

Targeting IL-17 in psoriatic arthritis

Elizabeth A. Wang¹, Erika Suzuki², Emanuel Maverakis¹, Iannis E. Adamopoulos²⁻³

Abstract

Psoriatic arthritis (PsA) is a chronic and progressive inflammatory arthritis intimately associated with psoriasis, and can be an impairing disease that leads to reduced quality of life and significant morbidity. Treatment often requires TNF antagonists, yet many patients with PsA are not responsive to the standard anti-TNF therapies. The interleukin-17 (IL-17)/IL-17 receptor (IL-17R) family has recently been implicated in the pathogenesis of PsA and psoriasis. Much enthusiasm has been generated for the development of biologics that target the IL-17 signaling pathway directly or indirectly, many of which have produced striking results in the setting of psoriasis and PsA. Herein, we review the role of IL-17 and the IL-17 receptor (IL-17R) in the pathogenesis of PsA, as well as the clinical evidence for IL-17 and IL-17R targeted therapeutics.

Keywords: Psoriatic arthritis, psoriasis, interleukin-17

Introduction

Psoriatic arthritis (PsA) is a chronic, inflammatory, and heterogeneous disease that can affect various distinct anatomical sites including peripheral and axial joints, entheses, skin and nails (1). PsA is grouped together with the other spondylarthropathies—i.e., arthritic diseases affecting the peripheral or axial spine. PsA is a seronegative arthritis not commonly associated with specific autoantigens or autoantibodies (2, 3). Although PsA is a form of inflammatory arthritis that shares characteristics with other arthritic diseases including rheumatoid arthritis (RA), it is a distinct entity defined in part by concomitant or preceding psoriatic skin findings.

Clinical features of PsA

In the vast majority of patients with PsA, psoriatic features commonly precede the development of bone or joint involvement; however, joint pain or bone destruction can also precede the emergence of psoriatic lesions. The transition from having skin-only manifestations of psoriasis (PsO) to concomitant PsA occurs in up to 40% of psoriasis patients (4, 5). Histologically, psoriasis is characterized by epidermal hyperplasia, hyperkeratosis, parakeratosis, Munro's microabscesses (neutrophilic granulocytes at the epidermis) and mixed dermal infiltrates including T cells, dendritic cells and macrophages, which together lead to the clinical features of raised erythematous skin with overlying silvery plaques (6, 7).

With respect to PsA, the most common clinical manifestation is a symmetrical polyarthritis that affects the joints equally. It resembles a rheumatoid-like pattern; however, it is differentiated from RA by the presence of distal interphalangeal joint involvement and the absence of subcutaneous nodules. Patients who are left untreated may experience progressive joint damage and deformity secondary to sustained inflammation, resulting in morbidity and disability. Dactylitis is also an important feature of PsA, and is a combination of enthesitis of the tendons or ligaments, and synovitis affecting joints in the digit (8). Enthesitis may occur at any site in PsA (8). Histologic changes in the joint are similar to those observed in common forms of arthritis such as RA; however, in PsA there is presence of enthesitis and increased synovial vascularity (9, 10). Increased monocytes, mast cells, neutrophils and mature monocytes CD163⁺ cells are also observed in PsA (11, 12).

Epidemiology

The precise etiology of PsA is not well understood, though it is recognized as a multifactorial disease whose pathogenesis arises from various genetic, environmental and immunological factors. The prevalence of PsA varies widely among different countries, from 1 per 100,000 in Japan, to 250 per 100,000 in the United States and to 470 per 100,000 in Australia (13-15). However, these geoepidemiological differences may be further complicated by environmental and immunological factors and genetic susceptibility. In addition to physical trauma, as evidenced by the Koebner phenomenon in which penetrating cuts in psoriatic skin lead to further psoriatic plaque formation, other environmental factors such as infectious agents, recurrent oral ulcers, or HIV infection play a role (16, 17).



Cite this article as: Wang EA, Suzuki E, Maverakis E, Adamopoulos IE. Targeting IL-17 in psoriatic arthritis. *Eur J Rheumatol* 2017; 4: 272-7.

¹ Department of Dermatology, UC Davis School of Medicine, CA, USA

² Department of Internal Medicine, Division of Rheumatology, Allergy and Clinical Immunology, University of California at Davis, CA, USA

³ Institute for Pediatric Regenerative Medicine, Shriners Hospitals for Children Northern California, CA, USA

*EAW and ES contributed equally

Address for Correspondence:

Iannis E. Adamopoulos, Institute for Pediatric Regenerative Medicine, Shriners Hospitals for Children Northern California, CA, USA

E-mail: iannis@ucdavis.edu

Submitted: 28.02.2017

Accepted: 23.08.2017

Available Online Date: 10.11.2017

©Copyright by 2017 Medical Research and Education Association - Available online at www.eurjrheumatol.org.

IL-17 and IL-17R

Interleukin 17 (IL-17) is a common denominator of various inflammatory diseases and has a crucial role in the pathogenesis of PsA and psoriasis. Experimental evidence, from psoriatic lesions and synovial fluid in humans to psoriatic-like and arthritis mouse models, support the development of therapies targeting the IL-17 pathway. Herein, we review the role of the IL-17 pathway in the pathogenesis of PsA, as well as the clinical evidence for IL-17 and IL-17 receptor (IL-17R) targeted therapeutics.

