



SHORT REPORT

Acute and delayed hypersensitivity reactions to infliximab and adalimumab in a patient with Crohn's disease

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Abstract

A 61 year old woman with active luminal Crohn's disease was successfully treated with infliximab induction therapy followed by 5 infusions every 8 weeks. However, symptoms returned in the weeks preceding the 7th and 8th infusions. The 9th infusion was therefore given only 4 weeks after the 8th infusion, but an acute severe anaphylactoid reaction occurred immediately after start of the infusion. Anti-infliximab IgG antibody concentration was high (100 U/ml) prior to the 8th infusion and up to 1 year after infliximab discontinuation (81 U/ml). Anti-infliximab IgE antibodies were not found, and the anti-infliximab antibodies did not cross react with adalimumab. One week after the anaphylactoid reaction to infliximab, adalimumab therapy was initiated. Twelve days after the first adalimumab administration (80 mg), a delayed hypersensitivity reaction occurred. This was likely caused by rapidly generated anti-adalimumab IgG antibodies (45 U/ml), as these antibodies appeared to be specific for adalimumab in that infliximab failed to compete with adalimumab/anti-adalimumab antibody binding *ex vivo*. In conclusion, immunogenicity to infliximab and adalimumab may be associated with both acute anaphylactoid reactions and delayed hypersensitivity reactions. Reactions may be precipitated by newly induced specific anti-drug antibodies rather than by cross-reactivity of previously generated antibodies.

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Abbreviations: ADA, adalimumab; Ab, antibodies; IBD, inflammatory bowel disease; IFX, infliximab.

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1. Introduction

The TNF- α inhibitors infliximab (IFX) and adalimumab (ADA) are generally well tolerated in patients with inflammatory bowel disease (IBD) but infusion/injection reactions occur.^{1–3} Acute infusion/injection reactions may be seen during administration and can be mild to moderate, or severe: Severe reactions necessitate immediate discontinuation because of hypotension, chest tightness, respiratory distress, and/or urticaria, and may necessitate hydrocortisone and antihistamine therapy. Mild to moderate reactions are usually self-limiting and resolve spontaneously after temporary cessation or reduction of infusion rate; typical symptoms are nausea, headache, fever, erythema, and itching.^{1,4,5} Delayed reactions occur 1–14 days after drug administration and are commonly associated with myalgias, arthralgias, headache, fever, rash, and fatigue.^{1,4,5}

Although the prevalence of acute and delayed reactions to IFX and ADA is relatively low, both types of reactions constitute a serious clinical problem because of the severity and the subsequent discontinuation of the drug.^{4,6} Little is known about the precise mechanisms underlying these reactions, including a possible role of anti-drug antibodies (Ab). We report a case of an acute severe hypersensitivity reaction to IFX followed by a delayed reaction possibly caused by anti-ADA Ab.

2. Case report

A 61 year old woman with previous history of fistulizing Crohn's disease, colectomy and ileorectal anastomosis presented with abdominal pain and diarrhea. Endoscopy revealed inflammation and stenosis of the anastomosis. Despite two courses of high dose hydrocortisone the disease still flared when hydrocortisone therapy was discontinued. Azathioprine was contraindicated due to liver toxicity. Consequently, the patient started IFX monotherapy (5 mg/kg). There was an immediate and substantial reduction of symptoms as well as clinical improvement after the induction phase (weeks 0, 2, and 6) which persisted at the subsequent five infusions given every 8 weeks. However, in the weeks preceding the 7th and 8th infusions the patient described recurrence of symptoms. Blood samples immediately prior to the 8th and 9th IFX infusion (trough level) were therefore obtained and stored in a biobank in order to retrospectively assess immunogenicity, if it was judged necessary by the treating physician. All anti-drug Ab test results were obtained after discontinuation of both IFX and ADA therapies. Anti-drug Ab and drug concentrations were measured using clinically validated commercially available radioimmunoassays.^{7–10}

