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CASE REPORT

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Anaphylactic reaction to infliximab in two rheumatoid arthritis patients who had previously received infliximab and resumed

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Abstract Here we report on two cases of anaphylactic reaction following infliximab infusion in patients with active rheumatoid arthritis (RA). Both individuals had received infliximab treatment during a clinical trial approximately 2 years prior to further therapy; subsequent infusion of this agent led to anaphylactic reactions in both cases. In light of these findings, we recommend that future treatments with infliximab in RA patients who have previously received this agent should be carefully monitored.

Key words Anaphylactic reaction · Human antichimeric antibody (HACA) · Infliximab · Rheumatoid arthritis (RA)

Introduction

A number of new biological agents that allow broader treatment options for individuals suffering from rheumatoid arthritis (RA) have recently been developed. Among the most notable is infliximab, which is a chimeric (part murine and part human) monoclonal antibody that binds with high affinity and specificity to tumor necrosis factor (TNF)-α in order to neutralize its biological activity.[1–3]

As with any infused protein-derived agent, clinical trials using infliximab have assessed the potential of the drug to elicit adverse events, including reactions caused by its infusion. Overall, the incidence of infusion reactions to infliximab is low (approximately 5%).[4] However, in some reported cases of Crohn's disease, in which the infliximab infusion intervals are longer than those for RA treatment, severe infusion reactions have been observed.[5,6]

Since November 2003, our institution has used infliximab to treat RA patients who have an inadequate response to conventional methotrexate (MTX) treatment. To date, 14 active RA patients have been treated with infliximab. Here we report on two RA patients who had previously received infliximab treatment during a clinical trial in Japan. Subsequent treatment, approximately 2 years later, elicited anaphylactic reactions in both cases.

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Case reports

Case 1

A 53-year-old woman with a 13-year history of RA participated in an infliximab clinical trial from January to September 2001. Prior to participating in the trial, she had been treated with an 8-mg weekly dose of MTX since November 1999, but had showed an inadequate response to this therapy. She experienced no adverse events from the infliximab (3 mg/kg) treatment during the trial period and a 20% improvement from the baseline was observed at 36 weeks according to the response criteria of the American College of Rheumatology (ACR20). Treatment with infliximab was discontinued at the end of the clinical trial and the patient was again treated with 12 mg weekly dose of MTX.

The clinical use of infliximab was approved in Japan in July 2003. Subsequently, infliximab treatment was resumed in this patient in January 2004. There was no reaction following the first infusion, and the swelling and tenderness caused by the arthritis decreased. However, on day 10 after the first infusion of infliximab, the patient had a fever of 38.5°C and a visible skin rash covering her whole body. Laboratory tests revealed an elevated white blood-cell count (16100/μl), and increased C-reactive protein (8.5 mg/dl) and lactate dehydrogenase (506 IU/l) levels. The patient was hospitalized and given 100 mg of hydrocortisone. After 2 days, she had recovered and was discharged. Prior to the next infusion, olopatadine hydrochloride (10 mg/day) was administered to prevent an allergic reaction. This time we maintained an infusion rate of 9 mg of infliximab per hour,

which is less than half the normal speed. Fifteen minutes after infusion, the patient experienced a skin rash and itching, followed by dyspnea and a swollen throat. Infusion was immediately stopped and the patient was given 50% oxygen, 200 mg of hydrocortisone, and 125 mg of methylprednisolone intravenously. We found no apparent abnormalities in other vital signs or laboratory data (body temperature, 36.7°C; blood pressure, 100/70 mmHg; heart rate, 70 beats/min; oxygen saturation, 100%). The symptoms had disappeared completely within 2 h of preventative treatment. The patient was observed overnight and was discharged the following day.

Case 2

A 49-year-old woman with a 16-year history of RA participated in an infliximab clinical trial from February to November 2001. She showed no adverse events during the trial period and an ACR20 response was observed at 36 weeks. Following the completion of the clinical trial, she was treated with 10.5 mg of MTX. After an interval of approximately 2 years, infliximab administration was resumed.