IL-17 (or IL-17A) is a homodimeric disulfide-linked glycoprotein and the most widely studied of the IL-17 family of cytokines (IL-17, IL-17B, IL-17C, IL-17D, IL-17E and IL-17F) (18). Th17 cells, gd T cells, and various other immune cells have been demonstrated to secrete IL-17 (19, 20). IL-17 and IL-17F share the greatest homology, and can form heterodimers, which also bind IL-17R. IL-17R is commonly expressed on epithelial cells, vascular endothelial cells, keratinocytes and fibroblasts as well as on cells of hematopoietic lineage, including monocytes, neutrophils, T and B cells, $\gamma\delta$ T cells, LTI cells and other innate-like lymphocytes (21, 22).

The dimeric IL-17R complex consists of IL-17RA and IL-17RC subunits (22, 23). IL-17 has differential affinities for binding to IL-17RA and IL-17RC, though the precise binding kinetics are not well defined under specific inflammatory

conditions. Interestingly, the distribution of IL-17R is also not uniform. Although IL-17RA is ubiquitously expressed in cells of hematopoietic cell origin, IL-17RC demonstrates variable expression. The variable expression observed with IL-17RC suggests that it may be rapidly internalized upon binding, differentially expressed under homeostatic conditions or bind additional, possibly unidentified ligands. Additionally, alternatively spliced soluble forms of IL-17RA and IL-17RC have recently been identified and are thought to negatively regulate IL-17 signaling (21, 22).

Binding of IL-17 to IL-17R leads to the recruitment of an adaptor molecule, Act1, which associates with inducible I κ B kinase (IKKi) and tumor necrosis factor receptor-associated factor (TRAF) proteins. Single nucleotide polymorphisms in *TRAF3IP2* (*Act1*) have linked IL-17-mediated immune regulation to PsA disease pathology (24). Interestingly, the Act1 mutation that has been associated with PsA susceptibility is suggested to differentially regulate TRAF2/5 and TRAF6 binding and downstream signaling. Phosphorylation of IKKi and binding of TRAF2 and TRAF5 lead to CXCL1 chemokine stabilization to drive neutrophil recruitment, whereas binding of TRAF6 leads to activation of mitogen-activated protein kinase (MAPK) and transforming growth factor β activated kinase-1 (TAK1), to induce translocation and transcriptional activity of nuclear factor κ B

(NF- κ B) activator protein (AP-1), CCAAT-enhancer-binding protein (C/EBP) and NF- κ B (25-27). The activation of these transcription factors leads to the secretion of various trophic factors including CXCL1, CXCL2, CXCL8, CCL2, CCL7, granulocyte colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) to promote myeloid cells and granulocyte recruitment, development and inflammatory effector function. Moreover, recent studies have highlighted the diverse heterogeneity of myeloid cells and granulocytes suggesting that IL-17 may mediate yet to be defined non-redundant inflammatory pathways, which are distinct from its classical activation within a particular disease.

IL-17 in PsA

IL-17 plays multiple critical roles in the pathogenesis of PsA and psoriasis (28). It is known to act on keratinocytes and synovial cells to produce pro-inflammatory mediators, bridging the innate and adaptive immune systems to sustain chronic inflammation (Figure 1) (28). IL-17 has protective roles in host defense at epithelial borders and defense against fungal and bacterial pathogens, as well as inflammatory roles in autoimmunity. Although IL-17 is a common denominator of many inflammatory diseases, the mechanisms that govern IL-17-mediated disease may differ. Moreover, IL-17 is commonly evaluated in relation to IL-23

