CLINICAL SCIENCE

Treat-to-target study for improved outcome in polyarticular juvenile idiopathic arthritis

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ABSTRACT

Background Juvenile idiopathic arthritis is one of the most prevalent chronic inflammatory diseases in children. Evidence suggests that early effective treatment minimises the burden of disease during childhood and in further life. We hypothesise that a guided treat-to-target (T2T) approach is superior to routine care in polyarticular juvenile idiopathic arthritis (pJIA) in terms of reaching a clinical remission after 12 months of treatment.

Methods Patients with early and active pJIA were enrolled. Targets for treatment were the following: Recognisable Juvenile Arthritis Disease Activity Score (JADAS) improvement after 3 months, acceptable disease at 6 months, minimal disease activity at 9 months and as primary endpoint remission after 12 months. Initially, patients received methotrexate. Failure to meet a defined target required treatment modification at the specified intervals. The choice of biologics was not influenced by the protocol. Finally, T2T patients were compared with a cohort of matched controls of patients with pJIA with unguided therapy documented by BIKER.

Results Sixty-three patients were enrolled. Treatment targets after 3/6/9 and 12 months were reached by 73%/75%/77% and 48% of patients. Fifty-four patients completed the protocol. Compared with matched controls, on T2T guidance significantly more patients reached JADAS remission (48% vs 32%; OR 1.96 (1.1–3.7); p=0.033) and JADAS minimal disease activity (JADAS-MDA) (76% vs 59%; OR 2.2 (1.1–4.4); p=0.028). Patients from the T2T cohort received a biologic significantly more frequent (50% vs 9% after 12 months; OR 9.8 (4.6–20.8); p<0.0001).

Conclusion The T2T concept was feasible and superior to unguided treatment. High rates of patients reached JADAS-MDA and JADA remission after 12 months. Approximately half of the patients achieved their therapy goals without a biologic.

Key messages

What is already known about this subject?
- A treat-to-target approach is successfully used in the treatment of rheumatoid arthritis.
- In juvenile idiopathic arthritis (JIA), it is known that an early response to treatment is associated with better outcome.

What does this study add?
- This study tested the treat-to-target approach for polyarticular JIA in clinical practice and compared it with unguided treatment for polyarticular JIA.
- It could be shown that patients with polyarticular JIA with targeted treatment strategy reached Juvenile Arthritis Disease Activity Score (JADAS) remission and JADAS minimal disease activity, and also more patients received biologics compared with an unguided treatment strategy.

How might this impact on clinical practice or future developments?
- A treat-to-target strategy can be easily implemented in routine care of JIA, with benefits for the patients.

INTRODUCTION

Over the last decades the outcome of patients with polyarticular juvenile idiopathic arthritis (pJIA) has improved significantly due to the availability of more efficacious antirheumatic therapies and improved treatment strategies.[1–5] Guidelines for the treatment of juvenile idiopathic arthritis (JIA) exist in Germany and other countries.[6–8] However, inadequate standardisation and poor penetration of therapies and recommendations in clinical practice may result in late or inadequate treatment. The standard of care in the management of rheumatoid arthritis currently is considered to include early diagnosis with prompt initiation of disease-modifying antirheumatic drugs (DMARDs), tight control monitoring of disease activity, and treatment adjustments aiming at the target of clinical remission or at least low disease activity.[9] Also in patients with JIA early DMARD treatment is associated with better disease control and outcome, such as drug-free remission in early adulthood.[10] An early response to treatment is associated with a better outcome.[11 12] This supports the concept of a 'window of opportunity' for JIA, which suggests that the long-term disease process can be altered by early successful disease control. This can be achieved by setting targets to monitor sufficient treatment response and using a step-up design, if targets are failed (treat-to-target (T2T)).[13] Guided treatment aims at monitoring disease activity at defined intervals with predetermined treatment targets and steps to be followed in case of failure to reach the target.

This open-label intervention study was designed to examine the T2T principle in a routine clinical setting and not to test or compare specific treatments. Thus, standard of care was to be maintained. According to national and international guidelines,

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all patients started with methotrexate (MTX). The choice of the biologic within the approved spectrum was an independent decision of the treating paediatric rheumatologist.

