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Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis

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Abbreviations: ACR, American College of Rheumatology; AE, adverse events; AGREE, appraisal of guidelines for research and evaluation; AWMF, Association of the Scientific Medical Associations; Bw, bodyweight; CAPS, cryopyrin-associated periodic syndromes; CD, cluster of differentiation; CIOMS, Council for International Organizations of Medical Sciences; CTLA-4, cytotoxic T-lymphocyte antigen 4; DELBI, German instrument for methodological guideline appraisal; DMARDs, disease modifying anti-rheumatic drugs; EBM, evidence based medicine; EMA, European Medical Agency; EULAR, European League against Rheumatism; FDA, Food and Drug Administration; GC, glucocorticoids; GKJR, German Society for Pediatric Rheumatology; GPs, general practitioners; IgG, immunoglobulin G; IL, interleukin; ILAR, International League of Associations for Rheumatology; JDM, juvenile dermatomyositis; JIA, juvenile idiopathic arthritis; MAS, macrophage activation syndrome; Max, maximum; MTX, methotrexate; NGT, nominal group technique; NSAID, nonsteroidal anti-inflammatory drug(s); SCT, stem cell transplantation; SLE, systemic lupus erythematodes; SoJIA, systemic onset of juvenile idiopathic arthritis; TNF, tumor necrosis factor; TPMT, thiopurinmethyltransferase.

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KEYWORDS
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Abstract Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children and adolescents. Immunomodulatory drugs are used frequently in its treatment. Using the nominal group technique (NGT) and Delphi method, we created a multidisciplinary, evidence- and consensus-based treatment guideline for JIA based on a systematic literature analysis and three consensus conferences. Conferences were headed by a professional moderator and were attended by representatives who had been nominated by their scientific societies or organizations. 15 statements regarding drug therapy, symptomatic and surgical management were generated. It is recommended that initially JIA is treated with NSAID followed by local glucocorticoids and/or methotrexate if unresponsive. Complementing literature evidence with long-standing experience of caregivers allows creating guidelines that may potentially improve the quality of care for children and adolescents with JIA.

1. Introduction

1.1. Background, aims and addressees

Juvenile idiopathic arthritis (JIA) is defined by the International League of Associations for Rheumatology (ILAR) [1]. JIA is a highly heterogeneous disorder. Some of the subtypes of JIA are clearly distinct from others, also in regard of immunopathophysiology, e.g. systemic onset of JIA is now thought to be an autoinflammatory disease. Treatment of JIA subtypes may thus vary significantly [2]. JIA shows substantial impact on patients' physical abilities, psychological function and quality of life [3,4]. Therefore, treatment goals are pain relief, the elimination of active disease, the normalization of physical function, the achievement of normal growth and development and improvement of quality of life. Appropriate initial management, continuous, comprehensive and consistent care offer the chance of the prevention of long term sequels [5,6]. The German consensus group for treatment of JIA systematically developed guidelines for treatment of JIA in 1999, 2005 and 2008 [7,8]. Our guideline is addressed to physicians in medical practices and hospitals, allied health professionals, physiotherapists, occupational therapists and all people who are involved in the treatment, care and follow-up of children or adolescents with JIA. Our aim is to provide clear, evidence- and consensus based recommendations for the treatment of children and adolescents with JIA within a multidisciplinary setting. The guideline focuses on JIA and does not cover the issue of treatment resistant cases, complex or unusual forms of arthritis and does not consider all ILAR subtypes of JIA individually. Subtype specific recommendations are highlighted separately, e.g. treatment schemes for oligo-, polyarticular or systemic onset JIA.

2. Methodology

2.1. Members of the consensus group and consensus conferences

Scientific societies and organizations (Table 1), representing pediatricians in medical practices and hospitals, adult and pediatric rheumatologists, orthopedic surgeons, ophthalmologists, surgeons, physiotherapists, psychologists, national and local support-groups for parents and children, nominated representatives for the participation in consensus conferences. The scope of the conferences was the implementation of evidence and consensus based guideline for the treatment of JIA in children and adolescents. Consensus conferences were held at Duesseldorf respectively Krefeld (Germany) on the 9th of May 2007, 1st of August 2007 and 15th of January 2010 and were all attended by >95% of the representatives.

2.2. Literature search and literature review

Based on existing guidelines [7,8] we conducted a systematic literature search in Medline (http://www.ncbi.nlm.nih.gov/pubmed/) (deadline of search: 15th January 2010; terms: "juvenile idiopathic (rheumatoid) arthritis" and "therapy"; limits: "humans", "published in the last 3 years", "all child: 0–18 years", "clinical trial"). Studies relating to diagnosis of JIA, uveitis, vaccination, transition, rofecoxibe, Ca-supplementation and costs were excluded manually. The exclusion was necessary due to varying target groups and loss of market approval by European Medical agency (EMA) respectively [9]. Final results of the literature review are as shown in Fig. 1. These studies were evaluated for quality of methodology, following the definitions of evidence level and recommendation grade as published by Feldmann et al. [10] (Table 2 and Table 3). Thirteen studies were judged as relevant for the 2010 update of treatment guidelines for JIA (Table 4). To draft guideline statements, the core conclusions of studies were discussed and formal consensus building followed the nominal group technique (NGT) [11] and Delphi method [12].

2.3. Consensus process

The consensus process was externally and independently supervised by the Association of the Scientific Medical Associations (AWMF), who has membership of Council for International Organizations of Medical Sciences (CIOMS). The AWMF coordinates the systematic development of diagnostic

Table 1 Representatives nominated for the consensus group by scientific societies and professional organizations.

Name	Representing scientific societies or professional organisations
Arbogast M	Association of Paediatric Orthopaedic Surgeons
Dannecker G	German Society of Paediatrics and Adolescent Medicine (DGKJ)
Dueckers G (coordinator)	
Foeldvari I	German Society for Paediatric Rheumatology (GKJR)
Frosch M	GKJR
Ganser G	GKJR
Guellac N (coordinator)	
Heiligenhaus A	German Society for Ophthalmology (DOG)
Horneff G	GKJR
Illhardt A	German Society for Psychology (DGPs)
Krauspe R	Association of Paediatric Orthopaedic Surgeons
Kopp I (moderator)	
Markus B	National support group of parents and children with JIA—Rheuma Liga
Michels S	GKJR
Niehues T (coordinator)	GKJR
Schneider M	German Society of Rheumatology (DGRh)
Singendonk W	Association of Paediatricians in private practice (BVKJ)
Sitter H (moderator)	Association of the Scientific Medical Associations (AWMF)
Spamer M	National Association of Physiotherapists
Wagner N	German Society of Paediatrics and Adolescent Medicine (DGKJ)

and treatment guidelines for medical, scientific societies and organizations in Germany.

