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RESEARCH ARTICLE

EFFECT OF BIMEKIZUMAB IN PSORIATIC ARTHRITIS: A NEW APPROACH

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ABSTRACT

Psoriatic arthritis is a complex, immune-mediated inflammatory disease affecting peripheral and axial joints, entheses, skin, and nails. The IL-17 cytokine family, which includes several dimeric isoforms with overlapping and distinct functions, has been implicated in the pathogenesis of psoriatic arthritis. In particular, IL-17A and IL-17F, which share 50% homology and exhibit overlapping proinflammatory activity, can form both homodimers and heterodimers. Increased expression of these cytokines has been observed in the synovial tissue, entheses, and skin of patients with psoriatic arthritis. Secukinumab and ixekizumab, IL-17A inhibitors, have shown efficacy and tolerability in treating psoriatic arthritis. Bimekizumab, a humanized IgG1 monoclonal antibody, selectively inhibits both IL-17A and IL-17F.To effectively reduce inflammation in psoriatic arthritis, both IL-17A and IL-17F need to be neutralized. This suggests that dual inhibition of these cytokines could be an effective treatment approach.

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INTRODUCTION

Psoriatic arthritis (PsA) is an inflammatory arthritis which is progressive in nature. Generally 20% of psoriatic population may affected by this condition (1). The causes and pathogenesis behind psoriatic arthritis was not clear yet. The disease involve an immune mediated inflammation on skin, joints and other organs as a result of interaction between genetic and environmental factors (2). The mechanical stress or infection related environmental stress resulted in chronic inflammation which produce a central cytokine IL-23, primarily in joints and skin (3, 4). Il-23 also produced from macrophages and dendritic cells. The gastrointestinal tract may act as a source of IL-23 when its barrier function is impaired or the microbiota is dysregulated (3, 4, 5). The spondyloarthropathy of animal models,IL-23 stimulates resident T cells, characterized by the CD3+, CD4-, CD8-, IL-23R+, and RORγt+ (6). This stimulation leads to the production of IL-17, IL-22, and TNF-α, which promote inflammation, bone loss with erosions, and osteoproliferation (7). CD8+ Tcells and other immune cells like CD4- T helper 17 cells that involve in the production of IL-17 and TNF-alpha (3,4).These proinflammatory cytokines recruit neutrophils to the synovial fluid, activating synoviocytes, promoting local angiogenesis, and stimulating osteoclasts, leading to bone destruction. Simultaneously, they induce osteoblasts to promote new bone formation (3, 4, 8, 9). Despite the significant improvement in clinical outcomes and HRQoL for PsA patients due to the introduction of biologic and targeted synthetic therapies, some patients may experience a lack or loss of response. This can lead to persistent pain, fatigue, functional limitations, and reduced HRQoL. Therefore, long-term data are crucial to assess sustained treatment responses (10, 11).

PREVALENCE OF PSORIATIC ARTHRITIS

The prevalence of psoriatic arthritis varies significantly, ranging from 0.05% to 0.25% in the general population to 6% to 41% in patients with psoriasis (12). This variability is partly attributed to underdiagnosis, as a meta-analysis suggests that up to 15.5% of psoriatic arthritis cases may go undiagnosed (13). Typically, the condition manifests in individuals in their 30s and 40s, affecting both men and women equally (14).

ETIOLOGY

Etiology is not fully understood. Genes associated with psoriatic arthritis include those within the HLA region, which are involved in antigen presentation and immune recognition. Non-HLA genes also contribute to the development of the disease, influencing immune activation, inflammation, intracellular signaling, cytokine expression, and T cell effector

function (15, 16). Genetic factors play a significant role in psoriatic arthritis such as HLA-B*08:01, HLA-B*27:05, HLA-B*38:01, HLA-B*39:01, HLA-B*44:02HLA-B*57:01, and HLA-C*06:02 (17).HLA-B*27:05 is linked to axial involvement, symmetric sacroiliitis, enthesitis, and dactylitis (15, 18). HLA-B38 and HLA-B39is associated with polyarthritis. HLA-B44:02/03 is protective and associated with milder disease. HLA-DR4, a gene associated with rheumatoid arthritis, is linked to symmetric polyarthritis in a subset of psoriatic arthritis patients (17). IL-23R is the non-HLA gene associated with psoriatic arthritis. It involves the production of proteins such as TNFAIP3, TNF3IP2, REL, FBX19, and PTPN22 that causes immune medicated inflammation (16, 17). Epidemiological studies suggest a link between streptococcal infection and recent antibiotic use with the development of psoriatic arthritis. Additionally, skin trauma, known to trigger psoriatic skin lesions (Koebner phenomenon), may also play a role (18, 19, 20, 21).