METHODS

Patients

In six German centres for paediatric rheumatology, a total number of 63 patients with early pJIA (disease duration <12 months) were recruited for this study. Inclusion criteria were the following: diagnosis of pJIA according to International League of Associations for Rheumatology criteria (seropositive, seronegative pJIA and extended oligoarthritis),[14] active disease with a baseline Juvenile Arthritis Disease Activity Score (JADAS) 10 of greater than 5.4 (inacceptable disease[15]), age 2–16 years and written informed consent of patient and parents/legal guardian to participate in the study (informed consent).

The study was performed in compliance with the Declaration of Helsinki. The study protocol was registered at the German clinical trials register, DRKS (Deutsches Register Klinischer Studien (German registry for clinical trials)), DRKS-ID: DRKS00010764.

As a control cohort, biologic-naive patients from the German biologics in JIA register (BIKER)[16] were selected, who also had a short disease duration of no more than 12 months, had an active disease at therapy start and started with MTX as their first DMARD between 2005 and 2011. These patients were matched to the study patients 3:1, matching criteria were JIA category, baseline JADAS and gender.

Table 1 Baseline patient characteristics of T2T cohort and matched controls from BIKER

	T2T screened patients, N=63	T2T patients completing protocol, N=54*	BIKER matched controls, N=162	P value †
Gender, female, n (%)	47 (74.6)	42 (77.8)	126 (77.8)	1.0
Age a treatment start, years, mean (SD)	9.4 (4.8)	9.1 (4.8)	8.8 (4.5)	0.68
Disease duration, years, mean (SD)	0.5 (0.7)	0.36 (0.2)	0.4 (0.22)	0.24
JIA category				
Rheumatoid factor – PA, n (%)	49 (77.8)	44 (81.6)	132 (81.6)	1.0
Rheumatoid factor + PA, n (%)	8 (12.7)	6 (11)	18 (11)	1.0
Extended oligo JIA, n (%)	3 (4.7)	4 (7.4)	12 (7.4)	1.0
Enthesitis-associated arthritis, n (%)	2 (3.2)	0	0	
Psoriatic arthritis	1 (1.6)	0	0	
Number of active joints, mean (SD)	10.0 (7.2)	9.9 (7.5)	11.2 (9.7)	0.37
Physician-assessed disease activity VAS, cm, mean (SD); 0–10	5.5 (1.8)	5.6 (1.8)	5.9 (2.1)	0.34
Patient-assessed disease activity VAS, cm, mean (SD); 0–10	5.4 (2.4.)	5.3 (2.2)	4.5 (2.5)	0.0625
CHAQ-DI, mean (SD); 0–3	0.99 (0.77)	0.92 (0.77)	0.81 (0.65)	0.31
ESR, mm/hour mean (SD)	25.1 (23.9)	25.5 (25.0)	28.3 (20.8)	0.42
CRP, mg/L, mean (SD)	16.1 (23.9)	16.0 (24.5)	19.4 (28.0)	0.43
JADAS10, mean (SD); 0–40	19.3 (5.0)	19.2 (5.2)	19.0 (5.4)	0.81
Systemic steroids baseline, n (%)	37 (63)	33 (61)	60 (37)	0.003

Matching 1:3 with the following criteria: JIA category, baseline JADAS and gender.
*Only data of patients treated according to study protocol are shown.
†Comparing T2T patients who completed the protocol and matched control, p-values <0.05 were considered significant.
CHAQ-DI, Childhood Health Assessment Questionnaire Disability Index; CRP, C reactive protein; ESR, erythrocyte sedimentation rate; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; PA, polyarthritis; T2T, treat-to-target; VAS, Visual Analogue Scale.

Study design

This was an open single-arm multicentre study investigating a T2T strategy.

All patients started MTX at the baseline visit in a dose of 10–15 mg/m^2 per week subcutaneously or orally as prescribed by the investigator. Concomitant treatment as non-steroidal anti-inflammatory drugs, bridging with systemic steroid or intra-articular steroids were allowed at the discretion of the treating investigator. The first assessment of treatment effectiveness was scheduled after 12 weeks. The required target was a JADAS improvement defined as a decrease in JADAS10 as validated by Horneff and Becker.[17] If the target was not met, a biologic should be started (online supplementary table 1S). The decision, which biologic was started and whether MTX was continued or not was the responsibility of the treating investigator and made in a shared decision with parents and patients after informing them of the options. Further effectiveness evaluations were scheduled after 24 and 36 weeks. Targets were set more rigorous with treatment duration requiring JADAS acceptable disease activity (ADA), defined as JADAS10 $\leq$5.4 at week 24 and JADAS minimal disease activity (MDA), defined as JADAS10 <3.8, at week 36.[15] If targets were not met, a modification of treatment, meaning either start of a biologic or switching to an alternative biologic was mandatory. Again the choice of treatment remained with the investigator, the only requirement being, that a treatment approved for the diagnosis in the approved dosing was used. The final assessment after 48 weeks determined if the study objective of JADAS remission was met.

