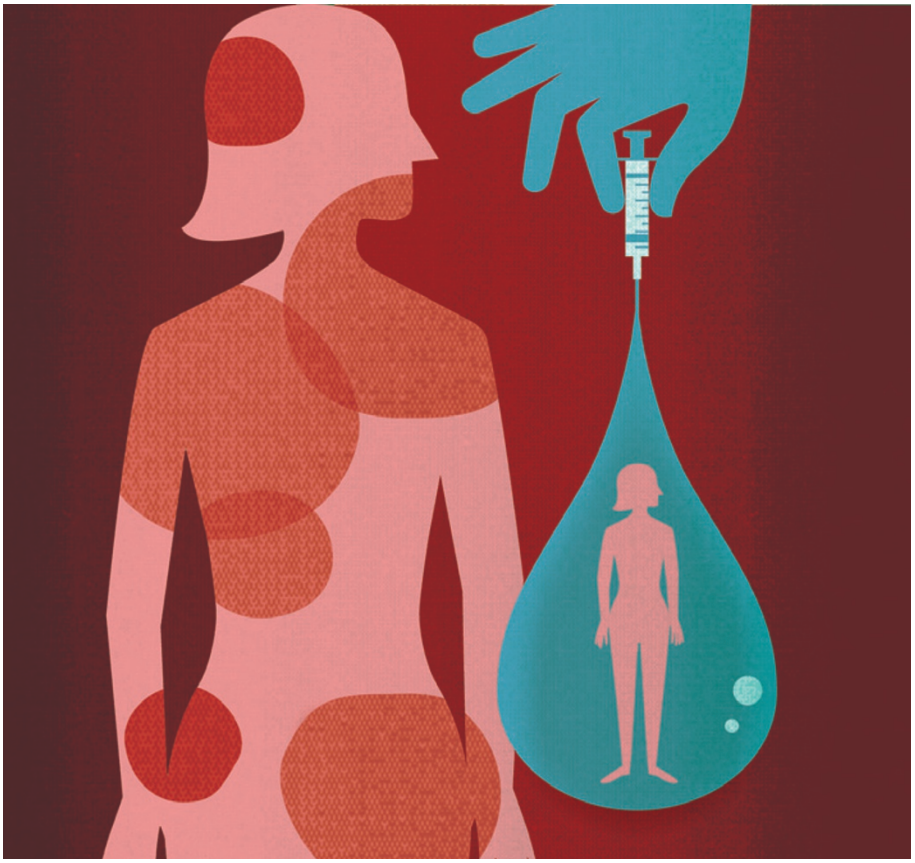

ANDREW BAKER

THERAPEUTICS

Silencing psoriasis

The latest drugs hold fantastic promise for people with severe psoriasis. But where are the treatment options for the far larger number with less serious cases?

BY JAMES MITCHELL CROW

There's a buzz among psoriasis researchers. A new generation of therapies are sailing through clinical trials, promising to bring the most debilitating cases of the inflammatory skin disease under control. Not quite a cure, but getting very close.

"It really is a phenomenal period," says Kim Papp, a clinical researcher at Probity Medical Research in Waterloo, Canada. Generating most excitement is a new class of drugs known as the anti-interleukin (IL)-17s. "The anti-IL-17s have demonstrated profound efficacy," says Papp. And he is well placed to judge, having conducted more than 100 clinical trials assessing new psoriasis therapies in the past decade.

Not only are the drugs effective, but so far they seem to be safe. "Given what we've seen in phase II, where all these therapies were well tolerated and continued to be effective, it is very unlikely that there will be something in phase III to prevent regulatory approval," says Papp.

The field sorely needs fresh treatment options. A survey[1] by the National Psoriasis Foundation, a patient advocacy organization based in Portland, Oregon, found that 40% of people suffering from this disorder are frustrated with the ineffectiveness of their current therapies. Yet most psoriasis patients will not benefit from expensive biologic drugs like the anti-IL-17s. Indeed, none of the antibody-based biologic drugs in development will have an impact on clinical practice for most psoriasis cases in the near term. That distinction is likely to belong to another class of psoriasis drugs entirely, which are proceeding rather more quietly through clinical trials.

COMPETITION TIME

The first biologic therapy for psoriasis was alefacept (Amevive), an anti-T-cell treatment approved by the US Food and Drug Administration (FDA) in 2003. Five other biologics followed, culminating in ustekinumab (Stelara) in 2009 (see 'Psoriasis through-flow'). These later drugs target different points in the cascade of immune-system signalling molecules, or cytokines, that triggers the skin-cell hyperproliferation characteristic of psoriatic lesions.

