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Bilateral Panuveitis at Etanercept Initiation for Juvenile Idiopathic Arthritis

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Abstract

Introduction: Uveitis is a well-known extra-rheumatological manifestation of juvenile idiopathic arthritis (JIA). Tumour necrosis factor (TNF) has been used to treat uveitis associated with inflammatory diseases. A new-onset uveitis under anti-TNF therapy is uncommon.

Case presentation: A 12-year-old male, affected since the age of 6 years, by a severe form of polyarticular JIA. When etanercept was started, he presented panuveitis bilaterally, so we switched to infliximab with good response.

Conclusions: The TNF-soluble receptor could be considered as a possible promoter in inducing endogenous new-onset uveitis in JIA.

Keywords: Anti-TNF therapy, etanercept, juvenile idiopathic arthritis, paradoxical effect, uveitis

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Uveitis is a well-known extra-rheumatological manifestation of JIA which may lead to severe functional impairment. Tumour necrosis factor (TNF)-alpha blocking agents are increasingly used to treat children with JIA refractory to conventional therapy. Most reports have demonstrated resolution of refractory uveitis under anti-TNFα. However, cases of new-onset uveitis under anti-TNFα therapy are rarely reported.

We report herein a new case of paradoxical new onset of uveitis occurring under etanercept treatment in a patient with JIA.

Case Report

A 6-year-old male child with no significant past medical or family history presented with progressive polyarthralgia and morning stiffness. Physical examination revealed bilateral arthritis of the wrists, proximal interphalangeal joint, knees and ankles. Laboratory findings showed an increase in C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR). The rheumatoid factor and antinuclear antibodies (ANA) titres were negative. Knee joint X-ray showed soft tissue swelling and wrist joint X-ray showed osteoporotic changes in the epiphysis of the lower end of radius and ulna. Ophthalmological exam was normal. A diagnosis of seronegative polyarticular JIA was established. Methotrexate treatment (10 mg/m2 weekly) was conducted, leading to complete resolution of articular manifestations. After 6 years of clinical remission under methotrexate, a severe arthritis flare occurred. His joint disease was active as shown by DAS 28 at 5.1, while ophthalmologic examination with slit lamp did not show any signs of uveitis. Laboratory findings again showed increased ESR and CRP levels. Etanercept was administered subcutaneously at 0.4mg/kg twice weekly and methotrexate was continued. Two weeks after the first injection, and for the first time during his longstanding disease, he presented with painful red eyes and photophobia. Ophthalmologic examination revealed anterior and posterior chamber inflammation of the two eyes. He was treated with oral steroids and beta-blocker ophthalmic drops. Etanercept was suspended and infliximab was started, with no side effects. There was a rapid decrease in his ocular inflammation and improvement in his eye disease. After 20 months, arthritis was stable and complete remission of uveitis was obtained.

Discussion

JIA is the most common cause of chronic anterior uveitis in childhood. Uveitis is strongly associated with the oligoarticular and seronegative polyarticular subgroups or the presence of ANA. Uveitis in JIA can worsen over time, with many sight-threatening complications, such as cataracts, keratopathies, synechiae and glaucoma. Posterior segment involvement in JIA is rare. This patient had no prior history of uveitis with regular ophthalmological control.

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Studies have shown that etanercept is associated with a risk of new-onset uveitis and uveitis flares in JIA patients. We are aware of only 13 cases of new-onset uveitis in JIA under TNF blockers, presented in *Table 1*.

