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Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis

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ABSTRACT

Background: Uveitis in juvenile idiopathic arthritis (JIAU) is frequently associated with the development of complications and visual loss. Topical corticosteroids are the first line therapy, and disease modifying anti-rheumatic drugs (DMARDs) are commonly used. However, treatment has not been standardized.
Methods: Interdisciplinary guideline were developed with representatives from the German Ophthalmological Society, Society for Paediatric Rheumatology, Professional Association of Ophthalmologists, German Society for Rheumatology, parents' group, moderated by the Association of the Scientific Medical Societies in Germany. A systematic literature analysis in MEDLINE was performed, evidence and recommendations were graded, an algorithm for anti-inflammatory treatment and final statements were discussed in a consensus meeting (Nominal Group Technique), a preliminary draft was fine-tuned and discussed thereafter by all participants (Delphi procedure).
Results: Consensus was reached on recommendations, including a standardized treatment strategy according to uveitis severity in the individual patient. Thus, methotrexate shall be introduced for uveitis not responding to low-dose (≤ 2 applications/day) topical corticosteroids, and a TNFalpha antibody (preferably adalimumab) used, if uveitis inactivity is not achieved. In very severe active uveitis with uveitis-related deterioration of vision, systemic corticosteroids should be considered for bridging until DMARDs take effect. If TNFalpha antibodies fail to take effect or lose effect, another biological should be selected (tocilizumab, abatacept or rituximab). De-escalation of DMARDs should be preceded by a period of ≥ 2 years of uveitis inactivity.
Conclusions: An interdisciplinary, evidence-based treatment guideline for JIAU is presented.

Introduction

Juvenile idiopathic arthritis (JIA), as defined by the current version of the internationally applied ILAR classification [110], is by far the most common chronic inflammatory rheumatic disease of childhood and adolescence [118]. In 9–13% of patients, JIA is associated with anterior uveitis (JIAU) [18,54], particularly in early disease onset, oligoarthritis subtype, and anti-nuclear antibody (ANA) positive patients [54,155].

JIAU patients are at high risk of uveitis-related complications and deterioration of visual acuity [25,27,34,60,68,77], but appropriate screening and modern treatment approaches have considerably reduced the rate of visual impairment [77,145,153]. A long period of chronic inflammation seems to be particularly critical, and even low anterior chamber (AC) cell grades (≥ 0.5 +) may be associated with an increased risk of structural complications and visual deterioration [158], and therefore patients must be assessed thoroughly [56].

While patients with JIAU cannot be treated curatively, complete suppression of inflammation with anti-inflammatory medication is

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anticipated. The primary objectives of treatment are preservation of sight, treatment of relapses, treatment of complications, treatment of underlying systemic diseases, prevention of recurrences and complications, and avoidance of adverse drug reactions. Evidence in the treatment of JIAU is still limited to three randomized controlled trials [113,117,144], but there is no doubt that in severe disease the long-term prognosis can be improved by the use of conventional synthetic (cs) or biological (b) disease-modifying anti-rheumatic drugs (DMARDs). This guideline was developed to reduce the existing practice variation in the treatment of JIAU and to promote therapy based on current evidence that is tailored to disease severity. The existing JIAU guideline [57] has been revised to take into account recently published data, particularly focusing on the increasing use of bDMARDs. The guideline is intended to aid decision-making in the treatment of JIAU.

Methods

The methods were designed according to international standards for high quality guidelines, as layed out in the AWMF Guidance document [36]. A comprehensive MEDLINE literature search on therapy for uveitis in JIA was done by two delegates each from the DOG (AH, CT) and the GKJR (HL,KM) to include publications with the previous 2 decades, up to January 30, 2017. The classifications of the International League of Associations for Rheumatology (ILAR) [110], and Standardization of Uveitis Nomenclature (SUN) [62] were taken into account. Thereby, 543 publications were identified (Supplement Table 1).

The delegates appraised the identified studies with regard to their design, quality of execution (risk of bias), and analysis. They took into account the clinical relevance of the studies' outcome measures of effectiveness, the applicability of the study results to the target group of patients and to the German healthcare system, cost aspects, and ease of implementation in physicians' daily routine. Evidence tables were established for the various treatment measures. Based on the algorithm for common treatment practice, key recommendations were drawn up and classified according to level of evidence (Supplement Table 2), and grade of recommendation (Supplement Table 3), and texts were drafted with adequate answers to clinical questions on the basis of the guideline synopsis. These texts and key recommendations were conveyed to all members of the guideline group for perusal before the conference.

The guideline group comprised representatives from the professional societies involved in diagnosis and treatment of JIAU, and a patient group. All members of the guideline group declared secondary interests using the AWMF standard form. The whole-day consensus conference took place in Muenster on 31 March 2017; 69.2% of the guideline group members were present. Nominal group process (NGP) technique was used to collect individual opinion, and to reach consensus. To accomplish this, the results of the literature review were presented in brief. The key statements, individual sections of the draft text, and algorithms were presented by the moderator (IK) and scrutinized by the participants, opinions and alternative wordings were clarified and substantiated, the preliminary draft and alternatives were fine-tuned and discussed, and the final consensus was fixed. In formal voting processes, participants with relevant CoI abstained.

The guideline and treatment algorithm were then sent to all members of the guideline group with the request for suggestions (Delphi Process). Their proposals for revision were sent to the coordinators, collated, and entered. All participants stated their agreement or dissent and provided suggestions for modification. The results of this first Delphi round were summarized and sent to the members of the guideline group; for sections where no consensus had been achieved, the proposed revisions were included in the second Delphi round.

The guideline manuscript was then sent for external review (by DOG, DGRh, GKJR) and subsequently voted on in writing within the guideline group (Delphi round 3). The draft of the complete guideline was then finally approved by all participants.

