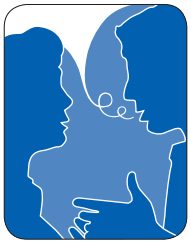
IN brief

Claims expose fatal events

Insurance claims could flag risks posed by some products, according to the first study of its kind conducted at the US Food and Drug Administration (FDA). Agency scientists collaborated with Wilmington, Delaware–based HealthCore, a subsidiary of insurance giant Wellpoint, to analyze retrospective insurance claims from over 69 million people. They analyzed claims contained in HealthCore's database related to Vivaglobin, a subcutaneous immunoglobulin treatment for immunodeficiency from CSL Behring of King of Prussia, Pennsylvania, discontinued in 2011. Recent product withdrawal-—Lachen, Switzerland–based Octapharma's Octagam and Omr-IgG-am by Omrix Biopharmaceuticals in Somerville, New Jersey-—highlighted the possible association between immunoglobulin products and thrombotic events, such as strokes and heart attacks. The study found Vivaglobin was associated with same day thrombotic event. People aged over 45 or with a history of prior thrombotic eventss and/or hypercoagulable states were at highest risk. "This is really a hypothesis-generating study," says Gayathri Sridhar, a research manager at HealthCore and one of the study authors. "The next step is validation." Claims databases are retrospective and can include errors, but their value, a spokesperson for the FDA-based authors pointed out, is in providing a "timely assessment of rare adverse events occurring after biologic product use." *Malorye Allison*

IN their words



"We simply don't have time to wait. Our life spans are much shorter than the [Food and Drug Administration] approval process." ALS sufferer Ben Harris explains why ALS patients began taking home-made preparations of sodium chlorite which they deduced was the active component present in the drug NP001, currently in phase 2 clinical trials. (*The Wall Street Journal*, 15 April 2012)

"If current trends continue, orphan drugs can become…larger than the entire global pharmaceutical industry today." Venture capitalist Bill Frezza, a fellow at the Competitive Enterprise Institute, predicts the trend will result in profit regulation, nationalization and, ultimately, stagnation. (*BioITWorld*, 3 April 2012)

Table 1 Biologicals targeting Th17 cells or IL-17 in autoimmunity

Company	Agent	Target	Indications	Stage
Eli Lilly	Ixekizumab, (LY2439821)	IL-17A	Psoriasis Rheumatoid arthritis	Phase 3 Phase 2 complete
Novartis	Secukinumab (AIN457)	IL-17A	Psoriasis Rheumatoid arthritis Ankylosing spondylitis Psoriatic arthritis Non-infectious uveitis Asthma Multiple sclerosis	Phase 3 Phase 3 Phase 3 Phase 3 Phase 3 terminated Phase 2 Phase 2
Amgen/ MedImmune	Brodalumab (AMG 827)	IL-17 receptor	Psoriasis Psoriatic arthritis Rheumatoid arthritis Asthma Crohn's disease	Phase 2 complete Phase 2 Phase 2 Phase 2 Phase 2 suspended
Janssen Biotech (J&J)	Stelara (ustekinumab) (CNTO 1275)	p40 subunit of IL-23 and IL-12	Psoriasis Crohn's Ankylosing spondylitis	Approved 2009 Phase 3 Phase 2
Merck	MK-3222 (SCH 900222)	p19 subunit of IL-23	Psoriasis	Phase 2 complete
Janssen Biotech (J&J)	CNTO 1959	p19 subunit of IL-23	Psoriasis	Phase 2
Amgen/ MedImmune	AMG 139	p19 subunit of IL-23	Crohn's	Phase 1

Sources: http://www.clinicaltrials.gov/, interviews with companies, company press releases.

Patient biopsy samples offer clues. "There is a dramatic ability of this [Amgen] antibody to turn off the underlying inflammation in the disease," says James Krueger, a dermatologist at Rockefeller University in New York, who has worked with both Amgen and Lilly to unpick the underlying biology. "Everything that defines psoriasis…the genes that are activated…the cellular infiltration, the tissue patterning, the hyperplasia, the clinical features of the disease, everything is reversed extremely well by blocking IL-17." All this happens within a few weeks of starting treatment. Surprisingly, not only is IL-17 signaling neutralized, but upstream IL-17 gene expression is reduced (along with that of other cytokines), suggesting a feed-forward inflammatory loop that amplifies drug effects (*J. Allergy Clin. Immunol.* 2012, in press).

Krueger speculates that such a loop may start with IL-17 inducing expression of antimicrobial peptides in keratinocytes, the predominant cell type in the epidermis. These peptides supposedly activate dendritic cells, which then stimulate the many T-cell types active in psoriatic lesions. Interrupting this loop with anti-IL-17 antibodies apparently chokes off the entire cascade of events. In addition, Krueger and others have shown that IL-17 synergizes with TNF-α to induce a large set of inflammatory genes, so it's likely that blocking IL-17 also indirectly blocks many of the downstream consequences of TNF-α activation in psoriasis.

Whatever the biological underpinning, efficacy is now a given. "Phase 2 efficacy results in psoriasis tend to be very predictive of what we see in phase 3," says Schmidt. "If there's any question around the product, it'll be around safety." Both the Amgen and Lilly antibodies were very well-tolerated in phase 2, but the trials enrolled only a few hundred patients, who were treated for less than four months. One concern is neutropenia, as IL-17 induces the secretion of chemokines that recruit neutrophils to sites of inflammation. Amgen and Lilly each reported two cases of asymptomatic neutropenia. "Neither of these patients had any infections," says Subhashis Banerjee, Lilly's senior medical director for ixekizumab. Banerjee adds that these two cases could be from defective neutrophil trafficking in blood (not from bone marrow suppression).

Another concern is fungal infections. People with inborn human genetic deficiencies of IL-17RA and IL-17F both suffer from chronic mucocutaneous candidiasis in the skin, nails and oral/genital mucosae, and are also prone to *Staphylococcus aureus* infection (*Science* **332**, 65–68, 2011). Individuals with this genetic (null) phenotype supply powerful evidence of IL-17's role in protecting against *Candida albicans*. Blocking IL-17 with antibodies is unlikely to leave patients unprotected, Krueger speculates, as the blockade is probably incomplete. No fungal infections were reported in the Amgen and Lilly phase 2 trials.

As far as efficacy goes, targeting the IL-17A cytokine (the Lilly and Novartis antibodies) and the receptor (Amgen's approach)