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ABSTRACT. ***Objective.*** Anti-TNF-α agents have significantly changed the management of juvenile idiopathic arthritis (JIA). We evaluated the safety and efficacy of adalimumab (ADA) and infliximab (IFX) for the treatment of JIA-associated uveitis in patients treated for ≥ 2 years.

Methods. Patients with JIA-associated uveitis treated with IFX and ADA were managed by a standardized protocol and data were entered in the ORCHIDEA registry. At baseline, all patients were refractory to standard immunosuppressive treatment or were corticosteroid-dependent. Data recorded every 3 months were uveitis course, number/type of ocular flares and complications, drug-related adverse events (AE), and treatment switch or withdrawal. Data of patients treated for ≥ 2 years were analyzed by descriptive statistics.

Results. Up to December 2014, 154 patients with ≥ 24 months followup were included in the study. Fifty-nine patients were treated with IFX and 95 with ADA. Clinical remission, defined as the absence of flares for > 6 months on treatment, was achieved in 69 patients (44.8%), with a better remission rate for ADA (60.0%) as compared to IFX (20.3%; $p < 0.001$). A significant reduction of flares was observed in all patients without difference between the 2 treatment modalities. The number of new ocular complications decreased in both groups but was lower for ADA ($p = 0.015$). No serious AE were recorded; 16.4% of patients experienced 35 minor AE and the incidence rate was lower with ADA than with IFX.

Conclusion. At the 2-year followup, ADA showed a better efficacy and safety profile than IFX for the treatment of refractory JIA-associated uveitis. (First Release April 15 2018; J Rheumatol 2018;45:1167–72; doi:10.3899/jrheum.171006)

Key Indexing Terms:
UVEITIS JUVENILE IDIOPATHIC ARTHRITIS TREATMENT ANTI-TNF AGENTS

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Juvenile idiopathic arthritis (JIA) is one of the most common rheumatic diseases in children and among its extraarticular manifestations, anterior uveitis (AU) is the most important[1]. The prognosis is still poor because of frequent sight-threatening complications. To date, chronic JIA-associated uveitis represents a challenge for pediatric rheumatologists and ophthalmologists because standardization of AU management is still pending, even though an early interdisciplinary approach significantly reduces the risk of severe visual impairment[1].

Therapy of chronic uveitis includes topical and systemic nonbiologic drugs such as corticosteroids and methotrexate, and biologic agents. In refractory patients, anti–tumor necrosis factor (TNF)-α agents have significantly changed uveitis course and related complications. Indeed, anti-TNF-α agents are strongly recommended as corticosteroid-sparing agents in severe uveitis[2]. Experience of the use of these drugs increased in recent decades, but more evidence is required regarding their safety and efficacy.

Since 2007 the Italian National Agency for Drugs has approved the use of infliximab (IFX) and adalimumab (ADA) as off-label treatments for refractory JIA-associated uveitis. Because of the lack of data concerning longterm safety and efficacy of these biologic agents, a National Italian Registry called ORCHIDEA (OculaR involvement in CHIldhood rheumatic DisEAses) was established. Thus, data of patients from 24 pediatric rheumatology and ophthalmology centers are prospectively collected in an online protected, anonymized database. This was the beginning of the cooperation between Italian pediatric rheumatologists and ophthalmologists.

MATERIALS AND METHODS

Since January 2007, patients with JIA-associated AU, treated with the anti-TNF-α agents IFX and ADA and refractory to standard immunosuppressive treatment and/or corticosteroid-dependent, were managed by a standard protocol and were entered in the ORCHIDEA Registry. Data were prospectively collected from 24 pediatric rheumatology and ophthalmology centers. All eligible patients were diagnosed as having JIA according to the International League of Associations for Rheumatology criteria[3], and AU according to the Standardization of the Uveitis Nomenclature Working Group criteria[4]. Uveitis was graded according to the number of cells in the anterior chamber; an anterior chamber cell grade of < 0.5+ was defined as inactive disease[4]. Uveitis flare was defined as the increase of 2 or more levels of cell score in the anterior chamber.

