Juvenile Idiopathic Arthritis: Towards Improving Clinical Care

Hissink Muller, P.

5.2

Treat to target (drug-free) inactive disease in DMARD naive Juvenile Idiopathic Arthritis: 24-months clinical outcomes of a three-armed randomised trial

P.C.E. Hissink Muller, D.M.C. Brinkman, D. Schonenberg-Meinema, W. B. van den Bosch, Y. Koopman-Keemink, I.C.J. Brederije, W.P. Bekkering, T.W. Kuijpers, M.A.J. van Rossum, L.W.A. van Suijlekom-Smit, J.M. van den Berg, S. Boehringer, C. F. Allaart, R. ten Cate

Published in Annals of the Rheumatic Diseases 2019 Jan;78(1):51-59

ABSTRACT

Question: Which is the best strategy to achieve (drug-free) inactive disease in Juvenile Idiopathic Arthritis (JIA)?

Methods: In a randomized, single-blinded, study in disease-modifying-anti-rheumatic-drug(DMARD)-naive JIA patients three treatment-strategies were compared 1: Sequential DMARD-monotherapy (sulfasalazine (SSZ) or methotrexate (MTX)), 2: Combination therapy MTX+ 6 weeks prednisolone, 3: Combination therapy MTX+ etanercept. Treatment-to-target entailed three-monthly DMARD/biologic adjustments in case of persistent disease activity, with drug-tapering to nil in case of inactive disease.
After 24 months, primary outcomes were time-to-inactive-disease and time-to-flare after DMARD discontinuation. Secondary outcomes were adapted ACRPedi30/50/70/90scores, functional ability and adverse events.

Results: 94 children (67% girls) aged median (InterQuartileRange) 9.1 (4.6-12.9)years were enrolled: 32 in arms 1 and 2, 30 in arm 3. At baseline VASphysician was mean 49 (SD 16) mm, VASpatient 53 (22) mm, ESR 12.8(14.7), active joints median 8(5-12), limited joints 2.5(1-4.8), and CHAQ score mean 1.0 (0.6).
After 24 months 71% (arm 1), 70% (arm 2) and 72% (arm 3) of patients had inactive disease and 45% (arm 1), 31% (arm 2) and 41% (arm 3) had drug free inactive disease. Time-to-inactive-disease was median 9.0 (5.3-15.0)months in arm 1, 9.0(6.0-12.8)months in arm 2 and 9.0(6.0-12.0)months in arm 3 (p=0.30). Time-to-flare was not significantly different (overall 3.0(3.0-6.8)months, p=0.7). Adapted ACRpedi-scores were comparably high between arms. Adverse events were similar.

Conclusion: Regardless of initial specific treatments, after 24 months of treatment-to-target aimed at drug-free inactive disease, 71% of recent-onset JIA patients had inactive disease (median onset 9 months), and 39% were drug free. Tightly-controlled treatment-to-target is feasible.
Dutch Trial Register 1574

Key words: Juvenile idiopathic arthritis, treatment-to-target, treatment strategy study, inactive disease

INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is the most common auto-immune disease in children[1]. In recent years, earlier introduction of conventional synthetic disease modifying antirheumatic drugs (csDMARDs) and the development of biologic (b)DMARDs have improved the outcome for JIA patients[2-4], but ongoing inflammation in JIA may still cause functional disability and joint damage[5]. Early inactive disease may be the optimal therapeutic target[6-10]. Studies in JIA support the window of opportunity hypothesis when the disease is optimally responding to treatment and chronicity may be prevented[10-14].

Once inactive disease is achieved, discontinuation of treatment might be possible[15-19]. Comparative drug studies have shown that initial treatment with csDMARD results in less rapid response than initial treatment including glucocorticoids or a bDMARD[10 20], but the latter two have not been directly compared. If the initial treatment is not effective, subsequent treatment adjustments should still aim at achieving the treatment target. In adults with rheumatoid arthritis, such targeted therapy has been proven effective in long term prevention of damage progression and maintaining functional ability, even irrespective of initial treatment success[21-23]. In JIA, continuous treatment-to-target therapy in a tight-control setting, with treatment adjustments based on frequent evaluations of disease activity, has not yet been studied. Recent recommendations agree that treatment-to-target should be implemented in daily practice[24].

The aim of the BeSt (acronym for Dutch 'treatment strategies') for Kids study was to investigate which of three treatment-to-target strategies, using treatment-to-target aimed at inactive disease, is most effective and safe. Here, we report the results of one of the first treat-to-target study in patients with recent-onset JIA.

METHODS

Patients

Patients, 2-16 years old, with new-onset (oligoarticular, juvenile psoriatic arthritis or rheumatoid factor (RF) negative polyarticular) JIA, without previous DMARD-therapy and symptom duration less than 18 months were eligible. RF-positive JIA patients were excluded because monotherapy might be inappropriate for this severe category. Also the number was too low to stratify. Uveitis at enrolment was an exclusion criterion. Rest of exclusion criteria are summarized in supplementary file 1.

Study design and medical intervention

The BeSt for Kids study is an investigator-initiated multicenter randomised study with 2 years of follow-up. To minimize the risk of bias of the open design, all outcome measurements were assessed by trained research nurses, physiotherapists and physicians who remained unaware of the allocated treatment strategy during entire study-period (single-blind design). Medical Ethics Committees of all 5 participating hospitals approved the protocol, and all parents and patients older than 12 years of age gave informed consent. The trial was registered in the Dutch Trial Register, number 1574.

Patients were enrolled starting October 2009 to April 2014 by diagnosing paediatric rheumatologists. Randomization was by variable block, stratified per centre and per oligo- or polyarticular disease, into three strategy-arms: 1. initial treatment with csDMARD monotherapy (methotrexate or sulfasalazine if preferred by treating physician); 2. Initial treatment with MTX and 6 weeks of tapered prednisolone ('bridging therapy'); 3. Initial treatment with MTX and etanercept. For all arms, the treatment protocol described a number of subsequent treatment steps in case patients failed to fulfil treatment targets (figure 1 and supplementary file 2).

In case of side effects, the responsible drug was reduced to the lowest tolerated dose, but if it wasn't tolerated at all or contraindicated, patients on monotherapy proceeded to the next step in the allocated treatment group, and patients on combination therapy continued with the other drug of the combination. Additional treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular injections with glucocorticoids were permitted without a maximum and registered per strategy. All patients on MTX received folic acid 5mg/week. The use of DMARD or oral glucocorticoids was only permitted as dictated by the protocol. All protocol violations were recorded.

After 3 months of treatment, the initial target was an adjusted ACRPedi50%, calculated as described previously[25] (supplementary file 3) and scored by a research nurse or physiotherapist who remained blinded to the allocated treatment group during the entire study period. Treatment was continued if this target was met, escalated according to protocol if not.

After 6 months of treatment, the treatment target was inactive disease, defined according to Wallace 2004 criteria[26] (supplementary file 3) modified by Physicians Global Assessment (PGA) <10 mm indicating no disease activity.

