To order reprints or e-prints of JDD articles please contact sales@jddonline.com

doi:10.36849/JDD.2020.4645



Copyright © 2020 ORIGINAL ARTICLE Journal of Drugs in Dermatology

# Clinical and Molecular Effects of Interleukin-17 Pathway Blockade in Psoriasis

Lawrence Green MD,[a] Jeffrey M. Weinberg MD,[b] Alan Menter MD,[c] Jennifer Soung MD,[d] Edward Lain MD,[e] Abby Jacobson[f]

[a]George Washington University School of Medicine, Washington, DC
[b]Icahn School of Medicine at Mount Sinai, New York, NY
[c]Baylor Scott & White, Dallas, TX
[d]Southern California Dermatology, Santa Ana, CA
[e]Austin Institute for Clinical Research, Pflugerville, TX
[f]Ortho Dermatologics, Bridgewater, NJ

## ABSTRACT

The interleukin-17 (IL-17) pathway plays a crucial role in the development of psoriasis. Briefly, naive T cells differentiate into helper T (Th17) cells through interaction with activated dendritic cells in the presence of IL-23, Th17 cells produce IL-17 cytokines, and keratinocytes stimulated by IL-17 ligands lead to aberrant differentiation and proliferation that promote production of proinflammatory chemokines and further recruitment of inflammatory cells, setting up a positive feedback loop. Currently, 3 US Food and Drug Administration–approved agents to treat psoriasis affect the IL-17 pathway: brodalumab, secukinumab, and ixekizumab. Brodalumab is a fully human IL-17 receptor A antagonist that blocks signaling of multiple downstream inflammatory cytokines involved in psoriasis. Secukinumab and ixekizumab selectively bind to and neutralize only IL-17A. Pharmacologic effects in patients with psoriasis include decreased keratinocyte hyperproliferation, reduced epidermal thickening, decreased inflammatory markers, and resolution of histologic and genomic features of psoriasis. In clinical trials, therapeutic doses of brodalumab, secukinumab, and ixekizumab have demonstrated skin clearance efficacy by psoriasis area and severity index and static physician's global assessment scores at 12 weeks. The immunomodulation of these agents is associated with a favorable safety profile. Overall, the clinical improvement and normalization of genetic hallmarks of psoriasis provide a strong case for the unique role of IL-17 receptor blocking as a therapeutic mechanism of action to treat psoriasis. Understanding the unique mechanisms by which treatments interact with the IL-17 pathway to inhibit downstream proinflammatory signal cascade can help physicians make informed treatment decisions when selecting the appropriate medication for patients.

*J Drugs Dermatol.* 2020;19(2)138-143. doi:10.36849/JDD.2020.4645

## INTRODUCTION

Psoriasis is a chronic, inflammatory, immune-mediated systemic disease with an estimated prevalence of 3.2% in the United States among individuals >20 years of age.[1] It is characterized by abnormal proliferation of keratinocytes, increased dermal vascularity, and dermal infiltration of multiple inflammatory cells and by clinical presentation of erythema, induration, and scaling.[2,3] Psoriasis has multiple symptoms with a substantial effect on both physical and emotional health-related quality of life, as well as a number of comorbid conditions.[4-6]

A complex series of immunologic events results in the formation of psoriatic plaques as well as the underlying systemic inflammation characteristic of psoriasis. Central to this process is the keratinocyte activation of dendritic cells. Inflammatory dendritic cells release interleukin-23 (IL-23) and IL-12 to activate helper T (Th17) cells, Th1 cells, and Th22 cells, which in turn produce psoriatic cytokines, including IL-17, tumor necrosis factor α (TNFα), and IL-22.[7-9] The initial causes (environmental and/or genetic) that trigger the aberrant immune response and resulting cascade of immunologic events in psoriasis pathology are still not completely defined.

The current understanding of the complex pathophysiology associated with psoriasis has spurred the development of a variety of important new therapeutic agents that selectively target proinflammatory cytokines (eg, IL-17, IL-23, TNFα) rather than suppressing the immune system in its entirety, resulting in favorable efficacy and safety profiles compared with those of less-selective immunosuppressive agents.[3] This review focuses on the central role of the IL-17 pathway in psoriasis pathophysiology and the clinical and molecular effects of the blockade of this pathway in the context of psoriasis treatment.

