Real-World Experience With Acute Infusion Reactions to Ustekinumab at 2 Large Tertiary Care Centers

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Background: Ustekinumab is approved for Crohn's disease and Ulcerative colitis with acute infusion reactions reported at a rate of 0.9%–4.5%.

Methods: A retrospective chart review was conducted on inflammatory bowel disease (IBD) patients experiencing an acute infusion reaction to ustekinumab at 2 large institutions.

Results: Acute ustekinumab infusion reactions occurred in 16 patients with Crohn's disease (CD) and Ulcerative colitis (UC), at a rate of 0.8%–3%. Patients were all naïve to ustekinumab, receiving their initial IV induction. Ninety-three percent subsequently tolerated the injection without issues.

Conclusions: In this large, real-world study of acute infusion reactions to ustekinumab, the rate was similar to that seen in clinical trials—0.8%–3%.

Lay Summary

Ustekinumab is a therapy for inflammatory bowel disease (IBD) given as an infusion followed by maintenance injections. We present here our real-world experience that only 0.8%–3% of patients have reactions to the infusion, and these reactions, for the most part, do not lead to reactions to injections.

Key Words: acute infusion reaction, ustekinumab, IBD

INTRODUCTION

Ustekinumab is a fully human monoclonal antibody directed against the p40 subunit of interleukins 12 and 23. It has been approved for use in psoriasis, psoriatic arthritis, Crohn's disease (CD), and Ulcerative colitis (UC). Within CD and UC, UNITI-1, UNITI-2, IM-UNITI, and UNIFI all reported on safety data, up to 96 weeks in IM-UNITI. The immunogenicity across these trials has been consistently low, with 2.3%–4.6%[1–3] developing antibodies across all treatment groups, making it markedly less immunogenic than many of the other biologic therapies.[4] Infusion reactions, often caused by mechanisms other than simple antibody formation,[5] are not well-described within these cohorts, but they are reported as occurring in 0.9%–4.5% of patients in UNITI-1, UNITI-2, and UNIFI.[1,3]

It is relatively common to observe infusion reactions with monoclonal antibody therapies, attributed to a variety of immune-mediated (hypersensitivity reactions) or non-immune-mediated causes.[6,7] In CD and UC, ustekinumab is given once as an intravenous (IV), weight-based loading dose followed by 90 mg subcutaneous (SC) injection maintenance doses. We aimed to report on the rate of acute infusion reactions given this singular IV dose as acute reactions that occur during the first exposure to the drug are, by definition, not immunologically mediated, since prior antigen exposure is required for a Type I hypersensitivity reaction.[8] However, the singular dose could still lead to pseudo-allergic (non-immune mediated) reactions, which are also worth reporting as they can be dangerous and require therapy.[9] Additionally, the implications of these pseudo-allergic reactions to IV therapy on subsequent SC drug administration have not been described.

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MATERIALS AND METHODS

A retrospective chart review was conducted on all inflammatory bowel disease (IBD) patients reported as experiencing an acute infusion reaction to ustekinumab at Infusion Center 1 during the period from January 1, 2017 to March 31, 2019 and Infusion Center 2 from November 1, 2016 to December 31, 2018. Billing data was gathered to describe the total number of ustekinumab infusions performed for IBD at the 2 centers.

In both infusion centers, patients are monitored and receive care from experienced nurses and clinical pharmacists. Standardized policies and procedures are followed; ustekinumab is administered based on protocols set forth by the FDA and Janssen Pharmaceuticals. All infusions are administered and monitored by a trained nurse. Use of premedication (eg, antihistamines, acetaminophen, and/or intravenous steroids) is determined by the referring physician. Ustekinumab was infused over a minimum 1-hour period. Patients' vital signs were obtained prior to and at completion of the infusion. Nursing staff record all patients experiencing acute infusion reactions, defined as those occurring during the infusion, as part of infusion center protocol.

Patient gender, age, race, and allergies were obtained. Diagnosis and phenotype data were noted. Data on prior exposure to biologics and any prior reactions to biologics were gathered. Infusion reaction to ustekinumab was described, with data collected on any concurrent steroid or immunomodulator use as well as premedication, and management approaches were recorded from the electronic medical record. Reactions were graded based on the criteria previously described by Cheifetz and Mayer.[10] Data on any delayed reactions were not obtained. Tolerance of subsequent SC administration of ustekinumab was also recorded in this cohort, and any reactions to injections were described. Data was collected on any ustekinumab concentration and anti-ustekinumab antibody testing performed.