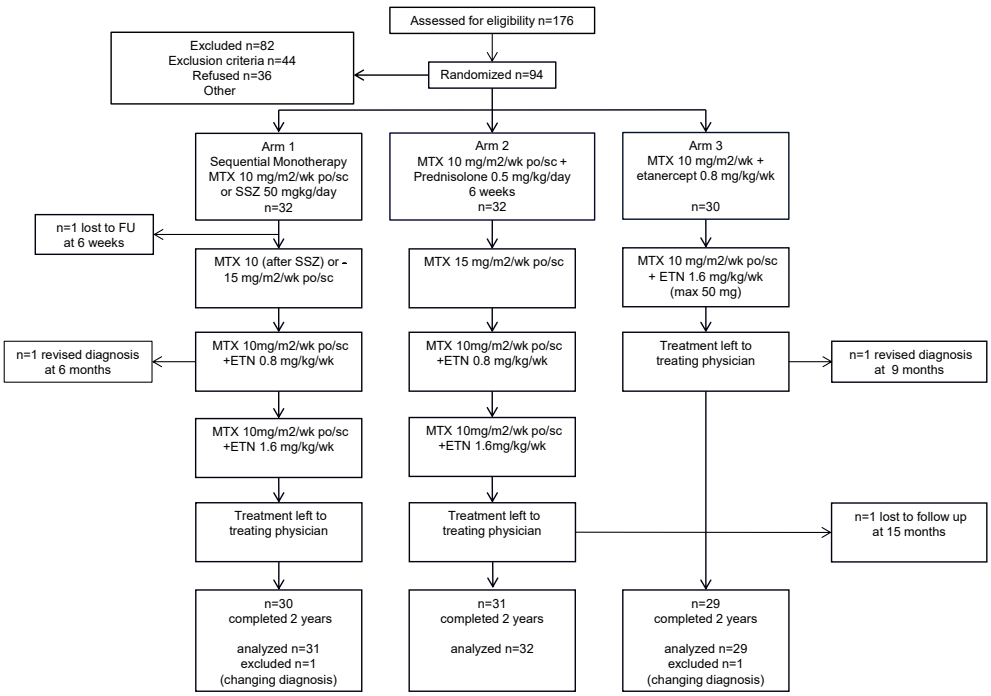


Figure 1 | Flow diagram of the three treatment strategies compared in the BeSt for Kids study;
Revised diagnosis were localized scleroderma with arthritis (arm 1) and polyarteritis nodosa (arm3)[32]. See patients and methods section for description of treatment groups. SSZ= sulfasalazine, MTX= methotrexate, ETN= etanercept, po= orally, sc= subcutaneous. n=21 patients had ≥18months of complaints' duration at first consultation, n=7 had comorbidities considered (relative) contra-indication for the DMARD therapy by either the pediatric rheumatologist or reason for (parents of) patients to refuse participation. These were morphea (1 patient), morbid obesity (n=1), hashimoto thyreoiditis (n=1), type 1 diabetes (n=1), previous uveitis (n=3).

In all three arms, in case of inactive disease for at least 3 (oligoarticular disease) or 6 (polyarticular disease) consecutive months, DMARD(s) were tapered and stopped. In case of combination therapy, first etanercept was tapered to once per 2 weeks, only once, directly followed by 50% dose reduction, then stopped. On the same requirements, methotrexate or sulfasalazine dose was reduced with 25% per week to zero. Following tapering strategies (supplementary file 4) , in case of a disease flare, defined by recurrence of arthritis (supplementary file 5), the last discontinued drug and/or the last effective dose was reintroduced. By protocol, prednisolone could not be restarted, and etanercept could be restarted but not discontinued for a second time.

Outcomes and analyses

Primary outcome measures are time-to-inactive-disease and time-to-flare after tapering and stopping all DMARD therapy. Time-to-flare was defined as the time between first moment of drug-free inactive disease (DFID) and the first arthritis judged as flare by the treating physician (supplementary file 5). Secondary outcome measures were adjusted ACRPedi30/50/70/90 scores, adverse events, functional ability. The Juvenile Disease Activity Score (JADAS)-10 score, JADAS-minimal disease activity (JADAS-MDA) and JADAS-inactive disease (JADAS-ID) were calculated as described previously (supplementary file 6)[27 28]. Functional ability was determined by the Childhood Health Assessment Questionnaire (CHAQ)[29]. Side effects were registered through open-end interviewing at each study visit combined with incidental reports in the intervals, and routine safety laboratory tests at each study visit (complete blood count, serum liver transaminases and creatinine). Severe Adverse Events (SAE) were defined as any adverse reaction resulting in any of the following outcomes: a life threatening condition or death, significant or permanent disability, malignancy, and (prolonged) hospitalization.

Sample size calculations

Percentages of time-to-inactive-disease were estimated since literature in 2008 [13 30 31] reported only on non-DMARD-naive JIA patients.

After three months of therapy an estimated difference of 10% inactive disease in arm 1 versus 60% in arm 3 could be detected with two groups of 30 patients by two-sided log rank test (α=0.05) with power > 90% assuming a hazard ratio of 8.70, a drop-out rate of 20% and 20% not treated according to initial treatment protocol. For an assumed hazard ratio of 4.11, with follow-up two years, a drop-out rate of 20%, a percentage not treated according to initial protocol of 20%, an alpha 0.05, a two-sided log rank test, two groups of 45 patients would be needed. The differences between arm 1 and arm 2 could be detected with two groups of 54, with a power of 80%, assuming a drop-out rate of 10% and no patients not treated according to initial protocol (HR = 2.12). Initially 60 patients per arm was aimed for. Due to slow inclusion rate, the study protocol was amended in 2012 to include 3 groups of 30 patients, leaving potentially enough power to compare arm 1 versus arm 3.

Statistical methods

Multiple imputation using package *mice* in software package R (version 3.4.0, http://r-project.org) was used to deal with missing values with n=10 imputed data-sets. Imputation variables were gender, age at inclusion, duration of symptoms, ANA positivity, diagnosis, number of affected joints, and all outcome variables. In case of drug free clinically inactive

disease often intentionally no blood was drawn causing non-random missing ESR, and here '0' was imputed for analysis of inactive disease.

Where measured repeatedly, measurements were treated as separate variables (wide format). Student's t-test was used to compare continuous normally distributed variables between groups. Non-parametric Kruskal-Wallis tests were used otherwise. For dichotomous variables, Pearson's chi-square test was used. A two-tailed probability value of P<0.05 was considered statistically significant. P-values were not adjusted for multiple statistical tests. Time-to-inactive-disease and time-to-flare was evaluated using log-rank test. The comparison of the groups over time in reaching aACRPedi 30/50/70/90, JADAS-10 and CHAQ-score was analyzed by generalized estimation equation models for continuous outcomes with time-by-strategy interaction as variable of interest. The third arm was treated as reference arm, since we hypothesized that arm 3 would be superior compared to arm 1 or arm 2, based on previous results[12 21].

Table 1 | Baseline demographic and disease characteristics*

	Arm 1 Sequential monotherapy (n=31)	**Arm 2 MTX + 6wks Prednisolone (n=32)**	**Arm 3 MTX+ Etanercept (n=29)**
Age (years), median (IQR)	9.0 (4.7-12.9)	10.2 (6.6-13.9)	8.6 (4.2-12.4)
Symptom duration (mo.), median (IQR)	8.1 (5.5-11.9)	5.9 (4.6-13.3)	8.6 (5.2-13.4)
ANA pos, n (%)	14 (45.2)	11 (34.4)	9 (31.0)
Female, n (%)	23 (74.2)	19 (59.4)	19 (65.5)
JIA Category:			
Oligo, n (%)	5 (16.1)	3 (9.4)	3 (10.3)
Oligoarticular <6 months	1	1	3
Oligoarticular >=6 months	4 (12.9)	2 (6.3)	0
Poly*, n (%)	24 (77.4)	25 (78.1)	24 (82.8)
Psoriatic, n (%)	2 (6.4)	4 (12.5)	2 (6.9)
VAS physician, mean (SD) in mm	46.4 ± 15.4	49.7 ± 16.1	51.2 ± 16.6
VAS patient/parent, mean (SD) in mm	48.9 ± 21.9	56.3 ± 21.4	54.6 ± 22.6
CHAQ, mean (SD)	0.9 ± 0.7	1.1 ± 0.6	1.1 ± 0.5
No. active joints, median (IQR)	7.0 (5.0-13.0)	7.5 (6.0-11.8)	8.0 (5.5-13.0)
No. limited joints, median (IQR)	2.0 (0-3.0)	2.0 (1.0-3.8)	3.0 (1.5-5.0)
ESR, median (IQR)	6.0 (2.0-11.0)	6.0 (2.0-23.5)	9.0 (3.5-26.0)
JADAS-10, mean (SD)	16.5 ± 4.2	18.8 ± 4.4	18.8 ± 5.4

MTX=methotrexate, oligo=oligoarticular JIA, poly=polyarticular RF-negative JIA, IQR=InterQuartile Range ANA=antinuclear antibodies, pos=positive, psoriatic=JIA with psoriasis, VAS=visual analogue scale. CHAQ=child Health Assessment Questionnaire, No.=number, ESR=erythrocyte sedimentation rate. JADAS-10=juvenile arthritis disease activity score in up to maximum 10 joints. Missing follow-up data occurred in 4% for active joint count, in 4% for limited joint count and physician VAS, 7% for parent/patient VAS, 7% for CHAQ score and 16% for ESR.

