

# Infusion reaction to infliximab biosimilar after transitioning from infliximab



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**Key words:** biosimilar; hidradenitis suppurativa; infliximab; infusion reaction.

## INTRODUCTION

Infliximab (IFX) (Remicade, Janssen Biotech Inc., Horsham, Pennsylvania) is a monoclonal antibody against tumor necrosis factor-alpha. It is currently approved by the United States Food and Drug Administration for treating rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, and inflammatory bowel disease. Recently, it has also been used as an off-label treatment for hidradenitis suppurativa (HS). Grant et al<sup>1</sup> outlined a significant improvement in HS disease severity among patients who received IFX therapy. IFX biosimilars, including infliximab-dyyb (Inflectra, Pfizer, New York City, New York), demonstrate a similar safety and efficacy profile as the original IFX product in patients with a variety of chronic inflammatory conditions.<sup>2-4</sup> However, there is a paucity of data examining patients, including those with HS, and how they responded to the IFX biosimilar in comparison with how they responded to IFX, especially with regard to side-effects data. We present a case report of a patient who experienced an infusion reaction after switching from IFX to the biosimilar.

## CASE REPORT

A 50-year-old Black woman with a past medical history significant for diabetes mellitus and morbid obesity presented for management of her HS. HS was Hurley stage III and predominantly affected the groin and buttocks. Prior and current treatments for HS included neodymium-doped yttrium aluminum garnet laser, wide local surgical excision, carbon dioxide laser excision, various oral and intravenous antibiotics, and IFX infusions. IFX was administered at 5-8 mg/kg every 6 weeks for 7 years with good

### Abbreviations used:

ADA: antidrug antibodies  
 HS: hidradenitis suppurativa  
 IFX: infliximab

control of HS and no adverse reactions. However, due to insurance coverage, the patient was switched to the IFX biosimilar at 6 mg/kg every 6 weeks. Within a few weeks of switching from IFX to the biosimilar, the patient noticed the onset of minor muscle aches and paresthesias, which would persist for a couple of days following each infusion. The severity of symptoms worsened with each subsequent infusion over 5 months with the eventual development of full-body arthralgias and paresthesias affecting the hands. Antibodies against IFX were obtained (from Mayo Clinic Laboratories, Rochester, Minnesota) due to concern for worsening infusion reactions and were elevated at 946 U/mL (reference value < 50 U/mL). The patient experienced anaphylaxis-like symptoms with her subsequent infusion, including throat tightening with associated nasal congestion and flu-like symptoms within 30 minutes of infusion initiation. The medication was immediately discontinued, and administration of an oral antihistamine led to resolution of the symptoms. The patient was then switched back to IFX, which she initially tolerated; however, she started experiencing similar infusion reactions after the second infusion. The patient was prescribed acetaminophen, diphenhydramine, and prednisone for preinfusion treatment and a 5-day course of prednisone post infusion if she experienced a reaction during the treatment. However, even with the

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Funding sources: None.

IRB approval status: Not applicable.

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JAAD Case Reports 2021;8:77-9.

2352-5126

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<https://doi.org/10.1016/j.jidcr.2020.12.011>

medications, she continued to experience significant adverse side effects. Currently, she is in the process of switching biologics, given her continued infusion reaction symptoms to IFX.

## DISCUSSION

The IFX biosimilars have been shown to be noninferior to IFX in terms of efficacy for psoriasis and other indications.<sup>2</sup> Previous randomized controlled trials have outlined a similar frequency of adverse events between switching to an IFX biosimilar or continuing treatment with IFX.<sup>3,4</sup> In contrast, here we report a case of an infusion reaction after switching from IFX to a biosimilar in a patient receiving treatment for HS, where IFX had previously been tolerated well.

Infusion reactions are immunologic reactions classified based on the timing and severity of symptoms and are not uncommon with the administration of IFX. Immediate infusion reactions often occur during or within 1-2 hours post infusion, while delayed infusion reactions often occur >24 hours after infusion.<sup>5</sup> Nausea, vomiting, chest pain, and dyspnea are common manifestations. The etiology of these reactions is not entirely understood, but some associations have been discovered. The presence of antidrug antibodies (ADA) predicts the development of these reactions among patients receiving IFX infusions.<sup>6</sup> ADA generally consists of immunoglobulin antibodies targeting the Fab fragment of the medication.<sup>7</sup> Consequently, ADA can increase immunogenicity and, thus, adverse reactions, due to the formation of IFX-ADA complexes, which activate complement and subsequently lead to infusion reactions.<sup>5</sup>