Immediately before the 8th IFX infusion, the circulating level of anti-IFX IgG Ab was high (100 U/ml = upper detection limit), and the serum IFX concentration was below the detection limit (<0.01 μ g/ml); see Fig. 1. The patient had no clinical effect of the 8th IFX infusion, and rapidly worsening of symptoms lead to a 9th infusion only 4 weeks later. Anti-IFX IgG Ab- and IFX concentrations prior to the 9th infusion were unchanged, again with a high level of Ab (100 U/ml) and undetectable IFX (<0.01 μ g/ml). At the 9th infusion, the patient reacted with anaphylaxis-like symptoms immediate-

ly after start of IFX infusion. The symptoms included severe malaise, severe dyspnoea, precordial chest pain, tachycardia, urticaria, and nausea. IFX was immediately discontinued and symptomatic treatment with intravenous antihistamine resulted in gradual regression of symptoms within one hour. Despite the clinical resemblance with an anaphylactic reaction, anti-IFX IgE Ab were negative as assessed before the 8th and 9th IFX infusions as well as 31, 140 and 333 days after the reaction (Fig. 1).

Due to continuous disease activity, ADA therapy was initiated one week after the IFX-induced reaction. Twelve days after the first ADA injection (80 mg), the patient presented in the emergency room with urticaria involving the whole body, headache, and severe fatigue. Based on the clinical appearance, and because the patients only medication was ADA, the treating physician concluded that the patient had experienced a delayed hypersensitivity reaction to ADA. ADA was therefore discontinued, and the patient received a three day course of high dose hydrocortisone and antihistamine. Anti-ADA Ab were negative at repeat assessments prior to ADA initiation. Nineteen days after the reaction, i.e. 31 days after the anaphylactoid reaction to IFX, anti-ADA IgG Ab were measured at a relatively high level (45 U/ml); anti-ADA IgE Ab was negative, ADA concentration was 0.39 μ g/ml, and anti-IFX IgG Ab were still present (100 U/ml); see Fig. 1. Thus, the delayed reaction was accompanied by anti-ADA Ab development. To address the etiology of the reaction, we also measured the ability of anti-IFX Ab to cross react with ADA using serum obtained prior to the 8th and 9th IFX infusion where high levels of anti-IFX Ab were demonstrated at a time where ADA had not yet been administered. Interestingly, these high-level anti-IFX Ab did not interfere in vitro with the binding between ADA and the later generated anti-ADA Ab.

Approximately one year after the hypersensitivity reactions, the serum levels of anti-drug Ab were reassessed. The patient had not received any biologic therapy or blood transfusions in this time period. The anti-IFX IgG Ab level was still high (81 U/ml at 333 days after the anaphylactoid infusion reaction to IFX). In contrast, anti-ADA IgG Ab were now undetectable (<10 U/ml at 326 days after the delayed reaction to ADA).

3. Discussion

Acute infusion reactions to IFX are reported in up to 40% of IBD patients, acute severe reactions in less than 5% of patients, and delayed reactions in approximately 2%.^{1,4,5} The prevalence of reactions to ADA is generally lower.⁶ The role of anti-drug Ab in these reactions is disputed.^{1,6,11,12} Clinical resemblance with anaphylactic reactions suggests that at least some acute severe infusion reactions to IFX might be caused by type 1 hypersensitivity reaction mediated by anti-IFX IgE Ab, and an IgE associated reaction to IFX has actually been described in a single child with Crohn's disease, and in three patients with rheumatoid arthritis.^{13,14} However, we have recently presented data strongly indicating that acute severe infusion reactions are usually not IgE-mediated anaphylactic reactions but rather associated with development of anti-IFX IgG Ab in IBD patients.¹¹