### Overview of the Central Role of the IL-17 Pathway in Psoriasis

For many years, the Th1 pathway had been considered the primary driver in psoriasis.[10] Research over the last decade,

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately at support@jddonline.com

To order reprints or e-prints of JDD articles please contact sales@jddonline.com



however, has demonstrated that pathogenic T cells producing high levels of IL-17 in response to IL-23 play a central role in the pathogenesis of psoriasis.[10] Activation of native immune cells results in production of proinflammatory cytokines (eg, TNFα and interferon-α), which stimulate myeloid dermal dendritic cells to produce IL-12 and IL-23.[3,9] These cytokines induce activation of T cells and differentiation into Th17 and Th1 cells, with greater differentiation into the Th17 lineage in the presence of IL-23.[9,11] Th17 cells produce IL-17A, IL-17F, IL-21, IL-22, and TNFα.[3] In addition to Th17-propagated cytokines, other ligands of the IL-17 receptor implicated in the proinflammatory cascade include IL-17C and IL-17E.[11,12]

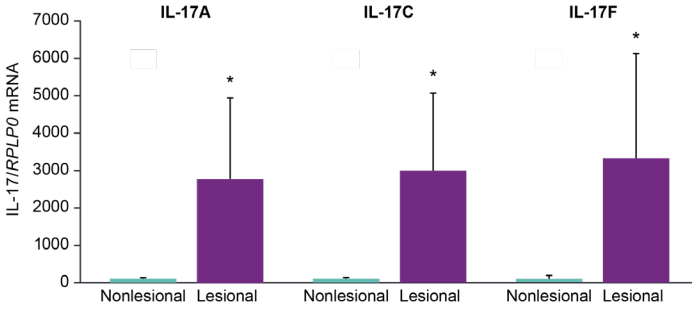
Keratinocytes stimulated by IL-17 ligands result in aberrant differentiation and proliferation that promote the production of proinflammatory chemokines, characterized by a self-amplifying inflammatory response.[13] IL-17A recruits immune cells to psoriatic lesions by enhancing keratinocyte chemokine expression, including chemokine (C-C motif) ligand 20 (which mediates recruitment of myeloid dendritic cells and Th17 cells) and chemokine (C-X-C motif) ligand 1 (CXCL1), CXCL3, CXCL5, CXCL6, and CXCL8 (which drive neutrophil recruitment), thus perpetuating the inflammatory process.[14,15] IL-17A also downregulates the expression of filaggrin, which binds to keratin fibers in epithelial cells, supporting the disruption of skin barrier function.[3] Neutrophils, mast cells, and Tc17 cells, all of which are found in psoriatic lesions, also produce IL-17A.[16]

IL-17C–stimulated endothelial cells lead to increased TNFα, and IL-17C/TNFα–stimulated keratinocytes have similar inflammatory gene response patterns as those induced by IL-17A/TNFα, contributing to a positive proinflammatory feedback loop between endothelial cells and the epidermis.[17] IL-17A, IL-17C, and TNFα additively and synergistically amplify the proinflammatory effects of one another.[11] IL-17E, also known as IL-25, signals via the IL-17 receptor A and IL-17 receptor B subunits and is overexpressed in keratinocytes located within psoriatic plaques.[12] Keratinocyte-derived IL-17E has been implicated in plaque formation and hyperproliferation. IL-17E–mediated macrophage activation leads to enhanced inflammation through recruitment of immune cells, including monocytes and neutrophils.[18]

**Rationale for Targeting the IL-17 Pathway in Psoriasis**

The IL-17 family of cytokines interact with the transmembrane receptors (IL-17 receptors A, B, C, D, and E).[14] These IL-17 receptors are expressed on keratinocytes, dendritic cells, and a variety of immune cells and mediate response to IL-17 cytokines.[15] IL-17A, IL-17F, and the IL-17A/F heterodimer share the same IL-17 receptor for signaling, resulting in downstream gene activation and proinflammatory activity.[16,19] IL-17C is also present in psoriatic lesions, localizing in keratinocytes, endothelial cells, and leukocytes, and is the most abundant IL-17 cytokine in psoriatic skin.[17] The effects of IL-17C on TNFα production and synergistic actions are similar to those of IL-17A, and the specific IL-17 receptor it interacts with shares a subunit (IL-17 receptor A) in common with that of IL-17A, IL-17F, and IL-17A/F.[14,15,17,19]

**FIGURE 1.** Expression of interleukin-17 (IL-17) isoforms in psoriatic skin.[20] *$P<0.01$ for lesional versus nonlesional skin. mRNA, messenger RNA.