PATHOPHYSIOLOGY

The key features of psoriatic arthritis involves immune dysregulation, altered cytokine expression and cellular phenotypes (22, 23).

Dysregulated Cytokine Expression: The skin and joint/ synovium in psoriatic arthritis are mostly pronounced with immune activation and associated proinflammatory cytokine expression. The skin exhibits higher levels of IL-17 expression, whereas the synovium shows elevated proinflammatory IL-6 expression.The cytokine expression patterns in synovium of psoriatic arthritis show a stronger correlation with gene expression patterns in psoriatic skin than with those in other forms of chronic arthritis, suggesting that cytokine expression in PsA may be more disease-specific than symptom-specific (22). IL-23, a heterodimeric cytokine composed of p19 and p40 subunits, is primarily secreted by innate immune cells like dendritic cells and macrophages and plays a crucial role in the IL-23/Th17 axis, which is central to the pathogenesis of psoriasis, especially skin disease (24). The IL-23R receptor, composed of IL-23R and IL-12Rb1 subunits, is expressed on the surface of lymphoid cells, including Th17 cells, and a subset of myeloid cells, such as macrophages and dendritic cells (25). IL-23R activation triggers the phosphorylation of Jak2 and Tyk2 kinases, which subsequently activate STAT3 and RORγ transcription factors, promoting Th17 cell differentiation and IL-17 production (26, 27).Notably, IL-17, in conjunction with TNF-α, induces the expression of matrix metalloproteinases (MMPs) in synovial fluid and cartilage, leading to collagen degradation and cartilage erosion (28). IL-17 can also stimulate osteoblasts to express receptor activator of nuclear factor kappa-B ligand (RANKL), which, upon binding to receptor activator of nuclear factor kappa-B (RANK) receptors on osteoclast precursors, promotes osteoclast differentiation and activation (29).

Innate Immune Cell Dysregulation: In murine models, the microRNA Let7b, a TLR-7 ligand, triggers skin inflammation characterized by CD68+ macrophage infiltration and increased expression of pro-inflammatory cytokines (IL-1β, IL-6, and IL-12) in joints. These stimulated skin macrophages exhibit a metabolic shift towards glycolysis.In the synovium of PsA patients, NK cells produce granulocyte macrophage colony-stimulating factor (GM-CSF), which drives the differentiation of monocytes into dendritic cells, crucial links between innate and adaptive immunity. They contribute to bone destruction, stimulate effector T cell responses, and induce fibroblast proliferation (30).

Altered Synovial Vascularization: Altered synovial vascularization in psoriatic arthritis is crucial for the development of synovitis and inflammation, leading to cartilage destruction and bone resorption. The PsA synovium exhibits increased vascularization, which facilitates the infiltration of innate and effector immune cells.The increased infiltration of immune cells, coupled with fibroblast proliferation, creates a hypoxic environment that further stimulates angiogenesis and immune cell infiltration, perpetuating inflammation. The elevated levels of VEGF, MMP-9, and EMMPRIN/CD147 in PsA synovium, along with several SNP and miRNA signatures associated with angiogenesis, highlight the crucial role of angiogenesis in the development of psoriatic arthritis (31, 32, 33).

CLINICAL FEATURES

The clinical presentation of psoriatic arthritis encompasses both articular and extra-articular features.

Articular/Periarticular characteristics of Psoriatic Arthritis

- Peripheral arthritis can have either an oligoarticular or polyarticular pattern.
- Periarticular manifestations include enthesitis, dactylitis, and tenosynovitis.
- Axial disease typically involves the sacroiliac joints in an asymmetric pattern.
- Spondylitis with discontinuous, bulky, non-marginal syndesmophytes.

Extra-Articular characteristics of Psoriatic Arthritis

- Psoriatic skin disease typically precedes the onset of arthritis, but it can also occur simultaneously or even before joint symptoms appear.
- Nail disease is observed by onycholysis, pitting, and splinter hemorrhages.
- Ocular disease in the form of uveitis (34, 35).

