

Etanercept therapy-associated acute uveitis: a case report and literature review

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ABSTRACT

A female patient diagnosed with ankylosing spondylitis experienced a new onset acute iritis following the initiation of etanercept therapy and recurrent episodes of iritis continues during the treatment of etanercept. Etanercept-associated iritis was suspected. Anti-TNF therapies can alleviate uveitis in some studies, but in some other anecdotal reports etanercept is considered as the main cause of uveitis. A literature review is presented below. For clinicians, more attention must be paid to the potential association between uveitis or iritis and etanercept, and more careful surveillance of patients under etanercept treatment is necessary.

Introduction

With the vast growth of life science, biological therapies are widely applied in the clinical practice of immuno-inflammatory diseases. In the early stage of this field, the Food and Drug Administration of USA categorized tumour necrosis factor-alpha antagonists as the first biological agents to treat auto-immune diseases. Soon after the approval of clinical use of TNF- α antagonist, etanercept began to show good clinical effects in the treatment of rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Uveitis, a symptom of AS, is considered as one of the side-effects of TNF antagonists, especially in etanercept treatment. As a hypothesis, we present a patient with a history of AS whose recurrent episodes of uveitis we believed to be temporarily connected with injections of etanercept.

Case report

A 27-year-old woman came to the Sixth People's Hospital affiliated to Shanghai Jiaotong University, complaining of a red-eye, pain, tearing and photo-sensitivity in her left eye for two days. Four months before, she had had gone to see a doctor because of a ten-month pain in her lower back and hips and difficulty for turning herself over in bed, had been diagnosed with AS and was treated with etanercept for six weeks, 25 mg ih twice a week. Computed tomographic (CT) scan showed severe sacroiliitis. The laboratory data of that examination is as

follows: HLA-B27 positive, rheumatoid factor negative, antinuclear antibody negative, IgG18.9g/L, IgA5.12g/L, C3 1.03g/L, C-reactive protein (CRP) 118.5mg/L, erythrocyte sedimentation rate (ESR) 120mm/h. She had no history of uveitis. She was diagnosed as having AS according to the modified criteria of New York in 1984, and was treated with sulfasalazine, methotrexate and folic acid for ten weeks. However because of the unsatisfactory curative effect, she switched to therapy with etanercept. One morning, six weeks after the initiation of etanercept therapy, she had a serious pain in her left eye, along with tearing and photo-sensitivity without any apparent cause. After the examination at ophthalmology, she was diagnosed with acute uveitis. The laboratory data showed that CRP 2.3mg/L, ESR 17 mm/h, which did not indicate a rheumatoid attack. Then steroids were administered topically and the uveitis was cured five days later. Eight weeks later, her iritis recurred in the left eye but with no joint pain. The laboratory data was CRP 3.1mg/L, ESR 12 mm/h. She recovered after a seven-day treatment with steroids topically but the story did not end there. Thirteen weeks later, she had another very painful episode of iritis, but this time in her right eye. The laboratory data showed that CRP and ESR were both normal. However, this time, the treatment with steroids topically was ineffective. Thus, 30 mg prednisolone was prescribed orally for five days and the dosage was reduced gradually over three weeks. During the last episode of uveitis, etanercept was considered to be the root of the cause and was stopped in time. The treatment of AS was changed to sulfasalazine and thalidomide for twenty-four weeks, and then switched to infliximab therapy with methotrexate. In the nine-month follow-up observation period, uveitis did not flare up again and the joint-pain was under control. Her CRP and ESR were normal.

Discussion

Today, the use of biological agents such as etanercept and infliximab are becoming more common in the treatment of AS (1). Among these, etanercept is a kind

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of human soluble TNF receptor antagonist (2). It was first approved in 1998 for rheumatoid arthritis at all levels: moderate to severe. It has since been used in nearly five hundred thousand patients worldwide. In Europe, etanercept was approved for the following conditions: RA (3, 4), AS (5), Polyarticular juvenile idiopathic arthritis (JIA) and psoriatic arthritis (PsA). Later, etanercept was gradually extended to the treatment of Behçet's syndrome (6), Sjögren's syndrome (7), and Wegener's granulomatosis (8).

Acute iritis or acute anterior uveitis is the most common extra articular complication in AS, with incidence from 10-30% of the all AS patients (9). The majority of patients complained of mild discomfort, blurred vision and occasional mild pain. Some patients complained of distending pain on the affected eye. Ciliary and iris hyperemia, corneal edema can affect the afflicted eye. There are few floating cells presented in the aqueous humour. Aqueous flare is apparent in the eyes of some other patients. In dealing with uveitis, steroids are often administered. In most cases, uveitis would be cured in four to eight weeks but it re-occurs quite often. With more severe uveitis, some patients would suffer a reduction of vision.

The link between etanercept and uveitis is quite complex and there are many controversies. Some observations suggest that etanercept may ease uveitis. According to the current studies, TNF is known to play a key role in ocular inflammation as shown by animal studies and it could be detected in the ocular fluids of the inflamed eyes of human. In some disorders, all types of anti-TNF agents are similarly efficacious. However, this does not appear to be so in the case of uveitis where infliximab at present has fewer side effects than etanercept (10).

On the other hand, some clinicians believe that etanercept may trigger uveitis in a susceptible patient, despite its efficacy in treating joint diseases. Taban

(11) makes a report of several ankylosing spondylitis cases with severe anterior uveitis flares following the administration of etanercept. In the literature reviewed pertaining to inflammatory eye diseases associated with the use of etanercept, seventeen cases of inflammatory eye disease (uveitis, scleritis, orbital myositis) which are believed to be associated with etanercept therapy are found. In Lim's study (12), cases involving uveitis which have occurred in the US are connected with etanercept, infliximab, or adalimumab therapy. Two thousand and six cases were reviewed in 2 spontaneous reporting databases prior to January 1. Overall, there are 43 cases of uveitis associated with etanercept, among which 14 are associated with infliximab, and 2 are associated with adalimumab. After normalizing for the estimated number of patients who were treated with these medications, it was found that etanercept is associated with a greater number of uveitis cases than infliximab ($p < 0.001$) and adalimumab ($p < 0.01$), while no such association was found between adalimumab and infliximab ($p > 0.5$). In order to avoid the inclusion of patients whose underlying disease is associated with uveitis, *a priori* criteria was used and the results were: 20 cases associated with etanercept, 4 cases with infliximab, and 2 cases with adalimumab. A repeating analysis continues to reveal many uveitis cases which are associated with etanercept ($p < 0.001$ versus infliximab). Consistent with previous studies and the former data, the results suggested that the relationship between etanercept and uveitis is drug-specific and is not correlated to TNF inhibitors as a whole. However, it cannot be concluded that the findings support the use of infliximab over etanercept; but rather, if a patient develops uveitis during etanercept therapy, then a switch to infliximab must be warranted.

In summary, the patient we presented had no prior history of uveitis. During etanercept treatment, uveitis occurred

when the AS activity level was under control, and when we switched to infliximab, the uveitis no longer flared up. Consequently, we believe that the patient's uveitis was a side effect of etanercept. As the TNF antagonists are adopted more widely in this disease, more attention should be paid to the adverse reactions of these novel biological agents, especially in the case of uveitis.

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