IL-17 inhibitors for psoriasis
So Yeon Paek, MD1,2; Jillian Frieder, MD1; Dario Kivelevitch, MD1; and M. Alan Menter, MD1,2

Abstract
The role of the Th17/interleukin (IL)-23 pathway has been well elucidated in psoriasis. The IL-17 family includes 6 cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. Two monoclonal antibodies targeting IL-17A (secukinumab, ixekizumab) and one antibody against the IL-17 receptor (brodalumab) have been approved for the treatment of moderate-to-severe plaque psoriasis. Clinical efficacy, safety, and tolerability of each agent is reviewed.

Semin Cutan Med Surg 37:148-157 © 2018 Frontline Medical Communications

The role of the Th17/interleukin (IL)-23 pathway has been well elucidated in psoriasis. The IL-17 family includes 6 cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F. Two monoclonal antibodies targeting IL-17A (secukinumab, ixekizumab) and one antibody against the IL-17 receptor (brodalumab) have been approved for the treatment of moderate-to-severe plaque psoriasis. Clinical efficacy, safety, and tolerability of each agent is reviewed.

Secukinumab
Secukinumab (Cosentyx®, Novartis Pharmaceutical Corporation, Basel, Switzerland), a fully human monoclonal IgG1-kappa antibody, selectively targets IL-17A, thereby preventing it from binding to its receptor (IL-17 receptor). It is approved in the United States and Europe for the treatment of moderate-to-severe plaque psoriasis (US Food and Drug Administration [FDA] approval 2015), psoriatic arthritis (FDA approval 2016), and ankylosing spondylitis. The recommended dosage for moderate-to-severe plaque psoriasis is two 150-mg (300-mg) subcutaneous (SC) injections at weeks 0, 1, 2, 3, and 4, followed by 300 mg every 4 weeks (Q4W). The same dosing regimen is also approved in the treatment of psoriatic arthritis with concomitant moderate-to-severe plaque psoriasis.

Clinical efficacy
Secukinumab was evaluated over 52 weeks in the phase 3 ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab versus Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis) placebo-controlled clinical trials.14 Week 12 Psoriasis Area and Severity Index (PASI) 90/100 response rates in ERASURE were significantly greater for secukinumab 300 mg (PASI 90: 59.2%; PASI 100: 28.6%) and 150 mg (39.1% and 12.8%, respectively) compared to placebo (1.2% and 0.8%, respectively; P < .001 for all comparisons). Both secukinumab doses achieved significant improvements in patient-reported symptoms such as itch, pain, and scaling (P < .001 for all comparisons). In the FIXTURE trial, secukinumab was superior to etanercept with regard to week 12 PASI 75/90/100 response rates, modified Investigator’s Global Assessment (IGA) 0/1 score, and Dermatology Life Quality Index (DLQI) 0/1 score, as well as maintenance of modified IGA 0/1 score and PASI 75 response through week 52. Biologic-naïve patients attained greater clinical responses compared to patients with prior biologic exposure (PASI 90: 300 mg: 58.1% versus 50.7%; 150 mg: 44.6% versus 29.4%). This is consistent with other reported data.15

In the phase 3 SCULPTURE trial, fixed-dosing maintenance therapy (300 mg: 78.2%; 150 mg: 62.1%) was superior to as-needed treatment (±20% loss of maximum PASI score improvement from baseline, or loss of PASI 75: 67.7%; 52.4%) in maintaining PASI 75 response through week 52.16 Of patients on as-needed treatment, 85% experienced at least 1 psoriasis relapse, with me-

1Division of Dermatology, Baylor University Medical Center, Dallas, Texas.
2Texas A&M Health Science Center College of Medicine, Bryan, Texas.

Disclosures: Drs Paek, Frieder and Kivelevitch have nothing to disclose; Dr Menter is a consultant, investigator, and speaker for the following companies: Novartis, Eli-Lilly, Ortho-Dermatologics.

Correspondence: So Yeon Paek, MD, FAAD; doctor.paek@gmail.com

Inherent deficiencies in IL-17A can lead to severe mucocutaneous infections with Candida spp or Staphylococcus.10,11 Currently, 3 IL-17 inhibitors have been approved for the treatment of psoriasis: secukinumab, ixekizumab, and brodalumab. Clinical efficacy, safety, and tolerability of each agent is reviewed and summarized in the Table.