Results

Anti-inflammatory treatment

Diagnostic procedures for JIA and associated uveitis are outlined in Supplement Text 1. The treatment of uveitis depends on the degree of inflammation, the presence of complications, and the presence of risk factors for deterioration of visual acuity. Four phases of treatment are recommended (Fig. 1(A)–(D)). Because the uveitis can take a very similar course in patients with JIA and those with ANA-positivity but no JIA, these two groups should be treated in the same way, which is in accordance with the recently published CARRA concensus treatment plans for anterior uveitis [3].

Local treatment of the eye and the management of any ocular complications shall be the province of the ophthalmologist. Patients with chronic active and/or severe uveitis should be referred to ophthalmologists with extensive experience in the treatment of JIAU. The indication for systemic anti-inflammatory treatment or administration of DMARDs to treat the uveitis shall be determined together with pediatric rheumatologists. Any DMARDs treatment should be monitored by a suitably experienced pediatric rheumatologist. The choice of medication must take into account the underlying JIA, often already requiring DMARD treatment. Mild and moderate adverse drug effects might occur during treatment with csDMARDs or bDMARDs [157]. Consequently, joint close monitoring by an ophthalmologist and a pediatric rheumatologist shall be put in place [72,86] and shall be continued under long-term treatment. Regular discussion between the treating physicians and the patient and/or parents is recommended, covering the disease course and the scope and frequency of follow-up (FU) examinations, so that they can come to a joint decision on the best further course of treatment.

To facilitate interdisciplinary communication, the ophthalmologist's or pediatric rheumatologist's discharge letter to the patient's tertiary care physician should document the relevant information. The ophthalmologist's discharge letter to the patient's tertiary care physician should document the relevant information characterizing the disease course and the patient's current condition, provided that this is not already known: age at diagnosis of uveitis, classification of the uveitis according to the SUN criteria, course of inflammation to date, disease course under previous treatment, current topical and systemic treatment, course of visual acuity anterior, chamber cell grade, intraocular pressure, structural ocular complications, and previous eye surgery.

The pediatric rheumatologist's discharge letter should document the following aspects, provided that this is not already known: age, gender, JIA category (according to ILAR classification), presence of antinuclear antibodies (ANA), HLA-B27 antigen, rheumatoid factor (RF), age at onset of arthritis, previous course of arthritis, response of arthritis to previous treatment, and current treatment, including tolerability and adverse drug reactions.

Treatment of active uveitis

Key statement 1

Active uveitis shall be treated.

The treatment of JIAU shall begin as soon as possible after diagnosis. Treatment is indicated from a grade of $\geq 0.5 + AC$ cells [62,158]. The goal of treatment of JIAU should be elimination of all AC cells. There is currently no consensus on whether endothelial precipitates alone should be considered in treatment [26,151].

If risk factors for impending deterioration of vision (see Supplement Text) are identified, the anti-inflammatory treatment shall be intensified. Presence of these risk factors point to the severity of the disease and, in the view of the guideline group, represent a criterion for DMARD treatment. On the other hand, anti-inflammatory therapy should be initiated or intensified without the presence of AC cells if macular edema, ocular hypotony [12,159], or iris rubeosis are demonstrated, as these often correlate with chronic inflammation of the affected tissues.

Algorithm for anti-inflammatory treatment

Treatment phase I

Key statement 2

Topical corticosteroids shall be used as initial treatment for active uveitis.

Topical corticosteroids

Topical corticosteroids shall be used as initial treatment for active uveitis. High-potency corticosteroids (e.g., prednisolone 1% or dexamethasone 0.1%) have been shown to be more effective than low-potency corticosteroids (e.g., rimexolone or loteprednol etabonate) in topical uveitis treatment [32,33,46]; therefore, high-potency corticosteroids should be preferred [138] (Table 1). To prevent amblyopia (particularly in patients <7 years of age), drops shall be applied when the child is awake, and ointment at night.

In the first 1–3 days of treatment after an uveitis attack is detected, drops should be given frequently (every 2 h, or hourly if $\geq 2+$ cells) during the waking hours. The dosage should then be reduced within 6 weeks according to the degree of inflammation; when stable inactivity ($<0.5+$ cells) is attained, the drops can be discontinued (Fig. 1(A)).

Even children who are being treated only with topical corticosteroids shall be monitored for possible topical (e.g., raised IOP) or systemic adverse effects (e.g., Cushing's syndrome). This risk increases with bilateral administration and high dosages of high-potency corticosteroids, particularly in children aged <4 years [80,105].

Key statement 3

Cycloplegics should be given to prevent or treat posterior synechiae in active uveitis

Anti-inflammatory treatment of active anterior uveitis should be combined with administration of cycloplegics to prevent or release posterior synechiae. In case of chronic inflammation, tropicamide may have to be given at night to prevent synechiae. Whenever cycloplegics are used, care shall be taken that no amblyopia is induced in young children.

Key statement 4

Topical and systemic nonsteroidal anti-inflammatory drugs shall not be used alone to treat active uveitis.

Nonsteroidal anti-inflammatory drugs (NSAIDs)

Topical NSAIDs (Table 2) play only a minor role in the treatment of JIAU, as they are less effective than topical corticosteroids [32,127].

