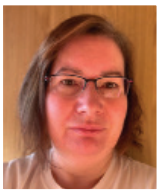
RECOMMENDATIONS FOR THE MANAGEMENT OF UVEITIS ASSOCIATED WITH JUVENILE IDIOPATHIC ARTHRITIS: THE CZECH AND SLOVAK ADAPTATION OF THE SHARE INITIATIVE

Malcová H.[1], Dallos T.[2], Bouchalová K.[3], Brejchová I.[4], Brichová M.[5], Bušányová B.[6], Fabianová J.[7], Fráňová J.[8], Furdová A.[9], Jarošová K.[10], Kobrová K.[11], Kostolná B.[6], Košková E.[12], Lokaj M.[13], Macků M.[8], Melocíková J.[14], Michaličková M.[5], Minxová L.[15], Moravčíková D.[14], Němcová D.[16], Pískovský T.[17], Říhová E.[5], Schüller M.[7], Skalická E.[18], Svozílková P.[5], Tomčíková D.[6], Vargová V.[19], Vrtíková E.[12], Doležalová P.[16], Heissigerová J.[5]

[1]Department of Rheumatology, Motol University Hospital, Prague, Czech Republic
[2]Department of Paediatrics, Faculty of Medicine, Comenius University and National Institute of Children's Diseases, Bratislava, Slovak Republic
[3]Department of Paediatrics, Faculty of Medicine, Palacký University and University Hospital Olomouc, Czech Republic
[4]České Budějovice Hospital, Czech Republic
[5]Department of Ophthalmology, General University Hospital and 1st Faculty of Medicine, Charles University in Prague, Czech Republic
[6]Department of Paediatric Ophthalmology, Faculty of Medicine, Comenius University and National Institute of Children's Diseases, Bratislava, Slovak Republic
[7]National Institute of Tumbercular and Pulmonary Diseases and Chest Surgery, Vyšné Hágy I, Vysoké Tatry, Slovak Republic
[8]Department of Paediatrics, Faculty of Medicine, Masaryk University and University Hospital, Brno, Czech Republic
[9]Department of Ophthalmology, Faculty of Medicine, Comenius University and University Hospital, Bratislava, Slovak Republic
[10]Institute of Rheumatology, Prague, Czech Republic
[11]Department of Paediatrics, Masaryk Hospital, Ústí nad Labem, Czech Republic
[12]National Institute of Rheumatic Diseases, Piešťany, Slovak Republic
[13]Department of Paediatric Ophthalmology, Faculty of Medicine, Masaryk University and University Hospital, Brno, Czech Republic
[14]2nd Paediatric Clinic, Slovak Medical University and Children's University Hospital and Clinic, Banská Bystrica, Slovak Republic
[15]Department of Paediatrics, Faculty of Medicine, Charles University and University Hospital, Hradec Králové, Czech Republic
[16]Department of Paediatric and Adolescent Medicine, 1st Faculty of Medicine, Charles University and General University Hospital Prague, Czech Republic
[17]Department of Paediatric Medicine, University Hospital Ostrava, Czech Republic
[18]Department of Paediatrics, Faculty of Medicine, Charles University and University Hospital Plzeň, Czech Republic
[19]Paediatric and Adolescent Clinic, Pavol Jozef Šafárik University, Košice, Slovak Republic

The recommendation was processed for the Paediatric Rheumatology Working Group at the Czech Paediatric Society and Slovak Paediatric Society, and the Czech and Slovak Ophthalmology Society

Received: 24. 2. 2020
Accepted: 6. 5. 2020
Available on-line: 30. 8. 2020



MUDr. Hana Malcová, Ph.D.
Oddělení revmatologie FN
v Motole
V úvalu 84
150 06 Praha 5
hana.malcova@fnmotol.cz

SUMMARY

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and uveitis is its most important extra-articular manifestation. Evidence-based recommendations are available only to a limited extent and therefore JIA associated uveitis management is mostly based on physicians' experience. Consequently, treatment practices differ widely, both nationally and internationally. Therefore, an effort to optimize and publish recommendations for the care of children and young adults with rheumatic diseases was launched in 2012 as part of the international project SHARE (Single Hub and Access Point for Pediatric Rheumatology in Europe) to facilitate clinical practice for paediatricians and (paediatric) rheumatologists.The aim of this work was to translate published international SHARE recommendations for the diagnosis and treatment of JIA associated uveitis and to adapt them for use in the Czech and Slovak Republics.

International recommendations were developed according to the standard methodology of the European League against Rheumatism (EULAR) by a group of nine experienced paediatric rheumatologists and three experts in ophthalmology. It was based on a systematic literature review and evaluated in the form of an online survey and subsequently discussed using a nominal group technique. Recommendations were accepted if > 80% agreement was reached (including all three ophthalmologists).

A total of 22 SHARE recommendations were accepted: 3 on diagnosis, 5 on disease activity assessment, 12 on treatment and 2 on future recommendations. Translation of the original text was updated and modified with data specific to the czech and slovak health care systems and supplemented with a proposal for a protocol of ophthalmological dispensarization of paediatric JIA patients and a treatment algorithm for JIA associated uveitis.

Conclusion: The aim of the SHARE initiative is to improve and standardize care for paediatric patients with rheumatic diseases across Europe. Therefore, recommendations for the diagnosis and treatment of JIA-associated uveitis have been formulated based on the evidence and agreement of leading European experts in this field.

Key words: juvenile idiopathic arthritis (JIA), uveitis, recommendation

Čes. a slov. Oftal., 76, 2020, No. 4, p. 182–196

INTRODUCTION

In 2012, within the framework of the SHARE project (Single Hub and Access Point for Paediatric Rheumatology in Europe), an endeavour was launched for the optimisation and publication of recommendations for the care of children and young adults with rheumatic diseases, in order to facilitate clinical practice for paediatricians and (paediatric) rheumatologists. The European League Against Rheumatism (EULAR) has already accepted a series of recommendations in the field of paediatric rheumatology (e.g. for juvenile dermatomyositis [1]) prepared according to a standardised procedure [2], which is a generally used tool for the compilation of recommendations: Appraisal of Guidelines for Research & Evaluation [3].

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease in children, and uveitis is its most common and potentially most serious extra-articular manifestation. Internationally accepted recommendations for the diagnosis and treatment of uveitis associated with JIA are not available, even if certain national recommendations exists, e.g. German and Spanish [4,5]. Care for these patients is therefore often based on the personal experience of the doctor, and as described in an extensive study by specialists in this field, considerable differences exist in clinical practice in the diagnosis and treatment of uveitis [6]. With the rapid development of new therapeutic possibilities of JIA, there is also an increasing requirement for clear recommendations for the management of uveitis, which should be based on the best available evidence and professional expertise (in the case of insufficient evidence from clinical trials), and which could help doctors caring for patients with uveitis upon a background of JIA. It is necessary to continue to update such compiled recommendations on a regular basis. Whereas the use of the majority of preparations in the treatment of arthritis is substantiated by evidence in the form of conducted clinical trials, for patients with uveitis there is either a lack of corresponding data, or the data is not on the level of evidence for the treatment of uveitis that would be sufficiently strong to justify its introduction into clinical practice.

Uveitis upon a background of JIA is most frequently chronic, affecting the anterior segment, and as a rule it is asymptomatic. However, but sometimes we may also encounter acute anterior uveitis, especially in the case of arthritis with enthesitis [7,8].

The aim of the expert group was to compile recommendations/strategies for the purpose of:

- preventing or reducing the probability of the development of uveitis in patients with JIA, and minimising the risk of damage to sight
- creating a strategy for the management of treatment, which effectively suppresses inflammatory activity and prevents the development of complications leading to irreversible damage to sight.

METHOD

A group of 12 specialists (AH, BV, CP, CE, SC-G, IF, JdB, JA, KW, RG, YU, NW – see acknowledgement) in paediatric rheumatology (n = 9) and ophthalmology (n = 3) contributed to the formation of the recommendations for uveitis associated with JIA. The recommendations were compiled using the standardised EULAR method, which defines the ways of stipulating best practice on the basis of reaching a consensus among experts, substantiated by published evidence [2,3]. For Czech and Slovak adaptation of the translation (HM), a working group of 30 specialists was created, representing the working group of paediatric rheumatology at the Czech and Slovak Paediatric Societies respectively (n = 19), and the Czech and Slovak Ophthalmology Society (n = 11).

Systematic literature search

During the course of February 2015, two working teams from SHARE, independently of one another, systematically searched publications from the years of 1970–2014 containing the term JIA (including known synonyms) in the electronic databases PubMed/MEDLINE, Embase and Cochrane. On the basis of predefined criteria, three specialists (TC, AP, VB) then selected articles relating to the examination and/or treatment of JIA associated uveitis,

which they submitted for an evaluation of validity. The fundamental criteria were exclusion of summary articles and case reports with less than 3 child patients.

Assessment of validity of publications

The selected articles were divided at random between pairs of specialists, who assessed each individual publication independently of one another, and evaluated its content and methodological quality. The data was extracted and evaluated with the aid of a predefined scoring system for diagnostic and therapeutic studies. Any discrepancies were resolved either by means of a discussion between the two specialists, or the statement of a third specialist. The level of evidence and the strength of the recommendations were determined on the basis of adapted classification tables for diagnostic, therapeutic and epidemiological studies [9-11].

Compilation of recommendations

In accordance with the standardised EULAR procedure, the main results and conclusions of each publication were formulated together with their validity and level of evidence. These source materials were summarised by five specialists (TC, GS, YU, RG, JdB), and used in order to formulate provisional recommendations, which were then reviewed by a panel of experts (IF, NW, JdB). The summary of evidence was submitted together with each preliminary recommendation to a specialist commission. The recommendations were systematically discussed and reviewed using the Nominal Group Technique (NGT [12]) for reaching consensus at a conference of 12 specialists held in March 2017. The process of the NGT was moderated by a non-voting expert (AR). The recommendations were accepted if a consensus of > 80 % (10 out of 12) was reached among the specialists (including all three ophthalmologists).

RESULTS

Research of literature

A systematic research of the literature found a total of 1,323 publications, after duplications were excluded there remained 1,259 unique articles. After a further re-evaluation on the basis of the baseline and exclusion criteria, 176 articles remained, which were further processed in the full text and forwarded for evaluation by the specialist commission. Of these, 117 were finally selected for the compilation of these recommendations.

