Methotrexate treatment may prevent uveitis onset in patients with juvenile idiopathic arthritis: experiences and subgroup analysis in a cohort with frequent methotrexate use

M.M. Kostik[1], E.V. Gaidar[1], A.Y. Hynnes[2], M.F. Dubko[1], V.V. Masalova[1], L.S. Snegireva[1], I.A. Chikova[1], E.A. Isupova[1], T.N. Nikitina[1], E.D. Serogodskaya[1], O.V. Kalashnikova[1], A. Ravelli[3,4], V.G. Chasnyk[1]

[1]Saint Petersburg State Paediatric Medical University, Saint Petersburg, Russia; [2]Eye Care Physicians and Surgeons, Winchester, VA, USA; [3]Universita degli Studi di Genova, Genova, Italy; [4]Istituto Giannina Gaslini, Genova, Italy.

Abstract

Objective

To evaluate the ability of methotrexate (MTX) to prevent the onset of uveitis in Russian children with juvenile idiopathic arthritis (JIA) .

Methods

The clinical charts for all consecutive patients who received a stable management for at least 2 years with or without MTX were reviewed. Patients who were given systemic medications other than MTX (except NSAID) and patients with systemic arthritis, rheumatoid factor-positive arthritis, or enthesitis-related arthritis were excluded. Each patient was examined after at least a 2-year follow-up period after the first visit to establish whether uveitis had occurred.

Results

A total of 281 patients with a median disease duration of 3.8 years were included. 191 patients (68%) were treated with MTX. During the observation period, 64 patients (22.8%) developed uveitis, a median of 1.6 year after disease onset. The frequency of uveitis was lower in MTX-treated than in MTX-untreated patients (11.5% vs. 46.7%, respectively, OR=6.7 (95%CI:3.7–12.3), p=0.0000001). Survival analysis confirmed that patients treated with MTX had a lower probability of developing uveitis (HR=4.35, p=0.000001). In subgroup analysis it was shown that MTX was more preventive in boys than in girls, and in patients with JIA onset age of over 5 years compared to those with disease onset less than 5 years. The data of survival analysis of MTX prevention has shown that benefits do not depend on the number of active joints and ANA status.

Conclusion

Our study corroborates a previous observation that MTX therapy may prevent the onset of uveitis in children with JIA. Randomised controlled trials are required to confirm our results.

Key words

juvenile idiopathic arthritis, uveitis, methotrexate

Mikhail M. Kostik, MD, PhD
Ekaterina V. Gaidar, MD
Alla Y. Hynnes, MD
Margarita F. Dubko, MD, PhD
Vera V. Masalova, MD
Ludmila S. Snegireva, MD
Irina A. Chikova, MD
Eugenia A. Isupova, MD
Tatiana N. Nikitina, MD, PhD
Elena D. Serogodskaya, MD
Olga V. Kalashnikova, MD, PhD
*Angelo Ravelli, MD**
*Vyacheslav G. Chasnyk, MD, PhD**

**These authors contributed equally to this study.*

Please address correspondence to:
Mikhail M. Kostik,
Saint Petersburg State Paediatric Medical University,
Lytovskaya 2,
Saint Petersburg,
194100 Russia.
E-mail: kost-mikhail@yandex.ru
mikhail.kostik@gmail.com

Received on December 12, 2015; accepted in revised form on February 26, 2016.

Competing interests: none declared.

