

Treating juvenile idiopathic arthritis to target: recommendations of an international task force

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Handling editor Dimitrios T Boupas

► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2018-213030>).

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Received 16 January 2018
Revised 20 March 2018
Accepted 26 March 2018
Published Online First
11 April 2018

ABSTRACT

Recent therapeutic advances in juvenile idiopathic arthritis (JIA) have made remission an achievable goal for most patients. Reaching this target leads to improved outcomes. The objective was to develop recommendations for treating JIA to target. A Steering Committee formulated a set of recommendations based on evidence derived from a systematic literature review. These were subsequently discussed, amended and voted on by an international Task Force of 30 paediatric rheumatologists in a consensus-based, Delphi-like procedure. Although the literature review did not reveal trials that compared a treat-to-target approach with another or no strategy, it provided indirect evidence regarding an optimised approach to therapy that facilitated development of recommendations. The group agreed on six overarching principles and eight recommendations. The main treatment target, which should be based on a shared decision with parents/patients, was defined as remission, with the alternative target of low disease activity. The frequency and timeline of follow-up evaluations to ensure achievement and maintenance of the target depend on JIA category and level of disease activity. Additional recommendations emphasise the importance of ensuring adequate growth and development and avoiding long-term systemic glucocorticoid administration to maintain the target. All items were agreed on by more than 80% of the members of the Task Force. A research agenda was formulated. The Task Force developed recommendations for treating JIA to target, being aware that the evidence is not strong and needs to be expanded by future research. These recommendations can inform various stakeholders about strategies to reach optimal outcomes for JIA.

INTRODUCTION

In the past two decades, there have been major changes in the management of juvenile idiopathic arthritis (JIA), which include earlier introduction of methotrexate (MTX), the more widespread use of intra-articular glucocorticoids, and most importantly the availability of biological disease-modifying antirheumatic drugs (DMARDs).¹ These advances have made remission, or at least minimal

levels of disease activity, an achievable goal for most, if not all, children with JIA. Complete disease quiescence is regarded as the ideal therapeutic objective because its attainment is associated with less long-term articular and extra-articular damage and physical disability.²

This therapeutic progress has been paralleled by the development and validation of standardised assessment tools for clinical trials and clinical practice, such as the JIA American College of Rheumatology Paediatric (ACR) response criteria,³ the definitions of clinical inactive disease (CID),^{4,5} and low (or minimal) disease activity (LDA),⁶ and the Juvenile Arthritis Disease Activity Score (JADAS).^{7,8} Cut-offs in the JADAS that correspond to the states of CID, LDA, and moderate and high disease activity have been established.^{9–11} The definitions of CID and LDA in JIA are presented in [table 1](#).

Studies in adults with rheumatoid arthritis (RA) have shown that patient outcomes are improved if low levels of disease activity are aimed for by frequent adjustments of therapy according to quantitative indices, regardless of the therapeutic agent chosen.^{12–14} These observations have suggested that the strategy of tight control, aiming for remission, is more important than the individual medications used to treat RA.¹⁵ In recent years, the paradigm of explicitly defining a treatment target and applying tight control and necessary therapeutic adjustments to reach the target has been incorporated into ‘treat-to-target’ recommendations for RA,^{16,17} axial and peripheral spondyloarthritis, including psoriatic arthritis,^{18,19} systemic lupus erythematosus²⁰ and gout.²¹ This principle has been also endorsed by the European and North American recommendations for the management of RA.^{22–25}

It is currently agreed that disease remission should be an over-riding goal in the management of JIA.^{26–30} However, the concept of targeted therapy has not yet been routinely implemented in paediatric rheumatology clinical care. For this reason, a Task Force was convened to discuss this issue and to reach a consensus on a set of recommendations aimed at defining a treat-to-target strategy for JIA, based on a systematic literature review (SLR).



To cite: Ravelli A, Consolaro A, Horneff G, et al. *Ann Rheum Dis* 2018;**77**:819–828.

Table 1 Instruments and criteria used for the definition of clinical inactive disease and low (minimal) disease activity in JIA

	Items included							Requirements for classification as CID or LDA
	PhGA	Pa/ChGA	AJC	ESR/CRP	Systemic features	Uveitis	Morning stiffness	
Criteria for CID								
Wallace's preliminary criteria ⁴	X		X	X	X	X*		Normal ESR/CRP and all other items at 0 or not present
ACR preliminary criteria ⁵	X		X	X	X	X†	X	Normal ESR/CRP, morning stiffness ≤15 min, and all other items at 0 or not present
JADAS criteria ⁹	X	X	X	X				JADAS≤1
cJADAS criteria ¹¹	X	X	X					cJADAS≤1
Criteria for LDA								
Magni-Manzoni criteria—Oligo ⁶	X		X					PGA≤2.5, AJC=0
Magni-Manzoni criteria—Poly ⁶	X	X	X					PGA≤3.4, Pa/PtGA≤2.1, AJC≤1‡
JADAS criteria ⁹	X	X	X	X				Oligoarticular course: JADAS≤2.0 Polyarticular course: JADAS≤3.8
cJADAS criteria ¹¹	X	X	X					Oligoarticular course: cJADAS≤1.5 Polyarticular course: cJADAS≤2.5

*Inactive uveitis was not defined.

†Inactive uveitis as defined by the Standardization of Uveitis Nomenclature Working Group.

‡In systemic arthritis, absence of systemic features is required.

ACR, American College of Rheumatology; AJC, active joint count; CID, clinical inactive disease; cJADAS, clinical JADAS; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; LDA, low disease activity; Oligo, persistent oligoarthritis; Pa/ChGA, parent's/child's global assessment of child's overall well-being; PhGA, physician's global assessment of overall disease activity; Poly, extended oligoarthritis, polyarthritis and systemic arthritis.

METHODS

At the beginning of this endeavour, a paediatric rheumatologist (AR) and a methodologist (JSS) invited paediatric rheumatologists from Europe and North America, selected on the basis of publication records, expertise in treating JIA and previous participation in similar activities, to form a Steering Committee (JS, AR, GH, DJL, RML, NMW). The Steering Committee met on 6 March 2017 in Vienna to discuss unmet needs in the treatment of JIA and the potential for using treatment targets in the management of JIA.