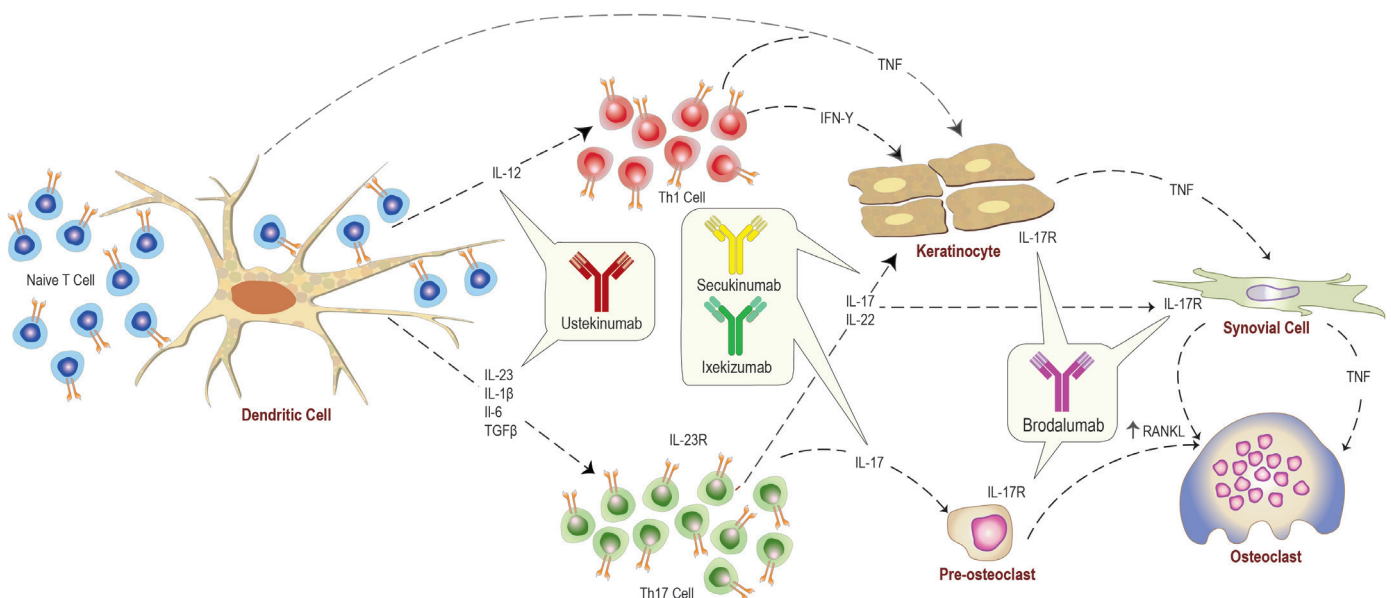


Figure 1. Mechanism of biologic agents for treatment of psoriatic arthritis. This figure is a schematic demonstrating blockade of cytokines secreted by dendritic cells, Th1 cells, Th17 cells, keratinocytes, and synovial cells. IL-12 is needed for differentiation of naïve T cells into IFN- γ -secreting Th1 cells, and IL-23 is needed to maintain IL-17-secreting Th17 cells. IL-1 β , IL-6, and TGF β also promote the differentiation of Th17 cells from naïve T cells. IL-17 secreted by Th17 cells act on keratinocytes, synovial cells, and pre-osteoclasts, which ultimately upregulate RANKL. Secukinumab is a fully human monoclonal antibody that targets IL-17A, while brodalumab is a fully human monoclonal antibody that targets the receptor. Ustekinumab is a fully human monoclonal antibody that targets p40, a subunit shared between IL-12 and IL-23. TNF is secreted by Th1 cells, keratinocytes and synovial cells, with downstream effects on osteoclasts.

Table 1. IL-17 and IL-17R targeted therapeutics for PsA in development

Drug name	Sponsor	Target	Type	Clinical/Development Status for PsA ^a
Secukinumab	Novartis	IL-17	Fully human mAb	Marketed
Ixekizumab	Eli Lilly	IL-17	Humanized IgG4 mAb	Registered (Lilly announced regulatory submission to FDA for psoriatic arthritis in 2017)
Brodalumab	Valient	IL-17RA	Fully human IgG2 mAb	Phase III (56)
RG7624	Genentech	IL-17/F	Humanized IgG1 mAb	Phase I ^b
ABT-122	AbbVie	IL-17/TNF	Humanized mAb	Phase II (57)
COVA322	Covagen	IL-17/TNF	FynomAb	Preclinical (58)
SCH 900117	Merck	IL-17	Humanized mAb	Phase I for RA, not yet in PsA

^aBased on ongoing clinical trials according to clinicaltrials.gov, as of January 2017

^bBased on Pharmaceutical Research and Manufacturers of America, Biologic Medicines in Development

and T cells, yet alternative pathways may exist in promoting pathogenicity at different stages of the disease. IL-17 is mechanistically relevant to PsA as IL-17 and other cytokines such as TNF are activators of NFκB, a key intracellular regulator of the innate immune that triggers transcription of several genes involved in the pathogenesis of PsA (29, 30). For instance, the receptor activator of nuclear factor κB ligand (RANKL) triggers the differentiation of osteoclast precursor cells into activated osteoclasts, resulting in bone resorption and subsequently joint deformity in PsA (31).

Experimental evidence in humans and mouse models has supported the development of IL-17-targeted therapies. At the clinical level, IL-17 and IL-17-producing cells have been found in the serum, psoriatic lesions, and within the synovial fluid of PsA patients—findings that have been shown to correlate with disease activity (32-34). It is likely that the IL-23/IL-17A axis is in fact essential to maintaining enthesal and joint inflammation in patients with PsA (35, 36). In addition, synovial fibroblasts isolated from PsA patients also contain elevated IL-17R expression and secrete increased IL-6, CXCL8 and MMP3 *ex vivo* compared to osteoarthritis patients (37).

We and others have shown using various animal models the importance of myeloid cells in IL-17-induced pathological features that resemble the human PsA (38, 39). Indeed IL-17 gene transfer is sufficient to induce the expansion of osteoclast precursors and concomitant elevation of biomarkers indicative of bone resorption (40) in parallel with epidermal hyperplasia hallmark phenotypic features of

PsA. This occurred at a time preceding noticeable joint inflammation, and suggested that IL-17A is critical for the induction of pathological bone resorption seen in PsA through direct activation of osteoclast precursors. Other groups have also shown evidence for crosstalk between IL-17A-mediated skin inflammation and bone loss. In fact, in mice with IL-17A-induced chronic skin inflammation, IL-17A inhibited osteoblast and osteocyte function through inhibition of Wnt signaling. Blocking IL-17A restored bone formation *in vivo* (41). Similarly, in a model of inflammatory arthritis, IL-17A deficiency promoted periosteal bone formation (42). Skin inflammation induced by the IL-17 family of cytokines has been elegantly studied in many types of IL-17 expressing models including a keratinocyte expressing IL-17C mouse model (K5-IL-17C) where keratinocyte expression of IL-17C induces a chronic skin specific inflammation (43). Taken together, these findings suggest that IL-17 is crucially involved in the pathophysiology of erosive bone disease and skin inflammation as observed in psoriatic arthritis.