Clinical remission on medication (CRM) was defined as the absence of flares for > 6 months on systemic treatment, with or without minimal topical treatment (corticosteroid and/or mydriatic-cycloplegic eye drops, used < 1 × per day).

Structural complications of uveitis and visual acuity outcomes were also recorded according to standardized methods. Complicated uveitis was defined as the occurrence of ≥ 1 structural complications such as posterior synechiae (involving ≥ 1 iris quadrant), band keratopathy, cataract, glaucoma, cystoid macular edema (CME), or ocular hypertension (defined as an intraocular pressure ≥ 22 mmHg for ≥ 3 mos, or a single measurement ≥ 30 mmHg).

Ophthalmological evaluation frequency ranged from once a week to once every 3 months, depending on the uveitis course. Clinical data, collected at baseline and during the followup, included the number of uveitis flares, new onset or worsening of preexisting ocular complications and drug-related adverse events (AE). A comparison was made between the frequency of uveitis flares and new-onset complications during the 12-month period before the introduction of anti-TNF agents and those occurring during the 24-month period of treatment.

All centers involved in this project adopted a "stepladder" algorithm for the treatment. New-onset uveitis was treated only with mydriatics and/or corticosteroids topical therapy. In case of recurrent or persistent AU activity for > 1 month, patients were prescribed systemic corticosteroids (oral prednisone 0.5–1 mg/kg/d) for a short period (1–2 mos). If intraocular inflammation was still refractory or steroid-dependent, immunosuppressive therapy with methotrexate (MTX; 10–15 mg/m^2/wk) or cyclosporine (CSA; 3–5 mg/kg/d) was prescribed. Indications to start anti-TNF treatment were intolerance or nonresponsiveness to ≥ 6 months MTX and/or CSA treatment, and/or oral prednisone dependency.

Anti-TNF-α agents were administered as "off-label" treatment, according to the Italian National Health System regulations, in case of intolerance or nonresponsiveness to standard immunosuppressive treatment for ≥ 6 months and/or oral corticosteroid dependency. Intravenous IFX infusions, at a dosage of 5 mg/kg, were scheduled at 0, 2, 6, and 12 weeks, and then continued every 6–8 weeks; ADA was administered subcutaneously every 2 weeks at a dosage of 1 mg/kg (max 40 mg).

MTX (10–20 mg/m^2/wk) and low-dose steroids (≤ 0.2 mg/kg/d), if present at baseline, were maintained, or when possible, tapered during the study period.

The collection of patient information was approved by the ethics committees of each center adhering to the ORCHIDEA Registry (Prot. no. 3305/AO/14). According to the Ethics Committee of Padua University Hospital, patients' written informed consent to publish the materials was not needed because all information was collected anonymously by each participating center.

Statistical analysis. Data of patients treated with anti-TNF agents for ≥ 2 years were anonymously retrieved from the ORCHIDEA Registry and analyzed by descriptive statistics. Quantitative variables were expressed as mean ± SD, and qualitative variables as n (%). Differences between the 2 groups (subjects who received ADA vs IFX) in baseline demographic characteristics and clinical variables at treatment start and after the first and second years of followup were analyzed using the chi-squared test or Fisher's exact test for categorical variables, and the Student t test or Mann-Whitney U test for continuous variables, where appropriate. McNemar tests were performed to examine within-group changes in the frequencies of uveitis flares and complications during the followup. Patients experiencing treatment shift from IFX or ADA to other treatments were included in the intention-to-treat analysis but excluded from IFX-ADA comparison on both efficacy and safety. The drug retention rate, defined as the proportion of patients who maintained the same anti-TNF agent in the 2-year period, was also determined. Safety data are presented as incidence rates (IR) with corresponding Poisson exact 95% CI, which were calculated as the number of events per 100 patient-years (PY) of exposure (no. patients with event/exposed PY × 100). PY of exposure were censored at the time of the first occurrence of an AE. For all statistical tests, a p value < 0.05 (2-tailed test) was taken to

indicate a significant difference. All data were processed using the statistical software PASW Statistic 18.0 (IBM-SPSS Inc.).

