Safety and efficacy of etanercept therapy in ankylosing spondylitis patients undergoing phacoemulsification surgery

Sir, AS is a chronic, progressive inflammatory disease that generally begins in the third decade of life. Ocular manifestations, namely acute anterior uveitis, or iridocyclitis are its most common extra-articular manifestations; 25–30% of the patients develop these symptoms in the course of the disease [1]. Besides traditional immunosuppressive agents, biological therapy, primarily TNF-α inhibitors, resulted in significantly better outcome in patients with AS. Among TNF-α blockers, etanercept is a 75-kDa dimeric soluble form of the p75 TNF-α receptor linked to human IgG, [2]. Although the number of AS patients treated with biologics is increasing, unfortunately there are scant data on the safety of etanercept therapy in surgically treated AS patients [3], in particular in cataract surgery. On the basis of the available data, it is proved that during the use of etanercept therapy there is a slightly increased incidence of bacterial infection; nevertheless, the risk of serious infections does not seem to be increased [4].

However, discontinuing TNF-α inhibitor therapy may result in exacerbation of AS [5]. AS patients present a challenge to the cataract surgeon because of chronic uveitis and sometimes locomotor deformities. Phacoemulsification is a routinely performed operation in cataract surgery, whereby the opacified crystalline lens is extracted through a 1.8- to 3.2-mm clear corneal, or scleral incision and an artificial lens is implanted. In the present study, we aimed to assess the possible effects of etanercept therapy in AS patients undergoing 1-day phacoemulsification surgery.

In our current study, 10 patients were on biological therapy (etanercept) (Group I), while 14 received non-biological therapy (Group II). The diagnosis of AS was established based on the New York classification criteria [6]. All the patients developed secondary cataract after anterior uveitis and required cataract extraction. The study was approved by the institutional ethics committee (Regional and Institutional Ethics Committee, Medical and Health Science Centre, University of Debrecen). Written informed consent was obtained from all patients.

Simultaneously, 14 patients also with definitive, advanced AS without receiving biological therapy were operated for cataract with phacoemulsification (Group II). Seven patients of Group II were administered 4 mg methylprednisolone daily for 3 weeks pre-operatively as steroid therapy (Group II/a); the remaining seven received no pre-operative steroid therapy (Group II/b). Disease activity of AS patients was monitored by the standard BASDAI, BASFI and BASMI, respectively. In addition, ESR and CRP levels, as biomarkers of systemic inflammation, were also determined pre-operatively. None of the patients had any episode of uveitis in the last 3 months before phacoemulsification, i.e. the uveitis was inactive in the last 3 months. The follow-up time was a minimum of 24 months.

Neither in Group I nor in Group II were there any intra-operative complications. Regarding the aqueous flare and cells, the Tyndall effect was greater on the first post-operative day and then declined rapidly in the first week and more gradually thereafter in a normal population without AS [7]. Out of 10 patients in Group I, 8 had an uneventful post-operative period with a regular healing rate. Only two patients developed mild post-operative anterior uveitis, i.e. Tyndall effect 1+, and none of them had posterior synechiae (adhesion between the anterior surface of the artificial posterior chamber intraocular lens and the iris). Anterior uveitis is successfully treated with combined local steroid (dexamethasone) and antibiotic (gentamycin) injection administered for 2 days.

During the follow-up period, none of the patients developed intraocular infection, or had any other complications. Concerning the 14 AS patients without biological therapy (Group II), 3 patients out of the 7 being administered pre-operative steroid therapy (Group II/a) had Tyndall effect 1+ and 1 had 2+ post-operatively. Two of them had posterior iris synechiae. Two patients of Group II/b had Tyndall effect 1+ post-operatively, two also had Tyndall phenomenon 2+, one had Tyndall effect 3+ and three of them had posterior synechiae.

We did not discontinue the otherwise highly effective etanercept therapy in patients, and indeed, we did not observe any complications in 8 out of these 10 patients. Only two patients had easily manageable, mild post-operative anterior uveitis. AS patients without biological therapy had a more severe form of post-operative anterior uveitis, whereas patients given etanercept had milder forms of uveitis and none had synechiae post-operatively.

Although some data have shown that TNF blockers can induce new uveitis flares [8], AS patients seem to have greater improvement in the frequency of uveitis flares after treatment with infliximab than etanercept [9]. Infliximab resulted in better clinical responses than etanercept in patients with JRA [10].

In summary, anti-TNF-α therapy, such as etanercept, may control the musculoskeletal disease, as well as uveitis simultaneously in patients with AS. Furthermore, if these patients need elective cataract surgery, the discontinuation of anti-TNF-α treatment is unnecessary.

**Rheumatology key message**

- Discontinuation of TNF-α inhibitor therapy during and after phacoemulsification is unnecessary.
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Colchicine-responsive chronic recurrent multifocal osteomyelitis with MEFV mutations: a variant of familial Mediterranean fever?

Sir, FMF is an autosomal recessive disease characterized by self-limited recurrent attacks of fever with serositis such as peritonitis, pleuritis and arthritis [1]. FMF is caused by mutations in the MEFV gene [2]. This gene had been considered to be responsible only for FMF in the past; however, recent reports show that the MEFV gene is associated with more than typical FMF and is linked to additional clinical presentations within the family of the autoinflammatory diseases [2–4]. Here, we describe a case of colchicine-responsive chronic recurrent multifocal osteomyelitis (CRMO) with MEFV gene mutations.

A 14-year-old female was referred with fever of unknown origin persisting for 15 days. Physical examination was unremarkable. Laboratory findings showed normal white blood cell count (3.9 × 10⁹/l), high levels of CRP (3.1 mg/dl), accelerated ESR (72 mm/h), normal levels of immunoglobulins and negative autoantibodies. Blood culture was negative. Unexpectedly, gallium (Ga) scintigraphy on Day 3 after admission demonstrated significant uptake in the bilateral proximal region of the tibia (Fig. 1A). Plain radiography showed no significant findings (Fig. 1D), but MRI demonstrated multifocal lesions whose intensity was low in the T₁-weighted condition and high in the T₂-weighted condition in bilateral tibia (Fig. 1E). Biopsy of the left tibia showed non-specific inflammatory changes and no malignant cells. The culture of bone marrow was negative. She had severe pain of the left heel on Day 21. MRI on Day 23 demonstrated multifocal lesions whose intensity was low in the T₁-weighted condition and high in the T₂-weighted condition in bilateral tarsal bones (Fig. 1F). Ga scintigraphy on Day 38 demonstrated significant uptake in left calcaneus and bilateral femur (Fig. 1B). From these findings, the diagnosis of multifocal recurrent osteomyelitis was made. No evidence of bone destruction or hyperostosis was observed at the time of diagnosis. High fever continued despite treatment with appropriate antibiotics and naproxen for 8 weeks. However, she was relieved dramatically from high fever soon after colchicine (2 mg/day) started. Mutation analysis demonstrated the heterozygous mutation E148Q-P369S-R408Q in cis on one allele of the MEFV gene. But no mutation was found in the LPIN2 gene. Colchicine dose was gradually decreased to 0.5 mg/day and daily colchicine therapy (0.5 mg/day) relieved her from febrile attacks for 1 year, although she had one episode of osteomyelitis in the left fibula (Fig. 1C) when she ceased to take colchicine.