2.4. Consensus building: nominal group technique (NGT)

Consensus building was headed by a professional moderators (H.S., I.K.). The moderator of the consensus conferences explained the purpose, method and procedure of consensus finding. Representatives gave brief presentations of literature and core conclusions for the guideline draft. A formal consensus process led to adoption of guidelines for treatment of JIA. As formal consensus procedure we used NGT, involving six stages:

1. Silent review of the guideline draft and noting of comments and ideas by the participants. During this period, participants did not consult or discuss with others.

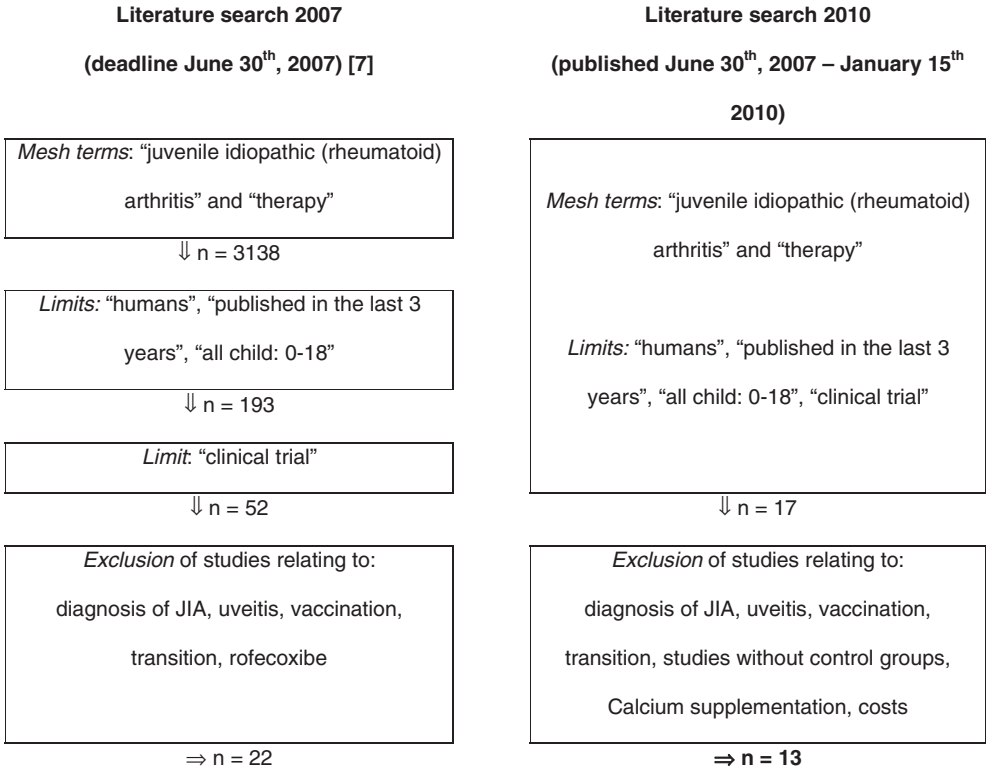

Figure 1 Literature search 2007 and 2010.

Table 2 Evidence level [10].

Evidence level	Definition
I	Evidence obtained from at least one properly designed randomized controlled trial.
II	Evidence obtained from well-designed controlled trials without randomization or from well-designed cohort or case–control analytic studies, preferably from more than one center or research group or from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
III	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

Table 3 Recommendation grade [10].

Recommendation grade	Definition
A	There is *good* evidence to support the recommendation that the intervention be performed.
B	There is *fair* evidence to support the recommendation that the intervention be performed.
C	There is *poor* evidence regarding the value or harm of the intervention; recommendations may be made on other grounds.
D	There is *fair* evidence to support the recommendation that the intervention not be performed.
E	There is *good* evidence to support the recommendation that the intervention not be performed.

2. Collocation of comments and ideas by the moderator, using the words of the participants.
3. Clarification and substantiation of comments and ideas on alternative guideline statements, by the participants.
4. Reconcilement of the manuscript and all alternative guideline statements.
5. Discussion of statements and further explanation of any of the comments that were not clear to all participants. Each member of the consensus group contributed to the discussion. The moderator kept the process as neutral as possible, avoiding judgment and criticism.
6. Final reconcilement for statements for guideline.

Table 4 Studies for 2010 update identified by the MEDLINE search algorithm (see Methodology).

	Drug/treatment	Mean age (age range) of participants at study (years)	Total number of patients (n)	JIA			
				Oligoarticular	Polyarticular	Systemic onset	Other subtypes
Foeldvari et al. [20]	Celecoxibe	10.3 (2–16)	264	128 (53%) [a]	114 (47%)	22 (9%)	
Céspedes-Cruz et al. [33]	MTX	8.2 (n.p.)	521	162 (31%) [b]	284 (55%)	75 (14%)	
Lovell et al. [45]	Etanercept	10.4 (4–17)	58	5 (9%) [c]	34 (58%)	19 (33%)	
Horneff et al. [83]	Etanercept	12.9 (4–17)	20	2 (10%) [b]	16 (80%)		2
Giannini et al. [46]	Etanercept	9.9 (2–18)	594	[d]	535 (90%)	58 (9.7%)	1
Lovell et al. [40]	Adalimumab	11.3 (4–17)	171		171 (100%) [e]		
Ruperto et al. [31]	Infliximab	11.2 (4–18)	121	28 (23%) [c]	74 (61%)	19 (16%)	
Lequerré et al. [51]	Anakinra	12.4 [f] (3–23)	20 [f]			20 (100%)	
Illowite et al. [50]	Anakinra	12 (2–17)	86	9 (10%) [c]	62 (72%)	15 (17%)	
Yokota et al. [53]	Tozilizumab	8.3 (2–19)	65			56 (100%)	
Ruperto et al. [54]	Abatacept	12.4 (6–17)	190	30 (16%)	122 (64%)	37 (20%)	1
Singh-Grewal et al. [58]	Vigorous exercise training	11.6 (8–16)	80	18 (23%)	34 (43%)	7 (9%)	21 (26%)
Brinkmann et al. [56]	Stem cell transplantation	8.5 (4–18)	22		4 (18%)	18 (82%)	

Abbreviations: n.p. = not provided.
[a] Not further specified.
[b] Only extended oligoarticular JIA.
[c] Pauciarticular onset with polyarticular course.
[d] Extended oligoarticular JIA were included into polyarticular JIA.
[e] All JIA with polyarticular course, with any type of onset, not further specified.
[f] Pediatric patients, total number of patients in extended report was 35 (15 were patients with adult onset of Still disease).