Messenger RNA levels (Figure 1) and protein levels of IL-17A, IL-17F, and IL-17C are highly upregulated in psoriatic skin.[20] Additionally, IL-17E has been shown to be produced at elevated levels in keratinocytes located within psoriatic plaques, further supporting the role of IL-17 cytokines in the immunopathologic mechanisms of psoriasis.[12] IL-17 receptor A expression, however, is no different among nonlesional and lesional psoriatic skin.[20] Furthermore, increased levels of both Th17 cells and IL-17 have been found in the blood as well as skin lesions in patients with psoriasis.[21,22] A proposed pathobiologic model of psoriasis suggests that a self-sustaining feedback loop is established, in which production of IL-17 in psoriasis pathogenesis leads to aberrant skin cell differentiation and proliferation (Figure 2).[11] Through the proinflammatory feedback mechanisms described previously, chronic activation of IL-17 signaling ultimately leads to the signs and symptoms of psoriasis.[16]

**Inhibition of the IL-17 Pathway in Psoriasis**

The central role of IL-17 in the pathogenesis of psoriasis makes it an attractive therapeutic target, and there are multiple approaches to inhibition of IL-17–mediated signaling. Mechanisms of action involve direct antagonism of IL-17 as well as indirect, upstream approaches.[23-25] Currently, 3 approved agents affect the IL-17 pathway directly, either by binding to the IL-17A ligand (secukinumab and ixekizumab) or by binding to IL-17 receptor A (brodalumab).[21,26] Brodalumab is a fully human anti–IL-17 receptor A monoclonal antibody that binds IL-17 receptor A with high affinity and prevents the signaling of multiple cytokines involved in psoriasis (IL-17A, IL-17F, IL-17A/F, and IL-17E [IL-25]).[21,27] Brodalumab undergoes selective, direct binding to IL-17 receptor A, resulting in inhibition of the induction of multiple downstream inflammatory factors (Figure 3).[11,25,27,28]

In contrast to brodalumab, secukinumab and ixekizumab target IL-17A, an IL-17 cytokine isoform that propagates inflammation

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately at support@jddonline.com

To order reprints or e-prints of JDD articles please contact sales@jddonline.com



**FIGURE 2.** Proposed model for the role of IL-17 in psoriasis pathogenesis[11] and IL-23/Th17–mediated effects on epidermal keratinocytes in psoriatic skin. The broad downstream effects of increased IL-23 and IL-17 signaling on various immune cell populations and keratinocyte biology are shown.[10] Blocking ligand interaction with IL-17 receptor A has been shown to reduce inflammatory markers upstream of the IL-17 signal cascade, including IL-23 and an IL-12 subunit, indicating the potential for a negative feedback loop within the IL-17 signal cascade.[28,34] CCL, chemokine (C-C motif) ligand; IFN-γ, interferon-γ; IL, interleukin; $T_c$, cytotoxic T cell; Th, helper T cell; TNF, tumor necrosis factor.

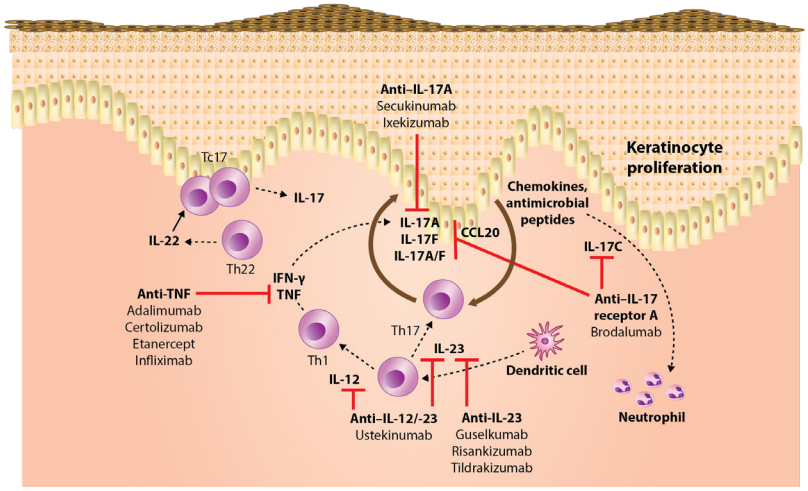
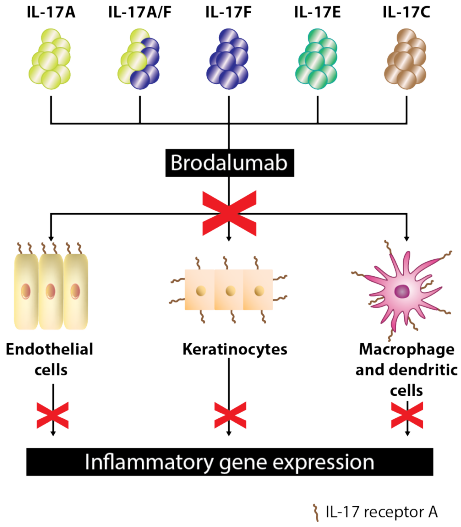