CASPAR Criteria (2006):Classification criteria for psoriatritic arthritis

- Skin psoriasis: Present - 2; Previously present -1; Family history, Patient not affected - 1
- Nail lesions: onycholysis, pitting, hyperkeratosis - 1
- Dactylitis: The patient with diagnosedpreviously diagnosed or presently disease which is documented by rheumatologist-1
- Negative rheumatoid factor (except by latex) - 1 point
- Juxta-articular bone formation: distinct from osteophytes – 1(36)

INVESTIGATION

Psoriatic arthritis cannot be definitively diagnosed with laboratory tests (37).Characteristic radiographic changes in psoriatic arthritis include erosive changes, severe joint destruction, joint space narrowing, and "pencil-in-cup"

deformities (38, 39).The simultaneous occurrence of bone destruction and new bone formation within the same digit or joint is a relevent feature of psoriatic arthritis (40).Axial features, such as sacroiliitis and spondylitis, are characterized by the formation of syndesmophytes (ossification of the annulus fibrosis) (41).Plain radiography, CT scans, ultrasound, and MRI are all imaging modalities useful for assessing patients with psoriatic arthritis (42).Musculoskeletal ultrasound (MSUS) and MRI are more sensitive imaging modalities than plain radiography for detecting early joint inflammation, damage, and axial changes, such as sacroiliitis (43).

CURRENT APPORACHES TOWARDS PSORIATIC ARTHRITIS

TNF inhibitors are consider as standard treatment for managing psoriatic arthritis now a days. IL-17 inhibitors, IL-12/23 inhibitors and IL-23 inhibitors are FDA- approved treatment for psoriatic arthritis.IL-17A and IL-17F play independent, yet pivotal roles in driving joint and skin inflammation in Psoriatic arthritis (44).IL-17A inhibitors, like secukinumab and ixekizumab, are currently available and have proven to be effective treatments for Psoriatic arthritis (45, 46).

BIMEKIZUMAB

A selectively inhibitor of IL-17A and IL-17F Bimekizumab, it binds to similar sites on the IL-17A and IL-17F molecules. It is a humanised monoclonal IgG1 antibody, inhibiting both homodimers and heterodimers. Effective reduction of inflammation requires dual neutralization of both IL-17A and IL-17F rather than neutralization of IL-17A alone. The inhibition of both IL-17A and IL-17F probably an effective treatment for psoriatic arthritis (47).

CLINICAL TRIALS CONDUCTED ON BIMEKIZUMAB IN PATIENTS HAVING PSORIATIC ARTHRITIS

A clinical trial was conducted by McInnes, Iain B *et al* to access efficacy and safety of bimekizumab in patients with active psoriatic arthritis who were naive to biologic disease-modifying antirheumatic drugs (DMARDs).BE OPTIMAL was a 52-week, Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-comparator (adalimumab) trial conducted at 135 sites across 14 countries.Eligible participants were adults aged 18 years or older with a confirmed diagnosis of adult-onset psoriatic arthritis(who met the Classification Criteria) for at least 6 months prior to screening.

Table 1. Clinical studies involving the effect of Bimekizumab in psoriatric arthritis

SL. NO	TITLE	AUTHORS	YEAR	SAMPLE SIZE	METHODOLOGY	RESULT
1	Bimekizumab in patients with Psoriatic arthritis, naïve to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL)	McInnes, Iain B *et al*	2023	1163	Phase 3, multicenter, randomized, double-blind, placebo-controlled, active-comparator (adalimumab) trial.	It was to access efficacy and safety of bimekizumab in patients with active psoriatic arthritis who were naive to biologic disease-modifying antirheumatic drugs (DMARDs). Bimekizumab demonstrated superior improvements in joint, skin, and radiographic outcomes at week 16 compared to placebo in treatment-naïve patients with psoriatic arthritis
2	Effect of Bimekizumab on symptoms and impact of disease in patients with psoriatic arthritis over 3 years: result from BE ACTIVE	Mease PJ *et al*	2022	206	randomized controlled trial was followed by aopen-label extension	The study used to monitoreffects of long-term bimekizumabtreatment on patient-reported outcome (PRO) measures, symptoms and the impact of PsA on patients. Bimekizumab treatment led to long-term sustained improvements in pain, fatigue, physical function, and quality of life, reducing the overall impact of PsA on patients for up to 3 years.
3	Bimekizumab treatment in biologic DMARD- naïve patients with active psoriatic arthritis: 52- week efficacy and safety results from randomised, placebo-controlled, active reference BE OPTIMAL study.	Christopher T Ritchlin *et al*	2022	1158	Double-blind, placebo-controlled	It aimed to evaluate achieve minimal disease activity across all domains, as assessed by stringent measures like American College of Rheumatology response criteria (ACR) ≥50% improvement, Psoriasis Area and Severity Index (PASI) 100% improvement and minimal disease activity (MDA).
4	Bimekizumab in patients with active psoriatric arthritis and previous inadequate response or intolerance to tumor necrosis factor alpha inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE)	Joseph F Merola *et al*	2022	556	Phase 3, multicenter, randomized, double-blind, placebo-controlled trial	It is assessed to evaluate the efficacy and safety of bimekizumab compared to placebo over 16 weeks in patients with active psoriatic arthritis who had previously failed or were intolerant to TNFα inhibitors. Bimekizumab demonstrated superior improvements in joint and skin outcomes at week 16 compared to placebo in patients with psoriatic arthritis who had previously failed or were intolerant to TNFα inhibitors.

