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Retrospective analysis of complications of immunosuppressive therapies (steroids and immunosuppressive therapies) in pediatric uveitis

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Abstract

Purpose The purpose of this study is to analyze the incidence rate of side effects occurring during systemic therapy (corticosteroids, methotrexate, azathioprine, cyclosporine A or biologic agents) of auto-immune uveitis.

Material and methods Retrospective study including 23 / 71 patients aged between 0-16 years old presenting with a chronic non-infectious uveitis. All children were treated in the Jules-Gonin Eye Hospital and paediatric rheumatology unit of the CHUV (Centre Hospitalier Universitaire Vaudois) between January 2000 and December 31st 2010. Side effects were reported as minor (without subsequent change in systemic medication), moderate (associated with a change in systemic dosage or class of immunosuppressive therapy or in the presence of Cushingoid face or weight gain) or severe (hospitalization or life threatening).

Results 52% of boys and 48% of girls are present in the cohort with a mean age at the first visit of 8.1 years (1.7–15.6). Intermediate uveitis consisted of the commonest aetiology with 8 patients (35%), juvenile idiopathic arthritis (JIA) in 7 (30%), Behçet's disease in 3 (13%) and others in 5 (22%). The overall length of therapy was longer for prednisone (26.6 ± 5.4 patient / year), but was similar between methotrexate (22.1 ± 5.4 patient / year) and azathioprine (15.2 patient / year). Moderate side effects were respectively 64% for corticosteroids therapy, 54% with methotrexate and 14% with azathioprine. One severe and one moderate side effect were observed with anti-TNFα respectively stage III anaphylactic shock and pain during injection associated with a redness of the site of injection and limping after the injection.

Discussion Immunomodulating agents allow a rapid decrease in corticosteroid therapy, but one severe side effect was observed with anti-TNFa agents. These agents are considered in most countries as third line therapeutic agents.

Key words Uveitis, pediatric, adverse events, corticosteroids, immunosuppressive agents

Retrospective analysis of complications of systemic immunosuppressive therapies (steroids and immunosuppressive therapies) in pediatric uveitis

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Introduction

Uveitis is defined as of inflammation of intraocular structures, such as the ciliary body, the choroid and the retina. In most cases, uveitis presents with breakdown of the blood-aqueous barrier, resulting in the presence of proteins and cells in the anterior chamber of the eye (SUN classification). [1] About 6 to 10% of all cases of uveitis occur in children. Uveitis presenting at birth or soon after birth are primarily related to congenital infections, while uveitis associated with auto-immune diseases occurs more frequently in young children. [2] The most common systemic associations are juvenile idiopathic arthritis (JIA), sarcoidosis and Behçet's disease. Uveitis in children remains a diagnostic and therapeutic challenge. Early diagnosis is mandatory to avoid severe ocular or systemic complications that may occur in the absence of adequate therapy. For instance, approximately 50% of eyes with JIA-associated uveitis will develop legal blindness in the absence of adequate therapy. [3] Therapy must be administered systemically, since topical corticosteroids are of limited efficacy on the posterior segment of the eye. [4]

Systemic corticosteroids have been the mainstay of therapy for uveitis affecting the posterior segment of the eye (posterior uveitis). Intravenous pulse administration of methylprednisolone during three consecutive days followed by oral prednisone has been widely used in sight-threatening uveitis. [5] However, systemic corticosteroid administration is associated with numerous systemic side effects, including growth retardation, Cushing's disease, bone calcium depletion, high blood pressure, salt retention, diabetes, and mood swings, or depression. [6] Long-standing topical corticosteroids also have the potential for side effects that affect the eye, such as cataracts, and ocular hypertension [7-9]; conversely, ocular hypertension may preclude further use of corticosteroids. [9]