**FIGURE 3.** Inhibition of downstream inflammatory processes due to brodalumab blockade of IL-17 receptor A.[11,25,27,28] IL, interleukin.




via the IL-17 receptor.[15,26,29] Ixekizumab is a humanized monoclonal antibody that selectively binds with IL-17A and inhibits its interaction with the IL-17 receptor.[26,30] Secukinumab is a high-affinity, fully human monoclonal antibody that selectively binds and neutralizes IL-17A.[29] Fully human monoclonal antibodies, such as brodalumab and secukinumab, have no murine sequence, whereas humanized monoclonal antibodies contain murine sequence–derived complementarity-determining regions engrafted into human-derived V regions.[31] Of note, fully human monoclonal antibodies may have a lower potential for immunogenicity than humanized monoclonal antibodies.[32]

**Pharmacologic Effects of IL-17 Pathway Inhibition in Psoriasis**

In early-phase human studies, brodalumab normalized psoriatic gene expression profiles and led to significantly decreased keratinocyte hyperproliferation, reduced epidermal thickening, and fewer numbers of infiltrating T cells in the skin of patients with psoriasis.[28,33] Within 1 week, expression of IL-23 and IL-12 subunit genes was reduced, indicating that brodalumab may reduce inflammatory markers upstream of IL-17 receptor A.[28,34] Within 2 weeks, IL-17A, IL-17C, and IL-17F were downregulated in a dose-dependent manner.[28] In a punch biopsy subset of patients enrolled in three phase 3 clinical trials of brodalumab, extensive improvement in clinical features of psoriasis was accompanied by near-complete resolution of histologic and genomic features of psoriasis, including a transcriptome of lesional skin that resembled nonlesional skin after brodalumab treatment.[34]

In an early study of secukinumab that included patients with plaque psoriasis, reductions in clinical disease activity were associated with reductions of histomorphologic signs of acanthosis and epidermal hyperplasia and changes in gene expression of IL-17A pathway markers.[35] For example, expression of IL-17A and IL-22 was markedly reduced after secukinumab therapy, as was the area occupied by dermal $IL17A^+CD3^+$ T cells.[35]

Skin lesions from patients with psoriasis in a phase 1 study of ixekizumab demonstrated significant dose-dependent reductions from baseline in keratinocyte proliferation, hyperplasia, epidermal thickness, and dermal and epidermal infiltration by T cells and dendritic cells.[36] These changes were accompanied by decreased expression of cytokines from multiple T-cell subsets, including interferon-γ, IL-17A/F, and IL-22 and the dendritic cell cytokine IL-23.[36]

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately at support@jddonline.com

To order reprints or e-prints of JDD articles please contact sales@jddonline.com



**TABLE 1.**

**Efficacy and Safety Profile of IL-17 Receptor Inhibitors at 12 Weeks of Treatment in Patients With Psoriasis**

| Drug | Study | Dose | sPGA 0/1, n (%) | PASI 75, n (%) | PASI 100, n (%) | Serious Adverse Events, n (%) |
|---|---|---|---|---|---|---|
| Brodalumab | AMAGINE-1[39] | 210 mg Q2W (n=222) | 168 (75.7) | 185 (83.3) | 93 (41.9) | 4 (1.8) |
| Brodalumab | AMAGINE-2[38] | 210 mg Q2W (n=612) | 481 (78.6) | 528 (86.3) | 272 (44.4) | 6 (1.0) |
| Brodalumab | AMAGINE-3[38] | 210 mg Q2W (n=624) | 497 (79.6) | 531 (85.1) | 229 (36.7) | 9 (1.4) |
| Ixekizumab | UNCOVER-1[37] | 80 mg Q2W (n=433) | 354 (81.8) | 386 (89.1) | 153 (35.3) | 20 (1.7) |
| Ixekizumab | UNCOVER-2[40] | 80 mg Q2W (n=351) | 292 (83.2) | 315 (89.7) | 142 (40.5) | -- |
| Ixekizumab | UNCOVER-3[37] | 80 mg Q2W (n=385) | 310 (80.5) | 336 (87.3) | 145 (37.7) | -- |
| Secukinumab | ERASURE[29] | 300 mg Q4W[a] (n=245) | 160 (65.3) | 200 (81.6) | 70 (28.6) | -- |
| Secukinumab | FIXTURE[29] | 300 mg Q4W[a] (n=323) | 202 (62.5) | 249 (77.1) | 78 (24.1) | 4 (1.2) |

