

Autoimmune

Biosimilars are threatening to chip away at established blockbusters. Industry giants are battling to devise better therapies for celiac, Crohn's and lupus even as they work around the clock to protect their turf in RA and psoriasis. Welcome to the autoimmune category—in which, **Rebecca Mayer Knutsen** explains, there's never a dull moment

The great biosimilar debate is overshadowing brisk innovation in the autoimmune disease category. The pipeline houses promising biologics for lupus and celiac disease, and competition for Novartis's recently approved IL-17A inhibitor for psoriasis, Cosentyx, is waiting on deck.

The prevalence of autoimmune disease, in which systemic inflammation assaults the body, is on the rise. Scientists are scrambling to counteract the immune system's inability to differentiate between healthy cells and outside invaders such as toxins, allergens and infections. The industry favors biologics, developed to target specific steps in the inflammatory process, over the conventional large-molecule approach to the entire immune system.

Biologics have emerged as safe targets for pharma, yielding high returns on investment. Humira (adalimumab), one of the best-selling drugs of all time, raked in \$12.5 billion in 2014. Four of last year's 10 best-selling drugs fell under the biologic autoimmune umbrella.

Genetically engineered from a living organism, biologics simulate the body's natural response to infection and disease. "Biologics target proteins, cells and pathways responsible for disease symptoms and damage of rheumatoid arthritis and other diseases," says Sandie Preiss, VP of advocacy and access at the Arthritis Foundation. Unlike chemically based compounds, however, biologics cannot be replicated. Biologics and their biosimilar knockoff versions can be therapeutically similar but are not the same product, raising safety and efficacy eyebrows.

"We're dealing with a live organism that tends to mutate and form polymorphisms," says Edward Buthusiem, a managing director at Berkeley Research Group.

The rheumatoid arthritis (RA) landscape is bursting with TNF inhibitors, like category leaders Amgen's Enbrel, Janssen's Remicade and AbbVie's super-blockbuster Humira. These biologics block the activity of tumor necrosis factor, a pro-inflammatory cytokine produced by macrophages and lymphocytes, to prevent inflammation in the joints.

Still, primarily due to the large price tag attached to biologics, patients rely heavily on conventional RA treatments: anti-inflammatory drugs, steroids and immunosuppressants like methotrexate. "As a group, anti-inflammatories will continue to top the best-selling drug list. These drugs are highly efficacious, have a favorable cost-utility profile and address a significant clinical need in inflammatory disease," says Jens Lindqvist, MD, director of life sciences for advisory firm N+1 Singer. Some of the most promising RA products in late-stage development are Eli Lilly/Incyte's once-daily oral kinase inhibitor baricitinib, Sanofi/Regeneron's IL-6 inhibitor sarilumab and Janssen/Glaxo-SmithKline's IL-6 inhibitor sirukumab.

The biosimilar "threat"

Biosimilars are hot on the heels of their biologic forebears. With 18 biosimilars authorized by the EMA, the biosimilars "threat" has been a reality in Europe for many years. FDA approval of

Sandoz's Zarxio in March opened the door for an established regulatory pathway here. Zarxio is biosimilar to Amgen's neutropenia drug Neupogen (filgrastim), originally licensed in 1991.

According to Lindqvist, the US entry of biosimilars will dent the sales of a number of individual branded biologic franchises, but the impact is likely to pale in comparison to the generic competition for "white pill" small-molecule drugs. Looking ahead, N+1 Singer analysts believe the biologics market will reach about \$300 billion in annual global sales by 2020, including about \$50 billion from biosimilars.

But the regulatory pathway for biosimilars is murky, Buthusiem says. "Zarxio's approval doesn't mean the floodgates will open. FDA will review the drugs on a case-by-case basis. Some drugs and organisms, from a biologic standpoint, could be easier to crack."

Biosimilars will have to sail through somewhat-uncharted waters to reach the market. The more complex monoclonal antibodies, in particular, will have to round more buoys than other biosimilars.

