



Short Report

# Immediate Infusion Reaction to Intravenous Ustekinumab in Three Crohn's Disease Patients: A Case Report and Review of the Literature

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## Abstract

Recently, ustekinumab has been approved for the treatment of Crohn's disease and ulcerative colitis. Treatment is started with an intravenous induction dose, followed by a subcutaneous dosage. We present details of three patients with therapy-refractory Crohn's disease who experienced an immediate infusion reaction to intravenous administration of ustekinumab. In two of these patients a subsequent reaction to subcutaneous injections occurred. Clinical features and pathophysiology are discussed.

**Key Words:** Ustekinumab, Crohn's disease, infusion reaction

## 1. Introduction

Ustekinumab is a humanized monoclonal antibody that binds to the p40 subunit of interleukin-12 [IL-12] and IL-23. It is approved for the treatment of Crohn's disease [CD],<sup>1</sup> and ulcerative colitis.<sup>2</sup> According to label, induction treatment starts with a weight-based intravenous [IV] loading dose, followed by subcutaneous injections of 90 mg every 8–12 weeks for maintenance treatment. Previously, two cases of infusion reaction following the IV administration and one case of infusion reaction following a subcutaneous administration have been reported.<sup>1–4</sup> Here we describe three cases of an immediate infusion reaction to the initial IV dose of ustekinumab, and a subsequent reaction to subcutaneous injections in two of these cases.

## 2. Case Report

### 2.1. Case 1

The first patient is a 41-year-old female with a medical history of ileocolonic CD, who previously underwent a right-sided hemicolectomy. In addition, her history includes allergic rhinitis, dust mite allergy and eczema but no reported episodes of asthma. Previously she was treated with azathioprine [discontinued due to pancreatitis], infliximab [immediate infusion reaction characterized by flushing and dyspnoea after four doses], methotrexate [stopped due to nausea], adalimumab [low trough levels and high levels of antidrug antibodies; insufficient clinical response], thioguanine [currently used] and vedolizumab [lack of clinical response]. She then started ustekinumab due to persistent disease activity.

After 10 min of IV administration of 390 mg ustekinumab, the patient experienced shortness of breath, difficulty breathing, chest discomfort, flushing and dizziness. Administration was stopped immediately and the IV line was flushed. Symptoms resolved completely within 10 min. No prednisone or clemastine was administered given the quick recovery. Two weeks later a 90 mg ustekinumab subcutaneous injection was initiated. After approximately 4 h she reported erythema, a warm sensation and pruritis at the injection site, slowly progressing in severity. Desloratadine was administered with subsequent resolution of symptoms. At day 2 she reported a mild dyspnoea and at day 3 oedema at the injection site re-occurred. The oedema responded to another dose of desloratadine, without effect on the dyspnoea. At day 4 the dyspnoea progressed and did not improve despite use of clemastine. Prednisone 20 mg orally was then started for 3 days with resolution of symptoms. Ustekinumab was discontinued permanently.

## 2.2. Case 2

The second case concerns a 23-year-old female with a medical history of colonic CD who previously underwent a subtotal colectomy followed by an ileo-anal pouch construction. Additionally, her history includes allergic rhinitis but no reported episodes of eczema or asthma. Previously she was treated sequentially with infliximab, adalimumab and methotrexate. After an initial insufficient response to infliximab and adalimumab with methotrexate, re-induction of infliximab 7 years later led to an immediate transfusion reaction with flushing and dyspnoea that responded well to prednisone and clemastine. Then adalimumab was re-introduced with mercaptopurine. Due to persistent disease activity after re-induction, adalimumab was discontinued and ustekinumab was prescribed. The last measured trough level of adalimumab was 1.4 µg/mL, 2 days before the first administration of ustekinumab.

Fifteen minutes after starting IV administration of 390 mg ustekinumab, she experienced dyspnoea, tingling of the lips and difficulty swallowing. The infusion was stopped and IV prednisone 25 mg was started. Symptoms resolved completely and administration of IV ustekinumab was restarted at a lower infusion speed. Within 5 min similar symptoms occurred and infusion was permanently ceased. After 2 h a subcutaneous injection of 90 mg was administered under the assumption that the IV route induced the infusion reaction. She directly experienced shortness of breath and flushing which was treated with clemastine 2 mg and another dose of prednisone 25 mg IV due to persistent symptoms. This medication was continued orally for 7 days with complete resolution of symptoms. She subsequently started vedolizumab with good clinical and biochemical response.

## 2.3. Case 3

The third case is a 54-year-old female with a medical history of stricturing ileocolonic CD and ileocecal resection, with no reported episodes of asthma or eczema. Previously she was treated with adalimumab [discontinued due to headache and malaise], infliximab [high trough levels, no antibodies; insufficient clinical response], vedolizumab [insufficient clinical response and adverse events including pruritus, rash and dry skin after the first dose, managed with clemastine and hydrocortisone prior to every dose; no trough levels available], azathioprine [discontinued due to oral ulcers, nausea] and methotrexate [discontinued due to pruritus and dyspnoea]. She was then prescribed ustekinumab and prednisone by her treating physician.

