Long-term control of non-infectious paediatric panuveitis refractory to traditional immunesuppressive therapy successfully treated with Adalimumab (Humira™)

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Abstract

Objectives

The aim of this paper is to present two cases of severe idiopathic non-infectious paediatric panuveitis, unresponsive to traditional therapy, successfully treated with Adalimumab (Humira™, Abbott Pharmaceutical Inc.) in the long term.

Methods

The data of the two cases are presented and the literature is reviewed.

Results

At base line, case 1 had 0.2 in the RE and 0.5 in the LE, while case 2 had 0.5 and 0.4 in the RE and LE, respectively. The anterior chamber (AC) of case 1 had 3+ cells and 3+ flare in both eyes, as well as diffuse keratic precipitates (Kps). Case 2 presented 2+ cells and 3+ flare in both eyes, as well as tiny Kps in the inferior part of the endothelium. The Binocular Indirect Ophthalmoscopy (BIO) score was +2 in both eyes of case 1 and case 2 at first examination. After Adalimumab initiation, both patients presented a dramatic resolution of the ocular inflammation, as well as a rapid improvement of the BCVA. Case 1 had 0.8 and 1.0 in the RE and the LE, respectively, while case 2 presented 1.0 in both eyes. At the last visit, both patients presented a quiet uveitis and stable BCVA: case 1 had 0.8 and 1.0 in the RE and the LE, respectively, while case 2 presented 1.0 in both eyes. No side effects were recorded during this time.

Conclusion

Adalimumab can be a promising drug for the therapy of severe, refractory paediatric uveitis, although further studies are needed on its application in uveitis.

Key words
adalimumab, uveitis, immunesuppression, paediatric

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Introduction

Uveitis is a sight threatening disease which can provoke irreversible damages, particularly in paediatric cases (1). Albeit systemic steroids are the mainstay of non-infectious bilateral severe forms, systemic immunesuppressive therapy is recommended in order to avoid unpleasant local and systemic side effects (2, 3).

Since tumour necrosis factor (TNF)-α represents one of the most important amplifying factors in the inflammatory reaction (4, 5), anti-TNF-α agents play a central role in the management of non-infectious uveitis. Adalimumab (Humira®, Abbott Pharmaceuticals Inc.) is a recombinant IgG1 monoclonal antibody targeting TNF-α, produced by recombinant deoxyribonucleic acid (DNA) technology, called "phage display", and classified as a fully humanised antibody.

Unfortunately, there is still a lack of data on non-infectious panuveitis treated with Adalimumab, either in children or young adults. We describe two cases of a non-responsive paediatric panuveitis successfully treated with Adalimumab.

Case report 1

In 2009, a young female from Liberia was referred to our Ocular Immunology Department. She presented with a severe bilateral panuveitis with no evidence of systemic involvement, under the light of a fully negative work-out for immunologic and infectious diseases.

She was treated in several uveitis centres since the age of 5. She had a long course of topical steroids and cycloplegics with a scarce control of the severe intraocular inflammation, she received 1 sub-Tenon and 1 intravitreal injection of triamcinolone in her right eye (RE), and 2 sub-Tenons injections in her left eye (LE). In the following months, the young patient developed a steroid-induced cataract. Since the panuveitis was getting progressively worse, she underwent phacoemulsification with no intraocular lens implant in both eyes and vitrectomy with internal limiting membrane peeling in the RE. The parents referred that at the same time she received a long course of systemic steroids: intravenous methyprednisolone at the dose of 500 mg was administered for 4 consecutive days, followed by oral steroids (1 mg/kg) tapered gradually, coupled with methotrexate (12.5 mg/week). Since the response to such therapy was partial, the young patient received a second course of intravenous steroids after one month and systemic cyclosporine A (CSA) was added (5mg/kg).

As soon as the dose of systemic prednisone was around 10 mg per day, the uveitis severely recurred and the patient was then referred to the Uveitis Service of the University of Ancona.

At presentation, the anterior chamber (AC) presented a bilateral severe inflammation with 3+ cells and 3+ flare in both eyes, as well as diffuse keratic precipitates (Kps). The patient was aphakic in both eyes. The vitreous had a severe involvement with an evident cells colonisation; the Binocular Indirect Ophthalmoscopy (BIO) score was 2+ in both eyes. The posterior pole presented a diffused cystoid macular oedema (CMO), confirmed by the optical coherence tomography (OCT, Fig. 1A-B). The best corrected visual acuity (BCVA) was 0.2 and 0.5 in RE and LE, respectively. The systemic work-up did not show any significant datum, excepted for anti nuclear antibody (ANA) positivity. Considering both the disease severity and the clinical history, all the treatments were stopped for 2 weeks and Adalimumab was introduced at the dose of 40 mg subcutaneously (SQ) every other week.