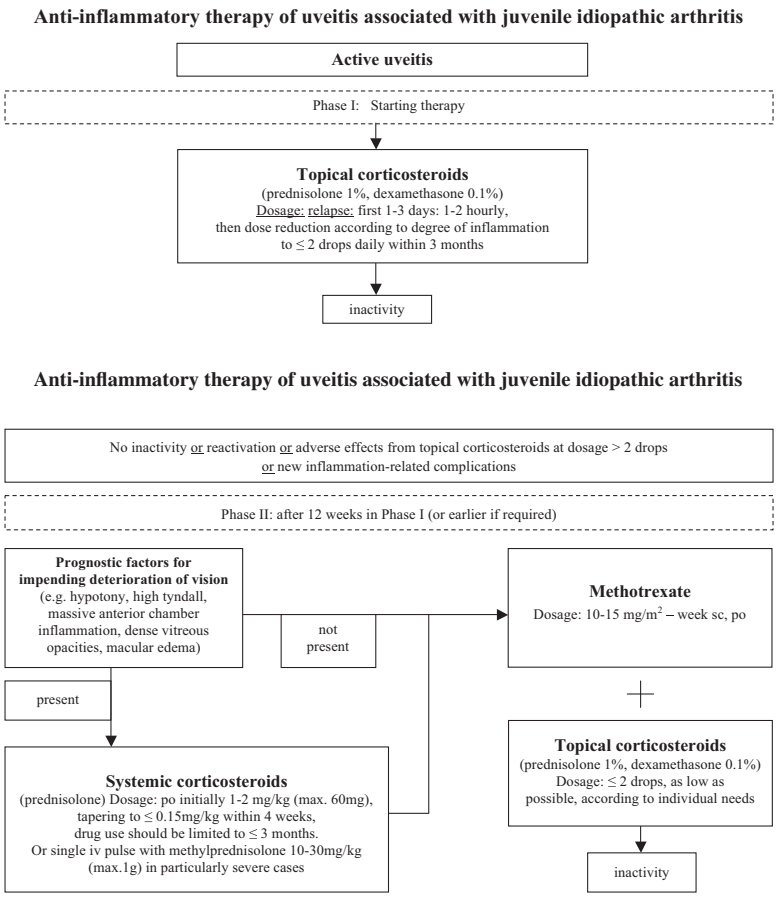
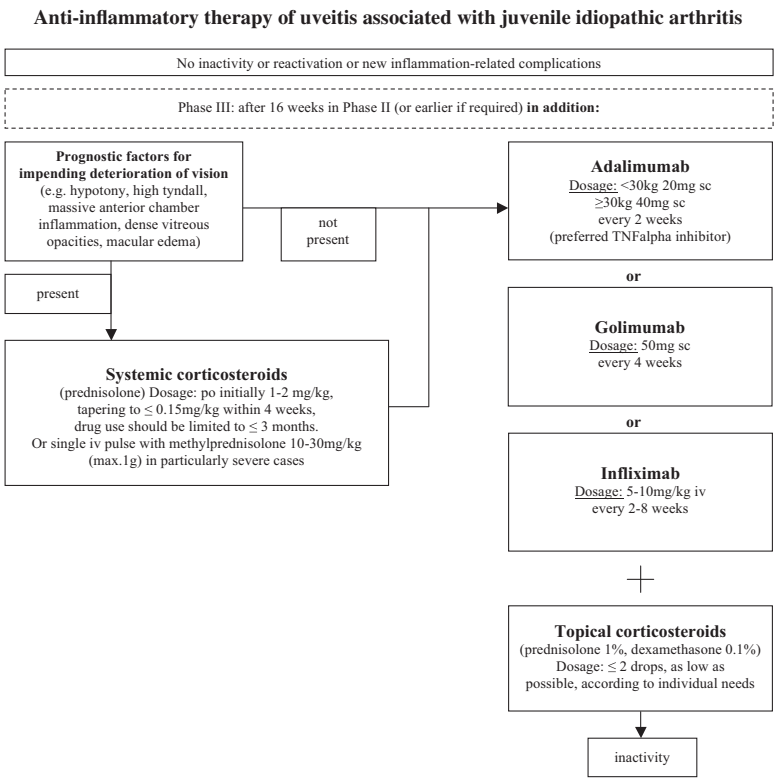


Fig. 1. (A) Anti-inflammatory therapy of uveitis associated with juvenile idiopathic arthritis: treatment algorithm, phase 1. (B) Anti-inflammatory therapy of uveitis associated with juvenile idiopathic arthritis: treatment algorithm, phase 2. The dosages are intended to provide orientation and should always be adapted to the circumstances of the individual patient. (C) Anti-inflammatory therapy of uveitis associated with juvenile idiopathic arthritis: treatment algorithm, phase 3. (D) Anti-inflammatory therapy of uveitis associated with juvenile idiopathic arthritis: treatment algorithm, phase 4.



