A report for Universitätsklinikum Schleswig-Holstein/Campus Kiel on shared decision making for juvenile idiopathic arthritis (glucocorticoids orally or intravenously vs. intraarticular glucocorticoid injections)

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LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
CCT	Controlled clinical trial
CI	Confidence interval
CDSR	Cochrane Database of Systematic Reviews
CPG	Clinical practice guideline
CRD	Centre for Reviews and Dissemination
DA	Decision aid
DARE	Database of Abstracts of Reviews of Effects
DMARD	Disease-modifying anti-rheumatic drug
FAQ	Frequently asked question
GC	Glucocorticoid
GIN	Guidelines International Network
GKJR	Gesellschaft für Kinder- und Jugendrheumatologie (German Society for Pediatric Rheumatology)
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HTA	Health technology assessment
ICU	Intensive care unit
INAHTA	International Network of Agencies for Health Technology Assessment
IQR	Interquartile range
IU	International unit
IV	Intravenously
JIA	Juvenile idiopathic arthritis
KSR	Kleijnen Systematic Reviews
MTX	Methotrexate
N/A	Not applicable
N	Sample size
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NR	Not reported
NSAID	Non-steroidal anti-inflammatory drug
PICOS	Participants, intervention, comparators, outcomes, and study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ROM	Range of motion
QoL	Quality of life
RCT	Randomised controlled trial
SD	Standard deviation
SDM	Shared decision making
STJ	Subtalar joint
TA	Triamcinolone acetonide
TH	Triamcinolone hexacetonide
TMJ	Temporomandibular joint
TNF	Tumour necrosis factor
UK	United Kingdom

1. PROJECT OBJECTIVE

A key aim of the research project “Making SDM a reality” is to inform patients as part of shared decision making (SDM).

To support this, Kleijnen Systematic Reviews (KSR) Ltd has prepared an evidence report with a synthesis of the evidence of the relevant treatment options.

The topic of this evidence report is to present a summary of outcomes resulting from treatment with glucocorticoids (GCs; orally or intravenously (IV) vs. intraarticular injection) in patients with juvenile idiopathic arthritis (JIA).

2. METHODS

2.1 INCLUSION CRITERIA

The research question underpinning the literature searches for this topic was developed in conjunction with clinical departments at Universitätsklinikum Schleswig-Holstein/Campus Kiel. The question was framed in terms of participants, intervention, comparators, outcomes, and study design (PICOS), see Table 1.

Table 1: Inclusion and exclusion criteria

	Included	Excluded
Population	Children (<18 years of age) with juvenile idiopathic arthritis (JIA) of unknown aetiology following the exclusion of other known causes of synovitis with onset prior to age 16 years and a minimum of 6 weeks duration with involvement of any number of joints: • Monoarthritis (one joint) • Oligoarthritis (up to 4 joints) • Polyarthritis (>4 joints)	Patients with skin, internal organs, muscles, ligaments and/ or tendon involvement
Intervention	Systemic glucocorticoids (orally or IV; with or without non-steroidal anti-inflammatory drugs (NSAIDs) and/or disease-modifying anti-rheumatic drugs (DMARDs))	None
Comparator	Glucocorticoid injections (intraarticular; with or without NSAIDs and/or DMARDs)	None
Outcomes	• Treatment duration and dosing • Use of analgo-sedation • Impact on inflammation • Time to resolution of symptoms/remission • Pain: acute and chronic • Joint(s) function/impact on mobility • Frequency of flare-ups • Reduction in swelling/redness • Quality of Life (QoL; any tool; patients and/or family) • Treatment-related risk including risk of calcifications • Adverse events	Those not listed
Study design	Systematic reviews, health technology assessments (HTAs) and guidelines; non-systematic reviews*; primary research including randomised controlled trials (RCTs), CCTs, cohort studies*	Expert opinions; letters
Effect modification / Subgroups	• Accompanied by NSAIDS and/or DMARDs • Based on number of joints involved/type • Based on previous therapy	Not applicable
* to be considered if evidence from systematic reviews/CPGs is scarce		

2.2 FREQUENTLY ASKED QUESTIONS

In consultation with the commissioner, the list of frequently asked questions (FAQs) asked by patients, in respect of outcomes identified in the literature, were developed:

1. **What does the treatment for JIA involve?**
    a. What is the procedure?
    b. Frequency of drug dosing
2. **Will I need anaesthesia?**
3. **Will treatment help my symptoms and for how long?**
    a. Resolution of symptoms/remission (including time to resolution)
    b. Decrease in inflammation
    c. Impact on pain and function
    d. Impact on concomitant treatments (e.g. DMARDs)
4. **Will treatment impact my QoL (individual and family)?**
5. **What are the side effects and treatment-related risks?**

2.3 LITERATURE SEARCHES

Literature searches were carried out to identify relevant systematic reviews and evidence-based guidelines on the treatment of children with JIA. To inform frequently asked questions (FAQs) a second targeted database search on JIA and shared decision making was also undertaken.

The search strategies were developed specifically for each database and the keywords adapted according to the configuration of each database. Searches were limited by date range for systematic reviews and guidelines to 2012-2020. Targeted searches on shared decision-making and JIA were limited to the last five years (2015-2020) as current and up-to-date evidence in this area was considered to be most relevant. Searches were not limited by language or publication status.

2.4 SEARCH SOURCES

Systematic reviews and guidelines

The following systematic review specific databases were searched from 2012 to present:

- Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/11/Iss11
- Database of Abstracts of Reviews of Effects (DARE) (www.crd.york.ac.uk): up to 2015/03
- Health Technology Assessment (HTA) database (www.crd.york.ac.uk): up to 2018/03
- INAHTA (https://database.inahta.org/): up to 2020/11/17
- KSR Evidence (https://ksrevidence.com/): up to 2020/11/17
- Epistemonikos (www.epistemonikos.org): up to 2020/11/17

The following guidelines resources were searched from 2012 to present:

- Guidelines International Network (G-I-N) (www.g-i-n.net): up to 2020/11/17
- NHS Evidence (www.evidence.nhs.uk): up to 2020/11/17
- ECRI Guidelines Trust (https://guidelines.ecri.org/): up to 2020/11/17
- NICE (www.nice.org.uk): up to 2020/11/17

Full details of all search strategies are presented in Appendix 1.

Targeted searches

To identify papers relevant to shared decision making, targeted searches were undertaken in the following databases from 2015 to present:

- EMBASE (Ovid): 1974-2020/10/20
- MEDLINE and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily: 1946- 2020/10/20
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): up to 2020/10/Iss10

Full details of all search strategies are presented in Appendix 1.

Handling of citations

Identified references from the bibliographic database searches were downloaded into EndNote bibliographic management software for further assessment and handling.

Supplementary searches

In addition, the website of an organisation supporting patients with JIA (National Rheumatoid Arthritis Society; www.jia.org.uk) was searched for any relevant patient friendly information about GCs.

ClinicalTrials.gov was searched for any ongoing or future studies (not yet recruiting; recruiting; enrolling by invitation or active, not recruiting) focused on GCs (orally, IV or intraarticular injection) using keyword “Juvenile Idiopathic Arthritis” or “JIA” on 24/11/2020. Records identified were screened based on the eligibility criteria in Table 1.

2.5 METHODS OF STUDY SELECTION, QUALITY ASSESSMENT AND DATA EXTRACTION

Study selection

A stepwise approach was used to identify the most recent and relevant evidence. Two reviewers independently screened the title and abstract of each record identified by the search and determined the potential relevance of each record. For potentially relevant records, the full paper was obtained, independently checked by two reviewers, and inclusion criteria applied. Any disagreements were resolved through discussion.

