

Successful switching to adalimumab in an infliximab-allergic patient with severe Behçet disease-related uveitis

Kaoru Takase · Shigeru Ohno · Haruko Ideguchi ·
Eiichi Uchio · Mitsuhiro Takeno · Yoshiaki Ishigatsubo

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Abstract Infliximab has demonstrated remarkable effects on controlling uveitis in patients with Behçet's disease (BD). However, there is no way except for discontinuation of infliximab treatment in patients who are intolerant to the agent due to hypersensitivity reactions. We here report successful switching from infliximab to adalimumab in a BD patient. Treatment with infliximab had maintained clinical remission in the patient having refractory ocular lesions to cyclosporine until the patient had experienced repeated infliximab-related infusion reactions. Discontinuation of the therapy led to another ocular attacks immediately. Switching to adalimumab induced clinical remission again. Our experience suggest adalimumab is a safe and effective option for patients having hypersensitivity to infliximab.

Keywords Uveitis · Behçet disease · Adalimumab

Introduction

There is accumulating evidence that treatment with infliximab, a chimeric human murine monoclonal anti-TNF-alpha antibody, is effective for sight-threatening uveitis in Behçet's disease (BD) [1, 2]. Clinical trials including open-label, prospective, and self-controlled studies have demonstrated that repetitive infliximab infusions successfully suppressed relapse of ocular attacks and progressive reduction of visual acuity even in patients who had refractory uveitis to conventional immunosuppressive therapy [2, 3]. Treatment with infliximab has been well tolerated in general. Although most of the adverse events are self-limiting, life-threatening infusion reactions can occur. In such cases, there is no choice but to discontinue treatment with infliximab.

We first report successful switching from infliximab to adalimumab, a fully humanized anti-TNF-alpha monoclonal antibody, in a BD patient who had repeated anaphylactoid reactions during infusion with infliximab.

Case report

A 42-year-old female had been suffering from recurrent ocular inflammatory attacks due to uveitis, oral aphthosis, genital ulcers, and erythema nodosum since November 2001. Based on the clinical manifestations and history, she had been diagnosed with BD. In spite of administration of oral corticosteroids and cyclosporine, she had repeated episodes of severe bilateral ocular attacks leading to the gradual reduction of vision in both eyes. After confirming no sign of latent tuberculosis infection and negative serological tests for hepatitis B and C virus, treatment with infliximab was initiated in June 2007. Intravenous infusion with 5 mg/kg of infliximab was given at 0, 2, 6, and 14 weeks

K. Takase · S. Ohno (✉) · H. Ideguchi
Center for Rheumatic Diseases,
Yokohama City University Medical Center, 4-57 Urafune-cho,
Minami-ku, Yokohama, Kanagawa 232-0024, Japan
e-mail: ohno@urahp.yokohama-cu.ac.jp

E. Uchio
Department of Ophthalmology,
Yokohama City University Medical Center,
Yokohama, Japan

M. Takeno · Y. Ishigatsubo
Department of Internal Medicine and Clinical Immunology,
Yokohama City University Graduate School of Medicine,
Yokohama, Japan

and then every 8 weeks with a combination of cyclosporine. Thereafter, she had been free of ocular attacks for more than 1 year.

In July 2008, she developed dyspnea, hypotension and hypoxemia at 20 min after the 9th infusion, in spite of pre-medication with D-chlorpheniramine maleate. Systolic blood pressure dropped from 120 mmHg to lower than 80 mmHg and oxygen saturation was 85%. The conditions recovered in the next 30 min by intravenous injection with methylprednisolone (40 mg) and oxygen inhalation. Because the episode was considered to be an anaphylactoid infusion reaction against infliximab, 40 mg of intravenous methylprednisolone in addition to D-chlorpheniramine maleate was given prior to infliximab at the 10th infusion in September 2008. Nonetheless, a similar anaphylactoid reaction developed again immediately after the initiation of an infliximab infusion. Besides another shot of methylprednisolone, infusion with infliximab was stopped before less than 50 mg of the agent was administered, leading to an improvement of the conditions. However, uveitis subsequently recurred during the next 2 months. This was the first attack since the infliximab therapy was initiated. Thus, anti-TNF therapy was considered to be essential to prevent ocular attacks. After obtaining the patient's written informed consent, therapy was switched in November 2008 from infliximab to 40 mg s.c. of adalimumab every 2 weeks. Thereafter, the patient experienced neither ocular attacks nor adverse effects for more than 6 months.