RESULTS

Patient characteristics

Baseline demographics and disease characteristics are summarized in Table 1. Figure 1 summarizes the study in a flow diagram. Ninety-four patients were randomized to one of three treatment groups: 32 patients were assigned to initial monotherapy (arm 1), 32 patients to initial combination of MTX with 6 weeks prednisolone-bridging therapy (arm2) and 30 patients to arm 3, initial combination of MTX/etanercept. Median symptom duration was 7.5 (IQR 5-12.5) months and median duration between diagnosis and inclusion was 6 (IQR 3-14) weeks. During follow-up 2 patients left the study because of revised diagnosis, one patient with localized scleroderma (in arm 1) and one (arm 3) with polyarteritis nodosa[32]. They were left out of further analyses. Two patients who were lost-to-follow-up, one in arm 1 after inclusion and one in arm 2 after 15 months, were included in the intention to treat (ITT) analysis.

Time-to-inactive-disease and time-to-flare

Median time-to-inactive-disease was 9.0(5.3-15.0)months in arm 1, 9.0(6.0-12.8)months in arm 2 and 9.0(6.0-12.0)months in arm 3 (Overall 9.0(6.0-12.0)months (log rank test p=0.3)). After one year 54% of patients in arm 1, 47% in arm 2 and 62% in arm 3 were in inactive disease (Figure 2).

During 24 months 59% (19 (3 oligo)/31 (61%) of patients in arm 1, 16 (1 oligo)/32 (50%) in arm 2 and 19(1 oligo)/29 (65%) in arm 3) had tapered and stopped all DMARDs (drug free inactive disease (DFID)), after median 15.0 (IQR 12.0-18.0) months (arm 1), 19.5 (12.0-24.0) months (arm 2) and 18.0 (12.0-21.0) months (arm 3) of therapy. However, 26% (6 (1 oligo) patients in arm 1, 3 in arm 2 and 5 in arm 3) subsequently had to restart treatment before the end of the study, in arm 1 median after 4.5(3.0-9.0) months, in arm 2 after 3.0(3.0-3.0) months and in arm 3 after 3.0(3.0-7.5) months (overall 3.0(3.0-6.8)months (p=0.7)). Three months later, inactive disease was regained by 10/14 (71%) (6 in arm 1, 1 in arm 2 and 3 in arm 3). After 24 months 71% (arm 1), 70% (arm 2) and 72% (arm 3) of patients had inactive disease and 45% (arm 1), 31% (arm 2) and 41% (arm 3) had DFID.

Adjusted ACRPedi30/50/70/90, JADAS-10 and CHAQ-score

Adjusted ACRPedi-scores were reached in similar high percentages over time in all three arms (figure 2 and supplementary table S1). JADAS-10 scores after 24 months improved comparably (figure 2), JADAS MDA and ID-criteria are in supplementary table S3. Overall, flares were characterised by a JADAS-10 of 9.7 (8.1-11.3), which improved 3 months after restart of treatment to JADAS-10 of 3.9(1.8-6.0). In all three arms CHAQ values improved from mean 1.0 (SD 0.6) to 0.5 (0.6).

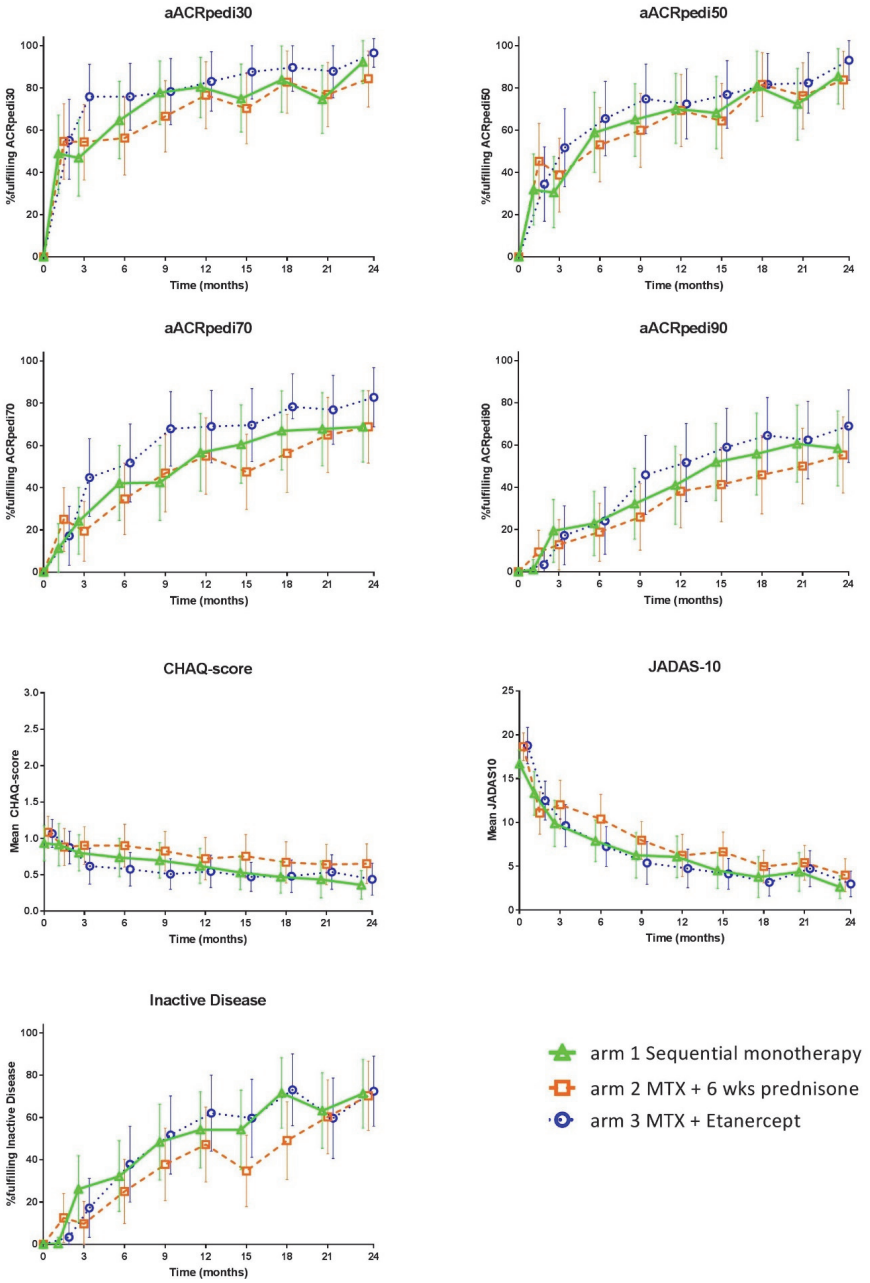


Figure 2 | Clinical outcomes after 24 months: adjusted ACRPedi30/50/70/90, inactive disease, CHAQ and JADAS-10 score, based on Generalised Estimating Equations (GEE)-analyses on imputed data. Error bars indicate 95% confidence intervals. Adjusted ACRPedi30/50/70/90= 30/50/70/90% improvement according to adjusted American College of Rheumatology Pediatric response criteria. CHAQ= Dutch version of the Child Health Assessment Questionnaire; JADAS-10=Juvenile Arthritis Disease Activity Score up to maximum of 10 joints.

