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Original Article

# Oral or Parenteral Methotrexate for the Treatment of Polyarticular Juvenile Idiopathic Arthritis

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## Abstract

**Objective:** Subcutaneous methotrexate injections are considered to be more effective or work faster than oral methotrexate. Therefore, the extent and the kinetics of response were analyzed in juvenile idiopathic arthritis patients treated with oral versus subcutaneous methotrexate.

**Methods:** The BIKER databank was searched for biologics-naive juvenile idiopathic arthritis patients treated with methotrexate as initial treatment. The Juvenile Arthritis Disease Activity Score-10 definition of remission and the pediatric American College of Rheumatology's response parameters were utilized as outcome criteria.

**Result:** A total of 410 polyarticular juvenile idiopathic arthritis patients receiving oral methotrexate were compared to 384 patients receiving subcutaneous methotrexate. Rheumatoid factor-negative polyarthritis was the most common juvenile idiopathic arthritis category (50%/51%) in this cohort followed by extended oligoarthritis (27%/26%), polyarticular psoriatic arthritis (18%/16%), and few had rheumatoid factor-positive polyarthritis (5%/8%). The oral cohort's disease duration (2.3 ± 3.0 vs. 1.9 ± 2.7) was significantly longer ($P = .04$), although their age at onset and baseline were similar. Furthermore, at baseline, disease activity (Juvenile Arthritis Disease Activity Score-10 16.5 ± 7.2 vs. 14.7 ± 8.2; $P = .001$ due to a higher active joint count 9.0 ± 10.1 vs. 7.4 ± 7.7; $P = .011$) was higher in the subcutaneous cohort. The weekly methotrexate doses were comparable with 13.6 ± 5.4 mg/m$^2$ and 13.3 ± 4.5 mg/m$^2$, respectively.

With oral/subcutaneous methotrexate, a pediatric American College of Rheumatology's 90 was achieved in 98(38.3%)/128(40.4%), while 96(38.1 %)/75(40.1%) attained Juvenile Arthritis Disease Activity Score remission after 12 months of therapy. There was no difference in the early kinetics of response according to Kaplan–Meyer analysis.

Adverse events including nausea, vomiting, and increased transaminases were considerably more common after methotrexate subcutaneous administration than after oral treatment.

**Conclusion:** In terms of effectiveness, but not safety, our retrospective analysis found some advantages of subcutaneous methotrexate. Adverse effects limit treatment continuance and thus must be considered a disadvantage. Furthermore, oral methotrexate eliminates the need for injections, which is especially essential for younger children. Controlled, randomized prospective trials in children and juvenile patients are necessary for definitive recommendations for the subcutaneous route of administration of methotrexate therapy.

**Keywords:** Juvenile idiopathic arthritis, methotrexate, juvenile arthritis disease activity score, remission

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## Introduction

Juvenile idiopathic arthritis (JIA) is an umbrella term used to describe diseases with unclear etiologies that are defined by persistent arthritis that restricts the patient's everyday activities and productivity. Disease start before the age of 16, and arthritis that lasts longer than 6 weeks are needed classification criteria for JIA diagnosis and definition.[1-3]

Juvenile idiopathic arthritis prognosis is thus far unpredictable in an individual youngster. Non-steroidal antirheumatic medications, primarily for symptomatic relief, and disease-modifying antirheumatic medicines (DMARDs) are used in the treatment of JIA. In the treatment of polyarticular JIA patients by the latter group, methotrexate (MTX) has become a cornerstone. Its effectiveness was proven 3 decades ago in a randomized, controlled experiment.[4] Following that, several controlled clinical trials indicated that MTX was effective as a first-line DMARD, according to various national treatment guidelines.[4-6]

When administered at a weekly dose of 10-15 mg/m$^2$ body surface area, it functions as an anti-inflammatory agent rather than a cytotoxic treatment.[8-10]

Methotrexate is usually started at a dosage of 10-15 mg/m$^2$ weekly in children with JIA, either orally or parenterally (subcutaneously (s.c.) or intramuscularly). At these typical levels, most pediatric rheumatologists prefer the oral route since it is easier to administer and provides better child comfort. Furthermore, neither the oral nor the parenteral administration methods appear to provide many benefits in terms of efficacy or safety.[11]

Some pediatric rheumatologists begin low-dose bridging treatment with prednisone (0.2-0.35 mg/kg/day) since the maximal therapeutic response appears not earlier than 4-6 months after the start of treatment and can take up to 12 months in some cases. In children who have only had a partial response to the medication or who have a more severe illness, a higher dose of up to 25-30 mg/m$^2$/week may be considered. Because of the drug's reduced oral bioavailability at higher doses, doses above 15-20 mg/m$^2$/week are generally given parenterally.[9]

Although a controlled prospective study comparing oral versus parenteral MTX administration in adult patients with rheumatoid arthritis (RA) observed that patients receiving parenteral MTX had significantly higher response rates to the American College of Rheumatology's (ACR) 20% improvement criteria, this has not been investigated in patients with JIA. However, the data suggest a number needed to treat 12.5 adult RA patients for 1 patient to benefit from s.c. MTX over oral MTX. In JIA patients, 2 non-randomized studies reported the successful use of parenteral MTX treatment in patients who failed oral treatment.[8,12]

There is nevertheless insufficient information available in literature concerning the effectiveness and safety of oral versus s.c. MTX for JIA therapy. The major objective of JIA treatment is to attain wellness with the least amount of adverse effects possible. The identification of response predictors aids in the development of recommendations for MTX usage, particularly for the initiation of MTX as well as a subsequent continuation or early cessation of MTX and the start of biological medication use. Subcutaneous MTX is considered to be more effective and works faster than oral MTX. As a result, we attempted to analyze the extent and kinetics of response in JIA patients treated with oral versus s.c. MTX in this study.

