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Review article

# Differential efficacy of biologic treatments targeting the TNF-α/IL-23/IL-17 axis in psoriasis and psoriatic arthritis

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ABSTRACT

Psoriasis and psoriatic arthritis cause significant physical and psychological burdens for afflicted individuals. An accelerated TNF-α/IL-23/IL-17 axis is their major pathomechanism; therefore, anti-TNF-α/IL-23/IL-17 biologics are very effective for the treatment of skin and joint lesions in psoriasis and psoriatic arthritis. Given that the IL-17 signature is more upregulated in the skin than in synovium in psoriatic arthritis, anti-IL-23/IL-17 agents seem to be superior to anti-TNF-α remedies in the treatment of skin lesions. In this review, we focus on the differential efficacy of anti-TNF-α/IL-23/IL-17 biologics in psoriasis and psoriatic arthritis.

## 1. Introduction

Psoriasis is a chronic, immune-mediated, inflammatory skin disorder with an approximately 0.1–3% prevalence in the general population [16,35,36]. As psoriasis preferentially affects visible areas, such as the face, scalp, hands and nails [18,31,32,74], patients with psoriasis experience a significant physical and psychological burden [4,9,48,80,83].

In addition, psoriasis is associated with arthritis, cardiovascular diseases, metabolic syndromes and autoimmune disorders. Psoriatic arthritis is characterized by spondyloarthropathies, enthesitis and elevated C reactive protein levels [8,16,129,133,146,147] and hampers quality of life [115]. Elevated comorbidity of psoriasis with cardiovascular diseases and metabolic syndromes has been documented not only in Caucasians but also in Asians [19,20,22,50,51,71,78,79,98,107,111]. Systemic inflammatory markers, such as neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, mean platelet volume and C reactive protein, are elevated in psoriasis [6,24,70,94,113,121,126,130].

Additionally, psoriasis tends to coexist with autoimmune disorders [3,38,68,82,85,114,127]. Psoriasis with HIV infection may exhibit a more severe course with sudden exacerbations and may be refractory to treatment [28,58]. Paradoxical onset of psoriasis and arthritis is also demonstrated in patients treated with biologics [72,122]. Anti-tumor necrosis factor (TNF)-α antibodies frequently induce increased levels of KL-6, which is a serum marker for interstitial pneumonia [47]. In addition, the onset and exacerbation of psoriasis have been reported in melanoma patients treated with the anti-programmed cell death protein 1 antibody nivolumab [64,97]. These phenomena are examples of the autoimmune or autoinflammatory nature of psoriasis.

Pathogenesis of psoriasis is multifactorial, including genetic [28,86,97,127,144], environmental [13,34,53,56,129,134,135,149] and immune-related factors [44,75,81,102,137]. Recent therapeutic success of anti-TNF-α, anti-interleukin (IL)-23 and anti-IL-17 antibodies has emphasized a pivotal role of the TNF-α/IL-23/IL-17 pathway in the pathogenesis of psoriasis [7,35,37,53,54,59,84,124,138,139]. Compiling evidence obtained from clinical trials unveils a difference in the efficacy among biologics targeting the TNF-α/IL-23/IL-17 axis.

In this mini-review, we focus on the differential efficacy of anti-TNF-α/IL-23/IL-17 biologics in psoriasis and psoriatic arthritis.

## 2. TNF-α/IL-23/IL-17 axis in psoriatic pathogenesis

Psoriasis is frequently triggered by skin surface injury, such as friction and scratching, via a process known as the Koebner phenomenon [61]. Cutaneous trauma induces expression of functional cathelicidin at the injured site [27]. Cathelicidin (LL37) is one of the antimicrobial peptides that is produced by keratinocytes and neutrophils [137]. An initial trigger of psoriasis is believed to involve activation of plasmacytoid dendritic cells (DCs) upon stimulation by complexes of host DNA and LL37 [75,81,102,137]. Activated plasmacytoid DCs and damaged keratinocytes produce interferon (IFN)-α, IFN-β and tumor

