

Overcoming methotrexate intolerance in a paediatric cohort of patients with rheumatic diseases: successful application of a large interval oral split-dose regimen

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Abstract Objective

Methotrexate (MTX) is the most commonly used disease-modifying anti-rheumatic drug to treat rheumatic diseases in children. In more than half of the patients, the conventional once-weekly dosage will lead to MTX intolerance. The objective of this study was to investigate whether pre-existing MTX intolerance can be overcome by switching to a large interval oral split-dose (LIOS) MTX regimen.

Methods

The clinical data of 26 paediatric patients with rheumatic diseases were analysed retrospectively. All patients included wanted to discontinue their once-weekly MTX therapy due to intolerance that did not improve with standard countermeasures. These patients were switched to the LIOS MTX regimen and received the pre-existing amount of MTX, divided into two equal oral doses three and four days apart. To compare side effects before and after changing the administration regimen, we used the Methotrexate Intolerance Severity Score (MISS), collected data on parental psychological distress, and analysed laboratory parameters.

Results

All patients were compliant with their MTX treatment for at least eight months after transitioning to the LIOS MTX regimen (median of 22 months). After six months, the average MISS values decreased from 12.3 to 2.8 ($p < 0.0001$), falling below the threshold of 6 points that indicates MTX intolerance. Additionally, parental psychological distress during drug administration improved in 24 out of 26 cases (92%). No significant changes were noted in disease activity or laboratory parameters.

Conclusion

Switching patients with MTX intolerance to the LIOS MTX regimen allows for long-term continuation of treatment and maintaining disease remission while significantly reducing side effects.

Key words

juvenile arthritis, methotrexate, adverse effects, drug therapy, immunosuppressive agents

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Introduction

Methotrexate (MTX) remains the most commonly used disease-modifying anti-rheumatic drug (DMARD) in juvenile idiopathic arthritis (JIA) and is widely used in treating uveitis, systemic connective tissue diseases, and vasculitis (1-3). MTX plays an important role in the reduction of glucocorticoids and prevention of anti-drug antibodies (1-6). Further advantages of MTX include its widespread availability and the highly favourable cost-effectiveness and efficacy-toxicity ratios (7). However, subjective side effects, such as intolerance, frequently occur during MTX treatment; this issue has not been adequately addressed (8, 9). In children with rheumatic diseases, a conventional once-weekly MTX dosage of 10–20 mg/m² leads to MTX intolerance in up to 50–73% of patients, with intolerance being the most common cause of non-compliance and MTX discontinuation in clinical practice (9-13). An effective countermeasure is the use of oral split-dose regimens, which, in adult patients, have been associated with reduced MTX side effects compared to oral single-dose regimens (14). Additionally, oral split-dose regimens offer superior bio-availability relative to oral single-dose regimens and demonstrate comparable efficacy to both oral and parenteral single-dose treatments (14-17). Based on these data, our study explored whether switching from the conventional once-weekly MTX dosage (either oral or parenteral) to a large interval oral split-dose (LIOS) regimen can overcome pre-existing MTX intolerance in children with rheumatic diseases.

Methods

Assessment of clinical data

Study participants were recruited and followed up by the Division of Paediatric Rheumatology, Department of Paediatrics, University Medical Center Rostock and University Medical Center Hamburg-Eppendorf following ethical approval and written informed consent (protocol no.: A 2019-0039).

We conducted a retrospective analysis of clinical data from 26 children and adolescents with rheumatic diseases and pre-existing MTX intolerance, who

were switched from a once-weekly MTX dosage (either oral or parenteral) to the LIOS regimen (demographic data are shown in Table I). The LIOS therapy regimen was implemented only if the patient refused to continue MTX in the conventional once-weekly dosage, despite the necessity for ongoing therapy, and if at least two of the following countermeasures against intolerance were unsuccessful: switching MTX administration from oral to subcutaneous or *vice versa*, using anti-emetics, or covert dosing by the parents.

