Juvenile Idiopathic Arthritis: Towards Improving Clinical Care

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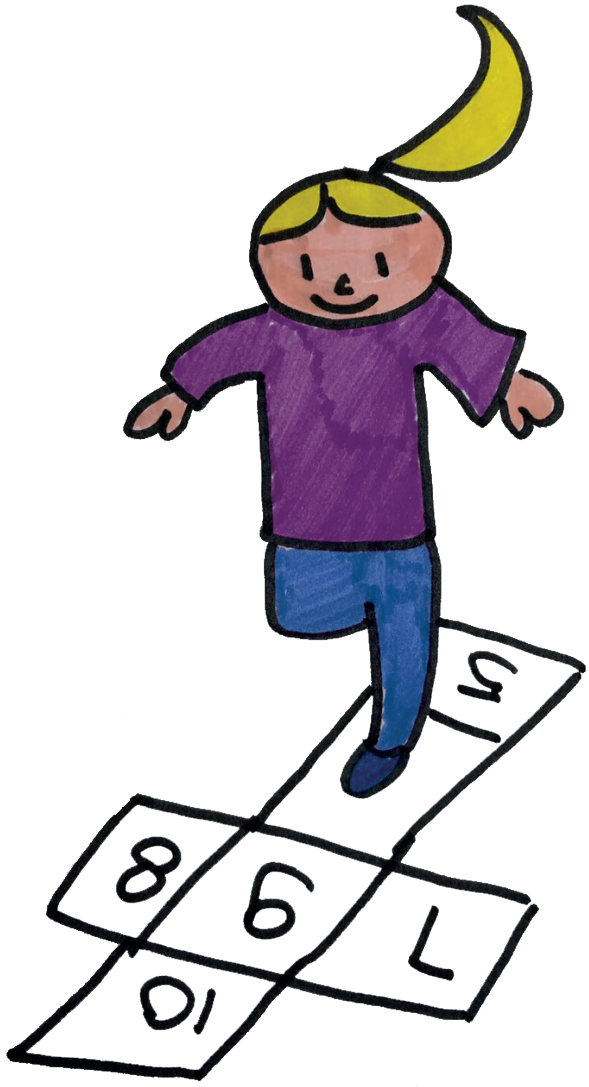
PART THREE

Discussion



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General discussion and conclusion

In the following chapter the main findings of this thesis are reviewed and discussed against the background of relevances in current clinical care.

PART 1 PATHOGENESIS OF JUVENILE IDIOPATHIC ARTHRITIS

Juvenile Idiopathic Arthritis

Juvenile Idiopathic Arthritis (JIA) is a collective name for a group of complex autoimmune diseases with a variable course and outcome. The main feature is arthritis of one or multiple joints in children. A general introduction on JIA and a brief history on therapeutic approach to JIA are given in Chapter 1. Pathogenesis has not been completely unravelled yet, but is currently viewed as a combination of genetic susceptibility and environmental triggers causing a disturbed balance between tolerance and inflammation. Due to the heterogeneous nature of JIA, biomarkers would be helpful in determining the window of opportunity and in selecting patients for particular treatments or strategies or help in determining the moment for tapering and stopping therapy. They can be used for diagnosis, response to therapy, or prediction of flare.

The role of biomarkers in the treatment of JIA

As such for example the myeloid related proteins (MRP's) have recently gained attention[1] as potential biomarker for a disease flare, although they are not incorporated routinely in clinical care yet. Other potential biomarkers could include the anti-Carp antibodies, already routinely screened in rheumatoid arthritis (RA)[2] and the composition of the collective gut flora including their genetic material, further referred to as the microbiome.

AntiCarp antibodies

To study the potential value of a new biomarker in RA for prediction of prognosis in JIA, we performed a pilot study in a group of JIA patients. The so-called anti-CarP antibodies are antibodies which are related to a poor prognosis/radiographic damage in RA, independent of the presence of RF or anti-CCP antibodies[3]. In our pilot study, anti-CarP antibodies are present in low percentages (8-13%) in JIA patients, even if (when) they are RF-negative and anti-CCP-negative. Most often however the three autoantibodies (Rheumatoid factor, anti-CarP antibodies and anti-CCP antibodies) could be demonstrated together, probably reflecting a more severe disease course. The exact role of the anti-Carp antibodies in the prognosis of JIA remains unclear. Future and ideally larger studies will have to be performed to investigate this in more detail. Probably the combination of several biomarkers will, in the future, help to predict responses and guide personalized medicine[4].

Microbiome in JIA

Over the last decade the gut microbiome has gained increased attention in the research field of inflammatory diseases, also in JIA[5]. We have performed a pilot study to investigate the diversity of microbiota in JIA as a potential biomarker, since it is easy to collect and

not invasive. We hoped to identify subsets of JIA patients, when compared with healthy controls by their gut microbiome, based on differences in the phylum Bacteroidetes, usually dominantly present in healthy children[6]. Almost simultaneously in 2016 microbiota aberrations were reported in non-systemic JIA[7] reflecting the same changes observed in type 1 diabetes, as in Enthesitis Related Arthritis (ERA)[8]. In the latter, associations with different states of disease activity were established. Intestinal dysbiosis has since long been implicated in the pathogenesis of spondylarthropathies. Therefore, research in the last years seems to focus on pediatric ERA patients[9, 10].

Indirect evidence for a role of the composition of the microbiota comes from studies linking environmental factors influencing the microbiota to the risk of developing JIA as described by Horton et al[11]. Microbiota research is complex due to complicated comparison of results when using different detection techniques, big data with complex statistical analysis and environmental differences. A recent study incorporating the use of microbiota analysis has found some clues that a lower relative abundance of a certain type of bacteria (Mogibacteriaceae) in oligoarticular JIA patients might play a role in predicting inactive disease in the first two years[12]. Further studies are needed to delineate the role of the microbiota and to appreciate its potential as therapeutic target in JIA.

PART II CLINICAL ASPECTS TREATMENT STRATEGIES

Medical treatment in JIA

The treatment of JIA has changed revolutionary over the last 2 decades. Improved understanding on pathogenesis in inflammatory diseases like RA and JIA and recognition of important mediators of inflammation have led to the development of TNF-blocking medicines on top of classical DMARDs like MTX and sulphasalazine (SSZ). The term refers to a group of therapeutic agents that specifically target a particular cell or cytokine involved in the inflammatory process of JIA. Especially with the biologicals inhibiting TNF-α (etanercept, infliximab and adalimumab)—clinical improvement is very significant. The introduction of TNF-blocking medication in the disease course has improved the outcome for JIA patients substantially. Additionally, increasing uniformity in monitoring the disease has further improved the outcome. Nowadays, treatment with Disease Modifying Antirheumatic Drugs (DMARDs) is started as soon as possible after diagnosis, resulting in more effective suppression of disease activity and substantial reduction of joint damage. Current treatment recommendations are based on national or international publications[13, 14]. The DMARD therapies recommended are all well-known. The optimal timing or combination is still a matter of debate.

Targeting Inactive disease

There are several indications that earlier or even immediate treatment with TNF-α inhibitors might even be more beneficial than reserving such treatment for patients who have failed on traditional DMARDs. Tynjala and Wallace et al both showed the beneficial effects of early aggressive treatment on outcome[15, 16]. Gradually even inactive disease has become the realistic goal that comes into view in JIA patients[17].

An important question remains when to initiate an TNF-blocking agent. Their place in the treatment of patients with recently diagnosed JIA and their effectiveness compared to other aggressive treatment strategies has yet to be determined[18].

In line with previous (RA) studies, these insights have led to the development of a practice-based study in JIA patients, comparing treatment strategies rather than individual drugs, called BeSt for Kids study.

The BeSt for Kids study

In this study three treatment strategies are compared (figure x page y).
1 Sequential monotherapy, where patients started with one DMARD: either methotrexate (MTX) or Sulphasalazine (SSZ), thereafter increasing MTX dose or switching to MTX, thereafter adding etanercept (anti-TNF) in case of insufficient response (n=31).
2 Initial combination therapy with MTX and prednisolone, where patients started directly with methotrexate and prednisolone bridging therapy (4 weeks 0.5mg/kg, tapering to 0 in 2 weeks), thereafter increasing MTX dose, thereafter adding etanercept (anti-TNF) in case of insufficient response (n=32).
*3 Initial combination therapy with etanercept and MTX (*anti-TNF) where patients started with a combination of the TNF-inhibitor etanercept and MTX (n=29).

Between October 2009 and April 2014, 94 JIA patients with recent onset active juvenile idiopathic arthritis (oligoarthritis, RF negative polyarthritis and juvenile psoriatic arthritis) were included and followed for 2 years. The initial target was to achieve an adjusted ACRpedi50% after 3 months of treatment and inactive disease from six months and onwards in all patients. To resemble the dynamics of daily practice, the patients moved through the treatment protocol and proceeded to the next step (increasing dose, switching to another drug, or adding another drug) in case of an insufficient response (no ACRpedi50% or no inactive disease). Tapering was commenced once a period of 3 (oligoarticular disease) or 6 (polyarticular disease) months of inactive disease was reached. Measurements of disease activity were performed every 3 months by a physiotherapist who was blinded for the allocated treatment strategy. The treating paediatric rheumatologists used the results of these core set criteria for the adjustment of therapy.