Table

<table>
<thead>
<tr>
<th>Agent</th>
<th>Approval</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab</td>
<td>FDA approval 2015, EMA approval 2015</td>
<td>Moderate-to-severe plaque psoriasis, psoriatic arthritis, ankylosing spondylitis</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>FDA approval 2016</td>
<td>Moderate-to-severe plaque psoriasis</td>
</tr>
<tr>
<td>Brodalumab</td>
<td>FDA approval 2016</td>
<td>Moderate-to-severe plaque psoriasis</td>
</tr>
</tbody>
</table>

1085-5629/13$-see front matter © 2018 Frontline Medical Communications
https://doi.org/doi: 10.12788/j.sder.2018.051
The pathophysiology of psoriasis begins with initial antigenic stimuli in the form of genetic, infectious, and/or environmental triggers. Native immune cells of the Th17/IL-23 and Th1 pathway are then activated, resulting in the production of pro-inflammatory cytokines such as TNF-alpha and IFN-alpha. These cytokines further stimulate dendritic cells to produce IL-12, which differentiates Th1 cells, and IL-23, which differentiates Th17 cells. Th17 cells then produce IL-17A, IL-17F, IL-21, IL-22, and TNF-alpha. This combination of cytokine activation leads to the cutaneous phenotype of erythema, induration, and scaling observed in psoriasis. ABBREVIATIONS: CAMP, cathelicidin antimicrobial peptide; CCL20, CC-chemokine ligand 20; IFN, interferon; IL, interleukin; mDC, myeloid dendritic cell; MHC, major histocompatibility complex; NF-kB, nuclear factor-kappaB; pDC, plasmacytoid dendritic cells; PMN, polymorphonuclear leukocyte; Th, T helper; TLR, toll-like receptor; TNF, tumor necrosis factor. Reprinted with permission from Macmillan Publishers Ltd: Nat Rev Dis Primers, 2:1-17 © 2016.
ter (FAE) systemic therapy in 202 patients with moderate-to-severe psoriasis naïve to systemic therapy (PRIME trial). A significantly greater proportion of patients on secukinumab 300 mg attained PASI 75 (89.5% versus 33.7%; P < .001), PASI 90 (81.0% versus 28.4%; P < .001), and DLQI 0/1 scores (71.4% versus 25.3%; P < .001) at week 24, compared to FAE.21 One phase 4 Japanese study evaluated the efficacy of secukinumab immediately following cyclosporine (CyA) therapy (≥12 weeks of treatment) in inadequate responders (PASI ≥10, IGA ≥ 2).22 As early as week 2, 41.2% of patients achieved PASI 50 responses. Week 16 PASI 75/90/100 and IGA 0/1 were achieved by 82.4%, 64.7%, 29.4%, and 70.6%, respectively. Ultimately, immediate secukinumab treatment after abrupt discontinuation of CyA leads to early clinical improvement without the commonly noted CyA withdrawal early relapse.22

Difficult-to-treat areas of psoriasis such as the nails and scalp have been evaluated in secukinumab clinical trials. In a 24-week phase 3b randomized controlled trial, secukinumab (300 mg) was beneficial for moderate-to-severe scalp psoriasis (Psoriasis Scalp Severity Index [PSSI] ≥12 plus ≥30% scalp surface area), attaining week 12 PSSI 90 and modified scalp IGA 0/1 response rates of 52.9% and 56.9%, respectively, compared to 2.0% and 5.9% for placebo (P < .001 for both).23 Clinical responses for secukinumab continued to increase up to week 24 (PSSI 90: 58.8%; IGA 0/1: 62.7%), with 47.1% of patients achieving complete scalp clearance (PSSI 100).23 In the phase 3b TRANSFIGURE nail psoriasis study, week 16 mean Nail Psoriasis Severity Index (NAPSI) score improvements from baseline were −45.3%, −37.9%, and −10.8% for secukinumab 300 mg, 150 mg, and placebo, respectively; further improvements were observed at week 32 (300 mg: −63.2%; 150 mg: −52.5%) and up to week 80 (−71.5% and −65.8%).24

Secukinumab has exhibited efficacy for recalcitrant, non-plaque forms of psoriasis such as palmoplantar and generalized pustular psoriasis (GPP). In the GESTURE phase 3b clinical trial for moderate-to-severe hyperkeratotic palmoplantar psoriasis (palmoplantar IGA score ≥3), week 16 palmoplantar IGA 0/1 score

