Biosimilar Adoption and Acceptance in Ireland—Still More to Be Done

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KEY POINTS

There was a significant time lag between regulatory approval and clinical acceptance of biosimilar infliximab CT-P13 in Ireland.

In this example from an Irish teaching hospital, the introduction of the biosimilar first to new patients, along with a switching study executed in parallel, helped to raise prescriber confidence.

Increased biosimilar medicine usage is of benefit to all stakeholders including patients, prescribers, healthcare payers, and manufacturers.

BIOSIMILAR OPPOSITION

In 2014, 6 of the top 10 blockbuster medicines were monoclonal antibodies. In recent times, small-molecule chemical entity (SMCE) blockbuster drugs like Viagra® (sildenafil citrate) and Lipitor® (atorvastatin), have been superseded by blockbuster biologics such as Humira® (adalimumab) and Enbrel® (etanercept), demonstrating the newly acquired prominence of biological medicines. However, these large-complex proteins (comprising or derived from living cells or organisms) are more complicated than traditional SMCEs due to their unique manufacturing process. Unlike generic drugs of SMCEs, biosimilar medicinal products (biosimilars) which aim to replicate originator biologic products, have given rise to concerns related to their pharmaceutical quality, safety, and efficacy. For this reason, biosimilars are not considered exact replicas of originator biologic medicines. While this uncertainty can prevent physicians from using biosimilars, this is not a problem for generic drugs of SMCEs. Therefore, knowing when it is most appropriate and timely to implement biosimilars into routine clinical practice can be difficult. In September 2014, a large acute teaching hospital was the first in Ireland to introduce biosimilar infliximab CT-P13 in place of originator brand infliximab (Remicade®), to treat inflammatory bowel disease (IBD).[1] The independent systematic evidence base behind the decision-making process used to introduce biosimilar infliximab in this hospital is one example of how healthcare professionals (HCPs) overcame biosimilar opposition.

> Work that aims to enhance the understanding of biosimilar medicines among stakeholders and to encourage best practice of biosimilar use is being conducted by a collaborative organization of various interested parties.[10]

IRISH CASE STUDY

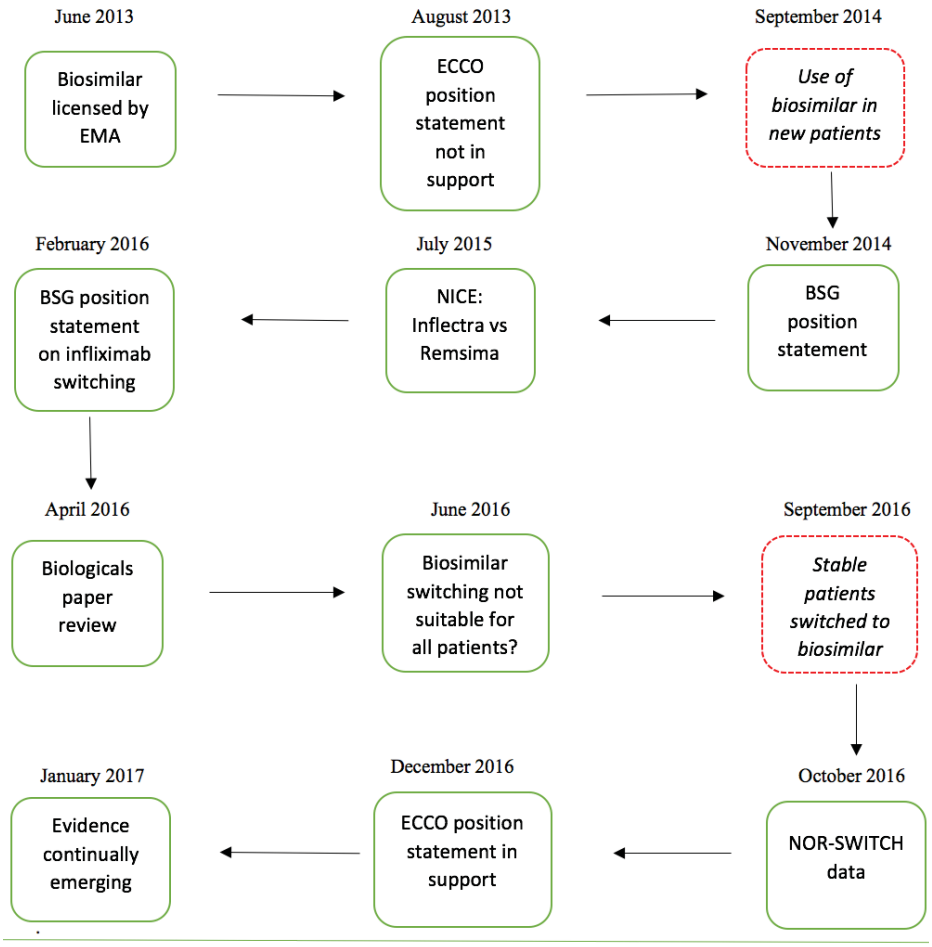
In June 2013, biosimilar infliximab CT-P13 was granted marketing authorization by the European Medicines Agency (EMA) for the same indications as Remicade®. A few weeks afterward, the European Crohn's and Colitis Organisation (ECCO) released a position statement articulating that the use of most biosimilars in patients with IBD should require testing in this particular patient population with comparison to the appropriate innovator product Remicade®, before approval.[2] Contrary to this guidance from the ECCO, the chief pharmacist and consultant gastroenterologist of a large acute Irish teaching hospital decided to introduce biosimilar infliximab CT-P13 for use in new patients in September 2014. Although this new prescribing practice could have been deemed hasty, the British Society of Gastroenterology (BSG) released a position statement 2 months later with updated guidance justifying the introduction of biosimilar infliximab CT-P13 in the clinical setting. During the summer of 2015, the National Institute for Health and Care Excellence (NICE) remarked positively on the topic of biosimilar prescribing. Their report concluded that the EMA was content that the pharmacokinetics, efficacy, safety, and immunogenicity profiles of biosimilars were similar to those of the originator products and concluded that the recommendations for infliximab could apply both to the originator product and its biosimilars.[3]