The primary clinical outcome was time to inactive disease and time to flare after tapering and stopping DMARD medication. Secondary outcomes were adjusted ACRPedi30/50/70/90% calculations, toxicity and physical function as measured by Child Health Assessment Questionnaire (CHAQ) every 3 months.

EARLY CLINICAL OUTCOMES

Adjusted ACRpedi improvements

After three months of therapy the target was ACRPedi50%. The patients who started with an initial combination of etanercept and MTX (arm 3) had a higher ACRpedi70% response after 3 months of 47% compared to arm 1 (25%) and arm 2 (19%) of treatment in comparison to the monotherapy strategy (arm 1, p=0.04). Less medication changes had occurred and toxicity was similar between the groups. These results are worldwide one of the first data on recent-onset DMARD-naive JIA patients treated DMARD naive with etanercept and MTX[19].

If we compare our data to the literature we find data on JIA patients with chronic severe disease course, previously treated with MTX or other DMARDs. In those patients after 3 months of etanercept treatment percentages of improvement ranging from 36% in original etanercept study[20] to 39%[21, 22] and 51%[23] depending on registry and JIA category.
This is relatively similar, although patients from both groups are not comparable in terms of disease duration before start of anti-TNF. The 3-months period is relatively short and outcome over a longer period is more important. Whether ACRpedi70% after 3 months is predictive for later outcome is subject of further study although results in literature previously reported on this[24-27].

If we focus on percentage of improvement we do not take the actual disease activity into account. Therefore, the JADAS-score was developed.

JADAS-score

The JADAS-score, first described in 2009[28] is a composite score of Physician Global Assessment (PGA), Patient/parent global assessment of well-being, ESR and number of active joints. JADAS-10 (joint count is up to a maximum of 10 active joints) scores after 3 months treatment were measured additionally, since this score was developed after finalizing the protocol for the BeSt for Kids study. As recently described[29] the difference in JADAS (ΔJADAS) compared to baseline is helpful and more easy to determine improvement. At baseline JADAS-10 scores were median 15.7 (13.5-20.2) in arm 1, 17.9 (15.2-21.9) in

arm 2 and 19.1 (13.8-23.2) in arm 3. ΔJADAS after 3 months of treatment was median 6.9 in arm 1, 5.7 in arm 2 and 10.2 in arm 3 (p=0.22). In literature JADAS-10 scores after 3 months of etanercept treatment were published[29], differentiating between baseline low, moderate or high disease activity. Cut-off values for improvement could be defined by the minimal decrease in the JADAS-10 in baseline class: low by 4, moderate by 10 and high by 17. Our patients are in the category of moderate disease activity corresponding with JADAS 15-25 at baseline. Our 3-months responses in ΔJADAS are in line with these responses in arm 3 only, underscoring the small but significant difference in ACRpedi70% responses after 3 months of therapy.

Clinical outcomes after 24 months of follow-up (see Chapter 5.2, figure 2).
Time-to-inactive-disease

Time-to-inactive-disease was not significantly different across the arms, median after 9 months. Between 12 and 24 months medication was tapered and stopped in case of prolonged inactive disease, giving rise to flares and therefore loss of inactive disease criteria explaining the bumps in the curves in the second year. After 2 years of treatment, in all three arms more than 70% was in inactive disease despite tapering strategies.

In literature, inactive disease after 54 weeks in ACUTE[16] was reached in 68% (infliximab), 40% (COMBO) and 25% (MTX). In TREAT[15] after 12 months numbers are 21% (arm1, MTX/etanercept/prednisolone) versus 7% (arm2, MTX with placebo prednisone/etanercept). The results of the extension study are in line with our results with prolonged periods of inactive disease in most patients and those not in clinical inactive disease had low levels of disease activity[30]. Differences in study design hamper the possibility to compare these results in further detail. In our study the much smaller and thus apparently non-significant differences can be explained since we used a dynamic treatment- to-target approach with a final common pathway in all three arms therefore final results tend to approach each other after 2 years. Flares in this specific study design are responsible for loss of inactive disease status.

Observational studies from the comparable time frame of our study (2009-2014) reach lower levels of inactive disease and all manuscripts discuss mainly *periods* of inactive disease instead of prolonged inactive disease, not mentioning tapering or stopping of DMARDs[31-35]. For example Ringold describes a cohort of patients with polyarticular disease, spending most of the follow up time in active disease[36]. A highly variable disease activity pattern was described by Albers et al, with, in general, a predictive course in the first two years for the course in the following 3 years[32]. Papsdorf, in 2011, has reported on 50% of patients reaching inactive disease on medication[33]. Anink has reported on the first episode

of inactive disease occurring after median 10 months in 77% of patients, but does not report on prolonged inactive disease state[34]. Minden reported on 20% inactive disease while 78% was still on therapy in the Jumbo registry in 2012[35].

Results from more recent observational studies reflecting daily current practice even with the most modern treatments earlier in the disease course, describe lower levels of inactive disease after 1 year[37-41] varying from 25-50% on average underscoring the importance of an additional treat to target (T2T) approach in JIA. For example, Mc Erlane reports that one third of patients is still in high disease activity at one year[37]. Worrisome is the fact that they lacked to find any improvement over the last 10 years possibly due to poor awareness and delays in referral. Solari et al report in 2012 that half the patients on etanercept reach inactive disease. After 24 months of continued therapy 57% was in the state of inactive disease[42].

Shoop-Worrall (2017) highlights that the majority of patients have persistent disease activity after 1 year of treatment in a large inception cohort[39]. Verrazza (2016)[40] also mentioned that half of the patients on etanercept reach complete disease quiescence. Sengler reports that the majority of patients with JIA reach the state of inactive disease within the first year of specialised care[41]. This cohort consisted mainly of oligoarticular JIA patients and therefore differed from our population.

Adjusted ACRPedi 30/50/70/90 improvements over 24 months (see Chapter 5.2 figure 2)

High percentages of improvement are reached in all three arms during 24 months, without significant differences over time between the 3 arms.

12 months outcome

Our study showed 69% ACRPedi70 in arm 3 after 1 year of treatment with etanercept and methotrexate combination from the start, compared to approximately 56% in the other 2 arms where etanercept, if needed, was initiated at a later stage. In 2004 early registries on etanercept describe in non-systemic established DMARD refractory JIA ACRpedi70 of 34% after 1 months to 64% improvement after 1 year of treatment[21]. Five years later the same authors describe 62% of ACRpedi70 improvement after one year of combination therapy with etanercept and MTX as compared to 45% for the etanercept only treatment. These registries contain the most severe JIA patients with long-lasting disease, in contrast to our study, where all children regardless of disease activity were included when they were in need of a DMARD. In the previously mentioned ACUTE study ACRpedi 75 after 54 weeks was primary end point. This high goal was reached in 100% (anti TNF), 65% (COMBO) en

50% (MTX) arm. The ACUTE study did not allow a tapering regime and was not blinded, two reasons probably contributing to the differences found in our results. Whether ACRpedi70% after 3 months is a predictor for long term outcome is subject of further study but this seems likely since more ACRPedi70% is reached in the third arm after 3 months and this result lasts over a period of 24 months.

24 months outcome

In our study even after 24 months, results continue to improve, mainly in ACRpedi30/50% in all arms without reaching a plateau phase yet. In arm 3 for ACRpedi 70 and 90 due to tapering and stopping therapy and therefore loss of improvement a plateau seems to have been reached, but not yet for arm 1 and 2. Earlier saturation of maximum clinical effect on group level might have been reached in arm 3 as an explanation to these graphs. This is special when we take tapering/stopping of DMARDs into account, mostly occurring between 12 and 24 months of follow-up as can be seen in figure chapter 5.2 figure 3. The continued improvement in all arms emphasize again the importance of a T2T-approach which can include a tapering and stopregime, but with careful monitoring and swift response in case of a flare. And again, although these percentages seem comparable, they do not allow us to compare actual disease activity.

JADAS-10 score

Since the development of the JADAS score[28] we added JADAS-10 score as secondary outcome measure after 24 months. JADAS-10 scores at baseline were calculated once more, since 2 patients were left out of the 24 months analysis due to changing diagnosis. Baseline JADAS-10 mean was 16.5 ± 4.2, in arm 2 18.8 ± 4.4, and in arm 3 18.8 ± 5.4. After treatment in this treatment-to-target regime JADAS-10 scores improved after 12 months to 6.1 (3.8-8.3) in arm 2 to 6.2 (3.8-8.6) and in arm 3 to 4.7 (2.6-6.8) (see figure Chapter 5.2 figure 2). All fulfil the criteria of improvement with ΔJADAS of at least >10 points from mediate baseline disease activity[29]. Numerically highest ΔJADAS was observed in arm 3. After 24 months of continued T2T-strategy, including tapering and stopping if predetermined criteria were met, JADAS-10 scores reached 2.6 (1.4-3.8) in arm 1, 4.0 (2.2-5.8) in arm 2 and 3.0 (1.6-4.4) in arm 3.

In accordance with previous results, JADAS-scores in all arms continue to go down and have not reached a plateau yet suggesting the on-going beneficial effect of the T2T-approach even allowing for tapering strategies.