During the meeting, it was unanimously agreed that defining therapeutic targets and an appropriate strategic treatment approach would be valuable, but there was concern that evidence for its validity could be lacking. It was therefore decided that—in line with respective recommendations^{31 32}—a comprehensive SLR was a mandatory initial step to serve as the basis for achieving consensus on the definition of treatment targets. After extensive discussion among the members of the Steering Committee, it was agreed that the SLR should primarily explore the current evidence regarding the following themes: (1) Is a treat-to-target strategy preferable to a non-steered management? (2) What is the best outcome to be used as target and with which instrument? (3) Which time should elapse before escalating treatment in patients with active disease? (4) What is the potential role of biomarkers and imaging methods in decision-making? (5) Does disease duration and JIA heterogeneity influence the strategy and choice of the target? (6) Does a longer time spent in CID lead to a better long-term outcome? (7) What is the impact of treat-to-target in terms of cost, safety and treatment burden? (8) What is the effect of treat-to-target on comorbidities, including uveitis, psoriasis, depression, infections and adverse events? (9) Does improved patient/parent understanding on the disease improve the outcome? (10) What is the impact of treat-to-target on functional status, health-related quality of life, burden of disease and effect on patient's family life? After the definition of a series of search questions aimed to address all these issues, the SLR was performed by author AC. The databases used for the SLR and the methodology employed to screen articles and extract data

are summarised in online supplementary file S1. The SLR was not limited to randomised controlled trials, but also included observational studies.

The SLR results were presented to the Steering Committee at a subsequent meeting, held in Munich on 24 August 2017. The literature search revealed that no strategic trials that addressed a target-oriented, steered therapy in comparison with conventional management had been published in JIA. Indirect evidence on optimal therapeutic approaches was, however, available to inform the next stages of the process. On this basis, the Steering Committee formulated a provisional set of recommendations in line with the European League Against Rheumatism (EULAR) standardised operating procedures (SOP).³¹

The day after the Steering Committee meeting in Munich, the SLR and the proposed recommendations of the Steering Committee were presented to a Task Force of 23 additional paediatric rheumatologists practising in various areas of the world (Africa, Asia, Australia, Europe, Latin America and North America). These invitations were a consequence of the individuals' contributions to the field and deliberations among members of the Steering Committee. After presentation, two breakout groups were formed, each chaired by a member of the Steering Committee: one group addressed the proposed overarching principles and proposed recommendations 7 and 8; the other group addressed the proposed recommendations 1–6 (see below). Further discussions took place during these breakout sessions and the suggested wording reformulated as deemed appropriate, with majority votes where controversy emerged.

The results obtained by the breakout groups were reported to the whole Task Force, which then discussed the proposals, amended them and arrived at final wordings that were subjected to an open voting process through a show of hands. Items that achieved at least a 75% majority vote were accepted as final recommendations in the same way as they had been worded. Items that did not attain such majority approval straight away were rediscussed, reformulated and revoted, until a 67% of majority vote or, subsequently, a >50% majority vote was achieved.

In line with the SOP, no representative of the company that provided the unrestricted grant was present to avoid any potential influence on the discussion or development of recommendations. This position has been a general principle in all treat-to-target procedures.

After the Munich consensus conference, all participants were asked to adjudicate via email their level of agreement with each overarching principle and recommendation on a 0–10 scale (0=no agreement at all; 10=full agreement).

The evaluation of the level of evidence (LoE) and strength of recommendation (SoR) was based on the Oxford Evidence-Based Medicine categorisation.³³

RESULTS

The evidence base

The SLR revealed that no randomised controlled trial had evaluated a targeted therapeutic approach in comparison with conventional therapy in JIA. There was, therefore, no direct evidence that a treat-to-target strategy was preferable to non-steered management. However, a randomised trial of early aggressive therapy in polyarticular JIA had employed therapeutic targets and predefined time requirements as endpoints to escalate therapy, although this applied only to the MTX monotherapy comparator arm, which was allowed to escalate to combination therapy with MTX, a tumour necrosis factor inhibitor and prednisolone, or to escape in case of disease flare.³⁴ The primary outcome was the JIA ACR 70 improvement at 4 months and the achievement of CID at 6 and 12 months. Another randomised study of aggressive drug therapy in very early polyarticular JIA had set the JIA ACR 75 as the minimum level of improvement, below which the dose of MTX had to be doubled and the route of administration switched from oral to parenteral.³⁵ Taken together, these trials provide examples that strategies aimed at intensifying therapy enable a sizeable proportion of patients to achieve CID. In systemic JIA, the rapid attainment of CID with early administration of interleukin-1 inhibitors^{36–37} has led to postulate that early intensive therapy may take advantage of a window of opportunity, in which disease pathophysiology can be altered to avoid the occurrence of chronic arthritis.³⁸ Indirect support regarding the time that should elapse before escalating treatment in a patient with persistently active disease was provided by several randomised clinical trials, non-controlled therapeutic studies and therapeutic recommendations formulated by expert panels.^{36–39–53} Nevertheless, given the lack of studies evaluating target-steered versus non-steered treatment, the LoE for the development of recommendations was anticipated to be low and mainly based on expert consensus.

The members of the Task Force also recognised that in contrast to adult RA, the heterogeneity of JIA (eg, polyarticular, oligoarticular or systemic) needed to be addressed and accounted for in the development of recommendations.

The consensus

The individual statements that received a positive vote by the majority of the Task Force members comprise six overarching principles and eight recommendations. These items are shown in table 2, together with the percentage of positive votes obtained at the consensus conference, LoE, SoR and level of agreement, and are discussed in detail below.

Overarching principles

A. The treatment targets and the therapeutic strategy should be based on shared decisions between the parents/patient and the paediatric rheumatology healthcare team.

It was recognised that involvement of the parents and, where appropriate, of the child in therapeutic decision-making is important and may lead to better adherence to treatment and potentially improve the outcome. The Task Force felt that the parents/patient must be informed about and agree with the selected target, the therapeutic options to reach the target and the reason for choosing the target, also in the light of the risks related to both the treatment and the disease. Parents/patient should be encouraged to participate fully in this discussion. The principle specifies that patient care should be delivered by a paediatric rheumatology healthcare team, recognising that the management of patients with JIA should be ideally conducted by a group of professionals with specific paediatric expertise. It was, however, argued that the healthcare team could vary in different countries. In this respect, because not all children will have access to paediatric rheumatology care, it was acknowledged that the formulated recommendations and principles should be also widely adopted by the adult rheumatology community when caring for children with JIA. This item achieved 90% of participants' votes; a few participants would have preferred the wording 'type of therapy' instead of 'therapeutic strategy'.