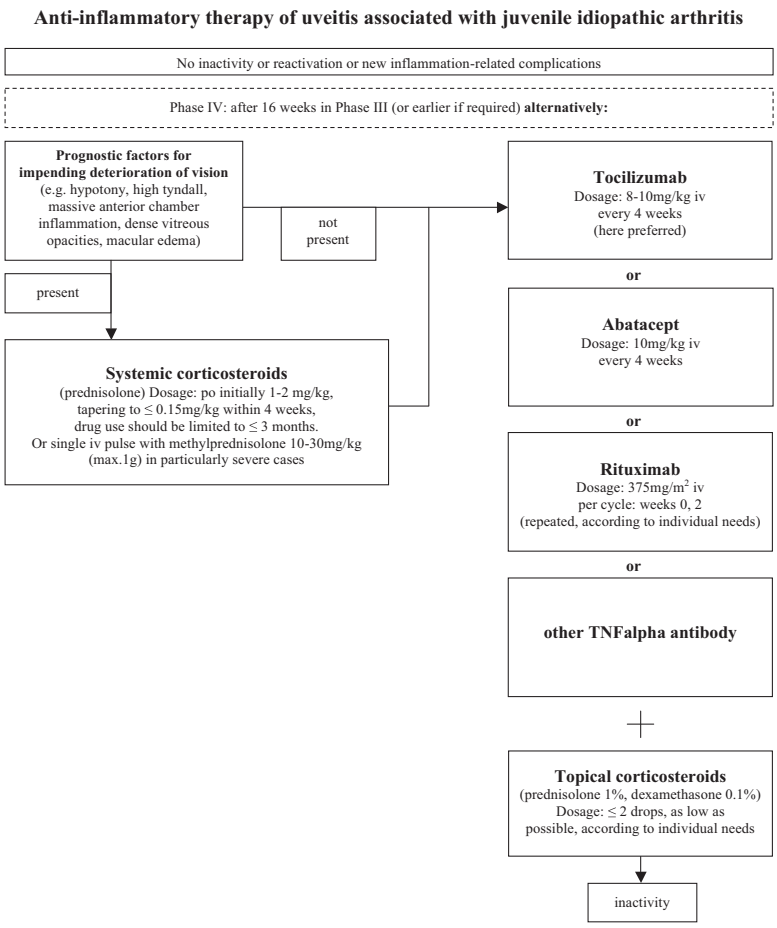


Fig. 1. Continued.

Table 1
Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Corticosteroids.

Topical corticosteroids[#,*]				
	Daily dosage	Comment	Level of evidence and recommendation	References
Prednisolone acetate 1%[*]	1x to hourly	Highly effective, high risk of glaucoma	IB	[42,46]
Dexamethasone phosphate 0.1%	1x to hourly	Highly effective; high risk of glaucoma	IB	[46,167]
Fluorometholone 0.1%	1x to 5x	Low effect	II0	[167]
Rimexolone 1%[**]	1x to 5x	Moderately effective	II0	[37,42]
Loteprednol etabonate 0.5%	1x to 5x	Moderately effective	II0	[138,148]
Systemic corticosteroid administration[#]				
	Dosage	Comment	Level of evidence and recommendation	References
Oral high-dose treatment	≥1–2 mg/kg BW/day prednisolone equivalent	Longer-term use (for several weeks) can be expected to result in significant adverse effects, depending on the cumulative dose	III0	[46]
Oral intermediate-dose treatment	>0.15 and < 1.0 mg/kg BW/day prednisolone equivalent	Longer-term use (for several weeks) can be expected to result in significant adverse effects, depending on the cumulative dose	III0	
Oral low-dose treatment	≤ 0.15 mg/kg BW/day prednisolone equivalent, max. 4–5 mg/day	Long-term adverse effects low; individually variable adverse effects, growth disorders possible	III0	
Bolus treatment	10–30 mg/kg BW/day methylprednisolone iv (max. 1 g/dose) for 3 days	Lower risk of long-term adverse effects than oral intermediate- or high-dose treatment	III0	[165]
Corticosteroids for orbital floor-, subtenon- or intravitreal injections.				
Drug	Dosage	Comment	Level of evidence and recommendation	References
Orbital floor or subtenon injections				
Dexamethasone phosphate	2–4 mg	Effective for 1–3 days; high risk of glaucoma	III0	[46,69]
Triamcinolone acetonide	20–40 mg	Effective for 1–2 months; high risk of glaucoma	III0	[121,122]
Intravitreal Injections				
Triamcinolone acetonide	2–4 mg	Effective for 1–2 months; high risk of glaucoma	II0	[5,121,125]
Dexamethasone acetonide implant[a]	700 μg	Effective for 2–4 months; high risk of glaucoma	II0	[58,112]

[#] Approved for this indication.
[*] Drops shall be applied when the child is awake, and ointment at night.
[**] Currently unavailable.
[a] Approved in adults

Systemic NSAIDs (Table 2) have also been reported to be less efficacious than high-potency topical corticosteroids [25,50,104]. In summary, NSAIDs can be considered only as adjuvant medication in children with low AC cell numbers (≤ 1 +).

Treatment of chronic uveitis

Key statement 5

Chronic uveitis shall be treated with topical corticosteroids at the lowest dosage depending on the individual course. If inactivity on a maintenance dosage of ≤ 2 drops daily is achieved within 3 months, systemic DMARD therapy shall not be introduced.

For chronic uveitis course, treatment with high-potency corticosteroid eye drops shall be initiated (Table 1, Fig. 1(A)). After 4–6 weeks, the patient can often be switched to lower-potency drugs (i.e., drugs causing fewer adverse effects) [37,42,46]; their lesser efficacy needs to be weighed against the more frequent administration and the problems associated with compliance.

In about 40% of all JIAU patients, chronic intraocular inflammation cannot be stabilized with topical corticosteroids alone, therefore requiring DMARDs [153]. Even with simultaneous DMARD therapy, commonly topical corticosteroids at low dosages are still required [16,21,53,55,68,152,154].

If high-dose treatment with eye drops is given for several months, the risk of adverse effects increases. Current knowledge is that administration of three or more doses of drug daily is associated with an increased risk of cataract and glaucoma [79,159]. Therefore, the dosage of corticosteroid eye drops should be kept as low as possible, and within 3 months of a flare, the number of daily doses should not exceed two. Occasionally, it may be sufficient to give the drops once daily on alternating days. Corticosteroid

Table 2
Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis.

Nonsteroidal anti-inflammatory drugs				
Drug	Daily dosage	Comment	Level of evidence and recommendation	References
Topical				
Indomethacin	2–3x	Low efficacy compared with corticosteroids	IIB	[127]
Diclofenac	2–3x	Low efficacy compared with corticosteroids	III0	[50]
Ketorolac trometamol	2–3x	Low efficacy compared with corticosteroids	III0	
Tolmetin	2–3x	Low efficacy compared with corticosteroids	II0	[32,170]
Bromfenac	2–3x	Moderate efficacy compared with corticosteroids	IIB	[167]
Systemic[##]				
Diclofenac	2–3 mg/kg BW divided into 3 doses; one single dose possible with delayed-release preparations	Long half-life time of new delayed-release preparations is beneficial; low efficacy compared with corticosteroids; approved from ≥ 14 years	III0	[104]
Ibuprofen	20–40 mg/kg BW divided into 3–4 doses	Availability in suspension is beneficial; low efficacy compared with corticosteroids; approved from ≥ 6 months	III0	
Indomethacin	1–3 mg/kg BW divided into 2–3 doses	Availability in suspension is beneficial; low efficacy compared with corticosteroids; approved from ≥ 2 years	III0	
Naproxen	10–15 mg/kg BW divided into 2 doses	Availability in suspension is beneficial; low efficacy compared with corticosteroids; approved from ≥ 1 year	III0	

[##] None of these drugs approved for uveitis. BW = body weight.

treatment should not be stopped abruptly in order to avoid a rebound effect.