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**Table 1**
Comparative efficacy of biologics for skin eruptions of psoriasis at 12 W posttreatment.

| | | | PASI75 (%) | PASI90 (%) | PASI100 (%) | Clinical trial name, Reference |
|---|---|---|---|---|---|---|
| | **Placebo** | | 6 | 3 | 1 | reSURFACE1, [118] |
| | | | 6 | 1 | 0 | reSURFACE2, [118] |
| | | | 4.5 | 1.2 | 0.8 | ERASURE, [76] |
| | | | 4.9 | 1.5 | 0 | FIXTURE, [76] |
| | | | 5.7 (16 W) | 2.9 (16 W) | 0.6 (16 W) | VOYAGE1, [15] |
| | | | 8.1 (16 W) | 2.4 (16 W) | 0.8 (16 W) | VOYAGE2, [117] |
| | | | 3.9 | 0.5 | 0 | UNCOVER-1, [41] |
| | | | 4 | 1 | 1 | UNCOVER-2, [43] |
| | | | 7.3 | 3.1 | 0 | UNCOVER-3, [43] |
| | | | 4.5 | 1.4 | 0 | ND, [42] |
| | | | 8 | 3 | 1 | AMAGINE-2, [77] |
| | | | 6 | 2 | 0.3 | AMAGINE-3, [77] |
| | **Methotrexate**<br>15–20 mg/W | | 41.9 (16 W) | 19.1 (16 W) | ND | RESTORE1, [12] |
| **Anti-TNF-α** | **Etanercept**<br>50 mg twice /W | A human soluble TNF-α receptor | 44 | 20.7 | 4.3 | FIXTURE, [76] |
| | | | 41.6 | 18.7 | 5.3 | UNCOVER-2, [43] |
| | | | 53.4 | 25.7 | 7.3 | UNCOVER-3, [43] |
| | | | 48 | 21 | 5 | reSURFACE2, [118] |
| | **Infliximab**<br>5 mg/Kg/shot | A chimeric anti-TNF-α mAb | 77.8 (16 W) | 54.5 (16 W) | ND | RESTORE1, [12] |
| | **Adalimumab**<br>80 → 40 mg/shot | A fully human anti-TNF-α mAb | 73.1 (16 W) | 49.7 (16 W) | 17.1 (16 W) | VOYAGE1, [15] |
| | | | 68.5 (16 W) | 46.8 (16 W) | 20.6 (16 W) | VOYAGE2, [117] |
| **Anti-IL-23** | **Ustekinumab**<br>45 mg or 90 mg/shot | A fully human anti IL-12/23 p40 mAb | 70 | 47 | 22 | AMAGINE-2, [77] |
| | | | 69 | 48 | 19 | AMAGINE-3, [77] |
| | | | 72 | 40 | 18 | ND, [110] |
| | **Briakinumab**<br>100 mg/shot | A fully human anti IL-12/23 p40 mAb | 80.7 | 61.6 | 32.2 | ND, [42] |
| | **Tildrakizumab**<br>200 mg/shot | A fully human IgG1 anti IL-23 p19 mAb | 62 | 35 | 14 | reSURFACE1, [118] |
| | | | 66 | 37 | 12 | reSURFACE2, [118] |
| | **Guselkumab**<br>100 mg/shot | A fully human IgG1 anti IL-23 p19 mAb | 91.2 (16 W) | 73.3 (16 W) | 37.4 (16 W) | VOYAGE1, [15] |
| | | | 86.3 (16 W) | 70 (16 W) | 34.1 (16 W) | VOYAGE2, [117] |
| | **Risankizumab**<br>90 or 180 mg/shot | A fully human IgG1 anti IL-23 p19 mAb | 93 | 77 | 45 | ND, [110] |
| **Anti-IL-17** | **Ixekizumab**<br>160 → 80 mg/shot | A fully human IgG4 anti IL-17A mAb | 89.1 | 70.9 | 35.3 | UNCOVER-1, [41] |
| | | | 89.7 | 70.7 | 40.5 | UNCOVER-2, [43] |
| | | | 87.3 | 68.1 | 37.7 | UNCOVER-3, [43] |
| | **Secukizumab**<br>300 mg/shot | A fully human IgG1κ anti IL-17A mAb | 81.6 | 59.2 | 28.6 | ERASURE, [76] |
| | | | 77.1 | 54.2 | 24.1 | FIXTURE, [76] |
| | **Brodalumab**<br>210 mg/shot | A fully human IgG2 anti IL-17 receptor A mAb | 86 | 70 | 44 | AMAGINE-2, [77] |
| | | | 85 | 69 | 37 | AMAGINE-3, [77] |