The conference guideline topics were reviewed and edited by working groups. After the first consensus conference, statements were adopted by NGT and additional proposals for schemes of treatment strategies of JIA were collated.

2.5. Consensus finding: method of Delphi

Three out of 15 statements remained without consensus after NGT. These statements comprise the utility of etanercept (treatment resistant polyarticular JIA), sulfasalazine (treatment resistant JIA) and anakinra (treatment for refractory SoJIA). Therefore, they were sent to all participants of consensus conferences via email. To each of them participants should state one of three votes ("agree", "do not agree" or "alternative proposal") (1st round of Delphi). The results were summarized and the statements, which remained with no consensus after 1st round of Delphi, were sent to participants again (2nd round of Delphi). After 2nd round of Delphi results were sent to external review.

2.6. External review and adoption

The guideline manuscript has been reviewed in 2007 by national experts in German Rheumatology: Huppertz (Bremen, Germany), Michels (Garmisch Partenkirchen, Germany) and Specker (Essen, Germany). The comments of external reviewers (H.I. Huppertz) to the 2011 manuscript were involved within the 3rd round of Delphi. External review enabled adoption of the guidelines' core conclusions and statements with strong consensus, i.e. 95% agreement by representatives of participating scientific societies and organizations.

3. Results: treatment guidelines

3.1. Drug-based therapy

Drugs used in treatment of JIA are summarized in Table 5. Proposed schemes of treatment of JIA are shown in Fig. 2. The following paragraphs will highlight specific adverse reactions and introduce the 13 studies relevant for the 2010 update of treatment guideline for JIA briefly. For detailed information about prescribing information including: indication, contraindication, drug dosage, route of administration, monitoring and product characteristics, the consensus group recommends consulting national drug data bases, e. g. www.roteliste.de (German database of drugs with national market approval) or www.fda.org or www.ema.europa.eu.

3.1.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

Commonly, NSAIDs are well tolerated. Main side effects of NSAIDs are stomach irritation, dyspepsia and—in rare cases—nephritis. Cephalgia and behavioral changes can be associated with the administration of ibuprofen. Pseudoporphyria is not uncommon in patients treated with naproxen. Pain relief has been demonstrated for Naproxen [13–15], Diclofenac [15,16] and Ibuprofen [17] (evidence level I) and for Indometacin [18] and Meloxicam [19] (evidence level II). Efficacy of Celecoxibe has been demonstrated in a randomized, double blind multicenter study [20]. 95% of 212 patients entered the 12 week open label phase, after a 12 week double blind phase in three treatment groups (Celecoxibe 6 mg/kg/d versus Celecoxibe 12 mg/kg/d versus Naproxen 15 mg/kg/d). Both dosages of Celecoxibe showed comparable efficacy compared to Naproxen. Safety, i.e. number of adverse events (AE) did not differ significantly between Celecoxibe versus Naproxen.

Consensus statement.

> NSAIDs are recommended for the treatment of JIA: Diclofenac, Naproxen, Ibuprofen and Indometacin (evidence level I, respectively II, recommendation grade A).
> If those drugs are contraindicated, Celecoxibe might be used (evidence level I, recommendation level B–C).

3.1.2. Glucocorticoids

3.1.2.1. Glucocorticoids (GC)—local administration. The use of intra-articular crystalline corticoids is highly potent and has a rather low rate of complications (evidence level II) [21,22]. They might be administered as first line therapy. Response rate was significantly higher with triamcinolone hexacetonide than with triamcinolone acetonide at 6 months and this difference was sustained to 24 months [21,22]. These findings were independent of duration and extent of disease [21,22]. Simultaneous intra-articular steroid injections are preferable to consecutive injections at different time points (limited suppression of hypothalamic–pituitary–adrenal axis) [23]. Side effects, e.g. local necrosis of fat tissue, are seen in approximately 2% of injections [22]. Working under sterile conditions, the risk of infection is low.

Consensus statement.

> Intra-articular injections of crystalloid corticosteroids (triamcinolone hexacetonide) are recommended and can be part of the first line treatment. Improvement of local inflammation, pain, swelling and range of joint movement has been demonstrated (evidence level II, recommendation grade A).
> Triamcinolone hexacetonide is more efficient than triamcinolone acetonide inducing local remission (evidence level I, recommendation grade B).

3.1.2.2. GC—systemic administration. GC can be administered as a fast acting drug in highly active disease. Indications for their use are: bridging time until DMARDs (disease modifying anti rheumatic drugs) become effective, treatment of severe systemic features of systemic-onset JIA (SoJIA), induction of remission in polyarticular JIA and in severe forms of uveitis. There are no controlled trials and no standardized therapeutic regimes for the use of systemic

Table 5 Drugs for the treatment of JIA.

Generic	Dosage	Age approval by European medical agency in pediatric rheumatology (EMA) [a]	Medical indication in pediatric rheumatology [a], [b]	Evidence level/ recommendation grade [10]	Literature
NSAIDs					
Diclofenac	2–3 mg/kg Bw/d p.o. (in 3 doses) Retard formulation: 1 dose	14 years	Arthritis	I–A	Haapasiri [16], Laxer [14]
Ibuprofen	20–40 mg/kg Bw/d p.o. in 3–4 doses	6 months	Pain, fever	I–A	Giannini [17]
Indometacin	1–3 mg/kg Bw/d p.o. in 3 doses	2 years	Arthritis	II–A	Stoeber [18]
Meloxicam	0.125–0.25 mg/kg Bw/d p.o.	15 years	Arthritis	II	Ruperto [19]
Naproxen	10–15 mg/kg Bw/d p.o. in 2 doses	1 year	Arthritis	I–A	Kvien [13], Laxer [14], Leak [15]
Celecoxibe	6 mg/kg Bw/d p.o. in 2 doses or 12 mg/kg Bw/d in 1 dose	No approval for children	Arthritis	I B-C	Foeldvari [20]
Glucocorticoids (GC)					
a) Systemic GC					
Prednisone/ Prednisolone	0.1–0.2 mg/kg Bw/d (max. 5 mg/d)		JIA: i.e. severe SoJIA, severe peri-/ myokarditis, severe uveitis (hypotonia or cystoid macular edema), intolerance to other drugs ("low-dose"); or as "bridging" therapy in higher doses e.g. 2 mg/kg Bw/d, until therapeutic effect of "DMARDs"	III	Prieur [28]
Prednisone as an oral high-dose therapy	≥1–2 mg/kg Bw/d prednisolone-equivalent			III	Prieur [28]
Prednisone as an oral medium-dose therapy	0.2 to<1.0 mg/kg Bw/d prednisolone-equivalent			III	Kirwan [24], Prieur [28]
Prednisone as an oral low-dose therapy	<0.2 mg/kg Bw/d Prednisolone-equivalent or <4 mg/m² body surface			III	Michels [25]
Prednisone as a i.v. pulse-therapy	>(5)–10 mg/kg Bw (p.o.) Prednisolone-equivalent, 10–30 mg/kg Bw/d Methyl-Prednisolone i.v for 1–3 d (maximum 1 g/dose)			III	Miller [26], Picco [27]
b) Intra-articular GC					
Triamcinolone hexacetonide	0.5–1 mg/kg Bw into large joints, dose adaption referring to size of joint, (e.g. max. 2 mg into interphalangeal joints [c])	5 months	Arthritis, tendo-vaginitis	I	Zulian [21,22]

