Drug survival of the infliximab biosimilar (CT-P13) in paediatric patients with non-infectious uveitis

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Abstract

Objective

Paediatric non-infectious uveitis (NIU) is an important cause of significant long-term complications and blindness in children. Infliximab (IFX) is a chimeric human/murine monoclonal antibody against TNF-α that is effective in NIU resistant to conventional therapies. In this study, we aimed to determine the efficacy and safety of an IFX biosimilar (CT-P13) in paediatric patients with NIU.

Methods

This was a non-interventional and retrospective study that included paediatric patients with NIU who received IFX biosimilar CT-P13 treatment between January 2016 and January 2020. Demographic data pertaining to patients and their disease were collected. The efficacy and safety of the IFX biosimilar were evaluated.

Results

Twenty-six patients (44 eyes) were enrolled in this study. The median age (interquartile range) at the diagnosis of uveitis was 9.41 (5–12.3) years. The most common site of involvement was anterior uveitis, and bilateral involvement was more commonly seen in the older age group (p=0.32). The primary diagnosis of 16 patients was juvenile idiopathic arthritis, three had Behçet's disease, six had idiopathic disease and one had sarcoidosis. All patients were treated with CT-P13 (22 patients were biologic-naïve, and four switched from adalimumab). The median follow-up time on IFX was 14 months (range 4–48). Complete recovery was achieved in 95.4% of eyes with active uveitis, while inactive disease was not achieved in two of them. We observed a reduction in the number of flares in all patients during the follow-up period (4.5±2.2 vs. 0.89±1, p=0.01). Treatment-emergent adverse events occurred in 26.9% of patients.

Conclusion

To our knowledge, this is the first study to assess the impact of CT-P13 treatment adherence on disease activity in children with NIU. The IFX biosimilar CT-P13 is remarkably safe and effective for the long-term treatment of paediatric NIU.

Key words

non-infectious uveitis, children, anti-TNF-α, infliximab, biosimilar

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Received on August 7, 2020; accepted in revised form on December 11, 2020.

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Competing interests: none declared.

Introduction

Uveitis is defined as inflammation of the iris, choroid, and/or retina, which are the uveal components of the eye (1). Uveitis is less common in children, who may constitute up to 14% of all uveitis patients (2). Non-infectious uveitis (NIU) is a significant cause of blindness and long-term complications in children.

Non-infectious uveitis may be associated with underlying systemic diseases such as Behçet's disease (BD), juvenile sarcoidosis/Blau syndrome, and juvenile idiopathic arthritis (JIA). In a significant number of patients, there are no additional associated symptoms or systemic diseases, and they are defined as having idiopathic uveitis (3, 4). Band keratopathy, glaucoma, hypotonia, synechiae, cataracts, cystoid macular oedema, and vision loss are the most common complications seen in patients with NIU. Vision loss can occur in up to 75% of these patients (3, 5, 6).

Although no standardised treatment approach has been established, early diagnosis and immediate treatment are required to maintain visual function. Local steroid treatment is recommended initially. The early implementation of corticosteroid-sparing therapy, mostly methotrexate, is recommended both to improve visual outcomes and prevent corticosteroid side effects due to long-term administration (7, 8). Biological treatments, such as anti-TNF drugs, are effective in patients with uveitis refractory to conventional therapies (8-11). It has been shown that some inflammatory cytokines, such as TNF-α, may play a role in the occurrence of uveitis (12, 13). Infliximab (IFX), a chimeric monoclonal antibody against TNF-α, has been shown to be effective for an average of 64.7% of paediatric uveitis patients (95% CI: 59.8 to 69.3%) (14).

Biosimilar drugs are reproductions of their original counterparts and are usually less expensive (15). CT-P13 (Remsima®, Inflectra®) is the biosimilar of the reference medicinal product (RMP) of IFX (Remicade®) and was the first approved biosimilar monoclonal antibody by the European Medicines Agency. CT-P13 and its RMP have a uniform amino acid sequence and extremely comparable higher-order structures (16, 17). CT-P13 was found to be effective and safe in clinical trials of rheumatologic diseases (the PLANETRA and PLANETA studies) (18, 19).

