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REVIEW ARTICLE

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

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Abstract Uveitis in juvenile idiopathic arthritis (JIA) is frequently associated with the development of complications and visual loss. Topical corticosteroids are the first-choice therapy, and immunosuppression is commonly used. However, treatment has not been standardized. Representatives from the German Ophthalmological Society, Society for Childhood and Adolescent Rheumatology, and the German Society for Rheumatology reached consensus on a standardized treatment strategy according to disease severity in the individual patient. The recommendations were based on a systematic literature analysis in MEDLINE and consensus expert meetings. Evidence and recommendations were graded, and an algorithm for anti-inflammatory treatment and final statements confirmed in a Delphi method. An interdisciplinary, evidence-based treatment guideline for JIA uveitis is presented.

Guidelines of the German Ophthalmological Society (DOG) and the Society for Childhood and Adolescent Rheumatology (GKJR) in collaboration with the following professional societies: Working group of the Scientific Medical Specialty Societies (AWMF), Professional Association of Ophthalmologists (BVA), German Society for Rheumatology (DGRh), Parents' Association for Children with Uveitis and Their Families.

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Preliminary comments

Uveitis in childhood can develop in conjunction with various inflammatory rheumatic diseases, and in particular with juvenile idiopathic arthritis (JIA). Indeed, chronic forms of these diseases are frequently associated with visual deterioration. In previous patient cohorts, the rate of blindness was high (up to 30%); however, this can be significantly reduced if screening is adequate and all currently available forms of treatment are exhausted [1, 2]. Nonetheless, compared to forms of uveitis that develop in adulthood, the risk of irreparable damage and the associated reduction in quality of life is still very high for children with JIA-associated uveitis. Thus, it is particularly important that these patients receive adequate treatment early on before permanent damage has developed.

Currently available studies of uveitis in patients with childhood arthritis have established certain clinical and laboratory parameters as prognostic factors. Long-term complications and a poor visual course were found particularly frequently if vision was poor at first presentation (<20/60), inflammatory activity was high at first diagnosis of uveitis, cataracts had formed, uveitis onset before arthritis had developed, interval between the onset of arthritis and uveitis was short (<6 months), early onset of disease, long duration of uveitis, macular edema, dense vitreous opacity, ocular hypotony, and glaucoma [1, 3–18].

The presence of complications at initial diagnosis represents an important prognostic criterion for further complications to develop [19], and a long period of chronic inflammation seems to be particularly critical. Even a low number of cells in the anterior chamber (>0.5+) is then associated with an increased risk of loss in visual acuity [16].

According to these studies, early diagnosis is highly important for long-term prognosis (evidence and recommendation level IIIA). Therefore, close screening should be commenced directly after arthritis has appeared. The screening intervals recommended to date in these studies are oriented on the incidence of uveitis for the various arthritis subtypes, presence of antinuclear antibodies (ANA), duration of arthritis, and the typical signs of uveitis (symptoms, red and painful versus no symptoms on the external white of the eye [19, 20]. Although no controlled studies have been conducted, the findings published prior to the screening era and before immunosuppressive drugs were used suggest that for a severe course of disease, the long-term prognosis can be improved by appropriate screening and the use of these substances.

Aims/goals

The treatment of uveitis in patients with JIA has not been standardized; therefore, the aim of the present guideline is

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to develop a standardized, state-of-the-art, and qualitatively high treatment strategy according to disease severity in the individual patient that is based on the current literature and expert consensus. To that end, we defined the following goals: improve patient care, implement the current status of evidence-based medicine on the subject of uveitis, establish reasonable diagnostic and screening intervals, and develop a treatment algorithm that includes a flow diagram and facilitates patient care in interdisciplinary networks.

Methods

These guidelines were based on the consensus statements for the treatment of JIA-associated uveitis from 2004 [21] and for "rheumatic uveitis" from 2007 [22] and the treatment of JIA [23]. Representatives from the specialty societies DOG, GKJR, and DGRh and from patient groups joined forces to develop these guidelines. The methodological concept followed the German Instrument for Methodological Guideline Appraisal (DELBI [24, 25]).

The guidelines coordinators (AH, TN, and CS) conducted a systematic search of the literature on the subject of "anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis".