(continued on next page)

Table 5 (*continued*)

Generic	Dosage	Age approval by European medical agency in pediatric rheumatology (EMA) [a]	Medical indication in pediatric rheumatology [a, b]	Evidence level/ recommendation grade [10]	Literature
DMARDs					
Sulfasalazine	30–50 mg/kg Bw/d in 2–3 doses	6 years	Arthritis	II	Van Rossum [36,37]
Cytotoxic or immuno-suppressive drugs					
Methotrexate	10–15 (20) mg/m² body surface once a week (p.o., s.c., i.v.) [e]	2 years	Polyarticular JIA, Psoriasis arthritis, uveitis, Collagenosis	I	Giannini [84], Ravelli [85], Woo [86]Cespedes-Cruz [33]
Azathioprine	1.5–3 mg/kg Bw/d p.o. in 1–2 doses	No approval for children		II	Kvien [34]
Leflunomide	No clear recommendation for children available. Bw<20 kg: d 1: 100 mg/kg from d 2: 10 mg/kg/d Bw 20–40 kg: d 1 to d 2: 100 mg/kg from d 3: 10–20 mg/kg/d Bw>40 kg: d 1 to d 3: 100 mg/kg from d 3: 20 mg/kg/d	No approval for children		II	Silverman [35,87]
Biologic agents **a) TNFα inhibitors**					
Etanercept [d]	0.8 mg/kg Bw s.c. 1×/week (max. 50 mg/week) or 0.4 mg/kg Bw s.c. 2×/week, (max. 50 mg/week)	4 years	JIA, Polyarthritis and insufficient efficacy of MTX	I	Giannini [46], Horneff [49], Lovell [38,88], Prince [41]
Adalimumab [d]	24 mg/m^2 body surface s.c. in 1 dose every 2 weeks Bw<30 kg: 20 mg/m^2 body surface Bw>30 kg: 40 mg/m^2 body surface (max. 40 mg per dose)	4 years to 17 years	Adalimumab in combination with methotrexate is indicated for the treatment of active polyarticular juvenile idiopathic arthritis, in children and adolescents who have had an inadequate response to one or more disease-modifying anti-rheumatic drugs (DMARDs).	I	Lovell [40]

Infliximab [d]	3–10 mg/kg Bw/dose i.v. Infusion at d 0, d 14, d 42, then every 8 weeks intervals of application remain unclear	No approval for children with JIA 6 years (approval for Morbus Crohn)		III	Ruperto [31]
b) IL-1 inhibitors					
Anakinra [d]	1–4 mg/kg Bw/d s.c. in 1 dose	No approval for children		II	Illowite [50], Lequerre [51]
Canakinumab [d]	4 mg/kg Bw/single dose s.c. every 4 weeks (max. 150 mg)	No approval for children with JIA, 4 years (approval for CAPS)		III	Ruperto [89]
Rilonacept [d]	1–2×4.4 mg/kg/week s.c (max. 320 mg) then 2.2 mg/kg/week s.c. (max.160 mg)	No approval for children with JIA 12 years (approval for CAPS)			Lovell [88,90,91]
c) IL-6 inhibitors					
Tocilizumab [d]	1 h Infusion every two 2 weeks Bw<30 kg: 8 mg/kg Bw>30 kg: 12 mg/kg	2 years of age or older	Since May 2011 EMA approval for pediatric patients with SoJIA who have responded inadequately to previous therapy with NSAIDs and systemic corticosteroids (Approval at Japan for SoJIA and polyarticular JIA since 2008) [c]	I	Yokota [53], Ruperto [92], de Benedetti [62]
d) Co stimulatory-antagonists					
Abatacept [d]	10 mg/kg i.v. Infusion at d 0, d 14, d 28, then every 4 weeks	6 years of age and older	Abatacept in combination with methotrexate is indicated for the treatment of moderate to severe active polyarticular (JIA) in pediatric patients who have had an insufficient response to other DMARDs including at least one TNF inhibitor	I	Ruperto [54,93,94]

Abbreviations: CAPS=Cryopyrine associated periodic fever syndrome; JDM=juvenile dermatomyositis; Bw=body weight; SoJIA=systemic-onset of JIA; SLE=systemic Lupus erythematodes.

[a] Compare www.ema.europa.eu.

[b] www.roteliste.de. (German database of drugs with national market approval).

[c] Intra-articular injection into same joint no more often than once every 3 months.

[d] A statement from insurance companies should be acquired before treatment initiation for off label treatment (if possible).

[e] Oral application is most feasible in childhood.