Recommendations

The following sections contain the individual recommendations of the specialist commission, supported by the published data [13-128]. Tables 1-4 summarise these recommendations, the level of evidence they provide, the strength of the recommendations and the percentage of specialists who agreed upon the recommendations.

Baseline condition

JIA is the most common chronic rheumatic disease of childhood age, with an incidence of 8.2 (7.5-9.0) / 100 000 children aged under 16 years per year, and a prevalence of approximately 70.2 (16-140) / 100 000 [129-130]. The differences in prevalence are attributed to the different conception of the included studies. In general it is assumed that the incidence worldwide differs only minimally [130]. The incidence of uveitis associated with JIA is estimated at approximately 1 / 100 000, and there is certain evidence that it is lower in oriental populations of patients with JIA [7,131].

Structural complications of uveitis associated with JIA, which may lead to irreversible damage to sight, include cataract, glaucoma, zonular keratopathy, macular edema, papilledema, retinal detachment and the consequences of chronic hypotonia. The course of JIA associated uveitis is usually gradual, it may be chronic or recurring, though most often concerns a chronic relapsing pathology persisting for several years. In the majority of cases it begins as anterior uveitis, in rare cases panuveitis develops. Uveitis associated with JIA most frequently occurs in the age group of 3-7 years, and is generally asymptomatic. In the case of heavy inflammation of the iris, however, it may lead to complaints

Table 1. Recommendations for diagnosis and screening of uveitis associated with JIA

Recommendation	L	S	Consensus (%)	Reference
1. In all patients with suspicion of JIA, exclusion of uveitis should take place as soon as possible in accordance with the current and audited protocol. Such a screening protocol should be available in all centres caring for patients with JIA.	2A	B	100	[13-32]
2. The frequency of follow-up examinations during subsequent ophthalmological monitoring must be differentiated according to the severity of the pathology and should be agreed upon in co-operation with a specialised ophthalmologist.	4	D	100	[13-27, 33-66]
3. After the completion of systemic therapy, patients with JIA have an increased risk of manifestation of relapse of uveitis, even after a previous long interval of inactivity of the pathology. All patients with JIA after the completion of systemic immunosuppressive therapy should be carefully examined by an ophthalmologist at minimum every 3 months for a period of at least 1 year.	2B	B	100	[67-70]

- *The consensus states the percentage of specialists who agreed on the recommendation during the final round of voting*
- *L, level of evidence; 1A, meta-analysis of cohort studies; 1B, meta-analysis of studies of cases and controls; 2A, cohort studies; 2B, studies of cases and controls; 3, non-comparative descriptive studies; 4, expert opinion*
- *S - strength of evidence; A - on basis of level 1 evidence; B - based on level 2 or extrapolated from level 1; C - based on level 3 or extrapolated from levels 1 or 2; D - based on level 4 or extrapolated from levels 3 or 4.*

Table 2. Recommendations for monitoring activity of pathology

Recommendation	L	S	Consensus (%)	Reference
4. Close co-operation between an ophthalmologist and paediatric rheumatologist in monitoring therapy and adjustment of treatment depending on the activity of the pathology is of fundamental importance.	3	C	100	[71]
5. It is necessary to determine the common criteria for evaluating the activity of uveitis which are to be used in deciding on adjustments of systematic treatment.	4	D	100	
6. At present no validated biomarker is available for monitoring the activity of uveitis.	2A	B	100	[4,21,29,31, 32, 37,41, 46,72-76]
7. At present no generally accepted definition of inactive disease is available for uveitis associated with JIA. The aim of treatment should be to achieve an absence of cells in the anterior chamber. The incidence of complications – macular edema, papilledema, ocular hypotonia and pseudo-rubeosis iridis may constitute a reason for initiation systemic treatment even in absence of cells in the anterior chamber.	2B	B	100	[4,69,78]
8. Reduction of systemic immunosuppressive therapy is recommended after a minimum of 2 years of inactive disease, without the administration of topical steroids.	3	C	92	[67]

- *The consensus states the percentage of specialists who agreed on the recommendation during the final round of voting*
- *L, level of evidence; 1A, meta-analysis of cohort studies; 1B, meta-analysis of studies of cases and controls; 2A, cohort studies; 2B, studies of cases and controls; 3, non-comparative descriptive studies; 4, expert opinion*
- *S - strength of evidence; A - on basis of level 1 evidence; B - based on level 2 or extrapolated from level 1; C - based on level 3 or extrapolated from levels 1 or 2; D - based on level 4 or extrapolated from levels 3 or 4.*

such as pain and reddening of the eye or changes of pupil width or irregularity of the pupil. These manifestations, if noticed by the parents, may cause the child to visit an eye specialist. In small children we encounter visual malfunction only exceptionally, in very severe cases, and this usually concerns a result of irreversible damage to the eye. Risk factors for the development of chronic anterior uveitis are the presence of antinuclear antibodies (ANA), oligoarticular form of JIA and early manifestation of arthritis. Timely identification of these risk patients is a priority for targeted screening. This text deals only with chronic anterior uveitis associated with JIA, and not with acute anterior uveitis, which we encounter in patients with the positive antigen HLA B27 and arthritis with enthesitis.

If ocular complications are present in a patient already at the first examination, at the time of diagnosis of uveitis, early and aggressive treatment is required. With regard to the variable course of the pathology, however, significant complications may develop even years after the commencement of treatment. There is still a considerable lack of consensus among experts on the issue of timing and indication for increasing treatment due to persistent activity [132-133].

RECOMMENDATIONS FOR DIAGNOSIS AND SCREENING

Screening of uveitis associated with JIA

It is suitable to conduct an ophthalmological examination on every patient with JIA according to the current protocol for monitoring of patients with JIA. Such a protocol should be available in all centres caring for patients with JIA [42], it is not necessary that screening is performed on the same institution as rheumatological care. It is especially important for all patients with suspicion of JIA to undergo an ophthalmological examination as soon as possible, and it is not necessary to wait for confirmation of a diagnosis of JIA in a rheumatological centre. It is the responsibility of every paediatric rheumatologist to ensure that patients with JIA are sent for a screening examination. As a result, it is necessary to build up a network of ophthalmological centres with a targeted focus on screening examinations for children with suspected JIA, and subsequent monitoring of patients with a confirmed diagnosis (Table 1). The literature published to date indicates that originally considered risk factors for the occurrence of chronic uveitis in the population of patients with JIA (early onset of arthritis, positive ANA and oligoarticular subtype of JIA) are insufficient. Although a series of screening protocols have been published, experts agree that none of them is better than the others [5,23,26,61,74].

To date no specific genetic markers have been identified with the exception of already published HLA subtypes associated with oligoarticular JIA and uveitis [14]. At present there is no evidence that genotyping would be of benefit in order to improve the effectiveness of the existing screening programmes. Despite advances in the subtyping of ANA antibodies in the case of other rheumatic diseases, there has been no advance in the understanding of the association between ANA antibodies and the risk of development of uveitis in JIA patients [28,34,35,41,60,67]. Publications are available on the role of antibodies against nuclear structures (such as histones and chromatin [21,41,52-54,64,77]) and also against ocular antigens [13,33,51,75]. Two studies have described that children with higher inflammatory activity (sedimentation of erythrocytes) at the time of manifestation of oligoarthri-

Table 3. Recommendations for treatment of uveitis associated with JIA

Recommendation	L	S	Consensus (%)	Reference
9. Active uveitis associated with JIA usually requires immediate initiation of treatment.	2B	B	100	[69,71, 78-80]
10. Topical steroids (priority given to prednisolone acetate or dexamethasone) are the first line of treatment of anterior uveitis.	4	D	100	[81]
11. Local and systemic nonsteroidal anti-inflammatory drugs (NSA) do not have a convincing effect in monotherapy, but may be used as a supplementary treatment.	3	C	92	[79,81,82]
12. If poor prognostic factors are present already at the first ophthalmological examination, it is recommended to start systemic treatment immediately. A further reason for commencing systemic immunosuppressive treatment is the appearance of poor prognostic factors or persistent activity of uveitis at any time later during the course of the illness.	2A		100	[4,19,22,29, 55,56,65, 78,83,84]
13. Systemic immunosuppressive treatment is recommended in the case that inactivity of uveitis has not been achieved after 3 months of local therapy, or if reactivation of activity has occurred following reduction of the dose of steroids.	2B	B	100	[55,59,68, 69,78,80, 85-87]
14. Methotrexate is the drug of first choice as systemic immunosuppressive treatment.	4	D	100	[68,84, 88-95]
15. In the case of insufficient effect or intolerance of methotrexate, it is recommended adding or switching to biological treatment.	3	C	92	[91-104]
16. In patients with uveitis that is resistant to treatment by DMARDs, especially methotrexate, it is recommended to use anti-TNF therapy (adalimumab > infliximab > golimumab).	3	C	100	[86,100, 101, 104-117,120-124,126,127]
17. Etanercept is not suitable for treatment of uveitis associated with JIA.	1B	A	100	[87,100, 109, 117-121]
18. In the case of insufficient effect of the first anti-TNF biological treatment, switch to another anti-TNF drug is recommended, although the evidence for the effectiveness of switching is based only on small case studies or as yet unpublished observations.	3	C	100	[87,113, 116,122]
19. In the case of insufficient efficacy of the existing treatment, it is recommended to examine the antibodies and antidrug level. If the patient has no antibodies but a low level of the drug, it is recommended to increase the dose or shorten the interval of administration.	4	D	100	
20. The drugs of choice for patients with an insufficient effect of anti-TNF drugs are tocilizumab, rituximab and abatacept.	3	C	100	[123-125]

- *The consensus states the percentage of specialists who agreed on the recommendation during the final round of voting*
- *L, level of evidence; 1A, meta-analysis of cohort studies; 1B, meta-analysis of studies of cases and controls; 2A, controlled studies without randomization; 2B, quasi-experimental studies; 3, descriptive studies; 4, expert opinion*
- *S - strength of evidence; A - on basis of level 1 evidence; B - based on level 2 or extrapolated from level 1; C - based on level 3 or extrapolated from levels 1 or 2; D - based on level 4 or extrapolated from levels 3 or 4.*

DMARD – disease-modifying anti-rheumatic drugs; NSA – nonsteroidal anti-inflammatory drugs; TNF – tumour necrosis factor

Table 4. Recommendations for future plans

Recommendation	L	S	Consensus (%)	Reference
21. It is necessary to create validated tools for evaluating activity of uveitis associated with JIA.	3	C	100	[73,126-128]
22. It is necessary to conduct further controlled clinical trials for the treatment of uveitis associated with JIA.	1B	A	100	[119,136, 141,149]

- *The consensus states the percentage of specialists who agreed on the recommendation during the final round of voting*
- *L, level of evidence; 1A, meta-analysis of cohort studies; 1B, meta-analysis of studies of cases and controls; 2A, cohort studies; 2B, studies of cases and controls; 3, non-comparative descriptive studies; 4, expert opinion (diagnostic study); 1A, meta-analysis of randomized controlled studies; 1B, randomized controlled study; 2A, controlled study without randomization; 2B, quasi-experimental study; 3, descriptive studies; 4, expert opinion (therapeutic studies);*
- *S - strength of evidence; A - on basis of level 1 evidence; B - based on level 2 or extrapolated from level 1; C - based on level 3 or extrapolated from levels 1 or 2; D - based on level 4 or extrapolated from levels 3 or 4.*

tis or polyarthritis have an increased risk of the development of uveitis [27,31]. The protocol of ophthalmological monitoring of patients with JIA should be adapted to the current possibilities of treatment, above all timely systemic therapy for arthritis [57,61,62,64]. The introduction of new biomarkers and genotyping in future will be able to improve the delineation of the risk population for screening.

