Letters to the Editors

Anti-interleukin 6 receptor antibody tocilizumab was not satisfactory for acute attack of Behçet's uveitis in three consecutive patients

Sirs,

Behçet's uveitis (BU) is a vision-threatening uveitis entity. Tocilizumab (TCZ), a recombinant humanised antibody binding interleukin 6 (IL-6) receptor, had been documented to be effective for refractory BU (1-8). In this context, we designed a single-arm observational study to investigate the potential role of TCZ for acute BU attack responded poorly to glucocorticosteroid or other biologics including tumour necrosis factor-alpha (TNF-α) antibodies and interferon (IFN)-α2a.

The first patient was a 22-year-old male with a 3-year history of Behçet's disease (BD) characteristic of oral and genital ulcers, pseudofolliculitis, epididymitis, and a 10-month history of BU. He presented in May 2018 with a relapse of bilateral pan-uveitis on prednisone 40 mg per day and cyclophosphamide (CYC) 100 mg every other day. Prednisone was then up titrated to 60mg per day for one month, which led to a transient improvement of visual acuity with remission of the retinal lesions in his right eye and paradoxical hypopyon in the left. A dose of 8 mg/kg TCZ was intravenously administered with CYC reduced to 50 mg every other day, and hypopyon in the left eye resolved one month after the infusion. However, he experienced another intense pan-uveitis attack one month after the second dose of TCZ.

The second patient was a 33-year-old male with a 10-year history of oral and genital ulcers, and a 30-month history of highly refractory BU. He presented in May 2018 due to a bilateral pan-uveitis attack with retinal haemorrhage and infiltration in the right eye and blurry fundus without retinal lesions in the left. He had responded poorly to 6 regular infusions of 3 mg/kg infliximab, and TCZ was then instituted based on prednisone 20mg per day, cyclosporin A (CsA) 75mg twice a day, and azathioprine (AZA) 50mg per day. Bilateral uveitis subsided during the first three monthly injections of 8 mg/kg TCZ. However, two days after the fourth injection, the patient experienced another episode of uveitis attack.

The third patient was a 25-year-old male with a 2-year history of mucosal ulcers, erythema nodosum, and pseudofolliculitis. He presented in April 2019 with blurry vision in the left eye. Examination revealed bilateral quiescent anterior chamber, vitritis with disseminated retinal haemorrhages and infiltrates in the left eye, and indiscernible fundus due to lens opacity in the right eye. At this presentation, he was on prednisone 40mg per day, tacrolimus 3 mg per day, and IFNα-2a 3MIU every other day. IFNα-2a was then switched to TCZ. Visual acuity in the left eye transiently improved after a single dose of 8 mg/kg TCZ but declined before the second monthly injection with bilateral pan-uveitis recurrence.

To date, several case series (1-8) have reported a generally favourable efficacy of TCZ for refractory BU patients. Before introduction of TCZ, all the 26 cases reported previously had failed corticosteroids combining conventional immunosuppressants [CsA (n=14), methotrexate (MTX) (n=12), AZA (n=11), CYC (n=4), and mycophenolate mofetil (MMF) (n=3)] initially, followed by insufficient response (n=21) or intolerance (n=5) to one or two biologic agent(s) [adalimumab (n=14), infliximab (n=13), golimumab (n=3), anti-IL-1 agents anakinra (n=1) and canakinumab (n=1), and the anti-IL-2 agent daclizumab (n=1)] later on. Ten cases were treated with TCZ monotherapy and 11 cases concurrently with a traditional immunosuppressant [GCS (n=2), AZA (n=3), MTX (n=2), CsA (n=2), and MMF (n=2)]. Of the 26 reported patients, 19 (73.1%) achieved "complete remission", "remission" or "inactivity", 6 (23.1%) reported improvement, and only 1 (3.8%) reported "no response", during a follow-up period between 1 to 24 months. In our present study, unexpectedly, TCZ failed to control uveitis attacks in three consecutive patients, which led to the early termination of this clinical trial. Future studies are needed to characterise the subgroup of refractory BU patients that might benefit from TCZ in the Chinese population.

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References

1. Hatemi G, Christensen R, Bang D *et al.*: 2018 update of the EULAR recommendations for the management of Behcet's syndrome. *Ann Rheum Dis* 2018; 77(6): 808-18.
2. Hirano T, Ohguro N, Hohki S *et al.*: A case of Behcet's disease treated with a humanized anti-interleukin-6 receptor antibody, tocilizumab. *Mod Rheumatol* 2012; 22(2): 298-302.
3. Calvo-Rio V, De La Hera D, Beltrán-Catalán E *et al.*: Tocilizumab in uveitis refractory to other biologic drugs: a study of 3 cases and a literature review. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S54-7.
4. Papo M, Bielefeld P, Vallet H *et al.*: Tocilizumab in severe and refractory non-infectious uveitis. *Clin Exp Rheumatol* 2014; 32 (Suppl. 84): S75-9.
5. Deroux A, Chiquet C, Bouillet L: Tocilizumab in severe and refractory Behcet's disease: Four cases and literature review. *Semin Arthritis Rheum* 2016; 45(6): 733-7.
6. Santos- Gómez M, Calvo-Río V, Beltrán E *et al.*: The effect of biologic therapy different from infliximab or adalimumab in patients with refractory uveitis due to Behcet's disease: results of a multicentre open-label study. *Clin Exp Rheumatol* 2016; 34 (Suppl .102): S34-40.
7. Alokaily F, Al Saata, Jawad A: Successful treatment of Behcet's uveitis with Tocilizumab. *Saudi J Ophthalmol* 2017; 31(1): 42-44.
8. Atienza-Mateo B, Calvo-Río V, Beltrán E *et al.*: Anti-interleukin 6 receptor tocilizumab in refractory uveitis associated with Behcet's disease: multicentre retrospective study. *Rheumatology* (Oxford) 2018; 57(5): 856-64.
9. Eser Ozturk H, Oray M, Tugal-Tutkun I: Tocilizumab for the treatment of Behcet uveitis that failed interferon alpha and anti-tumor necrosis factor-alpha therapy. *Ocul Immunol Inflamm* 2018; 26(7): 1005-14.