An evidence hierarchy was used to select the most appropriate study(ies) to populate the evidence tables. Where more than one study could provide evidence, the most relevant studies were selected using the following criteria: recency (most recent preferred), quality (highest quality preferred), representativeness (populations representative of the general target population preferred). Where there were gaps in the evidence (no systematic

review or guideline available), it was agreed to include and extract evidence from non-systematic reviews and high-quality primary evidence (RCTs).

Data extraction

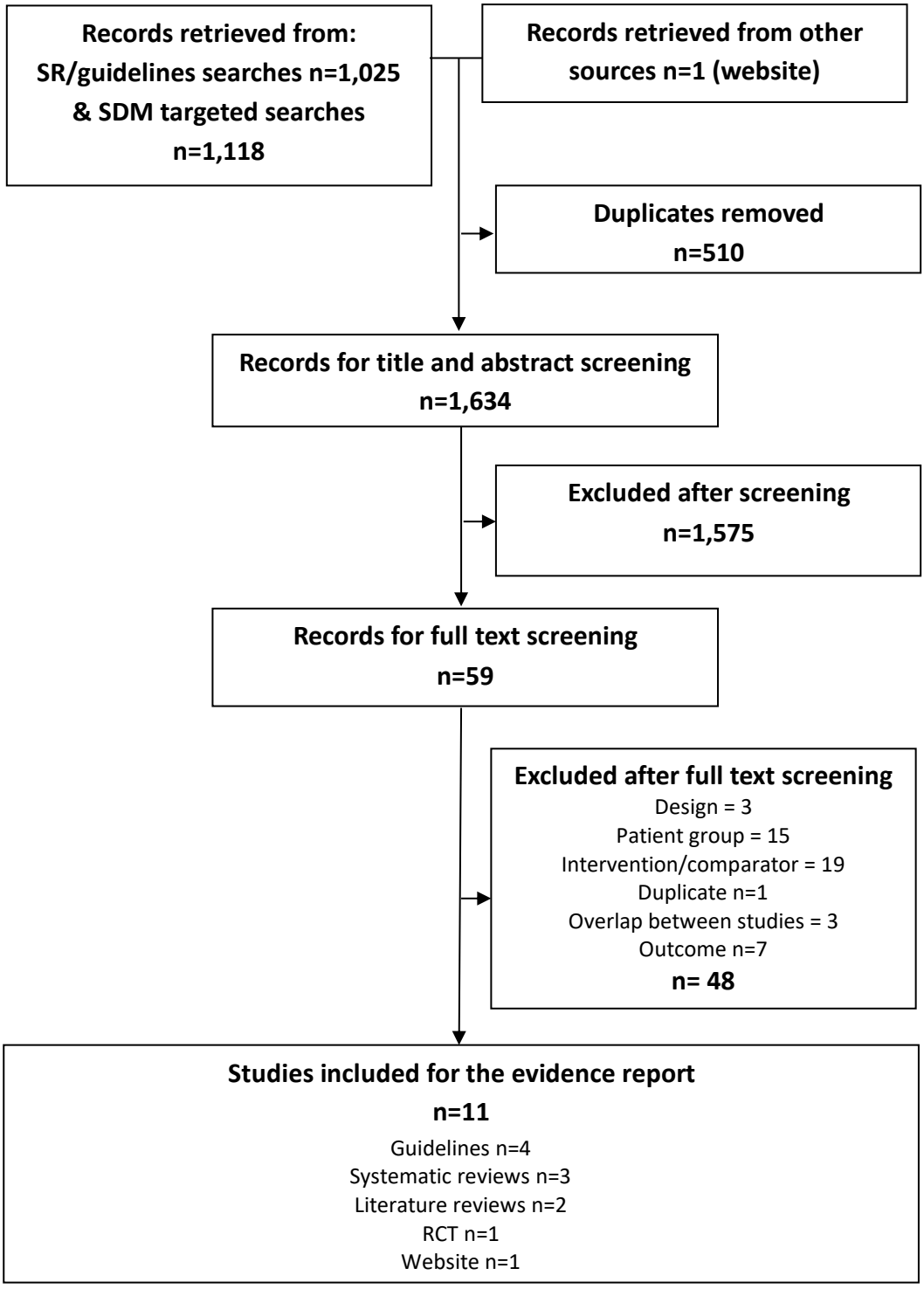
For studies which required data extraction, data were extracted by one reviewer and checked by another. Any disagreements were resolved by consensus.

3. RESULTS

3.1 LITERATURE SEARCH RESULTS AND INCLUSION ASSESSMENT

Searches were conducted in November 2020 to identify systematic reviews, health technology assessments or evidence-based guidelines. A total of 2,144 records were retrieved from the literature searches and a website. After removal of duplicate records, 1,634 titles and abstracts were screened by two reviewers. After screening, 59 records were selected for further assessment from which 11 were selected as meeting the inclusion criteria. A summary of the study selection process according to modified PRISMA reporting guideline[1] is reported in Figure 1.

Figure 1: Study selection process



3.2 Overview of the evidence

Table 2 summarises the sources of evidence used to answer the five FAQs. No comparative evidence from the primary studies was found (systemic GCs vs. intraarticular GC injections) for any outcomes that could inform any of the FAQs. No studies were identified that reported QoL of patients with JIA treated by GCs. However, other published primary studies were included in systematic reviews and guidelines described below.

Three guidelines were identified which provided background information on treatments and recommendations for patients with JIA: two were on any type of JIA - the German S2k (Oommen 2019[2]) and the international Task Force guidelines (Ravelli 2018[3]); one was specifically on polyarticular JIA – the American College of Rheumatology (ACR) guideline (Ringold 2019[4]). A fourth guideline was not focused on the JIA population, but it included recommendations for children treated with GCs, and thus, it was judged as relevant (ACR 2017; Buckley 2017[5]). The scope of included guidelines included GCs administered orally/IV[2-4] or as intraarticular GC injection.[2, 4] All guidelines were based on very low to moderate quality of evidence identified through mostly limited systematic review searches (i.e. inclusion of papers published in the English language only[4, 5]). Overall, the quality of guidelines was either low (Oommen 2019[2], Ravelli 2018[3]) or moderate (Ringold 2019[4], Buckley 2017[5]) due to methodological weaknesses.

Three systematic reviews were sources of information for intraarticular GC injections for either temporomandibular joint (TMJ) only (Antonarakis 2020[6], Stoustrup 2013[7]) or for joints in the lower limb (i.e. knee, ankle, subtalar and other foot joints; Jennings 2014[8]). Only the systematic review by Antonarakis 2020[6] provided pooled estimates of effectiveness with the other two systematic reviews[7, 8] providing a qualitative synthesis of findings due to substantial heterogeneity in the outcomes, and their definitions, as well as the small number of studies reporting the outcomes. The type of concomitant drugs, their frequency and period of use as well as the dosage in patients with JIA was underreported in all three systematic reviews. The quality of systematic reviews were judged as low (Antonarakis 2020[6]) or moderate (Stoustrup 2013[7], Jennings 2014[8]) due to methodological weaknesses (i.e. limited search strategies, the inclusion of English language papers only, lack of full data extraction). No systematic reviews were identified summarising the evidence on the use of systemic GCs (orally/IV) in patients with JIA.

To include more comprehensive information regarding the effect on symptoms and adverse effects, especially of systemic GCs, two literature reviews were included (Batu 2019[9], Cheng 2012[10]). The reviews did not focus on any type of JIA. The results should be interpreted with caution, as the quality of the reviews was judged as unclear due to limited information regarding their methodology.

