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Pathogenic role of IL-17 in psoriasis and psoriatic arthritis

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PALABRAS CLAVE

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Abstract Psoriasis is a chronic inflammatory skin disorder resulting from a complex network of cytokines and chemokines produced by various immune cell types and tissue cells. Emerging evidence suggests a central role of IL-17 and IL-23/T17 axis in the pathogenesis of psoriasis, giving a rationale for using IL-17-blocking agents as therapeutics.

Three agents targeting IL-17 signaling are being studied in Phase III clinical trials: secukinumab and ixekizumab (IL-17 neutralizing agents), and brodalumab (IL-17 receptor antagonist). Preliminary results are highly promising for all anti-IL17 agents, creating fair expectations on this class of agents as the new effective therapeutic approach for the treatment of psoriasis.

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Papel patógeno de la IL-17 en la psoriasis y en la artritis psoriásica

Resumen La psoriasis es un trastorno crónico inflamatorio de la piel resultante de un complejo sistema de citocinas y quimiocinas producidas por varios tipos de células inmunes y células tisulares. La evidencia incipiente sugiere un papel central de la IL-17 y el eje IL-23/T17 en la patogénesis de la psoriasis, lo que ofrece una base para el uso de agentes bloqueadores de la IL-17 como tratamiento.

Están siendo estudiados en estudios clínicos en fase III tres agentes enfocados en la señalización de la IL-17: secukinumab e ixekizumab (agentes neutralizantes de la IL-17), y brodalumab (antagonista del receptor de la IL-17). Los resultados preliminares son altamente prometedores para todos los agentes anti-IL17, lo que crea claras expectativas para esta clase de agentes como un nuevo planteamiento terapéutico eficaz para el tratamiento de la psoriasis.

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Introduction

Psoriasis is a chronic, disabling, inflammatory skin disease with a worldwide prevalence of about 2.5%.¹ It is estimated that 70%-80% of patients suffer from a mild form of psoriasis, usually treated with topical medications and phototherapy. The remaining 20%-30% show a moderate-to-severe form that requires a systemic treatment including conventional therapeutics (phototherapy, methotrexate, cyclosporine, acitretin) and biologic agents.

The pathogenic mechanism leading to the psoriatic plaque formation is not fully clarified though, in the last two decades, important advances in the understanding of psoriasis pathogenesis guided the identification of key pathogenic circuits, and consequently, the development of therapeutics that selectively target crucial psoriasis mediators, such as interleukin (IL)-17A (simply known as IL-17) and tumor necrosis factor alpha (TNF α).

Previously considered only a skin disorder, psoriasis is now recognized as a systemic disease: in fact, epidemiological, clinical, and pathogenic evidence associates psoriasis, particularly the severe form, with an increased risk of mortality and various comorbidities including arthritis, metabolic disorders (type II diabetes, obesity, metabolic syndrome), cardiovascular disease, hypertension, and depression.^{2,3} There is also a marked impairment of quality of life associated with a reduced productivity and poor social life^{4,5}.

New insights advanced our understanding of disease pathophysiology with important therapeutics implications, leading to the development of selective-targeting therapeutics. Chronologically, the first class of biologics designed for the treatment of psoriasis was represented by the anti-TNF α agents (adalimumab, etanercept, infliximab), followed by the anti-IL-12/IL-23p40 agents (ustekinumab and briakinumab), and lately, by emerging classes of agents blocking IL-17 signaling (brodalumab, ixekizumab, secukinumab) or the IL23p19 subunit (tildrakizumab and guselkumab), which are currently in the pipeline for psoriasis treatment.

New insights in the pathogenesis of psoriasis

Psoriasis is an immune-mediated disorder, resulting from the combination of genetic susceptibility and environmental/endogenous triggers. Previous conventional genetic linkage analyses identified 10 chromosomal *loci* (named PSORS1 to PSORS10) correlated to the onset of psoriasis. Lately, genome-wide association studies identified a greater number of susceptibility genes. Most of them are involved in the immune response characterizing psoriasis such as innate immunity-related genes (interferon [IFN], nuclear factor kappa-light-chain-enhancer of activated B cells [NF κ B]), IL-17-related genes (IL12B, IL23A, IL23R, TRAF3IP2, TYK2), while few genes (LCE3B and LCE3C) are linked to the keratinocyte differentiation process.⁶ Psoriasis histological hallmarks include epidermal acanthosis, hyperparakeratosis, tortuous and dilated blood vessels in the papillary dermis, and dense clusters of inflammatory cells infiltrating mainly the dermis, but also the epidermis.⁷

Activated CD4⁺ T cells, predominantly localized in the dermis, produce several pathogenic cytokines such as IFN γ and TNF α (so called Th1 cells), IL-17A, IL-17F, and IL-22 (Th17 cells), TNF α and IL-22 (Th22 cells). An important contribution in cytokine production derives from CD8⁺ T cells, Tc17, Tc1, and Tc22, respectively producing IL-17, IFN γ , and IL-22, infiltrating the epidermis.^{8,9} Though T cells are central to the pathogenesis of psoriasis, dendritic cells (DCs), and keratinocytes play an active role, in particular a psoriasis-specific myeloid DC subtype, named Tip-DCs, TNF α and inducible nitric oxide synthase (iNOS)-producing DCs. Tip-DCs, activated by various *stimuli* (IFN α , toll-like receptor agonists), express and secrete: a) pro-inflammatory mediators such as iNOS and TNF α ; b) IL-20, which stimulates keratinocyte proliferation, and c) both p40 cytokines, IL-23 and IL-12.¹⁰⁻¹²

Importantly, IL-12 and IL-23 induce the differentiation of naïve CD4⁺ T cells into Th1 and Th17, respectively, and both pathways are considered to be crucial in the pathogenesis of psoriasis. Similar to Th17, Tc17 activation and polarization are regulated by IL-23, whereas IL-12 influenced the differentiation of Tc1 cells.¹³⁻¹⁵ IL-23 is a heterodimer constituted by p19 and p40 subunits. The p40 subunit is common to IL-12, which also includes the p35 subunit.

Additionally to T1 (considering Tc1 and Th1 together), T17 (Tc17 and Th17), T22 (Th22 and Tc22), and Tip-DCs, other immune cells (plasmacytoid DCs, mast cells, neutrophils, natural killer cells [NK cells], macrophages) participate to psoriasis pathogenesis, and thus, to cytokine production. Tissue cells including fibroblasts, endothelial cells, and keratinocytes, are clearly involved in the psoriatic plaque formation process: particularly, keratinocytes, which are considered the key-responding cells to the inflammatory cytokine “storm”. Indeed, keratinocyte contribution is relevant to psoriasis phenotype as they sustain and amplify skin inflammation through the expression of antimicrobial peptides (AMPs) (i.e. HBD-2, S100A7, S100A8, S100A9, S100A12, LCN2), chemokines (CXCLs –chemokine [C-X-C motif] ligand–, CCL20 –chemokine [C-C motif] ligand–), cytokines (IL-6, TNF α), growth factors for neoangiogenesis, and matrix metalloproteinases.

The imprinting of IL-23/T17 axis on psoriasis pathogenesis

Psoriasis was dogmatically considered a Th1-mediated disease though increasing evidence suggested the centrality of the IL-23/T17 axis as main pathogenic pathway.^{16,17}

Human genetic studies identified various upstream and downstream genes related to IL23/T17 axis (Table 1) as psoriasis susceptibility genes, while they failed to prove an association with IL-12/T1-signature genes such as IL12A, IL12RB2, and IFN γ .¹⁸

Experimental models of psoriasis helped to clarify the pathogenic relevance of this pathway. Firstly, elevated transcript levels of T17 pathway-related genes (IL-17A, IL-17F, IL-23A, IL-12/IL-23p40, IL-22) were found in mice psoriasis-like lesions.¹⁹⁻²³ Further evidence derived from imiquimod-induced psoriatic inflammation that was suppressed in IL-23p19 or IL-17R- deficient mice.²³

Table 1 Psoriasis genetic susceptibility linked to upstream and downstream genes related to IL-17 pathway

Gene	Function	Relevance in IL-17 pathway
<i>IL23A</i>	IL-23 subunit	Upstream gene
<i>IL12B</i>	IL-23 subunit	Upstream gene
<i>IL23R</i>	IL-23 receptor	Upstream gene
<i>TYK2</i>	Tyrosine kinase involved in IL-23 signaling, belonging to JAKs protein family	Upstream gene
<i>TNFAIP3</i>	Involved in NFκB signaling	Up/downstream gene
<i>NFKBIA</i>	Involved in NFκB signaling	Up/downstream gene
<i>TNIP1</i>	Belonging to TNFAIP3 complex, it mediates NFκB signaling	Up/downstream gene
<i>TRAF3IP2</i>	Regulating IL-17 responses through NFκB	Downstream gene
<i>DEFB4</i>	Antimicrobial peptide whose expression is regulated by IL-17	Downstream gene

JAKs: Janus kinases; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells.