In this report, we examined the demographic, anatomical distribution, underlying systemic diseases, treatment outcomes and complications of children with NIU treated with an IFX biosimilar molecule.

Materials and methods

This non-interventional, retrospective, single-centre analysis collected medical record data of paediatric patients with NIU who received biosimilar IFX treatment at the referral centre for paediatric rheumatology between January 2016 and January 2020. The Local Ethics Committee of Umraniye Training and Research Hospital approved this study, and consent was waived (approval no: B10.1TKH.4.34.H.G.P.0.01).

Patients and data collection

Patients diagnosed with NIU aged ≤16 years and treated with an IFX biosimilar were included in the study. All patient examinations and follow-up visits were performed by the same team, including two paediatric rheumatologists and an ophthalmologist. Demographic data of patients, including age, sex, the time of the first episode, delay from first symptoms to the diagnosis date, number of attacks, number of visits, overall follow-up duration, laterality and chronicity of uveitis, underlying systemic diseases, local and/or systemic treatment modalities that were used, ocular surgeries that performed and/or ocular complications, were collected.

Patients with uveitis were first evaluated in detail for infectious and autoimmune diseases in terms of medical history, exposure status and family history. Next, all the patients underwent a comprehensive eye and laboratory examination. Human Leukocyte Antigen (HLA) typing and autoantibodies such as an antinuclear antibody (ANA) and angiotensin-converting enzyme (ACE) were studied during the evaluation of autoimmune causes. Magnetic resonance imaging (MRI) of the brain and

chest x-ray were also performed when needed. We used the "Standardization of Uveitis Nomenclature" (SUN) criteria to describe the improvement and worsening of the condition in patients (20). The diagnosis of JIA was made according to the International League of Associations for Rheumatology criteria (21). Patients who met the diagnostic criteria of the international study group of BD were diagnosed with BD (22). Additionally, patients were considered to have suspected cases of sarcoidosis when serum ACE levels increased, and the diagnosis of sarcoidosis was confirmed with histological investigation (23).

Patients diagnosed with NIU, after excluding infectious causes, were treated with local steroids, disease-modifying antirheumatic drugs (DMARDs) and/or anti-TNF alpha therapies according to current treatment protocols. Our study group consisted of patients diagnosed with NIU treated with an IFX biosimilar due to the presence of active uveitis under DMARDs and/or other biological treatments. An infliximab biosimilar was administered as an "off-label" treatment in cases of non-responsiveness to standard immunosuppressive treatment with the consent of patients and their legal guardians. All the data of patients treated with an IFX biosimilar were analysed.

Statistical Package for the Social Sciences (v. 23.0, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Univariate, bivariate, and multivariate analyses were performed. Univariate analysis was carried out to analyse the means and standard deviations of continuous variables and to report the distribution of frequency for categorical variables. A *p*-value of less than 0.05 was considered statistically significant.

Table I. Demographics and baseline characteristics of paediatric patients treated with infliximab biosimilar (CT-P13).

Demographics and clinical characteristic	Number of patients	% of population
Gender		
Female	13	50
Male	13	50
Systemic disease		
JIA	16	61.5
Extended oligoarticular JIA	11	68.7
Enthesitis-related arthritis	4	25
Juvenile psoriatic arthritis	1	6.3
Behçet's disease	3	11.5
Idiopathic uveitis	6	23
Sarcoidosis	1	4
Serology		
ANA positivity	15	
HLA B27 positivity	1	
Uveitis laterality		
Bilateral	18	
Unilateral	8 (5 right, 3 left)	
Uveitis location		
Anterior	21	
Intermediate	1	
Posterior	1	
Panuveitis	3	
Previous treatments prior to IFX starting		
Methotrexate (MTX)	21	
Adalimumab (ADA)	3	
Etanercept (ETN)	2	
Oral prednisone	10	
Azathioprine	6	

JIA: juvenile idiopathic arthritis; IFX: infliximab.