The systematic literature search described above identified one poster presentation (Bracciolini 2014[11]) providing information on an RCT of intraarticular GC injection with or without methotrexate (MTX) for joints in lower and upper limbs in patients

with oligoarticular JIA. The decision was made to obtain the full text for RCT (Ravelli 2017[12]) due to (1) limited availability of high-quality evidence, particularly lacking for joints located in upper limbs, and (2) lack of information on the effect of GCs used with concomitant therapies. The RCT was judged as moderate quality mostly due to the lack of masking and the lack of monitoring of MTX administration.

Table 2: Evidence sources

Reference	Evidence type	Intervention	**FAQ1:** treatment description, recommendations and/or drug dosage	**FAQ 2**: use of anaesthesia	**FAQ 3**: symptom relief	**FAQ 4**: QoL	**FAQ 5**: adverse events
Oommen 2019[2]	Guideline (German S2k)	GCs orally/IV	✓	-	-	-	-
		Intraarticular GC injection	✓	✓	-	-	-
Ringold 2019[4]	Guideline (ACR 2019)	GCs orally/IV	✓	-	-	-	-
		Intraarticular GC injection	✓	-	-	-	-
Ravelli 2018[3]	Guideline (Task Force)	GCs orally/IV	✓	-	-	-	-
Buckley 2017[5]	Guideline (ACR 2017)	-	✓	-	-	-	-
Antonarakis 2020[6]	SR with meta-analysis	Intraarticular GC injection	-	-	✓	-	-
Jennings 2014[8]	SR	Intraarticular GC injection	-	-	✓	-	✓
Stoustrup 2013[7]	SR	Intraarticular GC injection	-	-	✓	-	✓
Batu 2019[9]	Review	GCs orally/IV	-	-	-	-	✓
		Intraarticular GC injection	-	-	-	-	✓
Cheng 2012[10]	Review	Intraarticular GC injection	-	-	✓	-	✓
Ravelli 2017[12]	RCT	Intraarticular GC injection	-	-	✓	-	✓
National Rheumatoid Arthritis Society 2020[13]	Patient information	Intraarticular GC injection	✓	✓	-	-	-

GC – glucocorticoid; IV – intravenously; QoL – quality of life; RCT – randomised controlled trial; SR – systematic review

3.3 FAQ1: What does the treatment for JIA involve?

The following information was summarised mostly based on guidelines by Oommen 2019[2] (German S2k), Ringold 2019[4] and Ravelli 2018[3]. Supplementary evidence was gathered from systematic reviews (Jennings 2014[8], Stoustrup 2013[7]) and online resource for JIA patients[13].

This section includes background information and recommendations for practice along with drug dosage for both systemic GCs and intraarticular GC injections presented in Table 3. Summary of treatment plans for patients with various forms of JIA are presented in Figure 2. Systemic GCs are fast-acting and effective treatment; however, their use is not recommended to most patients with JIA, with exception of high disease activity, due to the severity of associated side effects[2, 4]. Intraarticular GC injections with triamcinolone hexacetonide (TH) are recommended to patients with any type of JIA due to their effectiveness in relieving joint pain with fewer side effects compared to systemic GCs[2, 4].

GC drugs are a synthetic version of steroid hormones that are present naturally in the human body with the ability to suppress inflammation. As the basis of any signs and symptoms in JIA are inflammatory processes, GCs emerged as one of the treatment options in patients with JIA[3].

GCs are most often combined with other drug treatments, such as NSAIDs and DMARDs, to achieve the necessary control of the inflammation, and consequently, desired treatment outcome[2]. NSAIDs are widely used drugs in symptomatic treatment to e.g. relieve mild to moderate pain or reduce inflammation. They are only used as adjunct therapy, particularly during initiation or escalation of other drugs, and are not appropriate as monotherapy[2, 4]. DMARDs, however, are drugs which interfere with the inflammatory pathways, thus, treating the underlying disease instead of only symptoms. They are used in the long-term treatments in rheumatology diseases in combination with other drugs. We can distinguish biological (e.g. etanercept or abatacept) or conventional synthetic (e.g. MTX) DMARDs[2, 4].

Moreover, non-drug therapies, such as physiotherapy or psychological support, are required to support the patients and their families[2].

The target of treatment for JIA, such as disease remission, and the therapeutic strategy should be a joint decision between patients and their parents along with the paediatric rheumatology healthcare team[3].

The summary of treatment plans, along with optional and non-drug therapies, and aims of treatment in patients with various forms of JIA is presented in Figure 2 (taken from Oommen 2019[2]).