German and English were taken as publication languages. For the MEDLINE search, we employed the terms "juvenile idiopathic arthritis" (including the ACR und EULAR classifications) und "uveitis and therapy". During the last years, numerous classifications for rheumatic diseases of childhood were employed; therefore, we included the International League of Associations for Rheumatology [26] classification, American College of Rheumatology [27], and European League Against Rheumatism [28, 29] classifications and extended the search terms to incorporate juvenile rheumatoid arthritis (ACR) and juvenile chronic arthritis (EULAR). Furthermore, the term iridocyclitis, which was frequently used before the current standardization of uveitis nomenclature [30] of anterior uveitis was implemented, was added to the search terms. Owing to the insufficient body of evidence on the subject, we considered publications from the past 15 years.

On the reference date 15 November 2009, 305 publications were found (Table 1). Restricting the search to "humans" reduced the number of publications to 198. The results were assessed for plausibility and completeness.

The primary literature was then graded concerning evidence and recommendations (Tables 2, 3). For the various treatment measures, evidence tables were created (Tables 4, 5, 6, 7). Using an algorithm of frequently used courses of therapy as orientation, we developed key recommendations with graded levels of evidence and recommendation and drafted corresponding texts and guideline synopses for clinical questions that had been adequately addressed. These were distributed to all conference participants beforehand.

The 1-day consensus conference took place on 5 February 2010 in Muenster, Germany, headed by Prof. I. Kopp (AWMF) and Prof. A. Heiligenhaus with a 92% participation. After thorough discussion during the conference, the key statements were reworked and a consensus formulated. By subsequently employing a Delphi procedure,

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

Key words	Publications (*N*)
Juvenile idiopathic (rheumatoid and chronic) arthritis and uveitis (iridocyclitis) and therapy	305
Limits: humans, published in the last 15 years	198
Limits: corticosteroids	32
Limits: nonsteroidal anti-inflammatory drugs	21
Limits: cyclophospamide	3
Limits: chlorambucil	3
Limits: methotrexate	41
Limits: cyclosporine	14
Limits: azathioprine	7
Limits: TNF-alpha inhibitors	33

PUBMED literature search (www.ncbi.nlm.nih.gov). "Manually" excluded: diagnostic studies, juvenile idiopathic arthritis, surgery, extraocular manifestations, and intermediate and posterior uveitis

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

Level	Evidence
I	>1 randomized, controlled study (RCT) of good quality
II	Single RCT, >1 controlled, but nonrandomized study or >1 RCT of poorer quality
	Cohort or case–control study preferred from more than one research group or from more than one center
	Observations showing a very clear effect in noncontrolled studies
III	Expert opinion, clinical experience, or descriptive studies, cohort- or case–control studies of poorer quality

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

Level	Recommendation
A	Strong recommendation
B	Recommendation
0	Open

Table 4 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (nonsteroidal antiphlogistics)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Topical			IB	
Indomethacin	2–3×	Low efficacy compared to corticosteroids		[38–40]
Diclofenac	2–3×	Low efficacy compared to corticosteroids		[41]
Ketorolac trometamole	2–3×	Low efficacy compared to corticosteroids		
Tolmetine				[34, 39]
Systemic[#]			III0	
Diclofenac	2–3 mg/kg body weight/day in 3 doses; 1 single dose possible	The long half-life of the retard drugs is beneficial. Low efficacy compared to corticosteroids		[40]
Ibuprofen	20–40 mg/kg body weight/day in 3–4 doses	Availability as suspension is beneficial. Low efficacy compared to corticosteroids		
Indomethacin	1–3 mg/kg body weight/day in 2–3 doses	Availability as suspension is beneficial. Low efficacy compared to corticosteroids		
Naproxen	10–15 mg/kg body weight/day in 2 doses	Low efficacy compared to corticosteroids		

[#] none of these drugs approved for this indication

the free text for the guidelines and the algorithms were discussed again and formally approved by a vote.

All individuals who were involved in developing the guidelines declared that they had no financial or other conflicts of interest that would systematically affect the content of the guidelines. The process for developing the guidelines was financially supported by DOG and GKJR.

Anti-inflammatory therapy

Treatment of patients with uveitis and inflammatory rheumatic diseases is not curative; these individuals can only receive symptomatic treatment to suppress the inflammation. Therefore, attempts to "eradicate the disease focus" such as by extracting teeth are superfluous unless the teeth actually require treatment because of specific findings (IIIA). The objectives of treatment are to manage acute episodes or complications, treat the systemic underlying disease, give prophylaxis for recurrence and complications, avoid undesirable drug effects, and preserve vision.

