Tocilizumab in refractory juvenile idiopathic arthritis with associated uveitis: a case report

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ACTA REUMATOL PORT. 2019;44:151-154

ABSTRACT

Introduction: We report a 9-year follow-up of a child with refractory juvenile idiopathic arthritis (JIA) with associated uveitis in which tocilizumab proved to be effective in achieving disease control.

Case Report: A 16-month child was diagnosed with JIA and at the age of 3 developed bilateral non-granulomatous anterior uveitis. Throughout the follow-up, the patient presented frequent joint and ocular flares. Refractory anterior uveitis and topical corticosteroid therapy resulted in the development of bilateral cataract and high intraocular pressure (IOP). The patient underwent multiple ocular surgeries along with corticosteroids, immunosuppressive therapy with methotrexate and adalimumab failing to reach disease control. Only after the introduction of tocilizumab a lower disease activity was achieved.

Discussion: Management of JIA-associated uveitis is challenging and requires a close collaboration between paediatric rheumatologists and ophthalmologists. Clinical remission can be difficult to achieve. However, one should always pursuit JIA inactivity with IOP and inflammation control. This report supports tocilizumab as a useful therapeutic option for JIA-associated uveitis.

Keywords: Tocilizumab; Juvenile Idiopathic Arthritis; Uveitis.

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is one of the most common rheumatic diseases of childhood with diverse musculoskeletal manifestations according to subtype[1,2]. Uveitis is the most frequent extra-articular manifestation of JIA, although it is generally quite rare in the paediatric age[3]. The aetiology of the condition is associated with immunological factors but the underlying pathogenic mechanisms remain unclear[4]. Ocular involvement may have different presentations, although its presence is not mandatory. JIA-associated uveitis is a sight-threatening condition which generally presents as a chronic, asymptomatic, anterior uveitis, typically associated with negative rheumatoid factor (RF) and positive antinuclear antibody (ANA)[4]. This is a silent condition, so in this setting, screening for JIA-associated uveitis is standard[5]. Early detection and treatment is warranted to prevent the development of complications leading to visual function loss. Ophthalmological adverse events include cataracts, glaucoma, band keratopathy and macular oedema. Moreover, chronic disease activity along with topical and systemic therapies also contribute to visual function impairment[3,4].

There is strong evidence that early introduction of systemic immunosuppressive therapies can reduce the need for topical and systemic corticosteroid[6,7]. However, remission may be challenging to achieve and some refractory patients require alternative therapeutic approaches[8].

The purpose of this clinical case is to report a 9-year follow-up of a child with severe and persistent ocular and joint impairment in which tocilizumab proved to be effective in achieving disease control.

CASE REPORT

A 16-month old caucasian female child was referred to evaluation by a Paediatric Rheumatologist due to oligoarthritis of both knee and ankle joints. She was diagnosed with oligoarticular JIA, with positive high ANA titre (1:1280), RF negative, and initially managed with corticosteroids. By the time of diagnosis, she was referred to our Department of Ophthalmology for

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screening of ocular involvement. She did not have other medical conditions and family history was unremarkable. Baseline full ophthalmological evaluation was uneventful and a 3-month ocular screening was proposed.

During the first year after diagnosis, due to an extended course of her oligoarticular JIA with other joints involved, patient started oral ibuprofen (30 mg/Kg/day), and afterwards deflazacort (0.5mg/Kg/ /day) and methotrexate (MTX) up to 15mg/m^2/week.

By the time she was 3 years old, the first evidence of uveitis was noticed. Slit lamp examination showed bilateral anterior non-granulomatous uveitis, initially treated with topical steroids. Despite treatment with corticosteroids, including intra-articular injections in knees and ankles, and methotrexate, ocular and joint activity persisted.

At the age of 5, the patient developed bilateral mild posterior subcapsular cataract (PSC) with a visual acuity of 20/30, in each eye. Intra-ocular pressure (IOP) rose in both eyes and was initially managed with topical drops of timolol 5.0mg/ml. However, there was a progressive need for more topical therapies to lower the IOP (brinzolamide 10mg/ml and brimonidine 2mg/ml). Due to the challenge in achieving disease control, with active joint and ocular inflammation, the patient was proposed to start on subcutaneous adalimumab (24mg/m^2/every two weeks), in addition to the oral MTX.

Despite all efforts to control IOP, the patient developed almost 360º peripheral anterior synechiae in her left eye (OS) with very high IOP (41 mmHg). Patient was proposed for glaucoma surgery and started on topical latanoprost 0.05mg/ml and oral acetazolamide 250mg per day until the day of the surgery. The procedure of choice was the implantation of an Ahmed Valve® device with a tube in the anterior chamber, covered with a bovine pericardium patch.