Monitoring during follow-up

The risk of development and/or relapse of uveitis persists also during the course of the illness in patients who initially respond well to treatment. Regular ophthalmological monitoring of patients with JIA is therefore an essential component of care. Specialists agree that the frequency of ophthalmological observation should be dependent upon the severity of the ocular manifestations, and should be based on close co-operation between a rheumatologist and an experienced ophthalmologist.

Monitoring after termination of treatment for uveitis

Methotrexate (MTX) is the immunosuppressive drug of choice for patients with uveitis upon a background of JIA (see recommendation no. 14, table 3). After achieving long-term remission of uveitis, there is usually an endeavour to terminate MTX treatment. It is not yet clear as to how long the optimum period of duration of remission would be before we begin discontinuing topical and systemic treatment. After the termination of MTX, patients have an increased risk of onset or relapse of uveitis, mainly during the first year after discontinuation, on the assumption that the termination of treatment was preceded by a long period of inactivity of the ocular inflammation. In a study published recently, a relapse of activity of uveitis occurred in the majority of patients within 24 months of the end of treatment [67-70]. As a result, all patients after treatment with MTX (for arthritis or uveitis) should be examined by an ophthalmologist every three months for a minimum period of 1 year. It is not yet clear as to which of the drugs it is better to discontinue earlier (MTX or biological drug), if the patient is being treated with a combination. Relapses of uveitis following the discontinuation of MTX are less frequent in older patients, and also in those who have been treated for a longer time [67]. Specialists agree that a reduction of the dose of MTX and other systemic treatment should be commenced at the earliest after 2 years of inactivity, without the administration of topical steroids [134].

It is essential to continue with the regular monitoring of patients also after the termination of treatment, primarily in the case of those patients who had undergone long-term treatment with topical or systemic drugs which maintained the disease under control. Specialists recommend ophthalmological follow-up examinations after the discontinuation of all treatments at a minimum interval of 3 months, for a period of at least 1 year. We do not yet have sufficient scientifically backed evidence on effective screening strategies that could ensure reliable long-term or lifelong remission for patients.

Proposal for protocol of ophthalmological monitoring of patients with JIA in the Czech and Slovak Republics

The proposed protocol of ophthalmological monitoring differentiates the frequency of follow-up examinations ac-

Table 5. Protocol of ophthalmological monitoring of patients with JIA in the Czech and Slovak Republics

Type of arthritis		Clinical situation	Ophthalmological examination
Oligoarticular, Polyarticular seronegative, Psoriatic	**Risk of arthritis**		
	High (JIA onset <6 years of age and/or ANA positive)	Manifestation of JIA	Without delay
		<6 months from manifestation of JIA	Every 2 months
		<6 months and <4 years from manifestation of JIA	Every 3 months
		>4 years from manifestation of JIA up to age 18 years	Every 6 months
		After age 18 years	Every 6-12 months
	Standard (JIA onset >6 years of age and concurrently ANA negative)	Manifestation of JIA	Within 1 month
		<4 years from manifestation of JIA	Every 3 months
		>4 years from manifestation to age 18 years	Every 6 months
HLA B 27 positive and concurrently ANA negative >11 years		From manifestation to **age 18 years**	Every 6 months
Systemic JIA (ANA negative)		From manifestation to **age 18 years**	
Polyarticular seropositive (ANA negative)		From manifestation to **age 18 years**	
Independent on JIA type and risk		**<1 year** from termination of long-term systemic treatment	Every 3 months
		Diagnosed uveitis	According to an ophthalmologist, but at minimum every 3 months

JIA – juvenile idiopathic arthritis

cording to the type of JIA. Systemic and polyarticular seropositive JIA generally have a very low risk of uveitis, in the case of arthritis with entesitis, uveitis is acute and symptomatic. As a result, for these forms of JIA, regular ophthalmological follow-up examinations are recommended every 6 months. The frequency of oligoarticular, polyarticular seronegative and psoriatic arthritis differ according to 2 categories of risk: children with a high risk of uveitis are considered to mean patients with at least 1 of 2 risk factors: age of manifestation of JIA < 6 years and ANA positivity, children with a standard risk of uveitis are considered to mean patients who do not meet the criteria of increased risk (i.e. without either risk factor) (Table 5).

Each patient with newly diagnosed JIA should undergo an ophthalmological examination without delay if clinical symptoms of uveitis are present (reddening, absence or asymmetry of photoreaction, medical history of photophobia etc.), or within 1 month of determination of the diagnosis of JIA if clinical symptoms of uveitis are not present. Children with newly diagnosed JIA with a high risk of uveitis, in whom it is not possible to exclude uveitis with certainty due to (repeated) lack of co-operation at an ophthalmological examination, are indicated for an ophthalmological examination under general anaesthesia. In children of any age with JIA with a high risk of uveitis, or with uveitis in their medical history, in whom long-term immunosuppressive treatment has been terminated, the frequency of the ophthalmological examinations is increased to 3-monthly intervals for a period of at minimum 1 year. Each child with JIA, regardless of the risk factors and type of JIA, must undergo an ophthalmological examination at minimum twice per year up to the age of 18 years. In the case of children in whom uveitis has been diagnosed previously, the frequency of the ophthalmological follow-up examinations is based on the activity of the pathology, according to the recommendations of an ophthalmologist, but is at least once every 3 months, regardless of the age of the child, subtype of JIA and presence of risk factors.

Within the context of this protocol, an ophthalmological examination is understood to cover a complete examination, including biomicroscopy of the anterior chamber of both eyes, and examination of the ocular fundus in mydriasis. Regular ocular monitoring of patients with JIA also includes measurement of intraocular pressure (IOP) and age-specific examination of vision. The examination should take place at an ophthalmological outpatient department co-operating with a paediatric rheumatology department, which has experience of child patients with uveitis.

Recommendations for evaluation of activity of uveitis associated with JIA

The main goal is timely diagnosis and effective treatment in order to avoid damage to sight. This occurs as a consequence of complications of inflammation such as glaucoma, macular edema, ocular hypotonia and amblyopia. Structural damage may also appear before the determination of the diagnosis, or may occur during the further course of the pathology as a consequence of insufficiently controlled inflammatory activity or corticosteroid therapy. Studies have repeatedly confirmed that the main risk factors of damage to sight are the following: late diagnosis with already ensuing complications, need for surgical procedures, overall length of observation [4,68,78]. For certain complications male sex and non-Caucasian race appear to be risk factors [18,19,37,56,65,71].

The aim of immunosuppressive treatment is therefore a reduction of activity evaluated with the aid of the agreed parameters, which cover the number of inflammatory cells and degree of flare in the anterior chamber, as well as the presence of macular edema. The suitability of individual parameters may differ according to the degree of damage or the stage of the disease [5,13]. In one study, an increase in the number of cells in the anterior chamber was linked with a worse prognosis, whereas immunosuppressive therapy was associated with a reduced risk of loss of sight, especially in the case of a result of 20/50 or worse (HR 0.40, P < 0.01) [78]. Other studies describe flare in the anterior chamber as a better predictor of damage to sight [63]. At present no validated biomarkers are available that could be used for prediction of the severity of the pathology or the strategy of treatment of uveitis, and this area requires further research (Table 3) [24,32,34,35,40,44,49,75-80]. Until reliable biomarkers are validated, the management of uveitis is dependent primarily upon repeated eye examination. However, in future, monitoring of the activity of uveitis could incorporate gene expression and proteomic profiling of serum, leukocytes of the peripheral blood and vitreous body; measurement of reactants of the acute phase; HLA typing and testing of ANA antibodies [74].

The recommendations of professional societies (German Ophthalmological Society, Society for Paediatric and Adolescent Rheumatology, German Society for Rheumatology) emphasise that macular edema, ocular hypotonia and pseudo-rubeosis are often linked with chronic inflammation, and these findings should lead to a commencement (or reinforcement) of treatment in the case of absence of cells in the anterior chamber [4]. An expert group also recommends that the goal of treatment of uveitis upon a background of JIA should be an absence of cells in the anterior chamber, although in practice this may be difficult to achieve (Table 6). With regard to the conclusions of the working group for the Standardisation of Uveitis Nomenclature (SUN), the international group MIWGUC (Multinational Interdisciplinary Working Group for Uveitis in Childhood) compiled a set of indicators of uveitis activity, which may provide a basis for evaluation of the severity of the pathology and its course, the risk of structural damage, the degree of damage to sight and assessment of the effect of treatment [74]. Its contribution would be invaluable in clinical trials, but it is still necessary to validate the proposed parameters for childhood age [136]. The basis of decisions on management of treatment remains good communication between the ophthalmologist and the paediatric

rheumatologist. Recently published instructions for the management of non-infectious uveitis in adults contain certain important principles for the treatment of panuveitis in all age groups [137].

Recommendations for treatment of uveitis associated with JIA

Active uveitis requires immediate start of treatment. In a comparison of two cohorts of patients with newly diagnosed JIA, patients in whom aggressive therapy was introduced early and who were intensively monitored manifested fewer complications in connection with damage to sight [80]. Factors connected with better results are early start of immunosuppressive therapy at a young age [69] and treatment by immunosuppressant drugs in general [71,78].