RESULTS

From January 2007 to December 2014, 236 patients with JIA-AU treated with IFX or ADA were entered in the ORCHIDEA Registry and 154 reached ≥ 2 years of followup (Figure 1). During this period, 32 patients (20.8%) changed treatment: 27 switched from IFX to ADA because of loss of efficacy (17 patients) and infusion reaction or intolerance (10 patients), 1 switched from ADA to IFX, 3 from ADA to abatacept, and 1 to rituximab (Figure 1).

Of the remaining 122 patients (99 female, 23 male) who maintained the same biological agent for 2 years, 90 were treated with ADA and 32 with IFX, with 94.7% and 54.2% retention rates, respectively ($p < 0.001$).

Demographic and clinical characteristics of the study group are summarized in Table 1. At treatment start, the mean age was 9.5 years and the duration of uveitis was 4.3 years. The mean age at arthritis onset was 4.4 years, and 5.2 years for uveitis onset. All patients included in our study had failed previous immunosuppressive treatments (MTX, CSA) and/or were corticosteroid-dependent. As shown, no significant differences were found comparing the 2 groups at baseline.

At the end of the 2-year treatment, the CRM (defined as the absence of flares > 6 months on systemic treatment) was achieved in 69 patients (44.8%), with a better remission rate for ADA (60.0%) compared to IFX (20.3%; $p < 0.001$; Figure 1).

As shown in Table 2, we observed a reduction in the number of flares in all patients treated with both anti-TNF-α agents at the end of the first year of treatment and during the whole followup period. Patients with ≥ 1 flare were 68 (75.6%) for ADA in the pretreatment period and 31 (34.4%) at the end of the 2-year followup ($p < 0.001$). For IFX, 23 subjects (71.9%) had ≥ 1 flare before treatment and only 12 (37.5%) during the followup ($p = 0.007$). Moreover, the rate of flares per 100 PY decreased significantly at the end of the first and second years of treatment both in the ADA and IFX groups ($p < 0.001$) without significant difference between the 2 treatment modalities ($p = 0.536$).

Moreover, we observed that in the ADA group, the rate of ocular complications per 100 PY progressively decreased both during first and second years of therapy ($p = 0.08$ and $p < 0.001$, respectively). A similar trend was also reported for patients taking IFX, without reaching significance ($p = 0.805$ and $p = 0.05$, respectively). A significant difference between the 2 groups was detected: the rate of complications per 100 PY was significantly higher in the IFX group than in the ADA group ($p = 0.015$).