Results

Patients' characteristics

Forty-four eyes of 26 patients treated with an IFX biosimilar were enrolled in this study. Twenty-two of the patients were biologic-naïve, and four were switched from adalimumab. All these patients had active uveitis findings at the initiation of IFX biosimilar therapy. The sex distribution was equal. The median age at admission to our clinic was 9.7 years. The median age (interquartile range (IQR)) at the diagnosis of uveitis was 9.41 (5–12.3) years, and at the diagnosis of primary (systemic) disease, it was 7.8 years. The median age at the initiation of the symptoms of systemic disease was also 6.6 years. The mean (±SD) number of uveitis episodes was 5.4±2.75. Bilateral involvement was more commonly encountered in the older age group (p=0.32). The most common involvement observed was anterior uveitis. Panuveitis, posterior uveitis and intermediate uveitis were the other types of presentations.

Of the 26 patients evaluated, the primary diagnoses of 16 were JIA, three had BD, six had idiopathic disease and one had sarcoidosis (Table I). Most JIA patients had the oligoarthritis subtype (68.7%) and enthesitis-related arthritis (ERA) subtype (25%) of uveitis, and the least common subtype was juvenile psoriatic arthritis (JPsA) (6.3%). Seven patients with JIA (n=16) had uveitis prior to arthritis (44%), and uveitis first emerged during JIA follow-up in nine patients. The median age (IQR) at diagnosis was 7 (2–17.1) years, with a median time from JIA diagnosis to uveitis of 3 (0–96) months. The mean age (IQR) at diagnosis was 17.7 (12.9–17.7) years in patients with BD and 8.2 (7.3–12.3) years in patients with idiopathic uveitis. Both the age at uveitis and primary diagnosis were lower in the JIA group than in the other groups (p=0.04).

Treatment characteristics

The median follow-up time on an IFX biosimilar was 14 months (range 8–48). Patients underwent an average of 18.7±12.5 (median 16) visits during treatment with an IFX biosimilar. Seven patients had a longer than 2-year follow-up, and 16 patients had a longer than one-year follow-up period prior to IFX biosimilar initiation. The mean induction dosage of an IFX biosimilar was 5.74±2.7 mg/kg (median=5 mg/kg) dosed every two weeks for the first

four weeks and then every four weeks thereafter for the whole population. Dosing was increased in six (23%) and maintained in 20 (77%) patients over the follow-up period according to the treatment response.

Twenty-one (80.7%) patients received concurrent methotrexate (MTX) once weekly (subcutaneous), five (19.2%) received azathioprine (AZA) daily (oral), and seven (27%) received mycophenolate mofetil (MMF) daily (oral) in at least one interval in the treatment period with an IFX biosimilar. A total of 80.7% (n=21) of patients were on MTX and 7.6% (n=2) were on AZA before IFX biosimilar therapy started, and the remaining patients were started after starting biosimilar IFX therapy. Biosimilar IFX was initiated after a median of 8 months (IQR: 3.7–28.2) following MTX or AZA in these patients.

Vision outcomes

While the rate of eyes with controlled uveitis was 95.4%, inactive disease was not achieved in two eyes with IFX biosimilar treatment. At presentation, there was good visual acuity (VA) (LogMAR VA <0.3, >20/40) in 72.7% of the eyes and significant improvement in VA after treatment in most eyes (95.4%). At the most recent visit, 92.3% (24/26) of patients had no active uveitis without topical steroids. We observed a reduction in the number of flares in all patients during the follow-up period (4.5±2.2 *vs*. 0.89±1, p=0.01) (Table II).

Complications were identified in 38.5% of the patients in the study population, and most of them were JIA patients (62.5% *vs*. 60%). We found that the most common complications were posterior synechiae and glaucoma (42.3%) at presentation and until the last visit. Posterior synechiae was significantly more common in the younger age group.

Biosimilar drug side effects

Overall, 26 patients were treated with an IFX biosimilar. Drug side effects were similar in naïve and switched patients. Under IFX biosimilar treatment, even at higher dosages, there was no opportunistic infection and no life-threatening adverse events requiring hospitalisation during the follow-up period. Seven patients (26.9%) experienced treatment-emergent adverse events (TEAEs) of an IFX biosimilar, three of whom discontinued therapy due to the emergence of a lupus-like syndrome. Upper respiratory tract infection, influenza-like illness, and mild urticaria were the most common TEAEs.