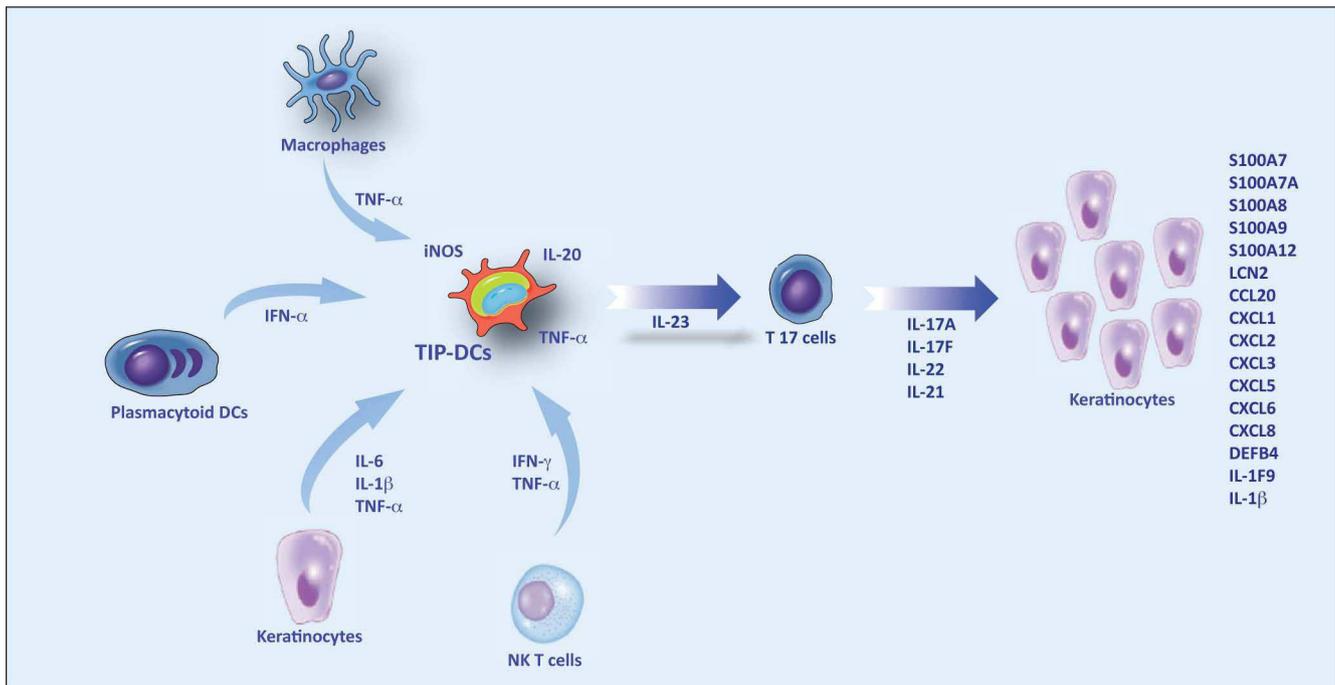


Figure 1 The IL-23/T17 axis in psoriasis. IL-23/T17 axis - related mediators are overexpressed in lesional psoriatic skin. TNF α /iNOS-producing dendritic cells, Tip-DCs, are activated by various cells and *stimuli*. They produce IL-20, TNF α , NO, and IL-23. IL-23 exerts its effects on T cells driving IL-17 and IL-22 expression. Keratinocytes are the key-responding cells to this pathway, expressing psoriasis-signature genes such as DEFB4, S100A12, and S100A7 (psoriasis).

Mice injected with recombinant murine (rm)IL-23, and not with rmlL-12, developed psoriasis phenotype including dermal inflammatory infiltrate, epidermal hyperplasia, and parakeratosis.²⁴

Moreover, both IL-17 and IL-22 have been demonstrated essential in mediating IL-23 effects as IL-17 or IL-22 knockout mice did not develop epidermal acanthosis when injected with IL-23.²⁰

Interestingly, administering anti-IL-17 antibodies prior to the injection of recombinant murine (rm)IL-23 in wild-type (WT) mice, epidermal hyperplasia was inhibited.²⁴ Conversely to IL-22, which is known to have a direct proliferative effect on keratinocytes, IL-17 has not been demonstrated to stimulate *in vitro* keratinocyte proliferation, but, most likely, it indirectly contributes to promote *in vivo* epidermal hyperplasia.

Similar to mice psoriatic skin, elevated levels of IL-17A, IL-17F, IL-22, IL-23 were detected in human lesional skin.²⁵⁻²⁸ Notably, IL-23 expression, and therefore the expression of both p40 and p19 subunits, was increased in lesional psoriatic skin compared to uninvolved skin, whereas the expression of IL-12p35 subunit did not result upregulated, likely suggesting a T17 differentiation skewing in psoriasis.^{24,29,30} Furthermore, circulating levels of T17-signature cytokines were higher in psoriatic patients compared to healthy subjects and they correlated with the severity of disease.³¹⁻³³

IL-17-downstream genes were also found upregulated in psoriatic lesional skin, in particular, keratinocyte-derived products such as CCL20, CXCL8, DEFB (defensin-B) 4 S100A7, LCN2, which are considered disease-defining genes (Fig. 1).

Table 2 Therapeutic agents targeting IL-17 signaling, which are currently under development in clinical trials

Agent	Target	Structure	Disease	Development	Manufacturer
Brodalumab	IL-17R	Fully humanized monoclonal IgG2 antibody	Plaque-type psoriasis/ psoriatic arthritis	III	Amgen
Ixekizumab	IL-17A	Fully humanized monoclonal IgG4 antibody	Plaque-type psoriasis/ psoriatic arthritis	III	Eli Lilly
Secukinumab	IL-17A	Fully humanized monoclonal IgG1k antibody	Plaque-type psoriasis/ psoriatic arthritis	Register/III	Novartis
RG4934	IL-17A	Fully humanized monoclonal antibody	Psoriatic arthritis	I	Roche
NI-1401 (RG7624)	IL-17A/ IL-17F	Fully humanized monoclonal IgG1 antibody	N/A	I	NovImmune/ Genentech/ Roche
ABT-122	IL-17A/ TNF α	Fully humanized monoclonal antibody	Rheumatoid arthritis	I	AbbVie
SCH 900117	IL-17A	Fully humanized monoclonal antibody	Rheumatoid arthritis	I	Merck

N/A: not available.

IL-17 directly or indirectly mediates multiple steps of the pathogenic cascade, and drives key-inflammatory circuits acting in synergism with TNF α .³⁴ For instance, IL-17-exposed keratinocytes secrete CCL20, which recruits CCR (CC chemokine receptors) 6+ cells, myeloid DCs and Th17 cells, to psoriatic lesions and, thereby, create reverberating pathogenic loops.³⁴ Moreover, IL-17 induces keratinocyte secretion of AMPs such as S100 proteins, β -defensins, that also show pro-inflammatory properties, attracting immune cells at the lesional site. IL-17 stimulates neutrophil migration inducing keratinocytes expression of neutrophil chemoattractants, namely CXCL-1, CXCL-3, CXCL-5, CXCL-6, CXCL-8, all binding CXCR-2 receptor, and it also seems to be responsible of neutrophil survival.³⁴⁻³⁶ Furthermore, it synergizes with IL-22 enhancing the expression of psoriasis transcriptome-related genes, in particular AMPs and neutrophil-recruiting chemokines.³⁷