Recently clinical (c)JADAS as adaptation of the original JADAS was developed[43]. The advantage is the lack of ESR in this score. Even more recently it was proposed that

cJADAS was able to identify patients in need of anti-TNF according to the Beukelman recommendations[13] and therefore it is a user-friendly tool easy to be used for T2T in JIA[44]. The patient VAS appeared to be a critical item in the cJADAS for the decision to escalate to anti-TNF. Since we know from previous studies[45] that patient VAS frequently overestimated disease activity when having pain and being functionally limited, these results need to be confirmed in future studies.

CHAQ

Functional ability was measured by the Dutch version of the Child Health Assessment Questionnaire (CHAQ)[46]. CHAQ levels were comparable at the start of the BeSt for Kids study on average (1.1± on a scale from 0-3) quite low, corresponding with between mild-to-moderate and moderate disability[47] yet comparable with CHAQ-levels in the TREAT (1.1±0.8 and 1.3±0.7) and ACUTE study (0.5-1.1±0.55-0.60)[15, 16]. Over time they improved in all three arms although CHAQ's in the second arm remained the highest numerically. The minimal clinically important differences (MCID) of the CHAQ both for improvement and worsening are often at or close to the level of the smallest potential difference, which is 0.13[48]. The problem in low disease activity is the fact that the CHAQ in its current form probably is too insensitive to determine important short term changes in health and disease for a given patient. If this problem was relevant in our study, it has affected all three groups in a similar way. Possibly also a so-called 'response shift' has occurred if patients, which means that although somewhat worsened or improved, the patients have become used to the altered health state and rate themselves as unchanged, even though an actual change in their health had taken place. For example in ACUTE study, baseline CHAQ in TNF arm was 0.5±0.1 and CHAQ after 54 weeks was 0.4±0.1, although 68% had reached inactive disease. Whether this response shift occurs in JIA patients is currently unknown. Interesting is that CHAQ scores in our study are low compared to for example the PRINTO-MTX study', where ACRpedi70 non-responders or even ACRpedi30 non-responders could be predicted by higher CHAQ scores (>1.0)[49]. Observational cohort studies in the TNF-era however describe low CHAQ levels (0.43-0.63) even before initiation of a biological[50] underlining the lack of sensitivity of the score in the lower ranges.

Medication changes in the BeSt for Kids study

More medication changes were needed in the first and second arm compared to arm 3.
In arm 3 all patients were treated with etanercept and methotrexate. In arm 2 after 1 year more than 50% started on etanercept and after 2 years 70% of patients used or had used it. In arm 1 50% of patients eventually needed etanercept at various time points according to protocol. Despite the different number of medication changes, comparable numbers of patients 1) reached inactive disease and 2) could taper and stop DMARD therapy, with 3) comparable numbers of flare.

It seems that the T2T approach is more important than initial treatment in terms of primary outcome measures: time-to-inactive disease and time-to-flare. Combination therapies were not superior in our study after 24months, as was previously reported in rheumatoid arthritis[51]. However, out of protocol use of glucocorticoids (see Chapter 5.2, Table S2 protocol violations) either oral, IM or intra-articular could have improved the outcomes of arm 1 and 2. More studies are needed to establish the optimal treatment strategies, although our study supplies proof-of-principle evidence that treatment-to-target is potentially equally/more important than the drug used as was previously described in RA[52, 53]. Consensus treatment plans (CTP) have been developed to study different initial treatment strategies outside of clinical trials, which are described further down.

Tapering and stopping DMARDS

In our study 59% of patients were able to taper and stop medication after on average 15-18 months of therapy. This duration of therapy is shorter in comparison to the patients previously described in literature, who were treated variably between 19 months and over 4 years[54-60] before tapering was attempted, although they had a more prolonged total disease duration and had started a biological later in the disease course.

In a large cohort of patients managed with contemporary treatments according to current standard-of-care, described by Guzman et al, probabilities of discontinuing treatment of 46% for oligoarthritis, 21% for RF negative polyarthritis and 44% for psoriatic arthritis are mentioned[61]. This large cohort contained patients with comparable patient characteristics in comparison to our study. Guzman explicitly states in the discussion that they report on *attaining* a clinical outcome, these results should not be interpreted as probabilities of *maintaining* these outcomes.

Chang et al describe a cohort of polyarticular JIA and Enthesitis related Arthritis[59]. 29% of RF negative polyarticular JIA could stop all DMARD therapy.

Recently, Minden et al describe higher chances of reaching drug-free remission is related to earlier initiation of biologicals, underscoring the concept of a window-of-opportunity[62]. Tapering and stopping therapy therefore is a logical step in the treatment of prolonged inactive JIA, especially when therapy was initiated early in the disease course. From our experiences in the BeSt for Kids study, motivation to be treated continually tends to decrease in JIA and patients/parents actively request for tapering and stopping therapy and this was observed previously[63].

At the end of our study about 39% in all arms were (still) in drug-free inactive disease. Although recent recommendations do not advice on tapering and stopping yet[64], in our experience, tapering and even stopping DMARDs was feasible in children with JIA once inactive disease had been reached for at least 6 months in polyarticular disease or 3 months in oligoarticular disease. More studies need to be done to recognize patients at risk for flare and to determine the optimal period of therapy before tapering since Klotsche et al describe less flares when inactive disease was maintained for 12 months before MTX withdrawal[65].

Time to flare

After tapering and stopping DMARDs, time-to-flare was not significantly different between the arms and occurred after on average 3.0 (3.0-6.0) months. Flares were described in 25% of cases in all three arms with the relative limited follow-up time up of 24 months.
A recent observational study by Chang et al[59] among polyarticular JIA and enthesitis related arthritis (n=335) describes a flare rate of 63% within the first year. More patients on combination therapy flared if they first stopped the TNF-blocker and continued MTX. This is not the case in our study. Long term data need to be collected to reflect on our flare percentages over longer period of time.
Data from another recent large observational study by Guzman show higher numbers of flare in up to 54.7% out of 1146 patients[60] depending on definition of flare and among all JIA categories. In this study significant flares, defined by the need to intensify therapy, occurred 26.6% (24% to 30%) within a year after achieving inactive disease and within a year after stopping treatment 25.0% (21% to 29%), respectively.

Flares in our study required restart of therapy in 4/6 patients in arm 1 (1 SSZ 3 MTX), 3/3 in arm 2 (MTX and n=1 one local injection) and 5/5 in arm 3 (MTX/etanercept). Numbers are in the same range as in the recent paper by Guzman[60] although comparability between our RCT in selected categories of JIA and this large prospective observational cohort study in all JIA categories is limited. Already known from Guzman et al is, that children with a severe disease course have higher chances for flare[60] yet there is a need for prediction of flares to determine in which patient therapy can be withdrawn safely.

Flares in our study were characterised by on average low disease activity: cJADAS 9.7 (8.1-11.3). After restart of last effective therapy (3 months later) cJADAS lowered substantially to 3.9 (1.8-6.0).

We were able to include a few oligoarticular JIA patients. In the n=11 oligoarticular patients in our study the amount of flares in oligoarticular patients (n=1 out of 5) was in proportion

with the amount of flares in polyarticular patients (n=13 out of 83), suggesting that 3 months of inactive disease in oligoarticular disease, before tapering needs further study. On the other hand, a recent study containing 40% oligoarticular JIA patients, described a lower flare rate in case of 12 months of inactive disease before MTX tapering[65].

Toxicity

Over 24 months toxicity was similar across the arms. Some severe adverse events occurred, all due to hospital admission for several reasons (see Chapter 5.2, table 2 Adverse events), in all three arms, none with permanent damage. In recent literature comparable data on toxicity can be found for patients treated with anti-TNF's or MTX/combinations[23, 66-69]. Concerns on serious infections[66, 69] exist but they seem to be mild on group-level. Long term pharmacovigilance remains of importance since the era of the use of biologicals in JIA patients is currently less than 20 years[70, 71]. Since we started and stopped biologicals early in the disease course we aim to reduce exposure to these drugs and thus diminish possible adverse events.

Protocol violations

In our study in all arms protocol violations occurred (see Chapter 5.2, table S2 protocol violations), mainly due to the wish of parent/patient or physicians wish not to increase therapy. Since this was a long term follow-up pragmatic clinical trial, we tried to mimic routine clinical care. Although parents and patients were informed and aware of the treatment protocol, we used shared decision making[64] as an important principle in the consulting room, and obviously this is complex in children when treated with TNF-blockers[72]. Protocol violations occurred in all arms in the study in comparable numbers. Previously described in the original BeSt-study, disagreement with the disease activity score (DAS) or the required treatment and dissatisfaction with the level of disease suppression were risk factors for non-adherence[73]. This is subject of further study from the results of our trial.

The use of glucocorticoids

In arm 2, 6 weeks of prednisone was administered as bridging therapy. Four weeks of 0.5mg/kg tapering in 2 weeks to 0. The six weeks results show a clear short-term benefit although the effects are short-lived and do not seem to sustain over longer time since we observed a 'rebound effect' in terms of adjusted ACRpedi improvements, inactive disease and JADAS10 score after withdrawal. The duration of administration of glucocorticoids in this trial is presumably too short for a lasting effect. Due to the inherent characteristics of glucocorticoids in children a prolonged use is not eligible. The optimal dose and duration for bridging purposes is subject of further studies although individual preferences exist among physicians[74].