PASI 75 and 100, psoriasis area severity index 75% and 100% improvement; Q2W, every 2 weeks; Q4W, every 4 weeks; sPGA 0/1, static physician's global assessment score of 0 or 1.
[a]After once-weekly dosing for 5 weeks.

**Clinical Efficacy of IL-17 Pathway Blockade in Psoriasis**

In clinical trials, therapeutic doses of brodalumab, secukinumab, and ixekizumab have all demonstrated substantial skin clearance efficacy following 12 weeks of treatment by psoriasis area and severity index (PASI) and static physician's global assessment (sPGA) scores (Table 1).[26,29,37-40] During the long-term extension phases (range, 52-60 weeks) in many of these trials, efficacy was maintained in large percentages of patients. For example, in AMAGINE-1, among those receiving brodalumab 210 mg every 2 weeks who had PASI 90% improvement response (PASI 90) and PASI 100 at week 12, 78.3% and 67.5% achieved PASI 90 and PASI 100, respectively, at week 52.[39] In AMAGINE-2 and AMAGINE-3, PASI 75, PASI 90, and PASI 100 rates at week 52 among those receiving brodalumab 210 mg every 2 weeks were 80%, 75%, and 56%, respectively, in AMAGINE-2 and 80%, 73%, and 53%, respectively, in AMAGINE-3.[38] Maintenance of response to ixekizumab was demonstrated in UNCOVER-3; PASI 75, PASI 90, and PASI 100 rates were 80%, 71%, and 52%, respectively, at week 60.[37] The 52-week efficacy rates for secukinumab ranged from approximately 75% to 80% and 60% to 65% for PASI 75 and PASI 90, respectively, and the 52-week efficacy rate for PASI 100 was ~40% in the ERASURE and FIXTURE trials.[29]

The efficacy results for brodalumab, secukinumab, and ixekizumab, all of which act within the IL-17 pathway cascade (by binding to the IL-17 receptor A [brodalumab] or the IL-17A ligand [secukinumab and ixekizumab]), compare very favorably with those of other biologics that target different pathways in the pathogenesis of psoriasis. For example, among the TNFα-blocking agents, efficacy rates by PASI 75 in phase 3 studies (range, 10-16 weeks) were 49%, 71%, and 80% for etanercept, adalimumab, and infliximab, respectively.[41-43] Interestingly, after 50 weeks of therapy in a phase 3 clinical trial of infliximab, the efficacy rate by PASI 75 was reduced to 61%.[43] Of note, both secukinumab and ixekizumab were superior to etanercept in terms of sPGA or modified PGA, PASI 75, PASI 90, and PASI 100 in their respective phase 3 trials that included an etanercept arm.[29,40] In the AMAGINE-2 and AMAGINE-3 studies, brodalumab 210 mg was superior to ustekinumab, a monoclonal antibody against IL-12 and IL-23, in terms of sPGA score of 0 or 1 response, PASI 75, and PASI 100.[38] Furthermore, in a study evaluating time to achieve clinically meaningful outcomes (defined as time for 25% of patients to achieve PASI 75), brodalumab exhibited the most rapid onset of efficacy (2.1 weeks), followed by the other IL-17 inhibitors ixekizumab (2.4 weeks) and secukinumab (3.0 weeks), whereas adalimumab, ustekinumab, and etanercept achieved onset of efficacy at 4.6, 4.6, and 6.6 weeks, respectively.[44]

**Safety Overview of IL-17 Pathway Blockade in Psoriasis**

As summarized in the updated 2019 joint American Academy of Dermatology and National Psoriasis Foundation guidelines of care for the management and treatment of psoriasis with biologics, the safety profile of IL-17 inhibitors is well established and understood.[45] IL-17 inhibitors are associated with an increased risk of infection and are not recommended in patients with a history of inflammatory bowel disease (IBD) but are not

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately at support@jddonline.com