Additional evidence of a central role of IL-23/T17 axis derived from mechanistic studies correlating the efficacy of antipsoriatic therapies such as cyclosporine and phototherapy, to the T17 pathway-suppression.^{38,39} Of relevance, even the effectiveness of a TNF α -neutralizing agent, etanercept, proved to be linked to the suppression of T17 pathway. In fact, the blockade of TNF α may interfere with the T17 pathway firstly because TNF α stimulates Tip-DCs in producing IL-23, and additionally due to its synergism with IL-17 in mediating key-inflammatory circuits.⁴⁰

Regarding psoriatic arthritis (PsA), monocyte-derived TNF α is considered the main immunological mediator, though a deeper understanding of the pathogenic circuits has recently revealed the involvement of novel key cytokines and T cells subsets to be targeted.⁴¹ In particular, recent studies have been focused on the emerging role of Th17 cells and their derived cytokine, IL-17. Experimental models of autoimmune arthritis (CIA) showed a critical role of the IL-23/IL-17 axis as IL-23 (and not IL-12) deficiency was protective against the development of CIA.⁴² Of note, IL-17 knockout mice developed less severe arthritis, likely because IL-17 contributes to: a) osteoclastogenesis;

b) destruction of the extracellular matrix; c) chondrocyte damage, and d) bone resorption, inducing the expression of receptor activator of NF κ B ligand (RANKL) and iNOS.⁴³⁻⁴⁶ IL-17 also acts in combination with other proinflammatory cytokines regulating cartilage degradation, osteoblasts and chondrocytes activity, and thus, mediating both synovial inflammation and joint destruction.⁴⁷⁻⁴⁹ Together with IL-17, IL-23 also seems to be essential in the instauration of enthesitis inducing IL-17 and IL-22 production that, in turn, promote signal transducer and activator of transcription 3 (STAT3)-dependent osteoblast-mediated bone remodeling.

IL-17/IL-17R anti-cytokine therapy in psoriasis and psoriatic arthritis: preliminary clinical efficacy data

IL-17 is a proinflammatory cytokine belonging to the IL-17 cytokine family that consists in 6 members, progressively named IL-17A up to IL-17F.⁵⁰ It is mainly produced by Th17 and Tc17 cells but also mast cells, neutrophils and γ/δ T cells contribute to the high levels of expression in lesional psoriatic skin⁵¹⁻⁵³. IL-17 sequence shows strong similarities with IL-17F, sharing 58% of their sequence at the protein level. The active form of IL-17 consists of either disulfide-linked homodimers or IL-17/IL-17F heterodimers.^{54,55}

IL-17A and IL-17F signal through the same receptor, namely IL-17R, consisting of two subunits, IL-17RA and IL-17RC. However, homodimeric IL-17 is biologically more active than heterodimeric IL-17/IL-17F or homodimeric IL-17F in inducing gene expression.⁵⁵

A new class of biologic agents targeting IL-17 signaling is now in the pipeline for the treatment of psoriasis, including: ixekizumab, brodalumab, and secukinumab. Secukinumab and ixekizumab neutralize IL-17, while brodalumab is an IL-17-receptor antagonist. Ixekizumab and brodalumab have successfully concluded Phase II trials and are presently tested in Phase III clinical studies. Secukinumab has recently published results in Phase III studies.⁵⁶

Table 3 Clinical outcomes of 12-week, dose-ranging, Phase II trial testing brodalumab⁵⁸

Study	Dose	Primary endpoint	Secondary endpoint at week 12		
		PASI 75 at week 12 (% patients)	PASI 90	PASI 100	sPGA 0-1 score
Brodalumab dose-ranging Phase II trial	Brodalumab 6 × 70 mg	33	18	10	26
	Brodalumab 6 × 140 mg	77	72	38	85
	Brodalumab 6 × 210 mg	82	75	62	80
	Brodalumab 3 × 280 mg	67	57	29	69
	Placebo × 6	0.0	0.0	0.0	33

As reported in Table 2, the above mentioned therapeutics are in a more advanced status of development compared to other anti-IL-17 agents, which are undergoing initial investigational studies.

Brodalumab

Brodalumab (AMG827, Amgen) is a human monoclonal antibody (mAb) blocking IL-17-receptor, and thereby inhibiting the response to IL-17A, IL-17F, and IL-17A/F heterodimer. The ability of brodalumab in treating psoriasis was initially showed by a proof-of-concept study.⁵⁷ In this study brodalumab treatment, administered in 10 patients, induced clinical, histological, and genomic improvement after only one week of therapy.⁵⁷ These outcomes have been confirmed by a recently published Phase II, double-blind, placebo-controlled, dose-ranging study.⁵⁸ Overall, 198 patients randomly received subcutaneous brodalumab at the dosage of 280 mg monthly, or 70 mg, 140 mg, 210 mg, or placebo at week 0, 1, 2, 4, 6, 8, and 10.

After 12 weeks of treatment the mean percentage improvement in term of PASI score was 45, 85.9, 86.3, 76, and 16% in patients treated with 280 mg, 210 mg, 140 mg, 70 mg brodalumab or placebo, respectively (< .001 for all comparisons vs. placebo).⁵⁸

The percentage of patients achieving PASI75 after 12 weeks was 77% and 82% in the 140 mg and 210 mg group, respectively (0% in the placebo group). While PASI90 improvement was experienced by 72% and 75% of patients treated with brodalumab at 140 mg and 210 mg dose, respectively, and the same dosages induced a complete remission in 38% and 62% of patients (Table 3). Decrease of the mean PASI score correlated with a significant amelioration of body surface area (BSA), static physicians' global assessment (sPGA), and dermatology life quality index (DLQI).⁵⁸

Regarding the safety profile, three serious adverse events were reported: one within the placebo group (ectopic pregnancy), one in the 70 mg brodalumab group (renal colic) and one occurred in the 210 mg brodalumab group (grade 3 asymptomatic neutropenia). Mild adverse events, more frequently observed within the 210 mg or 280 mg groups, included nasopharyngitis, upper respiratory tract infection and injection-site erythema.⁵⁸

Though anti-brodalumab antibodies were detected, they were not neutralizing.⁵⁸

Brodalumab is advancing through three Phase III clinical trials for plaque-type psoriasis and it will be investigated in Phase II studies for psoriatic arthritis. Among them, two head-to-head studies (AMAGINE-2/3 studies) comparing brodalumab with ustekinumab (anti-IL-23/IL-12p40 agent) are being performed.⁵⁹ Interestingly another Phase III trial (AMAGINE-1 study) is investigating brodalumab safety and efficacy using an intermittent administration scheme (withdrawal-retreatment) with 140 mg or 210 mg doses. Notably, a Phase I study is evaluating pharmacokinetic of a single brodalumab dose and brodalumab effect on midazolam pharmacokinetic in subjects with moderate to severe plaque psoriasis.⁵⁹

Ixekizumab

Ixekizumab (LY2439821, Eli Lilly) is a subcutaneously-administered fully humanized IgG4 mAb neutralizing IL-17A.

A Phase I, randomized, double-blind, placebo-controlled, dose-escalation, study assessed clinical, histological, and genomic response to ixekizumab in 40 patients affected by plaque-type psoriasis. Patients received placebo or subcutaneous doses of ixekizumab ranging from 5 to 150 mg, at week 0, 2, and 4. Histological evaluation of lesional psoriatic skin after 2 and 6 weeks of treatment showed a marked reduction of both inflammatory cell clusters (CD3+, CD11+, or CD-LAMP+ cells) and epidermal hyperplasia, compared with baseline.¹⁷ This inhibitory effect on keratinocyte proliferation was rapid and unexpected, suggesting a potential IL-17 role in regulating keratinocyte cell cycle, most likely, through mitogenic cytokines (i.e. IL-19). The amelioration in term of inflammatory infiltrates was associated with the suppression of AMPs expression and downregulation of multiple inflammatory markers, including IL-17-downstream and upstream genes, alike unrelated genes such as IFN γ , whose expression is not recognized to be IL-17-dependent.¹⁷ Notably, ixekizumab determined a faster and broader gene expression modulation compared to etanercept (an anti-TNF α agent) therapy, after only 2-week treatment, with a normalization by at least 75%, observed in 60% of the psoriasis transcriptome vs. 10% induced by etanercept.¹⁷

The results of this mechanistic study paved the way for designing Phase II trials.