One month later, the patient showed an encouraging improvement: the bilateral CMO was resolved as proven by OCT (Fig. 1C-D), no signs of inflammation were observed either in the AC or the vitreous (BIO score 0+ in both eyes), and the BCVA improved to 0.63 and 0.8 in the RE and LE, respectively. The patient had no significant side effects and the blood tests did not show any anomaly.

Two months later, the patient did not show any sign of active inflammation, the BCVA was 0.8 in the RE and 1.0 in the LE, with no evidence of CMO in both eyes.

The patient remained stable over time, maintaining her visual acuity in both eyes. At this time, she is continuing the same drug regimen, with 40 mg SQ every other week. No recurrence of

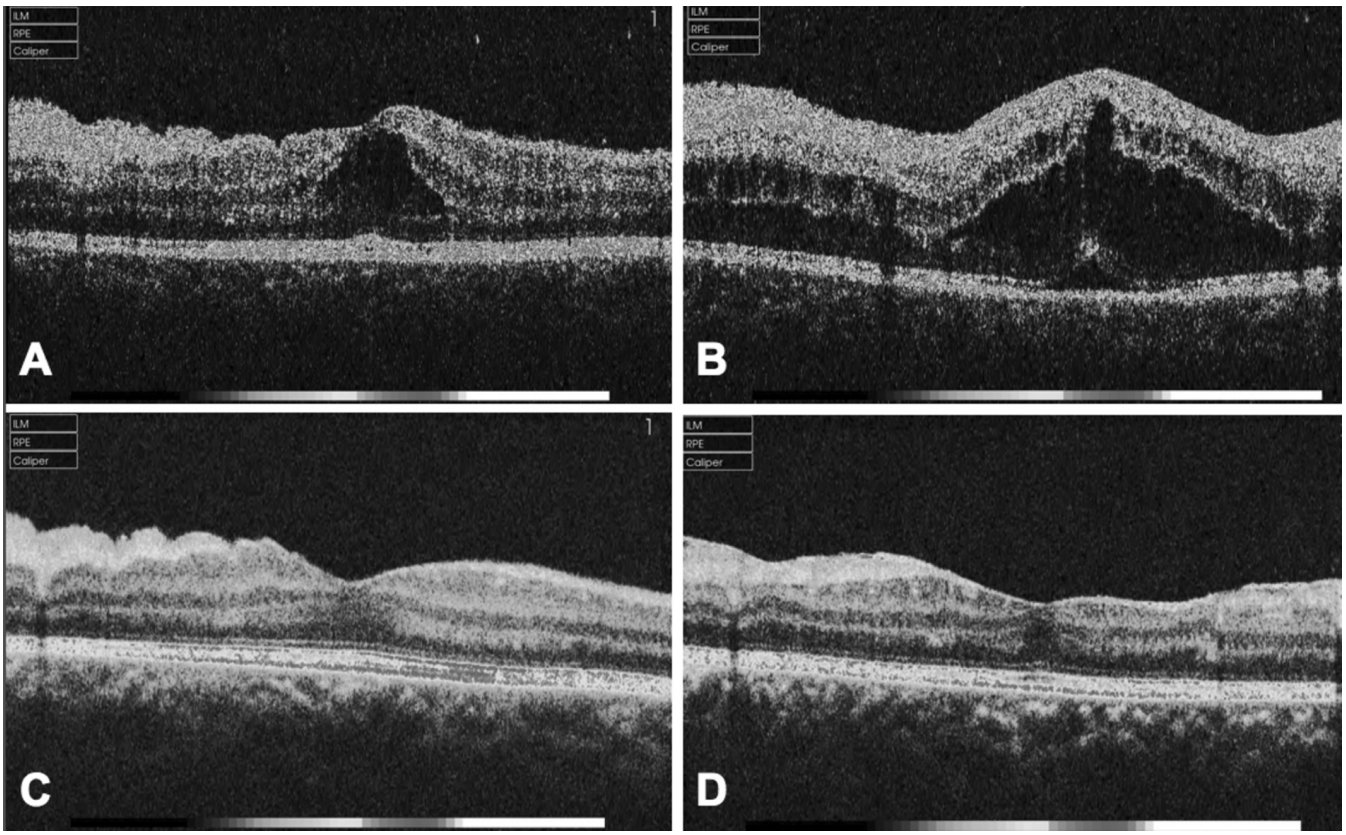

Fig. 1. Case 1: OCT showing intraretinal cysts (**A**), with an evident neurosensory detachment in the left eye (**B**).
Note the resolution of the oedema after one month with Adalimumab therapy (**C** and **D**).

