New biologic drugs get under the skin of psoriasis

New results on the clinical efficacy of two experimental psoriasis medications are creating a buzz among those who study and treat the skin disease. The drugs—ixekizumab from Indiana-based Eli Lilly and brodalumab from California's Amgen—are the first to exclusively target an immune signaling molecule known as interleukin-17 (IL-17) and its receptor. As such, new phase 2 data from both agents validate IL-17 as vital to psoriasis and offer the possibility of treatment for people who have failed existing therapies for this autoimmune disease.

"This patient population has had precious few rationale drugs over the decades," says Craig Leonardi, a dermatologist at St. Louis University School of Medicine and an author on the new studies of both ixekizumab and brodalumab, published simultaneously in late March. "I usually refer to the old days as the therapeutic wasteland. We were using tar coal, ultraviolet light and medicines with very significant toxicities. It's been an amazing renaissance to get where we are now."

In psoriasis, the body misidentifies skin cells as pathogens and sends T cells from the immune system to the skin, where they release cytokines, chemicals that activate inflammation pathways. The constant production of new skin cells causes red and white patches to form on surface; in some individuals, the internal inflammation associated with the condition can contribute to arthritis in the joints.

Existing biologic drugs on the market, including Humira (adalimumab) from Chicago-based Abbott Laboratories and Enbrel (etanercept) from Amgen, mostly target the cytokine known as tumor necrosis factor alpha, a major instigator of inflammation (see 'Biologic drugs set to top 2012 sales' on page 636). But over time the drugs can stop being as effective, and they can cause liver or gastrointestinal problems. More recently, however, companies have begun to develop monoclonal antibodies revolving around type 17 helper T cells (T_H17 cells), found in high levels in psoriatic lesions.

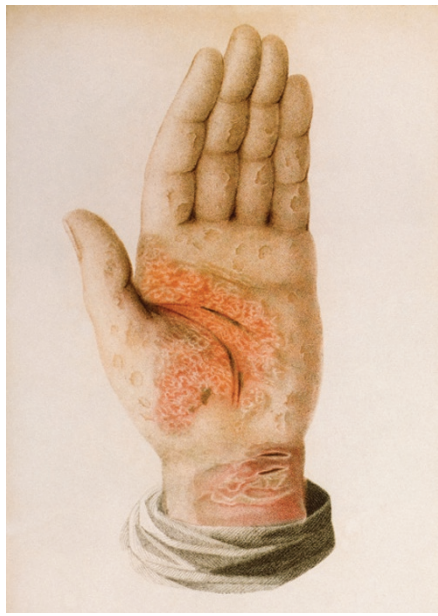
The most recent such psoriasis biologic to hit the market, Stelara (ustekinumab), made by Pennsylvania-based Janssen Biotech, blocks the protein domain p40 within two molecules, including interleukin-23, a cytokine that would otherwise promote the production of T_H17 cells. But the cells have some useful functions and blocking them entirely might end up being tough on the body in the long run. So other antibody-based therapies on the horizon block individual cytokines produced by the T_H17 cells, with the aim of producing fewer side effects and long-term toxicity.

The upside of downstream

Ixekizumab and brodalumab both work by stopping the production of IL-17 cytokines by T_H17 cells. "They're working on the same cascade of events but hitting it downstream," explains Leonardi.

In the trial of ixekizumab, 142 patients received either a placebo or one of four different doses of the drug injected into the skin. After three months, 82% of patients receiving the highest two doses of ixekizumab saw a reduction of at least 75% in psoriasis severity according to a common psoriasis scoring system; by comparison, less than 8% of those taking the placebo saw such improvement (*N. Engl. J. Med.* **366**, 1190–1199, 2012). In the similarly designed three-month trial of brodalumab, 198 patients received placebo or four doses of the drug. Around 86% of those taking the highest doses saw a 75% improvement in their disease, compared with 3% of those taking placebo (*N. Engl. J. Med.* **366**, 1181–1189, 2012).

Notably, both drugs work in about 10–20% more people than do the existing drugs, an exciting prospect for those who fall into the group of people unable to find psoriasis treatments that work. "The data shown in both the new papers have really outstanding numbers for efficacy, so I think what needs to be determined with these drugs is their long-term safety," says Alice Gottlieb, a dermatologist at the Tufts Medical Center in Boston who has studied Stelara and briakinumab, a similar experimental psoriasis antibody from Abbott Laboratories.



Mehau Kulyk / Photo Researchers, Inc.

Waving goodbye: Targeting IL-17 could be the key.

Because of the new biologics in development, analyst Bingnan Kang of Decision Resources, a Burlington, Massachusetts–based market research firm, expects the US psoriasis market to grow from $2.6 billion in 2010 to more than $5.6 billion by the end of the decade. But exactly which drug—ixekizumab, brodalumab or any of the other interleukin-directed agents in mid- to late-stage clinical development (see 'Rolling in the ILs')—will end up ahead is hard to predict, notes Kang, especially with such similar efficacy numbers coming out of the recent trials.

"The initial uptake will always be slow in the psoriasis market," she says, "and more information on long-term safety is really essential right now to convince physicians to switch to a new drug."

Ultimately, though, there are still needs for others types of psoriasis treatments—for both people whose psoriasis is not severe enough to warrant treatment with biologics and those who have more severe cases, Gottlieb points out. "There are needs in psoriasis that the biologics don't meet," she says. "A great unmet need is better topical treatments and also safer and more effective oral medications. Psoriasis is by no means a done deal."

Sarah C P Williams

Rolling in the ILs: Interleukin-directed antibodies in development for psoriasis.

Drug	Company	Target	Phase
Stelara (ustekinumab)	Janssen Biotech	IL-12/IL-23 (p40 subunit)	Approved
Briakinumab	Abbott Laboratories	IL-12/IL-23 (p40 subunit)	3
Ixekizumab	Eli Lilly	IL-17	2
Brodalumab	Amgen	IL-17 receptor	2
Secukinumab	Novartis	IL-17	3
Fezakinumab	Pfizer	IL-22	2
MK-3222	Merck	IL-23 (p19 subunit)	2
CNTO 1959	Janssen Biotech	IL-23 (p19 subunit)	2

Corrected after print 22 May 2012 and 6 December 2012.

Correction

In the May 2012 issue, in the piece "New biologic drugs get under the skin of psoriasis'" (*Nat. Med.* **18**, 638, 2012), sales numbers mistakenly cited for the US psoriasis market were actually sales numbers for the G7 (US, UK, France, Germany, Italy, Spain and Japan) markets. The correct numbers for the US market are $2.6 billion in 2010 and more than $5.6 billion in 2020 (rather than $3.9 billion in 2010 and more than $7.4 billion in 2020). The error has been corrected in the HTML and PDF versions of the article.

Correction

The table accompanying the article "New biologic drugs get under the skin of psoriasis" (*Nat. Med.* **18**, 638, 2012), which appeared in the May 2012 issue, misstated that the Novartis drug secukinumab was in phase 2 when in fact it was in phase 3. The error has been corrected in the HTML and PDF versions of the article.