Ustekinumab blocks two cytokines, IL-12 and IL-23, which are upstream of IL-17 in this cascade (see 'Deep exploration', page S56). This drug has become the yardstick against which all new biologic psoriasis drugs are measured. Psoriasis therapies are assessed by their PASI 75 score, which represents the percentage of patients achieving at least a 75% reduction in a disease measure called the Psoriasis Area and Severity Index (PASI). At week 12 of treatment, ustekinumab has a PASI 75 of 67% (ref. 2).

As with any drug designed to suppress the immune system, the main concern with ustekinumab is the risk of serious side effects. Such fears are well founded: the development of briakinumab, a biologic with the same mode of action, was halted after a series of major cardiovascular events during clinical trials. Ustekinumab has not been linked with any severe adverse events and, if confidence grows, it might be prescribed more. Severe side effects can take years to become apparent, however. In 2009 a biologic called efalizumab, approved six years earlier, was withdrawn after three patients developed progressive multifocal leukoencephalopathy, a potentially fatal brain disease.

Ustekinumab will soon be in competition with the three anti-IL-17 drugs now in phase III trials: brodalumab, ixekizumab and secukinumab. These agents are proving to be remarkably effective, says Christopher Griffiths, a dermatologist specializing in psoriasis at the University of Manchester, UK. Around half of the phase II trial participants receiving the anti-IL-17 drugs at high dose achieved PASI 100 — that is, complete clearance of psoriasis[3–5]. That's a similar proportion to the number who achieve PASI 75 with the current first-line biologics. And as Griffiths points out, "these are patients who have very difficult and recalcitrant disease".

The efficacy results are a surprise, says Rob Kastelein, who works on biologic psoriasis therapies at pharmaceutical giant Merck in Palo Alto, California. Animal studies suggested that blocking the cascade at IL-17 would not be as effective as upstream blockers such as ustekinumab, says Kastelein. "IL-23 is the only molecule where, if you inject it into the skin of a mouse, you get a psoriatic-type lesion." In fact, although ustekinumab targets both IL-12 and IL-23, its efficacy against psoriasis stems entirely from blocking IL-23, Kastelein adds. Armed with this insight, Merck is developing a new agent, MK-3222, that targets only IL-23. It therefore lowers the risk of side effects that might arise from unnecessary interference with IL-12.

Why the anti-IL-17s perform so well remains unclear, says Jonathon Sedgwick, research

fellow for biotechnology and autoimmunity at Eli Lilly in Indianapolis, Indiana — the pharmaceutical company currently developing ixekizumab. He adds that research into IL-17 is at an early stage. "There are a lot of unknowns."

Genetic studies hint at a reason. "The anti-IL-17s are impressive for the clinical outcomes, but even more impressive are the changes in gene expression in the psoriatic lesion," says Andrea Chiricozzi, a research dermatologist at the University of Rome Tor Vergata and the Rockefeller University in New York. Somehow these drugs are downregulating every major cytokine in psoriasis, even those upstream of IL-17 in the cascade. "You have very strong suppression of the psoriasis signature genes — it is even more effective than ustekinumab."

Potent as they may be, the anti-IL-17 drugs share a limitation with ustekinumab and the other biologics: for the time being, they are aimed only at severe psoriasis.

Psoriasis severity is typically measured by the percentage of a patient's body surface area (BSA) affected by lesions. A BSA of 3–10% is considered moderate, whereas 10% is the traditional cut-off for severe disease. "The patient at 9% is ineligible for these biologic therapies," says Papp. That's partly down to their cost, and partly down to safety concerns. In the United Kingdom, these treatments can amount to nearly £11,000 (US$17,500) per patient per year, a cost that insurers and healthcare providers are unwilling to bear for less-than-severe cases. There is also the risk–benefit ratio to consider. As the withdrawn drug efalizumab shows, it can take years to be sure that rare yet severe side effects will not emerge. For milder cases, this risk outweighs the benefit.

In the meantime, the 90% or so of psoriasis patients considered to have a moderate or mild form of the disease will not have access to the new biologic drugs. "By far the largest proportion of the psoriasis population is bereft of new therapies," says Papp.

MILD-MANNERED

Two drugs now in phase III trials might bring relief to patients with moderate psoriasis: tofacitinib from New York-based Pfizer (approved by the FDA in November 2012 as Xeljanz — a treatment for rheumatoid arthritis), and apremilast from drug developer Celgene, based in Summit, New Jersey. Both are small-molecule chemical therapies, which should make them cheaper to manufacture than biologic drugs. They can also be taken orally, whereas biologics must be injected. Tofacitinib works by targeting a group of molecules called Janus kinases (JAKs). Knocking out JAKs prevents the body from generating the docking sites needed to receive the cytokines associated with psoriasis. Apremilast, in contrast, works by blocking phosphodiesterase 4 (PDE4), which is essential for cytokine synthesis. "I'm hoping that some of the small molecules, where used as oral agents or introduced as topical agents, will find their way to treating patients who have less severe disease," says Papp.