---

**FIGURE 2.** The role of the Th17/IL-23 pathway in psoriasis has been well elucidated. IL-17 plays a role in neutrophil recruitment, stimulating IL-1 beta and TNF-alpha production and inducing TH2 response against extracellular organisms. Two monoclonal antibodies targeting IL-17A (Cosentyx®, secukinumab, US FDA-approved 2015; Taltz®, ixekizumab, FDA-approved 2016) and one antibody against the IL-17 receptor (Siliq®, brodalumab, FDA-approved 2017) have been approved for the treatment of moderate-to-severe plaque psoriasis. Bimekizumab, a new inhibitor of IL-17A and IL-17F, is currently under investigation. ABBREVIATIONS: FDA, Food and Drug Administration; IL, interleukin; Th, T helper; TNF, tumor necrosis factor. Reprinted with permission from Macmillain Publishers Ltd: Nat Rev Drug Discov 12:815-816 © 2013.
<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Trial Duration</th>
<th>Study Arms</th>
<th>Primary/Secondary Outcomes</th>
<th>End-of-Trial Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secukinumab Phase 3 (FEATURE)</td>
<td>177</td>
<td>48 weeks</td>
<td>(1:1:1) Secukinumab 300 mg, 150 mg, placebo</td>
<td>(Week 12) Secukinumab 300 mg PASI 75: 75.9% PASI 90: 60.3% PASI 100: 43.1% Secukinumab 150 mg PASI 75: 69.5% PASI 90: 48.5% PASI 100: 8.5% Placebo PASI 75: 0% PASI 90: 0% PASI 100: 0%</td>
<td>(Week 52) Secukinumab 300 mg PASI 75: 83.5% PASI 90: 68% PASI 100: 47.5% Secukinumab 150 mg PASI 75: 63.5% PASI 90: 50.3% PASI 100: 31.1%</td>
</tr>
<tr>
<td>Secukinumab Phase 3 (JUNCTURE)</td>
<td>182</td>
<td>48 weeks</td>
<td>(1:1:1) Secukinumab 300 mg, 150 mg, placebo</td>
<td>(Week 12) Secukinumab 300 mg PASI 75: 88% PASI 90: 55.6% PASI 100: 26.9% Secukinumab 150 mg PASI 75: 72.4% PASI 90: 40.4% PASI 100: 16.9% Placebo PASI 75: 3.3% PASI 90: 0% PASI 100: 0%</td>
<td>(Week 52) Secukinumab 300 mg PASI 75: 81.4% PASI 90: 64.1% PASI 100: 38.8% Secukinumab 150 mg PASI 75: 75.2% PASI 90: 57.4% PASI 100: 33.1%</td>
</tr>
<tr>
<td>Secukinumab Phase 3 (ERASURE)</td>
<td>738</td>
<td>48 weeks</td>
<td>(1:1:1) Secukinumab 300 mg, 150 mg, placebo</td>
<td>(Week 12) Secukinumab 300 mg PASI 75: 81.6% PASI 90: 59.2% PASI 100: 28.6% Secukinumab 150 mg PASI 75: 71.6% PASI 90: 39.1% PASI 100: 12.8% Placebo PASI 75: 4.5% PASI 90: 1.2% PASI 100: 0.8%</td>
<td>(Week 52) Secukinumab 300 mg PASI 75: - PASI 90: 60.0% PASI 100: 39.2% Secukinumab 150 mg PASI 75: - PASI 90: 36.2% PASI 100: 20.2%</td>
</tr>
<tr>
<td>Secukinumab Phase 3 (FIXTURE)</td>
<td>1,306</td>
<td>48 weeks</td>
<td>(1:1:1:1) Secukinumab 300 mg, 150 mg, etanercept 50 mg, placebo</td>
<td>(Week 12) Secukinumab 300 mg PASI 75: 77.1% PASI 90: 54.2% PASI 100: 24.1% Secukinumab 150 mg PASI 75: 67.0% PASI 90: 41.9% PASI 100: 14.4% Etanercept PASI 75: 44.0% PASI 90: 20.7% PASI 100: 4.3% Placebo PASI 75: 4.9% PASI 90: 1.5% PASI 100: 0%</td>
<td>(Week 52) Secukinumab 300 mg PASI 75: 83% Secukinumab 150 mg PASI 75: 82% Etanercept PASI 75: 73% PASI 90/100 data not available</td>
</tr>
</tbody>
</table>
### TABLE. Key phase 3 clinical trial results for IL-17 antagonists (continued)