Eighteen months later, despite control of musculoskeletal manifestations, ophthalmological disease was still active and with deterioration of visual function. Cataract showed progression with the development of dense PSC and visual function impairment in the right eye (OD). The visual acuity was 20/200 and 20/40, in the OD and OS respectively. Intra-ocular pressure was within the normal range with topical therapy. The patient was proposed to urgent cataract extraction in order to prevent amblyopia. However, surgery was delayed due to uncontrolled ocular inflammation (anterior chamber flare 2+ and cells 2+; according to the Standardization of Uveitis Nomenclature[9]) despite systemic and topical immunosuppressive therapies. As an alternative therapeutic approach, route of administration of MTX was changed to subcutaneous and adalimumab was switched to intravenous tocilizumab (12 mg/Kg/every two weeks).

Two months later, there was a favourable evolution of ocular disease with inactive uveitis and controlled joint disease, along with normalization of blood inflammatory markers. Cataract surgery (standard phacoemulsification) was then carried out safely, first in OD, and afterwards OS (Figure 1). Visual acuity dramatically improved to 20/25 in both eyes. Glaucoma surgery was needed to control IOP in her right eye (Ahmed Valve® implantation with a bovine pericardium patch).

Nevertheless, topical dexametasone and timolol, twice daily each, in both eyes, was still needed to fully control ocular disease. No adverse reactions occurred during treatment with tocilizumab.

In consideration of the persistent clinical benefit achieved, oral deflazacort was tapered to a residual dose.

During the course of the disease (before achieving clinical remission) the patient experienced multiple systemic adverse events, related to both JIA and treat-

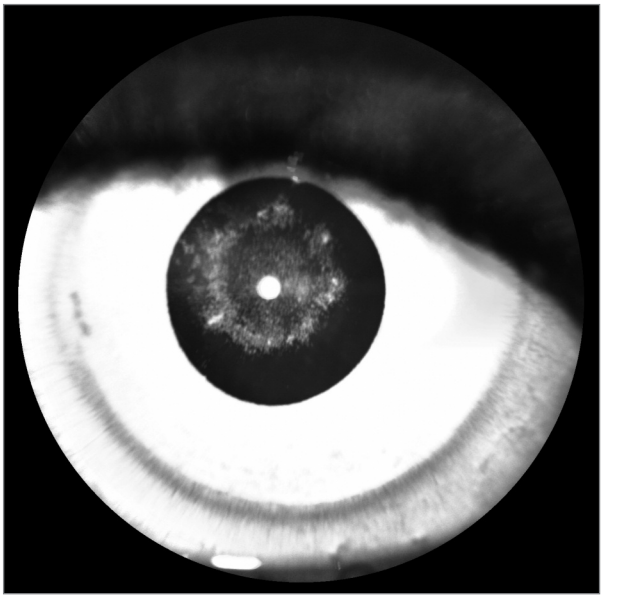

FIGURE 1. View of the anterior segment of the left eye showing a dense posterior pole subcapsular cataract (image acquired using anterior segment module of Spectralis® optical coherence tomography; Heidelberg Engineering)

ments, such as Cushing syndrome, low stature and inferior limbs muscle atrophy. Disease timeline is shown in Figure 2. Fundoscopic evaluation, including the optic disk, was uneventful during the follow-up. The child remains on sustained clinical remission with this therapy for the last 3 years (up to the latest visit).

DISCUSSION

The child, despite systemic steroid and methotrexate, developed chronic ocular inflammation. Throughout the 9-year follow-up of this child with JIA, chronic anterior uveitis with multiple ocular hypertensive flares resulted in visual impairment with the development of bilateral cataract and high IOP. These complications arise from both persistent ocular inflammation and prolonged steroid therapy. The child underwent cataract and glaucoma surgeries along with immunosuppressive therapy in order to control IOP and inflammation. Although controversial, a 3-piece intraocular lens (IOL) was implanted in the capsular bag. One should emphasize that the implantation of an IOL allows a more rapid visual function recovery and could prevent capsular contraction. However, it may raise ocular inflammation postoperatively so steroid therapy was intensified, before and after surgery, and the patient was closely monitored. The type of glaucoma surgery chosen was straightforward as the patient developed 360º anterior peripheral synechiae. Nevertheless, other procedures such as trabeculectomy are also plausible when dealing with uveitic glaucoma, however with a higher failure rate. Despite multiples systemic therapies, achieving joint and ocular disease activity control was challenging. In this JIA case refractory to conventional therapies, tocilizumab was the key to stop the inflammatory activity of the disease, both ocular and musculoskeletal.