Outcomes

Parent-reported or patient-reported outcomes included a global assessment of disease activity on a 10 cm Visual Analogue Scale (Pat VAS) and the functional status assessed by the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI; range 0–3). Physician-reported outcomes comprised the number of joints with swelling, range of motion limitations, tenderness or pain with motion, erythrocyte sedimentation rate (ESR) or C reactive protein (CrP) levels, as well as the physician's global assessment of the patient's disease activity (PGA) on a 10 cm VAS. Disease activity was additionally assessed by the JADAS10, calculated as a sum of the number of active joints up to a maximum of 10, the PGA, the Pat VAS and normalised to a 0–10 scale either ESR[18] or CrP[19] with a range from 0 to 40. The JADAS is recommend for the assessment and monitoring of disease activity as well as for the definition of a target to treat to.[19–22]

The primary outcome was percentage of patients reaching JADAS remission, defined as JADAS10 <1 at month 12. The secondary outcome measures were percentage of patients reaching JADAS MDA at months 9 and 12, JADAS ADA at months 6, 9 and 12 and JADAS improvement at months 3, 6, 9 and 12.[15 17]

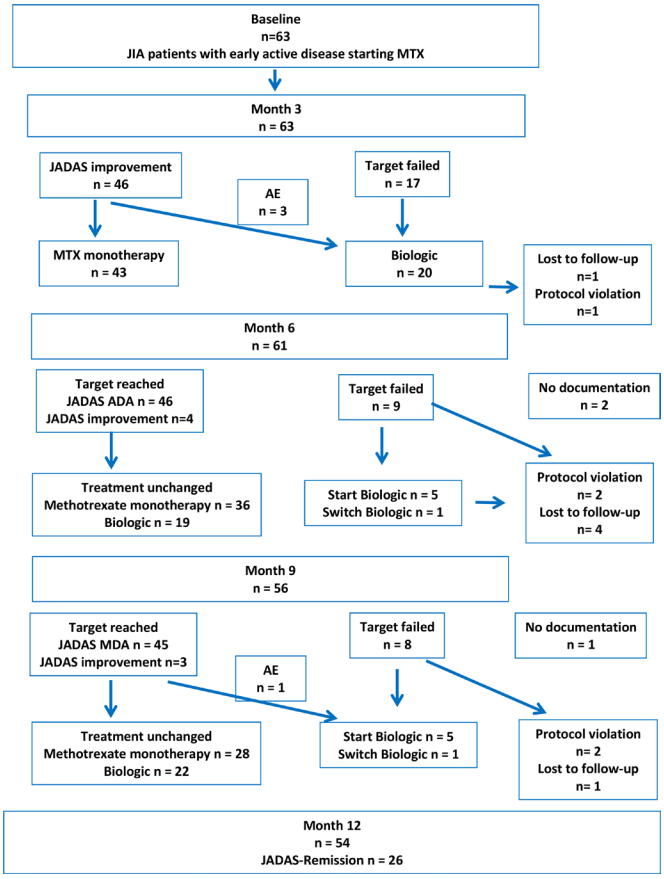

Figure 1 Patient flow. ADA, acceptable disease activity; AE, adverse event; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; MDA, minimal disease activity; MTX, methotrexate.

Statistical analyses

Mean values and SD were calculated for quantitative variables. Demographic and baseline characteristics were summarised by descriptive statistics. Efficacy and safety analyses were performed and the cohort completing the study according to protocol was compared with the matched control cohort. An intention-to-treat analysis was not performed because the assessment of the guided treatment protocol would not have been meaningful, if patients not adhering to protocol were included. Tests were two sided, and p-values <0.05 were considered statistically significant. Frequencies were compared using the χ^2 test or Fisher's exact test as appropriate. Data were entered in an Access 2010 database and analysed with Excel 2010 (Microsoft, Redmond, Washington, USA) or IBM SPSS V.23.