Pfizer's pending acquisition of Hospira has given the company a definitive leg up in the biosimilars field, Makovsky Health EVP Gil Bashe notes. "Having successfully navigated the biosimilar market in Europe, Hospira has regulatory savvy and physician/patient experience." Biosimilar CT-P13, sold as Remsima by Celltrion and as Inflectra by Hospira in other markets, was filed for review in the US last summer. If approved, Hospira will market the Remicade copycat. South Korea's Samsung Bioepis has submitted its infliximab biosimilar candidate for approval in Europe.

The competition isn't sitting still. Sandoz gained applicable experience from its early foray into growth hormone treatments and the accompanying uphill climb to win over physicians. But Amgen is the company with the most at stake. Expecting biosimilar competition for some of its own products, Amgen has gone on the offensive. Its Humira biosimilar ABP501 passed its second Phase-III study with flying colors—and pulled the company ahead of Cadila, Novartis and Boehringer Ingelheim, which are also looking to cash in on Humira's reigning profits as the drug nears patent expiration.

Beyond biosimilars

It goes without saying that there are new entries beyond biosimilars on the horizon.



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INC Research

The inflammatory disease space exalts the approval of moderate-to-severe plaque psoriasis treatment Cosentyx (secukinumab). "This is the first drug in the last 10 years with published studies showing clear superiority to the current standard of treatment," observes Marcin Ernst, MD, VP of clinical development at INC Research (see "Clinical Corner," p. 52).

Eli Lilly's ixekizumab and AstraZeneca/Amgen's brodalumab, both of which target the IL-17A cytokine, are expected to elbow their way into the picture. Both companies plan regulatory submissions for psoriasis this year.

A few companies are jockeying to bring the first celiac disease drug to market. Months-old start-up Celimmune acquired rights to Amgen's anti-IL-15 monoclonal antibody AMG 714 and is entering Phase-II studies for certain types of celiac disease (IL-15 is a cytokine thought to play a role in autoimmune disorders). Alba Therapeutics, on the other hand, is studying larazotide acetate for celiac disease. In other therapeutic areas:

- AbbVie and the newly rebranded Biogen are primed to submit for regulatory approval of daclizumab, a monthly biologic in development for patients with relapsing remitting multiple sclerosis, if they can iron out safety concerns.
- A pill could replace the use of injectables Remicade and Humira in the treatment of Crohn's disease. Mongresen, a biologic in early development by Italian pharma company Giuliani, shows promise for the digestive disorder.
- Lupus, a major unmet patient need, is a disease category to watch, according to Bashe. After a long dry spell, the developmental doors first reopened with the approval of Benlysta in 2011, but advances have slowed in recent years.
- AstraZeneca's MedImmune is moving its IFN pathway inhibitory molecule, anifrolumab, into Phase III trials for Lupus. Other lupus contenders in Phase-II studies include EMD Serono's recombinant fusion protein atacicept and Pfizer's anti-IL-6 antibody, also for Crohn's disease.



Cosentyx: Novartis's new interleukin-17A inhibitor for treating plaque psoriasis



CLINICAL CORNER

Novartis's first-in-class monoclonal antibody Cosentyx (secukinumab) received the FDA's stamp of approval in January for the treatment of moderate-to-severe plaque psoriasis. The highly anticipated selective interleukin-17A (IL-17A) inhibitor is already generating quite the buzz across the industry and among patients.

The CLEAR trial established Cosentyx as tackling psoriasis lesions more effectively than Johnson & Johnson's Stelara after a 16-week treatment. Extended studies demonstrated Cosentyx's superiority in achieving "clear or almost clear skin" over competitors.



Dhavalkumar Patel

"The immune system is designed to fight off infections and to fight against cancers. When it goes awry, it begins attacking itself," says Dhavalkumar Patel, MD, PhD, head of NIBR Europe and Global Head, Autoimmunity, Transplantation and Inflammation (ATI) Disease Area at the Novartis Institutes for BioMedical Research.

Before the drug had shown efficacy, doctors hoped to achieve a Psoriasis Area and Severity Index 75 response. "Essentially, they wanted 75% clearance of skin, which was thought to be good," Patel explains. "The results were far better than predicted or expected. We showed PASI 90 and 100 responses in trials, which should be the treatment goal."

Novartis is preparing to submit Cosentyx for additional indications, including ankylosing spondylitis and psoriatic arthritis, worldwide. "Currently marketed anti-TNFs don't work as well as we would like and often show reduced effect due to immunogenicity," Patel notes.