Aggregates form when 2 or more proteins assemble into stable complexes triggered by environmental stressors such as heat, oxidizing substances, or a change in pH that causes structural changes and subsequent protein misfolding or alteration.<sup>8</sup> The IFX biosimilar contains a slightly higher level of aggregates than IFX, which increases immunogenicity, and has been implicated in eliciting immune responses and infusion reactions.<sup>5,9</sup> Further, these insoluble aggregates can inherently illicit an immune response via dendritic cell activation and subsequent cytokine release.<sup>8</sup> Triggering these adaptive immune responses enhance the production of ADA, which further increases immunogenicity.<sup>8</sup> Previous studies have outlined that antibodies to IFX can recognize and crossreact with the IFX biosimilar and vice versa, indicating immunogenic similarity and sharing of immunodominant epitopes between these 2 agents.<sup>7</sup> Additionally, it has been found that in patients being treated for rheumatoid

arthritis, the presence of ADA to IFX increases the likelihood of developing ADA to adalimumab and, subsequently, to other biologics.<sup>10</sup> Thus, the development of additional ADA specific to IFX after switching from the biosimilar would be likely. These differences could explain why this patient developed a reaction to the biosimilar after switching from IFX and why the infusion reaction was sustained after switching back from the biosimilar.

In conclusion, we report a case of an infusion reaction following a switch from IFX to a biosimilar in a patient with HS. When switching from IFX to biosimilars, even if IFX was previously tolerated, clinicians should be aware and should monitor for symptoms of infusion reactions. These reactions have also been reported with IFX infusions after patients have tolerated treatment for several years. However, the sudden onset of an infusion reaction is an event that should be evaluated. Further studies are needed to elucidate these reactions' exact etiologies, develop appropriate preventative testing, and optimize patient selection. These must be balanced against the public health need for cost-effective treatment options for HS.

## Conflicts of interest

Drs Lyons and Narla are subinvestigators for Lenicura and General Electric. Dr Hamzavi has been an investigator for Lenicura and General Electric, is a consultant for Incyte, is on AbbVie advisory board (noncompensated), and is the current president of the Hidradenitis Suppurativa Foundation (noncompensated). Author Kashlan has no conflicts of interest to declare.

## REFERENCES

- Grant A, Gonzalez T, Montgomery MO, Cardenas V, Kerdel FA. Infliximab therapy for patients with moderate to severe hidradenitis suppurativa: a randomized, double-blind, placebo-controlled crossover trial. *J Am Acad Dermatol*. 2010; 62(2):205-217.
- Jørgensen KK, Olsen IC, Goll GL, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial. *Lancet*. 2017;389(10086):2304-2316.
- Park W, Hrycaj P, Jeka S, et al. A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. *Ann Rheum Dis*. 2013;72(10):1605-1612.
- Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis*. 2013;72(10):1613-1620.
- Lichtenstein L, Ron Y, Kivity S, et al. Infliximab-related infusion reactions: systematic review. *J Crohns Colitis*. 2015;9(9): 806-815.

6. Balint A, Rutka M, Végh Z, et al. Frequency and characteristics of infusion reactions during biosimilar infliximab treatment in inflammatory bowel diseases: results from Central European nationwide cohort. *Expert Opin Drug Saf.* 2017;16(8):885-890.
7. Hindryckx P, Novak G, Vande Castele N, et al. Incidence, prevention and management of anti-drug antibodies against therapeutic antibodies in inflammatory bowel disease: a practical overview. *Drugs.* 2017;77(4):363-377.
8. Morgan H, Tseng SY, Gallais Y, et al. Evaluation of in vitro assays to assess the modulation of dendritic cells functions by therapeutic antibodies and aggregates. *Front Immunol.* 2019; 10:601.
9. European Medicines Agency. Assessment Report: Inflectra; INN: infliximab. Procedure No. EMEA/H/C/002778/00002013. Accessed December 21, 2020. Available at: [https://www.ema.europa.eu/en/documents/assessment-report/inflectra-epar-public-assessment-report\\_en.pdf](https://www.ema.europa.eu/en/documents/assessment-report/inflectra-epar-public-assessment-report_en.pdf)
10. Benucci M, Grossi V, Manfredi M, et al. Laboratory monitoring of biological therapies in rheumatology: the role of immunogenicity. *Ann Lab Med.* 2020;40(2):101-113.