Case report

A case of refractory intestinal Behçet's disease treated with tocilizumab, a humanised anti-interleukin-6 receptor antibody

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ABSTRACT

We describe a young female patient who had refractory intestinal Behçet's disease that responded to tocilizumab, a humanised anti-interleukin-6 receptor antibody. The patient had suffered from long disease activity courses and was treated with multiple medications, and the disease became refractory when immunosuppressants (e.g. thalidomide, sulfasalazine and azathioprine) were limited for poor remission, methylprednisolone pulse therapy, cyclophosphamide, and biological agents (e.g. adalimumab or infliximab) were restricted due to side effects after administration. Therefore, tocilizumab was considered as a therapeutic option and the symptoms resolved during 9 months of administration. Tocilizumab may be a good choice for intestinal Behçet's disease refractory to conventional treatment.

Introduction

Behçet's disease (BD) is a systemic inflammatory disease characterised by recurrent oral aphthous and genital ulcers, skin and ocular lesions. In addition, there are some much less common manifestations (*e.g.* neurological, gastrointestinal, and vascular involvement). Intestinal BD occurs in 3-60% of patients with BD (1). The aetiology of BD is known that genetic and environmental factors interact with each other. Several studies (2) have shown that the serum levels of cytokines, including IL-2, IL-6, IL-8, IL-10, IL-17, IFN-γ, and TNF-α are elevated in patients with active BD. IL-6 is the only cytokine that has been found to be elevated in the cerebrospinal fluid of patients with neurological BD (3). Moreover, various studies have found a significant elevation of IL-6 in the ocular fluids derived from refractory uveitis patients and animal models (4). These findings indicate that IL-6 may play a pathogenic role in BD, and may be a potential a candidate target molecule for the treatment of BD. In the present case, we used tocilizumab to treat a patient with refractory intestinal BD.

Case report

Our patient, a 30-year-old female, diagnosed with BD in 2001 based on the presence of recurrent oral and genital ulcers, erythema nodosum on her lower extremities, and a positive pathergy test, which met the classification criteria for BD. The patient was initially treated with prednisolone in 1.0 mg/kg/d, but her disease often relapsed when prednisolone tapered below 0.5 mg/kg/d. In January 2009, thalidomide (50 mg/d) was added for disease relapse. In October 2009, she gradually developed lower abdominal pain, persistent diarrhoea (7–8 times/d), and gastrointestinal endoscopy revealed the presence of ulcers in the terminal ileum (Fig. 1a), consistent with intestinal BD. Initial blood monitoring revealed a raised ESR at 49 mm/h (normal<20mm/h) and CRP at 56.5 mg/L (normal<8mg/L), and the disease activity index for intestinal BD (DAIBD) (5) was 80, which indicated severe intestinal BD. Thalidomide (50 mg/d) and methylprednisolone pulse therapy (200 mg/d for 3 days, followed by oral prednisone in 1.0 mg/kg/d), and infliximab, a monoclonal chimeric antibody against TNF-α (dose of 5 mg/kg, at weeks 1, 2, and 3, then every two weeks, for a total of 12 times), which contributed to almost complete disease remission until it was suspended for tympanitis in August 2010. Then thalidomide (50 mg/d), prednisolone (0.5 mg/kg/d) and sulfasalazine (2000 mg/d) were used to control disease. When the