While Lilly and AstraZeneca/Amgen are gearing up to submit applications for IL-17A receptor inhibitors ixekizumab and brodalumab in psoriasis, Makovsky Health EVP Gil Bashe believes Cosentyx has taken and will keep the lead. Assuming a successful label expansion to psoriatic arthritis and ankylosing spondylitis, the agency predicts peak sales potential of just under \$3 billion for the three products in aggregate in these indications—with Novartis capturing the largest market share of about \$1.4 billion, based on its first-mover advantage. (Analysts expect brodalumab and ixekizumab to gain approval in 2016.)

According to Jens Lindqvist, MD, N+1 Singer's director of life sciences, the lowest-hanging fruit for these products is the market share currently held by TNF inhibitors. Stelara sales are also at risk, as both Cosentyx and brodalumab have outperformed the anti-IL-12/23 biologic in head-to-head Phase-III trials, he says.

With the new medications, patients can have complete clearance of skin lesions. "Psoriasis is not often thought to be a severe disease, but it is," Patel says. "Patients don't socialize because they don't want to be seen. With this drug, we can give patients a normal life. That's exceptional."

Based on interest within the patient community and by physicians, Novartis expects the drug to reach blockbuster status, bringing in up to \$2 billion a year. "In all head-to-head trials, the drug exhibited a remarkable profile against today's standards of care," Patel says.



In rheumatoid arthritis, Bashe advises interested parties to keep their eyes open as Lilly buys its way into a leadership position. The company recently agreed to collaborate with Korea-based Hanni Pharmaceutical on its HM71224, which is being studied for rheumatoid arthritis and lupus.

Although still tremendously crowded, the RA market anxiously awaits new treatment approaches. There has been nothing new in RA since Pfizer's tofacitinib gained FDA approval in 2012. Xeljanz is a first-in-class Janus kinase inhibitor, which targets a specific cellular process involved in the immune response and resulting inflammation. Pfizer is currently exploring the pill's application in plaque psoriasis.

Additionally, clinical trials face mounting difficulty in recruiting RA patients to participate. "More patients are being treated for the disease, so it narrows down the number of people who are candidates," INC's Ernst says.

A number of autoimmune drugs have the ability to target orphan diseases, thereby offering a vibrant incentive to attract pharma investment and attention. Big pharma will continue to seek out biologic solutions for RA by focusing on less prominent indications to reduce competition—and push profits up.

Change on the horizon

Recent premium-priced M&A activity encouraged investments in the early-stage autoimmune pipeline, Bashe says, but incentives for pharma to invest in these areas remain ever-changing. The Obama administration recently proposed slimming the 12-year exclusivity period—during which biosimilars of FDA-approved biologics cannot gain approval—down to seven years.

Ernst, for his part, questions how payers will react to biosimilars: Will there be a significant price war? Will payers pressure the companies owning the originator drug to lower prices in order to compete with biosimilars?

Biologics typically fall into specialty medication tiers, requiring patients to pay a percentage of the drug's cost (rather than a fixed price). If passed, the Patients' Access to Treatments Act would limit coinsurance payments for patients—which is critical, Preiss says. "With affordability comes greater adherence to medications."

In the absence of pressure from payers, the natural tendency will be to keep prices at current levels. Bashe believes competition will make pricing a factor with payers, and biosimilars will use discounts and rebates to secure strong tier status.

Biosimilar prices, then, will be set lower than the bio-therapeutic originators but will not be vastly different. The premium pricing is justified, Bashe says, because the recombinant products often require in-home patient training, 24/7 patient hotlines and significant physician marketing efforts and reimbursement services.

There is also some question of whether prescribing physicians will accept biosimilars with open arms. Unless the biosimilar is supported by data, Ernst—formerly a practicing physician—would choose the originator, owing to its efficacy and safety record.

Bets will continue to be wagered on the fate of biosimilars, as well as on whether biologics are immune to the forthcoming pricing competitions that have sent experts to opposite sides of the ring. "We're not where we thought would be with biosimilars," Ernst says. "Turns out they're not as easy and cheap as everyone originally thought." ■