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Hypersensitivity Reaction to Ustekinumab in Pediatric and Young Adult Inflammatory Bowel Disease Patients: A Case Series

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Abstract: Ustekinumab (UST) is a human IgG1K monoclonal antibody that binds to the p40 receptor subunit bound by cytokines IL-12 and IL-23. It is indicated in both Crohn's disease and ulcerative colitis as a second-line agent. The safety and efficacy of UST in children and young adults has not been thoroughly studied. We report a case series of six pediatric patients and young adults who developed hypersensitivity reactions during intravenous infusion with UST. These reactions ranged from mild allergic reactions to anaphylaxis, with no detectable antibodies if tested. We hypothesize the reaction could be secondary to ethylenediaminetetraacetic acid, which is present solely in the intravenous preparation. Patients who experience hypersensitivity reactions during their UST infusion may safely receive subcutaneous preparations of UST, as demonstrated by some patients who received it based on physician discretion. Further investigation is required to establish the etiology of infusion reactions.

Key Words: Crohn's disease, ulcerative colitis, EDTA

What Is Known

- Inflammatory bowel disease (IBD) responds to biologic therapies in children with similar or greater efficacy compared with adult populations.
- Ustekinumab is a FDA-approved biologic therapy for adults but also utilized as a second-line agent in children.

What Is New

- Patients receiving ustekinumab IV infusions may experience hypersensitivity reactions, including anaphylaxis, hypothesized to be secondary to an additive-like ethylenediaminetetraacetic acid (EDTA).
- Patients having hypersensitivity reactions to ustekinumab infusion can safely receive a subcutaneous ustekinumab formulation without recurrence.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammation of the gastrointestinal tract secondary to dysregulated immune response to gut microbiota. Biologic therapies are being increasingly utilized for the management of IBD in children, before FDA approval in pediatrics. Due to lack of response to anti-TNFα medications in about 30% of patients, off-label treatment with alternate biologics such as vedolizumab and ustekinumab (UST) are becoming more commonplace (1).

UST is a human IgG1K monoclonal antibody that binds to the p40 receptor subunit bound by cytokines IL-12 and IL-23 (2). Such cytokines are key mediators in inflammatory and immune responses in IBD such as activation and differentiation of natural killer cells and the CD4+ T cells. UST ligation to p40 on the T cells interrupts downstream signaling resulting in inhibition of the inflammatory pathways (3).

UST is currently approved for psoriatic arthritis, moderate-to-severe plaque psoriasis, and moderate-to-severe active Crohn's disease (CD) and ulcerative colitis (UC) in adult patients (4). It is delivered as an induction dose by infusion followed by subcutaneous injections. Few data exist regarding its safety and efficacy in pediatric IBD patients.

Each vial of UST contains 0.52 mg of ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate, which is an additive in the intravenous formulation of UST that improves the stability of this drug. EDTA salts have been used in a wide variety of applications such as cosmetics, medications, food, and in the treatment of heavy metal poisoning. Hypersensitivity reactions secondary to the use of EDTA have been reported (5).

We report a case series of six pediatric and young adult patients who developed hypersensitivity reactions during intravenous (IV) induction dose of UST, ranging from mild allergic reactions to anaphylaxis, with no antibodies detected if tested. We report the patient demographics, symptomology, onset, and management of hypersensitivity reactions encountered with IV UST and highlight that patients may still be able to safely receive subcutaneous preparations of UST without further hypersensitivity reactions.

METHODS

A retrospective review of six pediatric and young adult patients with IBD who exhibited hypersensitivity reaction during UST IV infusion at Nicklaus Children's Hospital and Children's Mercy Hospital was performed. Medical records review was approved by the Institutional Review Board (IRB).