Introduction

Juvenile idiopathic arthritis (JIA) is the most common cause of chronic anterior uveitis during childhood (1). Often JIA-associated uveitis is entirely asymptomatic, whether it affects one or both eyes, but could be sight-threatening (2). Late diagnosis and poor controlled inflammation in the eye often lead to cataract, band keratopathy, glaucoma and posterior sinechia formation, which leads to decreased visual activity up to blindness (3). The frequency of JIA-associated uveitis is near 20% and is strongly linked to the category of JIA. It often occurs in the first two years after onset of joint involvement (4-6). A short interval between joint involvement and uveitis onset is a predictor of poor uveitis outcomes (7). The main predictors of uveitis in JIA are oligoarticular (OA) category, ANA-positivity and younger age at JIA onset, but new studies have excluded OA from this set (4, 8). Methotrexate (MTX) is the main non-biologic disease-modifying anti-rheumatic drug used in the treatment of JIA and can lead to remission in up to half of the cases of JIA, depending on the category (9, 10). It is also known that MTX may lead to remission of JIA-associated uveitis in up to 73% of cases, but MTX withdrawal leads to uveitis flare (11, 12). Methotrexate (MTX) has been able to decrease the incidence of uveitis in JIA (13), but these data were obtained in Italian children and may not be extrapolated to other populations. The treatment of the OA category of JIA, which is often complicated by the development of uveitis, is initially based on the use of non-steroidal anti-inflammatory drugs (NSAIDs and intra-articular (IAC) steroid injection (14). In Russia due to limited access to long-acting intra-articular steroids (absent from the market), such as triamcinolone hexacetamide, in the case of relapse of arthritis or insufficient efficacy after NSAIDs or short-acting IAC, MTX therapy is often started. This treatment approach in Russia leads to a higher proportion of patients with JIA being treated with MTX with respect to Europe and North America.

These differences in therapeutic approaches between Russia and Europe and North America were the reasons that led us to investigate the possibility that MTX could prevent the onset of uveitis in a Russian cohort of JIA patients (13).

Patients and methods

Written consent was obtained according to the declaration of Helsinki. The protocol of this trial was approved by the local Ethics Committee of Saint Petersburg State Paediatric Medical University.

The clinical charts for all consecutive patients who had received a stable management for at least 2 years with or without MTX were reviewed. The diagnosis of JIA was established according to ILAR classification criteria (15). The study design was very similar to a previous one (13). Depending on the MTX therapy, the patients were divided into two groups: the first group - with MTX with or without NSAIDs and (short-acting) IACs and the second with only NSAIDs and (short-acting) IACs. The exclusion criteria were:

i) Any medications other than MTX, NSAIDs and IACs;

ii) Patients with systemic arthritis, rheumatoid factor-positive arthritis, or enthesitis-related arthritis, in which uveitis is rare or symptomatic,

iii) Patients in whom uveitis occurred before arthritis or first observation in our centre. Each patient was examined after at least a 2-year follow-up period after the first visit to establish whether uveitis had occurred. The start date of the observation of our cohort was 01 January 2005, and the end date 01 Jan 2013.

Patients from the MTX group received a stable dose of MTX 15 mg/m^2 per week. The root of administration was chosen only by the attending physician, with subcutaneous administration being most frequent (90.6%).

To identify uveitis, all the children were examined by ophthalmologists with over 20 years' experience in the daignosis and treatment of uveitis. Diagnosis of uveitis was based on the criteria of the SUN (Standardisation of Uveitis Nomenclature) Working Group (16, 17).

Statistical analysis

Descriptive statistics were reported

in terms of medians and interquartile ranges (IQRs) for continuous variables and in terms of absolute frequencies and percentages for categorical variables. The comparison of quantitative variables between groups was made using the Mann-Whitney U-test. The comparison of qualitative data was performed by means of the chi-squared test or the Fisher's exact test in case of expected frequencies <5. The ability of each variable to discriminate the risk of uveitis occurrence was evaluated with sensitivity and specificity analysis, AUC-ROC (area under receiver operating characteristic) curve with 95% confidence interval (CI), calculating odds ratio (OR) for detection of the best cut-offs of continuous variables. The higher values of OR of variables interact better with discriminatory ability. We used the "best" threshold obtained for the ROC curve analysis of our data because it provides the most appropriate mean between sensitivity and specificity. Survival analysis in each group, with first episode of uveitis as the event of interest, was conducted by means of the Kaplan-Meier method. Survival curves were compared by the log-rank test. Factors significantly associated with time of uveitis occurrence were then tested in a Cox proportional hazards regression model, calculating the Hazard-ratio (HR). For statistical analysis we used with the Statistica 6.0 (Tulsa, Oklahoma), Biostat, MedCalc and Microsoft Excel software. $p<0.05$ was considered as statistically significant.

Table I. Demographic characteristics of the entire study population and in reation to the occurrence of uveitis.