PSORIASIS THROUGH-FLOW

Five biologic drugs are in clinical use. Five more are close behind, along with new oral and topical therapies.

Name (trade name)	Manufacturer	Type	Target	Phase of development
Alefacept (Amevive)	Biogen	Biologic	T cells (CD2)	Approved 2003
Efalizumab (Raptiva)	Genentech	Biologic	T cells (CD11a)	Approved 2003, withdrawn 2009
Etanercept (Enbrel)	Amgen	Biologic	TNF-α	Approved 2004
Infliximab (Remicade)	Janssen Biotech (J&J)	Biologic	TNF-α	Approved 2006
Adalimumab (Humira)	Abbott	Biologic	TNF-α	Approved 2008
Ustekinumab (Stelara)	Janssen Biotech (J&J)	Biologic	IL-12, IL-23	Approved 2009
Brodalumab	Amgen	Biologic	IL-17 receptor	Phase III
Ixekizumab	Eli Lilly	Biologic	IL-17	Phase III
Secukinumab	Novartis	Biologic	IL-17	Phase III
MK-3222	Merck	Biologic	IL-23	Phase III
Apremilast	Celgene	Small molecule (oral)	PDE4	Phase III
Tofacitinib	Pfizer	Small molecule (oral)	JAK	Phase III
Tofacitinib	Pfizer	Small molecule (topical)	JAK	Phase II
CNTO 1959	Janssen Biotech (J&J)	Biologic	IL-23	Phase II
AN2728	Anacor	Small molecule (topical)	PDE4	Phase II

Phase II clinical trial data for both drugs seem underwhelming compared with the results for the biologics. In the tofacitinib study, 67% of patients achieved PASI 75 (ref. 6), while for apremilast the number was 41% (ref. 7). But because no significant side effects were linked to either drug, they could be just what is needed to treat less-severe forms of psoriasis. Apremilast, in particular, might be well suited for treating medium-severity cases, says Papp. One advantage it has is that there are good safety data from PDE4 drugs already in the clinic for other conditions. "Apremilast is potentially a sleeper in the panoply of products."

Chiricozzi agrees. "With apremilast, you don't have the very high efficacy of the biologic drugs," he says, "but you do have a very good safety profile." Although the long-term safety profile of the JAK inhibitors is less clear, they too could ultimately find a market in medium-severity cases, he adds.

Most psoriasis patients, however, have conditions that are too mild to warrant any systemic treatment, whether biologic or small-molecule. The good news for these patients is that it is possible to turn the new small-molecule drugs into ointments. Pfizer, for example, is developing a topical version of tofacitinib and has produced what Chiricozzi says appear to be "very encouraging results". Although Celgene has not announced the development of a topical apremilast formulation, another company, Anacor Pharmaceuticals, based in Palo Alto, California, does have a topical PDE4 inhibitor in development. Both therapies are part way through phase II trials.

Creams might seem to be the logical delivery mechanism for psoriasis treatments, but they present unique problems. The skin is a barrier, and it can be difficult to develop an agent that will penetrate the skin in sufficient quantity to have an effect, says Papp. "It takes a lot more to develop a cream than it does to develop a pill."

Once their safety is established, biologic treatments such as the anti-IL-17s might be prescribed for milder cases. This has happened for biologic drugs in other conditions, says Sedgwick. "But that will take some time."

Success in developing effective therapies for all psoriasis patients, no matter how mild their condition, would cap what has been a remarkable turnabout in psoriasis drug development. Until ustekinumab was approved, psoriasis medication largely consisted of adopted drugs, from organ transplant immunosuppression to rheumatoid arthritis. And now small-molecule therapies are catching up. "Psoriasis lends itself extremely well to clinical research," says Griffiths. "Psoriasis is now leading the field, rather than following." ■

James Mitchell Crow *is a freelance science writer based in Melbourne, Australia.*

1. Krueger, G. *et al. Arch. Dermatol.* **137,** 280–284 (2001).
2. Leonardi, C. L. *et al. Lancet* **371,** 1665–1674 (2008).
3. Papp, K. A. *et al. N. Engl. J. Med.* **366,** 1181–1189 (2012).
4. Leonardi, C. *et al. N. Engl. J. Med.* **366,** 1190–1199 (2012).
5. Rich, P. *et al. Br. J. Dermatol.* doi: 10.1111/bjd.12070 (2012).
6. Papp, K. A. *et al. Br. J. Dermatol.* **167,** 668–677 (2012).
7. Papp, K. *et al. Lancet* **380,** 738–746 (2012).