In the past 20 years, significant progress has been made in better understanding the pathomechanisms of psoriasis. Initially thought to be an epidermal disorder, psoriasis is now considered a chronic T-cell mediated autoimmune disease. Drugs targeting tumor necrosis factor alpha (TNF-alpha) have been effective in managing both cutaneous psoriasis as well as psoriatic arthritis, but they have limitations. Severe adverse events, such as opportunistic infections and tuberculosis, along with antibodies specifically to the TNF-alpha drug with loss of efficacy, have been reported. There has been a shift from approaching psoriasis as a primarily T-cell mediated disease to the development of biologic therapies that directly target cytokine signaling or T-cell function. More targeted treatment options with less impact on the immune system and fewer side-effects are desirable. Many new biologic treatments for psoriasis are undergoing clinical trial development with a more focused approach on specific aspects of cytokine signaling because it is a more targeted approach that may offer a better side effect profile than current evidence-based treatment modalities.

Understanding the role of cytokines in the pathogenesis of psoriasis has been critical in developing advances in therapeutic options. An appreciation of the interleukin (IL)-23/Th17 axis in the pathogenesis of psoriasis has shifted the cytokine paradigm from Th1 to Th17 cytokines, primarily focused on IL-17 and IL-22. The IL-23/Th17 pathway is becoming a therapeutic target for biologic agents and systemic therapies in psoriasis treatment. There is increasing evidence that IL-23 plays an important role in the pathogenesis of psoriasis, and IL-23 promotes the TH17 response. The IL-23 cytokine is produced by antigen-presenting cells and is required for the activation and survival of Th17 cells. In addition to Th17, IL-23 promotes the survival and expression of Th22 cells. Both IL-17 and IL-22 are highly expressed in skin lesions of psoriasis. Two isoforms of IL-17, IL-17A and IL-17F, are expressed by T cells both as homodimeric proteins and as an IL-17A/17F heterodimer. These three cytokines signal through the same IL-17 receptor complex. New advances in biologic agents have focused on modulating these cytokines and the IL-17 receptor complex to enhance the clinical response in patients with psoriasis.

**TARGETING THE P40 SUBUNIT OF IL-12/23**

The potential success of biologic therapy utilizing cytokine antagonists in the treatment of psoriasis was clearly demonstrated with the therapeutic efficacy of ustekinumab. Ustekinumab is a human monoclonal antibody that binds to the p40 protein subunit of both IL-12 and IL-23 with high affinity and specificity. As a result, IL-12 is blocked from promoting Th1 cell differentiation and IL-23 is blocked from promoting Th17 cell differentiation and subsequent production of IL-17 and IL-22. The PASI 75 response for ustekinumab 45mg at week 12, which was the primary endpoint of the Phoenix 1 and...
Phoenix 2 clinical trials, was > 66 percent for both studies. Over 40 percent of patients in Phoenix trials randomized to 45mg of ustekinumab obtained > PASI 90 response at week 12.

A similar drug, briakinumab (ABT874), a fully human monoclonal antibody, also targets the p40 subunit of IL-12 and IL-23. Briakinumab clinical trials demonstrated high levels of efficacy as measured by the PASI-75 response at 12 weeks. Unfortunately, the drug developer withdrew its Food and Drug Administration application after one of the clinical trial arms demonstrated an increased incidence of cardiovascular events.

**BIOLGICS TARGETING IL-17**

Ongoing research has indicated that IL-17 is an important factor in the pathogenesis of inflammatory and autoimmune diseases, including psoriasis. The two isoforms of IL-17, IL-17A and IL-17F, are expressed by T cells as both monodimeric proteins as well as an IL-17A/17F heterodimer. These cytokines signal through the IL-17 receptor complex. IL-17A and IL-17F are expressed at elevated levels in psoriatic skin. Several new biologic agents have been developed that only target IL-17A or block the IL-17 receptor, which inhibits all three isoforms of IL-17A/F. Many of these biologic agents are undergoing phase II clinical trial development.

Izekizumab (LY2439821) is a humanized IgG4 monoclonal antibody that neutralizes interleukin-17A. In a phase II, double-blind, placebo-controlled trial, izekizumab demonstrated significant clinical efficacy for chronic moderate-to-severe plaque psoriasis, as well as scalp and nail involvement. At 12 weeks, a greater than 75 percent reduction in PASI score was noted in over 75 percent of patients receiving 25mg, 75mg, and 150mg, compared to eight percent with the placebo. A PASI reduction of 100 percent was noted in 38 percent receiving 75mg and 39 percent of patients receiving 150mg. Izekizumab had a rapid onset of action with clinical improvement noted as early as one week.

There were no serious adverse events observed in this phase II trial for izekizumab, but assessment of safety is difficult due to the small number of patients enrolled in the trial (142 patients) and short duration (12 weeks). There were no major cardiovascular events, mycobacterial infection, or systemic fungal infections. Of interest, two of 115 patients (1.7 percent) developed neutropenia of a Common Terminology Criteria for Adverse Events (CTCAE) of grade 2, which is 1000 to < 1500 cells per cubic millimeter. Neither of the patients had any concurrent infection. The most common adverse events were nasopharyngitis, upper respiratory infection, injection site reaction, and headache.