In the paper by Guzman[61], the cumulative probability of attaining inactive disease after 2 years is high in patients with oligoarticular disease (86%) and RF negative polyarticular disease (70,9%), by using glucocorticoids relatively often and less biologicals compared to our cohort.
Throughout the study parenteral glucocorticoids were administered outside of protocol: in the first months in arm 1 and 2: 7 times compared to none in arm 3. These findings may indicate that the clinical efficacy of treatment in arm 3 was better, and that with less effective csDMARDs, additional glucocorticoid-courses are required to achieve similar results.

Radiographic outcome

As the time has come to include radiographic progression as outcome in JIA clinical trials[75] we evaluated radiological outcome in our cohort from recent onset active JIA patients in the BeSt for Kids study who were treated to target, early and with tight control.

Poznanski score

As determined by Poznanski[76] we found in the wrist no radiological damage, neither at baseline, nor at follow-up after 24 months of treatment. This result is remarkable since it was described previously that radiographic damage in polyarticular JIA mainly occurs in wrists[77, 78] both at baseline and with progression at follow-up, up to 10 years. Other studies describe variable degrees of damage[79, 80] and the potential of etanercept to reduce radiographic progression was recognized[81]. Patients in our study at first presentation were not as badly affected as they used to be 25 years ago, since Poznanski scores were comparable to a healthy population. Maybe patients are referred earlier although literature does not support that argument[37]. An explanation could be that current targeted treatments seem to prevent radiographic damage. Evidence for the hypothesis came from Malattia et al when they compared American College of Rheumatology paediatric (ACRpedi) response criteria and conventional radiography with MRI findings in a cohort of patients with JIA[82]. Exclusively patients reaching ACRpedi90 responses showed significant decrease in synovitis on MRI and the halting of structural damage. Those data strongly suggest that ACRpedi30 can no longer be considered a sufficient therapeutic response. Since MRI of the wrist in JIA is not yet validated for synovitis in JIA we still must view these results with caution since MRI abnormalities are sometimes seen in healthy children[83] and MRI data on healthy age matched controls are currently lacking.

Bone age and BMD

Additionally, by using BoneXpert, a validated and automated program to evaluate bone age and bone mineral density (BMD), previously it was found that a JIA population treated

with biologicals at some time in the disease course had delayed bone maturation and lower cortical BMD than healthy children[84]. In our study, bone age (BA) was comparable at start although differences occurred, that were interpreted as not clinically relevant. Changes over time also remained within 1 SD from 0, thus the normal range.
Additionally, BMD of the wrist was significantly reduced (>1SD) at baseline in arm 3 compared with arm 1 and improved significantly in subsequent post-treatment studies in arm 3. In treatment strategy studies in RA, the BeSt-study and the IMPROVED-study, BMD loss was detected and related to joint damage progression[85, 86]. In JIA, previously the relation between diminished BMD and disease activity was observed[87, 88], with exemptions[89], including the possibility for improvement of BMD after therapy[90, 91] although normalization of BMD over time was often not reached[92, 93].
The significant improvement in BMD in arm 3, the relatively preserved BMD in arm 1 and 2 and relatively preserved bone development underscore the importance of the T2T approach in the current era of early adequate treatment.

Patient perspective

Most outcome measurements of clinical studies focus on clinical and radiographic efficacy and do not take the patients' perspective into account. For successful enrolment in future studies such as the BeSt for Kids study, not only the outcomes of the study, but also the patients' willingness to participate in trials, their thoughts and ideas at study entry as well as later on, based on personal experiences are important. Are patients in equipoise at the beginning of participation in clinical trial? And how about later in the course of the study? Equipoise is genuine uncertainty on superiority of one intervention over the other. With those questions in mind we conducted an interview study with parents/patients in the study while the actual BeSt for Kids study was still ongoing so we could compare initial preferences with later ones, shaped by experiences. The results are described in chapter 6. Initial preferences of the majority of families were to be assigned to arm 3, initial treatment with etanercept/MTX combination, therefore preference as a proxy for equipoise was not present during enrolment. During the interview study preferences tended to change towards the actual treatment strategy, possibly reflecting positive experiences with the treatment strategy received. Adverse opinions towards prednisolone were strong at study enrolment. The core message of this manuscript is the importance to evaluate the so-called 'informed patient-group' equipoise in the development of future studies. The importance to include patients and families in all aspects of trial development was recently acknowledged by other groups[94]. Elaborating on this, the next research agenda for juvenile idiopathic arthritis will be made by a collaboration of the Dutch Juvenile Arthritis Association (jeugdreumavereniging) and the Dutch Society of Pediatric Rheumatology (NVKR) according

to the James Lind Alliance method in so-called Priority Setting Partnership (PSP)[95, 96] in which the author of this thesis is participating as a member of the steering group.

Clinical trials, Consensus treatment plans and treatment recommendations

Next to the observational studies with etanercept, clinical trials with a design of early aggressive treatment are scarce: two important in the last decade are the TREAT[15] and the ACUTE[97]. In the TREAT study (Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis) 85 polyarticular JIA patients were treated with either the combination of methotrexate, etanercept and prednisolone (arm1) or with methotrexate, placebo prednisolone and placebo etanercept (arm2). After 4 months ACRPedi70 was reached by 71% in arm 1 versus 44% in arm 2, which was significantly different (p=0.011), although not the primary outcome measure. An important result from the TREAT-study was the predictive value of disease duration. The shorter the disease duration at baseline, the more likely it was that clinical inactive disease would be achieved at 6 months.

The Aggressive Combination Drug Therapy in Very Early Polyarticular JIA (ACUTE) study[97] compared 3 treatment strategies in a multicenter, randomized, open-label trial: 1 MTX monotherapy, 2 MTX with infliximab and 3 MTX with SSZ and hydroxychloroquine. Sixty patients had an average disease duration of 2 months. If the target of ACRpedi75 was not reached by 12 weeks or thereafter in any of the treatment arms, methotrexate was doubled to 30 mg/m^2 weekly up to 25 mg and administered parenterally. At 6 months, modified clinical inactive disease was achieved in 60% of the patients in the MTX and infliximab arm, 30% in the combination arm, and 5% in the MTX only arm. Although for both studies the study design is different, as well as the number of included patients, JIA categories and the use of additional medications, the results provide evidence of the advantage of early aggressive therapy. Novel in our study in relation to the previous 2 clinical trials are the ongoing treatment to target (T2T) approach and the tapering and stopping strategy.

Due to difficulty performing clinical trials in JIA[98], several initiatives were launched to investigate[14, 99] optimal initial treatments for polyarticular course JIA. Comparative effectiveness studies could provide information reducing variation in care by evaluation of the comparative effectiveness of treatment timing and selection and collecting large numbers of patient[100].

The first initiative came from The Childhood Arthritis and Rheumatology Research Alliance (CARRA), a North American organization of pediatric rheumatologists who have joined together to facilitate research in pediatric rheumatology diseases[101]. The first plan was a step-up plan comparable with our arm 1, the second was a combination plan, comparable

with our second arm and the third plan was a biologic only plan, comparable with our arm 3 (although we used combination therapy in arm 3). Those plans were made based on consensus opinion as compared to the treatment recommendations from 2011[13] by Beukelman which were developed by using an evidence-based method, with limited room for expert opinion and not forcing consensus. CARRA used the physician global assessment (PGA), the ability to taper/discontinue glucocorticoids and the "patient much improved" statement as criteria for treatment evaluation. First results are awaited.

Subsequently in 2016 the German initiative by Horneff et al describes the design of 4 treatment plans: 1 adding a biological to MTX in case of insufficient response; 2 initial MTX thereafter biological monotherapy, 3 initial glucocorticoid pulse therapy with MTX and 4 initial multiple glucocorticoid joint injection with MTX. Improvement is more clearly defined, based on JADAS10 or delta JADAS (amount of improvement) cut off values[29]. After 3 months the target is minimal JADAS improvement as previously described. At six months the target is JADAS "parent acceptable disease activity" (JADAS10 ≤ 5.4)[102]. From 12 months the treatment goal is "inactive disease" (JADAS ≤ 1) or at least "low disease activity" (JADAS ≤3.8) . No advice for a treatment withdrawal is given after the first year. First results are awaited for this project as well.

Which target to address and when: is inactive disease too high to aim at?

The treatment-to-target concept has made it way in pediatric rheumatology[103], although it is still in its infancy[64]. Based on the results of our study, inactive disease has proven to be a feasible goal, which is necessary to aim at in trials and clinical care, before tapering and stopping can be considered. However, current consensus treatment plans or treatment recommendations do not advice on tapering and stopping of DMARD/biologics yet due to lack of evidence and still debate the optimal initial goal. Additionally, considerable variability exists on tapering regimes[104]. A previous attempt to study tapering strategies failed as insufficient patient number could be included (personal communication: ABC Stop study). Patients who could taper according to the treating physician, were not prepared to randomize between different tapering strategies, since they wanted to stop right away, emphasizing again the need to include the 'informed patient group' in developing new trial designs.