B. JIA is a heterogeneous group of diseases that requires distinct treatment approaches.

It is well established that JIA is not a single disease, but constitutes a heterogeneous group of disorders, all manifesting joint inflammation, but with different clinical phenotype, disease course and outcomes, as well as with distinct genetic background and pathophysiology. This variability implies that the therapeutic choices, optimal targets and treatment strategy may be different across disease categories. Differentiation of therapeutic approaches based on the disease phenotype is in keeping with the ACR recommendations for the treatment of JIA.^{45–50} It was also emphasised that the management of children with JIA requires the involvement of a multidisciplinary team of specialists, which should include, beside paediatric rheumatologists, ophthalmologists, physiotherapists, occupational therapists, orthopaedic surgeons, dermatologists, gastroenterologists, social workers, psychologists and others. This item was unanimously endorsed.

C. The goals of treating patients with JIA are to control signs and symptoms; to prevent structural damage; to avoid comorbid conditions and drug toxicities; and to optimise function, growth and development, quality of life, and social participation.

This principle was modified several times by changing the order of the individual therapeutic goals. It was decided unanimously to give priority to control of inflammatory signs and symptoms, followed by prevention of structural damage to joints. There was, however, an intense discussion regarding the importance of considering comorbidities, such as uveitis, psoriasis, osteoporosis, depression and infections, as well as medication-related toxicity, in making clinical decisions. It was widely agreed that caution should apply particularly to systemic glucocorticoids, whose side effects may have a devastating impact in the paediatric age group. Optimisation of linear growth and pubertal development was added to the therapeutic goals to highlight this unique paediatric issue and the specificity of the recommendations. For patients of adolescent age, the therapeutic strategy should be tailored in accordance with the broader process of transition from paediatric to adult rheumatology

Table 2 Recommendations to treat juvenile idiopathic arthritis (JIA) to target

	Percentage of positive votes at consensus conference	Level of evidence	Strength of recommendation	Mean±SD level of agreement
Overarching principles				
A. The treatment targets and the therapeutic strategy should be based on shared decisions between the parents/patient and the paediatric rheumatology healthcare team.	90			9.8±0.5
B. JIA is a heterogeneous group of diseases that requires distinct treatment approaches.	100			10
C. The goals of treating patients with JIA are to control signs and symptoms; to prevent structural damage; to avoid comorbid conditions and drug toxicities; and to optimise function, growth and development, quality of life, and social participation.	100			10
D. Abrogation of inflammation is essential to achieve these goals.	100			9.8±0.5
E. Long-term use of systemic glucocorticoids to maintain the target should be avoided.	100			9.8±0.5
F. Treatment to target by regularly assessing disease activity and adapting therapy accordingly is important to achieve these goals.	100			10
Recommendations				
1. The primary target for treatment of patients with JIA is clinical remission, which means the absence of signs and symptoms of inflammatory disease activity, including extra-articular manifestations.	85	2b	C	9.7±0.5
2. Minimal (or low) disease activity may be an alternative target, particularly in patients with long-standing disease.	97	2c	B	9.7±0.6
3. Setting the target, selecting the tools and the therapeutic decisions should be based on individual patients' characteristics and agreed on with the parents/patient.	100	5	D	9.7±0.6
4. Disease activity should be assessed and documented regularly using a validated composite instrument.	100	2c	C	9.8±0.5
5. The frequency of assessments depends on the category of JIA, level of disease activity and presence of extra-articular manifestations. This may require weekly assessments, such as in systemic JIA with active systemic manifestations; monthly to every 3 months evaluations for patients who have high/moderate disease activity; and less frequent assessments, in states of persistent clinical remission.	93	5	C	9.6±0.7
6. In all patients, at least a 50% improvement in disease activity should be reached within 3 months and the target within 6 months. In patients with systemic JIA with active systemic manifestations, resolution of fever should be attained within 1 week.	93	2b	B	9.2±0.9
7. Treatment should be adjusted until the target is achieved.	100	2b	C	9.7±1.0
8. Once the treatment target has been achieved, it should be sustained. Ongoing monitoring should occur to ensure maintenance of the target.	100	2b	C	9.9±0.3

care. During this process, there should be direct communication between paediatric and adolescent rheumatologist teams. Self-management support was widely recognised as a key aim of treatment. The term social participation encompasses participation in social life and school attendance, as well as participation in extracurricular activities. The final wording of this principle was voted for by 100% of the participants.

D. Abrogation of inflammation is essential to achieve these goals.

This principle underscores the key role of the inflammatory process underlying JIA in causing signs and symptoms of the disease and disease-related damage. A number of other terms were suggested instead of abrogation (including suppression, abolition, inhibition, resolution, remission, disappearance), but in the end the majority of participants felt that abrogation was the most appropriate. The final wording of this principle was voted by 100% of the participants.

E. Long-term use of systemic glucocorticoids to maintain the target should be avoided.

High-dose glucocorticoid therapy may be necessary to control the acute or life-threatening manifestations of systemic disease, and a short course of low-to-moderate-dose glucocorticoids is often prescribed in children with polyarthritis to achieve a rapid control of inflammatory symptoms

while awaiting the full therapeutic effect of a synthetic or biological DMARD.⁵⁴ Long-term administration of glucocorticoids to maintain the target is inappropriate because it indicates that the selected DMARD therapy is not sufficient to control the disease. This principle was added to the list of those originally formulated by the Steering Committee during the consensus meeting to highlight the serious side effects related to the prolonged administration of glucocorticoids in children, and was endorsed unanimously.

F. Treatment to target by regular assessment of disease activity and adapting therapy accordingly is important to achieve these goals.

Although the SLR had produced only indirect evidence for the utility of the treat-to-target strategy in JIA, the participants unanimously agreed that regular measurement of disease activity and the adjustment of therapy with persistently active disease were an overarching principle. This principle was endorsed by 100% of the participants.

Recommendations

1. The primary target for treatment of patients with JIA is clinical remission, which means the absence of signs and symptoms of inflammatory disease activity, including extra-articular manifestations.