In cases of aphakia or pseudophakia, it may be possible to administer higher dosages of topical corticosteroids (e.g., to decrease the number of giant cells on intraocular lenses). Lower-potency drugs may be beneficial in cases of steroid-induced ocular hypertension [37,46]. The course of the inflammation determines whether low-dose maintenance treatment is needed.

Treatment phase II

Key statement 6

If uveitis inactivity is not achieved by 12 weeks of topical corticosteroid treatment of ≤ 2 drops daily, or if the topical corticosteroids result in adverse effects, or if new, inflammation-related complications of uveitis occur, treatment with a csDMARD shall ensue. In very severe uveitis, the interval can be shortened accordingly. In very severe active uveitis with prognostic risk factors for impending uveitis-related deterioration of vision (e.g., hypotony, high Tyndall effect, massive anterior chamber inflammation, dense vitreous opacities, or macular edema) that potentially cause further worsening of vision in the short term, administration of systemic corticosteroids should be considered for bridging until DMARDs take effect.

A basic precondition for using DMARDs is the presence of uveitis activity with threatened or actual deterioration of vision, provided improvement or preservation of visual acuity is still feasible.

Short-term systemic administration of corticosteroids until csDMARDs take effect

Systemic corticosteroids alone are often less effective in reducing the AC cell count compared to topical therapy when used alone. For severe active uveitis with risk factors for impending uveitis-associated deterioration of vision (e.g., affecting the posterior eye segments) that can potentially lead to further deterioration in visual acuity, bridging with additional systemic corticosteroids for a short period until the anticipated onset of the csDMARDs effect should occur (Fig. 1(B), Table 1).

Systemic corticosteroids (Table 1) are generally given orally. A single intravenous methylprednisolone bolus therapy (for 3 days) can be considered in particularly severe cases [165]. Along with the numerous well-known complications of systemic corticosteroid treatment (e.g., increased IOP, cataract, weight gain, diabetic metabolism), in children the risk of growth retardation must be taken into account. Therefore, the oral dose should be tapered within 4 weeks to less than 0.15 mg/kg, and should be restricted to 3 months.

Treatment with conventional synthetic or biological disease-modifying anti-rheumatic drugs (DMARDs)

It has been shown that csDMARDs can clear uveitis and have a corticosteroid-sparing effect. These drugs are associated with a low rate of adverse effects if used properly and monitored [7,49,59,70,74]. The visual prognosis and the rate of complications in JIAU could be improved by using csDMARDs [103,109,153]. Low-dose maintenance treatment with corticosteroid drops (≤ 2 /day) often needs to be continued to ensure lasting inactivity [52,53].

Contraindications to the administration of csDMARDs or bDMARDs shall be ruled out first, compliance and monitoring for infections or malignancy [72,74] should be ensured. The vaccinations generally recommended for children should be completed before initiation of treatment. Having an up-to-date vaccination record is important before starting treatment. Whenever possible, vaccination should be completed 4 weeks prior to the first DMARD therapy.

Only a small number of randomized controlled trials or comparative studies of DMARD treatment in children with JIAU are available; most of the relevant publications are noncontrolled studies or case reports. Therefore, this guideline's recommendations regarding csDMARD treatment are based predominantly on consensus among the members of the guideline group.

Conventional synthetic DMARDs

Methotrexate

Methotrexate has been shown to be efficacious in treating JIA in randomized controlled studies [49]. The positive effect of methotrexate on JIAU has been reported in several case series and a few prospective studies [19,40,53,83,91,126,139,153,168] (Table 3). Although prospective controlled studies are lacking, methotrexate is currently the first-choice csDMARD for treating JIAU [9,14,57]. Methotrexate can be administered orally or, particularly for higher dosages, subcutaneously. The preferred dosage is 10–15 mg/m^2/week [9,14,40,53,57,123] (Table 3). Retrospective case series have shown that methotrexate can reduce the incidence of uveitis in JIA patients [75,107]. Methotrexate should be administered to children according to the existing recommendations [102].

Table 3
Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis.

Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)[##]				
Drug	Dosage	Comment	Level of evidence and recommendation	References
Methotrexate	10–15 mg/m^2/week	Orally or subcutaneously, currently preferred csDMARD	IIB	[19,40,49,53,75,83,91,123,126,139,153,168]
Cyclosporine A	≤5 mg/kg BW/day in two doses	Gel capsule or juice, cannot be recommended as monotherapy	III0	[38,47,73,76,132,150,166]
Azathioprine	2–3 mg/kg BW/day	Determination of thiopurine methyltransferase advisable to avoid severe hemato-toxicity	III0	[52,59]
Mycofenolate mofetil	1.200 mg/m^2/day in two doses, max. 2000 mg/day		III0	[7,20,31,88,146]
Sulfasalazine	500–2000 mg/day in two doses	In HLA-B27-positive patients	IIB for HLA-B27-positive patients	[8,50,61]
Cyclophosphamide, Chlorambucil		Cannot be recommended due to high rate of severe adverse effects	IIIB	[51,95,106]
Leflunomide	10–20 mg/day in one dose	Cannot be recommended	III0	[10]

[##] None of these drugs approved for this indication.