<table>
<thead>
<tr>
<th>Trial</th>
<th>n</th>
<th>Trial Duration</th>
<th>Study Arms</th>
<th>Primary/Secondary Outcomes</th>
<th>End-of-Trial Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Secukinumab</strong></td>
<td></td>
<td></td>
<td></td>
<td>(Week 16)</td>
<td>(Week 52)</td>
</tr>
<tr>
<td>Phase 3b (CLEAR)20, 56</td>
<td>676</td>
<td>48 weeks</td>
<td>(1:1) Secukinumab 300 mg and ustekinumab (dosed per recommendations)</td>
<td>Secukinumab 300 mg PASI 75: 93.1% PASI 90: 79.0% PASI 100: 44.3% Ustekinumab PASI 75: 82.7% PASI 90: 57.6% PASI 100: 28.4%</td>
<td>Secukinumab 300 mg PASI 75: 92.5% PASI 90: 76% PASI 100: 46% Ustekinumab PASI 75: 79.5% PASI 90: 61% PASI 100: 36%</td>
</tr>
<tr>
<td><strong>Ixekizumab</strong></td>
<td></td>
<td></td>
<td></td>
<td>(Week 12)</td>
<td>(Week 52)</td>
</tr>
<tr>
<td>Phase 3 (UNCOVER 1)37, 57</td>
<td>1,296</td>
<td>60 weeks</td>
<td>(1:1:1) Ixekizumab 160 mg at week 0 and 80 mg every 2 weeks (ixekizumab Q4W), every 2 weeks (ixekizumab Q2W), placebo</td>
<td>Ixekizumab Q2W PASI 75: 89.1% PASI 90: 70.9 PASI 100: 35.3% Ixekizumab Q4W PASI 75: 82.6% PASI 90: 64.6 % PASI 100: 33.6% Placebo PASI 75: 3.9% PASI 90: 0.5% PASI 100: 0</td>
<td>Ixekizumab 160 mg at week 0, then 80 mg Q2W until week 12; then 80 mg Q4W PASI 75: 92.3% PASI 90: 80.8% PASI 100: 48.7%</td>
</tr>
<tr>
<td>Phase 3 (UNCOVER 2)29, 30</td>
<td>1,224</td>
<td>60 weeks</td>
<td>(2:2:1) Ixekizumab 160 mg starting dose followed by 80 mg Q2W or Q4W, etanercept 50 mg twice weekly, placebo</td>
<td>(Week 12) Ixekizumab Q2W PASI 75: 89.7% PASI 90: 70.7% PASI 100: 40.5% Ixekizumab Q4W PASI 75: 77.5% PASI 90: 59.7% PASI 100: 30.8% Etanercept PASI 75: 41.6% PASI 90: 18.7% PASI 100: 5.3% Placebo PASI 75: 2.4% PASI 90: 0.6% PASI 100: 0.6%</td>
<td>(Week 60) Ixekizumab 160 mg at week 0, then 80 mg every 2 weeks until week 12, then 80 mg Q4W Ixekizumab Q12W (continued): 40.9% Maintenance of sPGA = 0/1 from week 12 through 60 after re-randomization: Ixekizumab Q12W (continued): 40.9% Ixekizumab Q4W (continued): 74.9%</td>
</tr>
<tr>
<td>Phase 3 (UNCOVER 3)29, 30</td>
<td>1,346</td>
<td>60 weeks</td>
<td>(2:2:2:1) Ixekizumab 160 mg starting dose followed by 80 mg Q2W or Q4W, etanercept 50 mg twice weekly, placebo</td>
<td>(Week 12) Ixekizumab Q2W PASI 75: 87.3% PASI 90: 68.1% PASI 100: 37.7% Ixekizumab Q4W PASI 75: 84.2% PASI 90: 65.3% PASI 100: 35% Etanercept PASI 75: 53.4% PASI 90: 25.7% PASI 100: 7.3% Placebo PASI 75: 7.3% PASI 90: 3.1% PASI 100: 0%</td>
<td>(Week 60) Ixekizumab 160 mg at week 0, then 80 mg Q2W until week 12, then 80 mg Q4W PASI 75: 83% PASI 90: 73% PASI 100: 55%</td>
</tr>
</tbody>
</table>
was attained by significantly more patients on secukinumab than placebo (300 mg: 33.3% versus placebo: 1.5%; \( P < .0001 \); 150 mg: 22.1%; \( P = .0002 \)). Secukinumab also demonstrated greater reductions in palmoplantar PASI scores at all assessed time points (week 16: 300 mg: −54.5%; 150 mg: −35.3%; placebo: −4.0; \( P < .0001 \) and \( P = .0006 \), respectively), as well as significant improvements in health-related quality-of-life outcomes.\(^{25}\) Secukinumab was evaluated for GPP in a phase 3 open-label Japanese study.\(^{26}\) All patients (n = 12) initially received weekly SC secukinumab 150 mg (weeks 0, 1, 2, 3, and 4), followed by monthly dosing maintained at 150 mg, or increased to 300 mg if inadequate improvement (based on Clinical Global Impression [CGI]). At week 16, treatment suc-
cess was achieved by 83.3% of subjects, based on CGI ratings of “very much improved” (n = 9) and “much improved” (n = 1). Improvements were maintained through week 52. Results from this small study support the potential benefit of secukinumab for the treatment of GPP.26