Figure 2: Summary of treatment plans for patients with various forms of JIA

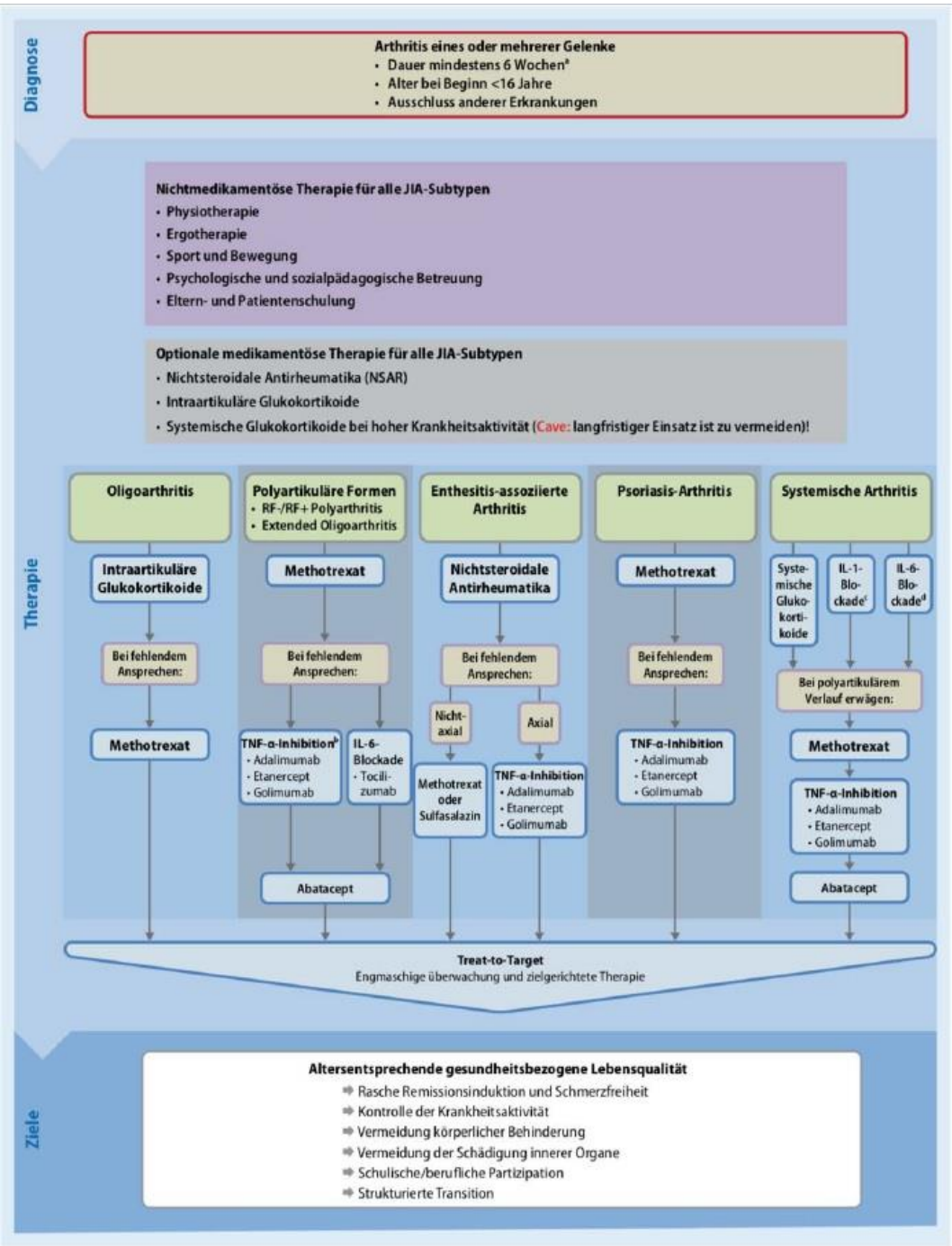


Table 3: Description of options

GCs (orally or IV)
GCs can be used systemically i.e. administered in the form of a pill (taken daily) or intravenous pulse therapy (intravenous infusion of medication over a short time period). GCs approved for JIA patients include: prednisolone/prednisone (converted to prednisolone in the liver) and methylprednisolone. The medications are administered based on guidance from a treating physician.[2] *Recommendations for practice* Importantly, Oommen 2019[2] states long-term use of GCs should not take place due to undesirable effects (discussed in FAQ5) and the availability of other forms of therapy (baseline therapy to impact disease processes with DMARDs and/or symptomatic treatment with NSAIDs). The recommendations are supported by other guidelines[3, 4], i.e. Ringold 2019[4] strongly recommends against including chronic low-dose GC therapy to patient's regimen, irrespectively of risk factors or disease activity (low level of evidence) due to known adverse effects of long-term GCs in children (see FAQ5). For patients with low disease activity in polyarthritis JIA, Ringold 2019[4] recommends against bridging therapy (therapy to control disease activity at the initiation or escalation of other drugs) with a limited course of oral GCs (<3 months). However, for patients with polyarthritis JIA with high or moderate disease activity, the same bridging therapy with a limited course of GCs (<3 months) is recommended (very low level of evidence) and may be of most utility in the setting of limited mobility and/or significant symptoms[4]. For patients with high disease activity, Oommen 2019[2] recommends that systemic application of GC should be used for systemic and non-systemic forms of JIA. *Drug dosage (Oommen 2019[2])* Long-term therapy: prednisolone/prednisone, methylprednisolone (any age) 0.1-0.2 mg/kg of body weight (max 5 mg/day; if necessary, higher dosage at initiation of therapy). Oral low dose therapy: <0.2 mg/kg of body weight or <4 mg/m2 of body surface prednisolone-equivalent. Oral medium dose therapy: 0.2-1.0 mg/kg of body weight prednisolone-equivalent. Oral high dose therapy: 1.0-2.0 mg/kg of body weight prednisolone-equivalent. Intravenous pulse therapy: 10-30 mg/kg of body weight IV methylprednisolone (max 1 g/dose for 1-3 days).

GC injection (intraarticular)

Intraarticular GC injection is a procedure during which the medications, such as TH or triamcinolone acetonide (TA), are injected directly into the painful joint(s). During the session, joints should be assessed to identify which require injection at the time of the procedure as this may change following the initial assessment. To alleviate any pain, patient will require some form of anaesthesia (pain relief) (see FAQ2)[13]. Intraarticular GC injections may require image-guidance (e.g. X-ray or ultrasound) to ensure a correct administration and placement of medications in the joint which can lead to fewer adverse events[7, 8].

Single or multiple joints can be treated in a single patient, however, the injection of several joints at the same time is preferable to a consecutive injection at different times[2]. Moreover, the same joint can be treated repeatedly with some limitations.

Management following intraarticular injection includes a brief period of rest; some form of physiotherapy and splinting of joints may also be recommended [13].

Recommendations for practice

Oommen 2019[2] recommends using intraarticular GC injection (injection of TH) to treat active arthritis in JIA (all types). Similarly, Ringold 2019[4] recommends intraarticular GC injections as adjunct therapy (low level of evidence) with strong recommendations for TH over TA in patients with polyarthritis JIA (moderate level of evidence). Ringold 2019[4] highlights that intraarticular GC injections for a large number of joints, or joints that have been injected multiple times, might not be appropriate treatment option with an escalation of systemic therapy being more appropriate.

Drug dosage (Oommen 2019[2])

TH can be administered in patients older than five months in large joints in a dose of 0.5-1 mg/kg of body weight (max 40 mg; dose adjusted accordingly in smaller joints).

3.4 FAQ2: Will I need anaesthesia?

This question was answered using the information from Oommen 2019[2], literature review by Cheng 2012[10], RCT by Ravelli 2017[12] and online resource for JIA patients[13].

A limited volume of evidence exists on the methods and effectiveness of any type of anaesthesia for patients undergoing intraarticular GC injections. To date, topical anaesthesia or subcutaneous therapy showed no advantages for procedural or post-procedural pain.

To ensure that intraarticular GC injection is as comfortable as possible for the patient, anaesthesia can be administered before the procedure[13]. However, an individual decision needs to be made about performing the procedure under short-acting anaesthesia, analgesic sedation or local anaesthesia[2].

To date, no advantages were proven for either topical local anaesthesia or subcutaneous therapy (e.g. cream or lidocaine injection) for procedural or post-procedural pain[2]. Data from one RCT described in Cheng 2012[10] states that application of 2.5g lidocaine/prilocaine

cream for 60-90 min before steroid injection into the knees of children with JIA did not show significant analgesic effect on pain. No other evidence regarding the effectiveness of different anaesthetics was identified.

Single analgo-sedation can be used to perform multiple injections during a single session[12]. The procedure will be carried out by a health professional and their team who have access to pain relief and are skilled in the intraarticular GC injections[13].

3.5 FAQ3: WILL TREATMENT HELP MY SYMPTOMS AND FOR HOW LONG?

The following information was summarised based on information in Oommen 2019[2], three systematic reviews (Antonarakis 2020[6], Jennings 2014[8], Stoustrup 2013[7]), literature review by Cheng 2012[10] and one RCT by Ravelli 2017[12].

Systemic GCs are fast acting substances with known symptom relief in patients with inflammatory conditions, including systemic JIA, however, no quantitative summary of evidence regarding symptom relief following administration of systemic GCs in the relevant population (patients with mono , oligo- or polyarticular JIA) was identified through the literature search. Some impact on the symptom relief following intraarticular GC injections in patients with TMJ involvement or lower limb joints was reported, however, the quality of evidence was weak or inconclusive. For patients with oligoarticular JIA, concomitant use of MTX alongside intraarticular GC injection is associated with only a small difference in remission of arthritis, but prolonged time to arthritis flare-up in injected joints.

GC (orally or IV)

Systemic GCs are fast acting substances with known symptom relief in patients with inflammatory conditions, including patients with systemic form of JIA[2]. The literature search did not identify any relevant papers that reported quantitative results regarding symptom relief following administration of systemic GCs (orally or IV) in the relevant population (patients with mono-, oligo- or polyarticular JIA).

GC injection (intraarticular) – TMJ involvement

In patients with TMJ involvement, intraarticular GC injection was associated with the pooled increase in maximal interincisal opening of 4.38 mm (95% confidence interval (CI) 2.76-6.00; n=6 studies; follow-up ranged 1.5 to 57 months) and pain resolution in 78% (95% CI 59%-90%; n=7 studies; follow-up ranged from 1.5 to 57 months) of patients[6]. Radiological improvement was reported in 48-83% of patients based on magnetic resonance imaging (n=4 studies) and 13% based on computed tomography findings (n=1 study)[7].

