

## Biosimilar infliximab (Inflectra)

Although biosimilars have already been used for several years in many countries, they are new to the US market. The hope is that availability of biosimilars will drive down drug costs and therefore improve patient access to these medications. The first biosimilar (infliximab-dyyb, aka CT-P13, US trade name Inflectra and marketed in Europe as Remsima) for use in rheumatology in the US is expected to be available in late 2016 making it critical that rheumatologists become familiar with the safety and efficacy data on biosimilars and regulations regarding their use. We will highlight available data regarding Inflectra and address issues important to biosimilars in general.

First, it is helpful to understand the definition of a biosimilar medication. This is a new concept in drug development and regulation regarding their approval has evolved at varying rates around the world. Due to the size and complexity of these molecules, it is impossible to make an identical molecule as one can do with smaller generic molecules. This fact has resulted in increased complexity of regulatory definitions and requirements.

The FDA considers a product to be “biosimilar” to a reference product if it is shown to have no clinically meaningful differences with respect to safety, potency and purity. Interchangeability is an additional statutory standard distinct from the assessment of biosimilarity based on having a greater data set. An interchangeable biosimilar is expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switching.

In the US, approval of biosimilars follows an abbreviated pathway. In order to obtain approval for a biosimilar, the manufacturer must submit an application showing data from analytical studies, animal studies and clinical studies assessing immunogenicity, pharmacokinetics and pharmacodynamics. At least one randomized clinical trial (RCT) is typically required to demonstrate that the efficacy, immunogenicity and safety of the biosimilar are comparable to its reference product. This RCT may enroll patients with any of the existing indications for which the reference product is approved. Extrapolation to additional indications may be allowed (as was the case when Inflectra was approved) based on scientific justification. As with all biologics, it is expected that post marketing surveillance will be performed to track adverse events.

As of November 2016, three biosimilars used in rheumatology have gained FDA approval (see table). None, to date, is considered interchangeable. Indeed, official FDA guidelines outlining the standards for interchangeable status have not, to date, been released.

Name	Trade Name	Manufacturer	Date of Approval
filgrastim-sndz	Xarxio	Sandoz	5/6/2015
infliximab-dyyb	Inflectra	Celltrion	4/5/2016
etanercept-szsz	Erelzi	Sandoz	8/30/2016
adalimumab-atto	Amjevita	Amgen	9/23/2016

Biosimilars in the US carry unique names to facilitate post-marketing surveillance. The 4 random letters after the generic name distinguish it from other, future infliximab biosimilar products. The letters themselves are random and do not hold any specific meaning. In approving Inflectra, the FDA relied on clinical data in rheumatoid arthritis (RA; a 1 year study in approximately 600 patients) and also utilized data in ankylosing spondylitis (AS; a 1 year study in 250 patients). These data were extrapolated to allow approval of other indications for which comparative clinical studies were not submitted. An assessment of safety and immunogenicity in patients undergoing switches in open label RA and AS extension studies was also submitted.

The safety of switching has been analyzed in a few studies from northern Europe, the most important of which to date is the NOR-SWITCH study presented at the 2016 ACR Annual Meeting. This trial provided real world data on maintenance of efficacy as well as adverse events after non-medical (that is, no medical indication to change drugs) switching from reference to biosimilar infliximab in 481 patients with a diagnosis of RA, psoriatic arthritis, spondyloarthritis, Crohn's disease, ulcerative colitis, or psoriasis. In this 52 week randomized, double-blind, non-inferiority trial, patients on stable treatment with originator Remicade were randomized 1:1 to either continue Remicade or switch to CT-P13 biosimilar infliximab at an unchanged dose. Switching from Remicade to CT-P13 was not inferior to continued treatment with Remicade and was not associated with an increased risk of adverse events. In addition, multiple abstracts at this year's ACR Annual Meeting presented data from observational cohorts after a switch to biosimilar infliximab suggesting similar efficacy and safety.

The biosimilar label is derived from the label for the reference agent and additionally contains the following statement:

"INFLECTRA (infliximab-dyyb) is biosimilar\* to REMICADE (infliximab) for the indications listed. \* Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

Across the country, legislation governing the use and especially substitution of biosimilars has been moving through state legislatures. These bills and laws vary to some extent but are fairly uniform in that they will allow for the substitution by a pharmacist with a lower cost biosimilar that the FDA has designated as interchangeable. Without interchangeable status, a new prescription must be obtained in order to switch. The laws also establish requirements for notification of the patient and prescribing provider after a substitution has been made. Some states allow notification to be delayed by as much as five business days.

Other features of state legislation have included defining FDA approval, allowing the prescriber to indicate "dispense as written" for the originator product, addressing patient notification and requiring the pharmacist to maintain records on which product was dispensed.

Wholesaler shipment of INFLECTRA began in the United States (U.S.) on November 21, 2016, and the biosimilar can now be ordered from various national and regional wholesalers across the country.

Pfizer holds commercialization rights to Inflectra in the U.S. According to Pfizer,

INFLECTRA is priced at a 15% discount to the current wholesale acquisition cost (WAC) for REMICADE. WAC is not inclusive of discounts to payers, providers, distributors and other purchasing organizations.

How such discounts will impact the price paid by pharmacy benefit managers (or out of pocket expenses for patients) remains to be seen.

An FDA biosimilar overview can be found online at <http://fdabiosimilars.e-paga.com> (1.5 CME hours).

Hotline Author: Kelly Weselman, MD Hotline Editors: Eric Ruderman, MD, Douglas White, MD, PhD, and Angus Worthing, MD. Disclosures: Dr. Weselman, consulting honoraria from UCB. Dr. Ruderman, consulting honoraria from Pfizer. Dr. White, nothing to disclose. Dr. Worthing, consulting honoraria from Abbvie.

The Hotline has been reviewed by the editors, the ACR Executive Committee and the Communications and Marketing Committee.

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