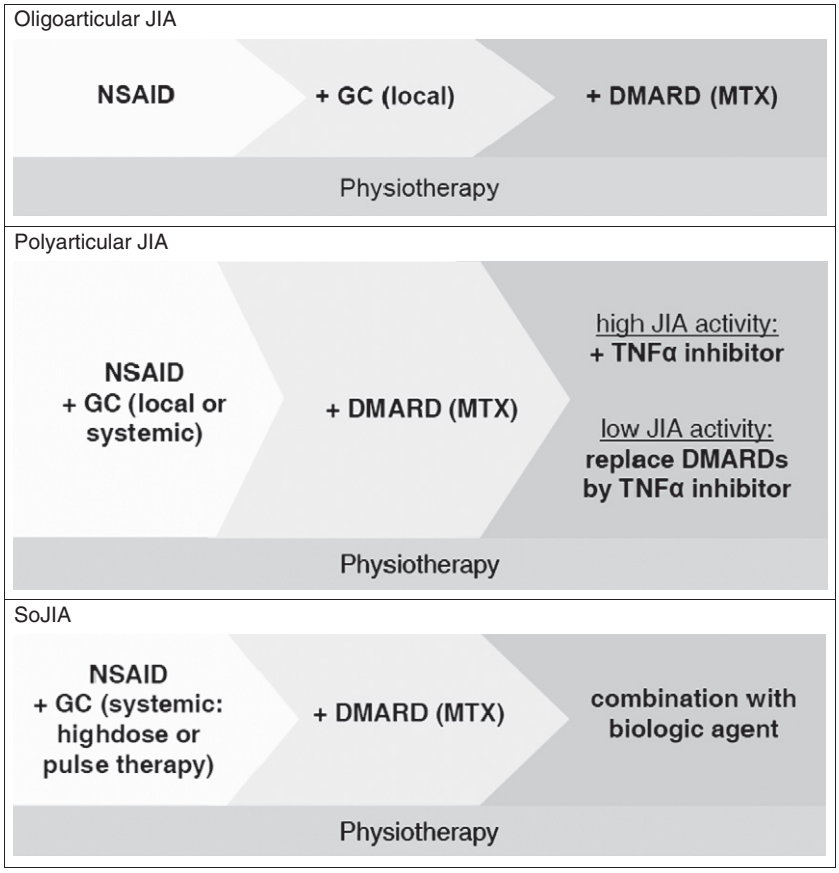

Figure 2 JIA treatment escalation schemes: + = addition of the drug (abbreviations: NSAIDs = non steroidal anti-inflammatory drug; GC = Glucocorticoids, DMARDs = disease modifying drugs, MTX = Methotrexate).

GC in JIA published, thus leading to "just" evidence level III. Different recommendations of dosage and therapy regimes are listed in Table 5 (evidence level III for all recommendations) [18,24–28]. Frequency and seriousness of deleterious effects correlate mainly to duration of therapy and dosage of GC administered. Main side effects are: iatrogenic Cushing's syndrome, growth disturbance, weight gain, mood changes. Higher dosage carry the risk of increased vulnerability to infection, hypertension, osteoporosis, thrombosis, diabetes, gastro-intestinal ulceration, cataract, glaucoma, atrophy of subcutaneous fatty tissue, steroid induced acne. To inform colleagues about GC treatment in a case of emergency and to reduce severe complications in long term treated patients, i.e. GC administration > 4 weeks, the supply of "Glucocorticoid ID cards" for patients might be useful.

Consensus statement.

The systemic use of GC is recommended as fast acting drugs in highly active JIA. GC are used for the treatment of children and adolescents with SoJIA, organ manifestations of JIA (e.g. uveitis, pericardial effusion), sero-positive polyarticular JIA and for bridging time until the complete therapeutic effect of DMARDs (evidence level III, recommendation grade A).

Consensus statement (*continued*)

Long-term use of systemic GC is not recommended. Continuous administration of ≥ 0.2 mg Prednisolone equivalent per kg bodyweight (Bw) carries a high risk of adverse events and therefore is not recommended (evidence level III, recommendation grade A).

3.1.3. Methotrexate (MTX), biologic agents and immunosuppressive agents

Consensus statement.

MTX, biologic agents and immunosuppressive agents are used for the treatment of children and adolescents with polyarticular JIA, if NSAIDs or local GC treatment do not succeed. The combination of those drugs with NSAIDs and GC is feasible. A common characteristic of MTX, biologic agents and immunosuppressive agents is the delayed onset of therapeutic effect, i.e. up to 3 months or even longer after commencing treatment.

Safe contraception is indicated during therapy with MTX, Azathioprine or Leflunomide and in the following 3 to 6 months after its discontinuation.

3.1.3.1. Methotrexate. Among DMARDs, MTX provides the mainstay of long-term therapy in JIA [29–32]. In case of side effects, e.g. dyspepsia or nausea, prophylaxis with folic acid can be recommended (1 × 1 mg per day or 5 mg once a week, 24–48 h after application of MTX). Safe contraception is mandatory while receiving MTX. Safety and efficacy of MTX and its impact on quality of life of children with JIA have been investigated. Significant positive impact of MTX on all health-related quality of life health concepts has been shown; although the study has its limit due to different MTX dosages used within participating JIA patients [33].

Consensus statement.

MTX administration can be recommended, due to its proven safety and efficacy to reduce disease activity. MTX is used in case of insufficient therapeutic effect of NSAIDs and/or local GC administration, continuous need for systemic GC and/or highly active disease. Efficacy of MTX (orally or subcutaneously administered) is frequently achievable with a dosage of 10–15 mg/m² body surface (evidence level I, recommendation grade A).

3.1.3.2. Purine analogs

3.1.3.2.1. Azathioprine. Efficacy has been investigated in a double blind placebo controlled study (32 patients). After 8 weeks of therapy the changes in disease activity measurement indicated a minor improvement in the Azathioprine group compared to the placebo group. At the end of the study, statistically significant differences between the groups were found for only 2 disease activity measurements [34]. Two patients were taken out of study, due to severe adverse events, e.g. leucopenia. Measurement of activity of Thiopurinmethyltransferase (TPMT) can be beneficial for avoidance of severe adverse events.

3.1.3.3. Pyrimidine analogs

3.1.3.3.1. Leflunomide. Within a double blind study (32 weeks, 94 patients) efficacy of Leflunomide was inferior in comparison to MTX but better than placebo. However, dosing of Leflunomide may not have been adequate in some children [35]. Contraindications for Leflunomide are: renal insufficiency, severe immunodeficiency, depressed myelopoesis, and pancytopenia. An extensive half-life period (approximately 14 days) has to be taken in account, when administering Leflunomide. In combination with hepatotoxic DMARDs the risk of severe adverse events might increase, e.g. increased blood pressure is seen frequently. Safe contraception is mandatory.

3.1.3.4. Antibiotic analogs and Hydroxychloroquine and Chloroquine

3.1.3.4.1. Sulfasalazine. Weak efficacy of Sulfasalazine was demonstrated within a placebo-controlled randomized study after 24 weeks (96 patients) [36,37]. One third of patients enrolled in the study discontinued treatment with Sulfasalazine, due to side effects, e.g. gastrointestinal symptoms, leucopenia [36]. Some experts use sulfasalazine in HLA-B27 positive JIA. Contraindications are Glucose-6-phosphatase deficiency and hypersensitivity against sulfonamides.

Consensus statement.

Administration of Sulfasalazine or Leflunomide is recommended, if MTX or Etanercept do not show sufficient efficacy or cannot be used for other reasons (evidence level II, recommendation grade B).

3.1.3.4.2. Hydroxychloroquine and chloroquine. Hydroxychloroquine and Chloroquine have been subject to clinical trials for the treatment of JIA, even though efficacy was limited. Within three consensus conferences held in 2007 and 2010 the consensus group decided not to give a consensus statement on the use of chloroquine or hydroxychloroquine treatment, despite the fact that those drugs still might be used by some caregivers.