Other conventional synthetic DMARDs

Azathioprine has been used for the treatment of JIA [81,131], and occasionally achieved JIAU inactivity and spared corticosteroids [52,59] (Table 3). It can be recommended for treating JIAU only when bDMARDs (e.g., TNFalpha inhibitors) are contraindicated or ineffective or the patient does not tolerate other DMARDs.

According to previous publications [38,47,73,76,132,150,166] (Table 3), cyclosporine A is only mildly effective for JIAU, and thus should not be employed as primary csDMARD. Cyclosporine A combined with methotrexate can be used as a reserve drug if other treatment has failed or bDMARDs are not tolerated [150].

In a few individual case reports, uveitis improved under treatment with cyclophosphamide or chlorambucil [51,95,106] (Table 3). However, as some patients suffered extremely severe side effects (e.g., infertility, leukopenia), they should no longer be used to treat JIAU.

Although mycophenolate mofetil is well tolerated and is associated with only a low rate of adverse effects [7,20,31,88,146] (Table 3), its role in the treatment of JIAU remains unclear.

Sulfasalazine significantly reduced the number of attacks of HLA-B27-associated acute anterior uveitis in adults [8,50,101], and the observations in children with HLA-B27-positive anterior uveitis were in part similarly positive [61] (Table 3).

As retrospective data concluded that leflunomide is less effective than methotrexate for JIAU [10] (Table 3), it cannot be recommended for the treatment of JIAU.

Drugs should be chosen according to the current guidelines, the individual factors of the patient being treated, and at the discretion of the treating physician [70,102,103].

Treatment phase III

Biological DMARDs

Key statement 7

If uveitis inactivity is not achieved by 16 weeks of methotrexate monotherapy and ≤ 2 drops of topical corticosteroids daily, or if new, inflammation-related complications of uveitis occur, a TNFalpha antibody therapy shall be used in combination with methotrexate. In very severe uveitis, this escalated treatment can be administered at shorter intervals. In very severe active uveitis with prognostic risk factors for impending uveitis-related deterioration of vision (e.g., hypotony, high Tyndall effect, massive anterior chamber inflammation, dense vitreous opacities, or macular edema) that potentially cause further worsening of vision in the short term, administration of systemic corticosteroids should be considered for bridging until bDMARDs take effect.

If stable uveitis inactivity cannot be achieved, the anti-inflammatory treatment shall be intensified, and csDMARD previously given alone should be complemented by a monoclonal anti-TNFalpha antibody (Table 4, Fig. 1(C)). The addition of a second csDMARD does not improve uveitis control and is associated with significant adverse effects [88].

The use of methotrexate in combination with TNFalpha inhibitors reduces the risk of drug-neutralizing antibodies, and the dose of methotrexate can often be lowered when used in combination with anti-TNFs. The guideline group is of the opinion that monotherapy with TNFalpha inhibitors can be considered in patients who do not tolerate methotrexate.

If the efficacy of monoclonal anti-TNFalpha antibodies dwindles, the serum concentration of neutralizing antibodies should be determined [14]. At low serum drug levels with negative neutralizing antibodies, the dose should be increased. In the presence of high drug concentrations and detectable neutralizing antibodies, the drug should be changed [14].

The introduction of bDMARDs led to a fundamental improvement in the treatability of JIA and associated uveitis. The drugs that have already been used to treat JIAU are directed against cytokines or cytokine receptors (TNFalpha, IL-6 receptor), lymphocyte-costimulating molecules (CD80/CD86), and lymphocyte antigens (CD20).

TNFalpha inhibitors

Etanercept

Etanercept is a fusion protein, formed of a human Fc molecule and two p75 TNF receptors, that binds free TNFalpha. A prospective study in JIAU showed that the efficacy of etanercept was initially good but then often decreased [119], while another prospective study found no difference in efficacy between the etanercept and the placebo control group [144]. Several studies have reported the risk of a first manifestation [48,64,65,74,129,133,135] or recurrence [43,48,133] of uveitis in JIA patients during treatment with etanercept. In several studies etanercept was less effective than infliximab against JIAU [39,44,86,130,163]. In comparison with infliximab or adalimumab, etanercept was associated with a significantly higher risk of uveitis occurrence in JIA patients [87]. The first manifestation or reoccurrence of uveitis may be a reason for discontinuation of etanercept treatment [147] and should prompt a switch to adalimumab or infliximab. Etanercept should not be used for the treatment of patients with JIAU (Table 4).

Adalimumab

Adalimumab is a human antibody to TNFalpha. The published studies show good efficacy of adalimumab against JIAU, therefore, it

Table 4
Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Biological disease-modifying anti-rheumatic drugs (bDMARDs).

TNFalpha inhibitors Drug	Dosage	Comment	Level of evidence and recommendation	References
Adalimumab[#]	<30 kg BW 20 mg, ≥ 30 kg BW 40 mg; then week 1, and every 2 weeks; if required, double initial dosage	Subcutaneous injection; currently, preferred TNFalpha inhibitor	IIA	[4,9,11,14,15,16,30,41,45,74,78,82,84,85,86,90,100,117,134,141,142,143,157,160,162,164,171]
Infliximab	5–10 mg/kg BW every 2–8 weeks	Intravenous administration; second-choice TNFalpha inhibitor due to infusion reaction	IIB	[6,9,14,39,43,44,63,84,85,86,92,115,120,130,136,137,140,141,143,157,162,163,171]
Etanercept	0.4 mg/kg BW 2x/week or 0.8 mg/kg BW 1x/week, max. 50 mg/week	Subcutaneous injection; occasionally initial manifestation or worsening of uveitis, therefore not recommended	II0	[29,39,44,48,64,65,87,119,129,130,133,144,147,163]
Golimumab	50 mg at ≥ 40 kg BW, 30 mg/m^2 at < 40 kg BW, every 4 weeks	Subcutaneous injection; approved from 40 kg BW	III0	[22,24,97,98,169]
Other biological DMARDs[a] Drug	Dosage	Comment	Level of evidence and recommendation	References
Tocilizumab (Anti IL-6)	8 mg/kg from 30 kg BW; 10 mg/kg < 30 kg BW every 4 weeks	Intravenous [b] administration	IIIB	[1,17,94,114,128,152,156,161]
Abatacept (Inhibition of lymphocyte co-stimulation (CTLA)–4)	10 mg/kg BW at 0, 2, 4 weeks, then every 4 weeks	Intravenous administration; occasional infusion reactions	III0	[2,13,35,71,93,154,172]
Rituximab (Anti-CD20)	375 mg/m^2 (max. 1 g) at weeks 0, 2	Intravenous administration	IIIB	[55,96,99]