The drug of first choice for acute and chronic anterior uveitis is topical cortocosteroids (priority is given to prednisolone or dexamethasone) [4,5,81,129]. Children with JIA and uveitis are often treated long-term with topical cortocosteroids, which increases the risk of development of complications, primarily cataract and glaucoma. One study demonstrated an increased risk of development of cataract in connection with the administration of high doses of topical corticoids, which was independent of the activity of uveitis or the presence of posterior synechiae [81]. The risk increased with the number of drops of local corticoids. It ensues from an analysis of the data

Table 6. Parameters proposed for evaluation of activity of uveitis associated with JIA (compiled by MIWGUC group) [74,153]

Parameter	
Number of cells in anterior chamber	Examination by slit lamp (evaluation according to SUN criteria)
Flare in anterior chamber	Examination by slit lamp for routine clinical practice and prospective trials (evaluation according to SUN criteria) Laser photometry for purposes of prospective trials
Number of follow-ups with active uveitis	Records of attending physician Duration of activity over period of minimum four follow-ups/year
Visual acuity (age-commensurate examination)	Best corrected visual acuity Threshold values: < 20/50, < 20/200 and blindness Proportion of amblyopia
Structural complications	Posterior synechiae Ocular hypotonia (< 5 mm Hg) Ocular hypertension (> 21 mm Hg) Glaucoma Cataract Zonular keratopathy in central cornea Macular edema on optic coherence tomography Papilledema Epiretinal membrane Dense vitreous opacities
Quality of life	Childhood Health Assessment Questionnaire Child Health Questionnaire Paediatric Quality of Life Inventory Tool for evaluating quality of life specific for uveitis EYEQL (not yet available for non-English speaking countries)
Overall affliction in connection with uveitis	Evaluation by parent, visual analogue scale (VAS 0-100) Evaluation by patient, VAS 0-100 Evaluation by ophthalmologist, VAS 0-100 Evaluation by rheumatologist, VAS 0-100
Social classification	Absence from school / kindergarten Number of days of hospitalisation in connection with uveitis Number of days of restriction of everyday activities due to uveitis
Anti-inflammatory treatment*	Reduce of dose of corticosteroids – topical/systemic
Surgical procedures*	Yes/No
Biomarkers	In research phase (not yet available)

**Suitable to document, although not part of evaluation of activity.*
SUN – Standardised Uveitis Nomenclature
EYEQL – The Effects of Youngsters' Eyesight QOL

that the long-term administration of low doses of topical corticosteroids (< 3 drops per day) (0.5 to 15 years, median 4 years) is linked with a low risk of development of cataract [81]. Upon the application of 2 drops or less per day, cataract practically did not appear within one year. There is no evidence to indicate that less effective topical corticosteroids are linked with a lower risk of adverse effects in these patients (Table 3). We try to use systemic corticosteroids minimally for children, primarily due to the risk of growth abnormalities and osteopaenia; in exceptional cases they are used in order to rapid control of inflammation or for macular edema.

In one retrospective study, the use of topical nonsteroidal anti-inflammatory drugs (NSA) was evaluated in the treatment of chronic uveitis in 14 patients, 8 with JIA and 6 with idiopathic iridocyclitis [82]. In all patients there was a reduction of the activity of uveitis following the addition of NSA to the existing therapeutic regimen, which enabled a reduction of the dose of corticosteroids. This date indicates that therapy with NSA may have a supplementary role in the treatment of chronic uveitis in children, but should not be applied in monotherapy.

The commencement of systemic immunosuppressive treatment is recommended in order to reduce the risk of complications in cases in which topical treatment does not lead to a remission of ocular inflammation, or when the patient requires high doses of topical corticosteroids. As previously mentioned, in patients with a multiple risk of loss of sight, it is suitable to commence systemic therapy very early [129]. In the case of the presence of poor prognostic factors in active uveitis, it is possible to commence systemic treatment immediately, already at the first ophthalmological examination. Some studies recommend the commencement of aggressive immunosuppressive treatment in high risk patients even before signs of development of complications appear [27,39]. Unfavourable prognostic factors include: uveitis preceding the manifestation of arthritis [19,22,74], presence of posterior synechiae [55,68,74,75], male sex [19,22,55], zonular keratopathy, glaucoma and cataract [55], malfunctions of vision initially, hypotonia, macular edema and dense vitreous opacities [55], and persistent activity during the course of observation (Table 3). Age at the time of the onset of uveitis does not appear to be a significant risk factor [22,56].

Definition of failure of treatment

Failure of treatment should lead to a change of dosage of drug, method of administration or character of drug, in which it is necessary to take into account the fact that the time until attainment of the optimal effect may differ in the case of individual drugs, as well as the fact that we only have a limited number of therapeutic modalities available. In a retrospective study which evaluated 23 patients with uveitis upon a background of JIA who were not responding to treatment by topical corticosteroids, an improvement was achieved in all the patients following the introduction of systemic immunosuppressive treatment [86]. Patients in whom treatment was commenced within 4-30 months after the manifestation of uveitis attained a better result in comparison with patients who received immunosuppressive treatment after 3 or more years ($p < 0.005$ in right and left eye together, $p = 0.0075$ for better eye, $p = 0.0375$ for worse eye). This data is supported by the conclusions of the SITE study, which states that the risk of loss of sight was reduced by approximately 60% in patients with uveitis and JIA who were treated with immunosuppressant drugs at a tertiary centre [78].

The expert group recommends the commencement of systemic immunosuppressive treatment if inactivity of uveitis is not achieved after 3 months of treatment with topical corticosteroids, or if a reactivation of inflammation occurs following a reduction of their dosage. The advantages of early introduction of immunosuppressive treatment are well known, and in patients who achieved a remission of uveitis systemic treatment was generally started earlier during the course of the illness in comparison with patients with a relapse of uveitis [55,59,68,78-87]. On the basis of knowledge about the effectiveness and safety of MTX from a series of studies, the expert group recommends this drug as the immunosuppressive therapy of first choice for patients with uveitis associated with JIA [68,84,88-90]. It is prefered subcutaneous application and a dose of 10-15 mg/m2 once a week [138]. Higher doses of MTX (15-20 mg/m2/week) lead to attainment of remission within a shorter time in comparison with doses of MTX < 15 mg/m2/week, with a comparable incidence of adverse effects [139].

In patients with uveitis, often in the case of failure of MTX, the effect of other immunosuppressant drugs has also been considered, such as azathioprine, sulfasalazine, mycophenolate mofetil, cyclosporine and leflunomide [91,95]. However, this mostly concerned studies with a small number of patients, and in the case of cyclosporine the clinical effectiveness was insufficient, with the authors of the original article noting that it has only limited effectiveness in this indication [94]. Results with other immunosuppressive drugs were more encouraging, but were on an even smaller number of patients [91-93,95]. They may represent an alternative to MTX in the case of intolerance or insufficient effect, especially in combination with biological treatment. In children there is a large amount of evidence on the better effectiveness of MTX in influencing arthritis in JIA in comparison with other conventional synthetic immunosuppressants. By contrast, in adult patients the administration of various immunosuppressive drugs is commonplace, without preference of MTX [91-95]. Specialists agree that in children and adults with uveitis which does not respond sufficiently to the administration of MTX (or another classic immunosuppressant), it is suitable to introduce biological treatment. There are a growing number of studies which support indication of biological therapy in the case of refractory uveitis [93-108], in which adalimumab is so far backed by the most evidence. Other biological drugs whose use in the treatment of uveitis is described in the literature are infliximab, golimumab, abatacept, tocilizumab and rituximab [96-108, 123-125].

The use of tumour necrosis factor (TNF) blockers in the treatment of uveitis is based on their demonstrable effectiveness in a series of systemic inflammatory pathologies, including JIA, rheumatoid arthritis and Crohn's disease [109]. An exception is etanercept, a recombinant dimeric fusion protein which antagonises TNF-α and has demonstrated effectiveness in the case of polyarticular JIA [118]. In the case of treatment of uveitis, however, etanercept has been linked with a high risk of relapses [87,100,109,117-121], and as a result it is not recommended in the treatment of uveitis associated with JIA [140].

Very few studies exist which would compare individual biological preparations mutually. One study determined that in children with refractory chronic uveitis associated with JIA, infliximab is significantly better than etanercept [100]. In another small study, adalimumab was more effective than infliximab if it was used as the TNF-α blocking treatment of first choice [106]. Adalimumab was more effective than infliximab in achieving remission, and had a better safety profile in patients with uveitis and JIA also in long-term observation [102,107]. On the basis of the SYCAMORE randomised controlled trial, comparing adalimumab with a placebo in patients with JIA uveitis following the failure of MTX, adalimumab was the first biological drug to be approved for the treatment of chronic anterior uveitis in children [136]. The data from

Table 7. Schema of therapeutic algorithm recommended for treatment of uveitis associated with JIA in the Czech and Slovak Republics. Adapted according to the Heiligenhaus Seminars in Arthritis and Rhematism (2019 [152]), Clarke Pediatric Rheumatol (2016 [7]) and Bou Rheumatol Int (2015 [5])

Active uveitis (number of cells in AC > 0.5+)	
Poor prognostic factors (malfunction of vision, hypotonia, glaucoma, cataract, macular edema, dense vitreous opacities)	
YES	**NO**
Topical corticosteroids (every 1-2 hours for a period of 1-3 days, then reduction of dose) + cycloplegic agent + systemic corticosteroids 1. Prednisone 1-2 mg/kg/day with gradual reduction down to discontinuation within 2-3 months, or 2. Methylprednisolone 10-30 mg/kg 3x max. 1g/dose and subsequently Prednisone 1-2 mg/kg/day with gradual reduction down to discontinuation	Topical corticosteroids (every 1-2 hours for a period of 1-3 days, then reduction of dose to < 2 drops per day) + cycloplegic
3 months (in individual cases earlier)	
Inactivity not achieved, relapse of activity at dose of < 2 drops per day, or occurrence of new complications	Improvement of uveitis (degree 0-0.5+ according to SUN, max. 1-5 cells in a field)
Add MTX (15-20 mg/m2 s.c.) if applicable + systemic corticosteroids in case of adverse prognostic factors (massive inflammation in AC, hypotonia, macular edema)	**Continue in treatment with topical corticosteroids with gradual reduction of dose**
3 months (in individual cases earlier)	
Inactivity not achieved, relapse of activity or occurrence of new complications **Add adalimumab (< 30 kg 20 mg s.c., > 30 kg 40 mg s.c. á 2 weeks)**	Inactivity of uveitis (degree 0-0.5+ according to SUN) **Continue in existing treatment (MTX) min. 24 months**
3 months	
Inactivity not achieved, relapse of activity or occurrence of new complications **Verify patient co-operation, measure level of drugs, antibodies against adalimumab** **Maximise dose of drugs (adalimumab 40 mg regardless of weight), optimise therapeutic interval and method of administration (adalimumab once a week)** Consider oral corticosteroids ± local intraocular application	Inactivity of uveitis (degree 0-0.5+ according to SUN) **Continue in existing treatment (MTX + adalimumab) min. 24 months**
3 months	
Inactivity not achieved, relapse of activity or occurrence of new complications **Replace adalimumab with other anti-TNF drug – infliximab, golimumab, or biological drug with different mechanism of action – tocilizumab, abatacept or rituximab**	Inactivity of uveitis (degree 0-0.5+ according to SUN) **Continue in existing treatment 24 months**