Targeted Therapeutics for PsA

TNF blockade

TNF blockade has been successfully used to treat various autoimmune and inflammatory diseases in clinical trials. The current FDA approved TNF therapies for PsA include infliximab, etanercept, adalimumab, golimumab and certolizumab pegol. Approximately 60-70% of patients with moderate to severe psoriasis were shown to achieve a 75% improvement in Psoriasis Area and Severity Index (PASI) 75 and 40-70% of patients with active

PsA achieved an American College of Rheumatology (ACR) 20 score (44). Thus, many patients with PsA are not responsive to the standard anti-TNF therapies. Moreover, some patients have also demonstrated exacerbated disease while taking TNF-targeted therapies (45). However, TNF blockade is also known to mediate the IL-23/IL-17 axis, which has been demonstrated at both the clinical and basic science level (46). Interestingly, patients non-responsive to etanercept show persistent levels of serum IL-17, while responders have shown a reduction in IL-17 levels (44).

IL-17 blockade

Recent clinical trials with various molecules blocking IL-17 signaling have evaluated the impact of dysregulated IL-17 signaling in the pathogenesis of inflammatory diseases. Many of these studies are currently ongoing to evaluate the efficacy of anti-IL-17 and anti-IL-17R antibodies in PsO, RA, and PsA (Table 1). The biologics targeting either IL-17 or its receptor that are being studied in the setting of psoriatic disease include secukinumab, brodalumab and ixekizumab. Each one has slightly different specificities targeting the IL-17 pathway (Figure 1). Secukinumab is a fully human anti-IL-17A monoclonal antibody, ixekizumab is a humanized anti-IL-17A monoclonal antibody, while brodalumab is a fully human IL-17 receptor (IL-17RA) monoclonal antibody.

Blockade of IL-17 has resulted in remarkable success in the treatment of psoriatic disease (47). In particular, IL-17 antagonists in the setting of psoriasis have been shown to achieve higher PASI 75, 90, 100 response rates (48). In patients with plaque psoriasis, clinical trials have shown that treatment with brodalumab results in prompt clinical improvement (49). Data from Phase I-III studies has also shown that ixekizumab is highly effective in treating patients with moderate-to-severe plaque psoriasis (50-52). Similarly, use of secukinumab has produced comparable results, and both ixekizumab and secukinumab have recently been approved for the treatment of psoriasis (53). Interestingly, the response rates of IL-17-targeted therapies in psoriasis have been successful, with moderate responses in PsA thus far, suggesting that additional variables including genetic susceptibility may be contributing to its pathogenesis. In PsA patients with mutations in *TRAF3IP2* or *IL23A/IL23R*, it may be possible that alternative pathways may be activated or working in synergy with IL-17. Recently, others have demonstrated experimentally that Act1-deficient mice demonstrate spontaneous IL-22-dependent skin inflammation,

which could not be rescued by anti-IL-17 antibodies (54). Although a panoply of biologics have been summoned to combat PsA including IL-23 and IL-23R biologics that can also target the development of Th17 cells and Th17 related cytokines including IL-22 and the aforementioned TNF, the development of IL-17 and IL-17R targeted therapies are summarized below (55).

Secukinumab

Secukinumab is a fully human IgG1k monoclonal antibody against IL-17A and is approved for the treatment of psoriasis, PsA and ankylosing spondylitis (53). Secukinumab did not reach significance in a double-blind, placebo-controlled, randomized phase IIa study, with moderate to severe PsA patients. However, there was a reduction in serum IL-17 and other cytokines with a trend of improved quality of life (59, 60). In a subsequent phase III study assessing the long-term efficacy and safety of secukinumab in subjects with PsA (FUTURE I), secukinumab was significantly more effective than placebo in improving the signs and symptoms of PsA, along with patient-reported physical functioning and quality of life, with responses sustained through 52 weeks of therapy (61). These improvements were seen alongside a significant reduction in radiographic progression in the treatment group as compared to the placebo, as well as improvements in the severity of plaque and nail psoriasis in those patients with a significant concomitant psoriasis burden in addition to their joint disease (61, 62). In a similar FUTURE II study, subcutaneous weekly doses of secukinumab vs. placebo were tested instead of intravenous loading doses for the first 4 weeks, and improvements in the primary endpoint (at least 20% improvement in the ACR20 at week 24) were seen in the active arm (63, 64).

Ixekizumab

Ixekizumab is an IL-17-targeted humanized monoclonal antibody that was studied in active PsA in a recent 24-week phase III trial (SPIRIT-P1), comparing subcutaneous ixekizumab (160 mg loading dose followed by 80 mg every two or four weeks) to subcutaneous adalimumab (40 mg every other week) or placebo in PsA patients who were naïve to biologic DMARDs (65). Significantly more patients treated with ixekizumab achieved a greater ACR20 response compared to placebo (62.1% in the q2week regimen and 57.9% in the q4), and treatment also reduced radiographic progression of joint damage. The adalimumab active reference arm also demonstrated a significantly greater ACR20 response at week 24 (57.4%) versus placebo (65). These findings

are in agreement with prior studies that have shown efficacy in the setting of chronic moderate-to-severe plaque psoriasis (50). For the SPIRIT-P1 trial, an extension period of 3 years will allow for longer-term assessment of safety and efficacy.