[#] Approved for this indication since September 2017.
[a] None of these drugs is approved for this indication.
[b] announced, subcutaneous.

is preferred for use in these patients [4,9,41,116]. A meta-analysis of publications from the period 2000 to 2012 compared the efficacy of various TNFalpha inhibitors against chronic uveitis in childhood; inactivity was achieved more frequently with infliximab and adalimumab than with etanercept [143].

Numerous prospective (one randomized, the others nonrandomized) and retrospective studies describe the attainment of uveitis inactivity in ≥ 75% of JIA patients after 4–12 weeks' treatment with adalimumab [11,15,16,30,39,43,45,82,84,90,100,116,117,155,164]. The treatment success is greater when adalimumab is used as first biologic [45,134,142,162] and when it is given early in the course of the disease [90,162]. Adalimumab has the potential to improve the further course of uveitis and prevent relapses [133,134,160].

Adalimumab can spare corticosteroids and csDMARDs [28,45,142]. Regression of macular edema has repeatedly been observed [28,30,45]. Adalimumab can help to reduce both the rate of complications of uveitis and the rate of subsequent ocular surgery [155]. The effect of adalimumab on achieving inactivity and decreasing the complication rate was greater than that of infliximab [141,143,171].

Several studies have demonstrated a long-term effect of adalimumab against JIAU over a period of years [15,171]. During long-term therapy the risk of secondary treatment failure was 20–60% after 2–4 years [15,16,30,78,141]. Treatment failure or the occurrence of adverse drug reactions [16,30,84,117,143] may then necessitate switching to another drug. DMARD treatment can significantly reduce the incidence of uveitis in patients with JIA [155]. In this regard, treatment with adalimumab has been found to be more effective than methotrexate monotherapy [41,153].

In summary, adalimumab shall be considered for use in patients with JIAU who have not responded to treatment with methotrexate (Table 4, Fig. 1(C)), which is in accordance with the recent CARRA consensus treatment plans for anterior uveitis [3].

Infliximab

Infliximab is a chimeric monoclonal antibody that binds to both circulating and membrane-bound TNF molecules. Combination with methotrexate reduces the risk of the development of antichimeric antibodies and subsequent loss of efficacy. Infliximab is not approved for the treatment of JIA.

A number of retrospective studies have described good efficacy of infliximab in JIAU [39,44,130]. Inactivity can be attained in 43–94% of cases [6,39,43,137,141,163], in as little as 2–3 months [43,63,130] or as long as 12 months [44]. When using infliximab, the dosages of topical corticosteroids [39,44,63,115,137] and systemic csDMARDs [120] can often be reduced. An enduring good effect on JIAU can be achieved with infliximab [92,115], but secondary loss of effect may occur [140,141]. High-dose infliximab treatment has shown rapid efficacy and good tolerability in the treatment of patients with uveitis refractory to corticosteroids and csDMARDs [6,63]. The rate of adverse drug reactions was no greater with high dosages of infliximab (10–20 mg/kg) than with standard dosages [149].

In summary, infliximab (preferably 6 mg/kg as a starting dose) should be considered in patients with JIAU that has proved refractory to csDMARDs combined with another monoclonal TNFalpha antibody and in cases of questionable compliance (Table 4, Fig. 1(C)).

Golimumab

Golimumab is a human antibody to TNFalpha and is approved for the treatment of polyarticular JIA in children weighing ≥ 40 kg. Case reports [22,169] and retrospective case series have shown a positive effect of golimumab in patients with JIAU refractory to treatment with csDMARDs and TNFalpha inhibitors. With golimumab treatment, disease inactivity, visual improvement, and amelioration of macular edema [24], steroid sparing [97], and a long lasting effect were achieved [98]. Therefore, golimumab may represent an effective treatment option in JIAU patients whose disease has not responded

to combined administration of a csDMARD and another TNFalpha inhibitor (Table 4, Fig. 1(C)).

Overall assessment of the use of TNFalpha inhibitors

Treatment with monoclonal TNFalpha antibodies can have a good and lasting effect in many children and adolescents with JIAU. Adalimumab is effective against polyarticular JIA and is approved for this indication in children from the age of 2 years upwards. It is also indicated for the treatment of children with enthesitis-related arthritis from the age of 6 years. Adalimumab is currently the preferred TNFalpha inhibitor in this phase of the treatment of JIAU owing to the good response rate, tolerability, and the published randomized controlled therapy trials (Table 4, Fig. 1(C)). Most recently, adalimumab has received approval for the treatment of chronic non-infectious anterior uveitis in children aged ≥ 2 years who have had inadequate response to or are intolerant to conventional therapy. However, discontinuation of treatment may be followed by recurrence of uveitis in a high proportion of patients [85,136]. Adalimumab reduces the risk of uveitis and should be the preferred drug considered for use in JIA children with a high risk of uveitis in whom treatment with a biologic is indicated. In the event of treatment failure and loss of adalimumab efficacy, a switch to golimumab or infliximab should be considered.

