

CASE REPORT

Anaphylaxis-Like Reaction to Infliximab in a Patient with Crohn's Disease

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Therapy with infliximab has been well tolerated with minimal and short-lived adverse effects (headache, nausea, upper respiratory tract infections, fatigue, and dizziness) and compares favorably with chronic corticosteroid and other immunomodulator therapy (1). However, unique to infliximab, the formation of autoantibodies and drug-induced lupus, human anti-chimeric antibodies (HACA), and human anti-human antibodies (HABA) with both acute and delayed hypersensitivity infusion reactions have been reported (2). These reactions have been "serum sickness"-type reactions with severe myalgias being the predominant clinical symptom. We report a case of an anaphylaxis-like reaction and discuss the potential safety issues surrounding monoclonal antibody therapy.

CASE REPORT

The patient is a 36-year-old man with a 16-year history of Crohn's disease that became refractory to standard anti-inflammatory therapy including corticosteroids, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, and home total parenteral nutrition at various times over the past two years. He had developed a serum sickness reaction to 6-mercaptopurine (6-MP). The disease involved the both the left and right colon and the ileum and included colonic fistulization. Clinical remission lasting 8 months was achieved with a single infusion of infliximab (5 mg/kg).

With the onset of a clinical relapse, the patient was given a repeat infliximab infusion (5 mg/kg) at home. He experienced nausea, dizziness, dysphagia, facial urticaria, pruritis, shortness of breath, and chest pressure after 5 min of the infusion. There was no wheezing, cyanosis, angioedema, or

hemodynamic instability. He was taken immediately to a nearby hospital where these symptoms resolved spontaneously in approximately 20 min, prior to receiving intravenous fluids, corticosteroids, and diphenhydramine. There was no history of previous drug sensitivities or allergic symptoms except for the 6-MP. The patient was electively admitted to the medical intensive care unit in our hospital for desensitization to infliximab, as it was unclear whether his reaction represented true anaphylaxis, an anaphylaxis-like reaction, or a vasovagal response. Because of high-dose corticosteroid use and malnutrition, he was not deemed an optimal surgical candidate.

The patient was in no distress. He appeared cushingoid. His temperature was 98.6°F, blood pressure 91/50, pulse 59, and respiratory rate 12. His height was 76 inches and weight was 150 lbs. The physical examination and laboratory studies were normal. Histamine level was at 20 mmol/liter. Electrocardiogram and chest radiograph were normal.

Infliximab was diluted 1:10 and 1:100 (v/v) in phosphate-buffered saline (PBS, pH 7.4). Percutaneous scratch testing was performed with undiluted infliximab, each dilution, positive control (histamine sulfate), and negative control (PBS). Skin was examined 20 min later for the presence of wheal and flair. There were appropriate reactions to the histamine control, but none of the three concentrations of infliximab caused a skin reaction in excess of that of the PBS alone. On the basis of these tests, an infusion of infliximab 5 mg/kg over 3 hr was planned. No premedication was given so that any infusion reaction could be detected. Our desensitization protocol called for a test dose of 1 ml of the drug (341 mg of infliximab in 250 ml normal saline) to be given with subsequent increases of 2, 4, and 8 ml given at 15-min intervals. Once the patients tolerated the 8-ml dose, the infusion was to be initiated as 2 ml/min.

Within 1 min of receiving the test dose of infliximab, the patient became nauseated, flushed, diaphoretic, and experienced severe back pain and difficulty speaking secondary to a sense of throat swelling. His blood pressure was 110/70, pulse 150 and respiration rate 24. His lungs were clear and cardiac examination revealed sinus tachycardia. There were no skin lesions or laryngeal symptoms noted. The infusion was stopped and two doses of 50 mg intravenous diphenhydramine and 20 mg intravenous famotidine were given with complete resolution of symptoms after 20 min. The patient was transferred to a monitored bed. Intravenous cyclosporine and hydrocortisone were initiated and after 48 h, the patient had significant clinical improvement. He

Manuscript received September 15, 2000; revised manuscript received October 5, 2001; accepted October 31, 2001.