ETHICAL CONSIDERATIONS

This study was approved by the Institutional Review Boards of both institutions.

RESULTS

During the study period, 16 patients, 14 at Infusion Center 1 and 2 at Infusion Center 2, were identified who had infusion reactions to ustekinumab. Patients were all receiving their initial IV weight-based induction dose of ustekinumab, and they were all naïve to prior ustekinumab therapy. At Infusion Center 1, there was a 3% rate of infusion reactions over the 2-year period from 2017 to 2018. At Infusion Center 2, there was a 0.8% rate of infusion reactions over the entire study period.

The patients mainly carried a diagnosis of CD (94%). The phenotypes of the cases are described in Table 1. Five (31%) of them were <18 years old. Females made up 63% of the cases. Regarding the patients' allergic histories, none of the patients had food allergies, and 4 (25%) had other drug allergies. A majority (81%) had previously received biologics other than ustekinumab with 3 patients (19%) experiencing an infusion or injection reaction. Two (13%) patients had infusion reactions previously to infliximab. Two of the prior reactions were related to the development of anti-drug antibodies, one with adalimumab and the other with infliximab; the development of anti-drug antibodies to infliximab occurred over a year after the initiation of infliximab. The final patient with a

TABLE 1. Patient Characteristics

	N (or median where noted)	% (or IQR where noted)
Male	6	37.5
Age (y)	Median: 24	IQR: 18–28
<18 yo	5	31.25
Race		
White, Ashkenazi Jewish	7	43.75
White, Non-Ashkenazi Jewish, Non-Hispanic	7	43.75
White, Hispanic	1	6.25
Unspecified	1	6.25
CD	15	93.75
Montreal classification		
A1	10	66.7
A2	5	33.3
L1	3	20
L2	1	6.67
L3	11	73.3
B1	10	66.7
B2	2	13.3
B3	3	20
PA dz	4	26.7
UC	1	6.25
Montreal classification		
E4	1	100.00
Prior biologic therapy		
Prior exposure to non-ustekinumab (non-UST) biologic therapy	13	81
Prior exposure to SC non-UST biologic therapy only		
Prior exposure to IV non-UST biologic therapy		
No prior biologic exposure	2	13
No information about prior medications	1	6
Reaction to prior non-UST biologic therapy (infusion or injection site reaction)	3	19

UST, ustekinumab.

reaction had reactions to both infliximab and adalimumab. The patient complained of fatigue, body aches, rash, and joint pains with the second infusion of infliximab; it was unclear if this was a hypersensitivity reaction or the onset of drug-induced lupus, and infliximab was discontinued. This patient also had hives at the injection site of adalimumab, which was being given as combination therapy with Imuran, at the first loading dose with associated nausea, lightheadedness, and joint pain.

None of the patients received pre-treatment prior to starting IV ustekinumab. Three patients (19%) had received either steroids or an immunomodulator within 4 weeks of the first infusion; one was on 40 mg of prednisone at the time of the infusion, one had recently stopped 15 mg of oral methotrexate the week before the infusion, and one was on 12.5 mg of oral methotrexate at the time of the infusion. Median time to onset of infusion reaction after the start of the infusion was 2 (Interquartile Range [IQR]: 2–4.5) minutes. Time to infusion reaction was notably different between sites with a median of 2 (Range: 1–5) minutes at Infusion Center 1 and a median of 27.5 (Range: 15–40) minutes at Infusion Center 2. The majority were classified as moderate (50%) or severe (38%), with only 6% each being mild and unclassified. The most common acute reaction was dyspnea/chest tightness, which occurred in 63%, followed by flushing, which occurred in 56%. Those classified as severe were done so for concern for bronchospasm due to acute onset cough in 2 (13%) and feeling of "lump in throat" or "throat closing" concerning for angioedema in 4 (25%). In all cases, medications were administered for the infusion reaction. The most common medications given were Benadryl (87.5%), Solucortef (75%), and Pepcid (63%). Both of the patients with cough received Albuterol and Atrovent. The symptoms of the infusion reactions and medications used are fully described in Table 2. Fifteen (94%) patients restarted ustekinumab IV after receiving medications for the infusion reaction, and all of these completed the infusion without issues. The one patient who did not restart the infusion did so out of personal preference; however, the infusion center nurses believed the infusion was safe to restart.