Participants were randomly assigned in a 3:2:1 ratio, stratified by region and baseline bone erosion number, to receive bimekizumab 160 mg every 4 weeks, placebo every 2 weeks, or adalimumab 40 mg every 2 weeks, all administered subcutaneously, using an interactive voice and web-response system.At week 16, patients in the placebo group switched to bimekizumab 160 mg every 4 weeks.The primary endpoint was the proportion of patients achieving at least a 50% improvement in American College of Rheumatology criteria response (ACR50) at week 16, using non-responder imputation. Bimekizumab demonstrated superior improvements in joint, skin, and radiographic outcomes at week 16 compared to placebo in treatment-naïve patients with psoriatic arthritis (48). A study was conducted by Mease PJ *et al* to monitoreffects of long-term bimekizumab treatment on patient-reported outcome (PRO) measures, symptoms and the impact of PsA on patients.A 48-week randomized controlled trial (NCT02969525) was followed by a 104-week open-label extension (NCT03347110), where patients continued to receive bimekizumab 160 mg every four weeks.Bimekizumab treatment led to long-term sustained improvements in pain, fatigue, physical function, and quality of life, reducing the overall impact of PsA on patients for up to 3 years (49).

A study was conducted byChristopher T Ritchlin *et al* to evaluate achieve minimal disease activity across all domains, as assessed by stringent measures like American College of Rheumatology response criteria (ACR) ≥50% improvement, Psoriasis Area and Severity Index (PASI) 100% improvement and minimal disease activity (MDA). The study was a 16-week, double-blind, placebo-controlled period followed by a 36-week treatment-blind period. Patients were randomized 3:2:1 to receive subcutaneous bimekizumab 160 mg every 4 weeks, placebo for 16 weeks followed by bimekizumab, or adalimumab 40 mg every 2 weeks.Bimekizumab demonstrated sustained efficacy in bDMARD-naïve patients with PsA from Week 16 to Week 52. Additionally, bimekizumab was well-tolerated, with no new safety signals identified (50).

A study was conducted by Joseph F Merola *et al* to evaluate the efficacy and safety of bimekizumab compared to placebo over 16 weeks in patients with active psoriatic arthritis who had previously failed or were intolerant to TNFα inhibitors.It was a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial conducted at 92 sites across 11 countries.Patients were randomized 2:1 to receive subcutaneous bimekizumab 160 mg every 4 weeks or placebo using an interactive voice and web-response system.Bimekizumab demonstrated superior improvements in joint and skin outcomes at week 16 compared to placebo in patients with psoriatic arthritis who had previously failed or were intolerant to TNFα inhibitors.The safety profile of bimekizumab was consistent with previous Phase 3 studies in plaque psoriasis and with the safety profiles of other IL-17A inhibitors (51).

CONCLUSION

Bimekizumab, a humanized monoclonal antibody targeting both IL-17A and IL-17F, was approved by the EU on August 20, 2021, for the treatment of plaque psoriasis. It is the first IL-17 inhibitor to target both these cytokines.Bimekizumab has shown superior efficacy compared to other therapies like secukinumab (an IL-17A inhibitor), ustekinumab (an IL-12/23 inhibitor), and adalimumab (a TNF inhibitor) in treating moderate-to-severe psoriasis, likely due to the inhibition of both IL-17A and IL-17F.

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