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REVIEW

Clinical Efficacy and Safety of Ixekizumab for Treatment of Psoriasis

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Abstract Psoriasis is a common, chronic, inflammatory skin disorder with a physical and emotional burden. Emerging evidence suggests that IL17-A is a key cytokine in the immunopathogenesis of psoriasis. Ixekizumab is a humanized IgG4 monoclonal antibody that acts by neutralizing IL-17A. Data from Phase I-III studies reveal that ixekizumab is highly effective in treating patients with moderate-to-severe plaque psoriasis. A large proportion of patients receiving ixekizumab achieved or maintained complete or near complete resolution of psoriatic lesions with an acceptable safety profile through week 60. These remarkable results introduce a paradigm shift in the medically management of psoriasis, where complete or almost completely clear skin becomes the new therapeutic goal.

PALABRAS CLAVE
Agentes anti IL-17;
Interleucina-17;
Ixekizumab;
Psoriasis

Eficacia y seguridad clínica del ixekizumab para el tratamiento de la psoriasis

Resumen La psoriasis es un trastorno cutáneo común, crónico e inflamatorio con una carga física y emocional. Las pruebas recientes sugieren que la IL17-A es una citocina clave en la inmunopatogénesis de la psoriasis. El ixekizumab es un anticuerpo monoclonal IgG4 humanizado que actúa neutralizando la IL17-A. Los datos de los ensayos fase III muestran una alta eficacia del ixekizumab para tratar pacientes con psoriasis en placas de moderada a grave. Una gran proporción de los pacientes que tomaba ixekizumab consiguió o mantuvo la resolución completa o prácticamente completa de las lesiones psoriásicas, con un perfil de seguridad aceptable en la semana 60. Estos notables resultados suponen un cambio de paradigma en la gestión médica de la psoriasis, donde una piel completamente o casi completamente libre de lesiones es el nuevo objetivo terapéutico.

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Introduction

Psoriasis is a chronic inflammatory skin disease affecting 1–3% of the adult population in western countries.[1] About 20–30% of patients develop psoriatic arthritis and an association with an increased risk for cardiovascular disease and other cardiometabolic comorbidities has also been described.[2,3]

Treatment options include topical therapy, phototherapy and systemic agents such as retinoids, cyclosporine and methotrexate. However, a significant proportion of patients do not respond, are intolerant or have contraindications to these therapeutic options. Over the past few years, the introduction of biologic therapies targeting selective inflammatory mediators, namely TNF-α (adalimumab, etanercept and infliximab) and IL12/IL23p40 (ustekinumab), has improved treatment options for patients with moderate-to-severe psoriasis. Nonetheless there is still a subset of patients that do not respond to these biologic agents, lose treatment response over time or do not reach the highest clearance rate.[4] These unmet needs lead to the development of biologic agents against other targets.[4] Anti-IL17 drugs (including secukinumab and ixekizumab) are a promising therapy for psoriasis that act by neutralizing IL-17A, a key cytokine in the pathogenesis of the disease. This article aims to review the role of IL-17 in psoriasis immunopathogenesis and summarizes the data on efficacy and safety of ixekizumab.

Biology of IL17

Psoriasis is an immune-mediated disease initially considered to be a result of a Th1 response with the signature cytokines INF-γ and IL-12. However, recent studies investigating the molecular basis of psoriasis identified the key role of the adaptive Th17 cells.[5]

The actual model of immunopathogenesis (Fig. 1) proposes that an unknown antigen or environmental trigger activates macrophages, natural killer (NK) T cells and plasmacytoid dendritic cells (DCs) to secrete TNF-α, INF-α, INF-γ, IL-1β and Il-6, which trigger myeloid DCs activation. Activated myeloid DCs produce IL-12 and IL-23, leading to the differentiation of Th1 cells and Th17 cells, respectively.[6,7] Th17 cells are important producers of IL-17A. Other cells, such as mast cells, neutrophils and NK cells, can also secrete IL-17A.[8–10]