Clinical and demographical data were collected including age, ethnicity, sex, disease characteristics, previous, and current treatment, as well as symptomatology, onset, and treatment of the infusion reaction with UST IV (Tables 1 and 2). Treatment of the

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TABLE 1. Patient cases with associated descriptive factors of infusion-related hypersensitivity reactions to ustekinumab IV

	Demographics	Disease	Previous medical treatments	Symptoms	Onset	Treatment	Current clinical course
Case 1	18-year-old Caucasian female	Ulcerative colitis	Steroids, Azathioprine, Infliximab, Vedolizumab, and an antibiotic cocktail	Chest pain, shortness of breath, cough, lip paresthesia, and tachycardia	30 minutes into 390 mg IV UST infusion	IV diphenhydramine with resolution of symptoms	Continues with subcutaneous UST with no further reactions
Case 2	11-year-old Caucasian female	Ileocolonic Crohn's disease	Steroids, Azathioprine, Methotrexate, Infliximab, and Adalimumab	Abdominal and chest pain, pruritis, cough, shortness of breath, nausea, dizziness, and laryngospasm	30 minutes into 390 mg IV UST infusion	IV diphenhydramine, methylprednisolone, and epinephrine with resolution of symptoms	Continues with subcutaneous UST with no further reactions
Case 3	19-year-old Hispanic female	Small bowel Crohn's Disease	Budesonide and Adalimumab	Erythematous rash, flushing, and cough	2 minutes into 390 mg IV UST infusion	Methylprednisolone with resolution of symptoms	Transitioned to infliximab
Case 4	14-year-old Caucasian male	Small bowel and colonic Crohn's disease	Adalimumab	Flushing, cough, and shortness of breath	Between 3 and 29 minutes into 390 mg IV UST infusion	Methylprednisolone with resolution of symptoms	Continues with subcutaneous UST with no further reactions
Case 5	22-year-old Caucasian male	Stenosing small bowel Crohn's disease requiring ileal resection for an acute small bowel obstruction	Infliximab	Flushing of the face and chest pain	Between 3 and 29 minutes into 390 mg IV UST infusion	Methylprednisolone with resolution of symptoms	Transitioned to adalimumab
Case 6	10-year-old Hispanic female	Ileocolonic Crohn's disease	Infliximab, Adalimumab, and methotrexate	Abdominal pain, shortness of breath, and rash	Immediately into 390 mg IV UST infusion	Methylprednisolone, IV diphenhydramine, and loratadine with resolution of symptoms	Continues with subcutaneous UST with no further reactions

TABLE 2. Frequency and relative frequency of symptomology, onset of symptoms, and treatment of infusion-related hypersensitivity reactions to ustekinumab IV

Descriptive factor	Frequency (*f*)	Relative frequency (*rf* = *f*/*n*)
Symptoms		
Cough	4	0.67
Shortness of breath	4	0.67
Chest pain	3	0.50
Flushing	3	0.50
Abdominal pain	2	0.33
Rash	2	0.33
Lip paresthesia	1	0.17
Tachycardia	1	0.17
Pruritus	1	0.17
Nausea	1	0.17
Dizziness	1	0.17
Laryngospasm	1	0.17
Onset of symptoms		
Immediately	1	0.17
2 min	1	0.17
3 to 29 min	2	0.33
30 min	2	0.33
Treatment		
Methylprednisolone	5	0.83
Diphenhydramine	3	0.50
Loratadine	1	0.17
Epinephrine	1	0.17

infusion reaction differed based on three different settings and protocols: Children's Mercy Hospital, Nicklaus Children's Hospital IBD Infusion Center, and Nicklaus Children's Hospital Outpatient Center. Descriptive statistics, including mean, range, frequency, and relative frequency, were calculated.