## Methods

Data were obtained from the German Biologics in Paediatric Rheumatology (BIKER) Registry established in 2001.[13] The registry is a long-term non-interventional project that has been authorized by the responsible ethics committee.[13] Patients who had just started using MTX as first-line therapy were added to the register in 2005 as a control group who were not exposed to biologics. For this analysis, data from patients admitted to the registry up through December 31, 2010, were included, who were then followed up further. Patients were included if they were documented as having been diagnosed with JIA according to the International League of Associations for Rheumatology (ILAR) definition and diagnosed with a JIA category for which MTX is approved in Germany (polyarthritis rheumatoid factor (RF)-positive, polyarthritis RF-negative, extended oligoarthritis, and psoriatic arthritis). Patients with systemic-onset JIA, Enthesitis related arthritis (ERA), or persistent oligoarthritis, those previously treated with or on current biologics therapy, simultaneous treatment with a second DMARD (other than MTX), or had previously been treated with MTX were excluded. Endpoint attained if therapy was stopped due to inefficacy, intolerance, or remission, changing the route of administration, start of biological agents, or uveitis occurred.

Data collection: the subject's/ parent's written consent was acquired prior to enrollment.

Baseline data that were included as follows: age at start-of-therapy, gender, duration of illness, JIA subtype, previous medical history, previous and current therapy, date of first MTX dose, prescribed MTX dose, clinical evaluation including weight, height, joint assessment, physician's assessment of global disease activity, and parent/patient global evaluation of overall activity, with measures on a 10-cm visual analog scale, Childhood Health Assessment Questionnaire disability index (CHAQ-DI), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) level The following data were gathered at a time of 3 and 6 months, following treatment, and every 6 months thereafter: MTX dose, missing MTX doses, concurrent treatment, adverse event (AEs), and clinical and laboratory testing, according to the abovementioned guidelines. The study's outcome has been analyzed at 3, 6, 12, 18, and 24 months for therapy. The date of the last MTX dosage and the causes for withdrawal were noted in the event of cessation. Intolerance (AEs), inefficacy, remission, or other explanations were indicated as justifications. More than 1 possible reason for stopping therapy was possible.

The patients were classified into responders and non-responders based on the American College of Rheumatology Pediatric (PedACR) 30, 50, 70, or 90 improvement criteria, which meant a 30%, 50%, 70%, or 90% improvement from baseline in at least 3 of the following 6 variables: Global physician assessment, global parent assessment, number of active joints, number of joints with limited range of motion, CHAQ-DI, and ESR with no more than one remaining variable deteriorating by more than 30%. The Juvenile Disease Activity Score (JADAS) is an essential tool for assessing clinically meaningful changes in disease activity, leading to a treat-to-target strategy that is increasingly focused on tight and comprehensive management of the patient's condition.[14]

The composite ratings are precisely built to track a child's illness progression over time. The availability of criteria for distinguishing high and low levels of activity, however, substantially enhances the value of these tools.

An AE is any unfavorable medical occurrence in a patient or clinical investigation subject who has been given a pharmaceutical product but does not necessarily have a direct link with this therapy. An AE was defined as any undesirable and unexpected sign (including an abnormal laboratory result), symptom, or disease that is temporally linked with the use of a medical (investigational) product, regardless of whether the medicinal (investigational) product is related to the AE.

Serious AE (SAE) are defined as any adverse medication experience that results in mortality, hospitalization/prolongation of hospitalization, congenital abnormality, and persistent or substantial disability/incapacity necessitating an intervention to prevent permanent impairment/damage. Data on adverse events were analyzed with comparative statistics.

## Statistical analysis

The patients in our study were divided into 2 groups: one group received MTX orally and the other group received it parenterally. Two sets of analyses were carried out. The "as-observed

analysis" was run on the patients who remained on the initial MTX treatment (oral and s.c.). Patients who discontinued therapy, altered the route of administration or added a biologic medication were included in the "intention to treat" (ITT) analysis. In the ITT data set, these patients were classified as non-responders.

For quantitative variables, the descriptive statistics are expressed as median with first and third quartiles or mean ± standard deviation (SD) and for qualitative variables, as absolute frequencies and percentages.

*t*-Tests, chi-square tests, and Wald tests are used to compare the 2 modes of MTX application in terms of short and long-term improvement duration. Using Kaplan–Mayer analysis, the velocity of improvement was statistically described. Patients were censored if they stopped taking MTX, switched to a different mode of application, or started receiving biologic therapy.