To date, no clinical trial has compared outcomes of JIA for progression of structural changes or improvement in quality of life when clinical remission (CR) rather than another state is targeted. However, there is indirect evidence to suggest that progression of damage is more effectively inhibited in states of CID/CR.² Considering that the recent therapeutic advances have made CR a realistic goal for potentially all patients with JIA, CR was set as the primary therapeutic target. The definition of CR was intended to be quite strict, that is, as complete absence of all signs and symptoms of inflammatory disease activity, in line with the Wallace criteria for CID in JIA^{4 5} or the JADAS criteria.^{9 11} The emphasis on the stringency of the criteria led to the elimination of the adjective 'significant' before inflammatory disease activity, as included in the preliminary version of this recommendation. Abrogation of inflammation should extend to extra-articular manifestations, such as fever and rash of systemic JIA, uveitis, enthesitis or psoriasis. Recognising that patients often require continued therapy to achieve and maintain a state of CR, ongoing treatment was considered acceptable. That achievement of the treatment target should not depend on the chronic use of glucocorticoids was not addressed here, since this important aspect has already been included as an overarching principle. The participants discussed in depth whether the adjective 'clinical' should be removed to leave only the term remission, owing to the potential role of biomarkers or imaging techniques in defining disease remission more reliably than clinical assessment. However, despite emerging evidence for biomarkers reflecting subclinical inflammation^{55 56} and several studies that indicate that there may still be residual active synovitis by MRI or sonographic evaluation in patients in CR,⁵⁷⁻⁵⁹ at present there is no established role for imaging in defining remission. Nevertheless, the definition of remission may have to be reconsidered based on emerging data in a future update of the recommendations. This statement was approved by 85% of the participants, with contrary votes being mostly explained by the disagreement about adding the adjective 'clinical' to remission.

2. Minimal (or low) disease activity may be an alternative target, particularly in patients with long-standing disease.

Although the Task Force did not intend to replace the target of CR by that of LDA, it was recognised that stringent remission, as defined in point 1, may be difficult to achieve in some patients, especially those with long-standing disease. These patients are generally those with the most aggressive systemic or polyarticular forms who have experienced persistently active disease, received multiple drug therapies or accumulated substantial joint damage or comorbidities. It was agreed on by 97% of the participants that in such patients, LDA^{6 9} is an alternative and valid target. LDA is differentiated from the state of CR by the existence of residual signs and symptoms. However, it is assumed that physical function and quality of life would not be substantially worse than in CR and that progression of structural damage, while possibly not halted, would be minimal.¹⁹ Importantly, by stating that LDA is an alternative goal to remission, the Task Force implied that any other, higher state, even moderate disease activity, would not be acceptable and its presence should prompt therapeutic adaptation.

3. Setting the target, selecting the tools to define the target and the therapeutic decisions should be based on individual patients' characteristics and agreed on with the parents/patient.

This recommendation emphasises the need to individualise the therapeutic target, the method used for its assessment and the therapeutic decisions based on patients' characteristics, which include the disease category (eg, oligoarthritis, polyarthritis or systemic arthritis), severity of arthritis, distribution of affected joints (eg, involvement of cervical spine or hip), and presence of extra-articular manifestations (eg, systemic features, uveitis, psoriasis, impending macrophage activation syndrome, MAS) or comorbidities (eg, osteoporosis, growth failure, infection). Therapeutic decision-making may be guided by the recent treatment recommendations for JIA issued by the ACR, which were tailored according to JIA phenotype, level of disease activity and the presence of features of poor prognosis.^{45 50} The rationale for choosing a particular treatment target and the means to achieve it should be properly communicated to the parents and the patient, and agreed on with them, in combination with appropriate information on the disease and the benefits and risks of different therapies (see also overarching principle A). This communication should include the explanation of the characteristics of the tools used to define the target and the indication that parent/patient-reported outcomes are an essential component of patient assessment and therapeutic decisions. In this regard, it may be difficult for parents to understand the need for this approach in patients with early disease or relatively mild symptoms. To this end, educational programmes supporting this initiative and involvement of parent and patient organisations were unanimously endorsed.

4. Disease activity should be assessed and documented regularly using a validated composite instrument.

There was full consensus that the use of composite measures of disease activity is the best way to estimate disease activity and response to therapy. Furthermore, it was agreed on that this assessment should be performed at each clinic visit. Two categories of composite measures are currently available to evaluate disease activity in JIA: those based on multiple criteria and the composite disease activity scores. The first group comprises the criteria for CID^{4 5} and LDA^{6 11}; the second includes the JADAS⁷ and its reduced version that lacks the acute phase reactant, the clinical JADAS (cJADAS).⁸ The definitions based on multiple criteria are suited to establish the presence of a disease state (ie, CR or LDA) at a particular visit, but cannot be used to quantify disease activity. Conversely, the JADAS and cJADAS are aimed to quantify the absolute level of disease activity by providing a number on a continuous scale. The JADAS and cJADAS cut-offs that correspond to CR and LDA in JIA were determined.^{9 10 60} Recently, the cJADAS was found to be potentially suitable to guide a treat-to-target strategy in JIA.⁶¹ During the consensus meeting, there was debate about the relative measurement properties and suitability for the treat-to-target strategy of the various tools. It was decided not to recommend the use of a specific instrument. Hence, to leave the choice open for the clinician, the neutral term 'composite instrument' was endorsed unanimously. These instruments are shown in table 1.

5. The frequency of assessments depends on the category of JIA, level of disease activity and presence of extra-articular manifestations. This may require weekly assessments, such as in systemic JIA with active systemic manifestations; monthly to every 3 months evaluations for patients who have high/

moderate disease activity; and less frequent assessments, in states of persistent clinical remission.

Owing to the clinical heterogeneity of JIA, the intervals between evaluations vary in relation to the disease phenotype, level of disease activity and presence of extra-articular manifestations. In the active stage of systemic arthritis, which is a highly inflammatory condition that is accompanied by high fever and may lead to potentially serious complications, such as pleuritis, pericarditis and MAS, there is a need for frequent assessment of the disease status (even weekly) to adjust treatment accordingly. Patients with non-systemic categories and high-to-moderate disease activity require less frequent evaluations, which may occur monthly in patients with severe polyarthritis or enthesitis-related arthritis with active sacroiliitis or every 3 months in patients with oligoarthritis. Patients in sustained remission should be assessed at certain intervals to ensure maintenance of the outcome and, in those who are still receiving therapy, to verify the lack of adverse events and avoid overtreatment. Most experts felt a 3-month interval to be unnecessary for this population of patients and the majority considered every 6 months sufficient. In the process of shared decision-making, patients and parents should be advised to return to the paediatric rheumatologist earlier than at the predetermined time point if they are concerned about a change in disease status. This recommendation was approved by 93% of the participants.

6. In all patients, at least a 50% improvement in disease activity should be reached within 3 months and the target within 6 months. In patients with systemic JIA with active systemic manifestations, resolution of fever should be attained within 1 week.