3.1.3.5. Biologic agents. Biologic agents are drugs, which selectively inhibit cytokines, cytokine receptors or directly bind to receptors of lymphocytes, e.g. CTLA-4, CD20. They include antibodies and fusion proteins. So far, all biological therapies are administered subcutaneously or intravenously.

3.1.3.5.1. TNFα-inhibitors. TNFα-inhibition with Adalimumab and Etanercept is efficient and safe (evidence level I) [38–41]. Both drugs have been approved for JIA with polyarticular course. TNFα-inhibitors have become an integral part of the treatment of JIA. Potential risks of therapy are vulnerability for infection and—in a rare occasion—the induction of autoimmune disease. Prior to the start of treatment with TNFα-inhibitors chronic infections needs to be excluded or treated sufficiently, e.g. tuberculosis, hepatitis B or C.

In children with JIA treated with TNFα-inhibitors, malignancies, e.g. Lymphoma, have been reported. It remains unclear, if the rate of malignancies is increased in patients compared to the risk by having JIA itself. In response to a previous letter of the FDA (as reviewed in [42]), the German Society for Pediatric Rheumatology (GKJR) has published official statements [43,44]. The GKJR states, that treatment with TNFα-inhibition should be used very carefully; physicians need to be aware of co-medication, e. g. immunosuppressive drugs, and should monitor those patients closely [43]. There is insufficient data on all biologic agents—including TNFα-inhibition—to judge about the long-term risk for children and adolescents.

3.1.3.5.1.1. Etanercept. Etanercept is a fusion protein consisting of the extracellular binding domain of soluble TNFα-receptor and Fc chain of human IgG1. Etanercept inhibits TNFα by direct binding of the cytokine. Efficacy has

been demonstrated in a randomized controlled withdrawal design trial for patients with polyarticular JIA [38]. Within an open extension study long term efficacy and safety have been documented over 8 years in 16/69 patients [39,45]. There is data on more than 2000 patients, registered in European registries [46–48]. Currently, retrospective data shows a somewhat better efficacy of combining MTX or other DMARDs with TNFα-inhibition versus anti-TNFα therapy as single therapy [49].

3.1.3.5.1.2. Adalimumab. Adalimumab is a humanized monoclonal IgG1 antibody directed against TNFα, which binds soluble and membrane bound TNFα. A randomized controlled withdrawal design trial demonstrated safety and efficacy of Adalimumab (24 mg/m² body surface every 2 weeks, max. 40 mg) for children and adolescents with polyarticular JIA (4–17 years of age, n=171) [40]. After 16 weeks "wash in" phase, responders (n=144/171) entered the 32 weeks randomized double blind phase. After 48 weeks twice the number of patients in the verum group met ACR 70 as compared to the control group (56 vs. 28%, $p<0.01$). Within the open extension phase Adalimumab dosage was fixed, i.e. 20 mg<30 kg Bw and 40 mg>30 kg Bw. There is lack of evidence showing superior efficacy of combining MTX (DMARDs) with Adalimumab versus Adalimumab as single therapy [40].

Consensus statement.

> Efficacy of Etanercept and Adalimumab for the treatment of polyarticular JIA has been demonstrated. Therapy with TNFα-inhibition is indicated in case of insufficient therapeutic effect of NSAIDs and local GC administration and lack of response to MTX (evidence level I, recommendation grade A).

3.1.3.5.1.3. Infliximab. Infliximab is a chimerical (human/mouse) monoclonal antibody, which binds soluble and membrane bound TNFα. A randomized controlled study in children and adolescents with JIA failed to demonstrate a significant difference of efficacy after treatment with Infliximab compared to placebo [31].

3.1.3.5.2. Interleukin-1-inhibitors. None of interleukin-1-inhibitors are approved for the treatment of JIA or SoJIA. They are commonly used in an off label setting.

3.1.3.5.2.1. Anakinra. Anakinra is an IL-1 receptor antagonist. Within a randomized controlled trial no significant efficacy of Anakinra for patients with polyarticular JIA could be demonstrated [50]. 50 of 86 patients were enrolled into blinded phase (1:1 Anakinra versus Placebo). No significant reduction of flare could be demonstrated in comparison to placebo. 29 of 50 patients completed the open label extension study. Two noncontrolled, nonrandomized studies have shown efficacy of anakinra in a proportion of patients with systemic-onset of JIA (SoJIA) [51,52].

3.1.3.5.2.2. Canakinumab. Canakinumab, an IL-1β antibody, binds IL-1β selectively without interfering with IL-1α or its physiological IL-1 receptor antagonist. Canakinumab has been approved for treatment of hereditary periodic IL-1 associated periodic fever syndromes, i.e. Cryopyrin-associated periodic syndromes. There are ongoing studies investigating safety and efficacy of Canakinumab for SoJIA.

3.1.3.5.3. Interleukin-6 inhibitors.

3.1.3.5.3.1. Tozilizumab. Tozilizumab is a humanized anti-IL-6 receptor monoclonal antibody. Efficacy has been demonstrated within a 12 week double blind, randomized controlled withdrawal trial in children with SoJIA (n=56, 2–19 years) in Japan [53]. After a 48 week open extension study ACR Pedi 30 was met by 47 patients (98%). At the time of our literature search Tocilizumab was approved for treatment of SoJIA and polyarticular JIA since 2008 in Japan. A multicenter European study investigating efficacy and safety of Tozilizumab in polyarticular JIA was ongoing at the deadline of literature search (www.clinicaltrials.gov, NCT00988221). No data on long term effects are currently available.

Consensus statement.

> The use of Anakinra or Tozilizumab can be recommended for treatment of children and adolescents with refractory SoJIA (evidence level II, recommendation grade A).

3.1.3.5.4. Co-stimulation inhibitors.

3.1.3.5.4.1. Abatacept. Abatacept is a recombinant fusion protein of extracellular domain of human cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) and IgG1-Fc-Fragment. It modulates T-cell co-stimulation. A randomized controlled double blind withdrawal design study of Ruperto et al. [54] demonstrated efficacy of Abatacept in patients with polyarticular JIA. 123 of 170 participants of study were enrolled in the 6 month double blind phase. Flares occurred in 33 of 62 (53%) patients who were given placebo versus 12 of 60 (20%) Abatacept patients during double blind phase. Adverse events (AE) did not differ in both groups, i.e. 37 AE in Abatacept versus 34 AE in placebo recipients. Some children may take 3 to 6 months or longer before their maximal response is achieved. 3% of patients developed reaction to the infusion [55]. Abatacept is approved by FDA and EMA for patients, who did not respond to prior MTX treatment. No data of long term effects of the use of Abatacept in JIA are available, due to the low numbers of patients treated so far.