Brodalumab

Brodalumab is a monoclonal antibody that targets and blocks the signaling pathway of IL-17R and has been proven effective in the treatment of psoriasis (66-68). It has been evaluated in PsA patients in a placebo-controlled phase II study, which showed significant and sustained response rates (68). At week 12 of treatment, the brodalumab groups demonstrated significantly higher rates of improvement in the outcome measure, the American College of Rheumatology response criteria (ACR20), than the placebo group. Commonly reported adverse events in the brodalumab groups in the trial were upper respiratory tract infection (12%, vs. 7% for placebo), fatigue (7% vs. 4%), and diarrhea (6% vs. 4%). Concern was raised during the development of brodalumab for psoriatic disease and axial spondyloarthritis in the United States after reports of suicidal thoughts and behavior were seen in clinical trial patients taking the drug (56). Phase III trials have either been completed (AMVISION-2; NCT02024646) or terminated (AMVISION-1; NCT02029495) (56). A critical review of the trial data, however, did not reveal a causal relationship between brodalumab use and suicidality (69). Given striking results seen in psoriasis patients (66, 67), the FDA has since approved brodalumab for moderate-to-severe psoriasis with a Boxed Warning on suicidal ideation and behavior (70).

IL-23 blockade

Recent research on the IL-23/IL-17 axis has enabled a better understanding of the pathogenesis of many chronic inflammatory diseases including inflammatory arthritis (46). With respect to PsA, it has been shown that single nucleotide polymorphisms in *IL23A*, *IL23R* as well as *TRAF3IP2* (Act1), a downstream target of IL-17R, confer susceptibility to the disease (71, 72). IL-12 is needed for differentiation of naïve T cells into IFN- γ -secreting Th1 cells, and IL-23 is needed to maintain IL-17-secreting Th17 cells (73). IFN- γ secreted by Th1 cells and IL-17/IL-22 secreted by Th-17 cells activates keratinocytes (Figure 1), which then proliferate and secrete IL-1 β and TNF.

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway modulate signaling in the IL-23/IL-17 axis and the subsequent generation of pathogenic Th17

cells in PsA patients. Therefore, inhibition of IL-23/IL-17 signaling may thus represent, at least in part, a plausible mechanism of action for the JAK inhibitor tofacitinib (74, 75).

With respect to biologic blockade of IL-23 in the setting of PsA, the fully human monoclonal antibody, ustekinumab, acts upon this pathway by targeting the p40 subunit shared between IL-12 and IL-23, thereby indirectly inhibiting the production of TNF. This targeted therapy has been well-studied in the setting of psoriasis (76). Of note, although IL-23 blockade targeting the p19 subunit is also in development for PsO and rheumatoid arthritis, it has not yet been extensively studied in the setting of PsA.

Ustekinumab

With regards to PsA, a phase II trial showed improvements in ACR20 response rates and significant improvement in skin disease, enthesitis, dactylitis and physical functioning (77). However, there was a higher dose requirement than that used for treating psoriasis. In a phase III PSUMMIT 1 trial, similar improvements were shown in PsA patients who were anti-TNF-experienced (78). In a PSUMMIT-2 phase III trial, data through week 60 indicated that ustekinumab induces long-term significant improvement in the joint, enthesitis/dactylitis and skin symptoms of active PsA (79). These findings supported the FDA approval of ustekinumab in the treatment of active PsA as of September 2013.

Insights and Conclusions

Psoriatic arthritis is a chronic and progressive inflammatory arthritis intimately associated with psoriasis, and can be an impairing disease that leads to reduced quality of life and significant morbidity. Treatment often requires TNF antagonists, yet many patients with PsA are not responsive to the standard anti-TNF therapies. Evidence from psoriatic lesions and synovial fluid in humans and psoriatic-like and arthritis mouse models have supported the development of therapies targeting the IL-17 pathway, which have demonstrated remarkable success in psoriasis and PsA. This is evidenced by secukinumab, the first anti-IL-17 based therapy that received FDA approval for treatment of PsA in January 2016. The IL-23/IL-17 axis is also mechanistically relevant to PsA and an important therapeutic target as seen through the successful use of ustekinumab. Clinical trials studying other anti-IL-17 therapies and even bispecific TNF/IL-17A inhibitors are ongoing and should provide new promising insight into new therapeutic options for PsA.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - E.A.W, I.E.A., E.S.; Design - I.E.A., E.S., E.A.W.; Supervision - I.E.A., E.M.; Resources - I.E.A., E.M.; Literature Search - E.A.W, E.S.; Writing Manuscript - E.A.W, E.S.; Critical Review - I.E.A, E.S., E.A.W, E.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

