GAfPA
Global Alliance for Patient Access

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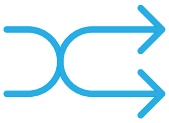
NOR-SWITCH

What will Norway's infliximab switching study tell us about the safety of switching patients from one biologic medicine to a biosimilar?

KEY TAKEAWAYS

Many physicians have questions about the effects of switching patients who are stable on one biologic medicine to a biosimilar.



NOR-SWITCH is a randomized, double blind study designed to evaluate the effects of switching patients once from the original biologic infliximab (Remicade®) to a biosimilar version (Remsima®) across six inflammatory diseases.

Data from this study may help define policies that govern switching, but it is important that policymakers understand what the data from this study will show and then develop policies accordingly.

BIOLOGIC AND BIOSIMILAR SWITCHING

The availability of biosimilars has the potential to increase the number of patients who can receive life-changing medicines. As biosimilars have become more widely used, one question that has arisen is: how does switching to a biosimilar affect patients who are stable on the original biologic? Physicians may question whether the switch may either cause an adverse reaction or adversely stimulate a patient's immune system, which may neutralize the medication and prevent it from providing clinical benefit. This, in turn, could narrow a patient's treatment options, since they may no longer respond to either the biosimilar or the original biologic.

This is of particular interest for one of the more recently approved biosimilars, infliximab.[1] Infliximab treats a range of inflammatory diseases, including those affecting the joints (rheumatoid arthritis), skin (plaque psoriasis), and bowel (inflammatory bowel disease). Infliximab is a monoclonal antibody, one of the largest and most complex types of biologic medicines.

SWITCHING, *a definition*

The treating physician switches one medicine for another with the same therapeutic intent in patients who are undergoing treatment. This can happen as a result of physician's choice, or may be dictated by a hospital, insurance company, or government policy.

Monitoring the effects of switching with this class of medicine compared with other biosimilars is important for two reasons: 1) infliximab may be more likely than other biologic medicines to stimulate a patient's immune system; 2) patients with the illnesses treated with infliximab eventually stop responding to the medicine as part of the normal course of their illness. Thus, for a patient who stops responding to treatment, it is may be difficult to determine whether this is as a result of a medication switch, or the natural progression of the disease.

WHAT ARE BIOLOGICS AND BIOSIMILARS?

Biologic medicines are used to treat many serious illnesses such as cancer, multiple sclerosis, and arthritis. Biologics are often made from tissue or living cells grown in a laboratory, and are large, complex molecules.

Because of this complexity, and the fact that they are made from living systems, identical copies of biologic drugs are not possible. Therefore, products created by manufacturers attempting to copy a biologic are called biosimilars.

Policymakers have established biosimilar guidelines and policies to ensure their safe prescribing and use. These include policies that ensure biosimilars and biologics have distinguishable names, enabling every member of the healthcare team to identify which medicine a patient has received; or requirements that a biosimilar product label has clear and complete information to facilitate clinical decision making.

[1]A biosimilar to infliximab (Remsima®) was approved for use in Europe in 2013, in Colombia in 2014, in Brazil and Venezuela in 2015, and in the US in 2016. Information on Remsima® is available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002576/human_med_001682.jsp&mid=WC0b01ac058001d124

WHY DOES SWITCHING MATTER?

Governments around the world are under pressure to reduce healthcare spending. One way this can occur is as a result of Europe's tender system, whereby a country's government invites bids from companies manufacturing medicines with the same active ingredient. Each company submits the price at which it is willing to sell its medicines, and the one with the lowest price often wins the right to sell the medicine to that country for a given period of time.

For the most part, where biosimilars have won the tender, the hospital does not force patients who are stable on one biologic medicine to switch to the biosimilar. All new (treatment-naïve) patients, however, will be started on the biosimilar. That said, many governments would like to expand these policies to switch all patients and thereby further reduce costs if such a switch was safe and medically appropriate.

While switching all patients to a biosimilar could reduce costs, some physicians are concerned about policies that necessitate wholesale switching of patients from one biologic to a biosimilar, without data to support the safety of such an approach. Currently, there are limited data available that enable an evaluation of the effects of a single switch from originator to biosimilar infliximab. No studies have examined the effects of multiple switches; it is a concerning possibility that a patient may be switched among multiple different biosimilars within the same product class during the course of his or her illness. The studies that do exist are either retrospective in nature, have a small sample size, do not have a randomized design, or are not sufficiently powered to enable definitive conclusions.[1-6]

WHAT IS NOR-SWITCH?

A biosimilar infliximab (Remsima®) was approved in Europe in 2013 and awarded the tender in Norway in both 2014 and 2015.[2] The Norwegian government wanted to assess the impact of switching patients who were stable on the original biologic to the biosimilar, and therefore funded NOR-SWITCH to evaluate this across all six inflammatory diseases for which infliximab is approved. The study was designed by a multidisciplinary and multiregional project group with special competence in performance of strategy trials, immunogenicity, and statistics led by Professor Tore Kvien at the Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway. Additionally, the group consisted of representatives from the three relevant patient organizations.

The study compares outcomes between those who undergo a single switch to the biosimilar and those who remain on the original biologic. Cost effectiveness will also be evaluated based on purchase price to the health authorities. The key elements of the study are summarized on the next page.

[2]The website for the Norwegian tender system is www.lisnorway.no.

This lack of data prompted the Norwegian government to fund a clinical trial to evaluate the effects of switching patients from an originator biologic infliximab to a biosimilar version.

UNDERSTANDING NOR-SWITCH: KEY STUDY DETAILS

Randomized, double-blind study to evaluate the effects of switching patients who are stable on the original biologic (Remicade®) to the biosimilar (Remsima®) across six inflammatory diseases.