disease relapsed again in June 2011, azathioprine (50 mg/d) was added to strengthen immunosuppressive therapy and her manifestations improved gradually for a long time. In February 2014, however, the patient developed a fever up to 40ºC in conjunction with severe abdominal pain. Endoscopy revealed multiple giant-ulcers in ileum and colon. Methylprednisolone pulse therapy was restricted due to femoral head necrosis, and cyclophosphamide was not administered for gastrointestinal side effects. Therefore, we started the administration of adalimumab, a fully humanised anti-TNF-α monoclonal antibody, with a dose of 40mg and every two weeks per time and her clinical manifestations of intestinal BD resolved gradually. However, it was discontinued for allergic reaction in the 13th treatment, which presented as obvious swollen and rash at the injection site, edema of her mouth and eyes, and severe dyspnea. Unfortunately, the patient was also hypersensitive to infliximab in a subsequent treatment attempt. Similarly, we chose etanercept (ETN, 25 mg per time, twice per week), a soluble TNF-α binding protein, as a potentially beneficial drug for our patient. However, the frequency of abdominal pain and diarrhoea deteriorated after two courses of ETN treatment. In that case, patient's symptom and endoscopy (Fig. 1b) were deteriorated and we considered tocilizumab as a therapeutic option. In July 2015, treatment with tocilizumab at a regular dose of 8 mg/kg following a defined treatment schedule (week 0, 2 and then every 4 weeks), as well as prednisolone (1 mg/kg/d, with rapid tapering and withdrew), azathioprine (50 mg/d), and thalidomide (50 mg/d). The disease manifestation gradually went into remission, and her serum concentration of IL-6 decreased from 337.3 pg/mL (normal<4pg/mL) to 11 pg/mL after the first infusion. During the course of treatment with tocilizumab, the clinical manifestation were recurrent mildly, was accompanied by enhanced levels of IL-6. Overall, her condition and endoscopy images (Fig. 1c) improved during the nine-month follow-up period, and there were no adverse events reported. Variation

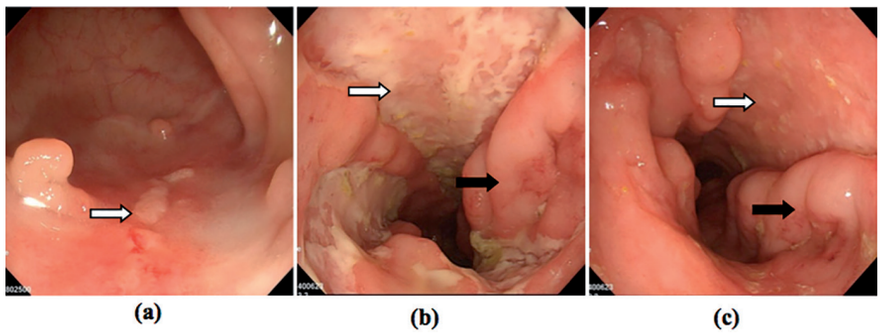

Fig. 1. Lower gastrointestinal endoscopic observations.
(**a**) First onset, lower gastrointestinal endoscopy revealed ulcers (white arrow) in the terminal ileum;(**b**) Before the initiation of tocilizumab, giant-ulcers (white arrow) in the colon with polypoid lesions (black arrow); (**c**) Three months after the treatment of tocilizumab, endoscopy revealed remission of the ulcers and lesions.

Fig. 2. Variation of DAIBD scores during the nine month of tocilizumab treatment.

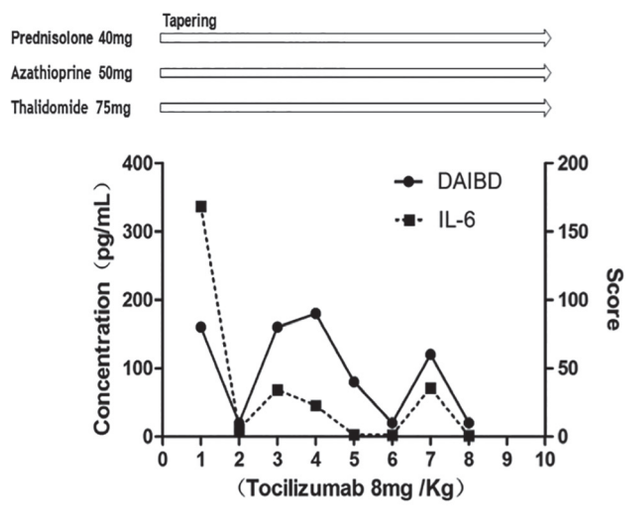

Fig. 3. Variation of symptom and serum concentration of IL-6, ESR, and CRP during the nine month of tocilizumab treatment.