Characteristics	All patients, n=281	Patients with uveitis, n=64	Patients w/o uveitis, n=217	*p*
Female	196 (69.8)	51 (79.7)	145 (66.8)	0.49
Age at JIA onset, Me (IQR), y	4.8 (2.3-8.6)	3.0 (1.9-5.6)	5.1 (2.6-9.0)	**0.0004**
Oligoarticular course	206 (73.3)	53 (82.8)	153 (70.5)	**0.05**
ANA positivity,(n =223)	90 (40.4)	31 (59.6)	59 (34.5)	**0.001**
ESR, mm/h	16.0 (5.0-25.0)	21.0 (9.0-25.0)	12.0 (5.0-25.0)	**0.04**
ESR >20 mm/h*, (n=266)	116 (43.6)	34/60 (56.7)	82 (39.8)	**0.02**
CRP, mg/l	2.6 (0.2-8.0)	5.2 (0.7-10.0)	2.0 (0.2-7.0)	0.06
NSAID,(n=278)	217 (78.1)	44 (71.0)	173 (80.1)	0.13
IACIs	80 (30.4)	19 (32.2)	61 (29.9)	0.74
MTX	191 (68.0)	23 (35.9)	168 (77.5)	**0.0001**
Active joints at onset	2.0 (1.0-5.0)	2.0 (1.0-3.5)	2.0 (1.0-5.0)	0.09
Cervical spine	21 (7.5)	5 (7.8)	16 (7.4)	0.91
TMJ	4 (1.4)	0 (0)	4/ (1.8)	0.27
Shoulder	9 (3.2)	1 (1. 6)	8 (3.7)	0.39
Elbow	28 (10.0)	6 (9.4)	22 (10.1)	0.86
Wrist	43 (15.3)	7 (10.9)	36 (16.6)	0.27
Ankle	110 (39.2)	26 (40.6)	84 (38.7)	0.78
Knee	214 (76.2)	51 (79.7)	163 (75.1)	0.45
Hip	34 (12.1)	6 (9.4)	28 (12.9)	0.45
Small joints of hand	73 (25.9)	11 (17.2)	62 (28.6)	0.07
Small joints of foot	42 (15.0)	5 (7.8)	37 (17.1)	0.07

*Calculated by the ROC-analysis.

Table II. Demographic characteristics of the entire study population and in reation to methotrexate treatment.

Characteristics	Patients treated with MTX, n=191	Patients treated w/o MTX, n=90	*p*
Female	132 (69.1)	64 (71.1)	0.73
Age at JIA onset, Me (IQR), y	4.4 (2.3-7.9)	5.3 (2.1-9.6)	0.17
Oligoarticular course	125 (65.5)	81 (90.0)	**0.000014**
ANA positivity, (n =223)	61 (40.4)	29 (40.3)	0.99
ESR, mm/h	17.0 (5.0-25.0)	11.0 (5.0-21.0)	0.04
ESR > 20 mm/h*, (n=266)	85 (47.2)	31 (36.1)	0.09
CRP, mg/l	3.8 (0.2-9.0)	2.0 (0.2-7.0)	0.45
NSAID, (n=278)	143 (75.7)	74 (83.2)	0.16
IACIs, (n=263)	53 (29.4)	27 (32.5)	0.61
Time between uveitis onset and onset of JIA, months	23.7 (12.2- 67.0)	17.1 (7.3- 35.3)	0.23
Uveitis, n (%)	22 (11.5)	42 (46.7)	**0.0000001**

*Calculated by the ROC-analysis.

Results

A total of 281 patients with a median disease duration of 3.8 years were included. The follow-up time ranged between 1.8 and 206.9 months. The group predominantly consisted of girls (69.8%) with early onset of the disease. ANA positivity was identified in 40.4% and oligoarticular category of JIA in 217 patients (77.2%). One hundred and ninety one patients (68%) were treated with MTX and 173 (90.6%) of them were received MTX subcutaneous. The time between JIA onset and start of MTX was 0.7 (0.3; 1.5) years.

During follow-up, 64 patients (22.8%) developed uveitis, a median of 1.6 year after disease onset (IQR=0.7; 3.8). The time lag between onset of arthritis and occurrence of uveitis ranged from 0.3 to 13.8 years.