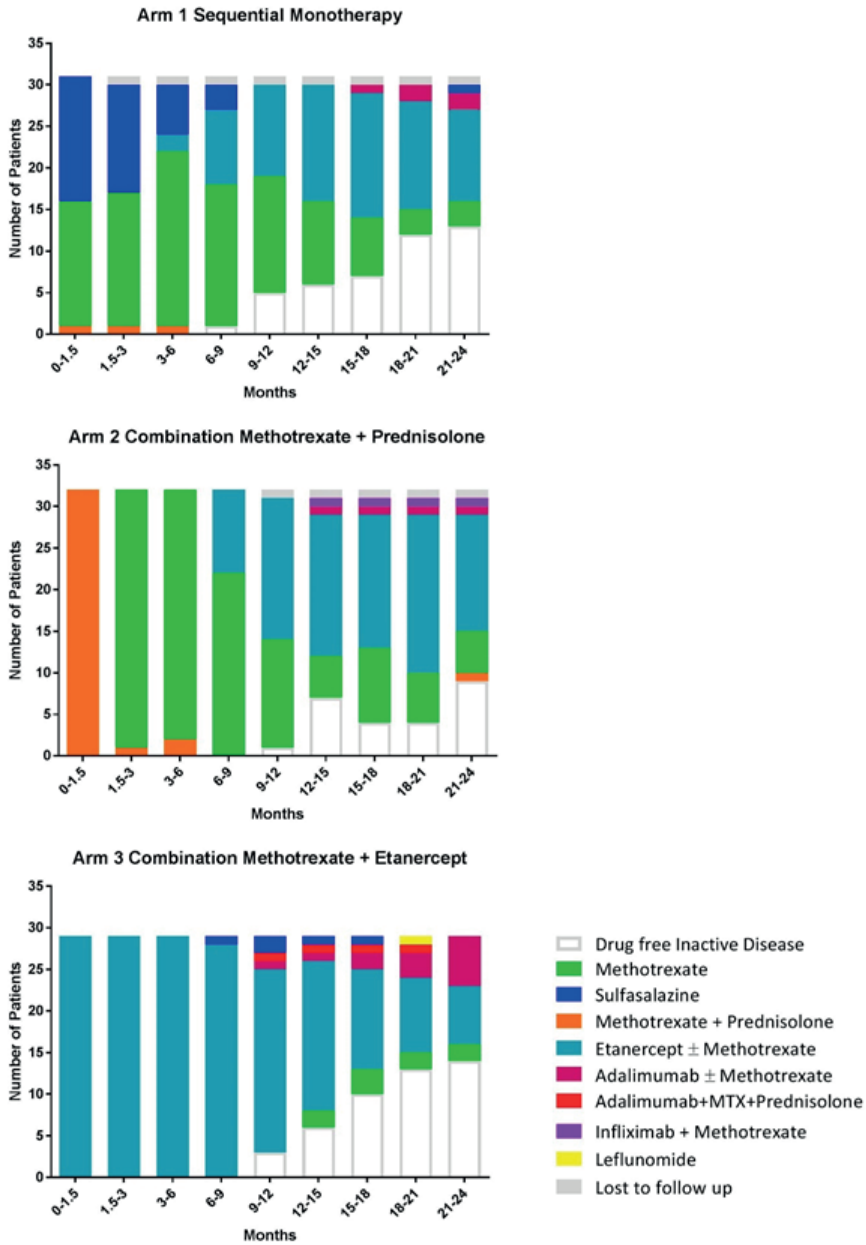


Figure 3 | Treatment of patients during two years of follow-up
Treatment was started and when necessary adapted to reach inactive disease. Within the first year of therapy more treatment changes occurred in arms 1 and 2 compared to arm 3. When inactive disease was reached for a consecutive period of 3 months in case of oligoarticular disease, and 6 months for polyarticular disease, all DMARDs where tapered and stopped according to protocol within approximately 2 months.

Medication changes and protocol violations

Figure 3 shows all medication actually used in the study per arm (i.e. including protocol violations). In arm 1 treating physicians prescribed SSZ (n=15) almost as often as MTX (n=17). By t=3 months 10/15 patients had switched from SSZ to MTX, 2 due to side effects, 8 because of insufficient response. After three months, patients who remained on SSZ had similar ACRPpedi50% scores as patients who started on MTX (data not shown). During 24 months in arm 1, 9 patients in arm 1 reached inactive disease while still on monotherapy, 4 on initial SSZ (one flared later) and 5 on initial MTX (3 flared later). In arm 2 (17/32) 53% of patients who started on MTX plus 6 weeks of prednisolone switched to MTX with ETN before end of year 1. Overall 17 patients (55%) in arm 1 and 23 patients (72%) in arm 2, progressed to a biological, at various time-points, according to protocol. Treatment was left to treating physician due to end of protocol in 4 patients in arm 1, versus 15 and 18 in arms 2 and 3. In arm 3 significantly less treatment adjustments were needed to achieve firstinactive disease: 0.6 (0.3-1.0) treatment steps compared to 1.4 (0.9-1.8) steps in arm 1 and 1.5 (1.0-1.9) steps in arm 2 (p=0.011). Across all arms, 10 (2 in arm 1, 2 in arm 2, 6 in arm 3) patients failed to achieve inactive disease on ETN and switched to adalimumab (9) or infliximab (1). After 24 months, five of these 10 patients gained inactive disease on the second anti-TNF.

Supplemental table S2 summarizes protocol violations including outside of protocol glucocorticoid-use across the 3 arms. Incorrect glucocorticoid treatments were given in the first months in arm 1 (3 times) and in arm 2 (4 times) compared to none in arm 3. Overall, treatment was not escalated according to protocol in all three arms for refusal to start or increase the dose of MTX or etanercept (table 3).

Adverse events

Adverse events (AE) were similar across the arms. AEs are summarized in Table 2. AEs were mild in general and involved mostly gastro-intestinal complaints, upper respiratory tract and other infections and general malaise. One patient in arm 1 while on MTX developed de-novo uveitis anterior after 6 months of treatment. No patients had permanent sequelae.

DISCUSSION

This is one of the first treatment-to-target studies, tightly-controlled and single-blinded, in newly diagnosed DMARD-naive JIA patients, aiming at inactive disease. Efficacy and safety of three treatment strategies were compared that are frequently used and comparable with the Childhood Arthritis and Rheumatology Research Alliance American Consensus

Table 2 | Adverse events in 92 patients with JIA in three treatment arms: sequential monotherapy, combination therapy MTX/prednisolone and combination therapy MTX/etanercept

	Arm 1 Sequential monotherapy n=31	**Arm 2 Combination MTX + 6 wks Prednisolone n=32**	**Arm 3 Combination MTX + Etanercept n=29**
	No. of events (No. pts)		
Common adverse events			
Nausea or abdominal pain	18 (12)	26 (16)	28 (13)
URTI	9 (9)	20 (13)	23 (14)
Gastro-enteritis	4 (4)	4 (4)	6 (6)
Other infections	8 (7)	12 (9)	12(8)
General malaise	11 (8)	12 (8)	7 (7)
New onset CAU*	1 (1)	0	0
Liver enzyme abnormalities	9 (5)	11 (8)	4 (3)
Other adverse events			
Headache and psychosomatic complaints**	10 (9)	12 (8)	4 (3)
Anemia	1 (1)	2 (2)	0
Leucopenia	8 (6)	2 (2)	1 (1)
Other	25	31	30
Severe adverse events			
Hospital admissions***	4 (3)	3 (3)	5 (5)

URTI=Upper Respiratory Tract Infections; No=number; pts=patients;
*CAU= Chronic Anterior Uveitis, treated additionally with local therapy.
**Psychosomatic complaints comprise: sleep disturbances, mood disturbances, concentration problems, temporary conversion disorder, eating disorder, dizziness.
***AE's with hospitalisation: In arm 1: 2 episodes of viral pneumonia with oxygen demand in one patient; one patient with prolonged vomiting on MTX for supportive care; one patient with varicella while on MTX; In arm 2 one case of scarlet fever; one patient with fever and confusion after to MTX, intake was observed; one case of hypovolemia in combination with skin infection while on MTX, cultures remained negative; In arm 3 one patient with pneumonia; 2 patients with gastro-enteritis who were admitted for supportive care; Campylobacter jejuni was cultured in one patient with complaints of diarrhea; one patient was observed for skin rash on SSZ which resolved spontaneously.