The neutralization of IL-17 by izekizumab has been demonstrated to have a rapid impact on the clinical features of psoriasis and inflammatory pathways. There were significant dose-dependent reductions from baseline in keratinocyte proliferation, epidermal thickness, hyperplasia, dendritic cell and T cell infiltration of the dermis and epidermis, and keratinocyte expression of innate defense peptides at only two weeks. An ablation of the disease-defining mRNA expression profile was noted by two weeks after the first dose. This study suggested that IL-17 was a key cytokine that activates the pathogenic inflammation in psoriasis.

Secukinumab (AIN457) is a fully human monoclonal antibody to IL-17A of the IgG1/K isotype. It has been evaluated in preliminary studies with psoriasis. A single administration of AIN457 (3mg/kg) resulted in a 63 percent reduction in PASI from baseline, compared to nine percent with placebo at week 12. The clinical response was associated with histologic findings of decreased acanthosis and epidermal hyperplasia, along with a reduction in the gene expression of markers of the IL-17A pathway. There was one serious adverse event noted in the study, which was the worsening of pre-existing congestive heart disease. A phase II dose-ranging study evaluated secukinumab (25-150mg) administered subcutaneously to patients with moderate to severe psoriasis. Fixed regimens of subcutaneously administered secukinumab 75mg every four weeks x 3 or 150mg every four weeks x 3 demonstrated efficacy in moderate to severe plaque psoriasis after 12 weeks. The PASI 75 response at 12 weeks was 81.5 percent for 150mg dosing, 57.1 percent for the 75mg dosing, and 9.1 percent for placebo. The more common side-effects were nasopharyngitis, upper respiratory tract infection, worsening of psoriasis, fatigue, and peripheral edema. Two patients experienced transient decreases in absolute neutrophils.

Brodalumab (AMG827) is a human, IgG2 mab that binds with high affinity to the human IL-17 RA (receptor) and prevents the binding and biologic activity of IL-17A, IL-17A/F, IL-17-F, and IL-25. In a phase I, randomized, placebo-controlled trial, subcutaneous and intravenous brodalumab was

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**TABLE 1. BIOLOGIC AGENTS IN DEVELOPMENT FOR PSORIASIS**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pharmaceutical Company</th>
<th>Target</th>
</tr>
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<tbody>
<tr>
<td>Stelara (ustekinumab)</td>
<td>Centocor/Janssen</td>
<td>p40 subunit of IL-12, IL-23</td>
</tr>
<tr>
<td>AIN457 (secukinumab)</td>
<td>Novartis</td>
<td>IL-17A</td>
</tr>
<tr>
<td>LY2439821 (izekizumab)</td>
<td>Lilly</td>
<td>IL-17A</td>
</tr>
<tr>
<td>AMG827 (brodalumab)</td>
<td>Amgen</td>
<td>IL-17RA (receptor)</td>
</tr>
<tr>
<td>ILV-094 (fezakinumab)</td>
<td>Pfizer</td>
<td>IL-22</td>
</tr>
<tr>
<td>SCH900222</td>
<td>Sanofi Pasteur MSD</td>
<td>p19 subunit of IL-23</td>
</tr>
<tr>
<td>CNT 1959</td>
<td>Centocor/Janssen</td>
<td>p19 subunit of IL-23</td>
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</tbody>
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Biologics With Other Targets. Biologics targeting the p40 subunit of IL-12 and IL-23, such as Ustekinumab, block both IL-12 and IL-23 signaling. The interleukin IL-12 is important for Th1 cell differentiation. IL-23, which is important for Th17 differentiation and survival, has two subunits: p19 and p40. By targeting the subunit p19, rather than p40, there is a specific inhibition of IL-23 without blocking IL-12. With preservation of the IL-12 pathway, Th1 stimulation is allowed to continue. Th1 immunity is preserved and risk of side effects may be decreased. The biologics targeting the p19 subunit of IL-23 are currently in phase I and II trials and include SCH900222 (Sanofi Pasteur MSD) and CNT 1959 (Centocor).5,6 A phase I study utilizing CNTO 1959 (Centocor) targeting the p19 subunit of IL-23 demonstrated encouraging results and was reported at the 6th International Congress of Psoriasis. The drug was evaluated for safety and tolerability following intravenous or subcutaneous administration in a single ascending dose study.16,17 Another major Th17/Th22 cytokine is IL-22. IL-22 regulates the expression of genes important in antimicrobial defense. There is a correlation between IL-22 levels and the severity of the disease.18 Fekazkinumab, an anti-IL-22 biologic, is currently undergoing phase I and phase II clinical trial development.5

CONCLUSION
An increase in the understanding of the pathomechanisms of psoriasis has led to expanding clinical trial development targeting recently discovered cytokine pathways. The IL-23/Th17 pathway is becoming a therapeutic target for evolving biologic treatments for psoriasis. Biologic agents are being developed that directly target cytokine signaling or T-cell function. With a more targeted approach on the immune system, newer biologic agents may have the potential to produce greater efficacy with an improved side effect profile. Most of the newer biologic agents for the treatment of psoriasis are in preliminary phase II clinical trials. The clinical efficacy and potential adverse events of these new agents will be more greatly appreciated as the clinical trials enter phase III studies. At the present time, the small number of patients treated and the short duration of the studies make accurate assessment of efficacy and safety difficult. The future of biologic therapy in the management of psoriasis remains challenging and exciting. ■

Dr. Bechtel is on the speakers bureaus for Abbott, Amgen, Janssen. Ms. Bechtel & Ms. Levinson have no relevant conflicts.

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