As a target CARRA aims at ACRpedi90 at 12 months[101] although this is a difficult target to calculate in daily clinical practice. The 'Protocols on classification, monitoring and therapy in children's rheumatology' (PRO-KIND) commission from Germany aims at JADAS remission or at least JADAS low disease activity[14]. On the other hand, from long term experience in rheumatology it is recognized that a goal set too high can hamper the effectuation of a

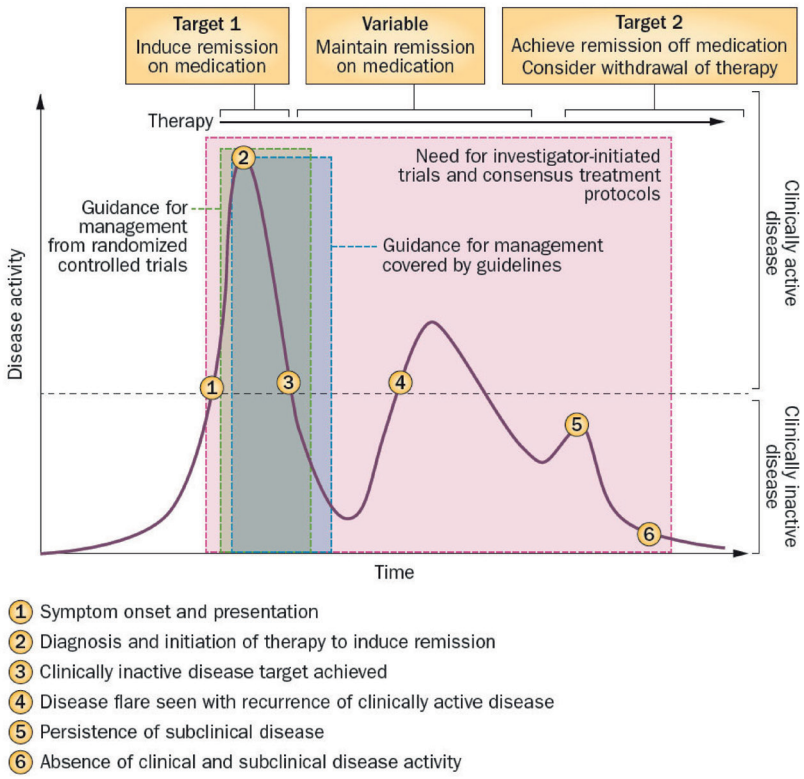

Figure 2 | Matching evidence-based guidance to individual disease courses in clinical practice. A typical disease sequence experienced by a patient with JIA begins with disease onset and diagnosis, after which disease activity (manifesting as periods of disease flare or disease remission) typically varies with time; scenarios of clinically inactive disease, in which subclinical disease persists, can also occur. Clinical practice guidelines and recommendations are founded on evidence-based statements, data from randomized controlled trials or consensus-derived definitions, but these are focused on particular aspects of the management of JIA such as initiation of therapy or achieving remission on medication. The disease activity patterns seen over time indicate other important long-term targets, including managing subclinical active disease, preventing disease flares and timing withdrawal of medication to achieve the ultimate goal of remission off medication. These targets are not yet adequately addressed by existing evidence or guidelines; thus, continued efforts to establish consensus-derived treatment strategies and undertake investigator-initiated trials are required.

Figure from: Management of juvenile idiopathic arthritis: hitting the target
Nature Reviews Rheumatology 2015;11(5): 290-300 (With permission of Prof Dr D Foell)

trial or treatment. Adherence to a DAS-steered protocol was better in the long run if the target was DAS ≤2.4 in the BeSt study, compared with the IMPROVED study aiming at a more strict DAS<1.6.[105] where protocol adherence diminished more over 5 years' time. In the latter study, protocol violations more often occurred against required treatment intensification. Perceived risks (side-effects or costs) of the required steps may reduce physicians' adherence to the protocol. Although not so dedicatedly studied, these results are in line with our experiences in the BeSt for Kids study. In all arms protocol violations occurred mainly against treatment intensifications and are important to keep in mind when developing future studies. Still, inactive disease seems is the right target. Reason to aim that high are the fact that, once treatment was started, we did not observe the development of damage, neither at the wrist, as was studied, nor in other joints. Undertreatment, with the risk of developing (permanent?) damage, is a greater risk for children with JIA than overtreatment, if you consider timely tapering and stopping regimens.

Which treatment strategy is the BeSt?

The evaluation of the three treatment strategies in early JIA as described in Chapter 5 and 6 in this thesis shows that all three arms are comparably effective after 24 months. These results may, next to early DMARD initiation, be attributed to tight control as achieved by intensive monitoring and immediate adjustment of medication.

Although the beneficial effect of tight control has just started to be recognized in JIA[106], the beneficial effect of early treatment and a few initial strategies has been previously described by Tynjala[16], Wallace[15] and Minden[62].

Heterogeneity in JIA categories as well as disease severity, additional use of glucocorticoids out of protocol and complicated estimations used for samples size calculations, have probably contributed to less than expected differences between the three arms.

In this study T2T and tight control seemed more important than the agents inducing it.

How to treat the individual JIA patient?

Reviewing the data from the BeSt for Kids study, it can be argued that, when starting a combination of drugs in all patients that present with JIA (oligo, poly or JIA with psoriasis) a considerable proportion of patients would have been 'overtreated'. Indeed after 2 years of follow up approximately 50% that started with initial monotherapy still showed good clinical response. What could argue against starting with monotherapy in (a subgroup of) JIA patient? In RA characteristics associated with poor prognosis could be overruled when starting early with a combination of drugs[107, 108]. Although diseases are not the same, treatment principles are similar. Therefore one could recommend for further study, based on these data, that JIA with features of poor prognosis as summarized by Beukelman[13]

should all start with combination therapy with MTX and anti-TNF or another biological (il-6 blockade), as nowadays occasionally is done by a pediatric rheumatologist (personal communication). Due to the well-known limitations in JIA patient numbers, we could apply this strategy as routine clinical care and observe the outcome[109].

Identification of patients with less severe disease, not in need of initial combination therapy is of major importance[44]. However, in general the risk of undertreatment seems higher than the risk of overtreatment with subsequent tapering and stopping[110] of combination therapy.

Methodological considerations of our design

The randomized clinical trial is the gold standard to provide evidence for good clinical practice. Alternative study designs have been applied in JIA patients due to several reasons. Trials in JIA patients are challenging[94, 98] mainly due to heterogeneity and rarity of juvenile idiopathic arthritis. In the BeSt for Kids study over 4 years were needed to recruite 'enough' patients. Sample size calculations were complicated since they were based on estimated percentages since actual data were lacking. The study was powered for time to inactive disease, although it tried to 1) evaluate effectiveness and safety of three initial treatment strategies, 2) evaluate the possibility to taper and stop DMARD therapy after prolonged clinical response 3) evaluate flare rates once medication was withdrawn. Although these goals were set (too?) high to answer all these questions we have given proof-of-principle that this type of study is feasible in JIA patients including all the pros and cons of this design.

Reasons for this slower than expected inclusion were delay in referral, passing the artificial 'window of opportunity' of 18 months as determined in the protocol, comorbidities prohibiting trial participation and refusal to participate, mainly at one inclusion site. Additionally, this study was not performed nationwide due to several reasons, which further hampered inclusion.

Our study is a combination between a clinical trial and a comparative effectiveness study and is performed as a large pragmatic trial. Facing the difficulties mentioned above it took a lot of time, perseverance and creativity to finalize the study. For example the inclusion of the oligoarticular patients was less than expected. Often, when a patient was referred as oligo-articular patient, during examination by our experienced physiotherapist, more joints with arthritis were recognized, changing diagnosis from oligo to polyarticular JIA. Probably oligoarticular disease was less severe in the past and by the time it remained active, the period of 18 months needed to be possibly included, had passed.

Inclusion and follow-up visits were time consuming, with single blinded joint examinations every 3 months, Clinical Record Forms (CRF) to fill in. Ideally we wanted to analyse oligoarticular JIA, psoriatic arthritis and polyarticular disease separately, although this did not seem sensible at the moment due to small numbers included of both the subgroups.

The JIA study design historically and future perspectives

In the eighties already it was recognized that performing clinical studies in JIA is challenging[111] and this is an actual issue ever since[98, 112].

Improved legislation in combination with collaboration through large research networks have improved the options for studies in JIA. Inventive study designs like utilizing an active comparator instead of placebo, adding an escape arm to minimize possible exposure to harm, and having an open-label extension for responders to assure direct benefit to research participants who respond well to the study drug. Including families in trial development as discussed in the previous chapter will enhance study appeal. Funding is needed and seems to be invested these days in comparative effectiveness studies and precision medicine (UCAN CAN DU). Several trial designs have passed in recent years, all with specific possibilities and challenges, the most important example is the randomized withdrawal trial[112]. The population under study is treated with a new drug in the first phase, secondly the responders are randomized to continue the drug or receive placebo. The outcome (time to flare) of the withdrawal trial is the efficacy of the drug to suppress a flare, instead of the true efficacy of a the drug. This study design does not support clinical equipoise since only responders are randomized. Secondly information on non-responders is lacking and carryover effect (carryover effect means that if the effect of the treatment carries on after the treatment is withdrawn, and the following response to a second treatment or placebo could be due in part to the previous treatment) will diminish changes to detect significant differences as occurred in the recent golimumab study[113].

To overcome these issues in future studies, extrapolation of efficacy data on adults is possible in diseases with similar progression and similar response to therapy, although studies for safety and drug-dosing always need to be performed in children. For biosimilars proof of similarity and extrapolation from adult studies is currently used, although immunogenicity can be different in less mature immune systems in children, advocating post-marketing studies in children.