Recently, guidelines for the therapy of severe uveitis were published, primarily with regard to adult uveitis. [9] The introduction of corticosteroid-sparing immunosuppressive agents is recommended if intraocular inflammation is not under control after one month of high dose corticosteroids (prednisone 1 mg/kg/day), if intraocular inflammation is not controlled with a

daily-dose of prednisone ≤ 10mg , in case of corticosteroid-side effects that require tapering or discontinuation of corticosteroids, or in the presence of an ocular inflammatory disease known to have poor prognosis with corticosteroids alone. [6;10] Regarding childhood uveitis, however, very few data are available with respect to the use of, the efficacy, and the potential side effects of systemic immunosuppressive therapy. Anti-TNFα agents are a new class of immunomodulating drugs that are widely used in the treatment of Behçet's disease, rheumatoid arthritis, JIA, spondylathropathies, Crohn's disease and psoriasis. [11] These agents may be combined to other immunosuppressive therapies to optimize therapeutic efficacy, as it was demonstrated in rheumatoid arthritis. [11]

The purpose of the current study was to analyze the side effects of three different categories of therapy (corticosteroids, immunosuppressive drugs and anti-TNFα agents) currently used in the management of intraocular inflammation in children.

Material and methods

Study population

All children presenting with non-infectious uveitis seen in the Uveitis unit of the Jules-Gonin Eye Hospital and the Unit of Paediatric Rheumatology of the CHUV (Centre Hospitalier Universitaire Vaudois) between January 2000 and December 31st 2010 were included in the study. Data analysis was primarily focused on patients treated with one of the 3 categories of therapy (systemic corticosteroid, antimetabolite agents, and biological agents).
The Jules-Gonin Eye Hospital and the CHUV have a general authorization that was delivered for retrospective analysis of the data. The protocol was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection

Patients were identified from a computerized database of uveitis patients followed at the Jules-Gonin Eye Hospital and in the CHUV. Data were collected via retrospective chart review and entered into a computerized database, and included demographics, clinical features of inflammatory eye disease, and diagnosis. Potential associated systemic diseases were thoroughly documented by systemic work-up that was performed in the Paediatrics Department as needed and during follow-up when systemic side effects occurred. Adverse

events were classified into three categories: minor (without subsequent change in systemic medication); moderate (associated with a change in systemic dosage or class of immunosuppressive therapy). In the presence of corticosteroids introduction of immunosuppressive therapy as corticosteroid-sparing agents, the presence of a Cushingoid face or weight gain was also considered as medium side effects; and severe (associated with hospitalization or life-threatening side effects). Side effects of therapy were analyzed according to clinical reports that were sent after each clinical visit to the child's paediatrician and according to laboratory work-up. Side effects that occurred most frequently were analyzed and documented. The average time interval between initiation of therapy and onset of side effects was also recorded for each of the 3 categories of therapy.

Statistical analysis

All statistical analyses were performed using the JMP software. Frequencies of demographic and clinical variables were calculated for each variable. Time of follow-up (reported as patient / year) was compared according with the Mann-Whithney rank sum test and incidence rate of complications were compared.

RESULTS

Seventy-one children with uveitis aged 0 to 16 years were identified in the chart review. All these patients were followed-up in the Uveitis Clinic of the Jules-Gonin Eye Hospital in Lausanne between January 2000 and December 2010. Of these 71 patients, 23 patients with uveitis and systemic therapy were included in the analysis. Demographics and diagnoses are summarized in table 1. There were 12 boys and 11 girls. Mean age at presentation was 8.1 years [range 1.7 to 15.6 years]. Localization of uveitis was unilateral in 4 patients and bilateral in 19 patients. Anatomical classification of uveitis was the following: anterior uveitis 52%, intermediate uveitis 35%, posterior uveitis 4% and panuveitis 9%. Intermediate uveitis consisted of the commonest aetiology with 8 patients (35%), juvenile idiopathic arthritis (JIA) in 7 (30%) and Behçet's disease in 3 (13%); distribution is detailed in table 1. All included patients were diagnosed with chronic uveitis (of more than 3 months' duration according to the SUN classification) [1] that was associated in some cases with rheumatologic disease.

The overall length of therapy was longer for prednisone (26.6 ± 5.4 patient / year), but was similar between methotrexate (22.1 ± 5.4 patient / year) and azathioprine (15.2 patient / year). These two agents are introduced usually as second line therapy. No difference in therapeutic time (in term of patient / year) was observed ANOVA $p \leq 0.2346$. Moderate and severe side effects were respectively 64% for corticosteroids therapy, 54% with methotrexate, 25% with anti-TNFα and 14% with azathioprine.