Table II. Improvement of the course and complications of uveitis during IFX treatment.

	Before IFX therapy	After IFX therapy
Frequency of uveitis episodes*	4.5 ± 2.21	0.89 ± 1.04
Good visual acuity (LogMAR <0.3)	32 (72.7%)	42 (95.4%)
Moderate visionloss (LogMAR 0.3–1.0)	9	2
Severe vision loss (LogMAR >.0)	3	0
Posterior Synechiae	9	2
Band Keratopathy	1	-
Cataract	1	3
Glaucoma	2	7

*mean±SD; IFX: infliximab.

Discussion

In the present study, we report the four-year follow-up results on the safety and efficacy of an IFX biosimilar in children with NIU. This is the first report on IFX biosimilar (CT-P13) efficacy and safety in paediatric patients with uveitis.

The prevalence of JIA uveitis varies from 11.6 to 30.0% in the literature due to differences in ethnic specificity and type of studies (24, 25). Sixteen patients had uveitis-associated JIA in our study. We found that seven patients (44%) with JIA had uveitis prior to arthritis, and nine developed new-onset uveitis during follow-up. Various researchers have reported the sex distribution, with slightly more affected girls, in previous studies (26-28). We found an equal sex distribution in our cohort. There was a predominance of anterior uveitis (47.7%) followed by panuveitis (6.8%) in our patients, as was also found in previous studies (26, 29, 30).

Uveitis-related complications were reported in 35.5 to 67% of children, and these complications were present in one-third of patients at the time of uveitis diagnosis. In a report, a last visual acuity of less than 20/200 was found in 12% and of less than 20/50 in 11 to 31% of eyes. Additionally, blindness widely appeared in 0 to 17.5% of the children with NIU (14). Ten patients had complications (nine had posterior synechiae, two had glaucoma, one had band keratopathy, and one had anterior subcapsular cataract) at presentation, and 10 patients developed complications (two had posterior synechiae, seven had glaucoma and three had cataracts) during follow-up. In the literature, the most prevalent complications included synechiae (27 to 33%), band keratopathy (15.7 to 29%), cataracts (8 to 31%), glaucoma (8 to 19%), macular oedema (6 to 25%), and macular fibrosis (4%) (14). Al-Haddad *et al*. noticed that anterior segment complications were more prevalent in younger children (p<0.05) (27). Approximately 21.7% of eyes in our cohort had anterior or posterior segment complications at admission.

The IFX response rate is variable in paediatric uveitis. Simonnini *et al*. reported an average response rate of 72% in 2014 (31, 32). Recently, Jari *et al*. observed an IFX response rate of 64.7% in 476 patients based on a meta-analysis (14). We found a high rate (95.4%) of IFX biosimilar effectiveness in our patient population. This result was not lower than that in the studies with the original molecule in the literature.

In some studies evaluating childhood non-infectious uveitis, less favourable results and/or the loss of effectiveness in IFX treatment administered with an interval of 6-8 weeks at a 5 mg/kg dose after initial q2 week loading doses were reported (33, 34). Previous studies support that higher doses of IFX treatment administered at 4-week intervals may be required to effectively control paediatric uveitis (35, 36). In our cohort, the median initial dosing of IFX biosimilar was 5 mg/kg dosed every two weeks for the first four weeks and

then every four weeks thereafter for the whole population. Dosing was increased in six patients (23%) during the follow-up period due to an insufficient treatment response. The optimal dosage and interval of IFX biosimilars have been determined empirically for paediatric NIU. The experience of Dincses *et al*. showed that IFX biosimilars may be a safe and effective alternative treatment for patients with BD refractory to conventional immunosuppressive treatments. They treated six patients with IFX biosimilars, and remission was achieved in four of them (37). In another adult study, Nikiphorou *et al*. analysed 395 rheumatic patients receiving IFX therapy (a biosimilar or the original molecule) and found that IFX biosimilar therapy was well tolerated and safe. Additionally, discontinuation due to inefficacy was much lower for biosimilars than the original IFX (38). Similar to these studies, IFX biosimilars were generally well tolerated and effective in our cohort. The drug was discontinued due to adverse events (lupus-like syndrome) in only three patients. In addition to opportunistic infection, hospitalisation or life-threatening adverse events were not seen even in those on higher dosages during the follow-up.