Treatment Plans[33]. Abrogation of inflammation by treating JIA to target has recently been recommended[24]. Our results show that after 24 months inactive disease was achieved by more than 70% of patients, irrespective of initial treatment, including tapering and stop-strategies. Fifty-nine percent achieved DFID, although early flares occurred that were successfully retreated.

After 3 months of treatment, more patients who started with methotrexate and etanercept (arm 3) had achieved rapid improvement as determined by aACRPedi70scores[34], but time-to-inactive-disease was similar across the arms. Due to treatment adjustments in case of active disease, which were needed more often in arms 1 and 2 than in arm 3, aACRpedi

improvement scores were met in similar percentages of patients over time across the arms. After 24 months of treatment-to-target JADAS-10-scores were considerably reduced and functional ability as assessed by CHAQ was lowered substantially across the arms.
Our results show higher percentages of patients achieving inactive disease than in the prospective randomised double-blinded TREAT-study[10] which included only polyarticular JIA patients (n=85) including 30-40% RF-positives. In the ACUTE-JIA study (n=59), 68% achieved inactive disease after 1 year in the infliximab arm[20]. This unblinded study allowed one treatment intensification step but did not include tapering or stop-strategies. In the daily practice-based ReACCh-out-cohort[35], polyarticular and oligoarticular JIA achieved inactive disease after 24 months in 71% and 86% mainly by additional glucocorticoid-use.
The current study also aimed at systematically tapering and discontinuing treatment when inactive disease was achieved. DFID was achieved by 54/92 (59%) of all patients, although in 14 patients (6 (1 oligo) in arm 1, 3 in arm 2 and 5 in arm 3), flares occurred, requiring restart of treatment, resulting in overall 39% of patients still in DFID at the 2 years endpoint. Time-to-flare was similar across the arms. Overall flare rates (26%) were lower than 37-60% mentioned in previous cohorts [16 17 36 37] which may also depend on our limited total follow-up period of 24 months.

Contrary to previous studies we included oligoarticular patients (n=11) because they can have substantial disease burden and adverse outcomes[38], but used a rapid drug-tapering scheme (tapering and stopping medication after 3 months of inactive disease, compared to after 6 months in polyarticular disease) as we hypothesized that DFID could be achieved earlier in patients with less inflamed joints. We could not establish this difference significantly, possibly due to low numbers. Only one oligo-articular patient out of 5 who achieved DFID, flared. These limited results suggest that oligoarticular JIA patients could benefit from a treatment-to-target strategy.

There are several limitations to our study. First, the sample size, which may obscure differences between groups that in a larger population might have become clear. This can be explained by rarity of the disease, delays in referral (21 patients had ≥18 months symptom duration at the first consultation), comorbidities preventing DMARD-use (7 patients) and reluctance of parents to enrol their children in a clinical trial. Data on the clinical course of non-participating patients, receiving 'routine care' are currently not available. Recent retrospective studies in polyarticular JIA showed that despite achieving inactive disease for some time, most patients had active disease during follow up[39-41]. Second, this study was performed in a single-blinded setting, with the clinical assessors remaining unaware of the treatment received. Third, there was a relatively high frequency of protocol violations or intra-articular injections. (Not-allowed) glucocorticoid treatments were given in the first

months in arm 1 (3 times) and 2 (4 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. These protocol violations suggest that physicians at least tried to follow the treatment-to-target approach. However, in a larger number of patients across the three arms the physicians did not follow protocol for various reasons, mainly reluctance to intensify therapy based on shared decision making[24].

Based on the results from our study we conclude that DFID is a feasible goal in treatment of children with JIA, as was recently recommended[24], resulting in over 70% achieving inactive disease and 39% stopping all DMARDs after 24 months. In addition, we showed that tapering and discontinuation of treatment is a realistic goal. On the other hand, treatment-to-target resulted in a relatively high use of bDMARDs, >50% of patients in all arms. The adverse events were nonetheless mostly mild, as previously reported[42]. Long term follow-up of the BeSt for Kids cohort, including radiology results, is initiated to investigate possible lasting positive results of treatment-to-target in JIA.

ACKNOWLEDGEMENTS

We would like to thank all partic ipating patients and parents as well as the following physiotherapists and research nurses: Ingrid Honkoop AMC, Annette Hummelman-van Dijk SKZ. Susan Moors physiotherapist SKZ, Jacqueline Bouts, LUMC, Piroska de Boer, LUMC, Veronique van de Lugt, ARC-Reade.

REFERENCES

1. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet 2007;369(9563):767-78.
2. 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 (Hoboken) 2011;63(4):465-82.
3. Stoll ML, Cron RQ. Treatment of juvenile idiopathic arthritis: a revolution in care. Pediatr Rheumatol Online J 2014;12:13.
4. Hinze C, Gohar F, Foell D. Management of juvenile idiopathic arthritis: hitting the target. Nat Rev Rheumatol 2015 May;11(5):290-300.
5. Ringold S, Seidel KD, Koepsell TD, et al. Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. Rheumatology (Oxford) 2009;48(8):972-77.
6. Wallace CA, Huang B, Bandeira M, et al. Patterns of clinical remission in select categories of juvenile idiopathic arthritis. Arthritis Rheum 2005;52(11):3554-62.
7. 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(4 Suppl 73):S157-62.
8. Martini A, Lovell DJ. Juvenile idiopathic arthritis: state of the art and future perspectives. Ann Rheum Dis 2010;69(7):1260-3.
9. Ravelli A, Martini A. Remission in juvenile idiopathic arthritis. Clin Exp Rheumatol 2006;24(6 Suppl 43):S105-10.
10. Wallace CA, Giannini EH, Spalding SJ, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum 2012 Jun;64(6):2012-21.
11. Woo P. Theoretical and practical basis for early aggressive therapy in paediatric autoimmune disorders. Curr Opin Rheumatol 2009;21(5):552-57.
12. Tynjala P, Vahasalo 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(9):1605-12.
13. van Rossum MA, van Soesbergen RM, Boers M, et al. Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: sustained benefits of early sulfasalazine treatment. Ann Rheum Dis 2007;66(11):1518-24.
14. Albers HM, Wessels JA, van der Straaten RJ, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum 2009;61(1):46-51.
15. Prince FH, Twilt M, Simon SC, et al. When and how to stop etanercept after successful treatment of patients with juvenile idiopathic arthritis. Ann Rheum Dis 2009;68(7):1228-29.
16. 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.
17. Baszis K, Garbutt J, Toib D, 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.
18. 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(13):1266-73.
19. Foell D, Frosch M, Schulze zur WA, et al. Methotrexate treatment in juvenile idiopathic arthritis: when is the right time to stop? Ann Rheum Dis 2004;63(2):206-08.
20. Tynjala P, Vahasalo 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(9):1605-12.
21. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146(6):406-15.
22. Heimans L, Akdemir G, Boer KV, et al. Two-year results of disease activity score (DAS)-remission-steered treatment strategies aiming at drug-free remission in early arthritis patients (the IMPROVED-study). Arthritis Res Ther 2016;18:23.

