

Infusion-related angioedema associated with infliximab-abda: Case report

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Purpose. A case of infusion-related angioedema associated with the use of an infliximab biosimilar (infliximab-abda) is reported in order to bring awareness that this adverse effect is still highly possible in biosimilars, similar to the reference infliximab biologic.

Summary. A 37-year-old white male with a past medical history significant for ileocolonic fistulizing Crohn's disease, depression, and gastroesophageal reflux disease (GERD) presented to an emergency department with shortness of breath, urticaria, and tongue swelling that had developed shortly after initiation of an infusion of infliximab-abda. The patient had no documented allergies at the time of presentation. The patient was taking oral budesonide 9 mg daily and oral azathioprine 50 mg daily for treatment of Crohn's disease. Other medications included oral omeprazole 40 mg every morning for GERD and oral sertraline 100 mg daily for depression. The patient's tongue swelling worsened, and he was intubated for airway protection. The patient received supportive care treatment for angioedema with intravenous (IV) dexamethasone 8 mg every 8 hours, IV diphenhydramine 50 mg every 8 hours, and IV famotidine 20 mg every 12 hours. He was extubated approximately 43 hours later and observed overnight in a medical intensive care unit. He was transferred to a general medicine unit the next day for further care. The total hospital length of stay was 4 days.

Conclusion. A 37-year-old man developed infusion-related angioedema with use of infliximab-abda. Discontinuation of the biosimilar product along with supportive care brought about resolution of angioedema. There are no prior published reports of infusion-related angioedema reactions secondary to infliximab-abda use.

Keywords: angioedema, biosimilar, Crohn's disease, infliximab, infliximab-abda

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Tumor necrosis factor α (TNF- α) inhibitors are used in the treatment of various chronic inflammatory diseases. Infliximab-abda (Renflexis, Merck) is a TNF- α inhibitor that is approved by the US Food and Drug Administration (FDA) as a biosimilar to infliximab (Remicade, Janssen Biotech).¹ Infliximab-abda is approved for the same indications as infliximab, which are adult and pediatric Crohn's disease, ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.¹ TNF- α is a key cytokine that contributes to inflammatory diseases.² TNF- α has been shown to be an important proinflammatory mediator in

many acute and chronic inflammatory processes.³ TNF- α recruits circulating inflammatory cells to local tissue sites of inflammation to induce edema and activate coagulation pathways, and it can play a pivotal role in granuloma formation.³

Infliximab was introduced in 1998 and was revolutionary in the treatment of many inflammatory diseases.⁴ Over the years, infliximab use has been associated with adverse events such as infection, malignancy, and infusion reactions.⁴ The incidence of infusion reactions and hypersensitivity with infliximab use is 5% to 10%. The development of antibodies to infliximab increases the risk of these reactions.⁵

For one of the 4 currently marketed infliximab biosimilars, infliximab-abda, there are currently no published reports of infusion reactions, such as anaphylaxis or angioedema; those reactions have been reported with use of the reference product. The etiology and pathogenesis of these reactions is not well defined, and characterization of their allergic/immune nature is often inconsistent.⁴ However, it is thought that the introduction of monoclonal antibodies can cause the immune system to react to these foreign antigens and cause the production of specific antibodies that lead to the induction of anaphylactic-like reactions or angioedema.⁵ Here we report a case of development of infusion-related angioedema in a patient treated with infliximab-abda and discuss the potential safety issues surrounding this biosimilar product.

Patient case

A 37-year-old white male presented to an emergency department (ED) with respiratory symptoms, urticaria, and tongue swelling after receiving a partial dose of infliximab-abda at a gastroenterology (GI) clinic. The patient had a past medical history significant for ileocolonic fistulizing Crohn's disease, depression, and gastroesophageal reflux disease. His surgical history included the placement and later removal of hardware from his right ankle and an exploratory laparotomy. He weighed 92 kg and was 170 cm tall. There were no documented allergies at the time of presentation. In addition to receiving infliximab-abda, the patient was also taking oral budesonide 9 mg daily and oral azathioprine 50 mg daily for treatment of Crohn's disease. Other medications included oral omeprazole 40 mg every morning for gastroesophageal reflux disease and oral sertraline 100 mg daily for depression.