Safety and tolerability
The most frequently reported adverse events (AEs) include nasopharyngitis, diarrhea, and upper respiratory tract infections (URIs). In placebo-controlled studies, rates of infection were reported as secukinumab (28.7%) and placebo (18.9%), with higher rates of serious infections for placebo (placebo: 0.3%; secukinumab: 0.14%).15 Comparable safety profiles were observed for secukinumab and etanercept in the FIXTURE trial, though numerically higher rates of candidiasis were seen for secukinumab (4.7% [300 mg]; 2.3% [150 mg]; 1.2% [etanercept]) and numerically higher injection site reactions for etanercept (secukinumab: 0.7%; etanercept: 11.0%). Both secukinumab and etanercept had low rates of neutropenia (grade 3: 1.0% for secukinumab and 0% for etanercept; grade 4: 0.3% for etanercept and 0% for secukinumab).14 In the CLEAR trial, secukinumab and ustekinumab exhibited similar safety profiles, with no unexpected AEs observed.20 Three-year safety data from an extension (n = 682) of the SCULPTURE trial reported no new or unexpected AEs, with the most common year safety data from an extension (n = 682) of the SCULPTURE trial reported no new or unexpected AEs, with the most common adverse events of special interest similar to all prior studies.17 A large pooled safety analysis including 10 phase 2 and 3 clinical trials reported incidence rates for Crohn disease and ulcerative colitis (UC) through 52 weeks of secukinumab exposure of 0.11 and 0.15, respectively.17 The package insert recommends caution when prescribing secukinumab to patients with a history of IBD, as up to 1 in 1,000 patients on secukinumab therapy develop Crohn disease and 2 in 1,000 develop UC. Full safety and prescribing information can be found in the package insert.12

Ixekizumab
Ixekizumab (Taltz®, Eli Lilly, Indianapolis, Indiana) is a humanized anti-IL-17A IgG4-kappa monoclonal antibody approved in the United States in 2016 for the treatment of moderate-to-severe plaque psoriasis and in 2017 for psoriatic arthritis. Ixekizumab is administered subcutaneously at a loading dose of 160 mg (80 mg × 2) at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, 12, and then Q4W for maintenance.28 The dosing regimen for psoriatic arthritis excludes the loading period but is otherwise identical.

Clinical efficacy
In the phase 3 UNCOVER-1 trial, ixekizumab was superior to placebo through week 12 for the treatment of moderate-to-severe psoriasis. Week 12 PASI 90/100 response rates in UNCOVER-1 were greater for ixekizumab 80 mg every 2 weeks (Q2W; PASI 90: 70.9%; PASI 100: 35.3%), compared to ixekizumab 80 mg Q4W (PASI 90: 64.6%; PASI 100: 33.6%) and placebo (0.5%, 0.0%, respectively).29 Improvement was noted as early as week 1 of treatment. Week 12 PASI 90/100 response rates in phase 3 UNCOVER-2 trial were greater for ixekizumab Q2W (PASI 90: 70.7%; PASI 100: 40.5%) and Q4W (PASI 90: 59.7%; PASI 100: 30.8%), compared to etanercept 50 mg twice weekly (PASI 90: 18.7%; PASI 100: 5.3%).30 Static physician’s global assessment (sPGA) score of 0 (clear) or 1 (almost clear) was achieved by 83% (ixekizumab Q2W) and 72% (ixekizumab Q4W) versus etanercept (36%) and placebo (2.4%). Patients receiving both ixekizumab dose frequency regimens reported significant improvement in itch severity and quality-of-life measures (DLQI). The UNCOVER-3 phase 3 trial confirmed ixekizumab superiority to etanercept with week 12 PASI 90/100 response rates for ixekizumab Q2W (PASI 90: 68.1%; PASI 100: 37.7%) and Q4W (PASI 90: 65.3%; PASI 100: 35.0%), compared to etanercept 50 mg twice weekly (PASI 90: 25.7%; PASI 100: 7.3%).30 sPGA responses were similar to those of UNCOVER-2. These results were sustained through 60 weeks of treatment. Patients in the UNCOVER-3 trial also entered a long-term extension period through week 108 of ixekizumab 80 mg Q2W or Q4W.31 Response rates as noted by PASI 75/90/100 and sPGA persisted through week 108.31

