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Delayed systemic reactions to infliximab retreatment in Crohn's disease

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Abstract

Objective: To improve the understanding of Delayed systemic reactions to infliximab retreatment.

Method: Two cases of anaphylactic reaction following infliximab infusion in patients with active Crohn's disease(CD) were reported. Both had previously received infliximab treatment over more than one year ago. Related literatures were reviewed.

Result: Two young male CD patients who obtained remission after infliximab treatment several years ago got flared and received infliximab infusion again. One got arthralgias and the other got myalgias. Both relieved after discontinuation.

Conclusion: A distant infliximab retreatment is associated with high rates of anaphylactic reaction. Careful monitoring should be adopted in those patients who receive infliximab retreatment.

Keywords: myalgias, arthralgias, infliximab retreatment, Crohn's disease

Introduction

Infliximab is a chimeric antibody to tumor necrosis factor-alpha targets on human immune system. It provided a dramatic improvement in our ability to care for refractory Crohn's disease(CD) patients. Since Infliximab came into commercial use in China in 2006, its adverse reactions are rarely reported.

Here we report two cases of infliximab retreatment in Crohn's disease, both had delayed systemic reactions. The diagnosis of CD was based on routine histological, endoscopic, radiological, and clinical criteria.

Case report

Case 1

A 18-year-old male student from Jiangxi Province was diagnosed as Crohn's disease(CD) in July, 2012. ASA was adopted but the disease flared in Jan 2013 and infliximab was infused. After that, autologous bone marrow-derived stem cell transplantation was done twice in some hospital but received no remission. Admission to our hospital was in Feb 2014 due to the flare of the disease. Five infusions of infliximab 5 mg/kg was adopted from 26th, Mar 2014 and got relieved from the symptoms of hematochezia and abdominal pain. From 1st, May, the student got myalgia in his right thigh and arthralgia in his right knee accompanied by elevated skin temperature and restricted bending. Adalimumab was administered in 29th, Oct 2014 and the reactions all tapered afterward.

Case 2

A 20 year-old male student from Jiangsu Province was diagnosed as CD in August, 2012 and received infliximab infusion from 15th, August the same year. Mild liver dysfunction was appeared after first infusion which got relieved from medication. The next 5 infusion got good results without liver dysfunction. He did not follow the doctor's advice and received no treatment after that. Due to the increase of stool frequency with blood, and colonoscopy examination showed multiple ulcers scattered in the terminal ileum and the whole colon on 8th, April 2018. He was admitted into our hospital and considered as flare of CD. Infliximab was adopted to him again on 27th, April. He got myalgias in hipbone which relieved from rest. He came to do second infusion on 26th, April, but he got rash in whole body and dizzy during the process with no itchy skin, no dyspnea, no abdominal pain or distension. So infusion was

suspended. Dexamethasone and oxygen inhalation was adopted. After these measures, rash and dizzy was relieved. The treatment was switched to mesalazine and got no myalgias.

Discussion

Infliximab consists of both human and murine portions. The murine binding portion, comprising 25% of the antibody, is antigenic. Previous reports are mostly of anaphylaxis when infliximab is used again in the treatment of rheumatoid arthritis and ankylosing spondylitis.

Infusion reaction of infliximab after re-administration could be divided into two kinds. One is acute systemic reactions, the other is delayed systemic reactions. Acute systemic reaction is anaphylactic/anaphylactoid reaction occurred during infusion or 24hs after infusion, manifested as drop in blood pressure, mucosal irritation, chest tightness, difficulty breathing, and "sense of impending doom". The vast majority of acute systemic reaction to IFX is not IgE-mediated[1]. Delayed systemic reactions happened after 48hrs of infusion. Most anaphylactic reactions are myalgia, arthralgia, arthritis, joint stiffness, leukocytosis and fever. These delayed retreatment reactions were of varying severity, ranging from mild to severe. Serious anaphylactic reactions are laryngeal edema, severe bronchospasm and even anaphylactic shock which rarely happen after infliximab infusion. These symptoms usually respond rapidly to corticosteroids[2]. Delayed infusion reactions in CD were reported in 25% of patients who received infliximab again after a 2–4 year interval without infliximab treatment[3-6].Subra Kugathasan et al[7] found delayed systemic reactions exclusively in adults(age>17yr) and occurred in eight patients treated for luminal Crohn's disease out of 86 adult and pediatric patients receiving 304 infusions of infliximab retreatment. Most severe systemic reactions occurred during the second infliximab infusion. Second infusion 20 weeks or more from the first infusion in CD was a notable risk factor for development of infusion reaction. In case 1 and 2, patients have myalgias and/or arthralgias after several days of re-administration. The interval of the reinfusion both exceeded 20 weeks.

Human antichimeric antibodies (HACA) formation has been associated with infliximab. A review of pooled safety data from clinical trials of infliximab found that 13% of patients developed HACA[8]. Patients who developed HACA were more likely to develop infusion reactions (36%) than those who did not (11%)[5]. In our cases, although we pretreated them with hydrocortisone to reduce the risk of HACA formation, both got reactions. Human

antichimeric antibodies were not tested because of patients' refusal. Although we were unable to measure its concentration in these cases, HACA is often not measured because it is undetectable when infliximab is also present in the serum[9]. Desensitization or induction of tolerance protocol may allow continuation of IFX therapy in CD patients with a history of immediate hypersensitivity reactions[1]. But to those who have severe reactions, it is suggested not to retreat with the same medicine[10]. Accent I Trial suggested that scheduled infusions will result in sustained remission and low rates of severe systemic reaction[11].

It is reported that severe myalgia associated with adalimumab in a patient with Crohn's disease[12]. Adalimumab is a fully human, immunoglobulin G1 monoclonal antibody that binds with high affinity and specificity to membrane and soluble TNF. We had thought that the murine portions in infliximab might play a large part in the acute and delayed reactions, but adalimumab also has these reactions. So until now, we are still in the mist why infliximab could induce the reactions. It needs more experiments and clinical researches.

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