The frequency of uveitis was lower in MTX-treated than in MTX-untreated patients (11.5% *vs*. 46.7%, respectively, OR=6.7 (95%CI: 3.7-12.3), p=0.0000001).

Patients treated with MTX had more active joints, had more often polyarticular arthritis with involvement of the wrist and small joints of the hand. Patients who developed uveitis comparatively had a lower age, had more often oligoarticular arthritis, less active joints, higher levels of ESR and ANA-positivity. There were no differences in uveitis frequency depending on MTX route of administration (oral or subcutaneous). Comprehensive demographic characteristics of the study population and relationship between MTX treatment and uveitis occurrence is presented in Tables I-II.

The main predictors of development of uveitis in JIA patients were female sex, oligoarticular course of JIA, ANA-positivity, increased ESR>20 mm/h, age

Table III. Predictors of uveitis occurrence in the entire study population.

Group	Rate (%)	OR (95% CI)	$p^{\dagger}$	HR*	$p^{\S}$
Girls	51/196 (26.0)	1.9 (1.0-3.8)	0.07	1.82	0.045
Boys	13/85 (15.3)				
Oligoarticular course	53/206 (25.7)	2.0 (1.0-4.1)	0.07	1.89	0.045
Polyarticular course	11/75 (14.7)				
ANA (+)ve	31/90 (34.4)	2.8 (1.5-5.3)	0.002	2.14	0.006
ANA (-)ve	21/133 (15.8)				
ESR>20mm/h	34/116 (29.3)	2.0 (1.1-3.5)	0.03	1.79	0.028
ESR≤20 mm/h	26/150 (17.3)				
Age of JIA onset ≤5 y	47/144 (32.6)	3.4 (1.8-6.3)	0.0001	2.56	0.0009
Age of JIA onset > 5 y	17/137 (12.4)				
MTX, no	42/90 (46.7)	6.7 (3.7-12.3)	0.0000001	4.35	0.000001
MTX, yes	22/191 (11.5)				

$^{\dagger}\chi^2$-test; §Log-Rank test; *Cox regression models.

Table IV. The ability of MTX to prevent uveitis in different subgroups.

Group	MTX, Y/N	Rate (%)	OR (95% CI)	$p^{\dagger}$	HR*	$p^{\S}$
Boys	N	9/26 (34.6)	7.3 (2.0-26.6)	0.001*	6.7	0.0007
	Y	4/59 (6.8)				
Girls	N	32/64 (50.0)	5.9 (3.0-11.9)	0.000001	3.6	0.000001
	Y	19/132 (14.4)				
Oligoarticular course	N	37/81 (45.7)	5.7 (2.9-11.3)	0.000001	4.0	0.000001
	Y	16/125 (12.8)				
Polyarticular course	N	4/9 (44.4)	6.7 (1.5-31.2)	0.007	3.7	0.02
	Y	7/66 (10.6)				
ANA (+)ve	N	20/29 (68.9)	10.1 (3.6-28.1)	0.000002	4.4	0.00002
	Y	11/61 (18.0)				
ANA (-)ve	N	13/43 (30.2)	4.4 (1.7-11.8)	0.0016	3.6	0.003
	Y	8/90 (8.9)				
Age of JIA onset ≤ 5 y	N	23/57 (40.4)	3.5 (1.7-7.3)	0.0006	2.3	0.003
	Y	18/111 (16.2)				
Age of JIA onset > 5 y	N	15/47 (31.9)	20.6 (4.5-95.2)	0.000001	22.2	0.000001
	Y	2/90 (2.2)				

$^{\dagger}\chi^2$-test; §Log-Rank test; *Cox regression models.