Prednisone therapy was used as first line therapy in 22 out of 23 patients (96%). Control of intraocular inflammation could be obtained in 5 patients (23%), allowing progressive tapering of the therapy. Whenever intraocular inflammation was not brought under control or in cases of long-standing corticosteroid therapy, a corticosteroid-sparing, immunosuppressive agent was used as a second line therapy. Among those agents, methotrexate was the most commonly used (13 patients, 57% of total) (Figure 1). A control of ocular inflammation could be achieved in 7 out of 13 patients. Azathioprine was used in 7 patients (30%), achieving control of intraocular inflammation in 4 patients, one patient was previously treated with methotrexate. Anti-TNFα agents were used as a third line therapy and whenever control of intraocular inflammation was not achieved using either systemic corticosteroid therapy or corticosteroid-sparing immunosuppressive drugs. Quiescence of uveitis was obtained in 20/23 patients minimal inflammation was still present in three patients see figure 1.

In our cohort of patients, minor metabolic side effects were observed in more than 95% of patients during the first weeks of therapy (our first line therapy consisted of prednisone 1mg/kg/day). On 22 patients who received a treatment of prednisone in the cohort 14/22 (64%) developed one or more moderate secondary effect. Among these moderate secondary effects, 9/22 (41%) cases of weight gain have been identified, 6/22 (27%) patients presented a change of the percentile of the weight and 5/22 (23%) patients developed a cuschingoïd facies. Among the other moderate secondary effects with prednisone, 4/22 (18%) patients developed an ocular hypertension, 3/22 (14%) had a lymphopenia, 3/22 (14%) developed a cataract, 1/22 (4.5%) developed a glaucoma, 1/22 patient presented an arterial hypertension and 1/22 patient presented a delay in the growth and the weight gain with a percentile under three. More than one side effect can be observed in the same patient. One patient stopped prednisone therapy one day after initiation of therapy in the presence of severe nausea and vomiting. The parents refused further use of corticosteroids. This event was reported in the moderate side effects in an intention to treat basis. No severe side effects were observed. Long term side effects were not reported in this study.

With regard to antimetabolites (methotrexate and azathioprine), the most frequently observed side effects was elevation of liver function tests SGPT and SGOT. Rarely, lymphopenia was documented. Regarding to the secondary effects of the immunomodulating therapies, there are more moderate side effects than with prednisone. 13 patients were treated with methotrexate and 9/13 (69%) patients developed some secondary effects. 2/9 (22%) patients developed a minor secondary effect, 4/9 (44%) patients developed a moderate secondary effect, 1/9 (11%) patient presented 2 moderate secondary effects and 2/9 (22%) patients developed a minor and a moderate secondary effect.

Concerning the minor secondary effect, there are 3 cases of lymphopenia and 1 case of liver toxicity. The moderate secondary effects are the following: 7 cases of liver toxicity with an elevation of the liver enzymes (ASAT/ALAT) and 1 case of severe lymphopenia.

7 patients were treated with azathioprine: among these patients, 4/7 (57%) patients developed a secondary effect. 1/4 (25%) patient presented a minor and a moderate secondary effect and 3/4 (75%) patients developed a minor secondary effect. The only 1/4 (25%) moderate secondary effect was a liver toxicity with an elevation of ASAT. There were 2 cases of liver toxicity which didn't require a change or a stop of the treatment, 1 case of thrombopenia associated with a leucopenia and 1 case which concern a decrease of the three bloodlines.

In the cohort of 23 patients, 1 patient was treated by cyclosporine and presented 1 minor secondary effect such as a thrombopenia.

Regarding the last possible line of treatment, 8 patients were treated by biological agents like anti-TNFα and 3/8 (37.5%) patients developed one or two secondary effects. There are few secondary effects with these agents. With anti-TNFα agents, only few side effects were observed, including slight pain upon injection or elevated liver function tests:

1/3 (33%) patient presented 2 minor secondary effects with two different molecules: etanercept (Enbrel®) and adalimumab (Humira®). 1/3 (33%) patient developed a moderate secondary effect and 1/3 (33%) developed a severe secondary effect. The 2 minor secondary effects were 1 pain during injection with adalimumab (Humira®), and 1 discrete liver toxicity with etanercept (Enbrel®). The moderate secondary effect was a pain during injection associated with a redness of the site of injection and limping after the injection concerning adalimumab (Humira®). Regarding the severe secondary effect it is an anaphylactic shock with an injection of infliximab (Remicade®). Side effects are summarized in table 2 and sides expressed as patient / year. Moderate side effects occurred in 14/22 patients with corticosteroids (64%). Antimetabolite-related liver toxicity was observed in 7/13 patients treated with systemic methotrexate (54%) (Subgroup analysis of oral or IM MTX) and

occurred after a mean time of 15.6 months, and in 1/7 patients treated with azathioprine (14%) after 6.3 months. Anti-TNFα therapy was associated with stage III anaphylactic shock in one patient after infliximab (Remicade®) infusion, and limp, pain and erythema in one other patient.

DISCUSSION

Approximately 32% of patients (23 out of 71 patients) in the studied group were treated with systemic therapy. Therapeutic approach included a stepwise approach consisting of corticosteroids as a first line therapy, antimetabolites methotrexate and azathioprine as a second line therapy, and eventually anti-TNFα whenever intraocular inflammation was not brought under control using the first two lines of therapy or if severe side effects were observed. Median time of therapy was longer for corticosteroids than for immunosuppressive or biological therapies. With anti-TNFα agents, only few side effects were observed, including slight pain upon injection or elevated liver function tests.

Stage III anaphylactic shock was the most severe side effect observed in one patient of this series and occurred with anti-TNFα perfusion (infliximab (Remicade®). This side effect result from idiosynchrasic reaction occurring after proteins perfusion. Infliximab (Remicade®) is a chimeric monoclonal antibody and anaphylactic adverse event requires cancellation of therapy, cardiopulmonary arrest was recently described in a 37-year-old man with no history of allergy or coronary heart disease. [12] Perfusion of infliximab (Remicade®) is mandatory in inpatient clinic, in the presence of unpredictable anaphylactic reaction (daycare hospitalization).

Most side effects were moderate and related to hepatotoxicity of immunosuppressive drugs, all cases were reversible after dosis change of switching to other therapies. A close follow-up of complete blood count, urea, creatinine and liver function tests values is mandatory during the follow-up of immunosuppressive therapy since this side effect was respectively observed in 54% of patients under MTX and 14% of patients under azathioprine. Infliximab (Remicade®) is associated with a better answer of the inflammation than etanercept (Enbrel®). [13] Infliximab (Remicade®) is better and generate less secondary effects than etanercept (Enbrel®). Etanercept (Enbrel®) is more frequently associated with ocular complications such as glaucoma or cataract. [14]

No significant difference was observed between the lengths of follow-up of the different group of patients. Corticosteroids were associated with a high rate of minor (more than 95%) and moderate metabolic complications. Multiples sides' effects were also observed in the same patients, high dosage of corticosteroids being more susceptible to produce severe sides' effects. This study was not designed to analyzed long term side effects such as osteoporosis or bone fractures which are classically described by corticosteroids use. In all patients corticosteroids could be stopped after initiation of immunosuppressive therapy or biological agents. This approach allows minimizing onset of cataract or corticosteroids-induced glaucoma. In this series less than 14% of patients developed a cataract and only one patient developed a glaucoma (4.5%). In a mean follow-up of 3.8 years, 27 out of 53 patients (51%) with JIA underwent cataract extraction in the series described by Sijssens et al, but JIA patients presents probably a higher risk of development of cataract. [8] Uveitis-induced glaucoma is observed in up to 20% of patients with a 5-years follow-up of uveitis and in more than 38% of patients with JIA. [7] The relative low rate of ocular complication of our series is probably related to the prompt introduction of immunomodulating agents allowing a rapid decrease in corticosteroids dosage and limiting topical administration of corticosteroids.

Anti-TNFα agents were shown to produce the highest degree of severity of sides' effects, but these events remains extremely rare. But the presence of a cardiopulmonary arrest after infliximab (Remicade®) therapy, in the absence of history of allergy justify their use as third line therapeutic agent. Humanized antibodies may be an excellent alternative, but their use is limited to third line therapy in most countries.