The analysis of the recent JIA clinical trials identified in the SLR showed that the maximum clinical benefit, expressed in terms of percentage of improvement, was usually not achieved before 3 months of treatment. In these clinical trials, which were performed for regulatory approval, the primary outcome measure has been a JIA ACR 30 response. However, because paediatric rheumatology practitioners are no longer satisfied with merely reaching a 30% change, a minimum improvement of 50% should be achieved. Thus, if an individual patient does not attain a minimum decrease of 50% in signs and symptoms of disease within 3 months from starting therapy, treatment should be adjusted. There was wide agreement that the attainment of CID or LDA before 6 months may not be realistic in patients with the most severe forms of JIA. A recent trial of early aggressive therapy in polyarticular JIA set the assessment of the primary outcome of CID at 6 months.³⁴ There was extensive discussion about whether the time intervals for drug therapy adjustment should vary in relation to the disease category or disease duration (early vs established). It was finally agreed that the above intervals should remain the same for all disease phenotypes, with the sole exception of patients with systemic JIA and active systemic manifestations, in whom resolution of fever should be obtained within 1 week. This tighter time frame was justified by the risk of patients with systemic arthritis to develop potentially serious complications, such as pleuritis, pericarditis and MAS, and by the recent demonstrations of dramatic improvement of systemic features within 1 week in many patients treated with appropriate therapy.^{36 47} Approval of this item was provided by 93% of the participants.

7. Treatment should be adjusted until the target is achieved.

Indirect evidence suggests that early clinical response or the achievement of CID is associated with improved long-term outcome.^{9 10 62} It is, thus, likely that pursuing the best possible target through treatment adjustment improves prognosis. Some participants argued that the word 'adjusted' sounds ambiguous and that 'modified' or 'escalated' could be more appropriate. It was, however, noted that the term adjustment covers both the modification and escalation of therapy. Several Task Force members emphasised the importance of non-pharmacological interventions, particularly physiotherapy and occupational therapy, optimisation of bone health, management of pain and psychological support. A concern was also raised that some targets may not be achievable for patients living in low-income countries, where costly biological DMARDs may not be available or affordable; however, others noted that the adaptation of treatment would have to be done with those options that are available. This recommendation was supported by 100% of the participants.

8. Once the treatment target has been achieved, it should be sustained; ongoing monitoring should occur to ensure maintenance of the target.

Once the agreed therapeutic target has been achieved, it should be maintained continuously. Both evidence and rationale exist in chronic arthritis that sustained/persistent remission leads to an optimal quality of life, enhances physical function and stops progression of structural joint damage.^{2 63-65} Conversely, an increase in disease activity during follow-up may lead to reduced quality of life and progression of the destructive process.⁶³⁻⁶⁵ Maintenance of the treatment target does not necessarily imply maintenance of treatment. However, the decision regarding whether therapy should be stopped or gradually tapered should be based on available evidence. A number of studies on tapering of therapy, especially dose reduction, spacing of administration intervals and even withdrawal of drugs have been performed in children with JIA who had achieved a state of CR.⁶⁶ The relapse rate after termination of both MTX and biological DMARDs is substantial. Unfortunately, there is currently a lack of evidence-based data from clinical trials and clinical care and of guidelines to aid in the withdrawal of medications after disease remission in JIA. A recent survey among North American paediatric rheumatologists conducted by the Childhood Arthritis and Rheumatology Research Alliance has shown a large variability in the preferences of medication withdrawal for CID.⁶⁷ No reliable clinical, biomarker or imaging indicators are currently available to identify patients at higher risk of experiencing disease flare after treatment discontinuation. Adherence to therapy has to be carefully monitored because non-adherent patients may be exposed to a high risk of flares. Safety aspects and drug cost should also be taken into account in designing the strategies for treatment tapering or discontinuation. This item was unanimously approved.

Adjudication of the level of agreement after the consensus meeting

The level of agreement on overarching principles and recommendations adjudicated by the Task Force members after the Munich consensus meeting was very high, as all items achieved

an average score greater than 9 and only one item had an average score lower than 9.6 (table 2).

DISCUSSION

In recent years, several sets of treatment recommendations have been developed for JIA.^{45 50 68–70} However, none of them has addressed specific treatment targets or described the strategy to reach the therapeutic goals. These objectives have been achieved in the present recommendations, which are primarily intended to provide expert guidance on general treatment approaches. A notable difference with the previous treatment recommendations is the absence of suggestions or advice regarding specific medications in any of the overarching principles or individual recommendations, apart from the avoidance of long-term glucocorticoid use. Consequently, these recommendations should be applicable and ideally adhered to in all regions and countries, irrespective of medication availability. Importantly, the recommendations are aimed at improving patient care in standard clinical practice and do not tackle the issue of registration trial design and conduct. However, the recommendations should be tested in respective strategic clinical trials.

The process was initiated by a Steering Committee, which followed the EULAR SOP for the development of recommendations.³¹ It was accomplished after discussions among the members of the Steering Committee and a Task Force of 23 additional international paediatric rheumatologists. In light of the wide international representation within the Task Force, the very high level of agreement for all statements supports the conclusion that the result of the efforts gained broad international consent.

The recommendations are aimed at paediatric rheumatology practitioners and other health professionals involved in the care of patients with JIA; official bodies, such as health authorities or payers, who may wish to use this document as a reference for the assessment of success in treating patients with JIA; and regulatory agencies, owing to the increasing interest of pharmaceutical companies for strategic trials. Parents and patients are another important audience that should be informed on these statements and their potential role in preventing or minimising damage and disability. In this respect, we recognise that the lack of participation of parent or patient representatives is a limitation of the project. However, the dissemination of the recommendations to parent/patient organisations and the request of their feedback are planned in the near future. An update of these recommendations will likely be required once parts of the research agenda have been addressed. With the next iteration, parents/patients and healthcare partners will be included.

Ideally, treatment recommendations should be based on available evidence. As mentioned, strategic therapeutic trials, in which therapy was consistently adapted to reach a prespecified treatment target and compared with a non-steered approach, are currently not available in JIA. While the SLR has provided indirect evidence from clinical trials which targeted specific endpoints,^{34 35} and thus supplied some information to the Task Force, the individual recommendations can only be regarded as consensus-based expert opinion and, therefore, call for further research in the field.

