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CASE REPORT | INFLAMMATORY BOWEL DISEASE

Hypersensitivity to IV Ustekinumab but Tolerance to Subcutaneous Ustekinumab in a Patient With Crohn's Disease

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ABSTRACT

Ustekinumab is a monoclonal antibody against the p40 subunit of interleukin (IL)-12 and IL-23 and is US Food and Drug Administration (FDA)-approved for plaque psoriasis, moderately to severely active Crohn's disease, and ulcerative colitis. We describe a case of an immediate hypersensitivity reaction to ustekinumab infusion with no reaction to subsequent ustekinumab subcutaneous maintenance therapy. We identify ethylenediaminetetraacetic acid as a unique excipient found in the intravenous formulation compared with the prefilled syringe used for subcutaneous injections, which is likely to account for this observation. No similar cases have been reported in the literature.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disease of the gastrointestinal tract. Patients with moderately to severely active disease are treated with glucocorticoids, immunosuppressants, and biological therapies. However, many of these therapies are associated with increased risk of infections, malignancies, and other adverse events.[1–5] Ustekinumab, a monoclonal antibody that inhibits the activation of interleukin (IL)-12 and IL-23 by blockade of the p40 subunit, is US Food and Drug Administration (FDA)-approved for plaque psoriasis, moderately to severely active CD, and most recently, ulcerative colitis. Studies in both psoriasis and CD have demonstrated ustekinumab's favorable safety profile, which is not associated with an increased risk of infections or malignancies and low prevalence of immunogenicity.[6–8] The induction dose for CD is an initial weight-based intravenous (IV) loading dose, followed by subcutaneous (SC) injections for maintenance. We describe a case of an immediate hypersensitivity reaction to ustekinumab infusion with clinical efficacy and no reaction to subsequent ustekinumab SC maintenance therapy.

CASE REPORT

A 26-year-old woman with a history of ileocolonic and perianal CD who previously underwent proctocolectomy with end ileostomy presented with oral ulcers and dysphagia. She was found to have active oral and esophageal CD. Her medical history included intolerance or inadequate response to infliximab (anaphylaxis), adalimumab with methotrexate (leukopenia), vedolizumab, certolizumab pegol, and off-label tofacitinib. She was prescribed ustekinumab at Crohn's dosing (260 mg IV followed by 90 mg SC q8w). At the time of IV loading infusion, she developed tachycardia, flushing, throat tightness, and difficulty breathing. Diphenhydramine 50 mg IV and methylprednisolone sodium succinate 100 mg IV were administered with rapid resolution of symptoms. A ustekinumab serum level obtained at day 50 postinfusion was 0.1 μg/mL without the presence of antidrug antibodies. We compared the list of excipients found in the IV formulation compared with the prefilled syringe used for SC injections and noted specifically that ethylenediaminetetraacetic acid (EDTA) was found to be in the infusion but not in the SC therapy (Table 1). The patient subsequently self-administered her first SC dose of ustekinumab and had no hypersensitivity reaction. EDTA was subsequently listed in her medical chart as an allergen. Her Crohn's-related oral and esophageal symptoms dramatically improved and has maintained deep remission at the 3-year follow-up.

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Table 1. Comparison of excipients found in the ustekinumab infusion and the prefilled syringe used for SC injection

Ustekinumab IV infusion (30 mL vial)	Ustekinumab SC injection (1 mL PFS)	Purpose of excipients
Ustekinumab 130 mg	Ustekinumab 90 mg	
EDTA disodium salt dihydrate (0.52 mg)		Chelating agent
L-Histidine (20 mg)	L-Histidine (1 mg)	Amino acid buffering agent
L-Histidine monohydrochloride monohydrate (27 mg)	L-Histidine monohydrochloride monohydrate (1 mg)	Amino acid buffering agent
L-Methionine (10.4 mg)		Amino acid—stabilizer
Polysorbate 80 (10.4 mg)	Polysorbate 80 (0.04 mg)	Surfactant—to prevent aggregation.
Sucrose (2210 mg)	Sucrose (76 mg)	Disaccharide –stabilizer

EDTA, ethylenediaminetetraacetic acid; PFS, prefilled syringe; SC, subcutaneous.

DISCUSSION

The approval of ustekinumab for the treatment of moderately to severely active CD added a safe and efficacious treatment option for both anti-TNF-naïve patients and patients who have failed anti-TNF therapy. The pivotal trials leading to the FDA approval of ustekinumab, UNITI-1, and UNITI-2 were studies of induction therapy of patients who failed anti-TNF therapy and those who were anti-TNF naïve, respectively, and demonstrated the clinical efficacy of weight-based induction dosing in contradistinction to the previous studies that led to regulatory approval for plaque psoriasis, in which no such loading phase was developed. Patients who completed the induction trials were continued in IM-UNITI to assess the maintenance of remission. The rates of infusion reactions occurring within 1 hour after an ustekinumab infusion were similar across the treatment and control groups in both UNITI-1 and UNITI-2. The rates of injection-site reactions in IM-UNITI, however, were higher in the treatment groups compared with the placebo arm (2.3% for 90 mg every 12 weeks group and 6.9% in 90 mg every 8 weeks group vs 0.8% in the placebo).[8,9] Ustekinumab is a biological therapy associated with very low immunogenicity; the induction trials reported ~0.09% (2 patients only) and 2.3% in the maintenance of antidrug antibody development.

We report a single patient with a type-I immediate hypersensitivity reaction to the IV infusion of ustekinumab, but not to the SC formulation. There were no antidrug antibodies. We hypothesized that our patient's infusion reaction to the IV formulation was because of EDTA, an excipient found in the induction infusion formulation and not the maintenance injection formula. EDTA has had numerous pharmacologic uses, one of which is being a chelating agents for the treatment of heavy metal poisoning but also preventing oxidation and antibacterial role by its ability to improve the stability of drug preparations by chelating divalent metal ions, which are essential for bacterial growth.[10,11]

We believe that this reaction may have occurred from the EDTA, a chelating agent previously described to induce immediate hypersensitivity reactions.[12] We suspect sensitization of EDTA developed from other therapy exposures (eg, propofol infusion). Her tolerance and clinical response to the SC formulation of ustekinumab supports this possibility, but careful consideration of other possible causes of hypersensitivity reactions and skin testing would confirm this allergy. We believe clinicians should be aware of this uncommon but serious reaction because it may not preclude further use of ustekinumab.

DISCLOSURES

Author contributions: NK Cleveland wrote and approved the final manuscript. A. Masching and DT Rubin approved the final manuscript and are the guarantors.

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