Basic treatment principles

Uveitis is treated with respect to inflammatory activity, complications, and risk factors for losing visual acuity. For medical treatment, the underlying inflammatory rheumatic disease must also be taken into consideration. ANA-positive patients with chronic anterior uveitis who have not previously shown any clinical signs of an inflammatory rheumatic disease should be treated like patients with JIA-associated uveitis as the two conditions are highly comparable (consensus group, evidence and recommendation level III0).

It is recommended that treatment comprises three phases (see Fig. 1). This is based on the evidence for or against a treatment according to the literature (Tables 2, 3) and on consensus from the guidelines group concerning preferred clinical treatment strategies. Information about the preferred therapy is presented. Key statements are listed in Table 8.

Diagnosis and treatment should best be jointly planned and monitored by the ophthalmologist and pediatrician (pediatric rheumatologist). The ophthalmologist is responsible for giving local treatment, recommending further systemic anti-inflammatory treatment of uveitis, and treating possible complications.

Patients with chronically active and severe uveitis should be referred to physicians who are competent in treating JIA-associated uveitis (in particular at uveitis centers with core expertise). If systemic immunosuppression is required, this should be given and monitored by an experienced pediatric rheumatologist upon the advice of an ophthamology specialist. For JIA therapy, we refer to the corresponding interdisciplinary S2 guidelines [23].

Managing a relapse of uveitis

Clearing uveitis with and without corticosteroid treatment

A prospective, randomized, double-blind study showed that a relapse of uveitis clears better by using local corticosteroids than placebo [31]. Thus, active uveitis should be

Table 5 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (Corticosteroids)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Topical[#]			IA	
Prednisolone acetate 1%	1 × up to hourly	High efficacy, high risk of glaucoma		[39, 46]
Dexamethasone phosphate 0.1%	1 × up to hourly	High efficacy; high risk of glaucoma		
Rimexolone 1%	1 × up to 5×	Moderately effective		[45, 46]
Subconjunctival or orbital floor injections			IIIA	
Dexamethasone phosphate	2–4 mg	Effective 1–3 days		
Triamcinolone acetonide	20–40 mg	Effective 1–2 months		
Intravitreal injections			IIIO	
Triamcinolone acetonide	2–4 mg	Effective 1–2 months		[101–104]
Systemic[#]			IIIA	[35]
Oral high-dose therapy	≥1–2 mg/kg body weight/day prednisolone equivalent	For a treatment duration of several weeks, relevant side effects can always be expected with respect to the cumulative drug dose		
Oral medium-dose therapy	0.2 and <1.0 mg/kg body weight/day prednisolone equivalent	For a treatment duration of several weeks, relevant side effects can always be expected with respect to the cumulative drug dose		
Oral low-dose therapy	≤0.15 mg/kg body weight/day prednisolone equivalent	Long-term side effects low; individually different side effects, growth retardation rare		
Intravenous pulse therapy	Normally 20–30 mg/body weight intravenous methylprednisolone (max. 1 g/dose) for 1–3 days	At intervals of ≥4 weeks lower long-term risk of side effects than for oral medium-or high-dose therapy; possibly indicated for ocular hypotony, vitreous body opacity and macular edema		[43]

[#] approved treatment for this indication

treated accordingly (IA) and commenced as early as possible.

The relevant criteria for assessing the efficacy of anti-inflammatory treatment are presently the subject of controversial debate. According to the recommendations of the Multinational Interdisciplinary Working Group for Uveitis in Childhood (MIWGUC), it is important—in addition to determining cells in the anterior chamber—to assess structural complications in the eye.

Indications for anti-inflammatory treatment

The goal of treating typical JIA-associated anterior uveitis should be "no cells in the anterior chamber." Treatment should be initiated when >0.5+ cells are present [16, 30].

Fibrin formation in the anterior chamber and keratocytic precipitates with corneal edema and loss of visual acuity also require treatment. The question of whether the presence of only endothelial precipitates or a positive Tyndall effect is important for therapeutic decision making is presently being controversially debated. Alone, however, they do not represent a clear indication for treatment. Increased flare values indicate a disorder in the blood-aqueous fluid barrier and correlate with presence of complications and a poor visual outcome [32].

Should prognostic factors for threatening loss of vision be confirmed, anti-inflammatory treatment should be intensified. According to comprehensive studies, these factors include poor initial vision, ocular hypotony, glaucoma, cataract, macular edema, and dense vitreous body opacification (>2+) [1–18, 33] (consensus group, IIIB).