Future perspectives: From care to cure

We realised that in our study more than 50% of patients intensified treatment with the need for anti-TNF medication, which is expensive and not equally accessible worldwide.

The value of combination therapy with relatively cheap conventional DMARDs: MTX, SSZ and plaquenil has been established in RA[114] with proven superiority of this triple therapy compared to MTX monotherapy after 1 year of therapy. Thanks to a ZOnMW grant on 'goed geneesmiddelen gebruik' number 80-83600-98-3172, we are currently investigating in a randomized multicenter single-blinded study, whether this superiority exists in JIA as well, while still applying the T2T-approach. The CHAMP study is successfully including JIA patients, over 49 patients in the last 12 months, and inclusion is ongoing. After coordinating and conducting the BeSt for Kids study, we realized how important it is to collaborate on larger scale to improve recruitment of JIA patients in studies. Therefore we are now investigating the possibility to enrol the study in countries for which this strategy would be particularly important, due to low accessibility to anti-TNF medication, like South Africa.

As mentioned previously the biggest challenge in JIA treatment is to provide the correct treatment at the right time. Since some patients can reach inactive disease with only 1 DMARD and others need many, personalized medicine is the way to proceed. Since the biological therapies are so effective, but we are still unable to predict which children need biological therapies and which can stop therapy without disease flare.

The recently launched UCAN CAN DU initiative has the goal to transform the care for JIA patients. The ultimate goal of this Canadian – Dutch Personalized Medicine Network in Childhood Arthritis and Rheumatic diseases is to address this gap in treatment approaches and support translational research in children with JIA.

The highly intruiging microbiome needs further exploration in larger scaled studies, financial support needs to be searched for. The role of the patients and parents will be increased in the research agenda to enhance the development of successful studies.

Potentially, personalized aspects should be added to treatment strategies with increasingly high and prolonged targets. This can be achieved among others by including pharmacogenomics, (will this drug be effective and not toxic in this patient?)[115-117] and by using (multiple) biomarkers that will help the clinician and patient in guiding therapy to personalize medicine.

Summary of lessons learned from this study

Treatment-to-target & tight control are feasible principles in a JIA clinical trial and give additional benefit in the short and long-term treatment of juvenile idiopathic arthritis.

Inactive disease should be the target to aim at after 6 months of treatment and onwards. Tapering strategies can be introduced in JIA studies safely since flare frequency was low and responses to restart of medication were good.

Radiographic damage did not occur on group level and BMD significantly increased after targeted therapy in the third arm.

Current research is focused on reaching inactive disease and therapy burden. Future research will focus on personalised therapies combined with treatment-to-target strategies aiming at inactive disease.

REFERENCES

1. Rothmund F, Gerss J, Ruperto N, Dabritz J, Wittkowski H, Frosch M, et al. Validation of relapse risk biomarkers for routine use in patients with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2014;66(6):949-55.
2. Trouw LA, Mahler M. Closing the serological gap: promising novel biomarkers for the early diagnosis of rheumatoid arthritis. Autoimmun Rev. 2012;12(2):318-22.
3. Trouw LA, Rispens T, Toes REM. Beyond citrullination: other post-translational protein modifications in rheumatoid arthritis. Nat Rev Rheumatol. 2017;13(6):331-9.
4. Ruperto N, Martini A. Current and future perspectives in the management of juvenile idiopathic arthritis. Lancet Child Adolesc Health. 2018;2(5):360-70.
5. Giancane G, Alongi A, Ravelli A. Update on the pathogenesis and treatment of juvenile idiopathic arthritis. Curr Opin Rheumatol. 2017.
6. de Meij TG, Budding AE, de Groot EF, Jansen FM, Frank Kneepkens CM, Benninga MA, et al. Composition and stability of intestinal microbiota of healthy children within a Dutch population. FASEB J. 2016;30(4):1512-22.
7. Tejesvi MV, Arvonen M, Kangas SM, Keskitalo PL, Pirttila AM, Karttunen TJ, et al. Faecal microbiome in new-onset juvenile idiopathic arthritis. Eur J Clin Microbiol Infect Dis. 2016;35(3):363-70.
8. Di Paola M, Cavalieri D, Albanese D, Sordo M, Pindo M, Donati C, et al. Alteration of Fecal Microbiota Profiles in Juvenile Idiopathic Arthritis. Associations with HLA-B27 Allele and Disease Status. Front Microbiol. 2016;7:1703.
9. Aggarwal A, Sarangi AN, Gaur P, Shukla A, Aggarwal R. Gut microbiome in children with enthesitis-related arthritis in a developing country and the effect of probiotic administration. Clin Exp Immunol. 2017;187(3):480-9.
10. Stoll ML. Gut microbes, immunity, and spondyloarthritis. Clin Immunol. 2015;159(2):134-42.
11. Horton DB, Scott FI, Haynes K, Putt ME, Rose CD, Lewis JD, et al. Antibiotic Exposure and Juvenile Idiopathic Arthritis: A Case-Control Study. Pediatrics. 2015;136(2):e333-e43.
12. van Dijkhuizen EHP, Aidonopoulos O, Ter Haar NM, Pires Marafon D, Magni-Manzoni S, Ioannidis YE, et al. Prediction of inactive disease in juvenile idiopathic arthritis: a multicentre observational cohort study. Rheumatology (Oxford). 2018;57(10):1752-60.
13. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, 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 (Hoboken). 2011;63(4):465-82.
14. Horneff G, Klein A, Ganser G, Sailer-Hock M, Gunther A, Foeldvari I, et al. Protocols on classification, monitoring and therapy in children's rheumatology (PRO-KIND): results of the working group Polyarticular juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2017;15(1):78.
15. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum. 2011.
16. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin 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(9):1605-12.
17. Wallace CA. Developing standards of care for patients with juvenile idiopathic arthritis. Rheumatology (Oxford). 2010;49(7):1213-4.
18. Berard RA, Laxer RM. Early aggressive therapy for patients with juvenile idiopathic arthritis: are we there yet? J Rheumatol. 2014;41(12):2343-6.
19. Hissink Muller PC, Brinkman DM, Schonenberg D, Koopman-Keemink Y, Brederije IC, Bekkering WP, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017;15(1):11.

20. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000;342(11):763-9.
21. Horneff G, Schmeling H, Biedermann T, Foeldvari I, Ganser G, Girschick HJ, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis. 2004;63(12):1638-44.
22. Horneff G, De BF, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68(4):519-25.
23. Prince FH, Twilt M, ten CR, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis. 2009;68(5):635-41.
24. Bartoli M, Taro M, Magni-Manzoni S, Pistorio A, Traverso F, Viola 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(3):370-4.
25. Albarouni M, Becker I, Horneff G. Predictors of response to methotrexate in juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2014;12:35.
26. Geikowski T, Becker I, Horneff G. Predictors of response to etanercept in polyarticular-course juvenile idiopathic arthritis. Rheumatology (Oxford). 2014;53(7):1245-9.
27. Otten MH, Prince FH, Armbrust W, ten CR, Hoppenreijs EP, Twilt M, et al. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. JAMA. 2011;306(21):2340-7.
28. Consolaro A, Ruperto N, Bazso A, Pistorio A, Magni-Manzoni S, Filocamo G, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum. 2009;61(5):658-66.
29. Horneff G, Becker I. Definition of improvement in juvenile idiopathic arthritis using the juvenile arthritis disease activity score. Rheumatology (Oxford). 2014;53(7):1229-34.
30. Wallace CA, Ringold S, Bohnsack J, Spalding SJ, Brunner HI, Milojevic D, et al. Extension Study of Participants from the Trial of Early Aggressive Therapy in Juvenile Idiopathic Arthritis. J Rheumatol. 2014.
31. Ringold S, Seidel KD, Koepsell TD, Wallace CA. Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. Rheumatology (Oxford). 2009;48(8):972-7.
32. Albers HM, Brinkman DM, Kamphuis SS, van Suijlekom-Smit LW, van Rossum MA, Hoppenreijs EP, et al. Clinical course and prognostic value of disease activity in the first two years in different subtypes of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2010;62(2):204-12.
33. Papsdorf V, Horneff G. Complete control of disease activity and remission induced by treatment with etanercept in juvenile idiopathic arthritis. Rheumatology (Oxford). 2011;50(1):214-21.
34. Anink J, Dolman KM, Merlijn vdB, van VM, Kuijpers TW, van Rossum MA. Two-year outcome of juvenile idiopathic arthritis in current daily practice: what can we tell our patients? Clin Exp Rheumatol. 2012.
35. Minden K, Niewerth M, Zink A, Seipelt E, Foeldvari I, Girschick H, et al. Long-term outcome of patients with JIA treated with etanercept, results of the biologic register JuMBO. Rheumatology (Oxford). 2012;51(8):1407-15.
36. Ringold S, Seidel KD, Koepsell TD, Wallace CA. Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. Rheumatology (Oxford). 2009;48(8):972-7.
37. McErlane F, Foster HE, Carrasco R, Baildam EM, Chieng SE, Davidson JE, et al. Trends in paediatric rheumatology referral times and disease activity indices over a ten-year period among children and young people with Juvenile Idiopathic Arthritis: results from the childhood arthritis prospective Study. Rheumatology (Oxford). 2016;55(7):1225-34.
38. Solari N, Palmisani E, Consolaro A, Pistorio A, Viola S, Buoncompagni A, et al. Factors associated with achievement of inactive disease in children with juvenile idiopathic arthritis treated with etanercept. J Rheumatol. 2013;40(2):192-200.
39. Shoop-Worrall SJW, Verstappen SMM, Baildam E, Chieng A, Davidson J, Foster H, 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(8):1381-8.