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was then given etanercept 25 mg subcutaneously twice weekly, and discharged home in stable condition. Clinical remission was again achieved, although the patient relapsed within two weeks of corticosteroid discontinuation. Etanercept was discontinued and thalidomide (200 mg by mouth, nightly) was initiated. Complete clinical remission was achieved after two weeks. The patient has recently undergone elective surgery to remove the most significantly involved areas of his terminal ileum and colon. The thalidomide has been discontinued, and the patient remains symptom-free.

DISCUSSION

We present a case of anaphylaxis-like reaction to infliximab. Two other similar experiences have been reported (3, 4). Our patient developed a reaction within 1 min of the initiation of the infliximab infusion. This immediate effect suggests a type I hypersensitivity reaction due to the release of immune mediators (histamine, leukotrienes, adenosine, prostaglandins, platelet-activating factor, proteoglycans or certain enzymes) from IgE-sensitized mast cells or basophils.

IgE-dependent drug reactions most commonly effect the gastrointestinal, integumentary, respiratory, and cardiovascular systems, with symptoms including urticaria, pruritis, nausea, vomiting, bronchospasm, and laryngeal edema possibly culminating in shock and death (5). It is less likely that our patient's reaction represents an immune-complex-mediated anaphylaxis. Circulating antibody-antigen complexes are responsible for this type of anaphylaxis with the antibodies usually of the IgM or IgG class. Symptoms from this type of allergic drug reaction usually develop within a week, but not immediately, after exposure to the drug and include serum sickness-type manifestations of fever, edema, nephritis, neuritis, and a papular, pruritic rash (5). No baseline IgE, histamine, C3, or C4 values were obtained on our patient; however, five days following the reaction, the patient's levels were all within normal range. Unfortunately, tryptase levels were ordered but never obtained. Although skin testing to infliximab was negative, this did not exclude the possibility of an IgE-mediated mechanism, as the dose used in the skin test was quite dilute (one drop of the standard concentration) and there is no commercially available infliximab-specific IgE test.

Type I hypersensitivity reactions have occurred with other monoclonal antibody therapies including rituximab, a chimeric monoclonal antibody that binds to the CD20 antigen on B lymphocytes used in non-Hodgkin's lymphoma; edrecolomab, a murine mono-

clonal antibody 17-1A used in gastrointestinal malignancies; and many others containing murine elements, partial murine and partial human combinations, and even all human components (6, 7). The immunogenicity of monoclonal antibodies varies with the amount of foreign (murine) material.

Antibodies produced against infliximab could potentially decrease its serum half-life and therapeutic efficacy (8, 9), although data are conflicting (10), and these antibodies would be of the IgM or IgG class. More importantly, these anti-infliximab antibodies could produce adverse effects through immune complex formation and complement fixation or immediate hypersensitivity (11). Studies reveal the formation of HACA with serum-sickness symptoms in up to 13% of patients with Crohn's disease after a single dose of the chimeric anti-TNF- α antibody (2, 11) and in up to 25% following multiple doses over an extended period of time with a long intervening period between dosing (12, 13). This increases the potential for subsequent infusion reactions, although with infliximab there appears to be a lower potential for delayed hypersensitivity reactions, and perhaps HACA formation when repeated doses are given within a shorter time interval (eg, less than one year apart) (14). Administration of concurrent immunosuppressive therapy with azathioprine or 6-mercaptopurine may also be associated with decreased HACA formation and prolonged remission (9).

One must consider several factors of immunogenicity when choosing monoclonal antibody therapy. All types of monoclonal antibody therapy have the potential to induce human anti-murine antibodies (HAMA), HACA, and human anti-idiotypic antibodies. Mouse-derived monoclonal antibodies appear to be more immunogenic (33–60% of patients treated with murine monoclonal antibodies develop human anti-mouse antibodies) (14), more so than chimeric and human products. However, recent data suggest antibody formation to a humanized TNF antibody may be similar to that of infliximab (3). The development of severe, systemic reactions with chimerized or humanized monoclonal antibodies is rare. The dose, route of administration, frequency of treatment, effects of concurrent immunosuppressive therapy and immunomodulatory effects of the antigen are as important as its components when considering immunogenicity. Infliximab is a significant advance in the treatment of Crohn's disease. However, future studies will be necessary to examine optimal patient subsets, dosage regimens, possible combination therapy, and means to diminish the immunogenicity of infliximab.

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