Discussion

It is now established that TNF is a therapeutic target, especially in BD patients with serious uveitis [1, 2, 4, 5]. In Japan, more than 300 patients with refractory uveitis have been receiving infliximab since the agent was approved in 2007. Treatment with infliximab is well tolerated in most BD patients as shown in several clinical trials. In our patient, who had sight-threatening bilateral panuveitis refractory to conventional immunosuppression, infliximab therapy effectively controlled ocular attacks until she developed anaphylactoid symptoms after the ninth infusion. Moreover, immediate recurrence of an ocular attack after discontinuation of infliximab suggested that TNF inhibitor greatly contributed to controlling the disease activity in the patient. Similarly, recurrent ocular attacks were frequently found after discontinuation of the infliximab therapy as a rebound phenomenon in patients who participated in the short-term clinical trial in Japan, (Ohno Trial). Moreover, we have previously shown that the relapses were associated with increasing numbers of circulating TNF secreting cells in peripheral blood mononuclear cells (Misumi ELISPOT), indicating that TNF plays a critical role in the development

of ocular inflammatory attacks and other manifestations in BD patients. Therefore, an alternative anti-TNF therapy was considered as being essential after infliximab was discontinued in the present patient.

Because infliximab is a genetically engineered antibody consisting of 25% murine sequences in the variable region of the antibody, some patients developed antibodies against infliximab, which is designated as human anti-chimeric antibody (HACA). In the published clinical trials, 14.5–17.1% of patients with Crohn's disease treated with infliximab developed HACA [6, 7]. The longer observation was associated with increased frequency of positive HACA in the clinical trial in Japan. The frequency relies on additional immunosuppressive therapies. In the ACCENT I randomized trial for Crohn's disease, HACA was detected in 8.2% of patients receiving any immunosuppressant agents, and in 17.2% of those without immunosuppressive therapy. However, it is uncertain whether HACA production is inhibited by cyclosporine, which is the most widely used immunosuppressant in BD patients in Japan.

HACA is clinically implicated in infusion reactions, including anaphylactoid reactions and attenuation of efficacy. The clinical course suggested the patient was positive for HACA, though it was not examined. Unlike infliximab, adalimumab is a genetically engineered and fully humanized IgG1 anti-TNF- α monoclonal antibody. Adalimumab has shown comparable efficacy to infliximab in rheumatoid arthritis, psoriasis, and Crohn's disease. The pharmacological profile of adalimumab is similar to that of infliximab except for administration route and interval. Because HACA does not bind to adalimumab, HACA related infusion responses and reduction of the efficacy can be circumvented, theoretically, by switching from infliximab to adalimumab. Indeed, clinical trials have shown that switching to adalimumab maintained clinical response in 50.8–85.0% of Crohn's disease patients who were intolerant to infliximab [8, 9]. Therefore, adalimumab was established as an alternative option for patients with Crohn's disease.

Data concerning the efficacy of adalimumab are still limited, though sporadic reports have shown that adalimumab is effective in maintaining remission in BD [10, 11]. Although etanercept, a soluble TNF receptor fusion protein, is considered as an alternative candidate for TNF blocker, the available data have suggested that etanercept is not as effective as infliximab on ocular inflammation [12–14]. Taken together, we decided to use adalimumab in the patient. As expected, switching to adalimumab has maintained the disease remission and prevented relapse. Adalimumab may be a safe and effective therapeutic option in BD patients who have an attenuated response or an anaphylactoid reaction to infliximab. It is important to accumulate such case reports until controlled trials of adalimumab evaluate the benefits and risks.

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