Week 24 results from the IXORA-S phase 3b, 52-week, head-to-head study comparing ixekizumab with ustekinumab demonstrated superiority of ixekizumab over ustekinumab.32 Patients received ixekizumab at the standard dosing regimen or ustekinumab 45 mg or 90 mg based on weight. By week 12 extending to week 24, response rates for PASI 75, PASI 90, PASI 100, sPGA, and DLQI were significantly higher for ixekizumab (ixekizumab: PASI 75: 91.2%; PASI 90: 83.1%; PASI 100: 49.3%; sPGA 0 or 1: 86.6%; DLQI 0.1: 66.2%) versus ustekinumab (ustekinumab: PASI 75: 81.9%; PASI 90: 59.0%; PASI 100: 23.5%; sPGA 0 or 1: 69.3%; DLQI 0.1: 53.0%). Reported AEs were similar between both treatment arms. Final results will be available at the conclusion of the study.

Ixekizumab treatment has been shown to improve short- and long-term work productivity as measured by the Work Productivity and Activity Impairment-Psoriasis tool.33 This instrument was administered to patients in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials at baseline and weeks 12, 24, 36, 52, and 60. Improvements in absenteeism, presenteeism, work productivity loss, and activity impairment were noted for ixekizumab compared to placebo, and in presenteeism, work productivity loss, and activity impairment compared to etanercept (P < .001 for both doses) in UNCOVER-2. Measurement of work productivity is a significant endpoint that should be considered in the cost burden of psoriasis.

Efficacy of ixekizumab in difficult-to-treat areas of psoriasis such as nails and scalp was also evaluated. In the UNCOVER-3 trial, NAPSI score of 0 or complete resolution was noted at week 12 in 19.7% and 17.5% of patients receiving ixekizumab Q4W and Q2W, respectively, compared to placebo (4.3%, P < .001) or etanercept (10.2%, P < .05 each comparison).34 At week 60, mean percent NAPSI improvement was 81.8% for ixekizumab Q4W and 83.6% for ixekizumab Q2W-Q4W. For scalp psoriasis, improvement in the PSSI was noted at week 12 and through week 60 for patients treated with both ixekizumab Q4W (PSSI 90: 75.6%; PSSI 100: 68.9%) and ixekizumab Q2W (PSSI 90: 81.7%; PSSI 100: 74.6%), compared to etanercept (PSSI 90: 55.5%; PSSI 100: 48.1%; P < .001) and placebo (PSSI 90: 7.6%; PSSI 100: 6.7%; P < .001).35

Ixekizumab has also demonstrated efficacy in nonpustular palmoplantar psoriasis,36 erythrodermic psoriasis, and GPP.37 In the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials, 28% of patients had palmoplantar involvement. Subpopulation analysis re-
vealed greater improvement in the Palmpoplantar Psoriasis Area and Severity Index (PPASI 50/75/100) by patients treated with ixekizumab (PPASI 50: 80%; PPASI 75: 70% with \( P < .05 \); PPASI 100: 50%-51.8%; \( P < .001 \)) versus etanercept (PPASI 50: 67.8%; PPASI 75: 44.1%; PPASI 100: 32.2%) and placebo (PPASI 50: 32.9%; PPASI 75: 18.85%); PPASI 100: 8.2%). Results were maintained or improved through week 60 of treatment. In a small 52-week, open-label, phase 3 study (UNCOVER-J) of Japanese patients with erythrodermic and GPP, 75% of erythrodermic patients and 60% of GPP patients achieved sPGA of 0 or 1 at week 52.47

In addition, Ixekizumab has been evaluated in the treatment of genital psoriasis, a form of psoriasis that has an approximate 60% incidence in the psoriasis population. Over 70% of patients on ixekizumab achieved clearing of their genital psoriasis versus 8% on the placebo arm. In addition, quality of life issues in genital psoriasis, eg, sexual activity, were significantly improved with ixekizumab therapy.