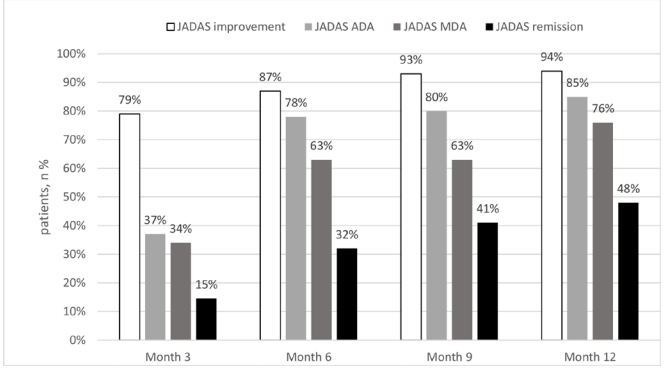

Figure 2 Response rates at months 3, 6, 9 and 12. ADA, acceptable disease activity; JADAS, Juvenile Arthritis Disease Activity Score; MDA, minimal disease activity.

RESULTS

Sixty-three patients were enrolled in the current study of whom 54 completely adhered to the protocol who finally were compared with 162 matched control patients selected from BIKER. Baseline patient characteristics of enrolled patients and matched controls from BIKER are shown in table 1.

All patients had highly active disease with a JADAS10 >10 and started MTX treatment at baseline and had the first follow-up documentation at month 3. According to the criteria for JADAS improvement, 46 patients had reached the target for month 3, the remaining 17 did not reach the target and a biologic was introduced (figure 1). A further three patients switched to a biologic because of intolerance of MTX treatment. Biologics used were etanercept (ETA) in 11 patients, tocilizumab (TOC) in 4 patients, adalimumab (ADM) in 3 and golimumab in 2 patients. In all, 43 patients remained on MTX monotherapy.

After 6 months, 61 patients were assessable. By then 46 patients had reached the target of JADAS ADA, 4 patients who had started a biologic at month 3 showed considerable JADAS improvement and 9 patients had failed to reach the target. While 54 patients continued their treatment (36 patients remained on MTX monotherapy and 19 patients continued the treatment they had initiated at month 3), 5 patients newly started a biologic treatment (ETA n=3, ADM n=1, TOC n=1) and one patient switched biologic from ETA to TOC.

At month 9, 56 patients could be evaluated according to protocol. Of the 56 patients, 43 patients reached the required target of JADAS MDA, and a further 4 patients who had started a biologic at month 6 had significant JADAS improvement and 8 patients failed to reach the target. Altogether 49 patients remained on their treatment with 27 on MTX monotherapy. While five patients newly started a biologic (ETA n=3, ADM n=1, TOC n=1), one patient switched from TOC to ETA. Of the patients starting a biologic, one patient had reached the month 9 target, but had to discontinue MTX due to intolerance.

Altogether, nine patients could not be evaluated for the final analysis. Six patients were lost to follow-up. Patients with protocol violation were also not considered for the outcome analysis at month 12 and are described here: In one patient, MTX was discontinued because of AE at month 3, but no biologic was started. Two patients (one was also lost to follow-up) had started a biologic (ETA, ADM) at month 3 and did not show JADAS improvement at month 6, but were not switched to another biologic. Two further patients failed to reach the month 9 target but treatment was not modified accordingly. Of the five patients not following the protocol, one patient reached the target of JADAS remission at month 12, the other four had JADAS scores of 5, 7, 9 and 12, respectively. (figure 2)

Outcome at month 12

After 1 year of treatment, 54 patients were assessable and had been treated according to protocol. Of these, 27 patients still received MTX monotherapy and 27 patients were on biologics.

The target of JADAS remission was reached by 48% (n=26) of patients, 16 patients with MTX monotherapy (59%) and 10 patients treated with biologics (37%). In all, 76% (n=41) of the patients reached JADAS MDA and 85% (n=46) JADAS ADA.

Of the patients remaining on MTX monotherapy, 23 (85%) reached JADAS MDA and 15 (56%) reached JADAS remission.