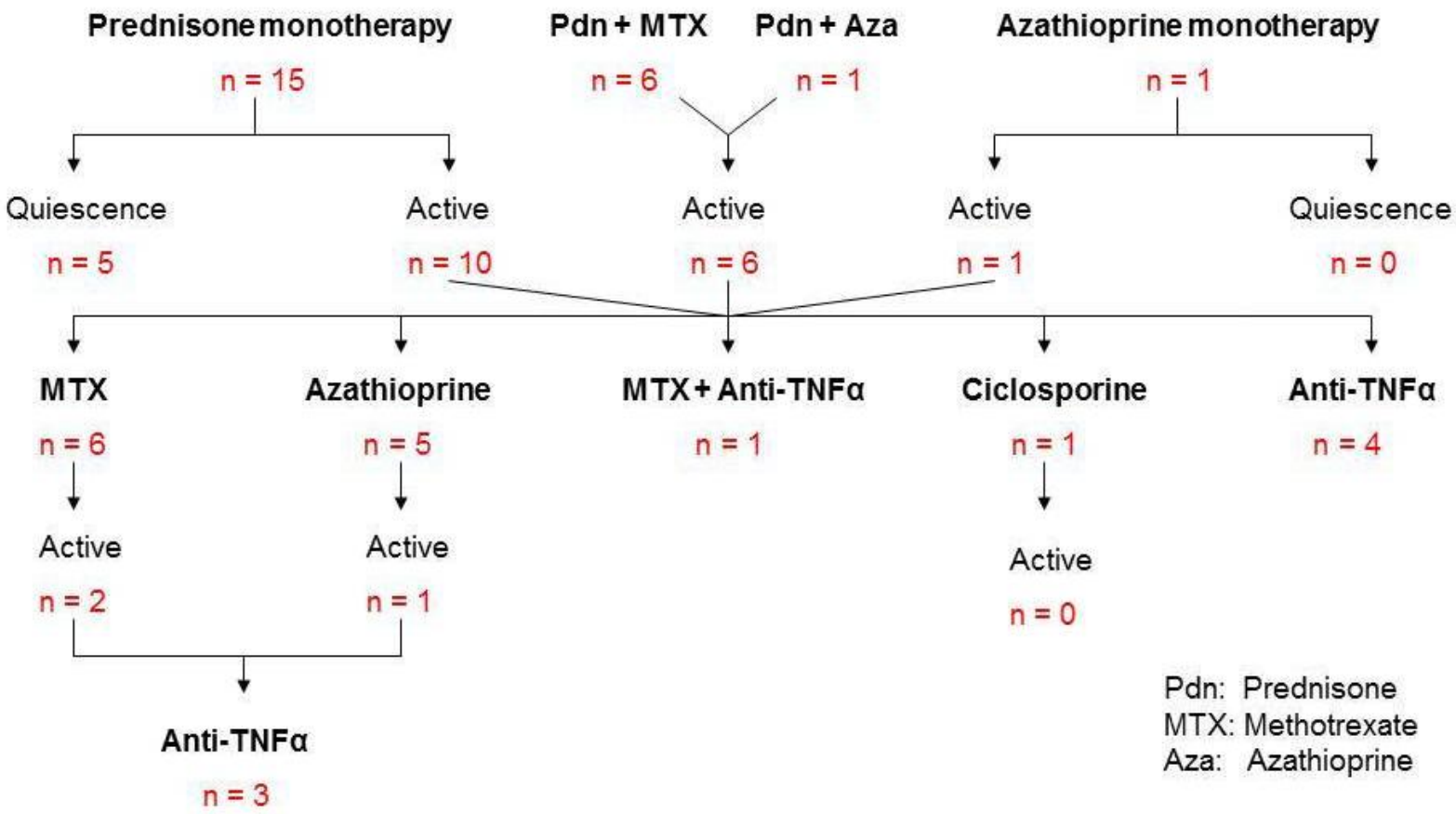
Table 1 Demographics and diagnosis

Number of patients	23
Sex	
Boys	12 (52%)
Girls	11 (48%)
Age at first consultation (year)	8.1 (1.7 - 15.6)
Localization of uveitis	
Anterior	12 (52%)
Intermediate	8 (35%)
Panuveitis	2 (9%)
Posterior	1 (4%)
Laterality of uveitis	
Unilateral	4 (17%)
Bilateral	19 (83%)
Associated disease	
Intermediate uveitis	8 (35%)
Juvenile idiopathic arthritis	7 (30%)
Behçet's disease	3 (13%)
HLA-B27	1 (4%)
Vogt-Koyanagi-Harada	1 (4%)
Idiopathic	3 (13%)
Number of patients treated by	
Prednisone	22 (96%)
Methotrexate	13 (57%)
Azathioprine	7 (30%)
Ciclosporine	1 (4%)
Anti-TNFα	8 (35%)