IL-17A is a pro-inflammatory cytokine that belongs to the IL-17 cytokine family, which comprises six members (IL-17A-F).[11] IL-17A,-C and-F expression is increased in psoriatic skin lesions.[12] IL-17A shows similarities with IL-17F and both cytokines bind to the same receptor IL-17RA. The biologically active form of IL-17A comprises either an IL-17A homodimer or an IL-17A-IL-17F heterodimer, although the first one has greater biological activity.[13,14]

Serum levels of IL-17A are significantly increased in patients with psoriasis compared with healthy individuals and IL-17A positive T cells are found in elevated number in psoriatic lesions.[15,16] The major pathogenic importance of the IL-23/Th17 axis over the IL-12/TH1 pathway is demonstrated by the higher expression of IL-23 in psoriatic skin lesions and its pathogenicity in inducing the psoriasiform phenotype in an experimental model injected with IL-23, but not with IL-12.[17,18] Besides, the IL23/Th17 axis contributes to genetic susceptibility of psoriasis, linked to specific IL23p19 gene variants and to other genes such as the IL-23 receptor gene.[19]

IL-17A action includes: (i) activation of STAT3 signaling in keratinocytes, inducing their proliferation and expression of proinflammatory cytokines associated with skin inflammation; (ii) overexpression of antimicrobial peptides (AMPs), such as S100 proteins and β-defensins, which also have pro-inflammatory properties, (iii) secretion of several chemoattractants (CXCL1, CXCL3, CXCL5, CXCL6 and CXCL8) responsible for neutrophils accumulation in psoriatic epidermis; and (iv) increased expression of CCL20, which can attract CCR6-expressing DCs and T cells, creating a proinflammatory loop in the skin.[20–24]

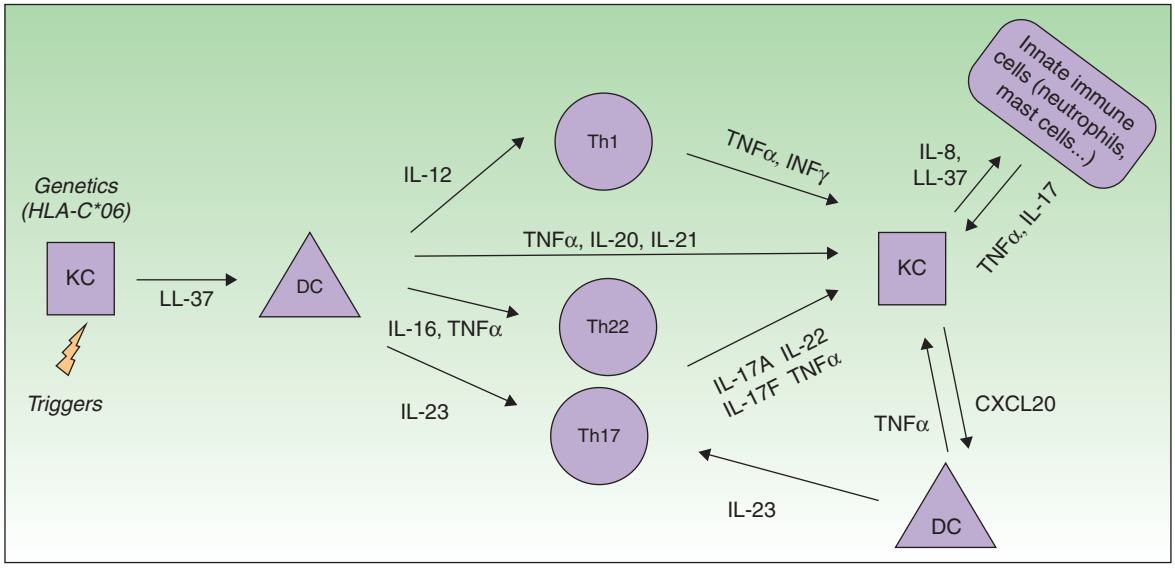

Figure 1 Immunopathogenesis model of psoriasis. DC, dendritic cell; KC, keratinocyte; Th, T helper cell.

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