The aim on all levels is to minimise the dose of topical corticosteroids to < 2 drops per day while attaining a number of cells in the anterior chamber of < (max. 1-5 cells in a field)
Key

this trial was later supported by the further randomised trial ADJUVITE, demonstrating the effect of adalimumab on JIA uveitis following the failure of topical corticosteroids and MTX [141]. As a result, the expert group recommends the commencement of anti-TNF therapy (in the order adalimumab > infliximab > golimumab) for patients with uveitis not responding to treatment with conventional disease-modifying anti-rheumatic drugs (csDMARD), especially MTX [86,100-127].

The conclusions of studies on small numbers of patients demonstrate that if treatment with one of the TNF-α blockers is insufficiently effective, it is suitable to change to another preparation from the same group [87,113,116,122]. The safety and effectiveness of adalimumab was evaluated in 26 children with JIA resistant to the current therapy (synthetic conventional DMARD in 17 cases and anti-TNF drugs in 9 cases). Change to adalimumab had a positive effect in controlling the disease in 17 (65.4 %) patients [113]. In another trial, 17 patients with severe refractory uveitis (resistant to etanercept, infliximab, adalimumab, rituximab or abatacept) were transferred to golimumab, and an improvement was achieved in 14 of them, in which 12 of these patients showed inactivity at the last examination (average period of duration 22 months, interval 6-29 months) [116]. Dhingra et al. published preliminary evidence showing that in 7 patients with refractory uveitis, a change to another biological drug (period of 5-24 months) led to better control of the intraocular inflammation [122]. Although no direct evidence about the influence of low levels of drugs or the formation of anti-drug antibodies (ADA) on the effectiveness of biological treatment in patients with uveitis was determined upon a review of the literature, the expert group nevertheless took into account the findings of other clinical trials and came to the conclusion that in the case of loss of effectiveness during the course of treatment it is necessary to conduct an examination of ADA and the level of the drug [142-143]. If the patient does not have presence of antibodies, but has a low level of the drug, it is suitable to consider increasing the dose or reducing the interval of administration [144]. By contrast, concomitant administration of immunosuppressive drugs, primarily MTX, suppresses the formation of ADA [145].

On the basis of data from smaller studies (see recommendation 18, table 3) on patients with uveitis and JIA who do not respond to conventional synthetic drugs and at least one drug from the group of TNF-α blockers, it is possible to consider application of another biological drug such as abatacept, rituximab or tocilizumab [123-125]. The effectiveness of intravenous tocilizumab in the treatment of JIA following failure of non-biological DMARDs and at least one anti-TNF biological drug have been demonstrated by two smaller retrospective studies [146-147]. There is an increasing amount of evidence for the positive effect of tocilizumab in influencing macular edema upon a background of uveitis [125,148]. A study is currently ongoing verifying the safety and effectiveness of subcutaneous tocilizumab in children with uveitis upon a background of JIA which does not respond to anti-TNF therapy [149].

The optimum time for performing surgical procedures on children with complications on a background of refractory uveitis was not discussed within the framework of these recommendations due to insufficient evidence. However, the current data shows that there are still a significant number of children with uveitis who require a surgical procedure due to the occurrence of complications [150].

On the basis of the European SHARE recommendations, a working group including the authors of this article agreed upon a therapeutic algorithm for the treatment of uveitis associated with JIA in the Czech and Slovak Republics, the schema is presented in table 7.

Recommendations concerning future plans for uveitis associated with JIA

Specialist societies feel the need to perform further clinical and longitudinal trials with the aim of comparing the costs and benefits in connection with the treatment of chronic uveitis associated with JIA [74]. In order to achieve this goal, the MIWGUC group proposes a set of parameters for the evaluation of activity of uveitis, for the purpose of standardisation of data and comparison of results (Table 6). The individual points should be approved both by research workers and by patients. Although the members of the working group unanimously agree upon the proposed set of parameters, they cannot yet be generally used in practice until they pass validation. They could subsequently provide a uniform evaluation in the case of intervention studies. Deterioration of sight has a significant impact on quality of life (QOL) of patients with uveitis associated with JIA, significantly influencing social, emotional and economic aspects of life, as well as the ability of individuals to perform everyday activities [126-128]. At present validation of a suitable tool for measuring the influence of uveitis on QOL is taking place, namely "The Effects of Youngsters' Eyesight QOL". A consensus reigns among experts concerning the need for further controlled clinical trials on children with uveitis upon a background of JIA, so as to increase the evidence in the field of diagnosis, screening, activity of the pathology and treatment, and to ensure optimal care for these patients.

DISCUSSION

Following a systematic study of the literature, using the Nominal Group Technique under the auspices of SHARE and EULAR, a total of 22 recommendations were accepted for diagnosis and screening, monitoring of activity, treatment and future planning for children with uveitis associated with JIA. These recommendations were accepted on the basis of a minimum of 80 % consensus of specialists. The recommendations compiled by experts on the basis of the available evidence should help improve the provision of optimal care for patients, above all where the evidence is based only on a limited number of subjects and changes quickly.

It is necessary to note that the level of evidence in these recommendations was generally relatively low, 13 of the 22 recommendations are of level 3 or 4, 7 level 2 and only 2 are on level 1. Many new drugs, especially from the field of

biological drugs, have been introduced only very recently, and further research shall follow in this area. At a time when the data search was taking place for the SHARE recommendations, almost no controlled clinical trials on children with uveitis upon a background of JIA were available. The results of the SYCAMORE randomised controlled trial (RCT) [97], comparing adalimumab with a placebo in children with uveitis upon a background of JIA who used a stable dose of MTX, were published only after the issuing of the SHARE recommendations. The study led to the approval of the indication of adalimumab for the treatment of chronic anterior uveitis in children from the age of 2 years by the European Medicines Agency (EMA) in 2017. The results of the study are not in conflict with the recommendations of the group of experts, but rather reinforce recommendation 15 in table 3: "In the case of insufficient effect or intolerance of methotrexate it is recommended to add or replace the treatment with a biological treatment." The only difference is that this recommendation is now supported by level 1 evidence rather than level 3. A further smaller RCT with adalimumab was published recently, demonstrating its effectiveness in the treatment of uveitis associated with JIA, in this trial flare was used as the primary goal of evaluation [141]. The study of further biological drugs is continuing with regard to their effectiveness in the treatment of uveitis upon a background of JIA, for example JAK inhibitors [151]. The conclusions of these studies are not incorporated in the original recommendations of the SHARE article published in 2017, and as a result it is necessary to update the existing recommendations for uveitis associated with JIA regularly, in order to provide a constantly higher level of evidence. In the Czech Republic, unlike the Slovak Republic, adalimumab does not have approved coverage by health insurance for administration to patients with JIA uveitis, and to date its application is therefore possible only with the special consent of health insurance company. The application of the recommendations in practice requires close co-operation between doctors and health insurance payers.