In conclusion, IFX biosimilar treatment is clearly safe and effective for the long-term treatment of children with NIU. A higher IFX biosimilar dosage and shorter intervals may be required to achieve successful control of uveitis in a certain percentage of patients. The side effects of corticosteroids and other medications and the emergence of complications in the long term were reduced by IFX biosimilar treatment. To our knowledge, this is the first study to evaluate the efficacy of IFX biosimilar (CT-P13) treatment on disease activity in children with NIU. The limitations of this study are that it was retrospective in nature, consisted of patients with heterogeneous primary disease, and lacked a control group. Prospective studies with larger patient groups are required to expand and verify these findings.

Acknowledgements

We are grateful to all participating children and their families.

References

1. SEN ES, DICK AD, RAMANAN AV: Uveitis associated with juvenile idiopathic arthritis, *Nat. Rev. Rheumatol* 2015; 11: 338-48.
2. BEN EZRA D, COHEN E, MAFTZIR G: Uveitis in children and adolescents. *Br J Ophthalmol* 2005; 89: 444-8.
3. WORETA F, THORNE JE, JABS DA, KEDHAR SR, DUNN JP: Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol* 2007; 143: 647-55.
4. THORNE JE, SUHLER E, SKUP M *et al*.: Prevalence of noninfectious uveitis in the United States: a claims-based analysis. *JAMA Ophthalmol* 2016; 134: 1237-45.
5. HOLLAND GN, DENOVE CS, YU F: Chronic anterior uveitis in children: clinical characteristics and complications. *Am J Ophthalmol* 2009; 147: 667-8, e665
6. ROSENBERG KD, FEUER WJ, DAVIS JL: Ocular complications of pediatric uveitis. *Ophthalmology* 2004; 111: 2299-306.
7. STROH IG, MORADI A, BURKHOLDER BM, HORNBEAK DM, LEUNG TG, THORNE JE: Occurrence of and risk factors for ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis. *Ocul Immunol Inflamm* 2017; 25: 503-12.
8. SABOO US, METZINGER JL, RADWAN A *et al*.: Risk factors associated with the relapse of uveitis in patients with juvenile idiopathic arthritis: a preliminary report. *J AAPOS* 2013; 17: 460-4.
9. CONSTANTIN T, FOELDVARI I, ANTON J *et al*.: Consensus-based recommendations for the management of uveitis associated with juvenile idiopathic arthritis: the SHARE initiative. *Ann Rheum Dis* 2018; 77: 1107-17.
10. 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, e783.
11. CAKAN M, EKINCI DY, KARADAG SG, AKTAY-AYAZ N: Etiologic spectrum and follow-up results of noninfectious uveitis in children: a single referral center experience *Arch Rheumatol* 2019; 34: 294-300.
12. CURNOW SJ, FALCIANI F, DURRANI OM *et al*.: Multiplex bead immunoassay analysis of aqueous humor reveals distinct cytokine profiles in uveitis. Invest *Ophthalmol Vis Sci* 2005; 46: 4251-9.
13. SIJSSENS KM, RIJKERS GT, ROTHOVA A, STILMA JS, SCHELLEKENS PA, DE BOER JH: Cytokines, chemokines and soluble adhesion molecules in aqueous humor of children with uveitis. *Exp Eye Res* 2007; 85: 443-9.
14. JARI M, SHIARI R, SALEHPOUR O, RAHMANI K: Epidemiological and advanced therapeutic approaches to treatment of uveitis in pediatric rheumatic diseases: a systematic review and meta-analysis. *Orphanet J Rare Dis* 2020; 15: 41.
15. KABIR ER, MOREINO SS, SIAM MKS: The breakthrough of biosimilars: a twist in the narrative of biological therapy. *Biomolecules* 2019; 24: 1-34.
16. EUROPEAN MEDICINES AGENCY: Committee for Medicinal Products for Human Use (CHMP). Assessment report: Remsima (infliximab). 2013. Available from: www.ema.europa.eu/docs/en_GB/document_library/EPAR_
17. JUNG SK, LEE KH, JEON JW *et al*.: Physicochemical characterization of Remsima. *MAbs* 2014; 6: 1163-77.
18. YOO DH, HRYCAJ P, MIRANDA P *et al*.: A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013; 72: 1613-20.
19. PARK W, HRYCAJ P, JEKA S *et al*.: A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. 2013; 72: 1605-12.
20. 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: 509-56.
21. PETTY RE, SOUTHWOOD TR, MANNERS P *et al*.: International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004; 31: 390-2.
22. Criteria for diagnosis of Behçet's disease. International study Group for Behçet's disease. *Lancet* 1990; 335: 1078-80.
23. HERBORT CP, RAO NA, MOCHIZUKI M: International criteria for the diagnosis of ocular sarcoidosis: results of the first international workshop on ocular sarcoidosis (IWOS). *Ocul Immunol Inflamm* 2009; 17: 160-9.
24. SEN ES, MORGAN MJ, MACLEOD R *et al*.: Cross sectional, qualitative thematic analysis of patient perspectives of disease impact in juvenile idiopathic arthritis-associated uveitis. *Pediatr Rheumatol Online J* 2017; 15: 58.
25. COSICKIC A, HALILBASIC M, SELIMOVIC A, AVDAGIC H: Uveitis associated with juvenile idiopathic arthritis, our observations. *Mediev Archaeol* 2017; 71: 52-5.
26. WORETA F, THORNE JE, JABS DA, KEDHAR SR, DUNN JP: Risk factors for ocular complications and poor visual acuity at presentation among patients with uveitis associated with juvenile idiopathic arthritis. *Am J Ophthalmol* 2007; 143: 647-55.
27. AL-HADDAD C, BOUGHANNAM A, ABDUL FATTAH M, TAMIM H, EL MOUSSAWI Z, ROLA N: Hamam patterns of uveitis in children according to age: comparison of visual outcomes and complications in a tertiary center. *BMC Ophthalmol* 2019; 19: 137.
28. WEISS AH, WALLACE CA, SHERRY DD: Methotrexate for resistant chronic uveitis in children with juvenile rheumatoid arthritis. *J Pediatr* 1998; 133: 266-8.
29. ANGELES-HAN ST, MCCRACKEN C, YEH S *et al*.: Characteristics of a cohort of children with juvenile idiopathic arthritis and JIA-associated uveitis. *Pediatr Rheumatol Online J* 2015; 13: 1-10.