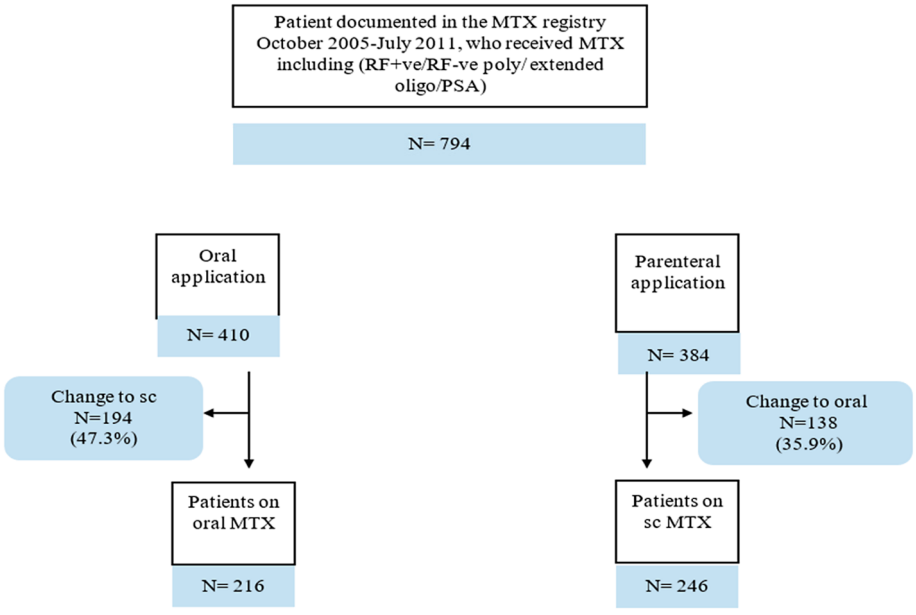


**Figure 1.** Flowchart showing the number of patients included in the study. MTX, methotrexate; RF+ve poly, rheumatoid factor-positive polyarthritis; RF-ve poly, rheumatoid factor-negative polyarthritis; PSA, psoriatic arthritis; s.c., subcutaneous.

## Results

The total number of patients enrolled in the MTX cohort in BIKER until September 2016 was 1517. Our study included 794 JIA patients who met all of the inclusion and exclusion criteria. Totally 410 individuals were treated with MTX orally and 384 parenterally. in the final analysis cohorts, 216 patients receiving MTX orally were compared to 246 patients receiving MTX parenterally (Figure 1).

Females represent 71% (299 patients) in the oral cohort and 78% (301) in the s.c. cohort. Seronegative polyarthritis is the most prevalent JIA category with over 50% in the 2 cohorts, while JIA RF+ve polyarthritis was the least involved. In the latter group, more statistically significant patients received MTX s.c. ($P=.04$). The age of onset and the age at which MTX therapy was initiated were comparable, but disease duration in the s.c. group was significantly shorter (1.8 ± 2.7 years) than in the oral MTX cohort (2.3 ± 3 years) ($P=.04$). Around 50% of our patients in both groups were Anti-nuclear Antibody (ANA) positive. Human leukocyte Antigen (HLA) B27 was found to be positive in 9.5% of the oral cohort and 11.7% of the s.c. group (Table 1).

When compared to the MTX oral cohort, the number of active joints in the MTX s.c. study population was substantially higher at baseline ($P=.012$) as well as the swollen joint count ($P=.006$) and painful joint count ($P=.009$). Morning stiffness was reported in 153 (51.2%) of the oral MTX patients, with a mean duration of 35.9 minutes. In the s.c. group, however, 265 patients (69.0%) had morning stiffness at baseline, with a mean length of 36.8 ± 53.7 minutes. In summary, the articular involvement analysis revealed higher disease activity in the MTX s.c. group at baseline, as well as substantially higher baseline ESR and CRP ($P=.0003$ and .036, respectively), indicating a higher inflammatory activity in the MTX s.c. group (Table 1).

### Treatment

The MTX dosage was comparable in both cohorts and there was no difference in corticosteroid concomitant therapy, both systemic and intraarticular. In the oral cohort, significantly more patients received NSAIDs (95.4% vs. 89%, $P=.0008$).

Response to treatment was analyzed by calculation of the PedACR30/50/70 and 90 responses as well as by the rate of patients reaching the disease state of acceptable disease, minimal disease activity, and remission for which the JADAS based definition was used.

With the exception of a higher PedACR90 response rate at month 6 in the MTX s.c. group, there was no significant difference in the rate of patients who reached a PedACR 30/50/70 or 90 response after 3, 6, 12, and 24 months of therapy in the as-observed population.

In the intention to treat population, response rates were lower than in the as-observed analysis since patients who discontinued treatment due to non-response, switching treatment, or adding a biologic were defined as non-responders. Here, with ongoing treatment, the PedACR 30/50/70 and 90 response rates were higher in the MTX s.c. cohort. These differences were statistically significant at month 18 and month 24 throughout all response measures (Figure 2).