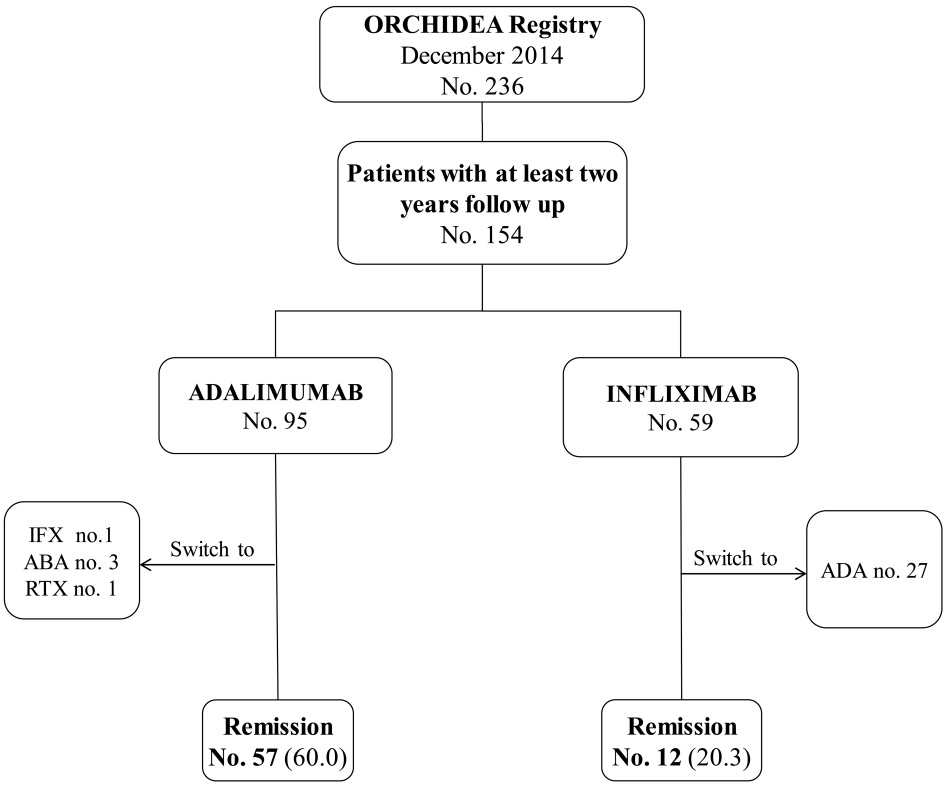

Figure 1. Disposition of the patients with JIA-associated uveitis treated for 2 years with anti-TNF agents. Data are n (%) unless otherwise indicated. JIA: juvenile idiopathic arthritis; TNF: tumor necrosis factor; ORCHIDEA: OculaR involvement in CHIldhood rheumatic DisEAses; IFX: infliximab; ABA: abatacept; ADA: adalimumab; RTX: rituximab.

Table 1. Patient baseline demographic and clinical characteristics. Values are n (%) or mean ± SD unless otherwise specified.

Characteristics	ADA, n = 95	IFX, n = 59	Overall, n = 154	p
Sex, F:M	1:5	1:3	1:4.3	0.301
Age, yrs	9.30 ± 4.47	9.95 ± 4.31	9.47 ± 4.42	0.474
Range	2.62–18.0	3.59–18.0	2.62–18.0	
Age at arthritis onset, yrs	4.13 ± 3.04	5.29 ± 3.29	4.43 ± 3.13	0.086
Range	1.08–16.67	1.05–13.88	1.05–16.67	
Age at uveitis onset, yrs	5.04 ± 3.24	5.61 ± 3.25	5.19 ± 3.24	0.403
Range	1.03–17.94	1.49–15.24	1.03–17.94	
Time interval arthritis/uveitis, yrs	1.61 ± 2.19	1.57 ± 2.49	1.61 ± 2.23	0.472
Range	0–10.03	0–9.04	0–10.03	
Uveitis duration, yrs	4.23 ± 4.17	4.38 ± 3.92	4.27 ± 4.09	0.854
Range	0–16.74	0.26–15.99	0–16.74	
Previous treatment				
MTX	78 (82.1)	50 (84.7)	128 (83.1)	0.219
CSA	4 (4.2)	2 (3.4)	6 (3.9)	0.188
Corticosteroid dependence	23 (24.2)	19 (32.2)	42 (27.3)	0.805

ADA: adalimumab; IFX: infliximab; MTX: methotrexate; CSA: cyclosporine.

Table 2. Uveitis flares and new ocular complications in the first and second years of anti-TNF treatment. Data are n (%) unless otherwise indicated.