RESULTS

Six cases were reviewed (Table 1). Four patients (67%) were female, and two patients were male (33%). Four patients (67%) identified themselves as Caucasian and two patients identified as Hispanic ethnicity (33%). Five patients (83%) were diagnosed with CD and one (17%) had UC. Three patients (50%) had a previous history of asthma. Treatment before UST induction included infliximab (67%), adalimumab (67%), corticosteroids (33%), azathioprine (33%), methotrexate (33%), vedolizumab (17%), budesonide (17%), and antibiotics (17%). From the 48 patients that are currently receiving UST amongst both centers, 13% developed a hypersensitivity reaction. Hypersensitivity reactions included cough, shortness of breath, chest pain, flushing, abdominal pain, rash, lip paresthesia, tachycardia, pruritus, nausea, dizziness, and laryngospasm. Onset of symptoms was observed over a short range of time (0–30 minutes). Resolution of symptoms was achieved after administration of methylprednisolone, diphenhydramine, loratadine, and epinephrine (Table 2). Current treatment of these six identified patients who experienced hypersensitivity to UST intravenous formulation includes subcutaneous UST (67%), infliximab (17%), and adalimumab (17%). Antibodies to UST (ATU) concentration were <1.6 U/mL for cases 4 and 6, whereas no antibodies were drawn for the other

patients. Change of formulation of UST from IV to subcutaneous was done in a controlled hospital-based setting.

DISCUSSION

Ustekinumab is used as a second-line biologic agent in the pediatric IBD population (6). Treatment with UST for IBD begins with a weight-based intravenous induction dose followed by subcutaneous injections every 8 weeks for maintenance therapy (2,7). Data on the safety and efficacy of UST in the pediatric population have not been established. In one of the largest studies to date in the pediatric population, 2 patients of 52 developed anaphylaxis during the initial IV induction of UST. These patients were treated with steroids and epinephrine, and later completed the induction infusion. One patient experienced an urticarial rash 1 day after IV induction (1). In another large pediatric study, a serious adverse event was seen in 2 patients after receiving one induction dose of UST but association with the medication was not clear (8). Additionally, in a recent pediatric study by Kim et al, 1 patient of 38 developed a suspected anaphylactic reaction to an intravenous reinduction dose but was able to continue with subcutaneous doses (9). In our studied population, hypersensitivity reactions occurred within the short range of 30 minutes, thus making it a good clinical practice to observe patients for 60 minutes postinfusion.

Furthermore, adult studies have shown similar tolerance to UST with limited severe adverse events. Clinical studies involving the safety of UST in 1,407 CD patients revealed similar rates of adverse events within 1 hour after infusion between the placebo and treatment groups for both the induction and subcutaneous trials. The rates of antidrug antibodies to UST were found to be low (2,10). Moreover, studies conducted in 961 UC patients revealed <3% adverse events related to an infusion or injection site reaction (7).

Although the exact pathogenesis of this infusion reaction remains unknown, it has been attributed to EDTA. EDTA has previously been described to cause hypersensitivity reactions when present in other formulations, including anesthetic and radiocontrast agents (5). Although none of our patients was previously treated with UST, it is possible our patients demonstrated a hypersensitivity type 1 reaction due to sensitization to EDTA from prior exposures to this additive. Moreover, 50% of our patients had a previous history of asthma but their predisposition of having a hypersensitivity reaction to EDTA is still to be studied.

Among our cases, 67% of our patients were able to continue with subcutaneous UST with no further reactions, whereas 33% were switched to another biologic due to physician preference and were never exposed to the subcutaneous formulation. We believe patients who develop this reaction with the IV formulation of UST should be treated with supportive measures. Patients who have reactions during induction may still be able to safely receive subcutaneous preparations, as demonstrated by patients included in this case series. Additionally, Krugliak Cleveland et al report an adult who was successfully switched to the subcutaneous formulation after having a hypersensitivity reaction with IV UST (11).

Limitations encountered in our case series are attributed to its retrospective design and small sample size. The biggest contribution of this case series is the identification of tolerance to subcutaneous UST despite prior hypersensitivity reaction with the intravenous formulation. We hypothesize that patients may tolerate the subcutaneous formulation as it lacks the additive EDTA. The recommendation of the contributing authors is to treat with supportive care, assess for the presence of UST antibodies, and trial a subcutaneous dose of UST in a controlled setting. Further investigations with skin prick testing or specific IgE levels to EDTA done by allergy and immunology are also recommended.

Further research is required to evaluate for a causal relationship between EDTA and the allergic reactions demonstrated with UST intravenous formulations, and, if established, the creation of an intravenous formulation without EDTA may be beneficial to the general population.

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