A randomized, double-blinded, placebo-controlled, Phase II study assessed ixekizumab safety and efficacy in 142 subjects

Table 4 Clinical outcomes of 12-week, dose-ranging, Phase II trial testing ixekizumab⁶⁰

Study	Dose	Primary endpoint	Secondary endpoint at week 12		
		PASI 75 at week 12 (% patients)	PASI 90	PASI 100	sPGA 0-1 score
Ixekizumab dose-ranging Phase II trial	Ixekizumab 5 × 10 mg	29	18	0.0	25
	Ixekizumab 5 × 25 mg	76.7	50.0	17.0	70
	Ixekizumab 5 × 75 mg	82.8	58.6	37.9	72
	Ixekizumab 5 × 150 mg	82.1	71.4	39.3	71
	Placebo × 5	7.7	0.0	0.0	8

affected by moderate-to-severe plaque-type psoriasis.⁶⁰ Patients were randomly distributed in five groups receiving 150 mg, 75 mg, 25 mg, 10 mg ixekizumab or placebo at week 0, 2, 4, 8, and 16. The primary endpoint was represented by the reduction in Psoriasis Area Severity Index (PASI) of at least 75% (PASI75) after 12 weeks of treatment. PASI75 was achieved by 82.1%, 82.8%, 76.7%, 29%, and 7.7% of patients treated with 150 mg, 75 mg, 25 mg, 10 mg ixekizumab doses compared with placebo ($P < .001$ for each comparison) with the exception of the lowest dose (Table 4).⁶⁰ As shown in Table 4, response rates in term of PASI90 were statistically significant for 150 mg (71.4%), 75 mg (58.6%), and 25 mg (50.0%) versus 0% of the placebo group ($P < .001$ for each comparison). A complete clearance of psoriasis (PASI100) was observed in 39.3% and 37.9% of patients treated respectively with 150 mg and 75 mg of ixekizumab, compared to placebo group (0%; $P < .001$ for both comparisons).⁶⁰ Satisfactory response was also observed for those hard-to-treat psoriasis localizations such as scalp and nails, measured by Psoriasis Scalp Severity Index (PSSI), and Nail Psoriasis Severity Index (NAPSI), respectively. In patients affected by psoriatic arthritis, ixekizumab significantly reduced joint-pain VAS score after 12-week treatment maintaining this improvement through 20 weeks.⁶⁰

During the study-period there were not reported serious adverse events across treatment groups while the occurrence of mild-to-moderate adverse events such as nasopharyngitis, upper respiratory tract infection, injection site reaction, and headache was similar throughout all study groups. However, a few patients interrupted the study because of hypertriglyceridaemia (placebo group), peripheral oedema (10 mg ixekizumab), hypersensitivity (10 mg ixekizumab) and urticaria (25 mg ixekizumab). Ixekizumab immunogenicity was not assessed.⁶⁰

Overall, five Phase III studies which are currently ongoing, include a head-to-head trial with etanercept (UNCOVER-3 study), and a regimen-finding study using 80 mg ixekizumab at varying intervals.⁶¹

Ixekizumab is also being tested in patients affected by psoriatic arthritis in comparison with adalimumab or placebo (SPIRIT-P1 study).⁶¹

Secukinumab

Secukinumab (AIN457, Novartis) is a fully humanized IgG1k neutralizing IL-17A. It has been tested as intravenous or

subcutaneous agents although larger studies have been performed using subcutaneous administration. In a proof-of-concept study, 36 psoriatic patients received a single intravenous dose of 3 mg Kg⁻¹ secukinumab or placebo.⁶² Secukinumab efficacy was significantly higher compared to placebo (58% vs. 4% as mean PASI reduction; $P = .0001$) and rapid as evaluated by Investigator Global Assessment (IGA) (83% of patients vs. 11% as reduction in IGA score category) at week 4. Benefits of secukinumab therapy lasted throughout the study period, until week 12.⁶² Clinical improvement reflected a decreased epidermal acanthosis, with reduced infiltrates IL-17+ and CD3+ cells, and normalized expression levels of both proliferation markers (K16) and inflammatory genes.⁶² Specifically, secukinumab downregulated Th17-related genes (IL-21, IL-22, IL-17F, IL-8, DEFB4), Th1 pathway genes (IFN γ , IL-12B), and other immune-related genes (TNF α , IL-6, IL-1 β , CCL20, IL-26).⁶² Another mechanistic study assessing skin histological and biomarker responses after 12-month therapy is ongoing as well as a Phase I pharmacokinetic study investigating the distribution into dermal interstitial fluid after a single subcutaneous administration of secukinumab in both healthy subjects and psoriatic patients.⁶³ The intravenous administration will be further tested in a Phase II, randomized, double-blind, multicenter study comparing the intravenous regimen of 10 mg Kg⁻¹ with subcutaneous 300 mg dose in a dose-escalation regimen, in case of partial response after 12-week treatment with secukinumab (subject who participated to CAIN457A2304).⁶³

In the subsequent Phase II trials, subcutaneous administration was mostly preferred to intravenous administration.

In a dose-ranging, double-blind, placebo-controlled, parallel-group, 12-week, Phase II study 125 subjects were randomly treated with subcutaneous secukinumab as single 25 mg dose, or at the dosage of 25 mg, 75 mg, 150 mg, or placebo as monthly administration (Table 5).⁶⁴ Higher dosages of secukinumab significantly improved psoriasis as 81.5 and 57.1% of patients respectively treated with 150 and 75 mg ixekizumab, achieved PASI75, compared to 9.1% of placebo-treated patients ($P < .001$ and $P = .002$ respectively).⁶⁴ IGA assessment confirmed secukinumab efficacy at higher dosages, reporting a response rate of 48.1% and 33.3% with 150 mg and 75 mg doses, respectively (Table 5). Conversely to PASI75 evaluation, IGA score improvement was significant only for the highest dose (150 mg) compared to placebo group ($P = .0005$).⁶⁴

Table 5 Efficacy end points in FIXTURE

End point	Secukinumab 300 mg	Secukinumab 150 mg
Coprimary efficacy end points at week 12 - no./total no. (%)		
PASI 75	249/323 (77.1)	219/327 (67.0)
Response of 0 or 1 on modified investigator's global assessment	202/323 (62.5)	167/327 (51.1)
Key secondary efficacy end points - no./total no. (%)		
PASI 90 at week 12	175/323 (54.2)	137/327 (41.9)
Maintenance of PASI 75 from week 12 to week 52	210/249 (84.3)	180/219 (82.2)
Maintenance of 0 or 1 response on modified investigator's global assessment from week 12 to week 52	161/202 (79.7)	113/167 (67.7)
Other efficacy end points		
PASI 100 at week 12 - no./total no. (%)	78/323 (24.1)	47/327 (14.4)
DLQI - mean score		
Baseline	13.3	13.4
Week 12	2.9	3.7
Absolute change	-10.4	-9.7

Regarding safety profile, secukinumab was proven overall safe though two cases of serious adverse events and two cases of permanent withdrawal because of adverse events, were reported. As common adverse events: worsening of disease, nasopharyngitis, and upper respiratory tract infection occurred.⁶⁴

The main outcome of this study was the identification of 150 mg secukinumab as the optimal dose that could be tested in further clinical studies, considering the achieved primary (PASI75 rates) and secondary (IGA, PASI90, and PASI50 rates) endpoints.

The 150 mg secukinumab dose was tested in a randomized, double-blind, placebo-controlled, parallel-group, regimen-finding, Phase II study including 404 subjects.⁶⁵ The study design was characterized by three induction schemes and two maintenance regimens. The induction schemes consisted in: *I. single dose* (at week 0); *II. monthly* (at weeks 0, 4, 8); or *III. early* (at weeks 0, 1, 2, 4). After 12-week induction period, PASI75 responders were re-randomized to two different maintenance therapeutic regimens (from week 12 to week 36) with secukinumab administered either at fixed intervals (as continuous treatment with administration at weeks 12 and 24) or as "withdrawn-retreatment" regimen (interruption during disease-free periods and retreatment at eventual disease-relapses).⁶⁵ "Early" and "monthly" regimens showed a superior efficacy compared to placebo in terms of PASI75 (54.5 and 42.0% vs. 1.5%, respectively; with $P < .001$ for both comparisons). The endpoint of PASI 90 was achieved by 31.8% and 17.4% of patients, treated with early and monthly regimen, respectively (1.5% by placebo group; $P < .001$ for both comparisons).⁶⁵ The maintenance period with secukinumab administered at fixed intervals proved more effective than treatment-at-relapse regimen, with 84.6% vs. 67.2% of patients achieving PASI75 at least once from week 20 to week 28.⁶⁵ Overall, secukinumab administered at loading-dose scheme (induction) followed by continuous, fix-interval treatment emerged as the optimal therapeutic regimen using 150 mg secukinumab.