In spite of the lack of evidence, the Task Force felt that the definition of treatment targets and strategy for JIA was necessary and timely for three main reasons: (1) the remarkable therapeutic advances of the past two decades have greatly improved the probability of achieving excellent outcomes and have, thus, mandated the establishment of more stringent treatment targets;

(2) JIA had not been previously addressed by ‘treat-to-target’ initiatives, such as those in RA and spondyloarthritis, for which treat-to-target recommendations were defined many years ago, have already been updated^{16–19} and adopted in management recommendations^{24 71}; and (3) the proposals originating from the consensus meeting and the formulation of a research agenda will likely foster and accelerate investigations towards providing the necessary evidence.^{17 19}

The present recommendations were aimed at defining treatment targets that would lead to the optimal outcome for the individual patient, but do not account for potential financial constraints or access to particular therapies. The Task Force raised the concern that different accessibility to certain medications may lead to disparities in the proportion of patients who are able to attain the desired target across countries or regions. However, studies in adult patients with RA have shown that a good outcome can be obtained in a large proportion of patients with easily accessible and affordable therapies, provided that a strategic treatment approach is pursued.^{12 72}

Looking at specific items, it is worth highlighting some important differences with the recommendations formulated for adult-onset diseases. First, the heterogeneity of JIA was accounted for by stating that therapeutic approaches, frequency of assessments and timeline for evaluation of improvement may be different across categories. It was, in particular, recognised that children with systemic arthritis and active systemic manifestations, particularly fever, require closer assessments and should have resolution of fever within 1 week. Another key point is that long-term administration of glucocorticoids to maintain the target is inappropriate, due to the devastating side effects related to prolonged administration of glucocorticoids in children. A further item specific to paediatric patients is the inclusion of the optimisation of linear growth and pubertal development in the therapeutic goals. Finally, the Task Force emphasised that care of adolescent patients be tailored in accordance with the broader process of transition from paediatric to adult rheumatology care. While this aspect was not specifically mentioned in the bullet point, it is mentioned in the accompanying text, which is part and parcel of the recommendations.

All Task Force members agreed unanimously that abrogation of inflammation (overarching principle D) is the most important goal in the treatment of JIA. Although there was also full agreement that this objective should be pursued by aiming at the state of disease remission, some experts were not in favour of adding the adjective ‘clinical’ to remission, in the light of the potential superiority over clinical assessment of more stringent targets, such as remission by biomarkers or ultrasonography. However, the majority considered that at this time remission should be defined on clinical grounds through the use of one of the existing criteria, as the evidence for other methods is scant.

Participants discussed that remission may not be achievable in all patients and, hence, formulated an alternative treatment target, especially for patients with long-standing disease, namely LDA (recommendation 2). Importantly, this conclusion implies that disease activity states other than CR or LDA should not be acceptable, unless justified for other reasons, such as comorbidity, parent/patient choice or treatment-related toxicity (recommendation 3).

There is ongoing discussion of the relative value of composite instruments for assessment of disease activity. There was concern that a recent study had shown that current criteria to capture CID and LDA do not always identify the same groups of patients.⁷³ A leading reason for the discordance was the inclusion of parent/patient global assessment in the JADAS^{7 8} but not in the criteria

Box 1 Objectives to be included in the future research agenda

- ▶ Implementation of strategic trials aimed to show the superiority of a steered treatment approach based on treat-to-target over a non-steered approach.
- ▶ Acceptance and applicability of treat-to-target strategies in clinical practice.
- ▶ Acceptance and applicability of treat-to-target strategies in low-income countries.
- ▶ Evaluation of whether treat-to-target strategies should have different characteristics in adolescent patients.
- ▶ Impact of parent/patient evaluation, particularly in the presence of particular pain sensitivity, in the assessment of targets.
- ▶ Comparison of remission defined clinically versus remission based on imaging methods or biomarkers in relation to structural and functional outcomes.
- ▶ Analysis of the best modalities of tapering and/or withdrawing treatments in patients with juvenile idiopathic arthritis reaching inactive disease or complete remission.
- ▶ Revision of treat-to-target recommendations in relation to the revision of the classification criteria for juvenile idiopathic arthritis, currently in progress.

for CID in JIA.^{4,5} However, it has been argued that integration of the parents' and children's perspective into clinical assessment may help with the physician's decisions and improve adherence to treatment.⁷⁴ It was finally decided not to recommend the use of a specific instrument, leaving the choice to the clinician.

This process highlighted the foremost importance of future research to underpin the next iteration of the recommendations. Some objectives that should be prioritised in the research agenda are listed in [box 1](#).

In conclusion, the recommendations to treat JIA to target are presented. The Task Force is convinced that transferring them into clinical practice will significantly improve the outcomes in patients with JIA (LoE 5, SoR D).

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Funding This activity was supported by an unrestricted educational grant from AbbVie to the Medical University of Vienna. No company representative had any influence on the procedure or content, nor was any company representative present at any of the meetings or received the manuscript before submission.

Competing interests AR has received grant support and/or speaking or consultant fees from AbbVie, Bristol-Myers Squibb, Novartis, Pfizer, Roche and Johnson & Johnson; AC reports personal fees from AbbVie and non-financial support from Pfizer; GH has received research funds, advisory board membership and honorary fees from AbbVie, Pfizer and Roche; RML has been consultant and/or participated in advisory boards for AbbVie, Eli Lilly, Novartis, Sanofi and Sobi; DJL reports grants/research support from the National Institutes of Health, NIAMS, and received consultancy fees from AstraZeneca, Bristol-Myers Squibb, AbbVie, Pfizer, Roche, Novartis, UBC, Forest Research Institute, Horizon, Johnson & Johnson, Biogen, Takeda, Genentech, GlaxoSmithKline, Boehringer Ingelheim, Celgene and Janssen, and speaker bureaus from Genentech; NMW reports research grants and/or consultant fees from AbbVie and Novartis; JDA has received consultant fees from Pfizer; SMA-M does not report competing interests; JA reports grant support and/or personal fees from AbbVie, Gebro, Pfizer, Novartis, Roche and Sobi; TA has received speaking and/or consultant fees from AbbVie, Boehringer Ingelheim and Pfizer; RAB does not report competing interests; MWB does not report competing interests; RB-V does not report competing interests; RC has received consultant fees from AbbVie, Alfa Wassermann and Novartis; FDB reports grants from Hoffmann-La Roche, Bristol-Myers Squibb, Novimmune, Novartis, Abbott, Pfizer and Sobi; ED does not report competing interests; DF reports grant support and/or personal fees from Pfizer, Novartis, Roche and Sobi; YI does not report competing interests; PL has received grant support from AbbVie; EMM does not report competing interests; PQ has received speakers' fees from AbbVie, Novartis, Pfizer, Roche and Sobi, grants from AbbVie, Pfizer and Novartis, and personal fees for consultancy from AbbVie, Novartis, Novimmune and Sanofi; NR reports personal fees from AbbVie, Amgen, Biogen Idec, Alter, AstraZeneca, Baxalta Biosimilars, Boehringer, Bristol-Myers Squibb, Celgene, CrescendoBio, EMD Serono, Hoffmann-La Roche, Italfarmaco, Janssen, MedImmune, Medac, Novartis, Novo Nordisk, Pfizer, Sanofi-Aventis, Servier, Takeda and UCB Biosciences, and other financial relationships from Bristol-Myers Squibb, GlaxoSmithKline, Hoffmann-La Roche, Novartis, Pfizer, Sanofi-Aventis, Schwarz Biosciences, Abbott, Francesco Angelini SPA, Sobi and Merck Serono; RR does not report competing interests; CS-M does not report competing interests; Ssa does not report competing interests; CS does not report competing interests; SSh has received speaking and advisory board fees from Novartis; JFS does not report competing interests; YU reports grant support and/or personal fees and/or non-financial support from AbbVie, Janssen, Novartis, Pfizer and Roche; SJV reports grant support from Sobi; JSS has received grant support from and/or provided expert advice to AbbVie, Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Celltrion, Gilead, Glaxo, Janssen, Lilly, Pfizer, MSD, Roche, Samsung, Novartis-Sandoz and UCB.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement The results of the systematic literature review are not to be presented in the study, but are available to anyone upon request to the corresponding author.