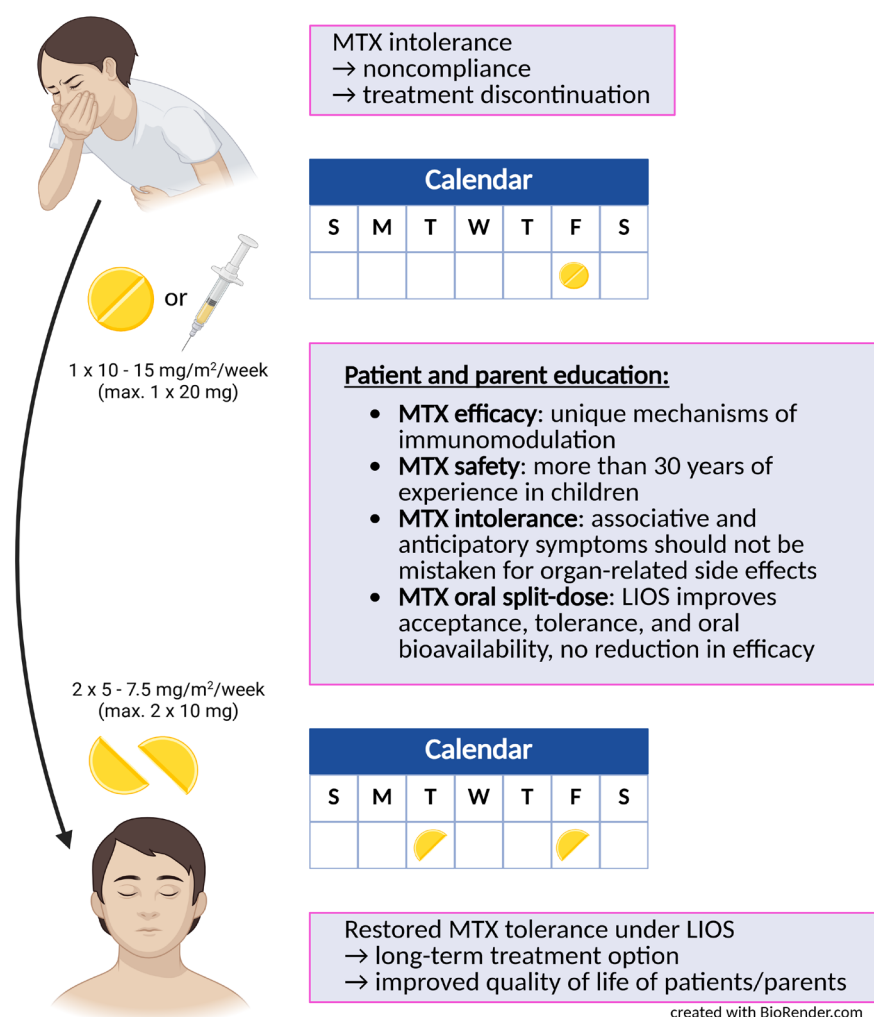
The LIOS regimen was applied as follows: The pre-existing once-weekly MTX dose of 10–15 mg/m²/week (maximum 20 mg) was divided into two reduced oral doses of approximately 50 % each (maximum 10 mg) at three- and four-day intervals. In case of unequal distribution of the single doses, *e.g.* 5 mg (Tuesday) and 7.5 mg (Friday), the higher dose was always taken in the evening on the weekend. It was recommended to administer folic acid at an unchanged dosage 24 hours after the weekend dose of MTX. The duration of LIOS MTX therapy depended on the course of the underlying disease, and in some patients, the MTX split-dose could be successfully reinduced following relapses.

To compare side effects before and after changing the administration regimen, we used the Methotrexate Intolerance Severity Score (MISS) (Supplementary Table S1) questionnaire (score range from 0 to 36 points, previously validated in JIA) (18) and added further questions, for example on mental stress of parents during the drug administration procedure (see online Supplementary file for details). The questionnaire covers the period before the switch to the LIOS MTX regimen and up to six months afterwards. The adherence to MTX intake and consent to the continuation of split-dose MTX therapy by patients and parents were documented during outpatient rheumatology visits conducted every three to six months. In case of relevant and persistent subjective or laboratory side effects, LIOS MTX therapy would have been discontinued immediately. We assessed complete blood count, liver function en-

zymes, lipase, renal function test, IgG, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) three and six months before and after the switch to the LIOS MTX regimen. Disease activity was monitored over the entire observation period in accordance with internationally recognised standards (19). Every three to six months, disease activity was monitored using physician global assessment and disease-specific validated activity scores, depending on the underlying diagnosis. These included the clinical Juvenile Arthritis Disease Activity Score (cJADAS) for patients with juvenile idiopathic arthritis, the childhood Myositis Assessment Scale (CMAS) for patients with juvenile dermatomyositis, and standardised clinical and laboratory assessments for other inflammatory rheumatic diseases. If present, the anti-rheumatic co-medication with NSAIDs or biologic DMARDs remained unchanged or was reduced during the course.