REFERENCES

1. Enders FB, Bader-Meunier B, Baildam E, et al. Consensus-based recommendations for the management of juvenile dermatomyositis. Ann Rheum Dis. 2017;76:329–340.
2. van der Heijde D, Aletaha D, Carmona L, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis. 2015;74:8–13.
3. Brouwers MC, Kho ME, Browman GP, et al. AGREE II: advancing guideline development, reporting and evaluation in health care. Can Med Assoc J. 2010;182: E839–842.
4. Heiligenhaus A, Michels H, Schumacher C, et al. Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Rheumatol Int. 2012;32:1121–1133.
5. Bou R, Adán A, Borrás F, et al. Clinical management algorithm of uveitis associated with juvenile idiopathic arthritis: interdisciplinary panel consensus. Rheumatol Int. 2015;35:777–785.
6. Zierhut M, Heiligenhaus A, deBoer J, Cunningham ET, Tugal-Tutkun I. Controversies in juvenile idiopathic arthritis-associated uveitis. Ocul Immunol Inflamm. 2013;21:167–179.
7. Clarke SLN, Sen ES, Ramanan AV. Juvenile idiopathic arthritis--associated uveitis. Pediatric Rheumatology. 2016;14(1):27.
8. Sen ES, Dick AD, Ramanan AV. Uveitis associated with juvenile idiopathic arthritis. Nat Rev Rheumatol. 2015;11:338–348.
9. Zhang W, Doherty M, Pascual E, et al. EULAR evidence based recommendations for gout. Part I: diagnosis. Report of a task force of the standing committee for international clinical studies including therapeutics (ESCISIT). Ann Rheum Dis. 2006;65:1301–1311.
10. Zhang W, Doherty M, Bardin T, et al. EULAR evidence based recommendations for gout. Part II: Management. Report of a task force of the EULAR Standing Committee for International Clinical Studies Including Therapeutics (ESCISIT). Ann Rheum Dis. 2006;65:1312–1324.
11. Dougados M, Betteridge N, Burmester GR, et al. EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. Ann Rheum Dis. 2004;63:1172–1176.
12. Van de Ven AH, Delbecq AL. The nominal group as a research instrument for exploratory health studies. Am J Public Health. 1972;62:337–342.
13. Uchiyama RC, Osborn TG, Moore TL. Antibodies to iris and retina detected in sera from patients with juvenile rheumatoid arthritis with iridocyclitis by indirect immunofluorescence studies on human eye tissue. J Rheumatol. 1989;16:1074–1078.
14. Giannini EH, Malagon CN, Van Kerckhove C, et al. Longitudinal analysis of HLA associated risks for iridocyclitis in juvenile rheumatoid arthritis. J Rheumatol. 1991;18:1394–1397.
15. Malagon C, Van Kerckhove C, Giannini EH, et al. The iridocyclitis of early onset pauciarticular juvenile rheumatoid arthritis: outcome in immunogenetically characterized patients. J Rheumatol.1992;19:160–163.
16. Murray KJ, Szer W, Grom AA, et al. Antibodies to the 45 kDa DEK nuclear antigen in pauciarticular onset juvenile rheumatoid arthritis and iridocyclitis: selective association with MHC gene. J Rheumatol. 1997;24:560–567.
17. Berk AT, Koçak N, Ünsal E. Uveitis in juvenile arthritis. Ocul Immunol Inflamm. 2001;9:243–251.
18. Zulian F, Martini G, Falcini F, et al. Early predictors of severe course of uveitis in oligoarticular juvenile idiopathic arthritis. J Rheumatol. 2002;29:2446–2453.
19. Chia A, Lee V, Graham EM, Edelsten C. Factors related to severe uveitis at diagnosis in children with juvenile idiopathic arthritis in a screening program. Am J Ophthalmol. 2003;135:757–762.
20. Chen CS, Roberton D, Hammerton ME. Juvenile arthritis-associated uveitis: visual outcomes and prognosis. Can J Ophthalmol. 2004;39:614–620.
21. Nordal EB, Songstad NT, Berntson L, Moen T, Straume B, Rygg M. Biomarkers of chronic uveitis in juvenile idiopathic arthritis: predictive value of antihistone antibodies and antinuclear antibodies. J Rheumatol. 2009;36:1737–1743.
22. Kalinina Ayuso V, Ten Cate HA, van der Does P, Rothova A, de Boer JH. Male gender as a risk factor for complications in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol. 2010;149:994–999.
23. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk factors for development of uveitis differ between girls and boys with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62:1824–1828.
24. 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;40:2088–2096.
25. Cole TS, Frankovich J, Iyer S, Lependu P, Bauer-Mehren A, Shah NH. Profiling risk factors for chronic uveitis in juvenile idiopathic arthritis: a new model for EHR-based research. Pediatr Rheumatol Online J. 2013;11:45.
26. 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;41:1416–1425.
27. Pelegrín L, Casaroli-Marano R, Antón J, et al. Predictive value of selected biomarkers, polymorphisms, and clinical features for oligoarticular juvenile idiopathic arthritisassociated uveitis. Ocul Immunol Inflamm. 2014;22:208–212.
28. Egeskjold EM, Johansen A, Permin H, Hoyeraal HM, Sorensen T. The significance of antinuclear antibodies in juvenile rheumatoid

arthritis associated with chronic bilateral iridocyclitis. Acta Paediatr Scand. 1982;71:615–620.
29. Cabral DA, Petty RE, Malleson PN, Ensworth S, McCormick AQ, Shroeder ML. Visual prognosis in children with chronic anterior uveitis and arthritis. J Rheumatol. 1994;21:2370–2375.
30. Haas JP, Truckenbrodt H, Paul C, Hoza J, Scholz S, Albert ED. Subtypes of HLA-DRB1*03, *08, *11, *12, *13 and *14 in early onset pauciarticular juvenile chronic arthritis (EOPA) with and without iridocyclitis. Clin Exp Rheumatol. 1994;12(Suppl 10):7–14.
31. Kotaniemi K, Kotaniemi A, Savolainen A. Uveitis as a marker of active arthritis in 372 patients with juvenile idiopathic seronegative oligoarthritis or polyarthritis. Clin Exp Rheumatol. 2002;20:109–112.
32. Zeggini E, Packham J, Donn R, et al. Association of HLA-DRB1*13 with susceptibility to uveitis in juvenile idiopathic arthritis in two independent data sets. Rheumatology. 2006;45:972–974.
33. Bloom JN, Ni M, Moore TL, Osborn TG, Hageman GS. Serum antiocular antibodies in patients with juvenile rheumatoid arthritis. J Pediatr Ophthalmol Strabismus. 1993;30:243–248.
34. Campanilho-Marques R, Bogas M, Ramos F, Santos MJ, Fonseca JE. Prognostic value of antinuclear antibodies in juvenile idiopathic arthritis and anterior uveitis. Results from a systematic literature review. Acta Reumatol Port. 2014;39:116–122.
35. de Boer J, Steijaert A, van den Bor R, Stellato R, Ossewaarde-van Norel J. Development of macular edema and impact on visual acuity in uveitis associated with juvenile idiopathic arthritis. Ocul Immunol Inflamm. 2015;23:67–73.
36. Ducos de Lahitte G, Terrada C, Tran TH, et al. Maculopathy in uveitis of juvenile idiopathic arthritis: an optical coherence tomography study. Br J Ophthalmol. 2008;92:64–69.
37. Edelsten C, Lee V, Bentley CR, Kanski JJ, Graham EM. An evaluation of baseline risk factors predicting severity in juvenile idiopathic arthritis associated uveitis and other chronic anterior uveitis in early childhood. Br J Ophthalmol. 2002;86:51–56.
38. Glass D, Litvin D, Wallace K, et al. Early-onset pauciarticular juvenile rheumatoid arthritis associated with human leukocyte antigen-DRw5, iritis, and antinuclear antibody. J Clin Invest. 1980;66:426–429.
39. Grassi A, Corona F, Casellato A, Carnelli V, Bardare M. Prevalence and outcome of juvenile idiopathic arthritis-associated uveitis and relation to articular disease. J Rheumatol. 2007;34:1139–1145.
40. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K, German Uveitis in Childhood Study Group. Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines. Rheumatology. 2007;46:1015–1019.
41. Ingegnoli F, Del Papa N, Comina DP, et al. Autoantibodies to chromatin: prevalence and clinical significance in juvenile rheumatoid arthritis. Clin Exp Rheumatol. 2004;22:499–501.
42. Kanski JJ. Screening for uveitis in juvenile chronic arthritis. Br J Ophthalmol. 1989;73:225–228.
43. Kodsi SR, Rubin SE, Milojevic D, Ilowite N, Gottlieb B. Time of onset of uveitis in children with juvenile rheumatoid arthritis. J Aapos. 2002;6:373–376.
44. Kotaniemi K, Sihto-Kauppi K. Occurrence and management of ocular hypertension and secondary glaucoma in juvenile idiopathic arthritis-associated uveitis: An observational series of 104 patients. Clin Ophthalmol. 2007;1:455–459.
45. Marvillet I, Terrada C, Quartier P, Quoc EB, Bodaghi B, Prieur AM. Ocular threat in juvenile idiopathic arthritis. Joint Bone Spine. 2009;76:383–388.
46. Mathur G, Biswas J. Systemic associations of anterior uveitis in a tertiary care ophthalmic centre in south India. Int Ophthalmol. 2012;32:417–421.
47. McGill NW, Gow PJ. Juvenile rheumatoid arthritis in Auckland: a long term follow-up study with particular reference to uveitis. Aust N Z J Med. 1987;17:305–308.
48. Melin-Aldana H, Giannini EH, Taylor J, et al. Human leukocyte antigen-DRB1*1104 in the chronic iridocyclitis of pauciarticular juvenile rheumatoid arthritis. J Pediatr. 1992;121:56–60.
49. Merayo-Lloves J, Power WJ, Rodriguez A, Pedroza-Seres M, Foster CS. Secondary glaucoma in patients with uveitis. Ophthalmologica. 1999;213:300–304.
50. Miller ML, Fraser PA, Jackson JM, et al. Inherited predisposition to iridocyclitis with juvenile rheumatoid arthritis: selectivity among HLA-DR5 haplotypes. Proc Natl Acad Sci U S A. 1984;81:3539–42.
51. Murray P. Serum autoantibodies and uveitis. Br J Ophthalmol. 1986;70:266–268.
52. Neuteboom GH, Hertzberger-ten Cate R, de Jong J, van den Brink HG, Feltkamp TE. Antibodies to a 15kD nuclear antigen in patients with juvenile chronic arthritis and uveitis. Invest Ophthalmol Vis Sci. 1992;33:1657–1660.
53. Ohno S, Char DH, Kimura SJ, O´Connor GR. HLA antigens and antinuclear antibody titres in juvenile chronic iridocyclitis. Br J Ophthalmol. 1977;61:59–61.
54. Ostensen M, Fredriksen K, Kass E, Rekvig OP. Identification of antihistone antibodies in subsets of juvenile chronic arthritis. Ann Rheum Dis. 1989;48:114–117.
55. Paroli MP, Abbouda A, Restivo L, Sapia A, Abicca I, Pivetti-Pezzi P. Juvenile idiopathic arthritis-associated uveitis at an Italian tertiary referral center: clinical features and complications. Ocul Immunol Inflamm. 2015;23:74–81.
56. Paroli MP, Speranza S, Marino M, Pirraglia MP, Pivetti-Pezzi P. Prognosis of juvenile rheumatoid arthritisassociated uveitis. Eur J Ophthalmol. 2003;13:616–621.
57. Reininga JK, Los LI, Wulffraat NM, Armbrust W. The evaluation of uveitis in juvenile idiopathic arthritis (JIA) patients: are current ophthalmologic screening guidelines adequate? Clin Exp Rheumatol. 2008;26:367–372.
58. Sabri K, Saurenmann RK, Silverman ED, Levin AV. Course, complications, and outcome of juvenile arthritis-related uveitis. J Aapos. 2008;12:539–545.
59. Saurenmann RK, Levin AV, Feldman BM, Rose JB, Laxer RM, Schneider R, Silverman ED. Prevalence, risk factors, and outcome of uveitis in juvenile idiopathic arthritis: a long-term followup study. Arthritis Rheum. 2007;56:647–657.
60. Schaller JG, Johnson GD, Holborow EJ, Ansell BM, Smiley WK. The association of antinuclear antibodies with the chronic iridocyclitis of juvenile rheumatoid arthritis (Still's disease). Arthritis Rheum. 1974;17:409–416.
61. Sim KT, Venning HE, Barrett S, Gregson RM, Amoaku WM. Extended oligoarthritis and other risk factors for developing JIA-associated uveitis under ILAR classification and its implication for current screening guideline. Ocul Immunol Inflamm. 2006;14:353–357.
62. Southwood TR, Ryder CA. Ophthalmological screening in juvenile arthritis: should the frequency of screening be based on the risk of developing chronic iridocyclitis? Br J Rheumatol. 1992;31:633–634.
63. Wakefield D, Herbort CP, Tugal-Tutkun I, Zierhut M. Controversies in ocular inflammation and immunology laser flare photometry. Ocul Immunol Inflamm. 2010;18: 334–340.
64. Wittemann B, Neuer G, Michels H, Truckenbrodt H, Bautz FA. Autoantibodies to nonhistone chromosomal proteins HMG-1 and HMG-2 in sera of patients with juvenile rheumatoid arthritis. Arthritis Rheum. 1990;33:1378–1383.
65. 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;143:647–655.
66. 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;90:91–95.
67. Kalinina Ayuso V, van de Winkel EL, Rothova A, de Boer JH. Relapse rate of uveitis post-methotrexate treatment in juvenile idiopathic arthritis. Am J Ophthalmol. 2011;151:217–222.
68. Papadopoulou C, Kostik M, Böhm M, et al. Methotrexate therapy may prevent the onset of uveitis in juvenile idiopathic arthritis. J Pediatr. 2013;163:879–884.
69. 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;17:460–464.
70. Shakoor A, Esterberg E, Acharya NR. Recurrence of uveitis after discontinuation of infliximab. Ocul Immunol Inflamm. 2014;22:96–101.
71. Dana MR, Merayo-Lloves J, Schaumberg DA, Foster CS. Visual outcomes prognosticators in juvenile rheumatoid arthritis-associated uveitis. Ophthalmology. 1997;104:236–244.
72. Arocker-Mettinger E, Asenbauer T, Ulbrich S, Grabner G. Serum interleukin 2-receptor levels in uveitis. Curr Eye Res. 1990;9(Suppl 1):25–29.
73. Kalinina Ayuso V, de Boer JH, Byers HL, et al. Intraocular biomarker identification in uveitis associated with juvenile idiopathic arthritis. Invest Ophthalmol Vis Sci. 2013;54:3709–3720.
74. Heiligenhaus A, Foeldvari I, Edelsten C, et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multina-