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REFERENCES

- Lovell DJ, Ruperto N, Giannini EH, *et al.* Advances from clinical trials in juvenile idiopathic arthritis. *Nat Rev Rheumatol* 2013;9:557–63.
- Magnani A, Pistorio A, Magni-Manzoni S, *et al.* Achievement of a state of inactive disease at least once in the first 5 years predicts better outcome of patients with polyarticular juvenile idiopathic arthritis. *J Rheumatol* 2009;36:628–34.
- Giannini EH, Ruperto N, Ravelli A, *et al.* Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202–9.
- Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290–4.
- Wallace CA, Giannini EH, Huang B, *et al.* American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. *Arthritis Care Res* 2011;63:929–36.
- Magni-Manzoni S, Ruperto N, Pistorio A, *et al.* Development and validation of a preliminary definition of minimal disease activity in patients with juvenile idiopathic arthritis. *Arthritis Rheum* 2008;59:1120–7.
- Consolaro A, Ruperto N, Bazzo A, *et al.* Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Rheum* 2009;61:658–66.
- McErlane F, Beresford MW, Baildam EM, *et al.* Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. *Ann Rheum Dis* 2013;72:1983–8.
- Consolaro A, Bracciolini G, Ruperto N, *et al.* Remission, minimal disease activity, and acceptable symptom state in juvenile idiopathic arthritis: defining criteria based on the juvenile arthritis disease activity score. *Arthritis Rheum* 2012;64:2366–74.
- Consolaro A, Ruperto N, Bracciolini G, *et al.* Defining criteria for high disease activity in juvenile idiopathic arthritis based on the juvenile arthritis disease activity score. *Ann Rheum Dis* 2014;73:1380–3.
- Consolaro A, Negro G, Chiara Gallo M, *et al.* Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. *Arthritis Care Res* 2014;66:1703–9.
- Grigor C, Capell H, Stirling A, *et al.* Effect of a treatment strategy of tight control for rheumatoid arthritis (the TICORA study): a single-blind randomised controlled trial. *Lancet* 2004;364:263–9.
- Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, *et al.* Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): A randomized, controlled trial. *Arthritis Rheum* 2008;58:S126–35.
- Smolen JS, Sokka T, Pincus T, *et al.* A proposed treatment algorithm for rheumatoid arthritis: aggressive therapy, methotrexate, and quantitative measures. *Clin Exp Rheumatol* 2003;21:S209–S210.
- Sokka T, Pincus T. Rheumatoid arthritis: strategy more important than agent. *Lancet* 2009;374:430–2.
- Smolen JS, Aletaha D, Bijlsma JW, *et al.* Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010;69:631–7.
- Smolen JS, Breedveld FC, Burmester GR, *et al.* Treating rheumatoid arthritis to target: 2014 update of the recommendations of an international task force. *Ann Rheum Dis* 2016;75:3–15.
- Smolen JS, Braun J, Dougados M, *et al.* Treating spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis, to target: recommendations of an international task force. *Ann Rheum Dis* 2014;73:6–16.
- Smolen JS, Schöls M, Braun J, *et al.* Treating axial spondyloarthritis and peripheral spondyloarthritis, especially psoriatic arthritis, to target: 2017 update of recommendations by an international task force. *Ann Rheum Dis* 2018;77:3–17.
- van Vollenhoven RF, Mosca M, Bertasi G, *et al.* Treat-to-target in systemic lupus erythematosus: recommendations from an international task force. *Ann Rheum Dis* 2014;73:958–67.
- Kiltz U, Smolen J, Bardin T, *et al.* Treat-to-target (T2T) recommendations for gout. *Ann Rheum Dis* 2017;76:632–8.
- Singh JA, Furst DE, Bharat A, *et al.* 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* 2012;64:625–39.
- Smolen JS, Landewé R, Breedveld FC, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
- Smolen JS, Landewé R, Bijlsma J, *et al.* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017;76:960–77.
- Wollenhaupt J, Albrecht K, Krüger K, *et al.* The new 2012 German recommendations for treating rheumatoid arthritis: differences compared to the European standpoint. *Z Rheumatol* 2013;72:6–9.
- Beresford MW, Cleary AG, Foster HE, *et al.* Comment on: Developing standards of care for patients with juvenile idiopathic arthritis. *Rheumatology* 2010;49:2227–9.
- Wallace CA. Developing standards of care for patients with juvenile idiopathic arthritis. *Rheumatology* 2010;49:1213–4.
- Consolaro A, Negro G, Lanni S, *et al.* Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2012;30:S157–62.
- Hinze C, Gohar F, Foell D. Management of juvenile idiopathic arthritis: hitting the target. *Nat Rev Rheumatol* 2015;11:290–300.
- Woerner A, Uettwiller F, Melki I, *et al.* Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. *RMD Open* 2015;1:e000036.
- Dougados M, Betteridge N, Burmester GR, *et al.* EULAR standardised operating procedures for the elaboration, evaluation, dissemination, and implementation of recommendations endorsed by the EULAR standing committees. *Ann Rheum Dis* 2004;63:1172–6.
- van der Heijde D, Aletaha D, Carmona L, *et al.* 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-Based Medicine: The Oxford 2011 Levels of Evidence. 2011.
- Wallace CA, Giannini EH, Spalding SJ, *et al.* Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. *Arthritis Rheum* 2012;64:2012–21.
- Tynjälä P, Vähäsalo P, Tarkiainen M, *et al.* Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. *Ann Rheum Dis* 2011;70:1605–12.
- Vastert SJ, de Jager W, Noordman BJ, *et al.* Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naïve patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. *Arthritis Rheumatol* 2014;66:1034–43.
- Nigrovic PA, Mannion M, Prince FH, *et al.* Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. *Arthritis Rheum* 2011;63:545–55.
- Nigrovic PA. Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? *Arthritis Rheumatol* 2014;66:1405–13.
- Lovell DJ, Giannini EH, Reiff A, *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis. *N Engl J Med Overseas Ed* 2000;342:763–9.
- Lovell DJ, Giannini EH, Reiff A, *et al.* Long-term efficacy and safety of etanercept in children with polyarticular-course juvenile rheumatoid arthritis: interim results from an ongoing multicenter, open-label, extended-treatment trial. *Arthritis Rheum* 2003;48:218–26.
- Lovell DJ, Ruperto N, Goodman S, *et al.* Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. *N Engl J Med* 2008;359:810–20.
- Gattorno M, Piccini A, Lasigliè D, *et al.* The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum* 2008;58:1505–15.
- Yokota S, Imagawa T, Mori M, *et al.* Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008;371:998–1006.
- Ruperto N, Lovell DJ, Quartier P, *et al.* Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. *Arthritis Rheum* 2010;62:1792–802.
- Beukelman T, Patkar NM, Saag KG, *et al.* 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. *Arthritis Care Res* 2011;63:465–82.
- Quartier P, Allantaz F, Cimaz R, *et al.* A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis* 2011;70:747–54.
- Ruperto N, Brunner HI, Quartier P, *et al.* Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2396–406.
- De Benedetti F, Brunner HI, Ruperto N, *et al.* Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2385–95.
- DeWitt EM, Kimura Y, Beukelman T, *et al.* Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res* 2012;64:1001–10.
- Ringold S, Weiss PF, Beukelman T, *et al.* 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Care Res* 2013;65:1551–63.
- Brunner HI, Ruperto N, Zuber Z, *et al.* Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. *Ann Rheum Dis* 2015;74:1110–7.