23. Markusse IM, Akdemir G, Dirven L, et al. Long-Term Outcomes of Patients With Recent-Onset Rheumatoid Arthritis After 10 Years of Tight Controlled Treatment: A Randomized Trial. Ann Intern Med 2016;164(8):523-31.
24. Ravelli A, Consolaro A, Horneff G, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis 2018;77(6):819-28.
25. Giannini EH, Ruperto N, Ravelli A, et al. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum 1997;40(7):1202-09.
26. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31(11):2290-94.
27. 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(7):2366-74.
28. Consolaro A, Ruperto N, Bazso A, et al. Development and validation of a composite disease activity score for juvenile idiopathic arthritis. Arthritis Rheum 2009;61(5):658-66.
29. Singh G, Athreya BH, Fries JF, et al. Measurement of health status in children with juvenile rheumatoid arthritis. Arthritis Rheum 1994;37(12):1761-69.
30. Lovell DJ, Reiff A, Ilowite NT, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum 2008;58(5):1496-504.
31. Giannini EH, Brewer EJ, Kuzmina N, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. The Pediatric Rheumatology Collaborative Study Group and The Cooperative Children's Study Group. N Engl J Med 1992;326(16):1043-9.
32. Hissink Muller PCE, Donze SH, ten Cate R. Polyarteritis Nodosa Mimicking Juvenile Idiopathic Arthritis: A Case Report, 2014: Ann Paediatr Rheum. 2014; 3(3): 141-145.
33. Ringold S, Weiss PF, Colbert RA, 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.
34. Hissink Muller PC, Brinkman DM, Schonenberg D, 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.
35. Guzman J, Oen K, Tucker LB, et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 2015;74(10):1854-60.
36. Guzman J, Oen K, Huber AM, et al. The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort. Ann Rheum Dis 2016 Jun;75(6):1092-8.
37. Lovell DJ, Johnson AL, Huang B, et al. Risk, Timing and Predictors of Disease Flare after Discontinuation of Anti-Tumor Necrosis Factor (TNF) Therapy in Children with Polyarticular Forms of Juvenile Idiopathic Arthritis (JIA) in Clinical Inactive Disease. Arthritis Rheumatol 2018 Mar 31. doi: 10.1002/art.40509.
38. Albers HM, Brinkman DM, Kamphuis SS, 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.
39. Anink J, Dolman KM, Merlijn vdB, et al. Two-year outcome of juvenile idiopathic arthritis in current daily practice: what can we tell our patients? Clin Exp Rheumatol 2012 Nov-Dec;30(6):972-8.
40. Ringold S, Seidel KD, Koepsell TD, et al. Inactive disease in polyarticular juvenile idiopathic arthritis: current patterns and associations. Rheumatology (Oxford) 2009;48(8):972-7.
41. McErlane F, Foster HE, Carrasco R, 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.
42. Tarkiainen M, Tynjala P, Vahasalo P, et al. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatology (Oxford) 2015 Jul;54(7):1170-6.

SUPPLEMENTARY FILE 1

Exclusion criteria BeSt for Kids study as per protocol

- Systemic JIA
- Rheumatoid factor positive JIA
- JIA with enthesitis
- Undifferentiated JIA
- Previous treatment with DMARDs or biologicals
- Known contraindication for one of the study drugs, such as G6PD deficiency
- Bone marrow hypoplasia
- Inborn conditions characterized by a compromised immune system
- Known HIV infection or other acquired forms of immune compromise
- Any significant concurrent medical or surgical condition which would jeopardize the patient's safety or ability to complete the trial
- Sepsis or risk of sepsis
- Significant cardiac [e.g. congenital heart disease, valvular heart disease, constrictive pericarditis myocarditis] or pulmonary disease, (e.g. cystic fibrosis);
- Asthma for which the patient has required the use of oral or parenteral corticosteroids for ≥ 2 weeks within 6 months prior to the baseline visit
- History or concurrent serious gastrointestinal disorders such as ulcer or inflammatory bowel disease, Crohn's disease, ulcerative colitis or other symptomatic lower gastrointestinal conditions, including ulcer and perforation
- Current or recent infections (last three months), including chronic or localized; evidence of active CMV or EBV, infectious hepatitis, active pneumocystis carinii, drug resistant atypical mycobacterium or other bacterial infections.
- Positive PPD and/or X-thorax (PPD is left out in patients that were vaccinated with BCG)
- History of lymphoproliferative disease including lymphoma or signs suggestive of possible lymphoproliferative disease, such as lymphadenopathy of unusual size or location (such as nodes in the posterior triangle of the neck, infraclavicular, epitrochlear, or periaortic areas), or splenomegaly.
- At increased risk of malignancy; history or presence of malignancy within the last five years
- Other comorbidity that prevents treatment with oral glucocorticoids and/or sulfasalazine and/or methotrexate and/or etanercept, or other comorbidity that, in the opinion of the pediatrician, prevents participation in the trial
- Vaccination with live vaccine in last 4 weeks, or expected to require such vaccination during the course of the study

- Current or prior history of blood dyscrasias. Abnormal safety baseline blood test e.g. haemoglobin ≤ 5 mmol/l; haematocrit ≤ 27%; platelet count ≤ 125 x 10^9 /L; white blood cell count ≤ 3.5 x 10^9 /L; serum creatinine ≥ 2 times the laboratory's upper limit of normal ; aspartate aminotransferase (AST [SGOT]) and alanine aminotransferase (ALT [SGPT]) ≥ 2 times the laboratory's upper limit of normal.
- Reasonable expectation that the subject will not be able to satisfactorily complete the study.
- History of or current psychiatric illness, alcohol or drug abuse that would interfere with the subject's ability to comply with protocol requirements or give informed consent.
- Receipt of any investigational drug within 3 months of screening visit.

SUPPLEMENTARY FILE 2

Extended Description of treatment strategies

In arm 1 (sequential monotherapy) the patients started with Sulfasalazine 50mg/kg up to 2000mg/day or (MTX10mg/m2/wk orally or subcutaneous (max 25mg/wk). After three months aACRPedi50 was calculated. If the patient did not reach aACRPedi50, patients on SSZ switched to MTX 10mg/m2/wk and patients on MTX increased the dose to 15mg/m2/wk, max 25mg/wk, preferably subcutaneous. After 6 months the target was inactive disease according to adapted Wallace definition (Supplementary appendix page 9). Subsequent steps for patients with an inadequate response were adding etanercept 0,8mg/kg/wk with MTX dose reduction to 10mg/m2/wk, followed by a three month period of increased dose of etanercept (1,6mg/kg/wk, max 50mg/wk). In case of still not reaching inactive disease, the treating physician could decide how to proceed.

In arm 2 (combination therapy with MTX and prednisolone) the patients started with MTX 10mg/m2/wk (max 25mg/wk) in combination with prednisolone orally 0,5mg/kg for four weeks, tapering by halving of the dose two times in two weeks to zero. If aACRPedi50 was not reached after three months, MTX dose was increased to 15mg/m2/wk, max 25mg, preferably subcutaneous. If after 6 months or every next step no inactive disease was reached, subsequent steps are (equal to arm 1) adding etanercept 0,8mg/kg/wk with MTX dose reduction to 10mg/m2/wk, and after that a three month period of increased dose of etanercept (1,6mg/kg/wk, max 50mg/wk). In case inactive disease was not realized with this regime, the next step was left to the treating physician.