Regarding safety profile, worsening of disease, nasopharyngitis and headache, were reported as the most common adverse events.⁶⁵

In the clinical trial pipeline, there are other dose-finding and regimen-defining studies (SCULPTURE and CAIN457A2304E1 studies), mainly testing secukinumab at the dose of 150 mg or 300 mg using different therapeutic schemes as fixed-interval treatment vs. withdrawal-retreatment (retreatment at start of relapse) and vs. placebo.⁶³ Moreover long-term clinical trials are being conducted up to 1 year (ERASURE study) and 2 years (extension study of CAIN457A230-2/-3 studies) for the treatment of moderate-to-severe plaque-type psoriasis.⁶³

Very recently 2 Phase III studies have been published. ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) were two randomized, double-blind, 52-week trials, Phase III trials including 738 and 1306 patients respectively. Both studies were conducted to assess the efficacy and safety of secukinumab, at a dose of 300 mg or 150 mg, administered as induction therapy (with assessment at week 12) and maintenance therapy (with assessment at week 52) in patients with moderate-to-severe plaque psoriasis.

At week 12 in the ERASURE study, 81.6% of patients with 300 mg of secukinumab and 71.6% of patients with 150 mg of secukinumab (4.5% of patients with placebo; $P < 0.001$ for all comparisons). At week 12 in the FIXTURE study, the endpoint of PASI 75 was achieved by 77.1%, 67.0%, 44.0% and 4.9% of the patients with 300 mg of secukinumab, with 150 mg of secukinumab, with etanercept, and with placebo, respectively ($P < 0.001$ for each secukinumab dose vs. comparators). The proportion of patients with a DLQI score of 0 or 1 at week 12 was significantly higher in each secukinumab-dose group than in the etanercept or placebo group ($P < 0.001$ for all comparisons). Although both studies were not designed to differentiate efficacy between the two secukinumab doses, the results suggest that the 300-mg dose may have been more effective than the 150-mg dose.

Regarding the response to secukinumab over the time, the curves suggest that the rates of response on the PASI increased during the period from week 12 to week 16

and then stabilized after week 16. In the FIXTURE study, the rates of response according to PASI 75, PASI 90, PASI 100 were higher with secukinumab than with etanercept through week 52.

The incidences of adverse events during the induction period and the entire treatment period in the FIXTURE study were similar in the secukinumab and etanercept groups.⁵⁶

In addition a few clinical trials are exclusively dedicated to specific forms of psoriasis such as palmoplantar psoriasis (GESTURE study) and nail psoriasis (TRANSFIGURE study).⁶³

Secukinumab was also tested as treatment for psoriatic arthritis in a double-blind, placebo-controlled Phase IIA clinical trials, safety and efficacy of secukinumab were tested on 42 patients affected by psoriatic arthritis. Secukinumab was administered 2 times with a 3-week interval, at the dosage of 10 mg Kg⁻¹.⁶⁶

The study design included as primary endpoint the achievement of American College of Rheumatology 20 score (ACR20) after 6 weeks of therapy.

ACR20 was obtained by 39% of patients vs. 23% of placebo-treated patients (not statistically significant difference, $P = .27$).⁶⁶ Secukinumab response was prolonged at week 12 (39%) and week 28 (43%) while, at the same timepoints, placebo response decreased to 15% and 18%.⁶⁶ ACR20 correlated with a reduction of both median C-reactive protein (CRP) serum levels and erythrocyte sedimentation rate.

Subsequently, other Phase III trials are currently investigating long-term safety, efficacy, and tolerability of secukinumab in the treatment of psoriatic arthritis with study period of 2 (FUTURE 1 study), 3, and 5 years.⁶³

IL-17 and inflammation: implications on atherogenesis

The epidemiological and clinical linkage between psoriasis and its comorbidities implicates immune mediators and circuits, which are commonly involved in the pathogenesis of these disorders.² Moderate-to-severe psoriasis represents a cardiovascular risk factor because chronic, severe, skin inflammation might promote the atherosclerotic process. According to the Fisman's model, pro-inflammatory cytokines, which are highly expressed in psoriasis (IL-23, IL-17, TNF α , IFN γ), may be considered pro-atherogenic as they are also involved in the pathogenesis of atherosclerosis.⁶⁷ Indeed, atherogenesis is characterized by an immune process including macrophages, dendritic cells, and T cells, and similarly to psoriasis, the pathogenic mechanism is driven by both Th1 and Th17 pathways. Specifically, Th1 cells are thought to be the initiators of the atherogenic process while Th17 cells seem to promote plaque instability.⁶⁸ Th1 and Th17 cells were found numerically increased in peripheral blood of patients with acute coronary syndrome, associated with high levels of both Th1 and Th17 cytokines. They act in synergism although Th1 seem to be responsible for atherosclerotic plaques initiation and inflammatory state perpetuation, while Th17 seem to promote intraplaque neoangiogenesis and haemorrhage, favoring plaque rupture.⁶⁸

However, evidence about the IL-17 role in atherosclerosis is controversial as it has been also reported as stabilizing

factor in atherosclerotic plaque formation.^{69,70} Increased expression of IL-17 in the plaques with a stable fibrotic phenotype compared to those having an unstable phenotype.⁷⁰

One would expect that the blockade of key-inflammatory mediators should improve, or, at least, not worsen, the atherosclerotic process. On the contrary, the use of a class of biologics designed for the treatment of psoriasis, the anti-IL-12/IL-23p40 agents, was correlated with the non-statistically significant occurrence of Major Adverse Cardiovascular Events (MACE), including non-fatal myocardial infarction, cerebrovascular accident, and cardiovascular death. This potential issue about cardiovascular safety appeared with both IL-12/IL-23p40 neutralizing agents, ustekinumab and briakinumab, though analysis are not consistent.⁷¹ Ustekinumab has been approved for the treatment of plaque-type psoriasis, whereas briakinumab passed Phase II trials, and its development was interrupted by the manufacturer in Phase III.

Comprehensively, integrated analyses about safety profiles of anti-p40 agents showed controversial results and the increased incidence of MACE was not powered by statistical significance compared to placebo and to anti-TNF α agents.⁷¹⁻⁷⁴

Regarding IL-17 blocking agents, preliminary safety data based on published peer-reviewed journals did not report an increased incidence of MACE, though the overall number of patients treated with any IL-17 blocker is actually limited. Further long-term safety studies and, especially, registry studies, which might be considered a more appropriate tool for safety evaluation, will help to evaluate safety of anti-IL-17 agents. Furthermore, functional and mechanistic studies will elucidate the IL-17 role in atherogenesis that is not fully understood.

Safety implications of anti-IL-17 therapy: IL-17 and infections

Although the exact role of the IL-17 in host defense against infection remains to be defined, it likely drives the innate immune response against bacterial, parasitic and fungal infections. As previously mentioned, IL-17 stimulates the production of antimicrobial peptides and the recruitment and activation of neutrophils, thus, regulating the immune response of surface epithelia. For instance, IL-17 or IL-17R-knockout mice are more susceptible to *Klebsiella pneumoniae* infection, showing an impaired neutrophil response in the airways.⁷⁵⁻⁷⁷ Conversely, recombinant adenovirus-induced IL-17 overexpression in mice lungs, proved protective against *K. pneumoniae*, enhancing bacterial clearance.⁷⁶ Moreover, IL-17R-deficient mice did not show a vigorous and effective response against *Klebsiella pneumoniae* with a markedly elevated mortality compared to wild-type mice.^{77,78}

IL-23/IL-17 axis has also a protective against *Candida albicans* as IL-23p19 or IL-17R deficient mice showed a reduced neutrophil recruitment and an increased susceptibility to oropharyngeal candidiasis.⁷⁹ Similarly, wild-type mice infected with *Pneumocystis jiroveci* displayed a worsening of fungal infection after administration

of neutralizing antibodies targeting either IL-23p19 or IL-17.⁸⁰ Susceptibility to intracellular parasitic infection of *Toxoplasma gondii* is observed in IL-17RA-deficient mice.⁸¹ Defensive role of IL-17 has been also reported against various pathogens including *Salmonella typhimurium* and *Pneumocystis Carinii*.^{82,83}

Similarly, in human being with impaired IL-17 response recurrent infections have been reported.^{84,85} Despite this evidence in favor of a critical role of IL-17 signaling against infections, human-phased trials did not show a significant increased risk of infections in patients treated with IL-17 blockers.