TABLE 2. Infusion Reaction Characteristics and Treatment

	N (or median where noted)	% (or IQR where noted)
Infusion reaction characteristics		
Dyspnea	10	62.5
Flushing	9	56.3
Stomach pain/nausea	5	31.3
"Lump in throat"/" Throat closing"	4	25
Cough	2	12.5
Diaphoresis	2	12.5
Hives	2	12.5
Brain fog	1	6.25
Palpitations	1	6.25
Tachycardia	1	6.25
Undescribed	1	6.25
Time to onset (min)	Median: 2	IQR: 2–4.5
Infusion reaction treatment		
Benadryl	14	87.5
Solucortef	12	75
Pepcid	10	62.5
Zofran	2	12.5
Claritin	2	12.5
Tylenol	2	12.5
Duoneb (Albuterol/ Atrovent)	2	12.5

Regarding subsequent injection therapy, 14 had received at least 1 injection by the study end. Of the 2 who had not received an injection, one had refused to restart the infusion and had instead started a different therapy. The other patient, the singular patient with UC, went to colectomy 8 weeks after the IV dose, and SC injections were never started. Thirteen of the 14 (93%) tolerated the injection without issues.

Pretreatment prior to the injections was used only in 3 patients (21%), one from Infusion Center 1 and both patients from Infusion Center 2. One received prednisone 40 mg for 2 days prior to the injection as well as diphenhydramine and acetaminophen just before the injection; this patient did not experience a reaction on initial injection and was subsequently lost to follow-up. Another received fexofenadine 30 minutes prior to the injection, did not experience an injection reaction, and continued fexofenadine with every injection on the advice of an allergist due to prior reactions to adalimumab and infliximab. The third patient who received pretreatment prior to the injection, with Tylenol and Benadryl orally, was the sole patient to experience a reaction to the injection. The patient was noted to have chest discomfort and was subsequently given Solucortef with resolution of symptoms. This occurred again with the second injection. With the third injection, pretreatment was given with IV Benadryl and Solucortef, and a tryptase level was drawn prior to and 2 hours after the injection, both of which were normal (3.3 prior, 3.1 two hours after). At this injection, the patient again noted chest discomfort that resolved immediately with the administration of an additional dose of IV Benadryl. No wheezing was ever noted in this patient. This patient elected to discontinue the medication after the third injection.

Regarding ustekinumab drug levels, 5 patients within the study had at least 1 ustekinumab drug concentration and antibody test by study end, with 9 total concentration and antibody tests performed. None of the patients developed anti-ustekinumab antibodies, and all of the patients had detectable levels of ustekinumab. Two of the concentrations were

performed 8 weeks following induction—1.1 and 3.0. The others were done at different intervals in maintenance (8 weeks following SC injection: 3.0, 1.7; 6 weeks following SC injection: 6.0, 6.2, 6.5; 4 weeks following SC injection: 8.8, 5.2).

DISCUSSION

Our real-world experience with ustekinumab infusions reflects a similar rate of infusion reactions (0.8–3%), as seen in the initial UNITI and UNIFI studies (0.9–4.5%).[1,3] Additionally, our experience highlights the safety of ustekinumab as all of the patients electing to continue treatment were able to complete the infusion after receiving treatment for the reaction. We have also found that reactions to injections, even without pretreatment, are uncommon, with 93% experiencing no reaction to the SC injection. Interestingly, all of the 11 that received no ustekinumab injection pre-treatment did not experience any reaction to the injection.

A majority of those who received prior therapy with another biologic (85%) had no history of infusion reactions. In those with a history, one was a result of anti-drug antibodies to infliximab occurring 1 year into therapy. Patients with a prior history of antidrug-antibody-associated infusion reactions should not be at higher risk for an acute infusion reaction to the first dose of ustekinumab as anti-drug antibodies are not found in those naïve to drug. The singular patient that had reactions unrelated to anti-drug antibodies to infliximab, adalimumab, and ustekinumab could represent a small subset of highly sensitive patients where caution and pretreatment should be used with the administration of any infusion therapy.