To order reprints or e-prints of JDD articles please contact sales@jddonline.com



associated with an increased risk of malignancy and may be used in patients with hepatitis B or C infections.[45] As shown in Table 1, the rates of serious adverse events with brodalumab, secukinumab, and ixekizumab ranged from 1.0% to 1.8%, comparable to the rates reported with placebo.[29,37-40] The most common adverse events reported with these agents included nasopharyngitis, upper respiratory tract infection, headache, and arthralgia.[29,37,38]

In a systematic review of clinical trials of patients with psoriasis or psoriatic arthritis, *Candida* infections were reported in 4.0% of patients treated with brodalumab, 1.7% of patients treated with secukinumab, and 3.3% of patients treated with ixekizumab compared with 0.3%, 2.3%, and 0.8% in those receiving placebo, ustekinumab, or etanercept, respectively.[46] The majority of *Candida* infections in anti–IL-17 biologic clinical trials occurred in the oral cavity and were of mild severity.[47] Exacerbation of IBD has also been reported in trials of anti–IL-17 agents in psoriasis, including 1 case of Crohn disease with brodalumab.[48] In a study of ixekizumab, incidence rates of Crohn disease and ulcerative colitis were 0.10 and 0.20 per 100 patient-years, respectively, and were 0.11 and 0.15 per 100 patient-years, respectively, in a study of secukinumab.[48] On the basis of these observations, caution should be used in patients with possible or diagnosed IBD.[48]

## SUMMARY

The IL-17 pathway plays a crucial role in the immunopathogenesis and development of psoriasis. Currently, 3 US Food and Drug Administration–approved agents affect this pathway for treatment of psoriasis (brodalumab, secukinumab, and ixekizumab) with others in development (bimekizumab).[49] Brodalumab is a highly selective IL-17 receptor A antagonist that blocks multiple downstream inflammatory cytokines that are elevated in psoriasis, including IL-17C and IL-17E, which may correlate with the observed efficacy of brodalumab. Secukinumab and ixekizumab selectively bind to and neutralize only IL-17A. Inhibition of the IL-17 pathway with these agents results in improvements in clinical, histologic, and genetic characteristics of psoriasis. The immunomodulation produced by these agents has been associated with a favorable safety profile. Overall, the clinical improvement and normalization of genetic hallmarks of psoriasis provide a strong case for the unique role of IL-17 receptor blocking as an important therapeutic mechanism of action in treating psoriasis. Understanding the unique mechanisms by which each of these biologics interacts with the IL-17 pathway to inhibit downstream proinflammatory signal cascade will be of benefit to dermatologists in making informed treatment decisions.

## DISCLOSURES

Lawrence Green has served as an investigator, consultant, or speaker for Amgen, AbbVie, Bausch Health, Celgene, Sun Pharma, Eli Lilly, and Novartis. Jeffrey M. Weinberg serves as an investigator for Boehringer Ingelheim, LEO Pharma, and Novartis and serves as a speaker for and/or advisor to AbbVie, Amgen, Celgene, Eli Lilly, LEO Pharma, and Novartis. Alan Menter has received compensation from or served as an investigator, consultant, advisory board member, or speaker for AbbVie, Allergan, Amgen, Anacor, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, Janssen Biotech, LEO Pharma, Merck, Neothetics, Novartis, Pfizer, Regeneron, Symbio/Maruho, Vitae, and Xenoport. Jennifer Soung has served as an investigator, consultant, advisory board member, or speaker for AbbVie, Actavis, Actelion, Allergan, Amgen, Boehringer Ingelheim, Cassiopeia, Celgene, Dr. Reddy, Eli Lilly, Galderma, GSK, Janssen, Kadmon, LEO Pharma, Menlo, National Psoriasis Foundation (nonprofit), Novan, Novartis, Ortho Dermatologics, Pfizer, Regeneron, and UCB. Edward Lain has received compensation from or served as an investigator, consultant, advisory board member, or speaker for AbbVie, Allergan, Boehringer Ingelheim, Celgene, Dermira, Eli Lilly, Galderma, LEO Pharma, Neothetics, Novartis, Pfizer, Sol-Gel, Endo Pharmaceuticals, Dr Reddy, Kadmon, Thync Global, Cassiopeia, Menlo, UCB, Kiniksa, Glenmark, Sienna, Sebacia, BMS, Vanda, Chemocentryx, Brickell, Aclaris, and Novan. Abby Jacobson is an employee of Ortho Dermatologics and holds stock and/or stock options in Bausch Health.

