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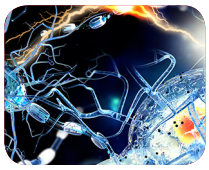

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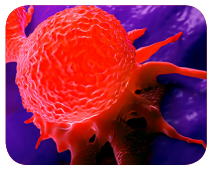

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First eczema biologic debuts but price could restrict use

The US Food and Drug Administration has approved the first biologic therapy for atopic dermatitis, the itchy skin condition better known as eczema. The drug is a human monoclonal antibody called Dupixent (dupilumab) that targets the interleukin-4 (IL-4) receptor alpha subunit, thereby blocking the signaling of two pro-inflammatory cytokines—IL-4 and IL-13—both of which are key mediators of the T helper type 2 (T_H2) immune response, thought to be the main driver of the disease.

Dupixent won approval on March 28 for treating people with severe-to-moderate eczema who can't get relief from existing topical corticosteroid therapies. For this population—an estimated 1–5% of the 32 million people in the US with the disease—"this is going to be a real lifeline," says Amy Paller, a dermatologist at Northwestern University's Feinberg School of Medicine in Evanston, Illinois, who has consulted for the two companies behind Dupixent, Regeneron of Tarrytown, New York, and Sanofi of Paris. "It's going to totally change practice. For the first time, we have a biologic that really works."

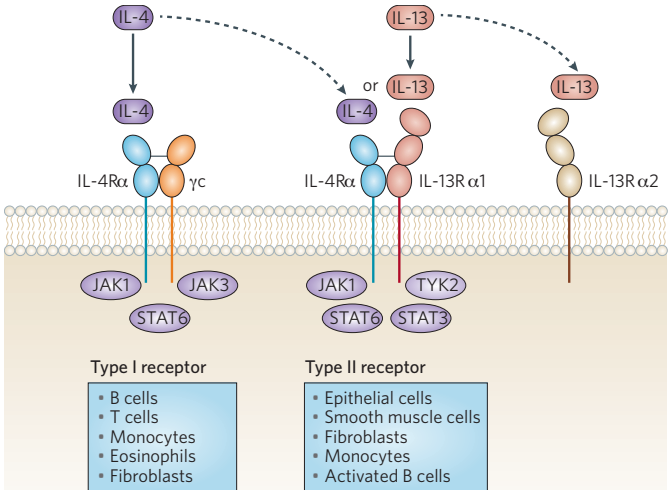
The drug doesn't come cheap, though. Its sticker price: $37,000 per year before discounts, which is well above the cost of topical steroids and immunosuppressants such as cyclosporine and calcineurin inhibitors. For this reason, healthcare analysts like Ian Love, who covers the eczema space for Decision Resources Group of Burlington, Massachusetts, expect insurance companies to balk at covering Dupixent until after patients have failed to respond to other therapies. "It's a tough sell," Love says—even though, as he points out, the Institute for Clinical and Economic Review, a Boston-based cost-effectiveness watchdog, concluded in a March 24 report that the new biologic offers good value for money, especially for patients with more severe disease.

Physicians like Robert Scheinberg may thus not have the freedom to prescribe Dupixent as often as they'd like. "I would probably want to use it as my first-line systemic medication after I have really exhausted very intense topical therapy," says Scheinberg, a dermatologist in private practice in the San Diego area. Reimbursement barriers could spell fewer prescriptions. Even so, at the high per-patient cost for Dupixent, "Sanofi and Regeneron will still see relatively high returns," notes Christina Vasiliou, an analyst at Datamonitor Healthcare in London. Consensus estimates put peak global sales forecasts at around $3 billion annually.

Three pivotal, phase 3 studies provided the data that led to the drug's approval. In two of these—the so-called SOLO trials—patients with moderate-to-severe eczema who had not responded well to topical therapy received 16 weeks of Dupixent or placebo injections without additional steroid treatment. Dupixent produced clear or almost clear skin in 37% of drug recipients—whether they got the active agent weekly or every other week—compared with just 9% among those on placebo (*N. Engl. J. Med.* **375**, 2335–2348, 2016). Close to half of all patients on Dupixent also improved by 75% from baseline on the Eczema Area and Severity Index, compared to fewer than 1 in 7 on placebo.

In the third trial, dubbed CHRONOS, participants continued taking topical corticosteroids alongside their Dupixent or placebo injections for 52 weeks. Placebo response rates were higher in this study than observed in the SOLO trials, but the magnitude of the difference between drug treatment and placebo was comparable on multiple efficacy measures.