The etiology of these infusion reactions is unclear. They, for the most part, happened very acutely within minutes of the start of the infusion, and they were all the first exposure of the patient to the drug. There was a significant difference in time to reaction between the 2 sites; however, the small number of cases at Infusion Center 2 is limiting in describing a potential cause for this difference. When considering infliximab, another monoclonal antibody therapy used in Crohn's disease, infusion reactions have been shown to be mainly non-allergic in nature with a rare few falling into the category of true IgE-mediated Type I acute hypersensitivity.[10] Symptoms of true allergic anaphylactic reactions include chest tightness, shortness of breath, flushing, hypotension, wheezing, and urticaria.[8] Additionally, in these IgE-mediated reactions, the tryptase level often rises due to mast cell degranulation.[11] A small study from 2003 showed that the tryptase level did not rise in 11 patients experiencing infliximab infusion reactions, leading the authors to conclude that the reactions were not IgE-mediated and likely not immune in nature.[12] However, there is debate over tryptase's use as a biomarker of IgE-mediated anaphylaxis as a more recent study showed that 36.6% of 102 patients did not have a rise in tryptase during an acute episode of anaphylaxis that was diagnosed clinically, and other biomarkers, such as platelet activation factor, chymase, carboxypeptidase A3, dipeptidyl peptidase I, basogranulin, and CCL-2, have been put forward as potential surrogates.[11,13]

Ustekinumab reactions should not be immune-mediated as there is no prior drug exposure to allow for antigen priming. Interestingly, in our cohort, there were a number of patients with complaints of shortness of breath and coughing classically thought of as true immune-mediated allergy symptoms, although there was no documentation of wheezing confirming true bronchospasm. Additionally, the singular patient with a clinical symptom following injection therapy did not have a rise in his/her tryptase following the administration of ustekinumab SC. Finally, and most importantly, the fact that 93% of patients tolerated a re-exposure to the drug, in SC form, without a reaction makes it unlikely to be an IgE-mediated reaction since an IgE-mediated reaction would occur with any repeated drug exposure.

It is worth noting that there is an exception to the rule that true hypersensitivity reactions cannot occur with the first infusion of a monoclonal antibody. Cetuximab, a chimeric mouse–human IgG1 monoclonal antibody against the epidermal growth factor receptor provokes a true IgE-mediated response in a subset of patients. This response was found to be a reaction to the galactose-α-1,3-galactose found in the Fab portion of the cetuximab heavy chain.[14] There is now a screening test for IgE antibodies specific for this oligosaccharide to identify patients at risk for anaphylaxis on first exposure.[15] The 5 patients in our study in whom anti-drug antibody testing was performed notably did not develop any anti-ustekinumab antibodies.

In general, there continues to be confusion over the nomenclature used in infusion reactions as they are still commonly called hypersensitivity reactions. However, hypersensitivity describes specific, immune-mediated events, falling into the classic Gell-Coombs 4 types: Type 1 driven by IgE, Type II driven by complement-mediated cytotoxic IgM or IgG antibodies, Type III driven by the formation and deposition of immune complexes, and Type IV driven by sensitized T lymphocytes.[8] Acute infusion reactions should be better described as immune- and non-immune-mediated reactions, with acute, immune-mediated events being Type I hypersensitivity reactions. The acute, non-immune-mediated infusion reactions are typically rate-related events, Red Man Syndrome with vancomycin being a classic example, or other mild, nonspecific, non-allergic symptoms such as headache or nausea that develop acutely at the time of the infusion, benefit from pre-treatment, and do not worsen with subsequent infusions.[9] It is likely that the reactions we observed with ustekinumab fall into this category of non-immune mediated given their occurrence at the first exposure of the drug, the ability to restart the infusion without issues following treatment, and, notably, the lack of reaction to the subsequent SC injection in a large majority of patients.

CONCLUSION

In conclusion, this is the largest real-world study of patients with IBD experiencing acute infusion reactions to ustekinumab. The rate was similar to that seen in clinical trials—0.8% to 3%. The patients were able to safely restart IV therapy after treatment for the acute reaction and, for the most part, tolerate SC injections without pre-treatment after experiencing an acute reaction to the IV form. None of the patients in whom concentration and antibody tests were performed developed anti-drug antibodies to ustekinumab.

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