## ACKNOWLEDGMENT

This study was sponsored by Ortho Dermatologics. Editorial assistance was provided under the direction of the authors by Angela Cimmino, PharmD, Rebecca Slager, PhD, and David Boffa, ELS, of MedThink SciCom, with support from Ortho Dermatologics.

## REFERENCES

1. Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. *J Am Acad Dermatol.* 2014;70(3):512-516.
2. Meephansan J, Subpayasarn U, Komine M, Ohtsuki M. Pathogenic role of cytokines and effect of their inhibition in psoriasis. Chiriac A, ed. *An Interdisciplinary Approach to Psoriasis:* London, UK: InTech Open; 2017.
3. Silfvast-Kaiser A, Paek SY, Menter A. Anti-IL17 therapies for psoriasis. *Expert Opin Bil Ther.* 2019;19(1):45-54.
4. Elmets CA, Leonardi CL, Davis DMR, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. *J Am Acad Dermatol.* 2019;80(4):1073-1113.
5. Prussick RB, Miele L. Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden? *Br J Dermatol.* 2018;179(1):16-29.
6. Takeshita J, Grewal S, Langan SM, et al. Psoriasis and comorbid diseases: epidemiology. *J Am Acad Dermatol.* 2017;76(3):377-390.
7. Baliwag J, Barnes DH, Johnston A. Cytokines in psoriasis. *Cytokine.* 2015;73(2):342-350.
8. Kim J, Krueger JG. The immunopathogenesis of psoriasis. *Dermatol Clin.* 2015;33(1):13-23.
9. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med.* 2009;361(5):496-509.
10. Hawkes JE, Chan TC, Krueger JG. Psoriasis pathogenesis and the development of novel targeted immune therapies. *J Allergy Clin Immunol.* 2017;140(3):645-653.
11. Martin DA, Towne JE, Kricorian G, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J Invest Dermatol.* 2013;133(1):17-26.
12. Senra L, Stalder R, Alvarez Martinez D, Chizzolini C, Boehncke WH, Brembilla NC. Keratinocyte-derived IL-17E contributes to inflammation in psoriasis. *J Invest Dermatol.* 2016;136(10):1970-1980.

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately at support@jddonline.com