Evidence of band keratopathy, synechiae, cataract, or glaucoma in inactive uveitis does not per se comprise an indication for anti-inflammatory therapy (consensus group, IIIA). Associated with persisting inflammation, however, these symptoms indicate severe disease and immunosuppression is recommended (consensus group, IIIA).

In contrast, macular edema, ocular hypotony, and rubeosis iridis require that anti-inflammatory treatment be initiated or intensified even if no cells are detected in the anterior chamber as these conditions are often associated with chronic inflammation of the affected tissue (consensus group, IIIA).

Table 6 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (immunosuppressive drugs)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Methotrexate	10–15 mg/m^2 week	Oral or subcutaneous administration	IIIA	[48, 52–59]
Cyclosporine A	≤3 mg/kg body weight/day in 2 doses	Gel capsules or syrup	III0 for monotherapy	[67, 69]
			IIIB for combination therapy	[65, 66, 68, 71]
Azathioprine	2–3 mg/kg body weight/day	Thiopurine methyltransferase levels should be determined to prevent severe hematotoxicity	IIIB	[62–64]
Mycofenolate mofetil	500–2,000 mg/day in 2 doses		III0	[78–80]
Sulfasalazine	500–2,000 mg/day in 2 doses		II0 for HLA-B27-positive patients	[81–83]
Chlorambucil	1–1.5 mg/kg body weight/day	High rate of adverse effects, thus not recommended	IIIA	[76, 77]

none of these drugs approved for this indication

Table 7 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (TNF-alpha inhibitors)

Drug	Dosage	Comment	Level of evidence and recommendation	Reference
Adalimumab	24 mg/m^2 at 4–13 years or ≥ 14 years 40 mg every 2 weeks	Subcutaneous injection; currently, preferred TNF-alpha inhibitor	IIIA	[74, 93, 105]
Infliximab	5–10 mg/kg body weight every 2–8 weeks	Intravenous administration; intensive care required because of possible reaction to the infusion. Currently, second-choice TNF-alpha inhibitor	IIA	[85–91, 95, 96, 105]
Etanercept	0.4 mg/kg body weight 2×/week or 0.8 mg/kg 1×/week	Subcutaneous injections; occasionally associated with first presentation or worsening of uveitis; thus, only limited recommendation	I0	[85, 90, 97, 99, 100]

none of these drugs approved for this indication

Algorithm for anti-inflammatory treatment

Treatment step 1

Topical corticosteroids High-potency glucocorticoids are more efficacious than low-potency preparations [31–35]; therefore, the high-potency drugs, such as prednisolone acetate 1% or dexamethasone 0.1%, should be used and not the low-potency alternatives, such as rimoxolone (consensus group IIIA). To prevent amblyopia (children under the age of 7 are at high risk), drops should be instilled when the children are awake and ointment applied for the night (consensus group IIIA).

In the first 3 days of a relapse, the drops should be applied frequently during the waking hours. How often the drops are instilled should be adapted to the severity of the inflammation (anterior chamber cells, fibrin, new synechiae), every 2 h or even hourly. The dosage should then be reduced within 6 weeks, according to the degree of inflammation (consensus group IIIA).

Even children who are being treated with topical corticosteroids need to be monitored for possible systemic adverse effects (e.g., Cushing syndrome). This risk increases with bilateral and high dosages (e.g., hourly) of high-potency corticosteroids (e.g., prednisolone 1%), particularly in young children (under 4 years) [36, 37].

Nonsteroidal antiphlogistics Topical nonsteroidal antiphlogistics play only a minor role in treating uveitis. Two