Table 2 Moderate and severe adverse events appearing with the systemic therapies

Therapies	Adverse events (moderate and severe)	Number/total patients	Mean time of onset (months)	Patient/year index
Prednisone	Nausea/vomiting	14/22 (64%)	0.1	26.6
	Weight gain and/or Cushing facies		8.1 (SD : 6.8)	
	Ocular affects (ocular hypertension or cataract or glaucoma)		7.2 (SD : 5.0)	
	Lymphopenia		5.5 (SD : 4.6)	
	Arterial hypertension		7.9	
	Delay in the growth and weight under percentile three		10.9	
Methotrexate	Hepatotoxicity (ASAT/ALAT)	7/13 (54%)	15.6 (SD : 8.8)	22.1
	Lymphopenia			
Azathioprine	Hepatotoxicity (ASAT/ALAT)	1/7 (14%)	6.3	15.2
Anti-TNFα	1) Limping, pain and erythema (Adalimumab (Humira®))	2/8 (25%)	0	14
	2) Stage III anaphylactic shock (Infliximab (Remicade®))		12.2	

Figure 1 Description of the different steps of treatment for the 23 children with quality of inflammation's control



Reference List

1. Jabs DA, Nussenblatt RB, Rosenbaum JT. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-16.

2. Basso A, Mansouri K, Frueh BE, Guex-Crosier Y. Granulomatous uveitis and congenital cataract: a rare association. Klin Monbl Augenheilkd 2010;227:306-8.

3. Cassidy JT, Sullivan DB, Petty RE. Clinical patterns of chronic iridocyclitis in children with juvenile rheumatoid arthritis. Arthritis Rheum 1977;20:224-7.

4. Saraiya NV, Goldstein DA. Dexamethasone for ocular inflammation. Expert Opin Pharmacother 2011;12:1127-31.

5. Wakefield D, McCluskey P, Penny R. Intravenous pulse methylprednisolone therapy in severe inflammatory eye disease. Arch Ophthalmol 1986;104:847-51.

6. Galor A, Jabs DA, Leder HA, et al. Comparison of antimetabolite drugs as corticosteroid-sparing therapy for noninfectious ocular inflammation. Ophthalmology 2008;115:1826-32.

7. Sijssens KM, Rothova A, Berendschot TT, De Boer JH. Ocular hypertension and secondary glaucoma in children with uveitis. Ophthalmology 2006;113:853-9.

8. Sijssens KM, Rothova A, Van D, V, et al. Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol 2007;144:574-9.

9. Thorne JE, Woreta FA, Dunn JP, Jabs DA. Risk of cataract development among children with juvenile idiopathic arthritis-related uveitis treated with topical corticosteroids. Ophthalmology 2010;117:1436-41.

10. Jabs DA, Rosenbaum JT. Guidelines for the use of immunosuppressive drugs in patients with ocular inflammatory disorders: recommendations of an expert panel. Am J Ophthalmol 2001;131:679.

11. Theodossiadis PG, Markomichelakis NN, Sfikakis PP. Tumor necrosis factor antagonists: preliminary evidence for an emerging approach in the treatment of ocular inflammation. Retina 2007;27:399-413.

12. Miki H, Okamoto A, Ishigaki K, et al. Cardiopulmonary arrest after severe anaphylactic reaction to second infusion of infliximab in a patient with ankylosing spondylitis. J Rheumatol 2011;38:1220.

13. Saurenmann RK, Levin AV, Feldman BM, et al. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. J Pediatr 2006;149:833-6.

14. Smith JR, Levinson RD, Holland GN, et al. Differential efficacy of tumor necrosis factor inhibition in the management of inflammatory eye disease and associated rheumatic disease. Arthritis Rheum 2001;45:252-7.