tional interdisciplinary working group for uveitis in childhood. Arthritis Care Res. 2012;64:1365–1372.
75. Walscheid K, Hennig M, Heinz C, et al. Correlation between disease severity and presence of ocular autoantibodies in juvenile idiopathic arthritis-associated uveitis. Invest Ophthalmol Vis Sci. 2014;55:3447–3453.
76. Manzotti F, Orsoni JG, Zavota L, Cimino L, Zola E, Bonaguri C. Autoimmune uveitis in children: clinical correlation between antinuclear antibody positivity and ocular recurrences. Rheumatol Int. 2002;21:127–132.
77. Massa M, De Benedetti F, Pignatti P, Albani S, Monestier M, Martini A. Lack of temporal association of iridocyclitis with IgG reactivities to core histones and nucleosome subparticles in pauciarticular juvenile chronic arthritis. Br J Rheumatol. 1995;34:507–511.
78. Gregory AC, Kempen JH, Daniel E, et al. Risk factors for loss of visual acuity among patients with uveitis associated with juvenile idiopathic arthritis: the Systemic Immunosuppressive Therapy for Eye Diseases Study. Ophthalmology. 2013;120:186–192.
79. Yuce BY, Yilmaz SG, Kose S, Uretmen O. Outcome of pediatric uveitis at an university clinic. Turk J Ophthalmol. 2013;43:395–401.
80. Kotaniemi K, Sihto-Kauppi K, Salomaa P, Säilä H, Ristolainen L, Kauppi M. The frequency and outcome of uveitis in patients with newly diagnosed juvenile idiopathic arthritis in two 4-year cohorts from 1990-1993 and 2000-2003. Clin Exp Rheumatol. 2014;32:143–147.
81. 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;117:1436–1441.
82. Olson NY, Lindsley CB, Godfrey WA. Nonsteroidal anti-inflammatory drug therapy in chronic childhood iridocyclitis. Am J Dis Child. 1988;142:1289–1292.
83. Wolf MD, Lichter PR, Ragsdale CG. Prognostic factors in the uveitis of juvenile rheumatoid arthritis. Ophthalmology. 1987;94:1242–1248.
84. Sijssens KM, Rothova A, Van De Vijver DA, Stilma JS, De Boer JH. Risk factors for the development of cataract requiring surgery in uveitis associated with juvenile idiopathic arthritis. Am J Ophthalmol. 2007;144:574–579.
85. Foster CS, Barrett F. Cataract development and cataract surgery in patients with juvenile rheumatoid arthritis-associated iridocyclitis. Ophthalmology. 1993;100:809–817.
86. Yu EN, Meniconi ME, Tufail F, Baltatzis S, Foster CS. Outcomes of treatment with immunomodulatory therapy in patients with corticosteroid-resistant juvenile idiopathic arthritis-associated chronic iridocyclitis. Ocul Immunol Inflamm. 2005;13:353–360.
87. Foeldvari I, Nielsen S, Kümmerle-Deschner J, et al. Tumor necrosis factoralpha blocker in treatment of juvenile idiopathic arthritis--associated uveitis refractory to second-line agents: results of a multinational survey. J Rheumatol. 2007;34:1146–1150.
88. Shetty AK, Zganjar BE, Ellis GS, Ludwig IH, Gedalia A. Low-dose methotrexate in the treatment of severe juvenile rheumatoid arthritis and sarcoid iritis. J Pediatr Ophthalmol Strabismus. 1999;36:125–128.
89. Foeldvari I, Wierk A. Methotrexate is an effective treatment for chronic uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2005;32:362–365.
90. Heiligenhaus A, Mingels A, Heinz C, Ganser G. Methotrexate for uveitis associated with juvenile idiopathic arthritis: value and requirement for additional anti-inflammatory medication. Eur J Ophthalmol. 2007;17:743–748.
91. Goebel JC, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Azathioprine as a treatment option for uveitis in patients with juvenile idiopathic arthritis. Br J Ophthalmol. 2011;95:209–213.
92. Huang JL, Hung IJ, Hsieh KH. Sulphasalazine therapy in chronic uveitis of children with chronic arthritis. Asian Pac J Allergy Immunol. 1997;15:71–75.
93. Sobrin L, Christen W, Foster CS. Mycophenolate mofetil after methotrexate failure or intolerance in the treatment of scleritis and uveitis. Ophthalmology. 2008;115:1416–1421.
94. Tappeiner C, Roesel M, Heinz C, Michels H, Ganser G, Heiligenhaus A. Limited value of cyclosporine A for the treatment of patients with uveitis associated with juvenile idiopathic arthritis. Eye. 2009;23:1192–1198.
95. Molina C, Modesto C, Martín-Begué N, Arnal C. Leflunomide, a valid and safe drug for the treatment of chronic anterior uveitis associated with juvenile idiopathic arthritis. Clin Rheumatol. 2013;32:1673–1675.
96. Rajaraman RT, Kimura Y, Li S, Haines K, Chu DS. Retrospective case review of pediatric patiens with uveitis treated with infliximab. Ophthalmology. 2006;113:308–314.
97. Vazquez-Cobian LB, Flynn T, Lehman TJA. Adalimumab therapy for childhood uveitis. J Pediatr. 2006;149:572–575.
98. Biester S, Deuter C, Michels H, et al. Adalimumab in the therapy of uveitis in childhood. Br J Ophthalmol. 2007;91:319–324.
99. Gallagher M, Quinones K, Cervantes-Castaneda RA, Yilmaz T, Foster CS. Biological response modifier therapy for refractory childhood uveitis. Br J Ophthalmol. 2007;91:1341–1344.
100. Tynjala P, Lindahl P, Honkanen V, Lahdenne P, Kotaniemi K. Infliximab and etanercept in the treatment of chronic uveitis associated with refractory juvenile idiopathic arthritis. Ann Rheum Dis. 2007;66:548–550.
101. Kotaniemi K, Säilä H, Kautiainen H. Long-term efficacy of adalimumab in the treatment of uveitis associated with juvenile idiopathic arthritis. Clin Ophthalmol. 2011;5:1425–1429.
102. García-De-Vicuńa C, Díaz-Llopis M, Salom D, et al. Usefulness of adalimumab in the treatment of refractory uveitis associated with juvenile idiopathic arthritis. Mediators Inflamm. 2013;2013:1–6.
103. Magli A, Forte R, Navarro P, et al. Adalimumab for juvenile idiopathic arthritisassociated uveitis. Graefes Arch Clin Exp Ophthalmol. 2013;251:1601–1606.
104. Zholobova E, Galstian L, Nikolaeva MN, Loskutova OY. Effectiveness of adalimumab in the treatment of juvenile idiopathic arthritis associated with uveitis. Pediatric Rheumatology. 2014;12(Suppl 1):O5.
105. Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrences i childhoodrefractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. Arthritis Care Res. 2011;63:612–618.
106. Simonini G, Taddio A, Cattalini M, et al. Superior efficacy of Adalimumab in treating childhood refractory chronic uveitis when used as first biologic modifier drug: Adalimumab as starting anti-TNF-& therapy in childhood chronic uveitis. Pediatr Rheumatol Online J. 2013;11:16.
107. Cecchin V, Zannin ME, Ferrari D, et al. Longterm safety and efficacy of adalimumab and infliximab for uveitis associated with juvenile idiopathic arthritis. J Rheumatol. 2018;45:1167–1172.
108. William M, Faez S, Papaliodis GN, Lobo AM. Golimumab for the treatment of refraktory juvenile idiopathic arthritis-associated uveitis. J Ophthalmic Inflamm Infect. 2012;2:231–233.
109. 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;45:252–257.
110. Richards JC, Tay-Kearney ML, Murray K, Manners P. Infliximab for juvenile idiopathic arthritis-associated uveitis. Clin Exp Ophthalmol. 2005;33:461–468.
111. Kahn P, Weiss M, Imundo LF, Levy DM. Favorable response to high-dose infliximab for refractory childhood uveitis. Ophthalmology. 2006;113:860–864.
112. Tynjälä P, Kotaniemi K, Lindahl P, et al. Adalimumab in juvenile idiopathic arthritisassociated chronic anterior uveitis. Rheumatology. 2008;47:339–3344.
113. Trachana M, Pratsidou-Gertsi P, Pardalos G, Kozeis N, Badouraki M, Kanakoudi-Tsakalidou F. Safety and efficacy of adalimumab treatment in Greek children with juvenile idiopathic arthritis. Scand J Rheumatol. 2011; 40:101–107.
114. Díaz-Llopis M, Salom D, Garcia-de-Vicuńa C, et al. Treatment of refractory uveitis with adalimumab: a prospective multicenter study of 131 patients. Ophthalmology. 2012;119:1575–1581.
115. Lerman MA, Burnham JM, Chang PY, et al. Response of pediatric uveitis to tumor necrosis factor – α inhibitor. J Rheumatol. 2013;40:1394–1403.
116. Miserocchi E, Modorati G, Pontikaki I, Meroni PL, Gerloni V. Long--term treatment with golimumab for severe uveitis. Ocul Immunol Inflamm. 2014;22:90–95.
117. Saeed MU, Raza SH, Goyal S, Cleary G, Newman WD, Chandna A. Etanercept in methotrexate-resistant JIA-related uveitis. Semin Ophthalmol. 2014;29:1–3.
118. Schmeling H, Horneff G. Etanercept and uveitis in patients with juvenile idiopathic arthritis. Rheumatology. 2005;44:1008–1011.
119. Smith JA, Thompson DJ, Whitcup SM, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum. 2005;53:18–23.