Regarding the targets to treat, the rate of patients reaching JADAS defined acceptable disease, minimal disease activity, and remission was calculated. Juvenile Arthritis Disease Activity Score-10 was substantially greater in the MTX s.c. group than in the oral MTX cohort at baseline, indicating increased disease activity. The incidence of patients in the MTX oral cohort who already had JADAS ≤ 5.6 (indicating acceptable disease activity) at baseline was substantially greater. In the observed population, over 80% of patients fulfilled the criteria for acceptable disease activity at month 24 of treatment, but the response rate in the intention to treat population was significantly lower. In terms of the rate of patients achieving acceptable disease state, no statistical difference between the MTX oral and MTX s.c. groups in the intention to treat and observed population data was found. Almost 80% of patients also had low JADAS-defined disease activity in the as-observed population with no difference between the oral and s.c. MTX cohorts. Approximately 60% of the ITT population achieved JADAS-Minimum disease activity (MDA) in both MTX oral and MTX s.c. cohorts. At month 6, there was a substantially higher

**Table 1.** Clinical and Disease Characteristics of Patients at Baseline

| | Oral, n = 410 | Subcutaneous, n = 384 | $\chi^2$-test or *t*-test |
|---|---|---|---|
| Female (%) | 299 (71) | 301 (78) | n.s |
| Age, mean ± SD, years | 7.6 ± 4.6 | 7.3 ± 4.6 | n.s |
| MTX dosage, mean ± SD, mg/m²/week | 13.5 ± 5.3 | 13.3 ± 4.5 | n.s |
| Disease duration, median [IQR1/IQR3), years, mean ± SD, years | 1.0 (0.4/3.0) 2.3 ± 3.1 | 0.7 (0.3/2.0) 1.8 ± 2.6 | *P* = .04 |
| JIA category | | | |
| RF-negative polyarthritis, (%) | 203 (49.7) | 159 (50.5) | n.s |
| RF-positive polyarthritis, (%) | 19 (4.6) | 31 (8) | *P* = .048 |
| Extended oligoarthritis, (%) | 111 (27) | 98 (25.5) | n.s |
| Psoriatic arthritis, (%) | 28 (22) | 9 (12.3) | n.s |
| Disease characteristic | | | |
| Number of active joints, mean ± SD | 6.1 ± 7.2 | 9 ± 10 | *P* = .012 |
| Number of tender joints, mean ± SD | 7.1 ± 8.1 | 8.7 ± 10 | *P* = .009 |
| Number of swollen joints, mean ± SD | 6.1 ± 7.2 | 7.6 ± 9.1 | *P* = .006 |
| Number of joints with LROM, mean ± SD | 6.7 ± 7.2 | 9.1 ± 10.8 | *P* = .0004 |
| Baseline JADAS, mean ± SD | 14.6 ± 8.1 | 16 ± 7.2 | *P* < .001 |
| Baseline ESR, mean ± SD | 21.4 ± 19.3 | 26 ± 24 | *P* = .0003 |
| Baseline CRP, mean ± SD | 12.1 ± 22.8 | 15.3 ± 26.9 | *P* = .036 |
| Baseline CHAQ, mean ± SD | 0.6 ± 0.62 | 0.7 ± 0.64 | *P* = .0008 |

MTX, methotrexate; IQR, interquartile range; SD, standard deviation; RF, rheumatoid arthritis; JADAS, Juvenile Arthritis Disease Activity Score; JIA, juvenile idiopathic arthritis; LROM, Low range of motion; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CHAQ, Childhood Health Assessment Questionnaire.

benefit of oral versus s.c. MTX, which was not sustained subsequently.

Juvenile Arthritis Disease Activity Score remission was reached in about 50% of patients in the as-observed population without a difference between oral and s.c. MTX. About 30% of patients in the ITT population reached JADAS remission. A significant advantage for oral MTX was observed at month 6 only without consistency thereafter (Figure 3).

The kinetics of response to MTX was assessed by Kaplan–Meyer analysis. In our study, Kaplan–Meier survival time was classified as not reaching pedACR 30,50,70,90, JADAS-minimal disease activity, or JADAS-remission. Patients who stopped taking MTX because of inefficacy or intolerance, switched routes of administration, or began using a biologic were censored. Kaplan–Meyer analysis showed no statistical significance between both populations in terms of kinetics of response. The findings were likewise consistent in terms of JADAS10 acceptable disease activity, JADAS10 minimum disease activity, and JADAS10 remission response (Figure 4).

### Safety

Reported adverse events are listed in Table 2. No significant differences regarding neutropenia, gastritis, appetite loss, or the incidence of severe adverse events were found between the MTX oral and MTX s.c. groups. The MTX s.c. cohort, on the other hand, had considerably higher adverse event rates for upper respiratory tract infection, nausea, vomiting, and elevated liver enzymes. However, they were generally mild not leading to discontinuation of medication.

Discontinuation: 175 of the 794 participants discontinued MTX. The major reason was inefficacy, which was 20% in the oral group and 20.5% in the s.c. MTX cohort. 64 individuals taking MTX orally stopped the medication due to adverse events, which is equivalent to patients receiving therapy parentally (62 patients).