Comparison with patients with unguided treatment

The JADAS outcome parameters at month 12 of the patients treated according to the T2T protocol were compared with patients with early active pJIA documented in the BIKER registry, who were biologic naive and started MTX within the first year of JIA onset. Patients were matched in a ratio of 1:3 using JIA category, gender and baseline-JADAS as criteria. The baseline characteristics of the 162 patients from BIKER are shown in table 1. Apart from higher concomitant systemic steroid use in the T2T cohort, there were no significant differences. The proportion of patients receiving intra-articular steroids at baseline was numerically but not significantly lower in the T2T cohort (n=12 (22%) vs n=59 (36%) in the control cohort (p=0.07)). Patients from BIKER had slightly more active joints at baseline, while the patients of the T2T cohort were slightly older and had a slightly higher CHAQ-DI at treatment start (table 1).

After 12 months of treatment, significantly more patients from the T2T cohort compared with the BIKER cohort (JADAS remission: n=52; 32%, JADAS MDA: n=96; 59%) had reached JADAS remission (OR 1.96; 95% CI: 1.05 to 3.68; p=0.033) and JADAS MDA (OR 2.2, 95% CI: 1.08 to 4.36; p=0.028) compared with patients from the T2T cohort. The proportion of patients reaching JADAS ADA in the BIKER cohort (n=119; 73%) was not significantly lower than that in the T2T cohort (p=0.068) (figure 3).

Compared with 9% of patients in the BIKER cohort, a significantly higher ratio (50%) of patients in the T2T cohort received biologic treatment at month 12 (OR 9.8; 95% CI: 4.6 to 20.8; p<0.0001). Also, fewer patients in the T2T cohort did receive systemic steroids after 12 months (5.6% vs 21.6%, p=0.007).

Safety

Altogether, 88 adverse events (AEs) were reported in 51 patients, of which 3 were serious AEs (SAEs) in 3 patients. In detail, the SAEs were norovirus gastroenteritis in a patient treated with TOC and MTX, Perthes disease and severe anaemia in MTX-treated patients. Most common AEs were infectious events (n=26), mainly of the upper airways (n=12), bronchitis (n=2) and gastroenteritis (n=3). MTX-related gastrointestinal symptoms (n=20) and elevation of liver enzymes (n=10) were also frequent events. AEs for both cohorts according to treatment are shown in table 2.

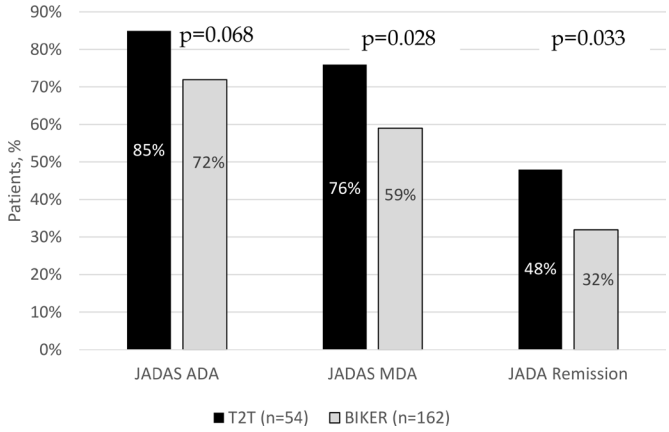

Figure 3 JADAS ADA, MDA and remission rates after 12 months of treatment compared between T2T study cohort and matched controls. ADA, acceptable disease activity; JADAS, Juvenile Arthritis Disease Activity Score; MDA, minimal disease activity; T2T, treat-to-target.

Table 2 Safety

n/number of pts (% of pts)	T2T cohort MTX only, n=63	T2T cohort biologic exposed, n=27	BIKER Control cohort MTX only, n=162	BIKER Control cohort biologic exposed, n=15
AE	69/45 (71)	19/14 (52)	104/61 (38)	14/7 (47)
Serious AE	2/2 (3.2)	1/1 (3.7)	1/1 (0.6)	0
Infectious AE	18/17 (27)	9/9 (33)	36/22 (14)	2/2 (13)
Uveitis	2/2 (3.2)	0	3/3 (1.9)	0
Gastrointestinal AE	21/20 (32)	4/4 (15)	38/30 (18.5)	2/2 (13)
Transaminases elevated	11/10 (16)	1/1 (3.7)	12/12 (7.4)	0

AEs are according to treatment and cohort. Gastrointestinal events were nausea, vomiting and abdominal pain.