**Safety and tolerability**

The most common treatment-emergent AEs were similar to those seen with other IL-17 inhibitors: nasopharyngitis, URI, injection site reactions, headaches, and arthralgias.48 Similar rates of nasopharyngitis, URIs, arthralgias, and headaches were observed as with placebo; ixekizumab induced a higher rate of injection site reactions (7.7% Q4W; 10.0% Q2W; versus 1.1% with placebo). Serious AEs, including infections, major adverse cardiovascular and cerebrovascular events, IBD, and cancer, were seen at similar rates with placebo.48 The overall rate of infections was higher during the induction period (first 12 weeks) of treatment with ixekizumab versus placebo (ixekizumab 27% versus placebo 23%) and did not increase during the maintenance period.49 In particular, infections with *Candida* were higher with ixekizumab versus etanercept or placebo (ixekizumab 4.3, 95% CI 2.9-6.5; etanercept 3.0, 95% CI 1.2-7.1; placebo 2.2, 95% CI 0.8-5.9). Incidence rates of staphylococcal infections, herpes zoster, and neutropenic infections were similar across treatment groups.49 Observed cases of neutropenia were mostly grade 1 or 2 and more frequent with ixekizumab and etanercept than placebo. No deaths were reported in the UNCOVER-2 and UNCOVER-3 trials. The rate of suicidal ideation or behavior was 1.39 per 1,000 patient years.50 In a Canadian study of secukinumab nonresponders who were switched to ixekizumab, 88.2% noted clinical efficacy to the new IL-17A agent, while 35.3% experienced an AE to ixekizumab.40 Analysis of adjudicated data from 7 ixekizumab trials evaluating IBD in treated psoriasis patients found an incidence rate for Crohn disease of 1.1 and UC of 1.9.41 The package insert for ixekizumab advises monitoring for onset or exacerbation of IBD.28

**Brodalumab**

Brodalumab (Siliq®, Ortho Dermatologics, Bridgewater, New Jersey; Kyntheon®, LEO Pharma, Ballerup, Denmark) is a fully human IgG2-kappa monoclonal antibody that uniquely blocks the anti-IL-17 receptor. It differs from secukinumab and ixekizumab by binding the IL-17 receptor, thus inhibiting binding of subunits IL-17A, IL-17E, and IL-17F. Brodalumab was approved in the United States for treatment of moderate-to-severe plaque psoriasis in 2017 and is currently under investigation for psoriatic arthritis. The recommended dosage for plaque psoriasis is 210 mg SC injections at weeks 0, 1, and 2, followed by 210 mg Q2W.42

**Clinical efficacy**

Three phase 3 trials, AMAGINE-1, AMAGINE-2, and AMAGINE-3, were conducted to evaluate the efficacy and safety of brodalumab for moderate-to-severe plaque psoriasis. AMAGINE-1 was only placebo-controlled, but both AMAGINE-2 and AMAGINE-3 were multicenter, randomized, double-blind, placebo-controlled, active-comparator (ustekinumab)-controlled, parallel-group studies with a 12-week induction period followed by a 40-week maintenance phase of brodalumab 210 mg or 140 mg.43 In AMAGINE-1, PASI 90 was achieved by 70.3% and 42.5% of patients receiving brodalumab 210 mg and 140 mg, respectively, and 41.9% and 23.3% achieved PASI 100 with brodalumab 210 mg and 140 mg, respectively.44 sPGA score of 0 (clear) or 1 (almost clear) was achieved by 75.7% (brodalumab 210 mg) and 53.9% (brodalumab 140 mg), versus placebo (1.4%, \( P < .001 \)). Patients also reported significant improvement in Psoriasis Symptom Inventory (PSI), including itch, compared to placebo (\( P < .001 \)).45 At week 12 of AMAGINE-2, PASI 90/100 was achieved for brodalumab 210 mg (PASI 90: 69.9%; PASI 100: 44.4%) and brodalumab 140 mg (PASI 90: 49.0%; PASI 100: 25.7%), compared to ustekinumab (PASI 90: 47.0%; PASI 100: 21.7%) and placebo (PASI 90: 1.9%; PASI 100: 0.6%).45 At week 12 of AMAGINE-3, PASI 90/100 was achieved for brodalumab 210 mg (PASI 90: 68.9%; PASI 100: 36.7%) and brodalumab 140 mg (PASI 90: 52.0%; PASI 100: 27.0%) compared to ustekinumab (PASI 90: 47.9%; PASI 100: 18.5%) and placebo (PASI 90: 2.9%; PASI 100: 0.3%).45 Secondary endpoints (sPGA, PSI, and PASI 100) at week 12 were greater for brodalumab compared to ustekinumab or placebo, but results were not statistically significant against ustekinumab.45 In an open-label extension study, brodalumab sustained significant clinical efficacy through week 120.46