- 52 Horneff G, Foeldvari I, Minden K, *et al.* Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. *Arthritis Rheumatol* 2015;67:2240–9.
- 53 Burgos-Vargas R, Tse SM, Horneff G, *et al.* A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. *Arthritis Care Res* 2015;67:1503–12.
- 54 Schiappapietra B, Varnier G, Rosina S, *et al.* Glucocorticoids in juvenile idiopathic arthritis. *Neuroimmunomodulation* 2015;22:112–8.
- 55 Foell D, Wulffraat N, Wedderburn LR, *et al.* Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. *JAMA* 2010;303:1266–73.
- 56 Hinze C, Foell D, Johnson A, *et al.* A68: The Role of Serum S100A12 Protein Levels in Maintaining Inactive Disease on Anti-tumor Necrosis Factor Therapy in Polyarticular Forms of Juvenile Idiopathic Arthritis. *Arthritis Rheumatol* 2014;66:S99–S100.
- 57 Magni-Manzoni S, Scirè CA, Ravelli A, *et al.* Ultrasound-detected synovial abnormalities are frequent in clinically inactive juvenile idiopathic arthritis, but do not predict a flare of synovitis. *Ann Rheum Dis* 2013;72:223–8.
- 58 Rebollo-Polo M, Koujok K, Weisser C, *et al.* Ultrasound findings on patients with juvenile idiopathic arthritis in clinical remission. *Arthritis Care Res* 2011;63:1013–9.
- 59 Brown A, Hirsch R, Laor T, *et al.* Do patients with juvenile idiopathic arthritis in clinical remission have evidence of persistent inflammation on 3T magnetic resonance imaging? *Arthritis Care Res* 2012;64:1846–54.
- 60 Consolaro A, Ravelli A. Defining criteria for disease activity states in juvenile idiopathic arthritis. *Rheumatology* 2016;55:595–6.
- 61 Swart JF, van Dijkhuizen EHP, Wulffraat NM, *et al.* Clinical Juvenile Arthritis Disease Activity Score proves to be a useful tool in treat-to-target therapy in juvenile idiopathic arthritis. *Ann Rheum Dis* 2018;77.
- 62 Bartoli M, Tarò M, Magni-Manzoni S, *et al.* The magnitude of early response to methotrexate therapy predicts long-term outcome of patients with juvenile idiopathic arthritis. *Ann Rheum Dis* 2008;67:370–4.
- 63 Smolen JS, Han C, van der Heijde DM, *et al.* Radiographic changes in rheumatoid arthritis patients attaining different disease activity states with methotrexate monotherapy and infliximab plus methotrexate: the impacts of remission and tumour necrosis factor blockade. *Ann Rheum Dis* 2009;68:823–7.
- 64 Radner H, Alasti F, Smolen JS, *et al.* Physical function continues to improve when clinical remission is sustained in rheumatoid arthritis patients. *Arthritis Res Ther* 2015;17:203.
- 65 Aletaha D, Funovits J, Breedveld FC, *et al.* Rheumatoid arthritis joint progression in sustained remission is determined by disease activity levels preceding the period of radiographic assessment. *Arthritis Rheum* 2009;60:1242–9.
- 66 Verazza S, Negro G, Marafon D, *et al.* Possible discontinuation of therapies after clinical remission in juvenile idiopathic arthritis. *Clin Exp Rheumatol* 2013;31:S98–101.
- 67 Horton DB, Onel KB, Beukelman T, *et al.* Attitudes and approaches for withdrawing drugs for children with clinically inactive nonsystemic JIA: a survey of the childhood arthritis and rheumatology research alliance. *J Rheumatol* 2017;44:352–60.
- 68 Dueckers G, Guellac N, Arbogast M, *et al.* Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. *Clin Immunol* 2012;142:176–93.
- 69 Davies K, Cleary G, Foster H, *et al.* BSPAR Standards of care for children and young people with juvenile idiopathic arthritis. *Rheumatology* 2010;49:1406–8.
- 70 Cellucci T, Guzman J, Petty RE, *et al.* Management of Juvenile Idiopathic Arthritis 2015: a position statement from the pediatric Committee of the Canadian Rheumatology Association. *J Rheumatol* 2016;43:1773–6.
- 71 Singh JA, Saag KG, Bridges SL, *et al.* 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Rheumatol* 2016;68:1–26.
- 72 Bakker MF, Jacobs JW, Welsing PM, *et al.* Low-dose prednisone inclusion in a methotrexate-based, tight control strategy for early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2012;156:329–39.
- 73 Shoop-Worrall SJW, Verstappen SMM, Baidam E, *et al.* How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. *Ann Rheum Dis* 2017;76:1381–8.
- 74 Giancane G, Ravelli A. Paediatric rheumatic disease: What is the best definition of clinical remission in JIA? *Nat Rev Rheumatol* 2017;13.