The patient's Crohn's disease had been diagnosed about 16 years previously. At another institution, he had received treatment with adalimumab, but it was discontinued due to development

Key Points

- The labeling of infliximab carries warnings of infusion-related reactions, including the severe reaction of angioedema, often requiring premedication prior to administration.
- Many new biosimilars to infliximab have seen increased use to yield cost savings for the healthcare system and carry similar risks of infusion-related angioedema.
- This is the first case report of infusion-related angioedema associated with use of an infliximab biosimilar, infliximab-abda.

of antibodies to the medication. After discontinuation of adalimumab, the patient had been initiated on infliximab, but that medication had since been discontinued for unknown reasons. Of note, per the available records he had never experienced any adverse reactions while taking infliximab, nor was there documentation of antibodies to infliximab. The first dose of infliximab-abda had been administered 2 weeks prior to the patient's arrival at the ED, with no reported complications. He had begun azathioprine therapy 1 month previously.

The patient had presented to the GI clinic to receive an infusion of infliximab-abda 450 mg/250 mL. This dose, which was appropriate based on his weight of 92 kg and recommended dosing for Crohn's disease (5 mg/kg), was the same dose he had received 2 weeks previously, and he had received no premedication prior to either infusion. The infusion rate and protocol can be found in [Box 1](#). He had received less than 50 mL of the infusion before developing generalized pruritus with a dry throat but no wheezing, oxygen saturation of 97% on room air, and mild erythema on his neck. In the GI clinic

he had received oral diphenhydramine 50 mg and was immediately transferred to the ED. Upon arrival to the ED, he had developed shortness of breath, urticaria, and tongue swelling. There were no other systemic symptoms or further symptoms of angioedema present. His vital signs included a blood pressure of 136/88 mm Hg, heart rate of 98 beats per minute, respiratory rate of 18 breaths per minute, and a temperature of 36.2°C. The first set of laboratory data obtained included results of a comprehensive metabolic panel, complete blood count, and International Normalized Ratio. There were no significant laboratory abnormalities except for a slightly below normal hemoglobin concentration of 12.9 g/dL, which was consistent with previously documented baseline values. No inflammatory markers were assessed. Single doses each of intravenous (IV) famotidine 20 mg and IV methylprednisolone 125 mg were given in the ED. The medical intensive care unit (MICU) team was called to evaluate the patient for admission. The patient was sitting up in a chair and able to speak complete sentences; however, his voice became muffled. The otolaryngologist at the bedside noted worsening in tongue swelling since the patient's initial examination, and a decision to intubate for airway protection was made. The patient received supportive care treatment for angioedema with IV dexamethasone 8 mg every 8 hours, IV diphenhydramine 50 mg every 8 hours, and IV famotidine 20 mg every 12 hours. These medications were continued until the time of discharge. He was extubated approximately 43 hours later and watched overnight in the MICU for observation. He was transferred to a general medicine unit the next day for further care. The total hospital length of stay was 4 days.

The patient was seen in the GI clinic for follow-up 5 days after discharge from the hospital, and no acute problems other than mild abdominal pain were reported. Oral budesonide 9 mg daily and oral azathioprine 50 mg daily were continued. At a 10-week follow-up

Box 1. Medication Protocols**Infliximab-abda administration protocol**

- 40 mL/h for 15 minutes; if tolerated, increase to:
- 80 mL/h for 30 minutes; if tolerated, increase to:
- 160 mL/h for remaining duration of infusion, for a total infusion time of 2 hours, plus 15 minutes for appropriate flushing of IV tubing

Premedication protocol (to be administered 30 minutes prior to infusion)

- Acetaminophen 650 mg orally once
- Diphenhydramine 50 mg IV once
- Methylprednisolone 125 mg IV once

GI clinic visit, no acute problems were reported except for mild abdominal pain. Budesonide therapy was tapered to 6 mg daily, and the azathioprine dosage was increased to 100 mg daily.