120. Saurenmann RK, Levin AV, Feldman BM, Laxer RM, Schneider R, Silverman ED. Risk of new-onset uveitis in patients with juvenile idiopathic arthritis treated with anti-TNFalpha agents. J Pediatr. 2006;149:833–836.
121. Kakkassery V, Mergler S, Pleyer U. Anti-TNF-alpha treatment: a possible promoter in endogenous uveitis? observational report on six patients: occurrence of uveitis following etanercept treatment. Curr Eye Res. 2010;35:751–756.
122. Dhingra N, Morgan J, Dick AD. Switching biologic agents for uveitis. Eye. 2009;23:1868–1870.
123. Zulian F, Balzarin M, Falcini F, et al. Abatacept for severe anti-tumor necrosis factor alpha refractory juvenile idiopathic arthritis--related uveitis. Arthritis Care Res. 2010;62:821-825.
124. Heiligenhaus A, Miserocchi E, Heinz C, Gerloni V, Kotaniemi K. Treatment of severe uveitis associated with juvenile idiopathic arthritis with anti-CD20 monoclonal antibody (rituximab). Rheumatology. 2011;50:1390–1394.
125. Mesquida M, Molins B, Llorenç V, Sainz de la Maza M, Adán A. Long-term effects of tocilizumab therapy for refractory uveitis-related macular edema. Ophthalmology. 2014;121:2380–2386.
126. Angeles-Han ST, Griffin KW, Lehman TJ, et al. The importance of visual function in the quality of life of children with uveitis. J Aapos. 2010;14:163–168.
127. Angeles-Han ST, Griffin KW, Harrison MJ, et al. Development of a vision-related quality of life instrument for children ages 8-18 years for use in juvenile idiopathic arthritis-associated uveitis. Arthritis Care Res. 2011;63:1254–1261.
128. Ezzahri M, Amine B, Rostom S, et al. The uveitis and its relationship with disease activity and quality of life in Moroccan children with juvenile idiopathic arthritis. Clin Rheumatol. 2013;32:1387–1391.
129. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet. 2011;377:2138–2149.
130. Thierry S, Fautrel B, Lemelle I, Guillemin F. Prevalence and incidence of juvenile idiopathic arthritis: a systematic review. Joint Bone Spine. 2014;81:112–117.
131. Yu HH, Chen PC, Wang LC, et al. Juvenile idiopathic arthritis-associated uveitis: a nationwide population-based study in Taiwan. PLoS One. 2013;5:8.
132. Shen CC, Yeh KW, Ou LS, Yao TC, Chen LC, Huang JL. Clinical features of children with juvenile idiopathic arthritis using the ILAR classification criteria: a community-based cohort study in Taiwan. J Microbiol Immunol Infect. 2013;46:288–294.
133. Heiligenhaus A, Heinz C, Edelsten C, Kotaniemi K, Minden K. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. Ocul Immunol Inflamm. 2013;21:180–191.
134. Sen, ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. Best Pract Res Clin Rheumatol. 2017;31:517–534.
135. Ramanan AV, Guly C. Adalimumab for childhood onset uveitis. Ann Rheum Dis. 2018;77: 961–962.
136. Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. N Engl J Med. 2017;376:1637–1646.
137. Dick AD, Rosenbaum JT, Al-Dhibi HA, et al. Guidance on Noncorticosteroid Systemic Immunomodulatory Therapy in Noninfectious Uveitis: Fundamentals Of Care for UveitiS (FOCUS) Initiative. Ophthalmology. 2018;125(5):757–773.
138. Ferrara G, Mastrangelo G, Barone P, et al. Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting. Pediatr Rheumatol Online J., 2018;16:46.
139. Wieringa WG, Ambrust W, Legger GE, Los LI. Efficacy of high-dose methotrexate in pediatric non-infectious uveitis. Ocul Immunol Inflamm. 2019;27(8):1305–1313.
140. LaMattina KC, Koreishi AF. What is new in pediatric uveitis? Curr Opin Ophtalmol. 2018;29: 412–418.
141. Quartier P, Baptiste A, Despert V On behalf of the ADJUVITE Study Group, et al. ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis. Annals of the Rheumatic Diseases. 2018;77:1003–1011.
142. Leinonen ST, Aalto K, Kotaniemi KM, Kivela TT. Anti-adalimumab antibodies in juvenile idiopathic arthritis-related uveitis. Clin Exp Rheumatol. 2017;35:1043–1046.
143. Skrabl-Baumgartner A, Erwa W, Muntean W, Jahnel J. Anti-adalimumab antibodies in juvenile idiopathic arthritis: frequent association with loss of response. Scand J Rheumatol. 2015;44:359–362.
144. Correll CK, Bullock DR, Cafferty RM, Vehe RK. Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis. Clin Rheumatol. 2018;37:549–553.
145. Skrabl-Baumgartner A, Seidel G, Langer-Wegscheider B, Schlagenhauf A, Jahnel J. Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis-associated uveitis. Arch Dis Child. 2019;104:246–250.
146. Calvo-Río V, Santos-Gómez M, Calvo I, et al. Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients. Arthritis Rheumatol. 2017;69:668–675.
147. Tappeiner C, Mesquida M, Adán A, et al. Evidence for Tocilizumab as a Treatment Option in Refractory Uveitis Associated with Juvenile Idiopathic Arthritis. J Rheumatol. 2016;43:2183–2188.
148. Mesquida M, Molins B, Llorenç V, et al. Twenty-four month follow--up of tocilizumab therapy for refractory uveitis-related macular edema. Retina. 2018;38:1361–1370.
149. Ramanan A, Dick AD, Jones AP, et al. A phase II trial protocol of tocilizumab in ati-TNF refraktory patients with JIA-associated uveitis (the APTITUDE trial). BMC Rheumatol. 2018;2:1.
150. Ferrara M, Eggenschwiler L, Stephenson A, et al. The Challenge of Pediatric Uveitis: Tertiary Referral Center Experience in the United States. Ocul Immunol Inflamm. 2018;15:1–8.
151. Pleyer U, Algharably EA, Feist E, Kreutz R. Small molecules as therapy for uveitis: a selected perspective of new and developing agents. Expert Opin Pharmacother. 2017;18: 1311–1323.
152. Heiligenhaus A, Minden K, Tappeiner C, et al. Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis, Seminars in Arthritis and Rheumatism. 2019;49:43–55.
153. Foeldvari I, Klotsche J, Simonini G, et al. Proposal for a definition for response to treatment, inactive disease and damage for JIA associated uveitis based on the validation of a uveitis related JIA outcome measures from the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC). Pediatr Rheumatol Online J. 2019;17(1):66.

Thanks

The SHARE initiative was approved by the Executive Committee of the European Society of Pediatric Rheumatology and the International Society of Systemic Autoimmune Diseases.

The authors of the Czech-Slovak adaptation of the recommendation thank the authors of the original text:

Tamas Constantin[1], Ivan Foeldvari[2], Jordi Anton[3], Joke de Boer[4], Severine Czitrom-Guillaume[5], Clive Edelsten[6], Raz Gepstein[7], Arnd Heiligenhaus[8,9], Clarissa A Pilkington[10], Gabriele Simonini[11], Yosef Uziel[12], Sebastian J Vastert[13], Nico M Wulffraat[13], Anne-Mieke Haasnoot[4], Karoline Walscheid[8], Annamária Pálinkás[1], Reshma Pattani[6], Zoltán Györgyi[1], Richárd Kozma[1], Victor Boom[14], Andrea Ponyi[1], Angelo Ravelli[15] and Athimalaipet V Ramanan[16]

[1]2nd Department of Pediatrics, Semmelweis University, Budapest, Hungary

[2]Klinikum Eilbek, Hamburger Zentrum für Kinder-und Jugendrheumatologie, Hamburg, Germany

[3]Department of Pediatric Rheumatology, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain

[4]Department of Ophthalmology, University Hospital Utrecht, Utrecht, The Netherlands

[5]Service de médecine des adolescents, CHU Bicêtre, AP--HP, 78, rue du Général-Leclerc, Paris, France

[6]Department of Ophthalmology, Great Ormond Street Hospital, London, UK

[7]Department of Ophthalmology, Meir Medical Center, Kfar Sava, Israel

[8]Department of Ophthalmology, Uveitis-Center, and Ophtha Lab, at St. Franziskus Hospital, Muenster, Germany
[9]University of Duisburg-Essen, Duisburg, Germany
[10]Department of Rheumatology, Great Ormond Street Hospital, London, UK
[11]Department of Paediatrics, Rheumatology Unit, Anna Meyer Children's Hospital, University of Florence, Florence, Italy
[12]Department of Paediatrics, Meir Medical Center, Sackler School of Medicine, Tel-Aviv University, Tel Aviv, Israel
[13]Department of Pediatric Rheumatology and Immunology, Wilhelmina Children's Hospital, University Medical Center Utrecht and University of Utrecht, Utrecht, The Netherlands
[14]Department of Internal Medicine, St. Antonius Hospital, Nieuwegein, The Netherlands
[15]Università degli Studi di Genova and Istituto Giannina Gaslini, Genoa, Italy
[16]University Hospitals Bristol NHS Foundation Trust & Bristol Medical School, University of Bristol, Bristol, UK