**Safety and tolerability**

As with secukinumab and ixekizumab, common AEs included nasopharyngitis, URI, headaches, and arthralgias.43 Neutropenia was observed more frequently during the induction phase with brodalumab versus placebo but was mild and not associated with serious infections (AMAGINE-2: 0.2% for 140 mg and 210 mg, versus 0.7% ustekinumab; AMAGINE-3: 0.8%, 140 mg; 1.1%, 210 mg, versus 0.3% ustekinumab). Infections with *Candida* were seen with greater frequency with brodalumab than with ustekinumab or placebo. Crohn disease occurred in 1 case with brodalumab during the maintenance phase. Per the package insert, brodalumab is contraindicated in patients with Crohn disease, which is linked genetically to psoriasis. During the induction phase, 1 death due to a cerebrovascular event occurred, and 5 deaths occurred through week 52 of AMAGINE-2 and AMAGINE-3. Causes of death included cardiac arrest (3), pancreatic carcinoma (1), and motor vehicle accident (1). Four additional deaths occurred after 52 weeks: 2 from completed suicide, 1 from cardiomyopathy, and 1 from hematophagocytic lymphohistiocytosis syndrome. As a result of the observed suicides, brodalumab has a boxed warning in its label for suicidal ideation and behavior.42 It is available only through the Siliq® REMS Program.
through a registered provider. Subsequent evaluation of the association of suicidality and brodalumab failed to identify a pathogenic mechanism. Additional studies have suggested that psoriasis patients are overall more likely to attempt suicide (odds ratio [OR] 1.32, 95% CI, 1.14-1.54) and complete suicide (OR 1.20, 95% CI, 1.04-1.39) than patients without psoriasis. Singh et al. identified a suicidal ideation pooled OR in psoriasis patients of 2.05 (95% CI 1.54-2.74). Furthermore, a comparison of depression in patients on biologic therapy in the Psoriasis Longitudinal Assessment and Registry found a lower incidence of depressive symptoms among psoriasis patients treated with biologics.

**Th17 inhibitors and IBD**

The association between psoriasis and IBD has been well documented. Higher prevalence rates of psoriasis have been reported in patients with Crohn disease and UC, and the same has been observed of IBD rates in psoriasis patients. Potential risk of exacerbation of both Crohn disease and UC was observed in trials of secukinumab and ixekizumab. Brodalumab is contraindicated in patients with Crohn disease because of observed worsening. Thus, Th17 inhibitors should be used with caution in patients with IBD.

**Expert opinion on IL-17 inhibitors in clinical practice**

In our experience, we have initiated 1 of the currently 3 approved IL-17 inhibitor drugs in 2 groups of patients:
- patients on a TNF-alpha or IL-12/23 agent with a significant flare of their psoriasis, and
- biologic-naïve patients with inflammatory, generalized plaque psoriasis with or without concomitant psoriatic arthritis. Thus, the ideal candidate for IL-17 inhibitor therapy would have no personal or family history of IBD or symptomatology consistent with IBD, may have concomitant psoriatic joint disease, and may or may not have failed previous biologic therapy. Choosing between the 2 IL-17A agents is difficult because both secukinumab and ixekizumab have high-quality early responses as well as maintenance of clinical improvement in the vast majority of patients. In addition, both are approved for psoriatic joint disease. Secukinumab has recently received FDA approval for label inclusion of data showing inhibition of joint structural damage progression in psoriatic arthritis. Ixekizumab has demonstrated positive results for treatment of genital psoriasis. The IL-17 receptor inhibitor brodalumab has also exhibited very rapid early response, especially in patients with a significant inflammatory flare of their disease. Frequently, the decision is driven by third-party payors.

**Conclusion**

Psoriasis has come of age as a systemic immune-mediated disease with multiple comorbidities, including cardiovascular disease and metabolic syndrome. While psoriasis originally lagged behind other autoimmune diseases such as RA and IBD (Crohn disease and UC), it has now leap ahead in the field of biologic systemic therapies with new molecules such as the 3 IL-17 agents discussed above with multiple new IL-23 biologic agents pending. With the systemic nature of psoriasis now better understood and the excellent clinical responses noted with current IL-17 and IL-23 agents, future research will hopefully enable dermatologists to utilize specific biomarkers to choose which appropriate biologic agent is likely to optimize long-term safe control in each individual patient. These are exciting times in the field of biologic psoriasis therapies.

**References**