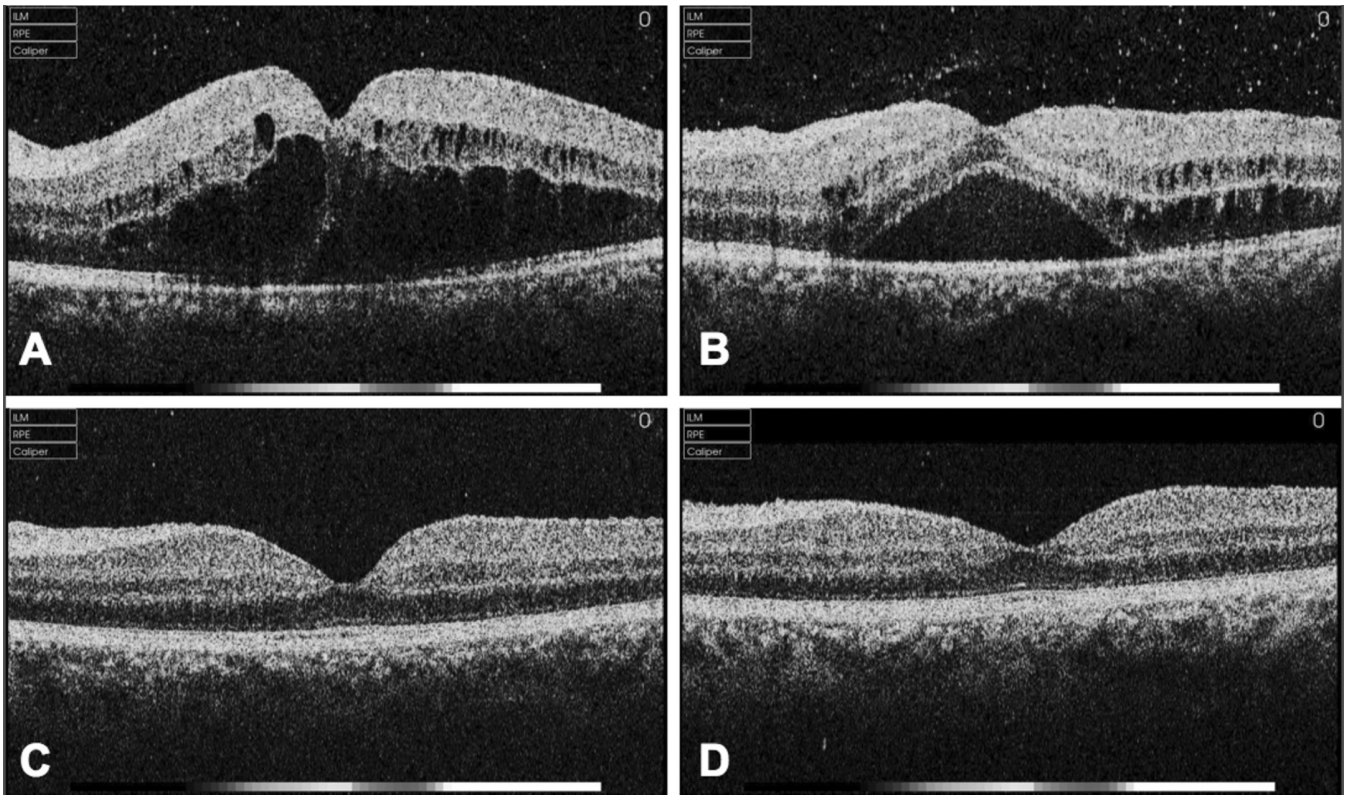

Fig. 2. Case 2: OCT showing the severe bilateral intraretinal oedema with neurosensory detachment at baseline (**A** and **B**), and after 2-month therapy with Adalimumab (**C** and **D**): no oedema is shown at that time with quiet uveitis.