Consensus statement:

> Patients with polyarticular JIA without systemic manifestation, refractory to treatment with MTX and TNF inhibition, might benefit from the use of Abatacept (evidence level III, recommendation grade C).

3.1.4. Autologous stem cell transplantation (SCT)

There are studies on autologous SCT for treatment of refractory and severe forms of JIA (evidence level III) [56]. 22

patients were enrolled in one study: 8 reached clinical remission, 7 were assessed as partial responders, 3 experienced relapse of the disease and 4 (18%) died as a consequence of MAS or immunosuppressive treatment [56]. Due to serious adverse events, including death, this therapeutic option is seen as the last treatment option.

3.2. Non-drug based therapy

3.2.1. Physiotherapy, occupational therapy and therapeutic appliances

Physio- and occupational therapy are integral parts of the therapeutic concept in children and adolescents with JIA [57,58]. Therapeutic goals of physiotherapy are: relaxation and pain relief, preservation or rehabilitation of physiological range of joint movement, prevention of contractures, stretching and activation of muscles, build-up of muscle force, and training of physiological movements.

Consensus statement.

Structured treatment by a properly trained physiotherapist/occupational therapist in combination with drug based therapy and instructions for disease adopted, self-sufficient daily exercise sessions are recommended to keep and to improve joint mobility (evidence level II, recommendation grade A).

Custom-made therapeutic appliances for correction of axial misalignment, prevention of false weight bearing, stabilization of joints (e.g. hand-, finger-, and foot-ortheses) are recommended individually. The use of therapeutic appliances follows individual physician-directed advice. Efficacy has been demonstrated (evidence level I, recommendation grade B).

Other forms of non-drug based therapeutic approaches rely on experts' opinion and are solely based on individual clinical experience. No controlled studies are available.

Consensus statement.

The implementation of thermotherapy, electro- or ultrasound therapy, massage and lymph drainage is recommended. Application of cold appliances for acute joint inflammation is indicated (evidence level II, recommendation grade A).

Electro- and ultrasound therapy are recommended for patients with tendosynovitis (evidence level III, recommendation grade B).

3.2.2. Sportive activity and exercise training

Positive impact of sportive activity on the general physical condition and on oxygen consumption has been demonstrated (evidence level II) [57–60]. Adequate exercise training supports the physiological development and helps coping with JIA [58]. Prospective controlled long term studies are currently not available.

Consensus statement.

Exercise training is recommended depending on the extent of inflammation, number of affected joints and global disease activity. Sports with minor stress on joints is favorable (evidence level I, recommendation grade A).

3.2.3. Surgical treatment

Toledo et al. investigated the role of arthroscopic synovectomy in JIA. They concluded that arthroscopy is a safe but only partially effective procedure in patients with oligoarticular JIA (evidence level/recommendation grade III/B) [61].

Consensus statement.

In individual cases the indication for open or arthroscopic synovectomy can be considered if conservative therapy does not succeed (evidence level III, recommendation grade B).

3.2.4. Psychological, social intervention or socio-pedagogical care

There are no controlled or open studies focusing on psychological, social and/or socio-pedagogical intervention in children or adolescents with JIA. Recommendations are based on expert's opinion and personal experience solely.

Consensus statement.

An early psychological support within standard pediatric rheumatological care should be implemented, to apprehend and treat mental issues and behavioral syndromes associated with physiological disturbances and physical factors (evidence level III, recommendation grade A).

Consensus statement.

A socio-pedagogical care with regard to integration at school, professional and everyday life and formal education of parents and patients is recommended (evidence level III, recommendation grade A).

4. Addendum

Since the deadline January 15th, 2010 new papers have appeared that are of interest in the context of our guideline [55,62–64], in particular we refer to the ACR recommendations [65] and the most recent literature on the risk of malignancies in JIA in context with TNF blocking agent and independent of medication [42], [66]. Moreover, there is a recent study on the use of Tocilizumab in polyarticular patients [67]. These papers will be discussed within the next consensus conference by NGT and considered for inclusion into the next edition of this guideline. On 6th of September 2011, our advanced search on www.clinicaltrial.gov (search terms: juvenile idiopathic arthritis; recruitment: open studies; study type: interventional study; age group: child (birth–17); intervention: drugs) led to 16 trials which are currently recruiting or will soon start recruiting.

5. Discussion

To develop clinical practice guidelines of high quality and validity, a formal consensus process and explicit methodological criteria for the production of guidelines are recommended [68–70]. Our guideline for the treatment of JIA in children and adolescents implements all these issues. The systematic literature search was terminated on 15th January 2010, leading to the most up to date guideline for JIA which is currently available. The deadline of the ACR recommendations as published recently by Beukelmann et al. was 5th of October 2009 [65]. By exclusion of case reports, trials without control groups, preliminary results published as abstracts on conferences and the strict graduation of the literature by the criteria of evidence based medicine, we aimed to give our guideline statements additional strength and a maximal validity. Newer original studies providing additional evidence for the treatment of JIA became available after our consensus process was finished, see Addendum. The results of these trials have to await the next NGT before inclusion into our recommendations.

Our updated systematic literature search in 2010 led to 13 relevant studies published after 30th June, 2007 (Fig. 1, Table 4). Their results have to be interpreted with caution. First, trials in JIA are mainly based on limited numbers of pediatric patients, as the recruitment of a sufficient number of pediatric patients remains challenging. Second, trials are mainly designed for patients with polyarticular JIA or with oligoarticular onset and a polyarticular course (Table 4). Most children with JIA do not have a polyarticular subtype of JIA, but an oligoarticular onset and course [71]. Thus, patients with oligoarticular JIA are heavily underrepresented in most of the current trials. Third, in 5 of the 13 studies the withdrawal study design has been used [40,45,50,53,54]. Lehmann reviewed the bias of withdrawal design trials in 2008 [72]. After a wash-in phase only responders to treatment are eligible for randomization. Thus the design preselects responders to the placebo effect who might retain their response throughout the entire study period. Further, there is a carryover effect of AE into the placebo group, so that significant differences in AE between groups may not become apparent. In the one placebo controlled trial without withdrawal design on TNFα-inhibition (Infliximab) no significant efficacy could be demonstrated between verum and placebo [31].