ND; Not Described. W; week. PASI75, PASI90 and PASI100; Rate of patients achieved 75, 90 and 100% reduction of Psoriasis Area and Severity Index. Most clinical trials are evaluated at 12 weeks after the initiation of treatment. Some studies were assessed at 16 weeks.

necrosis factor (TNF)-α, which result in further production of TNF-α and interleukin (IL)-23 by plasmacytoid and recruited inflammatory DCs (TNF/iNOS-producing DCs or TIP-DCs) [75,81,102,137]. IL-23 is critically involved in the generation and activation of IL-17- and IL-22-producing effector T helper (Th)17 and Th22 cells [44,137].

IL-17A upregulates the proliferation of keratinocytes and downregulates their differentiation [46]. IL-22 also drives epidermal hyperplasia primarily by downregulation of genes involved in terminal differentiation [17,123]. IL-17A acts on keratinocytes to induce chemokines that lead to neutrophil, TIP-DC, and Th17 cell influx into the skin [105]. IL-17A upregulates production of the neutrophil-attractive chemokines CXCL1, CXCL2 and CXCL8 by keratinocytes [37,60,119]. The accelerated TNF-α/IL-23/IL-17 axis coincides with the characteristic histopathology of psoriasis, such as epidermal hyperplasia, aberrant keratinocyte differentiation and neutrophilic microabscess, indicating that the TNF-α/IL-23/IL-17 axis is a canonical pathway to developing psoriatic lesions in humans [37].

## 3. Biologics targeting the TNF-α/IL-23/IL-17 axis and their safety

Topical application of steroids and vitamin D3 analogues inhibits psoriatic inflammation and normalizes epidermal differentiation [30,57,63,93,131,140]. Systemic treatments, such as methotrexate, cyclosporine and the phosphodiesterase 4 inhibitor apremilast, are useful for patients with extensive lesions [10,101,109]. Clinical trials have demonstrated the efficacy of the oral janus kinase inhibitor tofacitinib for psoriasis [1,5].

However, biologics targeting TNF-α, IL-23 and IL-17 signaling are much more efficacious in patients with moderate to severe skin lesions, arthritis or disturbed quality of life [7,53–55,59,84,124,138,139,145]. Biologics are useful for psoriatic patients who are unresponsive to cyclosporine [108]. Biologics are applicable in elderly patients, pregnant patients, patients undergoing hemodialysis, and patients with perioperational circumstances [2,67,96,103,116]. Switching of biologics is recommended for patients with primary failure, secondary failure and infusion reactions [52].

Genetic backgrounds are also related to treatment response to biologics [104,136]. Polymorphisms in *TNFAIP3*, *TLR10* and *CD84* are associated with treatment response to anti- TNF-α biologics [104,136,141]. The high cost of biologics limits access to these medications; however, cost-saving biosimilars are rapidly advancing to the market worldwide [23,26,132]. Regarding adverse effects, serious infection, reactivation of hepatitis B and C virus, interstitial pneumonia and oncogenesis are concerns common in biologics [39,62,148]. However, biologic therapies for psoriasis do not appear to be linked to a higher risk of cancer at least in the real-world clinical practice [39]. In addition, no significant increases in the risk of serious infection are observed in biologics for psoriasis [48], but monitoring of infection is