References

- Raychaudhuri SP, Wilken R, Sukhov AC, Raychaudhuri SK, Mavarakis E. Management of psoriatic arthritis: Early diagnosis, monitoring of disease severity and cutting edge therapies. *Journal of autoimmunity* 2017; 76: 21-37. [CrossRef]
- Alenius GM, Berglin E, Rantapaa Dahlqvist S. Antibodies against cyclic citrullinated peptide (CCP) in psoriatic patients with or without joint inflammation. *Annals of the rheumatic diseases* 2006; 65: 398-400. [CrossRef]
- Johnson SR, Schentag CT, Gladman DD. Autoantibodies in biological agent naive patients with psoriatic arthritis. *Annals of the rheumatic diseases* 2005; 64: 770-2. [CrossRef]
- Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. *Journal of the American Academy of Dermatology* 2008; 58: 826-50. [CrossRef]
- Gottlieb A, Korman NJ, Gordon KB, Feldman SR, Lebwohl M, Koo JY, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: Section 2. Psoriatic arthritis: overview and guidelines of care for treatment with an emphasis on the biologics. *Journal of the American Academy of Dermatology* 2008; 58: 851-64. [CrossRef]
- Nestle FO, Kaplan DH, Barker J. Psoriasis. *The New England journal of medicine* 2009; 361: 496-509. [CrossRef]
- Terui T, Ozawa M, Tagami H. Role of neutrophils in induction of acute inflammation in T-cell-mediated immune dermatosis, psoriasis: a neutrophil-associated inflammation-boosting loop. *Exp Dermatol* 2000; 9: 1-10. [CrossRef]
- Lloyd P, Ryan C, Menter A. Psoriatic Arthritis: An Update. *Arthritis* 2012; 2012: 176298. [CrossRef]
- Veale D, Yanni G, Rogers S, Barnes L, Bresnihan B, Fitzgerald O. Reduced synovial membrane macrophage numbers, ELAM-1 expression, and lining layer hyperplasia in psoriatic arthritis as compared with rheumatoid arthritis. *Arthritis and rheumatism* 1993; 36: 893-900. [CrossRef]
- Reece RJ, Canete JD, Parsons WJ, Emery P, Veale DJ. Distinct vascular patterns of early synovitis in psoriatic, reactive, and rheumatoid arthritis. *Arthritis and rheumatism* 1999; 42: 1481-4.
- Kruithof E, Baeten D, De Rycke L, Vandooren B, Foell D, Roth J, et al. Synovial histopathology of psoriatic arthritis, both oligo- and polyarticular, resembles spondyloarthropathy more than it does rheumatoid arthritis. *Arthritis research & therapy* 2005; 7: R569-80. [CrossRef]
- Noordenbos T, Yeremenko N, Gofita I, van de Sande M, Tak PP, Canete JD, et al. Interleukin-17-positive mast cells contribute to synovial inflammation in spondylarthritis. *Arthritis and rheumatism* 2012; 64: 99-109. [CrossRef]
- Hukuda S, Minami M, Saito T, Mitsui H, Matsui N, Komatsubara Y, et al. Spondyloarthropathies in Japan: nationwide questionnaire survey performed by the Japan Ankylosing Spondylitis Society. *J Rheumatol* 2001; 28: 554-9.
- Minaur N, Sawyers S, Parker J, Darmawan J. Rheumatic disease in an Australian Aboriginal community in North Queensland, Australia. A WHO-ILAR COPCORD survey. *J Rheumatol* 2004; 31: 965-72.
- Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, et al. Epidemiology of psoriatic arthritis in the population of the United States. *Journal of the American Academy of Dermatology* 2005; 53: 573. [CrossRef]
- Pattison E, Harrison BJ, Griffiths CE, Silman AJ, Bruce IN. Environmental risk factors for the development of psoriatic arthritis: results from a case-control study. *Annals of the rheumatic diseases* 2008; 67: 672-6. [CrossRef]
- Njobvu P, McGill P. Psoriatic arthritis and human immunodeficiency virus infection in Zambia. *J Rheumatol* 2000; 27: 1699-702.
- Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine & growth factor reviews* 2003; 14: 155-74. [CrossRef]
- Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. *Nat Rev Immunol* 2010; 10: 479-89. [CrossRef]
- Pantelyushin S, Haak S, Ingold B, Kulig P, Hepner FL, Navarini AA, et al. Ror-gamma-t+ innate lymphocytes and gamma-delta T cells initiate psoriasisiform plaque formation in mice. *J Clin Invest* 2012; 122: 2252-6. [CrossRef]
- Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol* 2009; 9: 556-67. [CrossRef]
- Toy D, Kugler D, Wolfson M, Vanden Bos T, Gurgel J, Derry J, et al. Cutting edge: interleukin 17 signals through a heteromeric receptor complex. *Journal of immunology* 2006; 177: 36-9. [CrossRef]
- Novatchkova M, Leibbrandt A, Werzowa J, Neubuser A, Eisenhaber F. The STIR-domain superfamily in signal transduction, development and immunity. *Trends Biochem Sci* 2003; 28: 226-9. [CrossRef]
- Huffmeier U, Uebe S, Ekici AB, Bowes J, Giardina E, Korendowycz E, et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. *Nat Genet* 2010; 42: 996-9. [CrossRef]
- Bulek K, Liu C, Swaidani S, Wang L, Page RC, Gulen MF, et al. The inducible kinase IKKi is required for IL-17-dependent signaling associated with neutrophilia and pulmonary inflammation. *Nat Immunol* 2011; 12: 844-52. [CrossRef]
- Sonder SU, Saret S, Tang W, Sturdevant DE, Porcella SF, Siebenlist U. IL-17-induced NF-kappaB activation via CIKS/Act1: physiologic significance and signaling mechanisms. *The Journal of biological chemistry* 2011; 286: 12881-90. [CrossRef]
- Fujioka S, Niu J, Schmidt C, Sclabas GM, Peng B, Uwagawa T, et al. NF-kappaB and AP-1 connection: mechanism of NF-kappaB-dependent regulation of AP-1 activity. *Mol Cell Biol* 2004; 24: 7806-19. [CrossRef]
- Lubrano E, Perrotta FM. Secukinumab for ankylosing spondylitis and psoriatic arthritis. *Therapeutics and Clinical Risk Management* 2016; 12: 1587-92. [CrossRef]
- O'Rielly DD, Rahman P. Genetics of susceptibility and treatment response in psoriatic arthritis. *Nature reviews Rheumatology* 2011; 7: 718-32. [CrossRef]
- Hayden MS, Ghosh S. NF-kappaB in immunobiology. *Cell research* 2011; 21: 223-44. [CrossRef]
- Adamopoulos IE, Mellins ED. Alternative pathways of osteoclastogenesis in inflammatory arthritis. *Nature reviews Rheumatology* 2015; 11: 189-94. [CrossRef]
- Mrabet D, Laadhar L, Sahli H, Zouari B, Haouet S, Makni S, et al. Synovial fluid and serum levels of IL-17, IL-23, and CCL-20 in rheumatoid arthritis and psoriatic arthritis: a Tunisian cross-sectional study. *Rheumatol Int* 2013; 33: 265-6. [CrossRef]
- Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, et al. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007; 8: 950-7. [CrossRef]
- Menon B, Gullick NJ, Walter GJ, Rajasekhar M, Garrood T, Evans HG, et al. Interleukin-17+CD8+ T Cells Are Enriched in the Joints of Patients With Psoriatic Arthritis and Correlate With Disease Activity and Joint Damage Progression. *Arthritis & Rheumatology* 2014; 66: 1272-81. [CrossRef]
- Lynde CW, Poulin Y, Vender R, Bourcier M, Khalil S. Interleukin 17A: Toward a new understanding of psoriasis pathogenesis. *Journal of the American Academy of Dermatology* 2014; 71: 141-50. [CrossRef]
- Sherlock JP, Joyce-Shaikh B, Turner SP, Chao CC, Sathe M, Grein J, et al. IL-23 induces spondyloarthropathy by acting on ROR-gamma-t+ CD3+CD4-CD8- enthesal resident T cells. *Nature medicine* 2012; 18: 1069-76. [CrossRef]
- Raychaudhuri SP, Raychaudhuri SK, Genovese MC. IL-17 receptor and its functional significance in psoriatic arthritis. *Mol Cell Biochem* 2012; 359: 419-29. [CrossRef]
- Suzuki E, Mavarakis E, Sarin R, Bouchareychas L, Kuchroo VK, Nestle FO, et al. T Cell-Independent Mechanisms Associated with Neutrophil Extracellular Trap Formation and Selective Autophagy in IL-17A-Mediated Epidermal Hyperplasia. *Journal of immunology (Baltimore, Md : 1950)* 2016; 197: 4403-12. [CrossRef]
- Ward NL, Loyd CM, Wolfram J, Diaconu D, Michaels CM, McCormick TS. Depletion of antigen presenting cells by clodronate liposomes reverses the psoriatic skin phenotype in KC-Tie2 mice. *The British journal of dermatology* 2011; 164: 750-8. [CrossRef]
- Adamopoulos IE, Suzuki E, Chao CC, Gorman D, Adda S, Mavarakis E, et al. IL-17A gene transfer induces bone loss and epidermal hyperplasia associated with psoriatic arthritis. *Annals of the rheumatic diseases* 2015; 74: 1284-92. [CrossRef]