In February 2016, the BSG updated their previous guidance stating that there was sufficient evidence to recommend that patients who were in stable clinical response or remission on Remicade® therapy, switch at the same dose and dose interval to biosimilar infliximab CT-P13. Despite the position statement from the BSG, this large acute Irish teaching hospital judged that it was premature to switch all of its patients from Remicade® to biosimilar infliximab >

CT-P13. Two months later, a review published in *Biologicals* journal concluded that while prudent switching practices should be employed, growing safety experience accumulated thus far with infliximab CT-P13 and other biosimilars was favorable and did not raise any specific concerns.[4]

In June 2016, *ScienceDaily* published a research article on its website, "Biosimilar switching not suitable for all patients,"[5] based on a study conducted in Spain.[6] At first, the consultant gastroenterologist and chief pharmacist of the hospital thought that this article would counteract previous evidence in favor of switching. However, when examined closely, the study results showed that when antidrug antibodies develop in response to Remicade®, these antibodies also cross-react with biosimilar infliximab CT-P13 as both biologics share structural properties. These findings suggested that antibody-positive patients being treated with Remicade® should not be switched to biosimilar infliximab CT-P13 since these antibodies would also interact with the biosimilar and potentially lead to a loss of response. Despite its misleading title, the results of the Spanish study actually emphasized the similarities between the originator and biosimilar brands of infliximab and reinforced the science behind the safety of switching. At this point, the chief pharmacist and consultant gastroenterologist decided to switch all patients from originator brand infliximab to biosimilar infliximab CT-P13, commencing in September 2016. In October 2016, explorative subgroup analyses of patients with IBD in the NOR-SWITCH study showed similarity between patients treated with originator infliximab and biosimilar infliximab CT-P13 with regard to efficacy, safety, and immunogenicity (The NOR-SWITCH study was one of the first large-scale controlled studies where biosimilar infliximab CT-P13 was tested in patients with IBD).[7] In December 2016, the ECCO released an updated statement revising previous guidelines. One of its prominent recommendations was that switching patients with IBD from the originator brand to a biosimilar product was now deemed acceptable. In this rapidly moving field, the evidence continues to grow supporting the case that biosimilar infliximab CT-P13 is just as safe and effective as the originator biologic (see Figure 1).

Figure 1. Independent systematic evidence base behind the decision-making process to implement biosimilar infliximab CT-P13 in a large acute Irish teaching hospital for the treatment of IBD.



BSG=British Society of Gastroenterology; ECCO=European Crohn's and Colitis Organisation; EMA=European Medicines Agency; IBD=inflammatory bowel disease; NICE=National Institute for Health and Care Excellence. Source: Reference [1].