Variables	Pretreatment, A	First-year Followup, B	Second-year Followup, C	p A vs B	p A vs C	p ADA vs IFX
ADA, n = 90						
Uveitis flares						
Patients	68 (75.6)	14 (15.6)	31 (34.4)	< 0.001	< 0.001	0.756
N	231	23	84			
IR (95% CI)	256.7 (224.6–292.0)	25.6 (16.2–38.3)	46.7 (37.2–57.8)	< 0.001	< 0.001	0.536
Complications						
Patients	27 (30.0)	16 (17.8)	24 (26.7)	0.043	0.678	0.140
N	45	23	38			
IR (95% CI)	50.0 (36.5–66.9)	25.6 (16.2–38.3)	21.1 (14.9–29.0)	0.08	< 0.001	0.015
IFX, n = 32						
Uveitis flares						
Patients	23 (71.9)	8 (25.0)	12 (37.5)	< 0.001	0.007	
N	90	13	26			
IR (95% CI)	281.3 (226.2–345.7)	40.6 (21.6–69.5)	40.6 (26.5–59.5)	< 0.001	< 0.001	
Complications						
Patients	13 (40.6)	9 (28.1)	13 (40.6)	0.481	> 0.999	
N	22	14	25			
IR (95% CI)	68.8 (43.1–104.1)	43.8 (23.9–73.4)	39.1 (25.3–57.7)	0.805	0.05	

TNF: tumor necrosis factor; ADA: adalimumab; IFX: infliximab; IR: incidence rate per 100 patient-years.

During the 2 years of followup, 63 new ocular complications (38 in 24 patients treated with ADA and 25 in 13 patients treated with IFX) were reported (Table 3). Cataract was the most commonly reported complication (25% with IFX, 11.1% with ADA), followed by band keratopathy, synechiae, CME, ocular hypertension, and vitreitis.

No significant difference between the 2 anti-TNF-α agents for the type of complication was observed, except for CME and cataract, which were less frequently found in the ADA group.

No variable such as duration of uveitis prior to treatment, sex, age at treatment start, and number and type of complication at baseline were significantly associated with the final outcome.

During the 2-year followup period, no serious or life-threatening AE related to anti-TNF-α treatment were recorded. As shown in Table 4, 20 patients (16.4%) experienced 35 minor AE and among these, 6 subjects had multiple AE. Interestingly, the IR was significantly lower in the ADA group (10.6 IR/100 PY) than in the IFX group (25.0 IR/100

Table 3. Onset of new ocular complications during the 2 years of anti-TNF treatment. Values are n (%) unless otherwise indicated.

Variables	ADA, n = 90	IFX, n = 32	p
Overall			
N	38	25	
IR (95% CI)	21.1 (14.9–29.0)	39.1 (25.3–57.7)	0.015
Cataract	10 (11.1)	8 (25.0)	0.080
Band keratopathy	7 (7.8)	4 (12.5)	0.441
Synechiae	10 (11.1)	3 (9.4)	0.785
Ocular hypertension	4 (4.4)	2 (6.3)	0.683
Vitreitis	3 (3.3)	3 (9.4)	0.216
CME	2 (2.2)	4 (12.5)	0.04
Ocular hypotension	1 (1.1)	1 (3.1)	> 0.999
Glaucoma	1 (1.1)	1 (3.1)	> 0.999

TNF: tumor necrosis factor; ADA: adalimumab; IFX: infliximab; IR: incidence rate per 100 patient-years; CME: cystoid macular edema.

PY, p = 0.008). In addition, more patients treated with IFX developed multiple AE (p = 0.014).

Infections (42.9%) were the most frequently reported AE, followed by headache (25.7%) and local skin reactions (8.6%). Among sites of infection, the involvement of the urinary tract was significantly more frequently associated with the use of IFX (p = 0.035).

DISCUSSION

Uveitis is the most serious extraarticular complication of JIA because it may lead to several sight-threatening conditions that may impair visual function.

To our knowledge to date, no standardized treatment approach has been established; therefore, an early diagnosis and prompt treatment are required to preserve visual function[2]. In particular, when the first-line treatment with topical mydriatics and corticosteroid drops fails, disease-modifying antirheumatic drugs such as MTX or anti-TNF-α agents such as IFX or ADA should be introduced to control ocular inflammation and prevent complications[2,5]. Unfortunately, data on the safety and efficacy of these biologic agents in this particular condition are scarce; therefore in 2007, the National Italian ORCHIDEA Registry was established. This registry includes a large cohort of patients with JIA-associated uveitis using a standardized protocol and receiving a homogeneous therapeutic dosing regimen.