Author and references	Gender	Age (years)	JIA subgroup	Age at the onset of AJI	Type of TNF blockers	Interval between TNF-blocker initiation and the onset of uveitis (months)	Type of uveitis	Treatment of uveitis	Modification of TNF blockers
V. Kakkassery et al. [1]	F	44	NS	14	Etanercept	6	Posterior uveitis	Oral corticosteroid	Switch to infliximab
	NS	24	NS	15	Etanercept	12	Anterior uveitis	Topical corticosteroid	Stop
	NS	16	NS	9	Etanercept	24	Anterior uveitis	Topical corticosteroid	Switch to infliximab
O. Kaipiainen-Seppänen et al. [2]	F	31	Juvenile SA	10	Etanercept	8	Anterior uveitis	Topical corticosteroid	Switch to infliximab
E. Martín-Mola et al. [3]	NS	NS	Juvenile SA	NS	Etanercept	NS	Anterior uveitis	NS	NS
	NS	NS	Juvenile SA	NS	Etanercept	NS	Anterior uveitis	NS	NS
R.K. Saurenmann et al. [4]	NS	NS	Psoriatic JIA	NS	Etanercept	NS	NS	NS	NS
	NS	NS	Extended oligoarticular JIA	NS	Etanercept	NS	NS	NS	NS
D. Wendling et al. [5]	F	6	NS	6	Etanercept	14	Anterior bilateral chronic uveitis	Topical corticosteroid	Switch to infliximab
	M	5	SA HLA-B27-	3.5	Etanercept	4	Chronic anterior bilateral uveitis	Topical corticosteroid	Switch to infliximab
H. Schmeling et al. [6]	F	17	Polyarticular, seronegative	6.5	Etanercept	10	NS	NS	NS
	F	10	Extended oligoarticular	5	Etanercept	12	NS	NS	NS
R. Scrivo et al. [7]	F	16	NS	8	Etanercept	28	Anterior uveitis	Topical corticosteroid	Switch to infliximab

Abbreviations: NS, not specified; JIA, juvenile idiopathic arthritis; SA, spondyloarthritis; F, female; M, male

Table 1: Cases of onset uveitis under TNF blockers

All these JIA cases were treated with etanercept.

The reason for the difference between the various TNF inhibitors and the risk of developing uveitis

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is unknown. In fact, the link between etanercept and uveitis is quite complex and there are many controversies. Some observations suggest that etanercept is not involved in generating uveitis. Schmeling and Horneff [6] reported a cohort of 229 JIA patients treated with etanercept. Of this cohort, only two patients developed new-onset uveitis after initiation of etanercept, whereas several others experienced a flare of their previously diagnosed uveitis. Despite this, the authors concluded that etanercept treatment did not influence the incidence and course of JIA-related uveitis.

Furthermore, some clinicians believe that etanercept may trigger uveitis in a susceptible patient, despite its efficacy in treating joint diseases. Scrivo reported a cohort of 350 patients treated with etanercept, in whom new-onset anterior uveitis occurred in four, including one with JIA[7]. The authors suggested that monoclonal anti-TNF treatment, especially adalimumab[8], is preferable to the soluble TNF receptor agent in patients experiencing recurrent uveitis flares. Uveitis onset may be considered as a paradoxical effect of anti-TNF therapy, so called because it appeared after the initiation of the anti-TNF drugs that are normally used to treat it. In the majority of the cases in the literature, uveitis appeared at a time during which rheumatic disease manifestations were fully controlled, but in our patient the uveitis occurred during a JIA flare. The uveitis onset occurred after an average duration of exposure to etanercept of 12.5 months (US registry) [9]. Our case is original since uveitis appears after the first injection and it was a panuveitis, suggesting that etanercept had a role in the onset of uveitis.

Treatment of new-onset uveitis under anti-TNF was local in most of the cases, with healing of the episode within 2 months. Discontinuation of anti-TNF could be necessary in some cases. In the US registry[9], four cases of uveitis under etanercept resolved after discontinuing the medication, with a recurrence of uveitis on rechallenge in two of these patients. In our case, uveitis resolved under oral corticosteroids and when etanercept was switched to infliximab. Adalimumab is considered the most effective anti-TNF in the treatment of uveitis associated with oligo- and polyarticular JIAs, but could not be afforded in our case and infliximab proved to be successful.

Learning points:

- Paradoxical uveitis can occur early after the initiation of etanercept.
- Consider bilateral panuveitis, which is, to our knowledge, the first case described as a paradoxical effect of TNFα blockers.
- Further randomized controlled clinical trials are necessary to investigate possible immune reactions associated with etanercept.

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