However, the most recurrent adverse events reported throughout Phase II trials are nasopharyngitis, headache, and diarrhea. Phase III trial ERASURE showed during the induction period higher proportions of patients with infections and infestations in the secukinumab groups (29.4% in the 300-mg group and 26.9% in the 150-mg group) than in the placebo group (16.2%). And during the entire treatment period rates of serious adverse events were reported as following: 6.3 events per 100 patient-years in the 300-mg secukinumab group; 6.4 events per 100 patient-years in the 150-mg secukinumab group; and 7.4 events per 100 patient-years in the placebo group.

On the other hand, in the FIXTURE study the incidences of adverse events during the induction period and the entire treatment period in the FIXTURE study were similar between the secukinumab and etanercept groups. In this same induction period, the proportions of patients who suffered infections and infestations were 26.7%, 30.9%, 24.5%, and 19.3% with the 300-mg dose of secukinumab, 150-mg dose of secukinumab, etanercept and the placebo group respectively. Infections by candida were more common with secukinumab than with etanercept during the entire treatment period (22 patients in the 300-mg and 11 patients in the 150-mg secukinumab group and none of them resulted in chronic mucocutaneous candidiasis).

The rates of serious adverse events in the FIXTURE study were 6.8 events per 100 patient-years in the 300-mg secukinumab group, 6.0 events per 100 patient-years in the 150-mg secukinumab group, 7.0 events per 100 patient-years in the etanercept group, and 8.3 events per 100 patient-years in the placebo group.

During Phase II studies there were reported cases of neutropenia (grade I or II), although none of them were clinically significant as they were not associated with severe infections. In Phase III FIXTURE study, grade 3 neutropenia occurred in 9 patients (1.0%) in the combined secukinumab dose groups and in no patients in the etanercept group; although no infections were reported in these patients. No patients with grade 4 neutropenia was reported in the secukinumab groups.

This reduction in absolute neutrophil count was also observed during brodalumab trial.⁵⁸

Similarly, the most commonly reported adverse events were nasopharyngitis (3-16% across brodalumab groups vs. 8% in the placebo group), upper respiratory tract infection (5%-12% across brodalumab groups vs. 8% in the placebo group).⁵⁸ As serious adverse events, two cases of asymptomatic Grade III neutropenia were reported, that resolved when the study drug was withheld.⁵⁸ Also the use

of ixekizumab was associated with no serious infections.⁶⁰ Nasopharyngitis (10%-14% across ixekizumab groups vs. 19% in the placebo group) and upper respiratory infection (3%-10% across ixekizumab groups vs. 4% in the placebo group) were the most commonly observed infectious adverse events. Grade II neutropenia was reported in two patients.⁶⁰

Overall, safety profile for all anti-IL17 agents appears favorable with no particular concerns. Indeed, an increased rate of opportunistic infections (mucocutaneous candidiasis and bacterial infections) would be expected as patients with atopic dermatitis/hyper-IgE syndrome (HIES) suffering from severe cutaneous and pulmonary *Staphylococcus aureus* infections and chronic mucocutaneous candidiasis, show an impaired development of IL-17 (and IL-22) because of heterozygous mutations in STAT3 sequence gene in T cells. Moreover, chronic mucocandidiasis disease is determined by complete deficiency of IL-17R gene.^{84,85}

Hopefully, the blockade of IL-17 signaling does not lead to a harmful immunosuppression as observed in these infectious disorders though the number of patients tested in Phase II trials is not elevated, and thus, further larger clinical studies are necessary to evaluate the risk of infections related to IL-17 blockade.

Safety implications of anti-IL-17 therapy: IL-17 and neoplasms

IL-17 function in cancer has been investigated though its role remains unclear since long-term studies are not available. Some studies reported a pro-tumoral role of IL-17, which may support tumor growth, probably stimulating angiogenesis.⁸⁶⁻⁸⁸ IL-17 increases tumorigenicity of human cervical tumors in nude mice.⁸⁹ In humans, the polymorphism within the IL-17 promoter significantly contributes to increase gastric cancer risk.⁹⁰ Chronic inflammation is recognized as promoter for colorectal tumorigenesis and IL-17, cooperatively acting with TNF α , likely stimulates aerobic glycolysis and growth factor production in cultured human colorectal cells.⁹¹

In contrast, other evidence suggested an anti-carcinogenic role of IL-17 that may boost a T cell-mediated tumor rejection.⁹²⁻⁹⁵

Conclusions

The identification of new T cell subsets and the recognition of various cytokines as pathogenic mediators revolutionized the concept of antipsoriatic therapy.⁹⁶ Crucial advances in the understanding of the psoriasis pathogenic mechanisms have been observed in the last three decades. Conspicuous evidence addresses IL-17 as key-mediator in psoriasis and as potential target for new therapeutics⁹⁷. Though several anti-IL-17 agents are being developed, brodalumab, ixekizumab, and secukinumab have showed a more advanced stage of development, as the first two agents, namely brodalumab and ixekizumab, are being currently tested in Phase III trials, whereas secukinumab completed Phase III trials heading the registration/pre-marketing phase. The promising outcomes

from Phase II trials found an important confirmation with the Phase III clinical trials testing secukinumab on a larger population. This evidence, together with the striking efficacy demonstrated by secukinumab over an anti-TNF α blocker, highlighted the winning strategy of blocking the IL-17 signaling and its centrality in the pathogenesis of psoriasis.

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Conflicts of interest

The author has no conflicts of interest to declare.