## Discussion

Methotrexate is a very effective second-line drug that is presently authorized for the treatment of RA and polyarticular JIA. There is a dearth of controlled studies comparing oral to parenteral MTX effectiveness and safety in JIA. While it may have a negligible immunosuppressive impact at the dosages used in RA, the quick start of action and predictability of disease flare upon cessation imply that its anti-inflammatory characteristics contribute to its effectiveness. The purpose of this study was to determine if parenteral MTX is preferable than oral MTX in terms of strength or kinetic response, response velocity, and safety. The cohort of patients in this research was drawn from the German BIKER Registry established in 2001, which has been collecting data prospectively on the efficacy and safety of long-term MTX treatment since 2005, the year MTX was authorized for the treatment of polyarticular JIA in Germany, and thus, a cohort of JIA patients not exposed to biologics was established as a control group for biologics exposed JIA patients until July 2011.Our retrospective study included 794 patients who were diagnosed with JIA using the ILAR definition and who fell into one of the JIA categories for which MTX is recommended (RF-negative polyarthritis, RF-positive polyarthritis, extended oligoarthritis, or psoriatic arthritis), and who met all inclusion criteria and none of the exclusion criteria. Patients were considered to have met the endpoint of the analysis if they discontinued MTX, switched the method of administration, or initiated biologic therapy. Data were analyzed (1) as-observed, which included patients who were receiving therapy and (2) as ITT, which included patients classified as non-responders if they met the endpoints discontinuing MTX, switching the method of administration, or initiating biologic therapy. Additionally, the

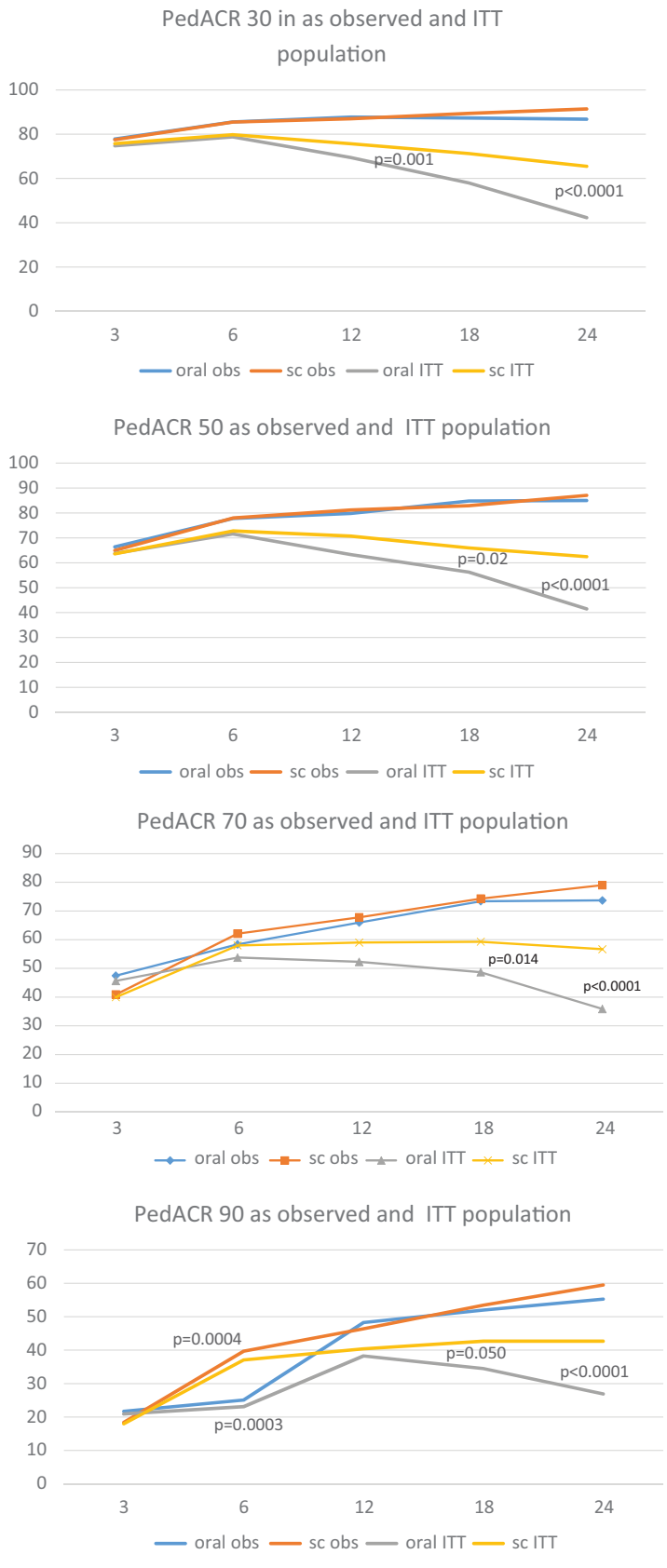


**Figure 2.** PedACR 39/50/70/ped90 response rates among oral and s.c. MTX cohorts in the as-observed and intention to treat population. At month 24 of treatment, the response rate was higher in the s.c. cohort in the intention to treat population ($P < .0001$, HR = 2.6 [1.8-3.7]) for PedACR 30; $P < .0001$, HR = 2.4 [1.65-3.34]) for PedACR 50; $P < .0001$, HR = 2.3 [1.64-3.32] for PedACR 70; $P < .0001$, HR = 2.02 [1.4-2.3] for PedACR 90) obs, observed; ITT, intention to treat; s.c., subcutaneous; HR, hazards ratio.