In our present study, we report the 2-year followup results on the safety and efficacy of anti-TNF-α treatment of JIA-associated uveitis. Regarding efficacy, we found a good response for both anti-TNF-α agents, with statistically significant greater remission rates among patients receiving ADA than in those taking IFX (60.0% vs 20.0%, p < 0.01).

These results confirm those reported after the first year of followup[6] and are comparable with other reports. In particular, 2 retrospective studies reported a good response rate on uveitis (57% and 76%) in patients with JIA treated with ADA[7,8]. However, in neither study was it possible to extract specific outcomes in the subset of patients who received ADA as first-line biologic treatment. In a meta-analysis including 5 studies of ADA, improvement in intraocular inflammation was reported in 87% of 31 patients with JIA, but again, the number of biologics-naive patients was not specified, and data on remission were available only for a few cases[9]. The only available study in which ADA was

Table 4. AE reported during the 2-year followup. Values are n (%) unless otherwise indicated.

AE	Overall, n = 122	IFX, n = 32	ADA, n = 90	p
Major AE	0	0	0	
Minor AE				
N events	35	16	19	
Patients	20 (16.4)	5 (15.6)	15 (16.7)	> 0.999
IR (95% CI)	14.3 (10.0–19.9)	25.0 (14.3–40.6)	10.6 (6.4–16.5)	0.008
Infections	15 (42.9)	8 (50.0)	7 (36.8)	0.433
URTI	7 (20.0)	4 (25.0)	3 (15.8)	0.677
HZV	4 (11.4)	0 (0.0)	4 (21.1)	0.109
UTI	4 (11.4)	4 (25.0)	0 (0.0)	0.035
Infusion reactions	2 (5.7)	1 (6.3)	1 (5.3)	> 0.999
Systemic symptoms				
Headache	9 (25.7)	4 (25.0)	5 (26.3)	> 0.999
Irritability	1 (2.9)	1 (6.3)	0 (0.0)	0.457
GI symptoms	2 (5.7)	1 (6.3)	1 (5.3)	> 0.999
Prolonged menses	1 (2.9)	0 (0.0)	1 (5.3)	> 0.999
BMI changes	1 (2.9)	1 (6.3)	0 (0.0)	0.457
Skin reactions	3 (8.6)	0 (0.0)	3 (15.8)	0.234
Fatigue	1 (2.9)	0 (0.0)	1 (5.3)	> 0.999

AE: adverse events; IFX: infliximab; ADA: adalimumab; IR: incidence rate per 100 patient-years; URTI: upper respiratory tract infection; HZV: herpes zoster virus; UTI: urinary tract infection; GI: gastrointestinal; BMI: body mass index.

used as first-line biologic treatment > 12 months in a small cohort of 15 patients reported remission in 60% of cases[10]; this remission rate is comparable to that found in our present study. Conversely, a lower response rate was found in a pilot study including 20 patients with JIA-associated uveitis in which 35% ocular improvement after a mean followup of 18 months was reported[11]. In that case, the low frequency of positive results was probably related to the prolonged uveitis duration at treatment start (mean 8.7 yrs) and to the fact that all patients were refractory to previous anti-TNF agents (IFX and etanercept).

The first double-blind randomized controlled trial investigating the effect of ADA in the treatment of JIA-associated uveitis in 90 patients has recently been published[12]. The results showed efficacy of ADA in controlling ocular inflammation, with a treatment failure of 27% at 18 months' followup in 60 patients with JIA-associated uveitis, which was significantly lower than in the placebo group (30 patients) treated with just MTX, where the treatment failure was 60%[12]. Although the uveitis duration at treatment start was not reported and the followup was 6 months shorter than in our study, the results obtained are very close to ours, confirming the overall efficacy of ADA in JIA-associated uveitis.