GC injection (intraarticular) – lower or upper limb joints

In patients with JIA in lower limb joints, weak or inconclusive evidence was reported for improvement in patient outcomes (Table 4) [8, 10].

Table 4: Impact on symptom relief (only of intraarticular GC injection) in lower limb joints

Reference	Outcome details	Nr of studies with an outcome	Follow-up range	Summary	Certainty of evidence	Assessment for use in DA
Jennings 2014[8]	Clinical response	13	N/A	Sustained clinical response reported in all studies (includes knee n=8 studies, knee and ankle n=1, STJ n=3 and midfoot joints n=1; significant difference in n=4 studies)	Weak or inconclusive evidence	- The evidence is insufficient to draw any conclusions on effectiveness of systemic GCs vs. intraarticular GC injections given no evidence for systemic GCs and weak or inclusive evidence for intraarticular GC injections
	Tenderness/pain	3		Some reduction in tenderness/pain in knee (n=2 studies) and ankle (n=1 study)		
	Swelling	2		Some decrease in swelling in knee		
	Synovitis	3		Some reduction in synovitis in lower leg joints; overall mean synovitis relapse time (n=1 study) 0.5 years (IQR 0.3-1.3) vs. mean remission time 0.9 years (IQR 0.6-1.9)		
	Effusion	1		Inconclusive evidence for any effect in knee		
	Hyperthermia	1		Inconclusive evidence for any effect in knee		
	Joint ROM	5		Increase in knee flexion (n=1 study), some improvement in knee ROM (n=2) increase in foot inversion and eversion (n=1) and ankle joint ROM normalisation/partial improvement (n=1); Mean duration of improvement in STJ was 1.2 years (SD ±0.9 years; n=1 study)		
Jennings 2014[8]; Cheng 2012[10]	Leg length discrepancy	3		Some decrease in the differences between limb length (n=2 studies) and knee joint circumference (n=1 study)		
Cheng 2012[10]	Gait pattern	1		Improvement in gait patterns (walking velocity and joint moments)		

DA = decision aid; IQR – interquartile range; ROM – range of motion; SD – standard deviation; STJ – subtalar joint

Low-quality evidence for prolonged remission in patients with JIA following intraarticular GC injections in combination with MTX was reported[10]. Results of a recent RCT[12], focused on oligoarticular JIA patients with lower and upper limb joints receiving intraarticular GC injection, showed only a slight difference in remission with or without MTX. For patients who received or did not receive MTX, remission of arthritis in all injected joints at 12 months was 34% and 39% (P=0.48), respectively. The incidence of new-onset arthritis was similar for both groups (no MTX: 37% vs. with MTX: 36%) as well as the proportion of patients who achieved inactive disease based on Wallace (no MTX: 26% vs. with MTX: 36%) and clinical Juvenile Arthritis Disease Activity Score criteria (no MTX: 27% vs. with MTX: 28%)[12]. Time to arthritis flare-up in injected joints was longer with concomitant MTX (no MTX: median six months, 95% CI 4.6 – 8.2; with MTX: median 10.1 months, 95% CI 7.6 – >16), however, the addition of MTX did not impact the odds of a flare-up of arthritis in injected joints (odds ratio 0.69, 95% CI 0.38 – 1.24, P=0.22).

3.6 FAQ4: Will Treatment impact my quality of life?

The literature search did not identify any relevant papers focusing of QoL of patients in JIA receiving any form of GCs.

3.7 FAQ5: What are the side effects and/or treatment-related risks?

The following information was summarised based on information in Buckley 2017[5]; two systematic reviews (Jennings 2014[8], Stoustrup 2013[7]); two literature reviews (Batu 2019[9], Cheng 2012[10]) and RCT by Ravelli 2019[12].

No comparative evidence was identified which evaluate the rates of adverse events of systemic GCs vs. intraarticular GC injections,however, localised administration of GCs (intraarticular GC injection) might be associated with lower rates and/or severity of adverse events given the well-known serious adverse events associated with systemic GCs. The impact of adverse events associated with concomitant drugs, such as DMARDs or NSAIDs, must be taken into account. Optimisation of calcium and vitamin D intake is recommended for children receiving GC ≥3 months due to the risk of development of GC-induced osteoporosis[5].

Please note that the list of adverse events related to systemic GCs or intraarticular GC injections mentioned below is not exhaustive and based on evidence for mixed types of JIA.

GCs (orally or IV)

Although no systematic reviews were found that reported the rates of side effects of systemic GCs in JIA, the review by Batu 2019[9] provided a summary. The frequency and severity of adverse events in systemic use of GCs correlates with the duration of therapy and the drug dose[2]. Long-term systemic use of GCs is associated with toxic and metabolic adverse events, especially at doses exceeding those found in healthy individuals (supraphysiological)[9]. In children with JIA, systemic use of GCs was found to be associated with the following critical adverse events: adrenal suppression/insufficiency, growth restriction (by promoting bone resorption, inhibition of bone formation or secretion of

growth hormone), osteoporosis, osteonecrosis (reduction or loss of blood supply to bone[9]), cataract, glaucoma, increased risk for viral, bacterial and fungal infections.

Other side effects include[2, 9]:

- Cushing's syndrome (a condition caused by elevated GC levels over a long period of time)
- weight gain
- atherosclerosis (build-up of fats, cholesterol and other substances inside arteries)
- arterial hypertension
- hyperlipidaemia (high levels of lipids in the blood)
- hyperglycaemia or corticosteroid-induced diabetes
- myopathy (loss of muscle strength)
- gastritis (inflammation of the stomach lining)
- gastrointestinal ulcers with bleeding (especially when combined with NSAIDs)
- steatohepatitis (liver inflammation with fat accumulation)
- skin pathologies (striae, skin atrophy, acne, impaired wound healing and others)
- psychosis, mood and behaviour changes.

GC injection (intraarticular)

Intraarticular GC injections are also associated with adverse effects; however, they are rare or insignificant[10].

In the systematic review by Jennings 2014[8] looking at intraarticular injections in the lower limb joints, the most commonly reported side effect was skin or subcutaneous layer atrophy (the reduction in the thickness of skin or subcutaneous fat loss, respectively due to prolonged exposure to GCs). However, the definitions of adverse events differed between studies. Other adverse events were rare and reported only in a small number of patients in 16 out of 21 studies (Table 5).

In the systematic review by Stoustrup 2013[7], examining intraarticular GC injections in TMJ, adverse events were reported in five out of seven studies (Table 6).