40. Verazza S, Davi S, Consolaro A, Bovis F, Insalaco A, Magni-Manzoni S, et al. Disease status, reasons for discontinuation and adverse events in 1038 Italian children with juvenile idiopathic arthritis treated with etanercept. Pediatr Rheumatol Online J. 2016;14(1):68.

41. Sengler C, Klotsche J, Niewerth M, Liedmann I, Foll D, Heiligenhaus A, et al. The majority of newly diagnosed patients with juvenile idiopathic arthritis reach an inactive disease state within the first year of specialised care: data from a German inception cohort. RMD Open. 2015;1(1):e000074.

42. Solari N, Palmisani E, Consolaro A, Pistorio A, Viola S, Buoncompagni A, et al. Factors Associated with Achievement of Inactive Disease in Children with Juvenile Idiopathic Arthritis Treated with Etanercept. J Rheumatol. 2012.

43. Consolaro A, Negro G, Chiara GM, Bracciolini G, Ferrari C, Schiappapietra B, 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 (Hoboken). 2014;66(11):1703-9.

44. Swart JF, van Dijkhuizen EHP, Wulffraat NM, de Roock S. Clinical Juvenile Arthritis Disease Activity Score proves to be a useful tool in treat-to-target therapy in juvenile idiopathic arthritis. Ann Rheum Dis. 2017.

45. Armbrust W, Kaak JG, Bouma J, Lelieveld OT, Wulffraat NM, Sauer PJ, et al. Assessment of disease activity by patients with juvenile idiopathic arthritis and the parents compared to the assessment by pediatric rheumatologists. Pediatr Rheumatol Online J. 2013;11(1):48.

46. Wulffraat N, van der Net JJ, Ruperto N, Kamphuis S, Prakken BJ, ten CR, et al. The Dutch version of the Childhood Health Assessment Questionnaire (CHAQ) and the Child Health Questionnaire (CHQ). Clin Exp Rheumatol. 2001;19(4 Suppl 23):S111-S5.

47. Dempster H, Porepa M, Young N, Feldman BM. The clinical meaning of functional outcome scores in children with juvenile arthritis. Arthritis Rheum. 2001;44(8):1768-74.

48. Brunner HI, Klein-Gitelman MS, Miller MJ, Barron A, Baldwin N, Trombley M, et al. Minimal clinically important differences of the childhood health assessment questionnaire. J Rheumatol. 2005;32(1):150-61.

49. Vilca I, Munitis PG, Pistorio A, Ravelli A, Buoncompagni A, Bica B, et al. Predictors of poor response to methotrexate in polyarticular-course juvenile idiopathic arthritis: analysis of the PRINTO methotrexate trial. Ann Rheum Dis. 2010;69(8):1479-83.

50. Horneff G, Klein A, Klotsche J, Minden K, Huppertz HI, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016;18(1):272.

51. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van ZD, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med. 2007;146(6):406-15.

52. Pincus T, Castrejon I. Evidence that the strategy is more important than the agent to treat rheumatoid arthritis. Data from clinical trials of combinations of non-biologic DMARDs, with protocol-driven intensification of therapy for tight control or treat-to-target. Bull Hosp Jt Dis (2013). 2013;71 Suppl 1:S33-40.

53. Sokka T, Pincus T. Rheumatoid arthritis: strategy more important than agent. Lancet. 2009;374(9688):430-2.

54. Prince FH, Twilt M, Simon SC, van Rossum MA, Armbrust W, Hoppenreijs EP, et al. When and how to stop etanercept after successful treatment of patients with juvenile idiopathic arthritis. Ann Rheum Dis. 2009;68(7):1228-9.

55. Remesal A, J DEI, Merino R, Garcia-Consuegra J. Discontinuation of etanercept after successful treatment in patients with juvenile idiopathic arthritis. J Rheumatol. 2010;37(9):1970-1.

56. Baszis K, Garbutt J, Toib D, Mao J, King A, White A, et al. Clinical outcomes after withdrawal of anti-tumor necrosis factor alpha therapy in patients with juvenile idiopathic arthritis: a twelve-year experience. Arthritis Rheum. 2011;63(10):3163-8.

57. Postepski J, Kobusinska K, Olesinska E, Osinska V, Opoka-Winiarska V. Clinical remission in juvenile idiopathic arthritis after termination of etanercept. Rheumatol Int. 2013;33(10):2657-60.

58. Pratsidou-Gertsi P, Trachana M, Pardalos G, Kanakoudi-Tsakalidou F. A follow-up study of patients with juvenile idiopathic arthritis who discontinued etanercept due to disease remission. Clin Exp Rheumatol. 2010;28(6):919-22.

59. Chang CY, Meyer RM, Reiff AO. Impact of medication withdrawal method on flare-free survival in patients with juvenile idiopathic arthritis on combination therapy. Arthritis Care Res (Hoboken). 2015;67(5):658-66.

60. Guzman J, Oen K, Huber AM, Watanabe DK, Boire G, Shiff N, et al. The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort. Ann Rheum Dis. 2015.

61. Guzman J, Oen K, Tucker LB, Huber AM, Shiff N, Boire G, et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis. 2014.

62. Minden K, Horneff G, Niewerth M, Seipelt E, Aringer M, Aries P, et al. The time of DMARD start in Juvenile Idiopathic Arthritis determines the likelihood of a drug-free remission in young adulthood. Arthritis Care Res (Hoboken). 2018.

63. Lipstein EA, Brinkman WB, Sage J, Lannon CM, Morgan Dewitt E. Understanding treatment decision making in juvenile idiopathic arthritis: a qualitative assessment. Pediatr Rheumatol Online J. 2013;11(1):34.

64. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018;77(6):819-28.

65. Klotsche J, Minden K, Niewerth M, Horneff G. Time spent in inactive disease before MTX withdrawal is relevant with regard to the flare risk in patients with JIA. Ann Rheum Dis. 2018;77(7):996-1002.

66. Davies R, Southwood TR, Kearsley-Fleet L, Lunt M, Hyrich KL. Medically Significant Infections Are Increased in Patients With Juvenile Idiopathic Arthritis Treated With Etanercept: Results From the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study. Arthritis Rheumatol. 2015;67(9):2487-94.

67. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis. 2008;67(8):1145-52.

68. Beukelman T, Xie F, Chen L, Baddley JW, Delzell E, Grijalva CG, et al. Rates of hospitalized bacterial infection associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum. 2012.

69. Becker I, Horneff G. Risk of Serious Infection in Juvenile Idiopathic Arthritis Patients Associated With Tumor Necrosis Factor Inhibitors and Disease Activity in the German Biologics in Pediatric Rheumatology Registry. Arthritis Care Res (Hoboken). 2017;69(4):552-60.

70. Swart JF, Pistorio A, Bovis F, Alekseeva E, Hofer M, Nielsen S, et al. The Addition of One or More Biologics to Methotrexate in Children with Juvenile Idiopathic Arthritis Increases the Incidence of Infections and Serious Adverse Events. The 5882 Pharmachild Cohort. Ann Rheum Dis 2015;74:91 doi:10 1136/annrheumdis-2015-eular 4397. 2015.

71. Swart JF, de RS, Wulffraat NM. What are the immunological consequences of long-term use of biological therapies for juvenile idiopathic arthritis? Arthritis Res Ther. 2013;15(3):213.

72. Lipstein EA, Lovell DJ, Denson LA, Moser DW, Saeed SA, Dodds CM, et al. Parents' information needs in tumor necrosis factor-alpha inhibitor treatment decisions. J Pediatr Gastroenterol Nutr. 2013;56(3):244-50.

73. Markusse IM, Dirven L, Han KH, Ronday HK, de Sonnaville PB, Kerstens PJ, et al. Evaluating Adherence to a Treat-to-Target Protocol in Recent-Onset Rheumatoid Arthritis: Reasons for Compliance and Hesitation. Arthritis Care Res (Hoboken). 2016;68(4):446-53.

74. Schiappapietra B, Varnier G, Rosina S, Consolaro A, Martini A, Ravelli A. Glucocorticoids in juvenile idiopathic arthritis. Neuroimmunomodulation. 2015;22(1-2):112-8.

75. Ravelli A. The time has come to include assessment of radiographic progression in juvenile idiopathic arthritis clinical trials. J Rheumatol. 2008;35(4):553-7.

76. Poznanski AK, Hernandez RJ, Guire KE, Bereza UL, Garn SM. Carpal length in children--a useful measurement in the diagnosis of rheumatoid arthritis and some concenital malformation syndromes. Radiology. 1978;129(3):661-8.

77. Giancane G, Pederzoli S, Norambuena X, Ioseliani M, Sato J, Gallo MC, et al. Frequency of radiographic damage and progression in individual joints in children with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2014;66(1):27-33.