During the first infusion, the patient's body temperature rose temporarily from 35.6° to 37.6°C, and then steadily decreased to the baseline level after treatment had ceased a few hours later. No adverse events were observed during the second and third infusions. However, during the fourth infusion, the patient experienced sweating and looked visibly pale 10 min after the commencement of infusion. Her systolic blood pressure (SBP) dropped from 150 to 78 mmHg with a normal range heart rate of 80 beats/min. No skin lesions or laryngeal swelling were observed. Infusion was immediately stopped, and the patient received 100 mg of hydrocortisone with lactate Ringer intravenously. Following this treatment, her SBP initially rose to 100 mmHg and finally reached 140 mmHg 2 h after infusion ceased. There was no significant difference in blood parameters before and after the infusion.

Discussion

Infusion reactions to infliximab can be categorized as either acute or delayed. An acute infusion reaction is defined as any adverse reaction, whether immunologically or nonimmunologically based, which occurs during, or within 24 h of, the infliximab infusion. A delayed infusion reaction is defined as any adverse reaction that occurs between 24 h and 14 days after the infusion. Severe anaphylactic or anaphylactic-like reactions – including hypotension, laryngeal/pharyngeal edema, and severe bronchospasm – rarely occur following infliximab infusion.[5,6] By contrast, delayed hypersensitivity- or serum sickness-like reactions have occurred in individuals with Crohn's disease who have received an initial therapy of infliximab and have subsequently undergone a 2- to 4-year break from treatment.[4,7]

The incidence of severe infusion reaction was approximately 0.5% in RA patients.[8,9] But up to the present severe infusion reactions, which occurred in RA patients who had previously undergone infliximab treatment and resumed at some intervals, have not been reported. In the present study, both patients had received previous infliximab treatment prior to the infusion that elicited an anaphylactic reaction. We therefore propose that for the cases described in this report, prior treatment with infliximab infusion was a risk factor for anaphylactic reaction.

It remains unclear what kind of immunological reaction occurs during such a serious infusion reaction. One possibility is the development of an antibody against infliximab. Recent clinical studies have shown that concurrent immunosuppressant and/or corticosteroid therapy reduces the frequency of human antichimeric antibody (HACA) formation, and that patients who develop HACA antibodies are more likely to develop acute infusion reactions.[10] However, another study found that the presence of HACA had little impact on the efficiency of a severe infusion reaction.[11] Compared with low dosages of infliximab, immunologic tolerance to infliximab was induced by higher dosages of

Table 1. Summary of both cases

	Case 1	Case 2
Interval from the final infusion of the clinical trial	28 months	24 months
Dosages of infliximab	3 mg/kg	3 mg/kg
Concomitant drug		
MTX/week	12 mg	10.5 mg
PSL/day	5 mg	0 mg
Infusion reaction		
Times/time from infusion	First time/10 days	First time/10 min
Symptom	Rash, fever	Fever
Anaphylactic-like reaction		
Times/time from infusion	Second time/15 min	Fourth time/10 min
Symptom	Rash, dyspnea, swollen throat	Hypotension
HACA		
First injection	Negative	Negative
Just before anaphylactic-like reaction occurred	Positive 1:1280	Positive 1:160

MTX, methotrexate; PSL, prednisolone; HACA, human antichimeric antibody

infliximab.[12] Although the mechanism that leads to decreased immunogenicity of infliximab at the higher dosages has not yet been explained, loss of infliximab in the serum may be relevant in inducing tolerance. Human antichimeric antibody levels are often not measured when infliximab treatment is administered at intervals of 8 weeks or less, because HACA is undetectable when infliximab is present in the serum. However, in the present cases HACA was identified (measured later) in the serum of both patients immediately before the infliximab treatment was resumed (Table 1).

In conclusion, we have reported two cases of anaphylactic reaction following infliximab infusion for the treatment of RA. These findings indicate that previous treatment with infliximab is a risk factor for severe infusion reaction in RA patients who are undergoing a new course of therapy with this agent. We therefore strongly recommend the careful monitoring of RA patients who receive infliximab treatment following a previous infusion, particularly after a lengthy interval.

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