To our knowledge there are two other guidelines that deal with the management of JIA as a whole (Table 6) [65], [73]. Other guidelines are limited to the use of single drugs in JIA, e.g. biologic agents [74], etanercept [75]. The Australian guideline (www.racgp.org.au/guideline/juvenileidiopathicarthritis) has not been published in a peer-reviewed journal. It is to provide recommendations for the early diagnosis and multidisciplinary management of JIA in the primary care setting for general practitioners (GPs) [73]. No recommendations are made regarding the use of GCs, DMARDs, immunosuppressive drugs or biologic agents [73]. The ACR recommendations uses the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument [65], [76] which does not fulfill criteria of a proper consensus process and carries the risk, that experts vote for peer opinion, which might not reflect the true value. We used an advanced and linguistically validated version of the AGREE instrument: the "German Instrument for Methodological Guideline Appraisal (DELBI)", which has been developed in cooperation of the AWMF among others [77,78]. We followed the highly structured Nominal Group Technique as described in Methodology. Our consensus group only considered formally board nominated representatives of multidisciplinary scientific societies and organizations (Table 1) and included patient's representatives, as this has been strongly recommended by the European League against Rheumatism (EULAR) recently [79]. The ACR mentions a parent representative within their task force panel, but leaves this representative anonymous. It remains unclear how ACR experts were selected and involved [65]. They defined treatment groups which have not been evaluated systematically so far. We used the ILAR classification system which has been repeatedly evaluated [80–82].

By content there are major differences between the ACR recommendations and our guideline. a) Our guideline provides a detailed and systematic list of 20 drugs commonly used in the treatment of JIA (Table 5), which has been an integrative part of our consensus conferences. The ACR recommendations do not provide information on approval status (Food and Drug Administration), indications for use and no specific differences on dosage regimes or frequency of daily application [65], e.g. it refers to the 2008 ACR recommendations for the use of DMARDs in adult rheumatoid arthritis. b) The ACR recommendations provide a more early aggressive approach in the treatment of JIA. The ACR recommends MTX as first line treatment in patients (<4 joints) with highly active disease [65]. To our knowledge there are only data to recommend MTX administration in cases of insufficient therapeutic effect of prior treatment with NSAID and/or GC [33]. c) The ACR recommends the use of TNFα inhibitors as escalation therapy for some patients with history of arthritis of 4 or fewer joints and refer to publications [38,40] conducted in patients with polyarticular JIA or pauciarticular JIA with polyarticular course [65]. There is no evidence that TNF is safe and efficient in patients with oligoarticular JIA, a systematic, controlled clinical trial on this issue has not been done yet. d) We regard a brief trial of local or systemic administration of GC plus NSAID as a feasible first line treatment for patients with polyarticular JIA. The ACR recommends MTX without regard to disease activity at the initial stage [65]. We reached consensus to recommend the use of GC as bridging therapy until full onset of

Table 6 Overview of recommendations/guidelines for treatment of JIA.

	USA	Australia	Germany
	ACR recommendations [65]	RACGP recommendations [73]	GKJR guidelines
Deadline of literature search	October 2009	January 2007	September 2010
Source of publications	Pub Med	Pub Med EMBASE, CINHAL Cochrane Library provisional Australian Guideline [95]	Pub Med Previous German Guidelines [7,8]
Definition used for JIA subgroups	Treatment groups defined by Core expert panel	Not specifically defined, Children with JIA < 16 years	ILAR criteria [1]
Consensus process/process validation	AGREE [76] RAND/UCLA appropriateness method [96]	AGREE [76]	DELBI [77] NGT Delphi method
Conferences	None	None	3 Formal consensus conferences
Addressees	Pediatric rheumatologists	General practitioner	Pediatric Rheumatologists Pediatricians General practitioners
Participating scientific societies or professional organizations			
Pediatric rheumatologist or rheumatologists for adolescents	Yes	Yes	Yes
General pediatrician:			
- In hospital	Yes	Yes	Yes
- In private practice	Yes	Yes	Yes
Researcher	Yes	No	Yes
Rheumatologists for adults	No	No	Yes
Ophthalmologists	No	No	Yes
Parents/patients support groups	Yes	No	Yes
Orthopedic surgeons	No	No	Yes
Pediatric orthopedic surgeons	No	No	Yes
Psychologists	No	No	Yes
Physiotherapists	No	No	Yes
Pediatric rheumatology nurses	Yes	No	No
Other scientific societies or organizations	ACR, BSPAR, PRINTO, PReS	RACGP, NAMSCAG, NHMRC	DGKJ, DGPs, DGRh, DGO, AWMF, BVKJ

(ACR = American College of Rheumatologists, AGREE = Appraisal of Guidelines for Research & Development, AWMF = Association of the Scientific Medical Associations, BSPAR = British Society for Pediatric Rheumatology, BVJK = Association of Pediatricians in private practice, CEP = Core expert panel, ILAR = International League against Rheumatism, CINHAL = Cumulative Index to Nursing and Allied Health Literature, DELBI = German Instrument for Methodological Guideline Appraisal, DGKJ = German Society of Pediatrics and Adolescent Medicine, DGO = German Society for Ophthalmology, DGPs = German society for Psychology, DGRh = German Society for Rheumatology, GKJR = German Society for Pediatric Rheumatology, NAMSCAG = National Arthritis and Musculoskeletal Conditions Advisory Group, NGT = Nominal Group Technique, NHMRC = National Health and Medical Research Council, PReS = Pediatric Rheumatology Society), PRINTO = Pediatric Rheumatology International Trial Organization, RACGP = Royal Australian College of General Practitioner, RAND/UCLA = Research and Development/University of California at Los Angeles).

therapeutic effect of DMARDs. The ACR recommendations do not provide any recommendation for the use of systemic GC for patients with oligo- or polyarticular course of JIA except systemic onset of JIA. e) The ACR recommendations do not cover the topic of non-drug based therapy at all, although there is strong evidence that e.g. exercise training is a useful addition to drug treatment [57,58,60].

6. Conclusion

In summary we present a treatment guideline for JIA on a consensus conference basis. We strongly advocate an interdisciplinary approach including surgery, physiotherapy, psychosocial intervention, physical therapy, medications, etc. and a strict formal consensus process in order to create statements that are most appropriate for the complex clinical situation of a child and family presenting with JIA and cover all aspects of JIA care. All German pediatric rheumatology sites are participating at the national pediatric rheumatologic database in the Deutsche Rheuma-Forschungszentrum at Berlin (DRFZ, www.drfz.de). It aims at quality assurance in Germany and monitors treatment behavior of pediatric rheumatologists by using internationally agreed criteria (e.g. joint count, global physician rating of disease activity, global parent rating of overall well-being, CHAQ, ESR, ACR-ped response or JADAS). The database will be used as a tool to monitor the application of our treatment guidelines.

Conflict of interest statement

Gregor Dueckers: Novartis Pharmaceuticals Corporation, Baxter (for all: travel grants for scientific meetings);
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