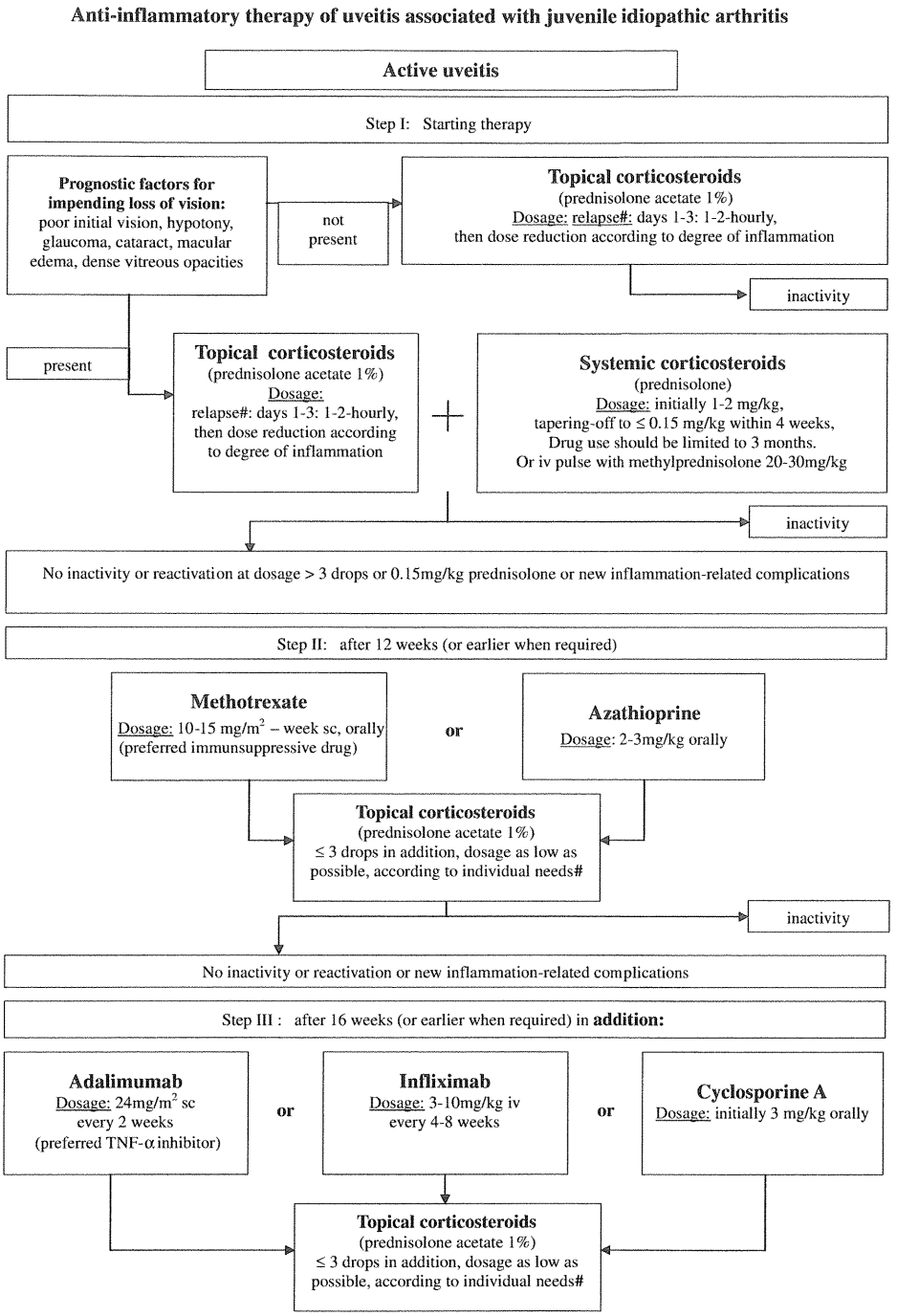

Fig. 1 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis. Algorithm for anti-inflammatory treatment

randomized, controlled studies showed that *topical* treatment using nonsteroidal antiphlogistics was effective, but not as good as topical corticosteroids for treating mild, acute uveitis [34, 38, 39] (IB). Therefore, treating uveitis attacks with nonsteroidal antiphlogistics alone is not recommended (IB). *Systemic* nonsteroidal antiphlogistics were also reported to be less efficacious than high-potency topical corticosteroids [8, 40, 41] (III0). All these studies were conducted in adults and not in children with JIA uveitis. In summary, nonsteroidal antiphlogistics could only be recommended as adjuvant medication in cases of low numbers of cells (≤1+) in the anterior chamber.