Across all trials, the drug proved safe. And as a T_H2 modulator, it doesn't carry the risk of infections or cancer that come with many of the T_H1-targeted biologics used for psoriasis (*Nat. Biotechnol.* **33**, 3–4, 2015). The worst symptom for patients taking Dupixent seemed to be an elevated risk of pink eye (conjunctivitis). "As biologics and systemic agents go, this has one of the cleanest safety profiles we have ever seen," says Jonathan Silverberg, a dermatologist and epidemiologist at Northwestern who was involved in the drug's trials.



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IL-4 and IL-13 functions overlap, facilitated, in part, by shared receptor subunits, to trigger T_H2 responses.

Whether Dupixent works predominantly through its action on IL-4 or IL-13 signaling remains "the million dollar question," says Emma Guttman-Yassky, a dermatologist from the Icahn School of Medicine at Mount Sinai in New York. Regeneron's senior vice-president of research Drew Murphy says the two cytokines work together to aggravate the disease, with "IL-13 more the tissue-effector and IL-4 more the immune-effector." So, he argues in favor of blocking both, as Dupixent does.

But other companies, including London-based AstraZeneca and Roche, of Basel, Switzerland, are banking on IL-13 being the primary culprit behind the disease. Those drug makers each have anti–IL-13 drugs that have completed phase 2 testing—and a host of other systemic therapies, both biologics and small molecules, are in the pipeline for atopic dermatitis as well (**Table 1**).

Many of these experimental agents target cytokines in the same T_H2 pathway—"and so," says Donald Leung, an allergist and immunologist at National Jewish Health in Denver, "you can imagine new therapies intervening up and downstream of IL-4 and IL-13."

One such drug is Chugai Pharmaceutical's nemolizumab, a humanized monoclonal antibody that targets IL-31 receptor, another cytokine produced by T_H2 cells and the key itch-inducing factor. In a 264-person, phase 2 trial published in March, monthly injections of nemolizumab reduced itching symptoms by around 60% at the two higher doses tested, versus around 20% in those who got placebo (*N. Engl. J. Med.* **376**, 826–835, 2017). A year-long extension of that study in which participants could take topical corticosteroids alongside their nemolizumab injections showed that itch and rash improvements compared favorably with results from the end of the CHRONOS trial with Dupixent. However, the anti–IL-31 drug seemed to tackle itch more quickly, whereas the anti–IL-4/IL-13 agent had a more rapid effect on rash clearance.

Because blocking the itch with nemolizumab seems to resolve all aspects of the disease, Thomas Ruzicka, a dermatologist at the Ludwig Maximilian University of Munich, Germany, argues that the anti–IL-31 data can finally help settle the long-running debate about which comes first in eczema: the rash or the itch. "Eczema is an itch that rashes, not a rash that itches," says Ruzicka, who led the nemolizumab trial.

Another drug target in the T_H2 pathway—one that Eric Simpson, a dermatologist at the Oregon Health and Science University in Portland, describes as "extremely attractive"—is thymic stromal lymphopoietin (TSLP), an epithelial-cell-derived cytokine that strongly activates dendritic cells to exacerbate immune activation. "It's a gateway to T_H2 inflammation, and it's a connection between your epithelium and your immunity," says Simpson, who led the SOLO trials for Dupixent and is involved in testing most other experimental eczema agents. AstraZeneca and its partner Amgen of Thousand Oaks, California, recently wrapped up a 100-person phase 2 trial of an anti-TSLP antibody called tezepelumab; top-line results are expected in the first half of this year.

Not all the drug development action is focused on the T_H2 axis, though. Guttman-Yassky, for example, recently received a grant from the US National Institutes of Health to run a 60-person phase 2 trial involving ILV-094, an human IgG1 antibody directed against the T_H22 cell-derived cytokine IL-22, which has been implicated in skin thickening and disrupted barrier functions that can make eczema patients susceptible to staphylococcal infections. As she reported at last month's Society For Investigative Dermatology Annual Meeting in Portland, Oregon, ILV-094 diminished the extent and severity of eczema even long after patients received their sixth and final bi-weekly shot. "The efficacy continues for many months," Guttman-Yassky says. "For such a small study, the results are quite exciting."