Table 5: Adverse events (only associated with intraarticular GC injection) in lower limb joints

Adverse event category	Adverse event as reported in Jennings 2014[8]	Nr of studies reporting adverse event	Rate of adverse event (% of patients)	Nr of patients with event	Certainty of evidence	Assessment for use in DA
Atrophy and/or skin hypo-pigmentation	focal cutaneous atrophy with ruptured popliteal cyst	1	6.7%#	1 out of 15	Weak or inconclusive evidence	- The evidence is insufficient to draw any conclusions on effectiveness of systemic GCs vs. intraarticular GC injections given no quantitative evidence for systemic GCs and weak or inclusive evidence for intraarticular GC injections
	local subcutaneous atrophy	7	1.1%# - 10%#	3 out of 30; 1 out of 94; 2 out of 24; 1 out of 40; 2 out of 23; 2 out of 21; 1 out of 23		
	skin hypopigmentation or subcutaneous atrophy	2	53%; 0.9% of joints*	- -		
	atrophic lesion	1	9.5%#	2 out of 21		
	skin atrophy with hypopigmentation	1	20%#	12 out of 60		
	subcutaneous lipolysis with spontaneous regression	1	10%	3 out of unclear nr of patients		
Calcification	asymptomatic periarticular calcification	1	8.3%#	2 out of 24		
Pain	short-lived pain and erythema	1	4.2#	1 out of 24		
	painful and red knee the day after injection	1	4.8#	1 out of 21		
Systemic events	flushing or redness	1	“a few”	-		
	flushed cheeks	1	1.7#	1 out of 60		
	increased appetite	1	5%#	3 out of 60		

Adverse event category	Adverse event as reported in Jennings 2014[8]	Nr of studies reporting adverse event	Rate of adverse event (% of patients)	Nr of patients with event	Certainty of evidence	Assessment for use in DA
	mood changes	1	5%[#]	3 out of 60		
Other	reversible apnoea (<20 sec duration during induction of sedation)	1	2.4%[#]	2 out of 85		

[*] n=1 study reported nr of joints injected instead of nr of patients that experienced the event; [#]Calculated based on the data available in the SR
DA = decision aid; SR = systematic review

Table 6: Adverse events (only associated with intraarticular GC injection) in the TMJ

Adverse event category	Adverse event as reported in Stoustrup 2013[7]	Nr of studies reporting adverse event	Rate of adverse event (% of patients)	Nr of patients with event	Certainty of evidence	Assessment for use in DA
Atrophy and/or skin hypo-pigmentation	subcutaneous/skin atrophy	2	4%[#]; 1.2%[#]	1 out of 25; 1 out of 83	Weak or inconclusive evidence	- The evidence is insufficient to draw any conclusions on effectiveness of systemic GCs vs. intraarticular GC injections given no quantitative evidence for systemic GCs and weak or inclusive evidence for intraarticular GC injections
	skin hypopigmentation	1	1.6%[#]	1 out of 63		
Calcification	intraarticular calcification	1	8%[#]	2 out of 25		
Swelling	transient swelling/pain	1	12%[#]	10 out of 83		
	swelling	1	3.2%[#]	2 out of 63		
	facial swelling	1	8.7%[#]	2 out of 23		
Other	fever	1	1.6%[#]	1 out of 63		
	TMJ stiffness/chewing dysfunction	1	-	-		
	scar	1	-	-		

[#]Calculated based on the data available in the SR. DA = decision aid; GC = glucocorticoid; SR = systematic review; TMJ = temporomandibular joint

In an RCT by Ravelli 2017[12] no adverse events at the site of intraarticular GC injections, or related to systemic absorption of injected GCs, were recorded in joints of lower or upper limbs in JIA patients. However, 17% (n=20) of patients who received intraarticular GC injection and MTX reported systemic adverse events including gastrointestinal discomfort (nausea, vomiting, or constipation; n=14), increased liver transaminases (n=8), fatigue (n=2), irritability (n=2), hair loss (n=1), and leukopenia (n=1).

Other adverse events, not covered by previous studies, include septic arthritis (probability of its occurrence in about 1 in 10,000 injections), rapid destruction of the femoral head, acute synovitis, Charcot's arthropathy, tendinopathy, Nicolau's syndrome or joint dislocation.[10]

Recommendations for treatment to mitigate adverse events

The 2017 ACR guideline[5] recommends particular treatments as follows; due to the known effects of prolonged use of GCs on the development of osteoporosis, for children ages 4-17 years treated with GCs for ≥3 months, it is recommended to optimise calcium (1000 mg/day) and vitamin D intake (600 IU/day). For children at the same age, but who have had an osteoporotic fracture and continue on GC at a dose of ≥0.1 mg/kg/day for ≥3 months, additional treatment with an oral bisphosphonate (or an IV bisphosphonate if oral treatment is not appropriate) is recommended along with calcium and vitamin D. Recommendations are conditional due to low or moderate quality of evidence from population other than JIA.

3.8 ONGOING STUDIES

The only eligible ongoing study is a randomised controlled trial of tumour necrosis factor (TNF)-inhibitors with added intraarticular GC injection vs. TNF-inhibitors with no injection. The study is not yet recruiting with estimated start and completion dates of 16/11/2020 and 16/11/2023, respectively. The trial aims to recruit 202 participants with non-systemic JIA with at least one joint with active arthritis (NCT04614311)[14]. Moreover, two other studies are currently recruiting with focus on oligoarticular JIA patients on abatacept with usual care vs. usual care only, where steroid injections are part of the usual care[14], and step-up and step-down approached to treat patients with oligoarticular JIA with intraarticular injections listed as part of step-down approach[15].

4. DISCUSSION

4.1 SUMMARY OF FINDINGS

This report is based on the results of the systematic literature search of any available evidence published between 2015 and 2020 and an additional search for systematic reviews published between 2012 and 2015. After screening 1,634 references, the content is based on 11 eligible resources including four guidelines with recommendations for practice (e.g. German S2k guideline), three systematic reviews, two non-systematic literature reviews, one RCT[12] and the online resource for JIA patients[13].

The volume of the evidence on outcomes for the decision aid (DA; see Appendix 2), for each of the FAQs, can be summarised as follows:

- FAQ1: What does the treatment for JIA involve?
    - Background information and recommendations for practice along with drug dosage for both systemic GCs and intraarticular GC injections presented in Table 3. Summary of treatment plans for patients with various forms of JIA presented in Figure 2.
    - Systemic GCs are fast-acting and effective treatment; however, their use is not recommended to most patients with JIA, with exception of high disease activity, due to the severity of associated side effects.
    - Intraarticular GC injections with TH are recommended to patients with any type of JIA due to their effectiveness in relieving joint pain with fewer side effects compared to systemic GCs.
- FAQ2: Will I need anaesthesia? (intraarticular GC injections only)
    - Limited volume of evidence exists on the methods and effectiveness of any type of anaesthesia for patients undergoing intraarticular GC injections. So far, topical anaesthesia or subcutaneous therapy showed no advantages for procedural or post-procedural pain.
- FAQ3: Will treatment help my symptoms and for how long?
    - Systemic GCs are fast acting substances with known symptom relief in patients with inflammatory conditions, including systemic JIA, however, no quantitative summary of evidence regarding symptom relief following administration of systemic GCs in the relevant population (patients with mono-, oligo- or polyarticular JIA) was identified through the literature search.
    - Some impact on the symptom relief following intraarticular GC injections in patients with TMJ involvement or lower limb joints was reported, however, the quality of evidence was weak or inconclusive.
    - For patients with oligoarticular JIA, concomitant use of MTX alongside intraarticular GC injection is associated with only small difference in

remission of arthritis, but prolonged time to arthritis flare-up in injected joints.

- FAQ 4: Will treatment impact my QoL (individual and family)?
    - No information was available on the effect of administration of systemic GCs or intraarticular GC injections on QoL of JIA patients.
- FAQ5: What are the side effects and treatment-related risks?
    - No comparative evidence was identified which evaluate the rates of adverse events of systemic GCs vs. intraarticular GC injections, however, localised administration of GCs (intraarticular GC injection) might be associated with lower rates and/or severity of adverse events given the well-known serious adverse events associated with systemic GCs.
    - Impact of adverse events associated with concomitant drugs, such as DMARDs or NSAIDs, must be taken into account.
    - Optimisation of calcium and vitamin D intake is recommended for children receiving GC ≥3 months due to the risk of development of GC-induced osteoporosis.

It was not possible to perform any subgroup analysis based on the available data. The only information on the potential effect of adding MTX (DMARD) to glucocorticoid GC injection is presented in RCT by Ravelli 2017[12] discussed in FAQ5.