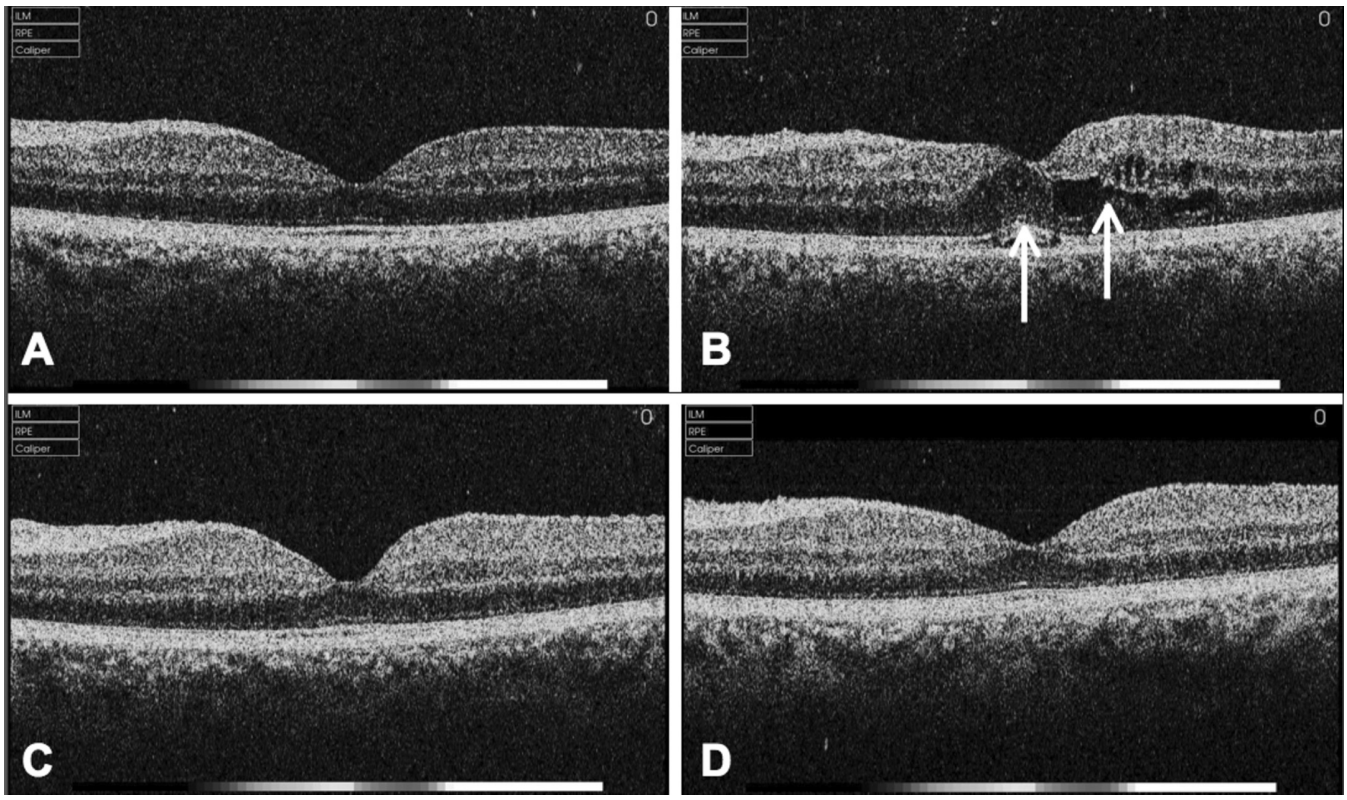

Fig. 3. Case 2: OCT at 16-month follow-up (**A** and **B**). Four months after the reduction of Adalimumab at 40 mg SQ every month, there is eveidence of intraretinal oedema with neurosensory detachment in the LE (**B**). Three weeks after the return to the standard regimen (40 mg SQ every other week), no evidence of uvetis is observed (**C** and **D**).

uveitis has been recorded to date, nor any serious or mild adverse events.

Case report 2

In 2008, a 14-year male patient was referred to the Ocular Immunology Service for a severe, bilateral, panuveitis complicated by a very thick CMO.

The young patient had been previously studied with a full immunologic screening, comprehending infectious diseases, with no evidence of any possible systemic trigger associated with such dramatic status. The parents referred that he had received intravenous steroids at the dose of 1 g intravenously for 5 days, followed by 1 mg/kg prednisone, coupled with CSA at the dose of 5 mg/kg/day. The CMO had improved temporarily, although a severe recurrence had occurred as soon as the daily dose reached 20 mg/day. The patient was newly studied with a full work-out for panuveitis, comprehending autoantibodies and infectous diseases. No positivity was recorded.