Table 8 Evidence-based, interdisciplinary guidelines for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis (Key statements)

1.	Active uveitis must be treated (IA)
2.	Topical corticosteroids should be used initially to treat active anterior uveitis (IA)
3.	Topical and systemic nonsteroidal antiphlogistics should not be used alone to treat active anterior uveitis (IB)
4.	For severe, active uveitis presenting with prognostic factors indicating uveitis-related, impending loss of vision (poor vision at initial presentation, hypotony, glaucoma, cataract, macular edema, or dense vitreous body opacification), systemic corticosteroids should be considered for a limited period of a few weeks in addition to topical therapy (IIIA)
5.	For chronic anterior uveitis, the dosage of topical corticosteroids should be as low as possible, according to the needs of the individual patient. If inactivity is achieved by maintenance therapy ≤3 drops daily within 3 months, systemic immunosuppressive treatment is not required (lIIIA)
6.	Systemic immunosuppression should be initiated if inactivity cannot be achieved under topical corticosteroids ≤3 drops and/or within 3 months while under systemic maintenance corticosteroid therapy (0.15 mg kg/body weight/day prednisolone equivalent) or if undesired adverse effects of the corticosteroids or new inflammation-related complications of uveitis develop. For a very severe course of uveitis, a correspondingly shorter interval can be chosen (IIIA)
7.	If inactivity cannot be achieved in the eyes after a maximum of 16 weeks of treatment with one immunosuppressive drug and topical corticosteroid therapy ≤3 drops daily or if new inflammation-related complications of uveitis develop, another immunosuppressive drug (e.g., cyclosporin A) or a biological (e.g., adalimumab) should be added to the regimen. For a very severe course of uveitis, a correspondingly shorter interval can be chosen (IIA)
8.	If immunosuppressive drugs are administered, the physician should have experience in administering and monitoring treatment with the respective drug (IIIA)
9.	For severe uni- or bilaterally active uveitis associated with prognostic factors indicating uveitis-related, impending loss of vision (hypotony, macular edema, or dense vitreous body opacification), corticosteroid injections to the eye can be considered as "rescue therapy" (III0)
10.	To prevent or treat posterior synechiae associated with active anterior uveitis, cycloplegics should be administered (IIIA)

Systemic corticosteroids Oral administration of corticosteroids is generally less effective in reducing the number of anterior chamber cells than frequently instilling eye drops ([8,42], consensus group) (see Table 8). Oral treatment with corticosteroids such as prednisolone is normally initially administered at a dose of 1–2 mg/kg body weight (consensus group, IIIA). Alternatively, high-dose intravenous administration of methylprednisolone (dosage 20–30 mg/kg for 3 days) can be considered [35, 43] (IIIA).

When children receive systemic corticosteroid treatment, not only do the numerous known complications need to be taken into consideration (e.g., increase in intraocular pressure, cataracts, weight increase, and diabetic metabolism situation) but also growth retardation. Therefore, the dose should be tapered to under 0.15 mg/kg body weight within 4 weeks and drug use be limited to 3 months. The development of intraocular pressure is dose dependent under systemic corticosteroid treatment, and secondary development of cataract is subject to individual propensity for this condition [17, 35, 44].

Treatment of chronic or chronic, recurring uveitis

For chronic or chronic, recurring uveitis, treatment with higher-potency corticosteroid eye drops should be initiated (e.g., prednisolone acetate 1%; IA). After 4–6 weeks, the patient can be switched to less effective drugs (hence, drugs causing fewer adverse effects: e.g., rimexolone) [35, 45, 46] (IA). In individual cases, the lesser efficacy of the anti-inflammatory preparations needs to be weighed against the problems associated with more frequent application and compliance.

In many children, chronic irritation can often be stabilized with topical corticosteroids alone. Frequently, however, long-term treatment over several years is required [3, 42] (consensus group IIIA).

If high-dose treatment with eye drops is given for several months, the risk of typical adverse effects increases. The individual propensity for this, however, varies highly. Currently, it is presumed that three doses of drug (e.g., prednisolone acetate 1% or dexamethasone 0.1%) daily over several months per year are associated with an increased risk of cataract and glaucoma [47]. Therefore, we should strive to give the lowest possible dose. During periods with inactivity, it may be sufficient to give the drops once daily on alternating days. Corticosteroid treatment should not be ended abruptly in order to avoid a rebound effect.

In cases of aphakia or pseudophakia, it may be possible, or even necessary, to give more generous dosages of topical corticosteroids (e.g., to decrease the number of giant cells on the intraocular lens) as long as the intraocular pressure does not increase.

Rimexolone may be effective in cases of steroid-induced ocular hypertension, but compared to prednisolone acetate 1% and dexamethasone 0.1%, it shows a lower anti-inflammatory effect [35, 45] (IA).