DISCUSSION

The ongoing development of effective treatment options for pJIA has led to a situation where remission of disease or at least MDA can be reached in a high percentage of patients. Also the concept of a window of opportunity[10 11] suggests that early treatment of pJIA alters the disease course. Hence, the aim of any treatment for pJIA should be early reduction of disease activity. To reach this goal in clinical practice, a guided standardised T2T concept seems a promising approach. A Dutch randomised single-blinded study with a T2T design in three different treatment arms (sequential DMARD monotherapy (sulfasalazine or MTX), combination therapy MTX + prednisolone or combination therapy MTX + ETA) with a step-up option within the treatment arm also showed promising response rates after 1 year with about 47%–62% of patients reaching inactive disease regardless of initial treatments.[23]

This T2T study showed that patients benefit from a tightly controlled T2T strategy. Significantly more patients reached MDA or remission in comparison to the control group. Interestingly, significantly more patients were treated with biologics to reach the target of JADAS remission/MDA. Although in the T2T cohort more patients initially received systemic steroids, steroid use was significantly lower in the T2T cohort after 12 months compared with the control cohort, further supporting this concept.

Another approach is an early aggressive treatment as tested in the multicentre, prospective, double blind, randomised, placebo-controlled TREAT trial, where patients after diagnosis of pJIA were either treated with ETA + MTX + oral steroids or with MTX monotherapy including a step-up option in case of insufficient response. MTX was given at a comparably high dosage of 0.5 mg/kg/week subcutaneously in both arms. While there was a trend toward a higher rate of patients in the combination therapy arm reaching the primary endpoint of clinical inactive disease at month 12 of induction, the difference was not statistically significant. In the extension of the TREAT, patients were treated as per provider's discretion. In this cohort, prolonged periods of clinically inactive disease could be observed in the majority of patients during follow-up regardless of the initial treatment arm with more than 50% of patients receiving biologics.[24 25] When looking at the data of our T2T study, it is remarkable that over half of the T2T patient cohort reached JADAS MDA on MTX monotherapy. This observation justifies the step-up regimen used here since biologics were not necessary to reach the target in every case. It seems important to start treatment early in the disease course, irrespective whether using initially a step-up

design or an aggressive therapy. With the step-up approach, overtreatment might be avoided.

It would be very interesting to be able to distinguish between patients showing a sustainable good response to MTX and patients needing biologics early in the disease course. It remains to be shown, if the patients who do not show a sufficient or sustained response to MTX might benefit from initial treatment with biologics.

The validated JADAS score for measuring disease activity was chosen, because it is an easy, time-efficient and flexible method to guide therapeutic interventions aimed to pursue tight disease control. Different validated levels of disease activity, i.e. for improvement of JADAS, ADA, MDA and remission are available, which are useful to gradually tighten the treatment goals.[15 17]The CARRA (Childhood Arthritis and Rheumatology Research Alliance) protocols[8] use the physician global assessment, ability to taper/discontinue steroids as well as a not clearly defined 'patient much improved' statement as criteria for treatment success. The recently published American College of Rheumatology guidelines[26] and the recently revised German consensus-based treatment guidelines for JIA [27] both recommend the JADAS10 to assess disease activity.

The T2T strategy used in this study has been shown to be applicable in clinical routine care. Such a standardised approach to treatment is transparent and easy to implement in clinical routine practice. The treating physician/paediatric rheumatologist is not influenced in the choice of the approved biologics and differences in known safety profiles as well as approval status and application can and should be taken into account. For a successful treatment, an early diagnosis and referral to a paediatric rheumatologist is of great importance.

Limitations of this study are the non-controlled and non-blinded approach. The comparison with a more or less historic cohort may pose a bias, in as far as physicians at present might be more generous in using biologics than in the past.

Also this analysis ended after the initial 12 months, long-term data regarding rates of patients remaining in remission and rates of patients who could successfully discontinue treatment are not available. Also the question of tapering or discontinuing JIA treatment in case of remission is not addressed by this study. Larger controlled studies are needed to address these issues.

CONCLUSION

A guided T2T strategy with early escalation of therapy was superior to unguided treatment in pJIA. Significantly more patients achieved JADAS MDA and JADAS remission after 12 months of treatment. Approximately half of the patients achieved their therapy goals without the use of a biologic. This approach is feasible and easy to implement in routine clinical care.

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