latter methodology enables the calculation of the impact of MTX in a cohort of patients who adhere to therapy. The limitation of our study is its non-randomized open approach; however, MTX was dosed essentially the same in both cohorts, allowing for direct comparison; yet, there were minor baseline variations between patients in the oral and sc MTX cohorts. Patients with RF-positive polyarthritis were more likely to get sc MTX, as were those with higher disease activity, as indicated by higher joint counts and a higher JADAS10 score. At baseline, patients who were started on s.c. MTX exhibited increased ESR and CRP, both of which are markers of active disease. They also had higher JADAS and CHAQ scores. These distinctions must be taken into account while discussing the results. In this study, we used the PedACR score of 30/50/70 and 90 to measure therapy response as well as the JADAS, particularly to calculate the rates of patients achieving well-defined targets such as JADAS remission, minimal disease activity, and acceptable disease activity.[15]

In one earlier study from BIKER, 563 patients were recruited and evaluated for factors that predicted poor response to a 6-month course of MTX in polyarticular patients (RF-negative, psoriatic arthritis, and enthesitis-related arthritis were excluded). The results revealed that the subgroup of patients with longer disease duration, ANA negativity, higher disability, and the presence of wrist activity was significantly assayed for factors that predicted poor outcome.[16] Patients were not analyzed individually for the method of MTX application in this research. According to Ravelli et al[17], the extended oligoJIA subtype is the greatest predictor of MTX effectiveness. These patients were equally represented in the MTX s.c. and MTX oral cohorts, but we did not perform analyses regarding different JIA categories.

Although an effective continuation of parenteral therapy with higher doses in non-responders to low-dose oral MTX has been demonstrated previously, no controlled, comparable trials are available.[18]

In the as-observed group, there was no statistically significant difference in the number of patients who achieved PedACR 30, 50, 70, and 90 and JADAS10 acceptable disease activity and JADAS10 minimum disease activity or remission during the course of 24 months of MTX therapy. However, in the ITT group, s.c. MTX was superior over oral MTX in achieving PedACR 30, 50, 70, and 90 responses, particularly after prolonged therapy of 18 and

