VIEWPOINT

Adalimumab and the Challenges for Biosimilars

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Biologic drugs are expensive therapeutic agents and represent a large and growing segment of pharmaceutical spending. In particular, at nearly $20 billion in sales in 2018, adalimumab (Humira) dominates the worldwide biologic market, with more than twice the annual sales of the second-highest selling drug, lenalidomide (Revlimid).[1]

Biosimilars have long been viewed as a solution to the high price of injectable biologic drugs like adalimumab. There are now 23 approved biosimilars in the United States with hundreds more likely under development, and the assumption is that a robust biosimilar market, once established, will substantially lower the price of biologic drugs and, consequently, spending. This appears to be happening in Europe, where biosimilar adalimumab products have led to discounts of 80% off the price of brand-name Humira.[1]

However, these deep discounts from biosimilar adalimumab are not available in the United States despite US Food and Drug Administration approval for 4 biosimilars, because each biosimilar manufacturer has agreed to delay their US launch until 2023 to settle patent disputes with AbbVie (maker of Humira).[2] By then, competition from newer (ie, patent-protected) biologics could erode the market share of adalimumab. In particular, the possibility of highly effective oral biologics or other oral treatment could substantially dampen the effect of biosimilars entering the marketplace.

> Specifically, will patients who transition to a more convenient or more effective biologic or oral therapy be willing to return to less convenient or effective injectable biosimilars to save money?

At issue for adalimumab and other biologics in the United States is the real possibility that patients who are receiving brand-name biologics will transition to more effective products before relevant biosimilars become available. Specifically, will patients who transition to a more convenient or more effective biologic or oral therapy be willing to return to less convenient or effective injectable biosimilars to save money? The answer to this question has major implications for the future of the biosimilar market.

This scenario is playing out in rheumatoid arthritis and related inflammatory diseases. Although tumor necrosis factor inhibitors remain a mainstay of treatment, other recently approved biologics have demonstrated impressive improvements in effectiveness. For example, the IL-23 antagonist risankizumab (Skyrizi) was found to be more effective than adalimumab in severe plaque psoriasis (90% improvement of skin lesions in 72% of 301 patients treated with risankizumab compared with 47% of 304 patients treated with adalimumab).[3]

Furthermore, the dosing schedule of risankizumab is potentially more convenient (every 12 weeks for maintenance vs every 2 weeks for adalimumab). Other IL-23 and IL-17 antagonists also have been proven effective for patients with psoriatic arthritis and are especially attractive for patients with concomitant severe skin disease. It is possible that these new biologics may be used preferentially over an adalimumab biosimilar. This is especially likely given the long delay in market entry for adalimumab biosimilars, and the fact that AbbVie manufactures both risankizumab and adalimumab, raising the likelihood of strategies to maintain market share over the adalimumab biosimilar, including combined rebate agreements (ie, rebate bundles).[4]

An additional factor that may limit biosimilar adoption for adalimumab is the possibility of effective oral small-molecule immunomodulatory drugs. This scenario will now likely play out with upadacitinib, which was approved by the US Food and Drug Administration on August 16, 2019, and, like risankizumab and adalimumab, is manufactured by AbbVie. Upadacitinib is an oral Janus kinase 1 inhibitor. Two other oral Janus kinase inhibitors (tofacitinib and baricitinib) are available, but these products have limitations in safety and efficacy that have made competition with adalimumab difficult.

On the other hand, there is evidence of greater effectiveness with upadacitinib compared with adalimumab. In the SELECT-COMPARE trial,[5] 1629 patients with rheumatoid arthritis who were continuing treatment with methotrexate were randomized to upadacitinib, placebo, or adalimumab. Upadacitinib was more effective for several measures of disease activity and symptoms, and adverse events were generally similar. The drug is under investigation for treatment beyond rheumatoid arthritis, including inflammatory bowel disease, dermatitis, and psoriatic arthritis.

A total of 21 active phase 3 trials of upadacitinib are listed on ClinicalTrials.gov, each studying the drug among patients who are naive or intolerant to biologic agents. Upadacitinib will compete directly with adalimumab, and it is anticipated that AbbVie will incentivize switching to its new brand-name oral rheumatoid arthritis therapy long before the biosimilar of Humira becomes available in 2023, ensuring continued dominance in the market.

Even though both risankizumab and upadacitinib are potential therapeutic substitutes for adalimumab, what if an oral version of adalimumab is developed to directly substitute for the injectable form? Technology that is in development will allow oral delivery of biologics,

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overcoming the obstacles that required these large and fragile proteins to bypass the gastrointestinal system. For example, Rani Therapeutics just completed its first human trial of the RaniPill, which delivers biologic drugs orally.[6] The pill has an enteric coating that delays activation until the intestine, where it pushes a tiny needle into the intestinal wall to deliver the biologic medication. Similarly, a group from the Massachusetts Institute of Technology developed a small capsule that can inject insulin into the stomach after being swallowed. These products, and others like them, portend a future in which expensive oral biologic products will compete with less expensive biosimilar injectables.

There are, of course, success stories for biosimilars. Infliximab (Remicade) now has 2 biosimilar competitors (Inflectra and Renflexis) that have contributed to a stabilization of list prices of the reference Infliximab product and a reduction in the net price with increasing rebates.[7] Similarly, the estimated net price of brand-name filgrastim (Neupogen) has declined by an estimated 30% after accounting for rebates and other discounts after the entry of 2 biosimilars (Zarxio and Nivestym).

Other biosimilar-like products, such as the follow-on biologic insulin Basaglar, also have contributed to reductions in price. There is also substantial potential for biosimilars bevacizumab (Avastin) and trastuzumab (Herceptin) to reduce drug spending in cancer. Moreover, once truly interchangeable biosimilars arrive (ie, products that may be substituted for the reference product without intervention by the prescriber), prices and spending on these agents are expected to decrease substantially.

However, is the window closing for biosimilars to have the large influence that was once expected? Biosimilars encounter many challenges, including rebate strategies that challenge substitution of the new product, manufacturing difficulty, patent disputes, and market uncertainty. These products also will encounter the same challenges small molecule generics have faced in the past, when brand-name manufacturers engaged in market tactics to maintain market share of their brand-name products. Added to these challenges is the likelihood that manufacturers of brand-name products will develop new oral products to supplant the injectable versions that lose patent protection, or improved injectable versions that make biosimilars obsolete. The example of adalimumab, including its biosimilar delay, injectable competitors, and now oral biologic competitors, should be a warning that speed is of the essence for establishing a robust biosimilar market in the United States.

ARTICLE INFORMATION

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