In arm 3 (combination therapy with etanercept and methotrexate) the patients started with a combination of etanercept 0,8mg/kg/wk sc and MTX 10mg/m2/wk. If after three

months aACRPedi50 was not accomplished, a three months dose increase of etanercept (1,6mg/kg/wk, max 50mg/wk) was advocated. In case of insufficient response after 6 months and onwards, the next step was left to the treating physician.
If inactive disease on medication is reached continue therapy in the same dose for 3 or 6 months (depending on type JIA: oligoarticular vs polyarticular).

SUPPLEMENTARY FILE 3

ACR Pedi calculations

The JIA Core Outcome Variables(1) consist of:

1. Physician Global Assessment of Disease Activity (10 cm Visual Analogue Scale (VAS))
2. Parent/patient global assessment of overall well-being (10 cm VAS)
3. Functional Ability (Childhood Health Assessment Questionnaire)
4. Number of Joints with Active Arthritis
5. Number of Joints with Limitation of Movement
6. ESR

For the efficacy assessment, patients will be evaluated as “improved” or “not improved” by comparing the values of core outcome variables at the post-dose assessment time points with baseline values.

Definition of Improvement in Juvenile Idiopathic Arthritis

ACRPedi30/50/70/90 improvement is defined as 3 of any 6 core outcome variables improved by at least 30/50/70/90% from the baseline assessments, with no more than 1 of the remaining variables worsened by more than 30%(1).
Changes in outcomes that remained within normal limits (ESR≤16 mm/hour and Physician Visual Analogue Scale (VAS) <1 cm (range 0-10cm) were not taken into account in ACRPedi-calculations and were corrected for, resulting in adjusted scores (aACRPedi30/50/70/90%).

Definition of inactive disease in Juvenile Idiopathic arthritis:

Criteria:
no clinical symptoms of active synovitis
no fever, rash, serositis, splenomegaly, or generalized lympadenopathy attributable to JIA
no active uveitis
normal ESR and/or CRP
Physician´s global assessment (PGA) of disease activity indicates no active disease;
Id est PGA<1cm*(0-10cm).
* adapted version of original definition by Wallace(2)

1. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis 14. Arthritis Rheum. 1997;40(7):1202-9.
2. Wallace CA, Ruperto N, Giannini E. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol. 2004;31(11):2290-4.

SUPPLEMENTARY FILE 4

Tapering regime a priori defined in the protocol

If inactive disease lasts 3 months in oligoarticular (2 consecutive visits) taper and stop DMARD therapy according to protocol.
If inactive disease lasts 6 months in polyarticular JIA (3 consecutive visits) taper and stop DMARD therapy according to protocol.

- How to stop the combination of etanercept (ETN) and MTX.
  After 3 or 6 months of inactive disease first taper ETN from 50mg/week to 25mg/week, then to 25mg every other week, then stop. (or full dose/week-> half dose/week-> half dose every other week-> stop). Next MTX is tapered with ¼ of the dose per week, rounding is allowed.
  In case of flare reintroduce ETN and MTX in the last effective and maximum tolerated dose. After the first flare further decisions will be according to the treating physician.
- How to stop MTX monotherapy.
  After 3 or 6 months of inactive disease, MTX is tapered with ¼ of the dose per week, rounding is allowed.
- How to stop SSZ monotherapy.
  After 3 or 6 months of inactive disease, SSZ is tapered with ¼ of the dose per week, rounding is allowed.

SUPPLEMENTARY FILE 5

Flare definition

If, after termination of the DMARDs according to the protocol, the arthritis becomes active again and the treating paediatric rheumatologist judges it as a flare, it is a flare.

Background

In the original protocol BeSt for Kids time to flare was defined as the duration of time until a flare of the disease occurred after tapering and stopping medication, defined as a minimum of 40% worsening in a minimum of 2 out of 6 outcome variables with no more than one of the remaining components improving by ≥30% as defined by Brunner in 2002(1).

During the study we noticed that worsening in % is impossible to compute starting from 0. Therefore the current definition of flare could not be maintained.
In 2013 in literature no consensus was reached concerning flare definition. Alternative definitions included loss of criteria for inactive disease(2) or recurrence of synovitis requiring treatment(3), or VAS physician/parent worsening of 20/100mm or worsening in 2 or more active joints(4).

Later, in 2016 Guzman et al(5), defined a flare as a recurrence of manifestations of active disease or a Physician Global Assessment ≥10 mm, and a significant flare as one requiring treatment intensification, analogous to the proposed definition of flare in rheumatoid arthritis(6).

In 2013 we amended the protocol with an alternative flare definition, which was approved 05-04-2013.

1. Brunner HI, Lovell DJ, Finck BK, Giannini EH. Preliminary definition of disease flare in juvenile rheumatoid arthritis. J Rheumatol. 2002;29(5):1058-64.
2. Foell D, Wulffraat N, Wedderburn LR, Wittkowski H, Frosch M, Gerss J, et al. Methotrexate withdrawal at 6 vs 12 months in juvenile idiopathic arthritis in remission: a randomized clinical trial. JAMA. 2010;303(13):1266-73.
3. Papadopoulou C, Kostik M, Gonzalez-Fernandez MI, Bohm M, Nieto-Gonzalez JC, Pistorio A, et al. Delineating the role of multiple intraarticular corticosteroid injections in the management of juvenile idiopathic arthritis in the biologic era. Arthritis Care Res (Hoboken). 2013;65(7):1112-20.
4. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Perez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet. 2008;372(9636):383-91.

5. 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.
6. Bingham CO, 3rd, Pohl C, Woodworth TG, Hewlett SE, May JE, Rahman MU, et al. Developing a standardized definition for disease "flare" in rheumatoid arthritis (OMERACT 9 Special Interest Group). J Rheumatol. 2009;36(10):2335-41.

SUPPLEMENTARY FILE 6

JADAS-10 score

The JADAS-10 score is the linear sum of 4 components, which yields a global score of 0-40(1).

1 PGA 0-10cm
2 Parent/patient Global Assessment 0-10cm
3 Active joint count up to max of 10 joints, any involved joint, irrespective of its type.
4 Normalized ESR according to formula: (ESR(mm/hour)-20)/10; before the calculation, ESR values<20 are converted to 0 and ESR values>120 are converted to 120.

JADAS Minimal disease activity definition(2)

For Oligoarticular JIA: JADAS10 < 2
For Polyarticular JIA: JADAS10 < 3.8

JADAS Inactive disease definition

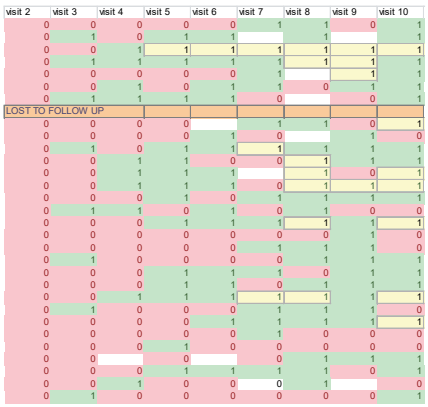
For oligo and polyarticular JIA: JADAS10 ≤ 1

1. 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.
2. 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.