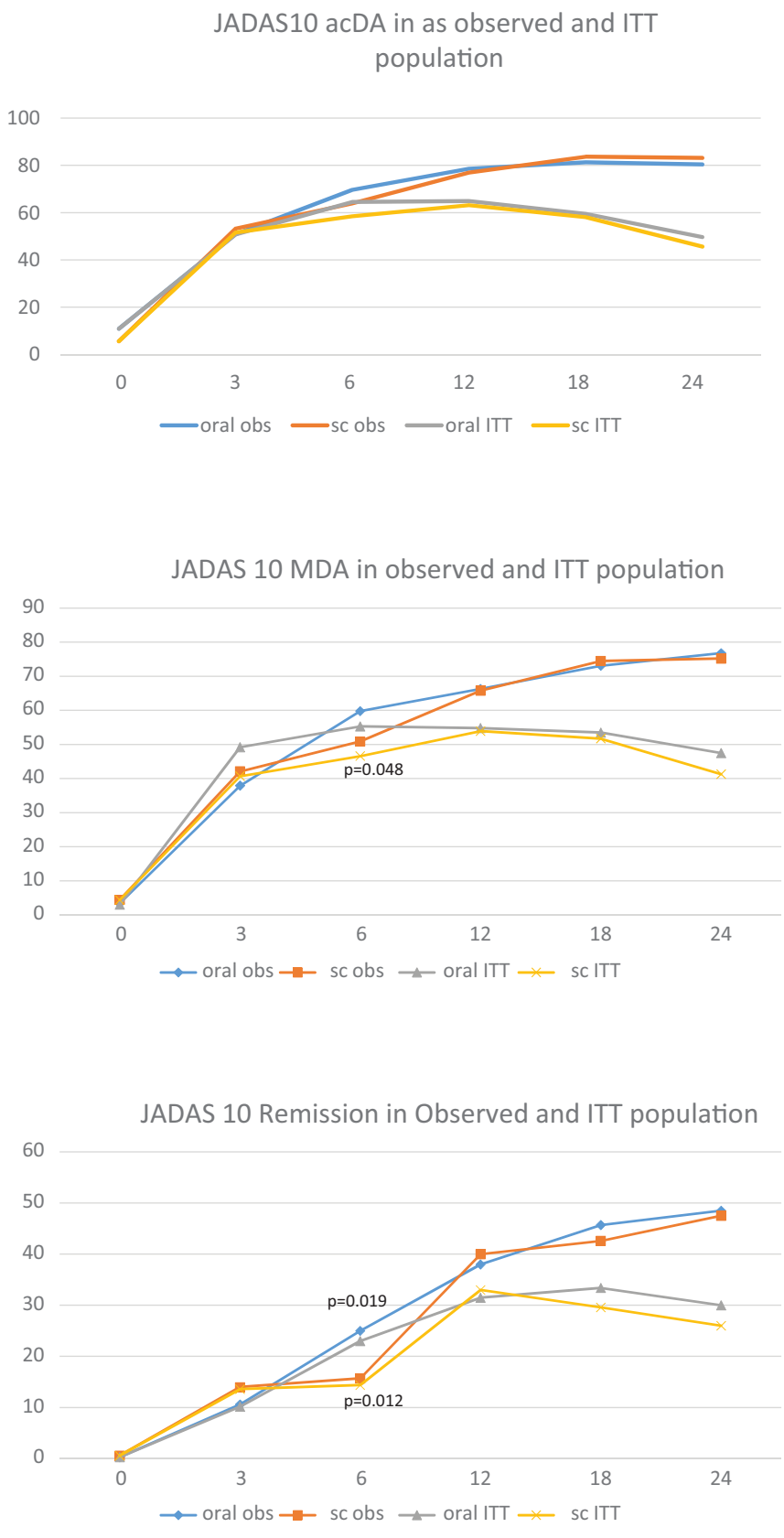


**Figure 3.** Treatment targets JADAS acceptable disease, minimal disease activity, and remission among oral and s.c. MTX cohort in the as-observed and intention to treat population. Only at month 6, statistically significant more patients reached JADAS MDA and JADAS remission upon oral MTX than upon subcutaneous MTX in the as-observed and in the intention to treat population ($P = .013$, HR = 1.7 [1.1-2.8] and $P = .012$, HR = 1.78[1.1-2.3]), respectively. JADAS, Juvenile Arthritis Disease Activity Score; MTX, methotrexate; HR, hazards ratio; s.c., subcutaneous.

24 months. Kaplan–Meier analysis revealed no statistically significant difference between oral and s.c. MTX in terms of kinetics of response in achieving acceptable disease activity, minimum disease activity, and remission as defined by PedACR 30,50,70, and 90 and JADAS10.

Our findings matched those of a short-term, prospective, open-label study that recruited 257 JIA patients at a single pediatric rheumatology clinic with 127 patients treated orally and 130 receiving intramuscular MTX. After 6 months of MTX therapy, the oral group had a response rate of 58 % which was comparable to that of the intramuscular group with a response rate of 61 %, with identical safety outcomes.[19]

A retrospective study of 55 JIA patients was conducted to document clinical practice using the treat-to-target approach and to substantiate the concept that achieving a greater therapeutic effect with an optimal dose of parenteral MTX is associated with clinically acceptable adverse effects comparable to those reported for oral treatment. 81.8 % of patients were initiated on parenteral MTX and were monitored every 3 months for 12 months. Not only was subcutaneous MTX correlated with a high response rate during the first 12 months of therapy but also with a low risk of severe adverse events requiring treatment discontinuation.[20]

When compared to the adult population, one prospective research was done from December 2004 to December 2005 to study the effectiveness, safety, and compliance of subcutaneous MTX in active RA patients. The trial enrolled 92 active RA patients over a 6-month period. The response rate was substantially greater in the s.c. group for the minimum ACR20 (93% vs. 80%, $P = .02$) and for the ACR50 (89% vs. 72%, $P = .03$). This advantage was not observed in the ACR70 response rate (11% vs. 9%, $P = .72$).[21]

Our study evaluated adverse events and showed that the s.c. cohort was more prone to nausea, vomiting, and increased liver enzymes than patients in the oral cohort which can likely be attributed to a higher drug availability after parenteral injection than after oral application. The adverse events of s.c. cohort, however, were relatively mild not leading to discontinuation of treatment.

Our study has numerous limitations. To begin, this is an unblinded, non-randomized study. Individuals with more severe illness were started on parenteral MTX more frequently