The course of the inflammation decides whether low-dose maintenance treatment is needed. The dosage and choice of corticosteroid should be based on the individual circumstances. If inactivity can be achieved, further steps are not required for the time being.

Treatment step II

If the inflammation in the eyes has not resolved within 12 weeks (even sooner after clinical judgement) under treatment with topical corticosteroids maximally 3 times daily or in cases of recurring uveitis under a systemic corticosteroid dosage of more than 0.15 mg/kg body weight or if new uveitis complications develop, the anti-inflammatory treatment needs to be intensified and immunosuppressives and/or biologicals added to the regimen.

Treatment with immunosuppressives and biologicals If uveitis persists after all the aforementioned drugs have been tried or if uveitis recurs under a high dose of corticosteroids and severe, undesired adverse effects of the drug develop, treatment with immunosuppressives should be initiated. According to current knowledge, biologicals should not be given before trying the classic immunosuppressives.

It has been repeatedly shown that immunosuppressives can clear uveitis and have a corticosteroid-sparing effect. Despite frequently expressed reservations, these drugs are associated with a low rate of adverse effects if used adequately and monitored [48–50]. By using immunosuppressive treatment, visual prognosis and rate of complications could be improved in JIA-associated uveitis [13, 51]. Although corticosteroids can be spared under immunosuppression, low-dose maintenance treatment with corticosteroid drops ($\leq$3/day) often needs to be continued. Whether treating JIA with immunosuppression early on prevents uveitis from developing later is the subject of controversial debate.

A basic precondition for applying immunosuppressive drugs or biologicals to treat persisting uveitis activity is the threat of loss of vision or further deterioration, presuming that it is still possible to improve or save vision.

Malignant conditions or other underlying diseases that may contraindicate immunosuppression must be excluded and compliance and monitoring of the medication ensured. The treatment plan should be worked out together with the patients and their parents. Information sheets for the individual immunosuppressive drugs are available via internet (http://gkjr.de/aufklaerungsboegen.html).

No randomized, controlled, or comparative studies are available yet for using immunosuppression to treat children with JIA-associated uveitis, only observational reports and case studies exist. Hence, the recommendations for immunosuppressive treatment in the present guidelines stem mainly from a consensus reached in our guidelines group.

Methotrexate Methotrexate has been shown to be efficacious in treating JIA in prospective, randomized studies [48]. The positive effect of methotrexate on JIA-associated uveitis has been reported in numerous case series [52–59].

Although prospective, controlled studies are lacking, methotrexate is currently the first-choice immunosuppressive drug for treating JIA-associated uveitis. A low rate of adverse effects has been reported for methotrexate [48]. Up to a third of patients did develop gastrointestinal problems and an aversion to the drug, however. It can be administered orally once per week or subcutaneously, in particular for higher dosages. The preferred dosage is 15 mg/m^2/week [60]. Methotrexate should be administered to children according to the present recommendations [61] (IIIA).

Azathioprine Azathioprine represents another drug for the long-term treatment of juvenile arthritis [62, 63]. There are only few published reports of the drug's effect on JIA-associated uveitis. However, these publications suggest that, by using azathioprine, inactivity can be achieved and corticosteroids spared [49, 64]. In summary, we can recommend azathioprine for treating uveitis in children (IIIB).

Cyclosporine A The efficacy of cyclosporine A in treating uveitis has been studied intensively in adults and has been clearly demonstrated. However, only a few publications exist on its efficacy in treating JIA-associated uveitis [65–71]. Consensus was reached that cyclosporine A alone was only mildly effective and thus should not be employed as the primary immunosuppressive to treat JIA-associated uveitis (IIIA). As it was more effective for treating patients who did not respond to previously administered immunosuppressive drugs, cyclosporine A can be administered as a combination drug if methotrexate or azathioprine treatment, for example, has failed (IIIB).

Cyclophosphamide and chlorambucil In a few individual case reports, uveitis improved under treatment with cyclophosphamide [72–74] or chlorambucil [75–77]. However, very severe side effects developed in the patients (e.g., infertility, leukopenia, thrombocytopenia, zoster infection, and others) and thus insofar as possible these drugs should not be used to treat childhood uveitis (IIIA).

Mycophenolate mofetil In recent years, mycophenolate mofetil has been applied as an immunosuppressive and corticosteroid-sparing drug. Although the substance is well tolerated and is associated with only few adverse effects, its significance for treating chronic JIA-associated uveitis has not been elucidated [78–80] (III0).