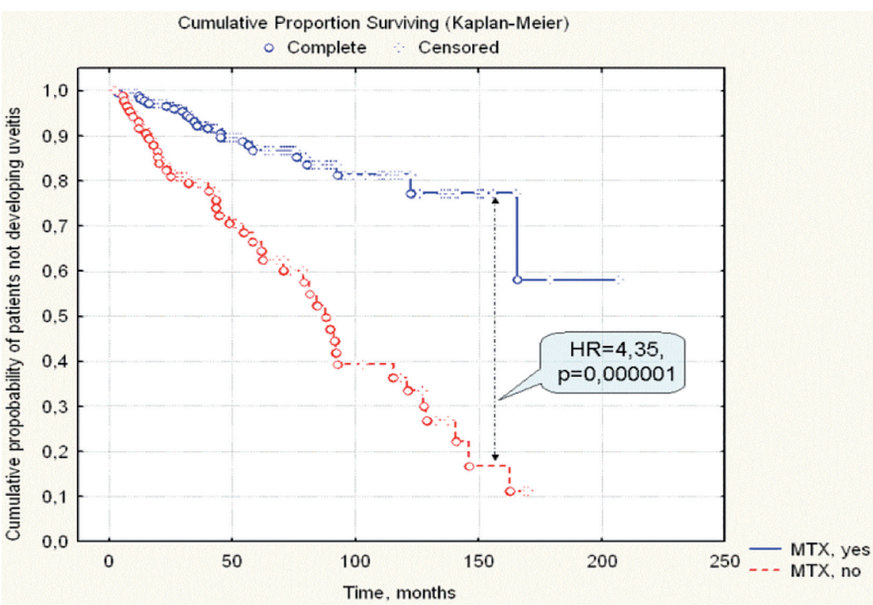

Fig. 1. Cumulative probability of patients not developing uveitis in relation to MTX therapy (Log-Rank).

of JIA onset less or equal than 5 years and absence of MTX therapy (data of analysis in Table III).

Survival analysis confirmed that patients treated with MTX had a lower probability of developing uveitis (HR=4.35, p=0.000001) (Fig. 1).

In subgroup analysis, it was shown that MTX was more preventive in boys than in girls and in patients with onset age more than 5 years than in those with disease onset of less than or equal to 5 years. Survival analysis showed that the effectiveness of MTX in uveitis prevention did not depend on the number of affected joints or the presence of ANA.

Discussion

Our study confirms the previous observation (13) that MTX may prevent the occurrence of uveitis in children with JIAIn the current study, one hundred and ninety one patients (68%) were treated with MTX, which is nearly double the number in the previous study (33.9%) (13). The frequency of uveitis in MTX-treated patients was 10.5% and 11.5% in both the previous and current study. However, the prevalence of uveitis in MTX-untreated patients was much higher in the present study (46.7% *vs*. 20.2%), which indicates that in our populations MTX decreased the frequency of uveitis up to 4–6 times. In addition, in the previous study MTX was given 1.5 times more frequently in patients who had not developed uveitis (p=0.049) whereas in the current study this parameter was two times greater (see Table I) (13). We observed that half of patients with uveitis from the MTX group developed it in the first 3 years, after which time the incidence was decreased. This association is doubtful, however, it could be an effect of MTX, but also a characteristic feature of JIA-associated uveitis (5). The explanation why MTX can prevent uveitis may lie in several experimental studies which have shown the possibility of MTX entering the eye and being accumulated in the ophthalmic tissues in a higher concentration than in blood (18, 19). The occurrence of uveitis in MTX-treated patients, (11.5% in current and 10.5% in previous studies), is,

however, an important clinical problem which needs to be addressed. The German registry "Biker" shows that the combination of MTX with biologics decreases the risk of uveitis "de novo" compared with biologic monotherapy (20). This finding underscores the major role of MTX in uveitis prevention. Altogether, these data suggest that early MTX administration may be indicated in target subgroups with higher risk of developing uveitis. Our study suggests that this decision should be independent on the pattern of joint disease, either oligoarticular or polyarticular. Our data may also be helpful to guide the choice between monotherapy with biologics or combination therapy of biologics and MTX in patients with high risk of uveitis whose joint disease fails to respond to MTX monotherapy. It can be speculated that MTX should not be discontinued in these patients, owing to its potential ability to prevent uveitis occurrence.

Our study has some limitations. Its non population-based nature can explain some differences in the rate of uveitis in subgroups, especially in MTX-untreated patients. Although the rate of uveitis in our cohort is 22.8%, which is similar to several previous reports, the exclusion of several JIA categories might have led to an artificial rise in the rate of uveitis. Our MTX-naïve group predominantly consisted of the oligoarthicular subtype (90%), a characteristic that might have been responsible for the increased rate of uveitis in the MTX-untreated subgroup.