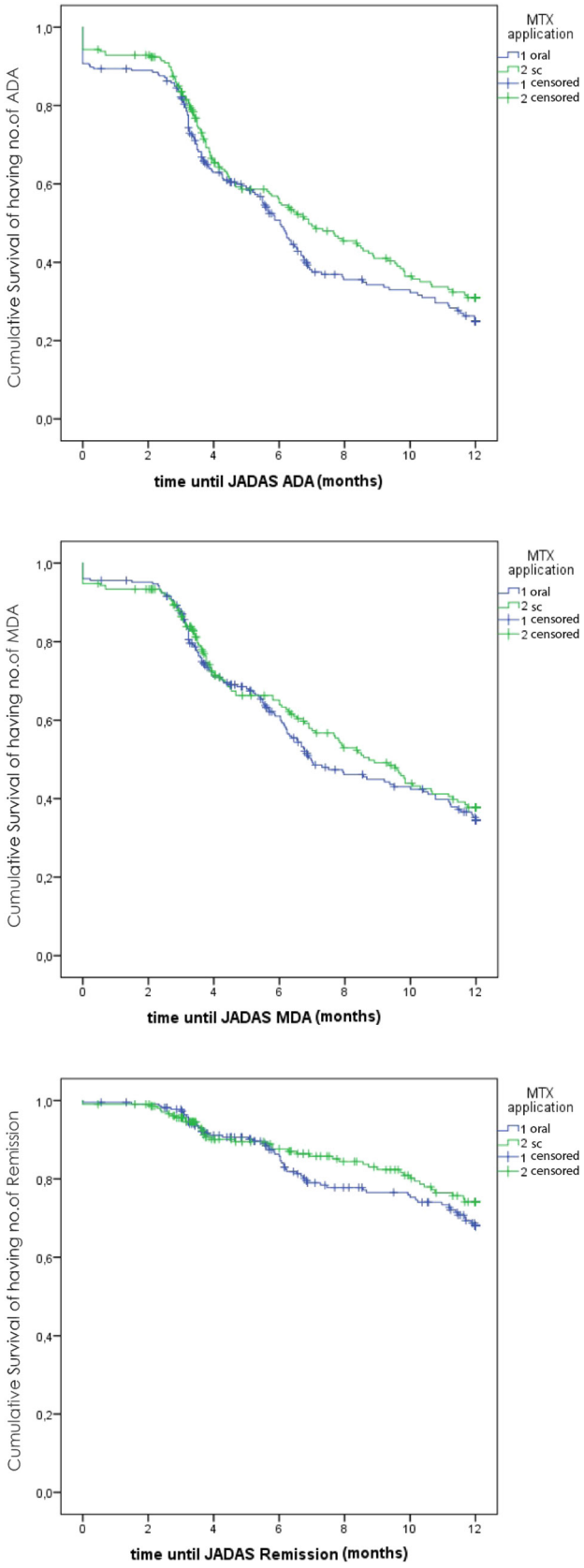


**Figure 4.** Kaplan–Meyer analysis during the first year of treatment. No differences in the kinetics of reaching treatment targets were noted. Obs, observed; s.c., subcutaneous.

based on our baseline disease parameters. Second, we could not be certain of the patient's compliance with MTX when it is taken orally versus when it is administered by injection by parents. Several patients switched from oral to subcutaneous MTX administration or from subcutaneous to oral MTX administration. Although we excluded such cases from the analysis, our data does not provide the causes behind this. Finally, some centers favor one method of administration over the other, while others administer both oral and subcutaneous MTX equally.

During 24 months of MTX therapy, there was a statistically significant difference in the proportion of patients meeting the definitions of PedACR 30, 50, 70, and 90, as well as JADAS10 acceptable disease activity, between the oral and s.c. populations in the intention to treat population. Kaplan–Meyer analysis revealed no statistically significant difference in the kinetics of response to MTX for PedACR 30, 50, 70, and 90 and JADAS10 acceptable disease activity, minimum disease activity, and remission between the 2 groups. The analysis of adverse events revealed that parenteral MTX caused more adverse events than oral MTX.

In conclusion, our retrospective analysis revealed some evidence in favor of s.c. MTX in terms of effectiveness but not in terms of safety. Possibly as a result of the higher blood levels achieved with injectable MTX, nausea, vomiting, and increased transaminases were considerably more frequent with s.c. than with oral administration. Such side effects significantly impair the ability to continue therapy and thus must be viewed as a significant disadvantage.

**Ethics Committee Approval:** Ethical committee approval was received from the Ethics Committee of Aerztekammer Duesseldorf, Germany University, (Approval No: 2/2015/7441).

**Informed Consent:** Written informed consent was obtained from the subject's and parent's.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – R.B., G.H.; Design – R.B., G.H.; Supervision – M.A.K., G.H.; Funding – G.H.; Materials – G.H.; Data Collection and/or Processing – R.B.; Analysis and/or Interpretation – R.B., M.A.K., G.H.; Literature Review – R.B., G.H.; Writing – R.B., G.H.; Critical Review – G.H.

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**Table 2.** Side Effects of MTX Among Oral and S.C. Cohort

| | | Oral, n = 410 | Subcutaneous, n = 384 | $\chi^2$-test *P*, odds ratio [95% CI] |
|---|---|---|---|---|
| Viral infections | Flu | 2 (0.5%) | 4 (1%) | n.s |
| | Gingivitis | 0 (0%) | 3 (0.8%) | n.s |
| | Lymphadenitis | 1 (0.2%) | 0 (0%) | n.s |
| | URTI | 23 (5.6%) | 37 (9.6%) | P=0.032, 1.7[1.0-3.08] |
| | Varicella | 1 (0.2%) | 3 (0.8%) | n.s |
| | Bronchitis | 11 (2.7%) | 9 (2.4%) | n.s |
| | Gastroenteritis | 9(2%) | 15 (4%) | n.s |
| Bacterial infection | Tonsillitis | 6 (1.5%) | 7 (1.8%) | n.s |
| | Otitis media | 3 (0.7%) | 5 (1.3%) | n.s |
| | UTI | 4 (1%) | 3 (0.8%) | n.s |
| GIT side effects | Nausea and vomiting | 144 (35%) | 198 (51%) | *P* > .000,1.9[1.47-2.6] |
| | Increased liver enzyme | 43 (10%) | 71 (18.4%) | *P* = .0001,1.9 [1.3-2.9] |
| | Loss of appetite | 3 (0.7%) | 5 (1.3%) | n.s |
| | Diarrhea | 5 (1.2%) | 3 (0.8%) | n.s |
| | Gastritis | 2 (0.5%) | 4 (1%) | n.s |
| Others | Leukopenia | 4 (1%) | 6 (1.6%) | n.s |
| | Leukemia | 1 (0.5%) | 1 (0.26%) | n.s |
| SAE | Patients with at least one SAE | 2 (0.5%) | 0 (0%) | n.s |
| | Fracture | 4 (1%) | 3 (0.8%) | n.s |
| | Infection | 5(1.2%) | 3(0.8%) | n.s |
| | Neutropenia | 0(0%) | 3(0.8%) | n.s |

URTI, upper respiratory tract infection; UTI, urinary tract infection; GIT, gastro intestinal tract; UTI, urinary tract infection; SAE, serious adverse events.

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