Tocilizumab is an effective and safe therapeutic, currently approved for systemic and polyarticular JIA in children aged 2 years and older[10-15], but not for oligoarticular JIA. Regarding ocular involvement, there is some recent evidence of the benefit of Tocilizumab in JIA associated uveitis[16-17]. Moreover, the first randomized clinical trial was published regarding safety, tolerability and bioactivity of Tocilizumab for adult patients with non-infectious uveitis (STOP-Uveitis study), with promising results[18]. Rationale for Tocilizumab use is suggested by animal studies that show that IL-6-deficient mice have an impaired Th17 response and lower ocular inflammation scores in experimental autoimmune uveitis. IL-6 inhibition re-

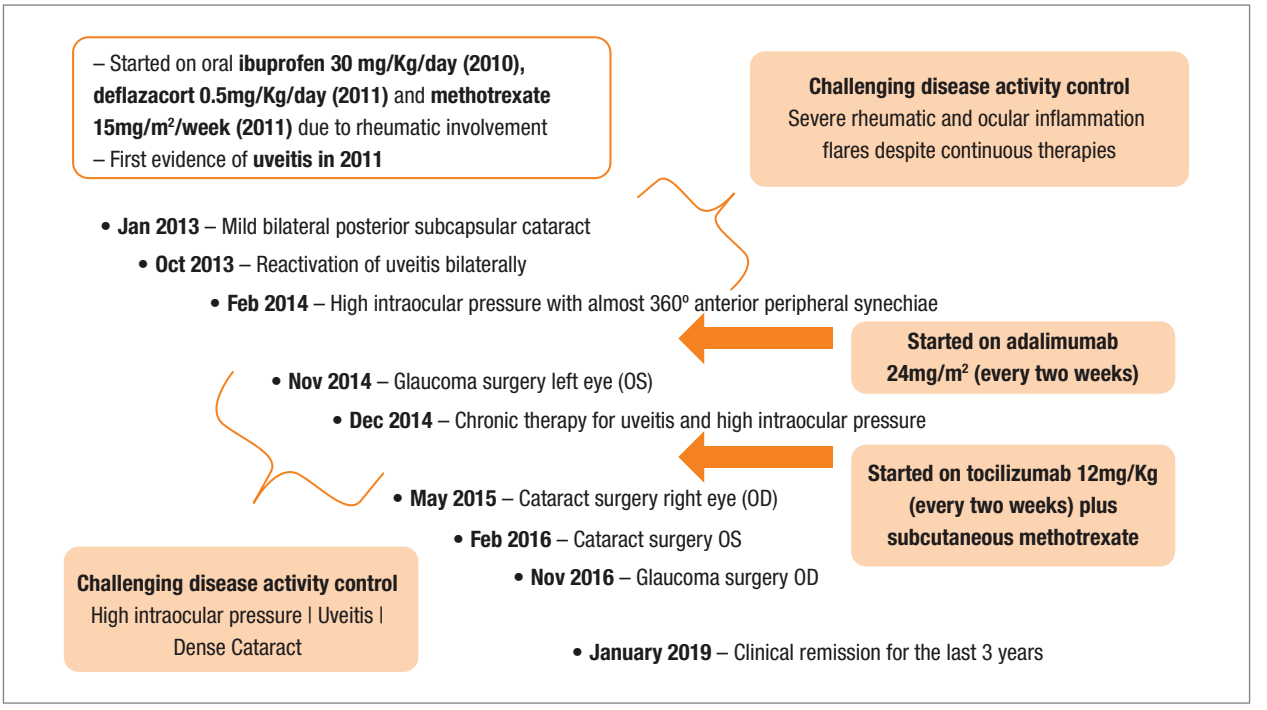

FIGURE 2. Timeline describing the course of the disease and the different therapeutic options employed

duces the risk of uveitis development in mice models[19].

This case report emphasizes the use of tocilizumab as an option in the management of JIA with associated uveitis, specifically when therapies targeting tumour necrosis factor-α fail to deliver significant clinical improvements. It also highlights the importance of a close collaboration between paediatric rheumatologists and ophthalmologists in order to obtain a proper management of JIA-associated uveitis. Disease inactivity may be difficult to achieve as shown in this case. However, one should always pursuit JIA remission with IOP and inflammation control, either by medical or surgical therapies.

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