The ophthalmic examination at baseline presented a bilateral severe inflammation in the AC with 2+ cells and 3+ flare in both eyes, as well as tiny Kps in the inferior part of the endothelium. The vitreous was severely involved: the BIO score was 2+ in both eyes, and the posterior pole had a diffuse CMO (Fig. 2A-B). The BCVA was 0.5 and 0.4 in the RE and the LE, respectively. Therefore, under the light of the negative tests and the temporary effect of the steroids, Adalimumab was commenced at the dose of 40 mg SQ every other week. At 2-month follow-up, the panuveitis dramatically reduced the severity, as well as CMO thickness (Fig. 2C-D). The BCVA improved to 1.0 in the RE and 0.8 in the LE. No signs of active uveitis were recoded at that time, either in the AC or the vitreous.

The patient continued the same therapeutic regimen until the 12th month, when the drug was tapered to 40 mg SQ monthly. After 4 months, a mild panuveitis occurred in his LE, as well as the CMO (Fig. 3A-B). The drug regimen was turned back to 40 mg SQ every other week, resolving within 3 weeks both the inflammation and the CMO (Fig. 3C-D). The patient remained stable until the last follow-up, without experiencing any serious side effect.

Discussion

The role of monoclonal antibodies can be defined as a hot topic in the modern ocular immunology. In monoclonal antibodies family, Adalimumab is one of the most evolved and newest drugs available.

Unlike the exiguous number of reports in the ophthalmic literature, Adalimumab has recently proven its efficacy in treating several rheumatic diseases (6-8). Moreover, much more evidence was provided supporting a primary role of TNF-α in uveitis (9).

In parallel with the "on-label" use of Adalimumab in rheumatic diseases, this drug is gaining scientific dignity in the "off-label use" for severe sight-threatening uveitis (10). While more evidence of the "off-label" use of Adalimumab in auto-immune uveitis in adults (11) are described in the medical literature, there are few reports of it in paediatric uveitis.

The mainstay of therapy in severe uveitic diseases are oral corticosteroids, even though serious systemic side effects can occur. For such reasons, immunosuppressive agents are considered (12). As soon as the traditional immunesuppressive agents do not control the ocular inflammation, anti-TNF-α agents are considered. Although some preliminary data seem to be promising (13), little information is available about the auto-immune uveitis. On the other hand, very recently, the potentiality of Adalimumab has been explored by Leccese *et al*. (14) and Olivieri *et al*. (15), who have proven the efficacy of Adalimumab in refractory Behçet's disease. Behçet's disease represents an excellent model of auto-immune uveitis in the light of its severity, pathophysiology and unpredictability. In both studies, the authors have proven that patients with Behçet's disease showing a scarce response or adverse events to infliximab may successfully be treated with Adalimumab, regardless of the reason for switching. Moreover, Adalimumab has shown to be effective in both the ocular and extra-ocular signs of Behçet's disease. For such reasons, the results provided by these studies may suggest a progressive employment of Adalimuamb in non-infectious uveitis.

In our cases, Adalimumab has been both effective and safe, with a promising propensity in resolving and controlling the ocular inflammation. In addition, both cases had a complete recovering of the BCVA, which is essential in paediatric cases: in the first case, the young patient had an improvement from 0.2 in the RE and 0.5 in the LE to 0.8 and 1.0 in the RE and the LE, respectively. The second case improved from 0.5 and 0.4 at base line to 1.0 in both eyes at last follow-up. Moreover, it is mandatory to highlight an important aspect of both cases: the occurrence of chronic CMO completely resolved after Adalimumab therapy, which can represent an indirect additional indicator of the drug efficacy. In addition, uveitic CMO is one of the potentially sight-threatening complications of uveitis, which can negatively affect the treatment outcome, particularly when serous retinal detachment occurs (16) such as in our two cases. The follow-up presented is more than 2 years in both cases, which can be interpreted positively in terms of long-lasting control of severe sight-threatening uveitis.

For such reasons, Adalimumab can represent a valid alternative for immune-mediated uveitis in children (13). On the other hand, it is still unclear when to initiate therapy and, moreover, how long to continue the treatment: in case 2, the tapering of the drug produced a mild recurrence and this fits well with the unsolved questions about the length of biologic therapy. On the basis of the results achieved, we invite to consider the undisputed qualities of the biologic therapy and the scarce rationale in continuing a traditional treatment when this is evidently ineffective, albeit further studies are mandatory to validate these preliminary data.

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