78. Selvaag AM, Kirkhus E, Tornqvist L, Lilleby V, Aulie HA, Flato B. Radiographic damage in hands and wrists of patients with juvenile idiopathic arthritis after 29 years of disease duration. Pediatr Rheumatol Online J. 2017;15(1):20.

79. Magni-Manzoni S, Rossi F, Pistorio A, Temporini F, Viola S, Beluffi G, et al. Prognostic factors for radiographic progression, radiographic damage, and disability in juvenile idiopathic arthritis. Arthritis Rheum. 2003;48(12):3509-17.

80. Cassone R, Falcone A, Rossi F, Magni-Manzoni S, Felici E, Buoncompagni A, et al. Unilateral destructive wrist synovitis in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2004;22(5):637-42.

81. Nielsen S, Ruperto N, Gerloni V, Simonini G, Cortis E, Lepore L, et al. Preliminary evidence that etanercept may reduce radiographic progression in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2008;26(4):688-92.

82. Malattia C, Consolaro A, Pederzoli S, Madeo A, Pistorio A, Mazzoni M, et al. MRI versus conventional measures of disease activity and structural damage in evaluating treatment efficacy in juvenile idiopathic arthritis. Ann Rheum Dis. 2013;72(3):363-8.

83. Muller LS, Avenarius D, Damasio B, Eldevik OP, Malattia C, Lambot-Juhan K, et al. The paediatric wrist revisited: redefining MR findings in healthy children. Ann Rheum Dis. 2011;70(4):605-10.

84. Anink J, Nusman CM, van Suijlekom-Smit LW, van Rijn RR, Maas M, van Rossum MA. Automated determination of bone age and bone mineral density in patients with juvenile idiopathic arthritis: a feasibility study. Arthritis Res Ther. 2014;16(4):424.

85. Guler-Yuksel M, Allaart CF, Goekoop-Ruiterman YP, de Vries-Bouwstra JK, van Groenendael JH, Mallee C, et al. Changes in hand and generalised bone mineral density in patients with recent-onset rheumatoid arthritis. Ann Rheum Dis. 2009;68(3):330-6.

86. Wevers-de Boer KV, Heimans L, Visser K, Kalvesten J, Goekoop RJ, van Oosterhout M, et al. Four-month metacarpal bone mineral density loss predicts radiological joint damage progression after 1 year in patients with early rheumatoid arthritis: exploratory analyses from the IMPROVED study. Ann Rheum Dis. 2015;74(2):341-6.

87. Lien G, Flato B, Haugen M, Vinje O, Sorskaar D, Dale K, et al. Frequency of osteopenia in adolescents with early-onset juvenile idiopathic arthritis: a long-term outcome study of one hundred five patients. Arthritis Rheum. 2003;48(8):2214-23.

88. Lien G, Selvaag AM, Flato B, Haugen M, Vinje O, Sorskaar D, et al. A two-year prospective controlled study of bone mass and bone turnover in children with early juvenile idiopathic arthritis. Arthritis Rheum. 2005;52(3):833-40.

89. Twilt M, Pradsgaard D, Spannow AH, Horlyck A, Heuck C, Herlin T. Joint cartilage thickness and automated determination of bone age and bone health in juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2017;15(1):63.

90. Reed AM, Haugen M, Pachman LM, Langman CB. Repair of osteopenia in children with juvenile rheumatoid arthritis. J Pediatr. 1993;122(5 Pt 1):693-6.

91. Simonini G, Giani T, Stagi S, de Martino M, Falcini F. Bone status over 1 yr of etanercept treatment in juvenile idiopathic arthritis. Rheumatology (Oxford). 2005;44(6):777-80.

92. Stagi S, Masi L, Capannini S, Cimaz R, Tonini G, Matucci-Cerinic M, et al. Cross-sectional and longitudinal evaluation of bone mass in children and young adults with juvenile idiopathic arthritis: the role of bone mass determinants in a large cohort of patients. J Rheumatol. 2010;37(9):1935-43.

93. Stagi S, Cavalli L, Signorini C, Bertini F, Cerinic MM, Brandi ML, et al. Bone mass and quality in patients with juvenile idiopathic arthritis: longitudinal evaluation of bone-mass determinants by using dual-energy x-ray absorptiometry, peripheral quantitative computed tomography, and quantitative ultrasonography. Arthritis Res Ther. 2014;16(2):R83.

94. Balevic SJ, Becker ML, Cohen-Wolkowiez M, Schanberg LE. Clinical Trial Design in Juvenile Idiopathic Arthritis. Paediatr Drugs. 2017;19(5):379-89.

95. Schoemaker CG, Prakken ABJ, Furth EF. [Patients and physicians creating a research agenda together: the method of the British James Lind Alliance]. Ned Tijdschr Geneeskd. 2017;161(0):D1764.

96. Schoemaker CG, Armbrust W, Swart JF, Vastert SJ, van Loosdregt J, Verwoerd A, et al. Dutch juvenile idiopathic arthritis patients, carers and clinicians create a research agenda together following the James Lind Alliance method: a study protocol. Pediatr Rheumatol Online J. 2018;16(1):57.

97. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin 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(9):1605-12.

98. Berard RA, Laxer RM. Learning the hard way: clinical trials in juvenile idiopathic arthritis. Ann Rheum Dis. 2018;77(1):1-2.

99. Ringold S, Weiss PF, Colbert RA, DeWitt EM, Lee T, Onel K, et al. Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2014;66(7):1063-72.

100. Beukelman T, Anink J, Berntson L, Duffy C, Ellis JA, Glerup M, et al. A survey of national and multi-national registries and cohort studies in juvenile idiopathic arthritis: challenges and opportunities. Pediatr Rheumatol Online J. 2017;15(1):31.

101. Ringold S, Weiss PF, Colbert RA, DeWitt EM, Lee T, Onel K, et al. Childhood arthritis and rheumatology research alliance consensus treatment plans for new onset polyarticular juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2013.

102. Consolaro A, Bracciolini G, Ruperto N, Pistorio A, Magni-Manzoni S, Malattia C, 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(7):2366-74.

103. Consolaro A, Negro G, Lanni S, Solari N, Martini A, Ravelli A. Toward a treat-to-target approach in the management of juvenile idiopathic arthritis. Clin Exp Rheumatol. 2012;30(4 Suppl 73):S157-62.

104. Horton DB, Onel KB, Beukelman T, Ringold S. 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(3):352-60.

105. Akdemir G, Markusse IM, Goekoop-Ruiterman YP, Steup-Beekman GM, Grillet BA, Kerstens PJ, et al. Rheumatologists' adherence to a disease activity score steered treatment protocol in early arthritis patients is less if the target is remission. Clin Rheumatol. 2017;36(2):317-26.

106. Consolaro A, Giancane G, Schiappapietra B, Davi S, Calandra S, Lanni S, et al. Clinical outcome measures in juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2016;14(1):23.

107. de Vries-Bouwstra JK, Goekoop-Ruiterman YP, Verpoort KN, Schreuder GM, Ewals JA, Terwiel JP, et al. Progression of joint damage in early rheumatoid arthritis: association with HLA-DRB1, rheumatoid factor, and anti-citrullinated protein antibodies in relation to different treatment strategies. Arthritis Rheum. 2008;58(5):1293-8.

108. Smolen JS, Van Der Heijde DM, St Clair EW, Emery P, Bathon JM, Keystone E, et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate with or without concomitant infliximab: results from the ASPIRE trial. Arthritis Rheum. 2006;54(3):702-10.

109. Vastert SJ, de Jager W, Noordman BJ, Holzinger D, Kuis W, Prakken BJ, et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol. 2014;66(4):1034-43.

110. Southwood TR. Paediatric rheumatic disease: Treatment of JIA in the biologic era: what are we waiting for? Nat Rev Rheumatol. 2014;10(3):132-4.

111. Lovell DJ, Ruperto N, Giannini EH, Martini A. Advances from clinical trials in juvenile idiopathic arthritis. Nat Rev Rheumatol. 2013;9(9):557-63.

112. Lehman TJ. Are withdrawal trials in paediatric rheumatic disease helpful? Lancet. 2008;372(9636):348-50.

113. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2018;77(1):21-9.

114. de Jong PH, Hazes JM, Han HK, Huisman M, van Zeben D, van der Lubbe PA, et al. Randomised comparison of initial triple DMARD therapy with methotrexate monotherapy in combination with low-dose glucocorticoid bridging therapy; 1-year data of the tREACH trial. Ann Rheum Dis. 2014;73(7):1331-9.

115. Becker ML, Leeder JS. Developmental pharmacogenetics in pediatric rheumatology: utilizing a new paradigm to effectively treat patients with juvenile idiopathic arthritis with methotrexate. Hum Genomics Proteomics. 2010;2010:257120.

116. Cobb J, Cule E, Moncrieffe H, Hinks A, Ursu S, Patrick F, et al. Genome-wide data reveal novel genes for methotrexate response in a large cohort of juvenile idiopathic arthritis cases. Pharmacogenomics J. 2014;14(4):356-64.

117. Bulatovic M, Heijstek MW, van Dijkhuizen EH, Wulffraat NM, Pluijm SM, de JR. Prediction of clinical non-response to methotrexate treatment in juvenile idiopathic arthritis. Ann Rheum Dis. 2012;71(9):1484-9.

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