4.2 Ongoing trials

The results of a non-systematic search for ongoing trials in ClinicalTrials.gov database revealed that only one study (NCT04614311[14]) focused on GCs use in patients with JIA is planned and aims to start recruitment shortly. Due to a lack of ongoing trials, it is unlikely that high-quality evidence for patients with JIA for the comparison of GC orally/IV vs. intraarticular GC injection will be available in the near future.

4.3 Strength, limitations and uncertainties

The report is based on thorough literature searches and the inclusion of the most up-to-date evidence from 2012. Although the report does not cover all outcomes of interest, the evidence base consists of guidelines, prepared by the organisations focused on advancing the practice and treatment of patients with JIA, and systematic reviews. However, it was necessary to include non-systematic reviews and one primary study.

The recommendations included in the guidelines were prepared based on low to moderate quality of evidence. There was no comparative evidence, i.e. studies that compared systemic GCs with intraarticular GC injection. The methodology of the only systematic review with meta-analysis[6] raised many concerns such as pooling the studies with a very wide range of follow-up times. Overall, the quality of all evidence included in this report was either low or moderate due to methodological limitations.

We were unable to find any evidence for FAQ4 (Will treatment impact my QoL?) for this patient group.

4.4 CONCLUSIONS

There is insufficient evidence to compare systemic GCs (orally/IV) with intraarticular GC injections for any patients group with JIA. The treatment choice should consider currently available recommendations and reflect a joint decision between patients, their parents and the paediatric rheumatology healthcare team.

5. REFERENCES

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APPENDIX 1: SEARCH STRATEGIES

SR/Guidelines searches

Database	Dates	Results
CDSR & CDSR Protocols	2012 – 2020/11/Iss11	38
DARE	2012 – 2015/03	14
HTA	2012 – 2018/03	14
INAHTA	2012 –20/11/17	16
KSR Evidence	2012 –20/11/17	320
Epistemonikos	2012- 20/11/17	264
NHS Evidence	2012-20/11/17	323
NICE	up to 20/11/17	26
GIN	up to 20/11/17	3
ECRI	up to 20/11/17	7
Total		**1025**

SDM database searches

Database	Dates	Results
Embase	2015-2020/10/19	556
MEDLINE & PreMedline	2015-2020/10/19	331
CENTRAL	2015-2020/10/Iss10	231
Total		**1118**

SR/Guidelines searches

Cochrane Database of Systematic Reviews (CDSR) (Wiley): up to 2020/11/Iss11
Searched: 17.11.20

#1 MeSH descriptor: [Arthritis, Juvenile] explode all trees 298
#2 ((Juvenil*) NEAR/3 (arthrit* or arthropath* or oligoarthritis or polyarthritis or "still disease" or "stills disease")) 919
#3 JIA:ti 131
#4 #1 or #2 or #3 975
#5 MeSH descriptor: [Arthritis] explode all trees 15650
#6 Arthrit*:ti,ab 20340
#7 #5 or #6 28721
#8 MeSH descriptor: [Adolescent] explode all trees 103483
#9 MeSH descriptor: [Child] explode all trees 55654
#10 MeSH descriptor: [Infant] explode all trees 31920
#11 (adolescen* or babies or baby or boy? or boyhood or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*):ti,ab 208733
#12 #8 or #9 or #10 or #11 289629
#13 #7 and #12 2242

#14 #4 or #13 with Cochrane Library publication date Between Jan 2012 and Dec 2020 1503

CDSR retrieved 33 records
CDSR protocols retrieved 5 records

Database of Abstracts of Reviews of Effects (DARE) (CRD): up to 2015/03
Health Technology Assessment (HTA) database (CRD): up to 2018/03
http://www.crd.york.ac.uk/CRDWeb/
Searched: 17.11.20
(Please note: both resources are now archive only and are no longer added to)
1 MeSH DESCRIPTOR Arthritis, Juvenile EXPLODE ALL TREES 26
2 ((Juvenil*) AND ((arthrit* or arthropath* or oligoarthritis or polyarthritis or "still disease" or "stills disease"))) 79
3 (#1 OR #2) 79
4 (#3) FROM 2012 TO 2020 28
5 (#4) IN DARE FROM 2012 TO 2020 14
6 (#4) IN HTA FROM 2012 TO 2020 14

Database: INAHTA up to 2020/11/17
https://database.inahta.org/
Searched: 17.11.20
(("Arthritis, Juvenile")[mh]) OR ((Juvenil*) AND (arthrit* or arthropath* or oligoarthritis or polyarthritis or "still disease" or "stills disease")) FROM 2012 TO 2021

INHATA retrieved 16 records

KSR Evidence: up to 2020/11/17
https://ksrevidence.com/
Searched: 17.11.20
Filtered by: PUBLICATION DATE 2021, 2020, 2019, 2018, 2017, 2016, 2015, 2014, 2013, 2012

1 Juvenil* or adolescen* or babies or baby or boy* or child* or girl* or infan* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler* or youth* in All text 31404 results
2 arthrit* or oligoarthritis or polyarthritis or "still disease" or "stills disease" or arthropath* in All text2296 results
3 #1 and #2 in All text 320 results

Epistemonikos: up to 2020/11/17
https://www.epistemonikos.org/
Searched: 17.11.20
(advanced_title_en:((Juvenil* OR adolescen* OR babies OR baby OR boy* OR child* OR girl* OR infan* OR neonat* OR neo-nat* OR newborn* OR new-born* OR paediatric* OR peadiatric* OR pediatric* OR perinat* OR preschool* OR puber* OR pubescen* OR school* OR teen* OR toddler* OR youth*) AND (arthrit* OR oligoarthritis OR polyarthritis OR "still disease" OR "stills disease" OR arthropath*)) OR advanced_abstract_en:((Juvenil* OR

adolescen* OR babies OR baby OR boy* OR child* OR girl* OR infan* OR neonat* OR neo-nat* OR newborn* OR new-born* OR paediatric* OR peadiatric* OR pediatric* OR perinat* OR preschool* OR puber* OR pubescen* OR school* OR teen* OR toddler* OR youth*) AND (arthrit* OR oligoarthritis OR polyarthritis OR "still disease" OR "stills disease" OR arthropath*))) [Filters: classification=systematic-review, protocol=no, cochrane=missing, min_year=2012, max_year=2021]

Epistemonikos retrieved 264 records

NHS Evidence (Internet): up to 2020/11/17
https://www.evidence.nhs.uk/
Searched 17.11.20

Limited to Guidance, Systematic reviews and Health Technology Assessments .
2012-Current

Search terms	Results
Juvenile idiopathic arthritis	195
Juvenile rheumatoid arthritis	128
Total	**323**

National Institute for Health and Care Excellence (NICE): up to 2020/11/17
https://www.nice.org.uk/
Searched 17.11.20

Limited to Guidelines

Keywords	Hits
(Juvenil* or child* or adolescen*) and arthrit*	26
Juvenile idiopathic arthritis	0/9 (duplicates)
Juvenile rheumatoid arthritis	0/5 (duplicates)
Total	**26/40**

Guidelines International Network (GIN) Library (Internet): up to 2020/11/17
http://www.g-i-n.net
Searched: 17.11.20

Search terms	Results
Juvenile idiopathic arthritis	3
Juvenile rheumatoid arthritis	0/1 (duplicate)
Juvenile arthritis	0/3 (duplicate)
Total	**3/7**

ECRI Guidelines (Internet): up to 2020/11/17
https://guidelines.ecri.org/
Searched 17.11.20