REGULATORY APPROVAL VERSUS CLINICAL ACCEPTANCE

The decision to treat new patients with and switch existing patients to biosimilar infliximab CT-P13 in this large acute Irish teaching hospital was a multifactorial one underpinned by a robust and extensive evidence-based trial that ultimately convinced prescribing physicians. Biosimilar infliximab CT-P13 was first licensed in June 2013, but prescribers decided to switch patients approximately 3 years later (September 2016). It is therefore evident that there was a significant time lag between regulatory approval and clinical acceptance. In fact, Ireland has the second lowest record of biosimilar use because of Irish HCPs' slow acceptance of biosimilars.[8,9] This is possibly due to a lack of confidence, unwillingness, or knowledge to prescribe biosimilars that is also seen in other European countries. Work that aims to enhance the understanding of biosimilar medicines among stakeholders and to encourage best practice of biosimilar use is being conducted by a collaborative organization of various interested parties.[10]

INTERCHANGEABILITY STATUS

Flixabi®, biosimilar infliximab SB2, received market authorization approximately 3 years (April 2016) after biosimilar infliximab CT-P13. Given its late entry to the Irish market relative to biosimilar infliximab CT-P13, it has been unsuccessful in penetrating this market so far. The chief pharmacist and consultant gastroenterologist of this hospital note that

Table 1. Areas Under Investigation in the Drafting of the Irish Biosimilar National Policy

Prescribing and Interchangeability	By focusing on the remit of biological medicine prescribing, it is hoped that the low uptake of biosimilars in Ireland can be increased
International Biosimilar Medicines Policies	International policies are being examined to decide which policy, if any, could be implemented in the Irish context
Education and Support	Educational programs and support are being researched from the perspectives of the patient, healthcare professionals, and pharmaceutical suppliers
Incentives and Disincentives	Incentives such as gain-sharing agreements and disincentives like patient copayment systems are being analysed
Tendering and Pricing Policies	Internal and/or external reference pricing arrangements as well as the various types of tendering processes used in different countries are being probed for their suitability in the Irish setting
Prevention of Inappropriate Business Practices	In addition to inappropriate business practices previously highlighted, exploration of such professional misconduct is underway

they would not be comfortable switching patients from biosimilar infliximab CT-P13 to biosimilar infliximab SB2 without conducting a comprehensive review of all available evidence, especially evidence from a switching study. This demonstrates that HCPs do not believe that all biosimilars should be subject to the same introduction process into the clinical setting.

IRISH BIOSIMILAR NATIONAL POLICY

The Irish Department of Health (DoH) is in the process of developing a national biosimilar medicines policy which aims to increase biosimilar use by creating a robust framework where biologicals and biosimilars can be used safely, cost-effectively, and confidently in the health service. It is hoped that this policy will address the inter-hospital variation to biosimilar medicine implementation between this teaching hospital and other secondary care settings in Ireland. Table 1 reveals some of the other topics of interest in this policy that are being considered.

COST SAVINGS

Too much money is spent on originator biologics when there are cheaper, equally effective alternatives available. Only 11 biosimilars are currently reimbursable by the Irish healthcare system. This is a concern as over €200 million is spent each year on biologic drugs that already have approved biosimilars or that will have available biosimilars in 2018. It is clear that the potential cost savings from using biosimilars instead of biologicals can be reinvested to increase patient access to other new medicinal products.

REFERENCE PRICING OF ORIGINATOR BIOLOGICS

Reference pricing of biologic products would increase biosimilar usage. Reference pricing of SMCE medicines has already resulted in savings of millions of euro in the Irish primary care setting. This was a powerful initiative to enforce generic substitution of these medicines. In addition, since pharmacists can legally substitute SMCE medicines, Ireland enjoys a high level of generic SMCE medicine market infiltration.

THE PATIENT VOICE

The Irish Platform for Patient Organisations, Science and Industry (IPPOSI) is a patient-led organization in Ireland that works with patients, government, industry, science, and academia to put patients at the heart of health policy and innovation. Its strategy aims to smooth the pathway for new treatments and technologies for unmet medical needs, but it is are also involved in other areas of health like that of biosimilars. In 2017, on behalf of the patients of Ireland, IPPOSI submitted a positive response to the public consultation on the Irish biosimilar national policy. In addition, the Health Products Regulatory Authority (HPRA) in Ireland has launched patient-specific guidance in the form of a leaflet, *Biological and Biosimilar Medicines: What Patients Should Know*, in conjunction with an educational video.

KEY MESSAGE

Undisputedly, increased biosimilar medicine usage is of benefit to all stakeholders: increased access for patients, more treatment options for prescribers, sustainable healthcare budgets for payers, and more business opportunities for manufacturers.

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Additional Information:

For more information on biosimilars in general and on the current Irish biosimilar landscape, please visit: http://gabi-journal.net/biosimilar-infliximab-introduction-into-the-gastroenterology-care-pathway-in-a-large-acute-irish-teaching-hospital-a-story-behind-the-evidence.html.