30. ANGELES-HAN ST, PELAJO CF, VOGLER LB *et al*.: Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry. *J Rheumatol* 2013; 40: 2088-96.
31. UTZ VM, BULAS S, LOPPER S: Effectiveness of long-term infliximab use and impact of treatment adherence on disease control in refractory, non-infectious pediatric uveitis. *Pediatr Rheumatol Online J* 2019; 17: 79-84.
32. 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.
33. DEITCH I, AMER R, TOMKINS-NETZER O *et al*.: The effect of anti-tumor necrosis factor alpha agents on the outcome in pediatric uveitis of diverse etiologies. *Graefes Arch Clin Exp Ophthalmol* 2018; 256: 801-8.
34. SIMONINI G, TADDIO A, CATTALINI M *et al*.: Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res* (Hoboken) 2011; 63: 612-8.
35. KAHN P, WEISS M, IMUNDO LF, LEVY DM: Favorable response to high-dose infliximab for refractory childhood uveitis. *Ophthalmology* 2006; 113: 860-4, e862.
36. SUKUMARAN S, MARZAN K, SHAHAM B, REIFF A: High dose infliximab in the treatment of refractory uveitis: does dose matter? *ISRN Rheumatol* 2012; 7 65380.
37. DINCSES E, ESATOGLU SN, OZGULER Y *et al*.: Biosimilar infliximab for Behçet's syndrome: a case series. *Clin Exp Rheumatol* 2019; 37: 111-5.
38. NIKIPHOROU E, HANNONEN P, ASIKAINEN J *et al*.: Survival and safety of infliximab bio-original and infliximab biosimilar (CT-P13) in usual rheumatology care. *Clin Exp Rheumatol* 2019; 37: 55-9.