Keywords	Hits
'Juvenile idiopathic arthritis'	4
Juvenile rheumatoid arthritis	3
Total	**7**

SDM Searches

Embase (Ovid): 1974-2020/10/19
Searched: 20.10.20
JIA + SDM (2015-C)
1 exp juvenile rheumatoid arthritis/ or JIA.ti,ab,ot. (23384)
2 (Juvenil$ adj3 (arthrit$ or oligoarthritis or polyarthritis or "still disease" or "stills disease" or arthropath$)).ti,ab,ot,hw. (23454)
3 or/1-2 (25012)
4 exp Arthritis/ (471463)
5 Arthrit$.ti,ab,ot. (262757)
6 or/4-5 (506679)
7 exp *adolescence/ or exp *adolescent/ or exp *child/ or exp *childhood disease/ or exp *infant disease/ or (adolescen* or babies or baby or boy? or boyhood or girlhood or child or child* or child*3 or children* or girl? or infan* or juvenil* or juvenile* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,kw. (2696981)
8 6 and 7 (43500)
9 3 or 8 (52262)
10 limit 9 to yr="2015 -Current" (16983)
11 *decision making/ or *patient decision making/ or *shared decision making/ (66243)
12 exp *decision support system/ (12356)
13 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (52293)
14 (decision$ adj2 aid$).ti,ab. (8843)
15 ((decision$ or choice$) adj3 (making$ or support$ or behaviour$ or behavior$)).ti,ab. (234843)
16 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (98260)
17 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (9081)
18 (person centred or person centered).ti,ab. (6643)
19 sdm.ti,ab. (3479)
20 or/11-19 (408020)
21 10 and 20 (556)

Child facet based on Children Filter – EMBASE: Ovid. Ovid expert searches [Internet]. 2020 [accessed 20.10.20]. Available from: https://tools.ovid.com/ovidtools/expertsearches.html

MEDLINE (Ovid) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily 1946-2020/10/19
Searched: 20.10.20

1 Arthritis, Juvenile/ or JIA.ti,ab,ot. (11719)
2 (Juvenil$ adj3 (arthrit$ or arthropath$ or oligoarthritis or polyarthritis or "still disease" or "stills disease")).ti,ab,ot,hw. (13344)
3 or/1-2 (13886)
4 exp Arthritis/ (261156)
5 Arthrit$.ti,ab,ot. (180711)
6 or/4-5 (318274)
7 exp *adolescent/ or exp *child/ or exp *infant/ or (infant disease* or childhood disease*).ti,ab,kf. or (adolescen* or babies or baby or boy? or boyfriend or boyhood or girlfriend or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*).ti,ab,kf. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).jn,jw. or (pediatric* or paediatric* or infan* or child* or adolescen* or young).in. (3375518)
8 6 and 7 (30262)
9 3 or 8 (32077)
10 limit 9 to yr="2015 -Current" (8459)
11 exp Decision Making/ (204589)
12 exp decision support techniques/ (77824)
13 exp Decision Theory/ (12169)
14 ((share$ or sharing$ or inform$) adj3 (decision$ or deciding$ or choice$)).ti,ab. (37909)
15 (decision$ adj2 aid$).ti,ab. (6001)
16 ((decision$ or choice$) adj3 (making$ or support$ or behaviour$ or behavior$)).ti,ab. (172134)
17 ((patient$ or consumer$) adj2 (involve$ or involving or participat$)).ti,ab. (62690)
18 ((patient-centred or patient centred or patient-centered or patient centered) adj2 care).ti,ab. (6558)
19 (person centred or person centered).ti,ab. (5396)
20 sdm.ti,ab. (2679)
21 exp Informed Consent/ (41292)
22 (informed adj3 (consent$ or agree$ or assent$)).ti,ab. (38827)
23 or/11-22 (555039)
24 10 and 23 (331)

Child facet based on OVID Children search filter – MEDLINE: Ovid. Ovid expert searches [Internet]. 2020 [accessed 20.10.20]. Available from: https://tools.ovid.com/ovidtools/expertsearches.html

Cochrane Central Register of Controlled Trials (CENTRAL): up to 2020/10/Iss10
Searched: 20.10.20

ID	Search	Hits
#1	MeSH descriptor: [Arthritis, Juvenile] explode all trees	297

#2 ((Juvenil*) NEAR/3 (arthrit* or arthropath* or oligoarthritis or polyarthritis or "still disease" or "stills disease")) 906
#3 JIA:ti 129
#4 #1 or #2 or #3 960
#5 MeSH descriptor: [Arthritis] explode all trees 15572
#6 Arthrit*:ti,ab 20170
#7 #5 or #6 28507
#8 MeSH descriptor: [Adolescent] explode all trees 103174
#9 MeSH descriptor: [Child] explode all trees 55465
#10 MeSH descriptor: [Infant] explode all trees 31836
#11 (adolescen* or babies or baby or boy? or boyhood or girlhood or child* or girl? or infan* or juvenil* or kid? or minors or minors* or neonat* or neo-nat* or newborn* or new-born* or paediatric* or peadiatric* or pediatric* or perinat* or preschool* or puber* or pubescen* or school* or teen* or toddler? or underage? or under-age? or youth*):ti,ab 205947
#12 #8 or #9 or #10 or #11 286643
#13 #7 and #12 2222
#14 #4 or #13 2365
#15 #14 with Cochrane Library publication date Between Jan 2015 and Dec 2020 1299
#16 MeSH descriptor: [Decision Making] explode all trees 3889
#17 MeSH descriptor: [Decision Support Techniques] explode all trees 2441
#18 MeSH descriptor: [Decision Theory] explode all trees 166
#19 ((share* or sharing* or inform*) NEAR/3 (decision* or deciding* or choice*)):ti,ab 4140
#20 (decision* NEAR/2 aid*):ti,ab 1598
#21 ((decision* or choice*) NEAR/3 (making* or support* or behaviour* or behavior*)):ti,ab 12145
#22 ((patient* or consumer*) NEAR/2 (involve* or involving or participat*)):ti,ab 15114
#23 ((patient-centred or patient centred or patient-centered or patient centered) NEAR/2 care):ti,ab 6063
#24 (person centred or person centered):ti,ab 1039
#25 sdm:ti,ab 389
#26 MeSH descriptor: [Informed Consent] explode all trees 719
#27 (informed NEAR/3 (consent* or agree* or assent*)):ti,ab 58277
#28 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 95430
#29 #15 and #28 233

Central retrieved 231 records

APPENDIX 2: KEY FOR DA

Type of Arrow	Assessment for use in DA
⇧	**"Proof or strong indication of effect"** **Difference in favour of group A versus B based on high to moderate quality data*** **The effect estimate ideally should be significant, but may sometimes be only borderline significant but from several studies indicating a trend (that according to KSR should be mentioned)**
⇗	**"Indication or hint of effect"** **Difference in favour of group A versus B based on low quality data that appears reportable in the DA (e.g., large effect on survival based on registry data, consistently very convincing effects from observational studies supported by one small RCT with same direction of effect)**
⇔	**"No Proof/Indication of effect or a hint of effect that is too weak to report"** **No difference shown among groups based on moderate to high quality data** **or difference shown but does not seem reliable enough to be reported based on low or very low quality data**
.	**No data to report: no difference shown from low/very low quality studies or no studies**
⇩	**Proof of harm, i.e., risks outweigh benefits**

*The term "Data Quality" includes assessment of evidence (level of evidence, risk of bias assessment) as well as transferability of study results to our target population. This should be either taken from original reviews/meta-analyses or provided by KSR for studies where no external evidence assessment exists.