Table 1 Therapies in development for atopic dermatitis

	Drug	Lead developer	Target	Stage
Biologics	Dupixent (dupilumab)	Regeneron	IL-4Ra	Approved
	Nemolizumab	Chugai	IL-31R	Phase 2 published
	Stelara (stekinumab)	Janssen	IL-12/23p40	Phase 2 published
	Tralokinumab	AstraZeneca	IL-13	Phase 2 completed
	Lebrikizumab	Roche	IL-13	Phase 2 completed
	ILV-094	Pfizer	IL-22	Phase 2 completed
	Tezepelumab	AstraZeneca	TSLP	Phase 2 completed
	Cosentryx (secukinumab)	Novartis	IL-17	In phase 2
	GBR830	Glenmark	OX40	In phase 2
	BMS-981164	Bristol-Myers Squibb	IL-31	Phase 1 completed
	CNTO 7160	GlaxoSmithKline	IL-33R	In phase 1
Small molecules	Eucrisa (crisaborole)[a]	Pfizer	PDE4	Approved
	OPA-15406	Medimetriks Pharmaceuticals	PDE4	Phase 2 completed
	Timapiprant	Atopix Therapeutics	CRTH2	Phase 2 completed
	ZPL-389	Ziarco Pharma	Histamine H4 receptor	Phase 2 completed
	Baricitinib	Eli Lilly	JAK1/2	Phase 2 completed
	PF-04965842	Pfizer	JAK1	In phase 2
	Upadacitinib	AbbVie	JAK1	In phase 2
	INCB18424[a]	Incyte	JAK1/2	In phase 2
	LEO 124249[a]	LEO Pharma	Pan-JAK	In phase 2

[a]Topical therapies. Source: *J. Allergy Clin. Immunol.* **139**, S65–S76 (2017); BioMedTracker; clinicaltrials.gov

ILV-094 entered phase 1 testing a decade ago. But when Pfizer acquired the rights to the drug in its 2009 buyout of Wyeth, the New York–based drug makers decided not to take the experimental therapy any further. In light of Guttman's new data, however, spokesperson Steven Danehy says Pfizer executives are now "considering our options."

A handful of orally available janus kinase (JAK) inhibitors are also in mid-stage development to help uncouple cytokine signaling from the downstream gene activation that contributes to autoimmune dysfunction. These include baricitinib from Eli Lilly of Indianapolis, a JAK1/2-blocking pill that US regulators shot down last month for patients with rheumatoid arthritis, citing concerns over safety and dosing, as well as JAK1 inhibitors from New York–based Pfizer and AbbVie of North Chicago, Illinois.

Brett King, a dermatologist at the Yale University School of Medicine in New Haven, Connecticut, has treated more than a dozen patients off-label with a different JAK-targeted pill from Pfizer, Xeljanz (tofacitinib), which is currently approved only for rheumatoid arthritis. "It works great," King says, with around half achieving clear or almost clear skin clearance at the doses he has tried.

Pfizer had been testing a topical version of Xeljanz, but it stopped further development in 2015 after completing a small phase 2 study. And while the company "is further exploring topical indications for some of our next-generation assets," Danehy says, Pfizer's main focus for treating mild-to-moderate eczema has been on its recently approved ointment, Eucrisa (crisaborole), a non-steroidal drug that blocks the phosphodiesterase-4 enzyme that promotes skin inflammation. After it snagged the thumbs-up in December 2016 for patients two years and older, Eucrisa became the first new eczema drug to hit the US market in 15 years.

At a wholesale price of $580 for a 60-gram tube, Eucrisa costs almost a hundred times more than a comparable tube of mid-potency corticosteroid, which means "it'll be too expensive to become the cream of choice for most people," says Paller, who led the phase 3 trials of Eucrisa. But according to Linda Stein Gold, another trial investigator from the Henry Ford Health System in West Bloomfield, Michigan, the drug should find its niche as an add-on therapy to corticosteroids, for treating certain body sites such as on the face (where steroids can thin the skin), and for patients who experience side effects on steroids. "To have a drug that's not a steroid, that has a very well-tolerated side-effect profile, and can be used anywhere on the body, I think, is a very good addition to the treatment armamentarium," she says.

Yet, Stein Gold reserves her more exalting praise for Dupixent and other biologics that target the T_H2 pathway. These, she says, are "a game changer for patients with severe atopic dermatitis that potentially will allow them to live normal lives."

Elie Dolgin *Somerville, Massachusetts*