References

- Schäfer T. Epidemiology of psoriasis. Review and the German perspective. *Dermatology*. 2006;212:327-37.
- Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J Invest Dermatol*. 2010;130:1785-96.
- Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. *Dermatology*. 2006;212:123-7.
- Burden AD. Health economics and the modern management of psoriasis. *Br J Dermatol*. 2010;163:670-1.
- Vardy D, Besser A, Amir M, Gesthalter B, Biton A, Buskila D. Experiences of stigmatization play a role in mediating the impact of disease severity on quality of life in psoriasis patients. *Br J Dermatol*. 2002;147:736-42.
- Bergboer JG, Zeeuwen PL, Schalkwijk J. Genetics of psoriasis: evidence for epistatic interaction between skin barrier abnormalities and immune deviation. *J Invest Dermatol*. 2012;132:2320-1.
- Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature*. 2007;445:866-73.
- Ortega C, Fernández AS, Carrillo JM, Romero P, Molina IJ, Moreno JC, et al. IL-17-producing CD8⁺ T lymphocytes from psoriasis skin plaques are cytotoxic effector cells that secrete Th17-related cytokines. *J Leukoc Biol*. 2009;86:435-43.
- Hijnen D, Knol EF, Gent YY, Giovannone B, Beijin SJ, Kupper TS, et al. CD8(+) T cells in the lesional skin of atopic dermatitis and psoriasis patients are an important source of IFN- γ , IL-13, IL-17, and IL-22. *J Invest Dermatol*. 2013;133:973-9.
- Lowes MA, Chamian F, Abello MV, Fuentes-Duculan J, Lin SL, Nussbaum R, et al. Increase in TNF- α and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). *Proc Natl Acad Sci USA*. 2005;102:19057-62.
- Zaba LC, Krueger JG, Lowes MA. Resident and "inflammatory" dendritic cells in human skin. *J Invest Dermatol*. 2009;129:302-8.
- Nestle FO, Turka LA, Nickoloff BJ. Characterization of dermal dendritic cells in psoriasis: autostimulation of T lymphocytes and induction of Th1 type cytokines. *J Clin Invest*. 1994;94:202-9.
- Ciric B, El-behi M, Cabrera R, Zhang GX, Rostami A. IL-23 drives pathogenic IL-17-producing CD8⁺ T cells. *J Immunol*. 2009;182:5296-305.
- Huber M, Heink S, Grothe H, Guralnik A, Reinhard K, Elflein K, et al. A Th17-like developmental process leads to CD8⁺ Tc17 cells with reduced cytotoxic activity. *Eur J Immunol*. 2009;39:1716-25.
- Croft M, Carter L, Swain SL, Dutton RW. Generation of polarized antigen-specific CD8 effector populations: reciprocal action of interleukin (IL)-4 and IL-12 in promoting type 2 versus type 1 cytokine profiles. *J Exp Med*. 1994;180:1715-28.
- Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. *Trends Immunol*. 2013;34:174-81.
- Krueger JG, Fretzin S, Suárez-Fariñas M, Haslett PA, Phipps KM, Cameron GS, et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol*. 2012;130:145-54.e9.
- Martin DA, Towne JE, Kricorian G, Klekotka P, Gudjonsson JE, Krueger JG, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J Invest Dermatol*. 2013;133:17-26.
- Tonel G, Conrad C, Laggner U, Di Meglio P, Gryk K, McClanahan TK, et al. Cutting edge: A critical functional role for IL-23 in psoriasis. *J Immunol*. 2010;185:5688-91.
- Rizzo HL, Kagami S, Phillips KG, Kurtz SE, Jacques SL, Blauvelt A. IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A. *J Immunol*. 2011;186:1495-502.
- Dong C. Th17 cells in development: an updated view of their molecular identity and genetic programming. *Nat Rev Immunol*. 2008;8:337-48.
- Wolk K, Witte E, Wallace E, Döcke WD, Kunz S, Asadullah K, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: a potential role in psoriasis. *Eur J Immunol*. 2006;36:1309-23.
- Van der Fits L, Mourits S, Voerman JS, Kant M, Boon L, Laman JD, et al. Imiquimod-induced psoriasis-like skin inflammation in mice is mediated via the IL-23/IL-17 axis. *J Immunol*. 2009;182:5836-45.
- Chan JR, Blumenschein W, Murphy E, Diveu C, Wiekowski M, Abbondanzo S, et al. IL-23 stimulates epidermal hyperplasia via TNF and IL-20R2-dependent mechanisms with implications for psoriasis pathogenesis. *J Exp Med*. 2006;203:2577-87.
- Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol*. 2009;160:319-24.
- Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. *J Invest Dermatol*. 2008;128:1207-11.
- Li J, Chen X, Liu Z, Yue Q, Liu H. Expression of Th17 cytokines in skin lesions of patients with psoriasis. *J Huazhong Univ Sci Technolog Med Sci*. 2007;27:330-2.
- Guttman-Yassky E, Lowes MA, Fuentes-Duculan J, Zaba LC, Cardinale I, Nogales KE, et al. Low expression of the IL-23/Th17 pathway in atopic dermatitis compared to psoriasis. *J Immunol*. 2008;181:7420-7.
- Piskin G, Sylva-Steenland RM, Bos JD, Teunissen MB. In vitro and in situ expression of IL-23 by keratinocytes in healthy skin and psoriasis lesions: enhanced expression in psoriatic skin. *J Immunol*. 2006;176:1908-15.
- Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, et al. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med*. 2004;199:125-30.
- Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. *J Invest Dermatol*. 2010;130:1373-83.

32. Caproni M, Antiga E, Melani L, Volpi W, Del Bianco E, Fabbri P. Serum levels of IL-17 and IL-22 are reduced by etanercept, but not by acitretin, in patients with psoriasis: a randomized-controlled trial. *J Clin Immunol.* 2009;29:210-4.
33. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17, and IL-18 in patients with active psoriasis and correlation with disease severity. *Mediators Inflamm.* 2005;2005:273-9.
34. Chiricozzi A, Guttman-Yassky E, Suárez-Fariñas M, Nogralas KE, Tian S, Cardinale I, et al. Integrative responses to IL-17 and TNF- α in human keratinocytes account for key inflammatory pathogenic circuits in psoriasis. *J Invest Dermatol.* 2011;131:677-87.
35. Nogralas KE, Zaba LC, Guttman-Yassky E, Fuentes-Duculan J, Suárez-Fariñas M, Cardinale I, et al. Th17 cytokines interleukin (IL)-17 and IL-22 modulate distinct inflammatory and keratinocyte-response pathways. *Br J Dermatol.* 2008;159:1086-91.
36. Dragon S, Saffar AS, Shan L, Gounni AS. IL-17 attenuates the anti-apoptotic effects of GM-CSF in human neutrophils. *Mol Immunol.* 2008;45:160-8.
37. 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.
38. Haider AS, Lowes MA, Suárez-Fariñas M, Zaba LC, Cardinale I, Khatcherian A, et al. Identification of cellular pathways of "Type 1", Th17 T cells, and TNF- and inducible nitric oxide synthase-producing dendritic cells in autoimmune inflammation through pharmacogenomic study of cyclosporine A in psoriasis. *J Immunol.* 2008;180:1913-20.
39. Johnson-Huang LM, Suárez-Fariñas M, Sullivan-Whalen M, Gilleaudeau P, Krueger JG, Lowes MA. Effective narrow-band UVB radiation therapy suppresses the IL-23/IL-17 axis in normalized psoriasis plaques. *J Invest Dermatol.* 2010;130:2654-63.
40. Zaba LC, Suárez-Fariñas M, Fuentes-Duculan J, Nogralas KE, Guttman-Yassky E, Cardinale I, et al. Effective treatment of psoriasis with etanercept is linked to suppression of IL-17 signaling, not immediate response TNF genes. *J Allergy Clin Immunol.* 2009;124:1022-30.
41. Novelli L, Chimenti MS, Chiricozzi A, Perricone R. The new era for the treatment of psoriasis and psoriatic arthritis: Perspectives and validated strategies. *Autoimmun Rev.* 2014;13:64-9.
42. Murphy CA, Langrish CL, Chen Y, Blumenschein W, McClanahan T, Kastelein RA, et al. Divergent pro- and antiinflammatory roles for IL-23 and IL-12 in joint autoimmune inflammation. *J Exp Med.* 2003;198:1951-7.
43. Nakae S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. *J Immunol.* 2003;171:6173-7.
44. Bush KA, Farmer KM, Walker JS, Kirkham BW. Reduction of joint inflammation and bone erosion in rat adjuvant arthritis by treatment with interleukin-17 receptor IgG1 Fc fusion protein. *Arthritis Rheum.* 2002;46:802-5.
45. Chabaud M, Garnero P, Dayer JM, Guerne PA, Fossiez F, Miossec P. Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. *Cytokine.* 2000;12:1092-9.
46. Kotake S, Udagawa N, Takahashi N, Matsuzaki K, Itoh K, Ishiyama S, et al. IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. *J Clin Invest.* 1999;103:1345-52.
47. Chabaud M, Fossiez F, Taupin JL, Miossec P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J Immunol.* 1998;161:409-14.
48. Katz Y, Nativ O, Beer Y. Interleukin-17 enhances tumor necrosis factor alpha-induced synthesis of interleukins 1, 6, and 8 in skin and synovial fibroblasts: a possible role as a "fine-tuning cytokine" in inflammation processes. *Arthritis Rheum.* 2001;44:2176-84.
49. LeGrand A, Fermor B, Fink C, Pisetsky DS, Weinberg JB, Vail TP, et al. Interleukin-1, tumor necrosis factor alpha, and interleukin-17 synergistically up-regulate nitric oxide and prostaglandin E2 production in explants of human osteoarthritic knee menisci. *Arthritis Rheum.* 2001;44:2078-83.
50. Gaffen SL, Kramer JM, Yu JJ, Shen F. The IL-17 cytokine family. *Vitam Horm.* 2006;74:255-82.
51. Res PC, Piskin G, De Boer OJ, Van der Loos CM, Teeling P, Bos JD, et al. Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. *PLoS One.* 2010;5:e14108.
52. Laggner U, Di Meglio P, Perera GK, Hundhausen C, Lacy KE, Ali N, et al. Identification of a novel pro-inflammatory human skin-homing Vc9Vd2 T cell subset with a potential role in psoriasis. *J Immunol.* 2011;187:2783-93.
53. Lin AM, Rubin CJ, Khandpur R, Wang JY, Riblett M, Yalavarthi S, et al. Mast cells and neutrophils release IL-17 through extracellular trap formation in psoriasis. *J Immunol.* 2011;187:490-500.
54. Gaffen SL. Recent advances in the IL-17 cytokine family. *Curr Opin Immunol.* 2011;23:613-9.
55. Gaffen SL. Structure and signalling in the IL-17 receptor family. *Nat Rev Immunol.* 2009;9:556-67.
56. Langley RG, Elewski BE, Lebwohl M, Reich K, Griffiths CE, Papp K, et al, for the ERASURE and FIXTURE Study Groups. Secukinumab in plaque psoriasis – results of two phase 3 trials. *N Engl J Med.* 2014;371:326-38.
57. Russell CB, Kerkof K, Bigler J, et al. Blockade of the IL-17R with AMG827 leads to rapid reversal of gene expression and histopathologic abnormalities in human psoriatic skin [abstract]. *J Invest Dermatol.* 2010;130:S46.
58. Papp KA, Leonardi C, Menter A, Ortonne JP, Krueger JG, Kricorian G, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med.* 2012;366:1181-9.
59. Available on: <http://clinicaltrials.gov/ct2/results?term=BRODALUMAB+AND+PSORIASIS&Search=Search>
60. 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.
61. Available on: <http://clinicaltrials.gov/ct2/results?term=IXEKIZUMAB+AND+psoriasis+dated>
62. 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. *Sci Transl Med.* 2010;2:52-72.
63. Available on: <http://clinicaltrials.gov/ct2/results?term=SECUKINUMAB+AND+PSORIASIS&Search=Search>
64. Papp KA, Langley RG, Sigurgeirsson B, Abe M, Baker DR, Konno P, et al. Efficacy and safety of secukinumab in the treatment of moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled phase II dose-ranging study. *Br J Dermatol.* 2013;168:412-21.
65. Rich P, Sigurgeirsson B, Thaci D, Ortonne JP, Paul C, Schopf RE, et al. Secukinumab induction and maintenance therapy in moderate-to-severe plaque psoriasis: a randomized, double-blind, placebo-controlled, phase II regimen-finding study. *Br J Dermatol.* 2013;168:402-11.
66. 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. *Ann Rheum Dis.* 2014;73:349-56.