Forty minutes after initiation of IV administration of 390 mg ustekinumab she experienced a swollen throat, coughing, headache and fatigue. Infusion was stopped and clemastine was administered, after which symptoms resolved completely. Infusion was re-initiated at a lower infusion speed. Similar symptoms occurred within 5 min and ustekinumab was stopped permanently.

## 3. Discussion

In this case report, we describe three patients with well-documented infusion reactions to their first IV ustekinumab administration. Ustekinumab has been approved for the treatment of psoriasis, arthritis psoriatica, CD and ulcerative colitis. IV induction is used solely for the treatment of inflammatory bowel disease, according to label. Phase II and phase III studies in CD have reported only two immediate infusion reactions out of 1407 CD patients treated with ustekinumab.<sup>1,4</sup> These studies described one patient who experienced symptoms consistent with anaphylaxis after a single subcutaneous administration, and one patient who experienced symptoms consistent with a hypersensitivity reaction after the initial IV ustekinumab dose. Both patients were treated with antihistamines and/or corticosteroids with quick resolution of symptoms.

Biologicals can cause infusion reactions in IBD patients. In those treated with infliximab, infusion reactions occur in 5–23% of patients.<sup>5</sup> The high rate of infusion reactions during infliximab therapy has generally been explained by antidrug antibody formation.<sup>5–7</sup> Antidrug antibody formation occurs more frequently [up to 65%] with infliximab due to the variable domain derived from murine cells and strategy of episodic administration of the drug after approval in the late 1990s.<sup>8,9</sup> Injection site reactions have been reported in 20% of patients using adalimumab, and allergic reactions in 1% of patients using adalimumab.<sup>10</sup> Adalimumab is a humanized monoclonal antibody and antidrug antibody formation occurs less frequently, in only about 0.3–38% of patients on adalimumab.<sup>8,10</sup>

The pathophysiology of infusion reactions to ustekinumab remains unknown. Neither a classic hypersensitivity type I reaction, nor cross-reactivity between immunogenicity to biologicals or allergic reactions to excipients seem likely in our patients. First, a classic type I hypersensitivity reaction seems less likely as this usually requires a previous encounter with an allergen for the induction of antibodies [sensitization] before mast cells can be activated.<sup>11</sup> However, an IgE-mediated hypersensitivity reaction during a first dose of a biological has been reported, and histamine release independent of IgE may also play a role.<sup>12</sup> Second, we considered cross-reactivity due to the presence of antidrug antibodies directed at a different biological, which may have resulted in these immediate infusion reactions. Previously, two studies assessed cross-reactivity between antidrug antibodies directed at one biological to another biological. Both studies observed no cross-reactivity between infliximab and adalimumab.<sup>13,14</sup> This may be due to different immunogenic epitopes between these biologicals. Therefore, it is unlikely that antidrug antibodies directed at a certain biological will cross-react with another biological. Third, an allergic response towards an excipient in the IV or subcutaneous formulation seems unlikely. All described patients have previously used a biological with similar excipients as ustekinumab. In one of these patients ethylenediaminetetraacetic acid [EDTA] may have resulted in a hypersensitivity reaction, which has been reported before in the context of an infusion

reaction to ustekinumab.<sup>3</sup> Although no blood tests are available to determine IgE-mediated hypersensitivity to EDTA, intradermal skin tests and basophil activation tests have been performed previously.<sup>15</sup> However, these tests often produce false positive results and may incorrectly suggest that the subcutaneous administration of ustekinumab which does not contain EDTA is safe. This may also incorrectly lead to withholding specific treatment options. Furthermore, two patients received a subcutaneous injection of ustekinumab and they experienced similar symptoms following the subcutaneous injection compared with the IV administration. Similarly, a reaction to the excipient L-histidine-mono-hydrochloride-mono-hydrate was considered to potentially cause these reactions, because other biologicals used in the treatment of CD do not contain this excipient. Although biogenic amines, such as histidine, might play a role in non-specific release of histamine, no IgE- or T-cell-mediated hypersensitivity reactions to L-histidine-mono-hydrochloride-mono-hydrate or histidine in general have been described to date.

#### 4. Conclusion

We report three patients with infusion reactions to their first IV ustekinumab while two out of three patients had a history of infusion reactions to infliximab. Awareness and immediate management with corticosteroids during infusion reactions with IV ustekinumab is warranted and rechallenge should be avoided. Future research is needed for a better understanding of the pathophysiology underlying these adverse events.

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#### Conflict of Interest

P.W.A.T. and G.F. have no conflicts of interest to declare. R.L.W. has participated in advisory boards or as a speaker or consultant for the following companies: Abbvie, Janssen. F.H. has served on advisory boards, or as speaker or consultant for Abbvie, Celgene, Janssen-Cilag, MSD, Takeda, Celltrion, Teva, Sandoz and Dr Falk, and has received unrestricted grants from Dr Falk, Janssen-Cilag, Abbvie and Takeda.

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#### Author Contributions

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