodies.<sup>131</sup> These drugs are characterized by the ability to achieve the complete or near-complete psoriatic improvement, as indicated by PASI100 and PASI90 responses, respectively, with a high safety profile.<sup>16,17</sup> In this scenario, we performed a narrative review with the purpose of the functioning of the IL-23/Th17 axis, its dysregulation in psoriasis pathogenesis, and the therapeutic potential of its inhibition.

As regards anti IL-17, four biologic drugs have been approved. In particular, secukinumab and ixekizumab act on IL-17A, bimekizumab on IL-17A/F and brodalumab on IL-17RA. All of these drugs showed high levels of effectiveness in both clinical trials and real-life experiences.

The excellent profile in terms of efficacy of anti-IL17, was confirmed also in response maintenance. However, long-term data for bimekizumab are still absent. Nasopharyngitis, upper respiratory infections, injection-site reactions, headache, mild neutropenia, and diarrhea are the commonest adverse effects reported for anti-IL17. Of interest, candida albicans mucocutaneous infections seems to be a specific risk associated with IL-17 inhibitors, since IL-17A plays a crucial role in mucocutaneous microbial defence against extracellular pathogens. The higher frequency of oral candidiasis in bimekizumab-treated patients could be explained by its additional inhibitory role on IL-17F. Fortunately, all cases of Candida infections related to IL-17 inhibitor treatment were mild or moderate, with none being systemic, often not requiring treatment discontinuation.

Furthermore, the inhibition of IL-17 or its receptor has been associated, less frequently, with worsening or new-onset outbreaks of IBD. Finally, some concerns regarding the safety of brodalumab have been raised after then four suicides were reported in the AMAGINE trial. However, the lack of evidence for a causal relationship between brodalumab and suicidal ideation has been demonstrated.

Guselkumab, risankizumab and tildrakizumab are anti-IL23 p19 biologic drugs approved for the management of moderate-to-severe plaque psoriasis. Clinical trials and real-world evidence widely confirmed the efficacy of these classes of biologics. Effectiveness data were also confirmed in long-term trials. As regards the safety, unlike IL-17 inhibitors, drugs inhibiting IL-23 are not associated with worsening or the onset of IBD. Additionally, risankizumab seems to be effective for IBD management. A recent analysis suggested that risankizumab was associated with significantly disproportionate CVA. However, these results were criticized. Globally, anti-IL23 biological drugs seem to be characterized by an excellent profile in terms of safety and efficacy.

Moreover, real-life studies and experiences showed both anti-IL17 and anti-IL23 as safe drugs also in patients with severe infections (eg tuberculosis, viral hepatitis) and oncological diseases,<sup>132–135</sup> as well as during COVID-19 pandemic.<sup>136–140</sup>

Finally, it should be discussed that anti-ILs seems to be safer than anti-TNF $\alpha$ .<sup>132</sup> A recent study investigating the effect of biological treatments on routine laboratory parameters showed that anti-TNF $\alpha$  were more effective in reducing inflammation parameters (neutrophil lymphocyte ratio and C-reactive protein) whereas IL antagonists were safer in terms of biochemical parameters (AST, ALT, and creatinine values were found to be statistically significantly higher in the anti-TNF group compared to the IL inhibitor group).<sup>141</sup> Moreover, anti-TNF $\alpha$  have some contraindications which are not confirmed for anti-IL17 and anti-IL23 such as advanced congestive heart failure and multiple sclerosis.<sup>142</sup> Similarly, anti-IL17 and anti-IL23 seems to be safe also in patients with severe infections, as previously discussed.<sup>132–135</sup>

To sum up, the introduction of biologic drugs revolutionized the therapeutic scenario of several dermatological diseases, allowing clinicians to have several weapons to use. Certainly, further studies will allow for better characterization of biologics' profile, in order to administer the right drug for the right patients at the right moment.

## Conclusion

Psoriasis is an inflammatory skin disease that is associated with multiple comorbidities and strong impact on patients' quality of life. The IL-23/IL-17 axis in psoriasis has been a real breakthrough especially for patients who are non-responders to conventional treatments and/or anti-TNF or ustekinumab, for those with severe disease and/or those with comorbidities contraindicating other therapies. Numerous clinical trials are available on IL17 and IL23 inhibitors for psoriasis treatment in both short and long-term supporting their key role in managing psoriatic disease.

## Data Sharing Statement

All data are reported in the current study.

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## Disclosure

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