67. Fisman EZ, Motro M, Tenenbaum A. Cardiovascular diabetology in the core of a novel interleukins classification: the bad, the good and the aloof. *Cardiovasc Diabetol*. 2003;2:11.
68. Armstrong AW, Voyles SV, Armstrong EJ, Fuller EN, Rutledge JC. A tale of two plaques: convergent mechanisms of Tcell-mediated inflammation in psoriasis and atherosclerosis. *Exp Dermatol*. 2011;20:544-9.
69. Taleb S, Romain M, Ramkhelawon B, Uyttenhove C, Pasterkamp G, Herbin O, et al. Loss of SOCS3 expression in T cells reveals a regulatory role for interleukin-17 in atherosclerosis. *J Exp Med*. 2009;206:2067-77.
70. Taleb S, Tedgui A, Mallat Z. Adaptive T cell immune responses and atherogenesis. *Curr Opin Pharmacol*. 2010;10:197-202.
71. Puig L. Cardiovascular risk and psoriasis: the role of biologic therapy. *Actas Dermosifiliogr*. 2012;103:853-62.
72. Reich K, Langley RG, Lebwohl M, Szapary P, Guzzo C, Yeilding N, et al. Cardiovascular safety of ustekinumab in patients with moderate to severe psoriasis: results of integrated analyses of data from phase II and III clinical studies. *Br J Dermatol*. 2011;164:862-72.
73. Tzellos T, Kyrgidis A, Zouboulis CC. Re-evaluation of the risk for major adverse cardiovascular events in patients treated with anti-IL-12/23 biological agents for chronic plaque psoriasis: a meta-analysis of randomized controlled trials. *J Eur Acad Dermatol Venereol*. 2013;27:622-7.
74. Ryan C, Leonardi CL, Krueger JG, Kimball AB, Strober BE, Gordon KB, et al. Association between biologic therapies for chronic plaque psoriasis and cardiovascular events: a metaanalysis of randomized controlled trials. *JAMA*. 2011;306:864-71.
75. Ye P, Rodríguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, et al. Requirement of interleukin 17 receptor signaling for lung CXCL chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J Exp Med*. 2001;194:519-27.
76. Ye P, Garvey PB, Zhang P, Nelson S, Bagby G, Summer WR, et al. Interleukin-17 and lung host defense against *Klebsiella pneumoniae* infection. *Am J Respir Cell Mol Biol*. 2001;25:335-40.
77. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat Med*. 2008;14:275-81.
78. Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, et al. Divergent roles of IL-23 and IL-12 in host defense against *Klebsiella pneumoniae*. *J Exp Med*. 2005;202:761-9.
79. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. *J Exp Med*. 2009;206:299-311.
80. Nigam P, Kwa S, Velu V, Amara RR. Loss of IL-17-producing CD8 T cells during late chronic stage of pathogenic simian immunodeficiency virus infection. *J Immunol*. 2011;186:745-53.
81. Kelly MN, Kolls JK, Happel K, Schwartzman JD, Schwarzenberger P, Combe C, et al. Interleukin-17/interleukin-17 receptor-mediated signaling is important for generation of an optimal polymorphonuclear response against *Toxoplasma gondii* infection. *Infect Immun*. 2005;73:617-21.
82. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, et al. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes *Salmonella* dissemination from the gut. *Nat Med*. 2008;14:421-8.
83. Rudner XL, Happel KI, Young EA, Shellito JE. Interleukin-23 (IL-23)-IL-17 cytokine axis in murine *Pneumocystis carinii* infection. *Infect Immun*. 2007;75:3055-61.
84. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. *Science*. 2011;332:65-8.
85. Milner JD, Brenchley JM, Laurence A, Freeman AF, Hill BJ, Elias KM, et al. Impaired T(H)17 cell differentiation in subjects with autosomal dominant hyper-IgE syndrome. *Nature*. 2008;452:773-6.
86. Petanidis S, Anastakis D, Argyraki M, Hadzopoulou-Cladaras M, Salifoglou A. Differential expression of IL-17, 22 and 23 in the progression of colorectal cancer in patients with K-ras mutation: Ras signal inhibition and crosstalk with GM-CSF and IFN- γ . *PLoS One*. 2013;8:e73616.
87. Numasaki M, Fukushi J, Ono M, Narula SK, Zavodny PJ, Kudo T, et al. Interleukin-17 promotes angiogenesis and tumor growth. *Blood*. 2003;101:2620-7.
88. Kato T, Furumoto H, Ogura T, Onishi Y, Irahara M, Yamano S, et al. Expression of IL-17 mRNA in ovarian cancer. *Biochem Biophys Res Commun*. 2001;282:735-8.
89. Tartour E, Fossiez F, Joyeux I, Galinha A, Gey A, Claret E, et al. Interleukin 17, a T-cell-derived cytokine, promotes tumorigenicity of human cervical tumors in nude mice. *Cancer Res*. 1999;59:3698-704.
90. Rafiei A, Hosseini V, Janbabai G, Ghorbani A, Ajami A, Farzmandfar T, et al. Polymorphism in the interleukin-17A promoter contributes to gastric cancer. *World J Gastroenterol*. 2013;19:5693-9.
91. Straus DS. TNF α and IL-17 cooperatively stimulate glucose metabolism and growth factor production in human colorectal cancer cells. *Mol Cancer*. 2013;12:78.
92. Hirahara N, Nio Y, Sasaki S, Minari Y, Takamura M, Iguchi C, et al. Inoculation of human interleukin-17 genetransfected Meth-A fibrosarcoma cells induces T cell-dependent tumor-specific immunity in mice. *Oncology*. 2001;61:79-89.
93. Benchetrit F, Ciree A, Vives V, Warnier G, Gey A, Sautès-Fridman C, et al. Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism. *Blood*. 2002;99:2114-21.
94. Hirahara N, Nio Y, Sasaki S, Takamura M, Iguchi C, Dong M, et al. Reduced invasiveness and metastasis of Chinese hamster ovary cells transfected with human interleukin-17 gene. *Anticancer Res*. 2000;20:3137-42.
95. Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev*. 2003;14:155-74.
96. Krueger JG. Hiding under the skin: a welcome surprise in psoriasis. *Nat Med*. 2012;18:1750-1.
97. Chiricozzi A, Krueger JG. IL-17 targeted therapies for psoriasis. *Expert Opin Investig Drugs*. 2013;22:993-1005.