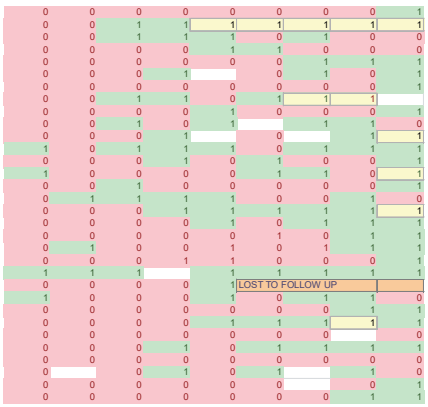
SUPPLEMENTARY FILE 7

Heat map representing active or inactive disease in arm 1, 2 and 3 for individual patients

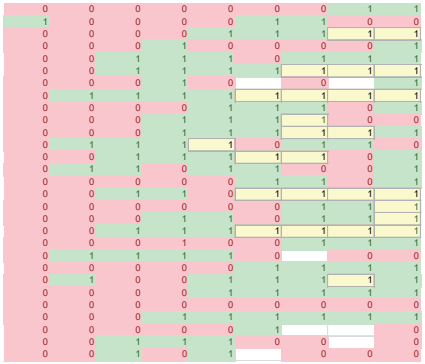
0 active disease
1 inactive disease
1 inactive disease, ESR missing due to no blood draw due to drug free inactive disease



Arm 1 initial sequential monotherapy



Arm 2 Initial MTX and prednisolone



Arm 3 Initial etanercept and MTX

Table S1 | Clinical results BeSt for Kids study after 24months per arm

	Arm 1 Sequential monotherapy n=31	Arm 2 MTX+ Prednisone n=32	Arm 3 MTX+ Etanercept n=29	Arm 1* p; OR (CI)	Arm 2* p; OR (CI)
aACRPedi30 (%) (CI)	92.2 (82,1-102.4)	84.4 (71.2-97.5)	96.6 (89.8-103.3)	0.84; 0.99 (0.93-1.09)	0.56; 0.97 (0.92-1.05)
aACRPedi50 (%) (CI)	85.5 (72.4-98.6)	83.8 (70.1-97.4)	93.1 (83.7-102.4)	0.89; 0.99 (0.92-1.07)	0.49; 0.98 (0.92-1.04)
aACRPedi70 (%) (CI)	69.0 (52.1-85.9)	68.8 (51.6-85.9)	82.8 (68.8-96.8)	0.92; 1.00 (0.93-1.07)	0.46; 0.98 (0.92-1.04)
aACRPedi90 (%) (CI)	58.4 (40.6-76.1)	55.3 (37.3-73.3)	69.0 (51.8-86.1)	0.72; 0.99 (0.93-1.05)	0.39; 0.98 (0.92-1.03)
Inactive disease (%) (CI)	71.3 (55.0-87.6)	70.3 (53.9-86.7)	72.4 (55.9-89.0)	0.99; 0.99 (0.94-1.06)	0.82; 0.99 (0.93-1.06)
VAS physician, mean (CI)	4.4 (1.2-7.7)	5.0 (1.2-8.9)	4.6 (1.2-8.0)	0.48; 0.85 (0.54-1.34)	0.61; 0.89 (0.57-1.38)
VAS patient/parent, mean (CI)	14.9 (6.9-22.9)	25.5 (16.2-34.8)	18.0 (10.4-25.8)	0.79; 0.92 (0.51-1.67)	0.48; 1.20 (0.72-2.01)
CHAQ, mean (CI)	0.4 (0.2-0.5)	0.7 (0.4-0.9)	0.4 (0.2-0.6)	0.14; 0.99 (0.98-1.00)	0.90; 1.00 (0.99-1.01)
No. active joints, mean (CI)	0.6 (0.1-1.1)	0.9 (0.1-1.7)	0.6 (0.1-1.2)	0.54; 0.96 (0.84-1.10)	0.52; 0.95 (0.83-1.10)
No. limited joints, mean (CI)	0.8 (0.1-1.4)	0.6 (0.3-1.0)	1.3 (0-2.7)	0.39; 0.96 (0.88-1.05)	0.53; 1.02 (0.95-1.10)
ESR, mm/hour mean (CI)	8 (4-12)	9 (5-12)	7 (3-11)	0.31; 0.90 (0.72-1.10)	0.29; 0.91 (0.76-1.09)
JADAS-10 mean (CI)	2.6 (1.4-3.8)	4.0 (2.2-5.8)	3.0 (1.6-4.4)	0.61; 0.96 (0.82-1.13)	0.97; 1.00 (0.87-1.16)

*Results from GEE-analysis on imputed data, arm 3 was used as reference arm; Vs=versus, OR=Odds Ratio, CI=95% confidence interval, aACRpedi30/50/70/90= adjusted ACRpedi 30/50/70/90 improvement scores; CHAQ=Child Health Assessment Questionnaire; JADAS-10= Juvenile Arthritis Disease Activity Score with maximum up to 10 active joints.

Table S2 | Protocol violations per arm

	Arm 1 Sequential monotherapy n=31	Arm 2 MTX+6 wks Prednisone n=32	Arm 3 MTX+ Etanercept n=29
Glucocorticoid treatments out of protocol 0-6 months			
IM kenacort injection*[1]	2	0	0
Oral prednisolone course*[2]	1	2	0
Intra-articular injection*[3]	0	2	0
6-24 months			
Oral prednisolone course*[4]	0	1	1
Intra-articular injection*[5]	0	6	2
0-24 months Cumulative			
Oral	60 mg/kg (n=1)	16.6mg/kg (n=32) + 36mg/kg (n=2) + 2w DU*[6]	216mg/kg (n=1)
Parenteral (IM;IA)	2 (n=2)	8 (n=5)	2 (n=2)
No change of therapy against protocol			
No MTX dose increase or restart due to:			
Preference parent/patient	5		
Preference physician	1	1	
Unknown	1		
No start etanercept, due to:			
Preference parent/patient	2	1	NA
Preference physician	4	4	NA
Unknown	2	1	
No etanercept dose increase, due to:			
Preference parent/patient	1		1
Preference physician	2	2	6
Tapering violation*[7]	1	1	1
Skipped time point(s)	10 visits in 9pts	6 visits in 4 pts	4 visits in 4 pts

IM =intramuscular, IA= intra-articular, MTX=methotrexate, NSAID=non-steroidal anti-inflammatory drugs, Pts=patients

*1 In arm 1: in 2 patients a single kenacort IM injection was administered after 6 weeks;
*2: In arm 1: 1 patient received oral prednisone : 4 months 0.5mg/kg,
in arm 2: 2 patients received 3 months of prednisone 0.4-0.5mg/kg,
*3: In arm 2 in the first 6 months one proximal interphalangeal (PIP) joint was injected with methylprednisolone in 1 patient, and one knee joint in another patient was injected with triamcinolonhexacetonide.
*4: in arm 2: one patient received a 1-2 week course of prednisone prescribed by the general practitioner due to irritation of enthesis, dose unknown.
In arm 3 one patient received 15mg/day tapering to 7.5mg/day after six months, tapering to 0 the next 6 months.
*5 In arm 2 the same PIP joint was injected in 1 patient; Five knees in 4 patients at 5 time points. In arm 3 one wrist injection and one knee injection in 2 different patients.
*6 DU=prednisone dose unknown for 2 weeks by the general physician.
*7 In arm 1 one patient did not taper MTX when appropriate according to protocol. Likewise in arm 2 one patient did not taper etanercept when in inactive disease for 6 months. In arm 3 one polyarticular patient tapered etanercept too soon, MTX was continued too long.

Table S3 | JADAS MDA and JADAS inactive disease after 1 and 2 years (based on imputed data)

JADAS MDA	Arm 1 (n=31)	Arm 2 (n=32)	Arm 3 (n=29)
Oligoarticular JIA JADAS < 2.0	1y: 2 of 5	1y: 2 of 3	1y: 0 of 3
	2y: 3 of 5	2y: 2 of 3	2y: 1 of 3
Polyarticular JIA JADAS < 3.8	1y: 12.3 of 26	1y: 13.3 of 29	1y: 17 of 26
	2y: 18.3 of 26	2y: 17.9 of 29	2y: 20.8 of 26
Total	1y: 46%	1y: 48%	1y: 59%
	2y: 69%	2y: 62%	2y: 75%
JADAS ID JADAS ≤ 1			
Total after 1 year	8.4 (27%)	9 (28%)	9 (31%)
Total after 2 years	16.2 (52%)	14.1 (44%)	12.5 (43%)

1y: after 1 year, 2y: after 2 years.

5
8
6
7
10