A total of 481 enrolled patients at 40 sites across Norway (19 in gastroenterology, 16 in rheumatology and 5 in dermatology) between October 2014 and June 2015

- **247 patients with inflammatory bowel disease** (155 with Crohn's disease, 93 with ulcerative colitis)
- **199 patients with inflammatory joint disease** (78 with rheumatoid arthritis, 91 with spondyloarthritis, and 30 with psoriatic arthritis)
- **35 patients with plaque psoriasis**

Patients who were stable on the original biologic either remained on the original biologic or were switched once to the biosimilar (randomized 1:1).

Patients were followed for 1 year, after which they could roll over into a 6-month open extension study, where everyone received the biosimilar. This meant that everyone in the study switched medicines once, either at the study start, or at the start of the extension phase.

An extensive biobank has been acquired. Serum samples were collected from each patient at every visit, and a complete blood sample for every patient was collected at the study start. This will enable an evaluation of whether or not the switch to the biosimilar has stimulated a patient's immune system, and whether or not the immune system has been activated to neutralize the medicine.

The effects of the switch on disease worsening, disease-specific outcomes, safety, immunogenicity, and cost-effectiveness will be analyzed.

Data will be available at United European Gastroenterology Week, 15-19th October, 2016 in Vienna, then at the American College of Rheumatology annual meeting 11-16th November, 2016 in Washington.

Results of the extension study will be available in spring 2017.

More information on the study can be found at **www.clinicaltrials.gov** (NCT 02148640)

WHAT WILL DATA FROM NOR-SWITCH SHOW?

It is helpful to understand what conclusions can be drawn from the NOR-SWITCH study.

NOR-SWITCH will provide information as to whether patients can safely switch once from the original biologic to the biosimilar. The study does not evaluate the potential clinical scenario of switching multiple times or switching among different biosimilars within a product class.

The effects of the switch will be evaluated by combining the disease worsening outcomes from 481 patients across all six diseases studied. Some have questioned whether this approach will limit the ability to draw firm conclusions as to the effects of the switch, since each illness is very different with regard to duration of response and clinical measures.

The study is not powered to provide definite conclusions about the effects of the switch within each specific disease. For example, it may be hard to say with any certainty whether or not the switch hastens the time to disease worsening in patients with psoriatic arthritis, as there are only 30 patients with this disease enrolled in the study. However, results within each disease will be provided as secondary outcomes.

NOR-SWITCH **WILL** SHOW	NOR-SWITCH **WILL NOT** SHOW
✓ Whether or not patients can be switched once from the original biologic to the biosimilar without: • Increased occurrence of disease worsening, or • Increased incidence of the most frequently occurring adverse events.	✗ The effects of a single switch from the original biologic to other biosimilars not evaluated in this study.
✓ Results from a pooled population of patients with Crohn's disease, ulcerative colitis, rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, and psoriasis.	✗ Definitive data on the effects of a single switch in the individual diseases studied.
✓ Whether or not patients can be switched once from the original biologic to the biosimilar without stimulating a patient's immune system.	✗ The effects of multiple switches. For example, from the original biologic to a biosimilar, then to a different biosimilar, etc.
✓ Whether or not the immune system is neutralizing the effects of the medicine.	✗ The effects of switching in different diseases treated with other biologics and biosimilars not studied in NOR-SWITCH.
	✗ The effects manifesting beyond the study treatment period.

POLICY IMPLICATIONS OF NOR-SWITCH DATA

What remains to be determined is how data from NOR-SWITCH will impact health policy. Will data from this study be used inappropriately to justify policies that mandate:

- Switching of any biosimilar within a class?
- Multiple switches over the course of a treatment period?
- Switching in any disease where biosimilars are available?

In short, will data from this study be inappropriately applied to support polices deemed financially advantageous without regard for clinical implications and patient safety?

We believe that policies concerning switching between biologics and biosimilars must be equally safe and efficacious – and supported by data. Finally, decisions about switching between biologics and biosimilars should remain in the hands of the treating physician and his or her patient.

The results from the NOR-SWITCH study create an opportunity to engage policymakers on the topic of switching and the importance of data to support switching policies.

We believe that **decisions about switching** should remain in the hands of the treating physician and his or her patient.

Education to facilitate an understanding of the issues is critical for physicians and patients, if they are to become advocates for appropriate biosimilar policies. Patients often have the loudest voice when it comes to influencing policies that affect their care, and advocacy around biosimilar policies will be no exception. Physicians must take an active role in educating their patients concerning policies affecting access to biologics and biosimilars.

In conclusion, the availability of biosimilars represents an unprecedented opportunity to reduce healthcare costs and expand treatment options. Studies like NOR-SWITCH are important in providing data to inform policies that govern their safe use. It is important, however, that all stakeholders understand what the data do and do not show, so that patients can benefit from biosimilars' appropriate use.

GAFPA'S PHYSICIANS WORKING GROUP MEETING ON NOR-SWITCH

On June 13, 2016, the Global Alliance for Patient Access convened a working group of leading clinicians in the fields of gastroenterology, rheumatology and dermatology; pharmacologists; researchers; and patient advocates to gain an understanding of the NOR-SWITCH study and the implications of data from this study on the clinical use of biosimilars.

Clinical coordinators for the study, Dr. Guro Lovik Goll (rheumatology) and Dr. Kristin Kaasen Jorgensen (gastroenterology), presented an overview of the study and discussed the study design with participants.

Participants discussed the implications of data from the study on patients, physicians and policymakers around the world.

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