Using the adverse reaction probability scale of Naranjo et al,⁶ we assigned this case a score of 6, which suggested a probable adverse reaction to infliximab-abda. The case was reported to FDA's MedWatch program. Additionally, infliximab-abda was listed in the patient's medical record as a documented allergen whose use resulted in life-threatening angioedema.

Discussion

Infliximab has been used worldwide for over 20 years for inflammatory diseases such as irritable bowel disease, Crohn's disease, rheumatoid arthritis, and psoriatic arthritis. Introduction of the first form of infliximab was a breakthrough in treatment of Crohn's disease; however, its administration has a well-documented association with acute infusion reactions.⁷ Infliximab is a chimeric monoclonal antibody with higher immunogenicity than humanized monoclonal antibodies. Acute infusion reactions have been reported to occur in about 1% to 6% of infliximab infusions and 5% to 27% of infliximab-treated patients. Reactions range from mild reactions such as fever, chills, dyspnea, pruritus, and urticaria to severe reactions such as anaphylaxis,

convulsions, and hypotension.⁸ Since 2016, 4 infliximab biosimilars have been approved by FDA: infliximab-dyyb (Inflectra, Pfizer), infliximab-qbtx (Ixifi, Pfizer), infliximab-axxq (Avsola, Amgen), and infliximab-abda (Renflexis). The labeling of the biosimilars carries the same warnings regarding infusion reactions as the reference product.⁹

Angioedema is an abrupt swelling of the skin, mucous membrane, or both that can include tissues of the respiratory and gastrointestinal tracts. Swelling of the larynx, pharynx, and tongue may also occur.¹⁰ Angioedema is the consequence of a local increase in permeability of subcutaneous or submucosal capillaries and postcapillary venules causing local plasma extravasation in response to mediators such as histamine and bradykinin.¹¹ The swelling can last up to 72 hours. Our patient presented with urticaria prior to the development of angioedema, which is not uncommon; as many as 40% of patients with urticaria may also experience angioedema.¹⁰ Idiopathic angioedema and urticaria associated with Crohn's disease have been well described. While management remains unclear, given the similarities between cytokine derangements in idiopathic angioedema and urticaria and those associated with Crohn's disease, medications that target these cytokines should be effective in both situations.^{12,13} While

such idiopathic reactions can possibly occur coincidentally in patients with Crohn's disease taking TNF- α inhibitors, we believe that in our patient this was unlikely, given the sudden onset of symptoms and the patient reporting that he had never before developed angioedema.

The exact etiology and pathogenesis of infusion reactions to infliximab are often unclear, and findings regarding their allergic/immune nature are inconsistent. The lack of a mechanism-based rationale for prevention, combined with the absence of adequate, well-controlled studies, has led to the use of diverse empirical administration protocols, often involving preventative medications.⁴ In the case described here, our patient did not receive any preventative medications prior to receiving an infusion of infliximab-abda. The angioedema was severe enough to require intubation and mechanical ventilation for about 43 hours. The administration of famotidine, dexamethasone, and diphenhydramine, in addition to supportive care, brought about a resolution of angioedema.

It was written in the medical record that our patient had previously developed antibodies to adalimumab. It was not documented in the medical record that our patient had developed antibodies to infliximab, even though he had previously received the reference product. Our patient had been using azathioprine and infliximab-abda concomitantly for approximately 2 weeks. While that is a relatively brief period of time, it has been discussed that concomitant use of TNF- α inhibitors and thiopurine immunomodulators can reduce the development of antidrug antibodies to TNF- α inhibitors.¹⁴ This strategy has become the standard to increase response to TNF- α inhibitors and reduce immunogenicity. However, in clinical practice many patients are switched to TNF- α inhibitor monotherapy after 6 to 12 months to prevent potential toxicity such as development of lymphoma.¹⁵