Treatment phase IV

Key statement 8

If treatment with TNFalpha antibodies fails to take effect or loses effect, another biological should be selected.

Other biological DMARDs

If treatment with TNFalpha antibodies fails to take effect or loses effect, another biological should be selected. Here, tocilizumab is preferred by the guideline group, and abatacept, rituximab, or another TNFalpha inhibitor are other treatment options (Fig. 1(D)).

Interleukin-6 blockers

Tocilizumab is a humanized monoclonal antibody to the interleukin-6 receptor (IL-6R). Case reports and retrospective case series have described efficacy of anti-IL-6R treatment with tocilizumab in patients with JIAU [17,152,156,161] in whom no uveitis inactivity could be achieved with a csDMARD (mostly methotrexate) combined with one or more TNFalpha inhibitors. In retrospective studies tocilizumab achieved amelioration of the uveitis and sparing of corticosteroids [17,156]. According to previous observations, improvement of uveitic macular edema can be attained with tocilizumab [1,17,94,114,156] (Table 4).

Inhibition of lymphocyte costimulation

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) prevents costimulation of T lymphocytes by preventing the binding of CD28 to CD80/CD86. Abatacept is a recombinant fusion protein formed of the Fc component of an IgG1 immunoglobulin and the extracellular portion of CTLA-4.

Several case reports indicate a positive effect of abatacept on uveitis refractory to treatment with various csDMARDs and bDMARDs [2,35,71,93]. While in one study amelioration of uveitis was described in $>80\%$ of patients given abatacept [172], it was mostly ineffective or had only a short-term effect [154], or was only moderately effective [13] in other studies. In summary, the data on the efficacy of abatacept for the treatment of JIAU are inconsistent (Table 4).

Anti-CD20 treatment

Histopathological and immunohistochemical studies have demonstrated dominance of B-cells and plasma cells in the nongranulomatous inflammatory infiltrate found in the iris of patients with JIAU [67,108], suggesting that B-cell blockade might represent a promising treatment option. Rituximab is a chimeric mouse–human monoclonal antibody that is directed against the CD20 surface molecule of B-cells and can induce apoptosis.

Inactivity was achieved in seven of 11 patients treated with rituximab in a case series [55] and in 7 of 8 patients in another study [96]. A study with a longer follow-up period indicates good long-term efficacy of rituximab in JIAU [99] (Table 4). Because rituximab has not been approved for the therapy of JIA, however, it should currently be used secondarily.

Duration of treatment with methotrexate and biologicals

Key statement 9

De-escalation of treatment with DMARDs should be preceded by period of at least 2 years of uveitis inactivity.

In the event of long lasting uveitis inactivity under treatment with methotrexate, discontinuation of therapy can be considered. Retrospective data show that uveitis flares up again in a large proportion of patients (69%) after methotrexate is stopped (46% ≤ 12 months) [66]. According to this study, long-term treatment (≥ 3 years) and a long period of disease inactivity before discontinuation of methotrexate (≥ 2 years), all at the age of ≥ 8 years at the time of withdrawal, may reduce the risk of recurrence after treatment is stopped. There are currently no published data to show whether gradual dose reduction should be preferred to abrupt discontinuation.

Retrospective studies have documented frequent recurrence of uveitis (50–65%) even after conclusion of treatment with TNFalpha inhibitors [85,136] in patients with lasting inactivity of both arthritis and uveitis. In the opinion of the guideline group, de-escalation of DMARDs should be considered in patients whose eyes are stable and show no sign of active disease. De-escalation should be preceded by an activity-free period of at least 2 years. Because recurrence cannot be ruled out, the patients should be examined by an ophthalmologist at regular intervals during the de-escalation period.

Better long-term prognosis with earlier initiation of immunomodulating treatment

Prospective studies have demonstrated that early immunomodulating therapy can improve the long-term outcome of JIAU, and that initiation of csDMARD treatment soon after the onset of arthritis may even prevent the occurrence of uveitis. Commencement of methotrexate therapy within 1 year of the onset of JIA was associated with a low risk of uveitis [153,155], and reduced the risk of uveitis flaring up again after a 1-year remission [124]. Early use of methotrexate can therefore be considered in JIA patients judged to be at high risk of uveitis.

Intra- and periocular corticosteroid injections

Key statement 10

In unilateral or bilateral severe active uveitis with prognostic risk factors for impending uveitis-related deterioration of vision (e.g., hypotony, macular edema, or dense vitreous opacities), ocular injection of corticosteroids can be considered as rescue therapy in individual cases after exhaustion of all other treatment options.

If severe uveitis with dense vitreous infiltration, hypotony, or macular edema is insufficiently controlled by topical corticosteroids, adjuvant subconjunctival, orbital floor or intraocular injections of triamcinolone or dexamethasone can be considered (Table 1). Dexamethasone injections have a rapid effect of short duration. The principal advantage of injections over oral administration is a lower rate of systemic adverse effects. If a high intraocular concentration of the active agent over a period of weeks is required, intraocular injections of triamcinolone acetonide [5,121,122,125] or surgical intravitreal placement of a sustained release dexamethasone implant can be considered [23,89,111,112] (Table 1). However, they may be

associated with greater cataract development and a higher rate of increased IOP possibly leading to glaucoma, and in many youngsters a short anesthesia is required.

The guideline group believes that intravitreal dexamethasone or triamcinolone injection is appropriate only as rescue therapy in selected JIAU cases of particularly severe disease with impending deterioration of visual acuity, and in patients in whom inactivity cannot be achieved with topical and systemic corticosteroids, csDMARDs and bDMARDs.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.semarthrit.2018.11.004.

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