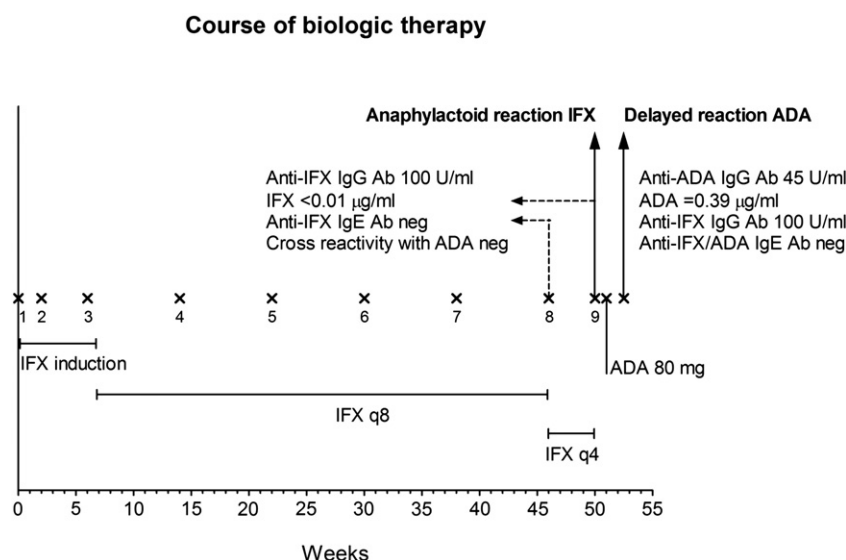


Figure 1 Course of biologic therapy. Course of infliximab (IFX) and adalimumab (ADA) therapy (q is frequency of administrations) in a patient with acute severe anaphylactoid reaction to IFX associated with anti-IFX IgG antibodies (Ab) and delayed injection reaction possibly to ADA associated with anti-ADA IgG Ab. Cross reactivity of anti-IFX Ab with ADA before the reaction to ADA was negative.

We present a case of a severe anaphylactoid reaction to IFX (i.e. a reaction resembling anaphylaxis but apparently not caused by IgE Ab), which was associated with high levels of circulating anti-IFX IgG Ab in an individual patient, and not with IgE Ab. Anaphylactoid reactions may be difficult to distinguish clinically from 'true' IgE-mediated anaphylaxis, and current data indicate that anaphylactoid reactions are a more common cause of acute severe infusion reactions to IFX as compared to IgE-mediated anaphylaxis.^{5,11,15} However, it should be noted that other mechanisms not involving anti-IFX Ab, e.g. cytokine release syndrome, may underly such reactions.^{5,16}

Even though immunological tolerance to IFX may be induced in some patients with previous acute severe infusion reactions to the drug,⁵ the most common approach to continued biological therapy is switching to ADA, which was also the case here. Twelve days after the first ADA injection, the patient developed a generalized urticaria-like skin reaction accompanied by severe fatigue and headache. The timing and symptoms are typical for delayed drug reactions, and in this case, the patient did not receive other medications at this time.^{4,17,18} The last IFX infusion was 19 days prior to the delayed reaction, and at this time only very little IFX was infused because the patient developed an acute severe anaphylactoid infusion reaction immediately after start of infusion. Thus, the last complete IFX infusion was 47 days prior to the delayed reaction. Delayed reactions usually occur 1–14 days after administration, and the timing of the reaction therefore indicates that it was caused by a reaction to ADA rather than to IFX.¹⁷ Despite the patient having high levels of anti-IFX Ab at the time of ADA administration, testing at multiple time points showed that anti-IFX Ab did not bind to ADA making it unlikely that the delayed reaction was caused by cross reaction between anti-IFX Ab and ADA. On the other hand, the delayed reaction was associated with development of anti-ADA IgG Ab.

The kinetics by which Ab against IFX and ADA are generated are largely unexplored. Disappearance of anti-IFX Ab during maintenance therapy has been reported, and

anti-IFX Ab may have a relatively short half-life following IFX discontinuation.^{19,20} In our case, anti-IFX IgG Ab were still highly elevated one year after IFX discontinuation having only decreased from 100 to 81 U/ml. In contrast, anti-ADA IgG Ab was undetectable 11 months after ADA discontinuation having decreased from 45 U/ml.

In conclusion, IgG Abs to IFX and ADA were associated with the development of an acute severe anaphylactoid reaction and a delayed hypersensitivity reaction.

Competing interests

Morten Svenson is an employee at Biomonitor A/S. Within the last three years, Klaus Bendtsen has served as a speaker for Pfizer, Wyeth, Roche, Novo-Nordisk, Bristol-Meyers Squibb, and Biomonitor A/S; and owns stocks in Biomonitor A/S. Ole Østergaard Thomsen has served as a speaker and consultant for Schering-Plough, UCB, and Zealand Pharma. Casper Steenholdt, Jørn Brynskov, and Mark Andrew Ainsworth have no interests to declare.

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CS participated in the design and coordination of the study, data collection, data analysis, and manuscript drafting. MS carried out the samples analyses and participated in the data analysis. KB participated in the design of the study, data analysis, manuscript drafting, and provided

significant scientific advice. ØØT, JB, and MAA participated in the design of the study, data analysis, manuscript drafting, and provided significant scientific advice. All authors read and approved the final manuscript.

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