41. Uluçkan Ö, Jimenez M, Karbach S, Jeschke A, Graña O, Keller J, et al. Chronic skin inflammation leads to bone loss by IL-17-mediated inhibition of Wnt signaling in osteoblasts. *Science translational medicine* 2016; 8: 330ra37-ra37.
42. Shaw AT, Maeda Y, Gravalles EM. IL-17A deficiency promotes periosteal bone formation in a model of inflammatory arthritis. *Arthritis Research & Therapy* 2016; 18: 104. [CrossRef]
43. Golden JB, Wang Y, Fritz Y, Diaconu D, Zhang X, Debanne SM, et al. Chronic, not acute, skin-specific inflammation promotes thrombosis in psoriasis murine models. *Journal of Translational Medicine* 2015; 13: 382. [CrossRef]
44. Zaba LC, Cardinale I, Gilleaudeau P, Sullivan-Whalen M, Suarez-Farinas M, Fuentes-Duculan J, et al. Amelioration of epidermal hyperplasia by TNF inhibition is associated with reduced Th17 responses. *J Exp Med* 2007; 204: 3183-94. [CrossRef]
45. Wallis DE, Waldron NM, Korendowych E. Ustekinumab for resistant psoriatic arthritis. *J Rheumatol* 2013; 40: 207. [CrossRef]
46. Lubberts E. The IL-23/IL-17 axis in inflammatory arthritis. *Nature reviews Rheumatology* 2015; 11: 415-29. [CrossRef]
47. Kang EJ, Kavanaugh A. Psoriatic arthritis: latest treatments and their place in therapy. *Therapeutic Advances in Chronic Disease* 2015; 6: 194-203. [CrossRef]
48. Wu D, Hou SY, Zhao S, Hou LX, Jiao T, Xu NN, et al. Efficacy and safety of interleukin-17 antagonists in patients with plaque psoriasis: a meta-analysis from phase 3 randomized controlled trials. *Journal of the European Academy of Dermatology and Venereology*: JEADV 2017.
49. Farahnik B, Beroukhim K, Abrouk M, Nakamura M, Zhu TH, Singh R, et al. Brodalumab for the Treatment of Psoriasis: A Review of Phase III Trials. *Dermatology and Therapy* 2016; 6: 111-24. [CrossRef]
50. Leonardi C, Matheson R, Zachariae C, Cameron G, Li L, Edson-Heredia E, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med* 2012; 366: 1190-9. [CrossRef]
51. Gordon KB, Leonardi CL, Lebwohl M, Blauvelt A, Cameron GS, Braun D, et al. A 52-week, open-label study of the efficacy and safety of ixekizumab, an anti-interleukin-17A monoclonal antibody, in patients with chronic plaque psoriasis. *Journal of the American Academy of Dermatology* 2014; 71: 1176-82. [CrossRef]
52. Griffiths CEM, Reich K, Lebwohl M, van de Kerkhof P, Paul C, Menter A, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *The Lancet*; 386: 541-51. [CrossRef]
53. Burkett PR, Kuchroo VK. IL-17 Blockade in Psoriasis. *Cell* 2016; 167: 1669. [CrossRef]
54. Wang C, Wu L, Bulek K, Martin BN, Zepp JA, Kang Z, et al. The psoriasis-associated D10N variant of the adaptor Act1 with impaired regulation by the molecular chaperone hsp90. *Nature immunology* 2013; 14: 72-81. [CrossRef]
55. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006; 203: 2271-9. [CrossRef]
56. Greig SL. Brodalumab: First Global Approval. *Drugs* 2016; 76: 1403-12. [CrossRef]
57. Ahmed GF, Goss S, Jiang P, Mansikka H, Padley RJ, Othman AA. FRI0156 Pharmacokinetics of ABT-122, A Dual TNF- and IL-17A-Targeted DVD-IG™, After Single Dosing in Healthy Volunteers and Multiple Dosing in Subjects with Rheumatoid Arthritis. *Annals of the rheumatic diseases* 2015; 74: 479. [CrossRef]
58. Silacci M, Lembke W, Woods R, Attinger-Toller I, Baenziger-Tobler N, Batey S, et al. Discovery and characterization of COVA322, a clinical-stage bispecific TNF/IL-17A inhibitor for the treatment of inflammatory diseases. *mAbs* 2016; 8: 141-9. [CrossRef]
59. McInnes IB, Sieper J, Braun J, Emery P, van der Heijde D, Isaacs JD, et al. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Annals of the rheumatic diseases* 2014; 73: 349-56. [CrossRef]
60. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Science translational medicine* 2010; 2: 52ra72. [CrossRef]
61. Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, van der Heijde D, et al. Secukinumab Inhibition of Interleukin-17A in Patients with Psoriatic Arthritis. *N Engl J Med* 2015; 373: 1329-39. [CrossRef]
62. Gottlieb AB, Mease PJ, McInnes IB, Kirkham B, Kavanaugh A, Rahman P, et al. Secukinumab, a Human Anti-Interleukin-17A Monoclonal Antibody, Significantly Reduces Psoriasis Burden in Patients with Psoriatic Arthritis: Results from a Phase 3 Randomized Controlled Trial. 2014 ACR/ARHP Annual Meeting 2014: Abstract #537
63. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *The Lancet*; 386: 1137-46. [CrossRef]
64. Bu X, Mahoney KM, Freeman GJ. Learning from PD-1 Resistance: New Combination Strategies. *Trends in Molecular Medicine*; 22: 448-51. [CrossRef]
65. Mease PJ, van der Heijde D. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naïve patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. 2017; 76: 79-87.
66. Papp KA, Leonardi C, Menter A, Ortonne J-P, Krueger JG, Kricorian G, et al. Brodalumab, an Anti-Interleukin-17-Receptor Antibody for Psoriasis. *N Engl J Med* 2012; 366: 1181-9. [CrossRef]
67. de Carvalho AV, Duquia RP, Horta BL, Bonamigo RR. Efficacy of Immunobiologic and Small Molecule Inhibitor Drugs for Psoriasis: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Drugs in R&D* 2016.
68. Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med* 2014; 370: 2295-306. [CrossRef]
69. Chiricozzi A, Romanelli M, Saraceno R, Torres T. No meaningful association between suicidal behavior and the use of IL-17A-neutralizing or IL-17RA-blocking agents. *Expert Opinion on Drug Safety* 2016; 15: 1653-9. [CrossRef]
70. Pharma. F. FDA advisory panel backs Valeant's psoriasis drug brodalumab, with suicide risk-mitigation plan [media release]. . 2016.
71. Suzuki E, Mellins ED, Gershwin ME, Nestle FO, Adamopoulos IE. The IL-23/IL-17 Axis in Psoriatic Arthritis. *Autoimmunity reviews* 2014; 13: 496-502. [CrossRef]
72. Bowes J, Orozco G, Flynn E, Ho P, Brier R, Marzo-Ortega H, et al. Confirmation of TNIP1 and IL23A as susceptibility loci for psoriatic arthritis. *Annals of the rheumatic diseases* 2011; 70: 1641-4. [CrossRef]
73. Adamopoulos IE, Bowman EP. Immune regulation of bone loss by Th17 cells. *Arthritis Res Ther* 2008; 10: 225. [CrossRef]
74. Raychaudhuri SK, Abria C, Raychaudhuri SP. Regulatory role of the JAK STAT kinase signaling system on the IL-23/IL-17 cytokine axis in psoriatic arthritis. *Annals of the rheumatic diseases* 2017. [CrossRef]
75. O'Shea JJ, Kontzias A, Yamaoka K, Tanaka Y, Laurence A. Janus Kinase Inhibitors in autoimmune diseases. *Annals of the rheumatic diseases* 2013; 72: ii111-5. [CrossRef]
76. Langley RG, Lebwohl M, Krueger GG, Szapary PO, Wafiq Y, Chan D, et al. Long-term efficacy and safety of ustekinumab, with and without dosing adjustment, in patients with moderate-to-severe psoriasis: results from the PHOENIX 2 study through 5 years of follow-up. *British Journal of Dermatology* 2015; 172: 1371-83. [CrossRef]
77. Gottlieb A, Menter A, Mendelsohn A, Shen YK, Li S, Guzzo C, et al. Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009; 373: 633-40. [CrossRef]
78. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; 382: 780-9. [CrossRef]
79. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Annals of the rheumatic diseases* 2014; 73: 990-9. [CrossRef]