In conclusion, our study confirms the previous observation that therapy may prevent the development of uveitis in patients with JIA. Randomised trials are needed to define the indications of MTX administration and delineate the role of MTX in therapeutic protocols with biologics in subgroups of JIA patients with a high risk of uveitis.

References

1. SAURENMANN RK, LEVIN AV, FELDMAN BM *et al*.: Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term follow-up study. *Arthritis Rheum* 2007; 56: 647-57.
2. ROSENBERG KD, FEUER WJ, DAVIS JL: Ocular complications of paediatric uveitis. *Ophthalmology* 2004; 111: 2299-306.
3. DE BOER J, WULFFRAAT N, ROTHOVA A: Visual loss in uveitis of childhood. *Br J Ophthalmol* 2003; 87: 879-84.
4. CALANDRA S, GALLO MC, CONSOLARO A *et al*.: Female sex and oligoarthritis category are not risk factors for uveitis in Italian children with juvenile idiopathic arthritis. *J Rheumatol* 2014; 41: 1416-25.
5. VERAZZA S, ALLEGRA M, LATTANZI B *et al*.: Time of onset of iridocyclitis (IC) in children with juvenile idiopathic arthritis (JIA). *Pediatr Rheumatol Online J* 2008; 6 (Suppl. 1): 77.
6. TAPPEINER C, KLOTSCHE J, SCHENCK S, NIEWERTH M, MINDEN K, HEILIGENHAUS A: Temporal change in prevalence and complications of uveitis associated with juvenile idiopathic arthritis: data from a cross-sectional analysis of a prospective nationwide study. *Clin Exp Rheumatol* 2015; 33: 936-44.
7. ZANNIN ME, BUSCAIN I, VITTADELLO F *et al*.: Timing of uveitis onset in oligoarticular juvenile idiopathic arthritis (JIA) is the main predictor of severe course uveitis. *Acta Ophthalmol* 2012; 90: 91-5.
8. ANGELES-HAN ST, PELAJO CF, VOGLER LB *et al*.: CARRA Registry Investigators. Risk markers of juvenile idiopathic arthritis-associated uveitis in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry. *J Rheumatol* 2013; 40: 2088-96.
9. GIANNINI EH, BREWER EJ, KUZMINA N *et al*.: Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. *N Engl J Med* 1992; 326: 1043-9.
10. RUPERTO N, MURRAY KJ, GERLONI V *et al*.: Pediatric Rheumatology International Trials Organization. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. *Arthritis Rheum* 2004; 50: 2191-201.
11. SIMONINI G, PAUDYAL P, JONES GT, CIMAZ R, MACFARLANE GJ: Current evidence of methotrexate efficacy in childhood chronic uveitis: a systematic review and meta-analysis approach. *Rheumatology* (Oxford) 2013; 52: 825-31
12. AYUSO VK, VAN DE WINKEL EL, ROTHOVA A, DE BOER JH: Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. *Am J Ophthalmol* 2011; 151: 217-22.
13. PAPADOPOULOU C, KOSTIK M, BOHM M *et al*.: Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. *J Pediatr* 2013; 163: 879-84.
14. BEUKELMAN T, PATKAR NM, SAAG KG *et al*.: 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* 2011; 63: 465-82.
15. PETTY RE, SOUTHWOOD TR, MANNERS P *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.
16. BLOCH-MICHEL E, NUSSENBLATT RB: International Uveitis Study Group recommendations for the evaluation of intraocular inflammatory disease. *Am J Ophthalmol* 1987; 103: 234-5.
17. 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.
18. PUCHTA J, HATTENBACH LO, BAATZ H: Intraocular levels of methotrexate after oral low-dose treatment in chronic uveitis. *Ophthalmologica* 2005; 219: 54-5.
19. DE SMET MD, STARK-VANCS V, KOHLER DR, SMITH J, WITTES R, NUSSENBLATT RB: Intraocular levels of methotrexate after intravenous administration. *Am J Ophthalmol* 1996; 121: 442-4
20. FOELDVARI I, THME N, HORNEFF G: Methotrexate is protective against the new onset of uveitis under etanercept treatment. Data from the German Etanercept Registry. *Ann Rheum Dis* 2010; 69 (Suppl. 3): 626.