To order reprints or e-prints of JDD articles please contact sales@jddonline.com



13. Giunta A, Ventura A, Chimenti MS, Bianchi L, Esposito M. Spotlight on ixekizumab for the treatment of moderate-to-severe plaque psoriasis: design, development, and use in therapy. *Drug Des Devel Ther.* 2017;11:1643-1651.
14. Gooderham M, Posso-De Los Rios CJ, Rubio-Gomez GA, Papp K. Interleukin-17 (IL-17) inhibitors in the treatment of plaque psoriasis: a review. *Skin Therapy Lett.* 2015;20(1):1-5.
15. Kirkham BW, Kavanaugh A, Reich K. Interleukin-17A: a unique pathway in immune-mediated diseases: psoriasis, psoriatic arthritis and rheumatoid arthritis. *Immunology.* 2014;141(2):133-142.
16. Girolomoni G, Mrowietz U, Paul C. Psoriasis: rationale for targeting interleukin-17. *Br J Dermatol.* 2012;167(4):717-724.
17. Johnston A, Fritz Y, Dawes SM, et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. *J Immunol.* 2013;190(5):2252-2262.
18. Senra L, Mylonas A, Kavanagh RD, et al. IL-17E (IL-25) enhances innate immune responses during skin inflammation. *J Invest Dermatol.* 2019;139(8):1732-1742.e17.
19. 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(4):174-181.
20. 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(2):319-324.
21. Roman M, Chiu MW. Spotlight on brodalumab in the treatment of moderate-to-severe plaque psoriasis: design, development, and potential place in therapy. *Drug Des Devel Ther.* 2017;11:2065-2075.
22. 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(5):1373-1383.
23. Leonardi CL, Gordon KB. New and emerging therapies in psoriasis. *Semin Cutan Med Surg.* 2014;33(2 suppl 2):S37-41.
24. Chiricozzi A, Romanelli P, Volpe E, Borsellino G, Romanelli M. Scanning the Immunopathogenesis of Psoriasis. *Int J Mol Sci.* 2018;19(1).
25. Miossec P, Kolls JK. Targeting IL-17 and TH17 cells in chronic inflammation. *Nat Rev Drug Discov.* 2012;11(10):763-776.
26. Leonardi C, Matheson R, Zachariae C, et al. Anti-interleukin-17 monoclonal antibody ixekizumab in chronic plaque psoriasis. *N Engl J Med.* 2012;366(13):1190-1199.
27. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med.* 2012;366(13):1181-1189.
28. Russell CB, Rand H, Bigler J, et al. Gene expression profiles normalized in psoriatic skin by treatment with brodalumab, a human anti-IL-17 receptor monoclonal antibody. *J Immunol.* 2014;192(8):3828-3836.
29. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326-338.
30. Liu L, Lu J, Allan BW, et al. Generation and characterization of ixekizumab, a humanized monoclonal antibody that neutralizes interleukin-17A. *J Inflamm Res.* 2016;9:39-50.
31. Harding FA, Stickler MM, Razo J, DuBridge RB. The immunogenicity of humanized and fully human antibodies: residual immunogenicity resides in the CDR regions. *MAbs.* 2010;2(3):256-265.
32. Silberstein S, Lenz R, Xu C. Therapeutic Monoclonal antibodies: what headache specialists need to know. *Headache.* 2015;55(8):1171-1182.
33. Papp KA, Reid C, Foley P, et al. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. *J Invest Dermatol.* 2012;132(10):2466-2469.
34. Tomalin LE, Russell C, Garcet S, et al. IL-17 receptor A inhibition with brodalumab rapidly normalizes molecular and cellular phenotype of patients with moderate-to-severe psoriasis vulgaris. 27th European Academy of Dermatology and Venereology Congress; September 16-18, 2018; Paris, France.
35. Hueber W, Patel DD, Dryja T, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. *Sci Transl Med.* 2010;2(52):52ra72.
36. Krueger JG, Fretzin S, Suárez-Fariñas M, et al. IL-17A is essential for cell activation and inflammatory gene circuits in subjects with psoriasis. *J Allergy Clin Immunol.* 2012;130(1):145-154.e149.
37. Gordon KB, Blauvelt A, Papp KA, et al. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. *N Engl J Med.* 2016;375(4):345-356.
38. Lebwohl M, Strober B, Menter A, et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. *N Engl J Med.* 2015;373(14):1318-1328.
39. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2016;175(2):273-286.
40. Griffiths CE, Reich K, Lebwohl M, 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. *Lancet.* 2015;386(9993):541-551.
41. Menter A, Tyring SK, Gordon K, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. *J Am Acad Dermatol.* 2008;58(1):106-115.
42. Papp KA, Tyring S, Lahfa M, et al. A global phase III randomized controlled trial of etanercept in psoriasis: safety, efficacy, and effect of dose reduction. *Br J Dermatol.* 2005;152(6):1304-1312.
43. Reich K, Nestle FO, Papp K, et al. Infliximab induction and maintenance therapy for moderate-to-severe psoriasis: a phase III, multicentre, double-blind trial. *Lancet.* 2005;366(9494):1367-1374.
44. Papp KA, Lebwohl MG. Onset of action of biologics in patients with moderate-to-severe psoriasis. *J Drugs Dermatol.* 2017;17(3):247-250.
45. Menter A, Strober BE, Kaplan DH, et al. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J Am Acad Dermatol.* 2019;80(4):1029-1072.
46. Saunte DM, Mrowietz U, Puig L, Zachariae C. Candida infections in patients with psoriasis and psoriatic arthritis treated with interleukin-17 inhibitors and their practical management. *Br J Dermatol.* 2017;177(1):47-62.
47. Frieder J, Kivelevitch D, Fiore CT, Saad S, Menter A. The impact of biologic agents on health-related quality of life outcomes in patients with psoriasis. *Expert Rev Clin Immunol.* 2018;14(1):1-19.
48. Hohenberger M, Cardwell LA, Oussedik E, Feldman SR. Interleukin-17 inhibition: role in psoriasis and inflammatory bowel disease. *J Dermatolog Treat.* 2018;29(1):13-18.
49. Papp KA, Merola JF, Gottlieb AB, et al. Dual neutralization of both interleukin 17A and interleukin 17F with bimekizumab in patients with psoriasis: Results from BE ABLE 1, a 12-week randomized, double-blinded, placebo-controlled phase 2b trial. *J Am Acad Dermatol.* 2018;79(2):277-286 e210.

## AUTHOR CORRESPONDENCE

**Lawrence Green MD**
E-mail:.....drgreen@looking-younger.com

This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately at support@jddonline.com

JO00220