Injection (tocilizumab)	Diarrhoea (times/d)	IL-6 (pg/mL)	ESR (mm/h)	CRP (mg/dL)
1st	6-8	337.3	14	21.2
2nd	2-3	11	1	1
3rd	4-6	68.9	2	1.58
4th	3-4	45.6	3	1.36
5th	2-3	2.9	<1	<1
6th	2-3	2.5	12	13
7th	4-6	71.2	10	14.1
8th	2-3	1.5	<1	<1

tendency of the DAIBD scores, symptom and serum concentration of IL-6, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels are presented in Figures 2 and 3.

Discussion

Behçet's disease (BD) is an inflammatory disorder, and the widely accepted criteria were published by the International Study Group for BD in 1990 (6). Diagnosis requires recurrent oral ulceration (three episodes within any 12-month period) plus any two of the following: recurrent genital ulceration, eye lesions, skin lesions or a positive pathergy test. Intestinal BD occurs in 3–60% of patients with BD (1). Gastrointestinal manifestations of BD typically occur 4.5–6 years after the onset of oral ulcers, with common symptoms consisting of abdominal pain, diar-

rhoea, and gastrointestinal bleeding. BD can involve any segment of the alimentary tract, and classically manifest as deep ulcers in the ileocecal region (7). A younger age at diagnosis (<35 years), higher serum CRP level (1.5 mg/dL), and a higher DAIBD score (≥60) independently predicted the likelihood of a clinical relapse (8). The patient presented according to above circumstances, which involved multiple relapses during the combined treatment using glucocorticoid, and immunosuppressants. There was a consensus that infliximab and adalimumab should be used as a second-line therapy for patients with glucocorticoid-resistant BD (7). Unfortunately, in the present case, hypersensitivity in response to both agents occurred after repeated infusions. Regarding ETN, we are aware of one case of successful ETN treatment in a paediatric patient with refractory intestinal BD, which was treated simultaneously with tacrolimus, prednisolone, and mizoribine (9). To date, ETN has not been reported to have a role in the management of refractory intestinal BD, as described in our report.

IL-6 plays a central role in the host defense against environmental stress, such as infection and injury. Dysregulated IL-6 production has been implicated in the development of various autoimmune conditions, chronic inflammatory diseases, and even cancer. Recent case reports and studies (10) have reported the efficacy of tocilizumab for the treatment of various other autoimmune and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, and Castleman's disease. Hirano *et al*. (11) reported that a BD patient with refractory uveitis responded to tocilizumab, who was restraint to colchicine, prednisolone, cyclosporine A and infliximab. This indicates that tocilizumab may be considered as a therapeutic option for refractory BD. In the present case, we believe that clinical improvement, as well as the improvement in the DAIBD score was due to the tocilizumab treatment.

It is known that tocilizumab inhibits the pro-inflammatory activities of IL-6, and also affects the function of effector T cells. One study found that the serum IL-17 levels were higher in cases of active BD than those in remission (2). Moreover, recent studies have found that the highly pro-inflammatory Th17 cells play a pivotal role in the development of human uveitis, and other experimental autoimmune diseases (12). It has also been reported that IL-6, together with transforming growth factor β (TGF-β), induces the differentiation of naive T cells into Th17 cells, while IL-6 inhibits TGF-β-induced regulatory T cell (Treg) differentiation (13). Therefore, the dysregulation of IL-6 production causes an imbalance in the Th17/Treg ratio. Tocilizumab functions to inhibit the pro-inflammatory activities of IL-6, and also affects the function of effector T cells.

In conclusion, an IL-6 blockade may constitute an optional treatment strategy for refractory BD, although further clinical studies are required to elucidate the efficacy and safety of tocilizumab for BD.

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