In our present study, we also found that both anti-TNF-α agents have proven to be effective in reducing the number of uveitis flares compared with the year preceding the beginning of the treatment, both after 1 year and after 2 years of anti-TNF-α therapy. Indeed, ADA was more effective than IFX ($p = 0.015$) in limiting the onset of new ocular complications, with a reduction of IR both at first and second years of followup. On the contrary, no changes among patients treated with IFX were recorded. This confirms previous reported results at 12 months' followup[6,13].

Both anti-TNF-α agents have proven to be safe in the medium- to long term. No major adverse events occurred during the 2-year followup and only 16.4% of the patients experienced minor side effects. However, ADA showed a better safety profile than IFX ($p = 0.008$). Interestingly, we found a much lower rate of AE for ADA than in the German Biologics JIA registry (10.6 vs 50.9 per 100 PY, respectively)[14]. In this registry, however, all JIA subtypes with various comorbidities are included and this may explain the difference. In agreement with previous studies, infections represented the most frequent AE for both ADA and IFX[6,12,15].

Hence, the lower incidence of minor AE, the easier and more comfortable administration, and the greater efficacy may explain the higher retention rate at 2 years for ADA (94.7%) than for IFX (54.2%, $p < 0.001$).

The 2-year followup data confirm that ADA has a better efficacy and safety profile in the medium term than IFX for the treatment of refractory JIA-associated uveitis.

REFERENCES

1. Sen ES, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. Nat Rev Rheumatol 2015;11:338-48.
2. Levy-Clarke G, Jabs DA, Read RW, Rosenbaum JT, Vitale A, Van Gelder RN. Expert panel recommendations for the use of anti-tumor necrosis factor biologic agents in patients with ocular inflammatory disorders. Ophthalmology 2014;121:785-96.
3. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al; International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390-2.
4. Jabs DA, Nussenblatt RB, Rosenbaum JT; Standardization of Uveitis Nomenclature (SUN) Working Group. Standardization of uveitis nomenclature for reporting clinical data. Results of the First International Workshop. Am J Ophthalmol 2005;140:509-16.
5. Reiff A, Kadayifcilar S, Özen S. Rheumatic inflammatory eye diseases of childhood. Rheum Dis Clin North Am 2013;39:801-32.
6. Zannin ME, Birolo C, Gerloni VM, Miserocchi E, Pontikaki I, Paroli MP, et al. Safety and efficacy of infliximab and adalimumab for refractory uveitis in juvenile idiopathic arthritis: 1 year follow up data from the Italian Registry. J Rheumatol 2013;40:74-9.
7. Kotaniemi K, Saila H, Kautiainen H. Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. Clin Ophthalmol 2011;5:1425-9.
8. Magli A, Forte R, Navarro P, Russo G, Orlando F, Latanza L, et al. Adalimumab for juvenile idiopathic arthritis-associated uveitis. Graefes Arch Clin Exp Ophthalmol 2013;251:1601-6.
9. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti-tumor necrosis factor α treatment efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach of individual drugs. Arthritis Care Res 2014;66:1073-84.
10. Simonini G, Taddio A, Cattalini M, Caputo R, De Libero C, Naviglio S, et al. Prevention of flare recurrences in childhood refractory chronic uveitis: An open-label comparative study of adalimumab versus infliximab. Arthritis Care Res 2011;63:612–8.
11. Tynjala P, Kotaniemi K, Lindahl P, Latva K, Aalto K, Honkanen V, et al. Adalimumab in the treatment of juvenile idiopathic arthritis associated uveitis. Rheumatology 2008;47:339-44.
12. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al; SYCAMORE Study Group. Adalimumab plus Methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637-46.
13. Simonini G, Zannin E, Caputo R, Falcini F, de Martino M, Zulian F, et al. Loss of efficacy during long-term infliximab therapy for sight-threatening childhood uveitis. Rheumatology 2008;47:1510-14.
14. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol 2014;66:2580-9.
15. Tarkiainen M, Tynjälä P, Vähäsalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatology 2015;54:1170-6.