Immunogenicity of biosimilars to their respective reference products should be considered as a possible contributing factor in the case reported here. Biosimilars are considered to be too complex and heterogeneous to be completely characterized; therefore, a reference product and its biosimilar could never be shown to be identical, only highly similar. In clinical studies conducted as required by the FDA biosimilars approval pathway, immunogenicity always should be evaluated. Data from European Public Assessment Reports available on the European Medicines Agency website confirm that while there are always small differences between biosimilars and reference products, these differences have no apparent impact on immunogenicity, which has proved to be comparable in all cases.¹⁶ Specifically for infliximab, a systematic review found that no clinically significant differences in the immunogenicity of biosimilars and reference products have been reported in “one-way” switching studies; however, whether multiple switches pose a risk of immunogenicity remains unclear.¹⁷ We can infer that differences in immunogenicity between the reference product and biosimilar likely had little to no contribution to our patient’s adverse reaction.

Alternative biologic therapies might have been considered for treatment of Crohn’s disease in our patient. While he was continued only on azathioprine and budesonide at postdischarge follow-up, there are future biologic therapy considerations. Some options would be an alpha 4 beta 7 ($\alpha 4\beta 7$) integrin receptor antagonist, such as vedolizumab; an interleukin-12/23 antagonist, such as ustekinumab; or the third TNF- α inhibitor approved by FDA for treatment of Crohn’s disease, certolizumab pegol.¹⁸ For patients who experience life-threatening angioedema, clinicians should use extreme caution when considering a retreat of another biosimilar of the same reference molecule. In patients for whom all treatment options have been exhausted, another consideration

would be desensitization to infliximab. This approach, which has been previously described as effective in a small number of patients, involves administration of desensitizing doses starting at 0.1 mg/mL and increasing up to the full treatment dose over 4 to 6 hours.¹⁹ If this treatment option is pursued, it should be carried out under close medical supervision with emergency medication (on a crash cart) available at the bedside for use in the event of a reaction.

Infusion-related angioedema is a medical emergency. Given FDA’s efforts to expedite approval of biosimilars and the major cost savings these products offer (spending on biosimilars is expected to reduce direct spending on biologic drugs by an estimated \$54 billion during the period 2017-2026), their use will only continue to increase.²⁰ It is pivotal that clinicians are aware that these reactions can occur not only with use of infliximab but also with use of infliximab biosimilars. Early detection is essential for appropriate therapeutic intervention as it can save lives and help prevent these reactions from becoming life-threatening. Treatment should involve discontinuation of the offending biosimilar and supportive care, including use of antihistamines and corticosteroids. Development and implementation of premedication protocols including acetaminophen, antihistamines, and corticosteroids like those used for infliximab should likely be used for infliximab-abda infusions as well. An example of such a premedication protocol can be found in [Box 1](#). Further studies to increase knowledge and understanding of the infusion-related reactions described here are needed.

Conclusion

A 37-year-old man who had been treated with infliximab-abda presented with infusion-related angioedema that required intubation and intensive care. The reaction completely resolved after discontinuation of infliximab-abda and provision of

supportive care. To our knowledge, this is the first case report describing infusion-related angioedema associated with use of infliximab-abda.

Disclosures

The authors have declared no potential conflicts of interest.

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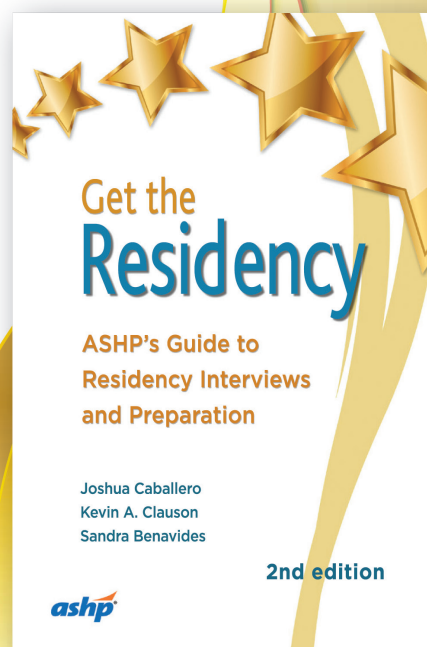
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