Sulfasalazine In a controlled study, sulfasalazine reduced the number of attacks of HLA-B27-associated acute

anterior uveitis in adults [81]. Another randomized, controlled study in 22 adults with ankylosing spondylitis demonstrated that sulfasalazine significantly reduced the number of uveitis attacks over a 3-year period [41, 82]. The data published on arthritic children with uveitis were in part positive [83]. However, the guidelines group assessed the efficacy as being low.

Choice and dosage of immunosuppressive drugs A drug should be chosen according to the personal experience of the physician, be based on the current guidelines, and depend on individual factors of the patient being treated [50, 51, 60, 84]. The dosages recommended in Fig. 1 should serve as orientation and must always be adapted to the individual patient. Under immunosuppressive treatment, corticosteroid eye drops should be reduced to the lowest possible dosage and in the intermediate term not exceed more than three daily applications. If uveitis inactivity can be achieved, further treatment is not required for the time being.

Treatment step III

If uveitis persists in the affected eyes or recurs under a maximum of 3 times daily topical corticosteroids or a systemic corticosteroid dosage of >0.15 mg/kg body weight or new complications of uveitis develop while under immunosuppressive treatment, the anti-inflammatory treatment should be intensified. In addition to the previous treatment with one immunosuppressive drug, a TNF-alpha inhibitor or cyclosporin A should be administered. The dosage of corticosteroid eye drops should be reduced to a minimum and in the intermediate term not be given any more than three times daily.

Infliximab (IIA) and adalimumab (IIIA) are highly effective and can thus be recommended [53, 74, 85–93]. Adalimumab is a completely humanized antibody that can effectively treat severe JIA/polyarthritis [94] and has been approved for treating children over 4 years of age. In this step of treating uveitis, adalimumab is currently the preferred TNF-alpha inhibitor.

In contrast, etanercept is less effective. Occasionally, even first or recurring severe attacks of uveitis have been reported under treatment with this drug [85, 92, 95–100] (I0).

Corticosteroid injections to the eye In the acute phase of severe uveitis associated with dense infiltration of the vitreous body, ocular hypotony, or macular edema, the physician may consider additional subconjunctival or orbital floor injections of methylprednisolone or dexamethasone (2–4 mg) if the topical corticosteroids are not effective. The injections act rapidly but are only effective for a short period [35]. The significant advantage of injections over oral administration is the lower rate of systemic side effects. Disadvantages include the possibly increased risk of development of cataract and more frequent increases in intraocular pressure with possible glaucoma damage. Short-term anesthesia for the injection is also often required.

If the goal of treatment is highly effective intraocular levels of drug over several weeks and a delay in treatment effect is acceptable, orbital floor injections (20–40 mg) or intraocular injections (2–4 mg) of a crystal suspension of triamcinolone acetonide can be considered to treat uni- or bilateral uveitis associated with dense vitreous body infiltration, hypotony, or macular edema (when topical corticosteroids are not effective) [101–104] (IIIA). Not enough data are available concerning the efficacy of surgically implanting biodegrable dexamethasone device into the eyes of children with anterior uveitis associated with inflammatory rheumatic diseases (III0).

Steroids injections should not be given to patients known to develop steroid-induced increases in intraocular pressure in order to prevent uncontrolled and long-term pressure increases.

For the treatment of JIA-associated uveitis, the guidelines group only considers intravitreal triamcinolone injections suitable in individual cases when the course of disease is particularly severe (impending loss of vision, for example, due to hypotony, macular edema, or dense infiltration of the vitreous body) and if the patient has not responded adequately to topical or systemic corticosteroids and immunosuppressives and biologicals (so-called rescue therapy) (III0).

Additional treatments Cycloplegics. Anti-inflammatory treatment of active anterior uveitis should be combined with cycloplegics to avoid posterior synechiae from developing or for their lysis. During acute attacks, the pupils should be dilated with scopolamine (IIIA).

Fresh synechiae should be treated as soon as possible. Cycloplegics can be administered alone (atropine, scopolamine, cyclopentolate, neosynephrine, or tropicamine), or initially possibly combined with each other as drops or given as a one-time subconjunctival injection (IIIA).

To treat chronic disease course, tropicamide should be applied during the night as a synechiae prophylaxis (IIIA). When using cycloplegics, care should be taken that pupils dilated for several days do not develop synechiae as a result and induce amblyopia in younger children.

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