Data analysis

Statistical analysis was performed using GraphPad Prism version 10.2.1 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). For the statistical analysis of the MISS subgroups, two-way ANOVA with the Sidak multiple comparisons test was calculated. For the statistical analysis of total MISS values before and after the switch, a paired t-test was performed. Due to the retrospective nature of the study, data on countermeasures against nausea, pre-administration discussions, need for psychological support, tiredness, hair loss, and susceptibility to infections before and after the switch to the LIOS MTX regimen are not complete for all analysed parameters. Therefore, in these cases, statistical analysis was performed with a mixed-effects model and Sidak multiple comparison test. For statistical analysis of laboratory parameters, data were analysed for normal distribution. As the data passed the normality test, analysis was performed with one-way ANOVA and Tukey test for multiple comparisons. *p*-values are indicated in cases of statistical significance (**p*<0.05, ***p*<0.01, ****p*<0.001, *****p*<0.0001). INKSCAPE ([https://](https://inkscape.org/de/)



Graphical abstract

Table I. Patients' characteristics.

Characteristics	Patients, n=26
Sex, female, n (%)	19 (73.1)
Age, mean (min-max), years	11.5 (3-22)
Diagnosis, n (%)	
Juvenile idiopathic arthritis	16 (61.5)
Uveitis (idiopathic)	3 (11.5)
Juvenile dermatomyositis	3 (11.5)
Sjögren's disease / systemic lupus erythematosus	4 (15.4)
MTX dosage, mean (SD), mg/week	
single-dose	12.9 (3.4)
LIOS	13.6 (2.8)
Folic acid, mean (SD), mg/week	
single-dose	5.4 (2.5)
LIOS	6.8 (2.7)

inkscape.org/de/) was used to produce the figure.

Results

Patients' characteristics

Study enrolment from 2017 to 2019 included a cohort of 26 patients, com-

prising children, adolescents, and one young adult patient in transition to adult care. Table I summarises demographic characteristics and diagnoses. At the time of switching to the LIOS MTX regimen, all 26 patients were in remission of their underlying rheumatic

disease and showed no laboratory evidence of adverse drug reactions despite pronounced subjective MTX intolerance that did not respond to standard countermeasures. Without a change in treatment regimen, all patients refused to continue taking MTX at the time of enrolment. The average duration of pre-treatment with the conventional once-weekly MTX dosage, whether administered orally or parenterally, was 3.5 years.

The follow-up period under the new LIOS MTX regimen varied individually, ranging from 8 months to 7 years. All 26 patients were followed up until at least 2020 (first observational period, median duration of LIOS MTX therapy 22 months). Data for a subgroup of patients continued to be collected until 2024 (second observational period, median duration of LIOS MTX therapy 72 months).

After switching to the LIOS MTX regimen, the total weekly dose of MTX and folic acid was slightly higher than at baseline (Table I). The rationale for this approach was the assumption that the LIOS MTX regimen would result in better MTX tolerance allowing for optimisation of the previously low individually tolerated MTX dosages. A slightly increased dose of folic acid, partly administered as a split dose, was given by some parents independently as a preemptive measure and not as a reaction to documented side effects under the new regimen. This practice was tolerated by the study physicians.

The effect of LIOS MTX regimen on MTX intolerance

We used the MISS questionnaire to quantify MTX intolerance (Supplementary Table S1) (18). Following the introduction of the LIOS MTX regimen, after six months, there was a highly significant reduction in the level of MTX intolerance, from 12.3 to 2.8 ($p < 0.0001$, Fig. 1A), bringing it below the intolerance threshold of 6 points.

At the first evaluation in 2020, all 26 patients were still receiving LIOS MTX, which corresponded to a treatment duration ranging from 8 to 39 months (median 22 months). During the further course of treatment, 12 out

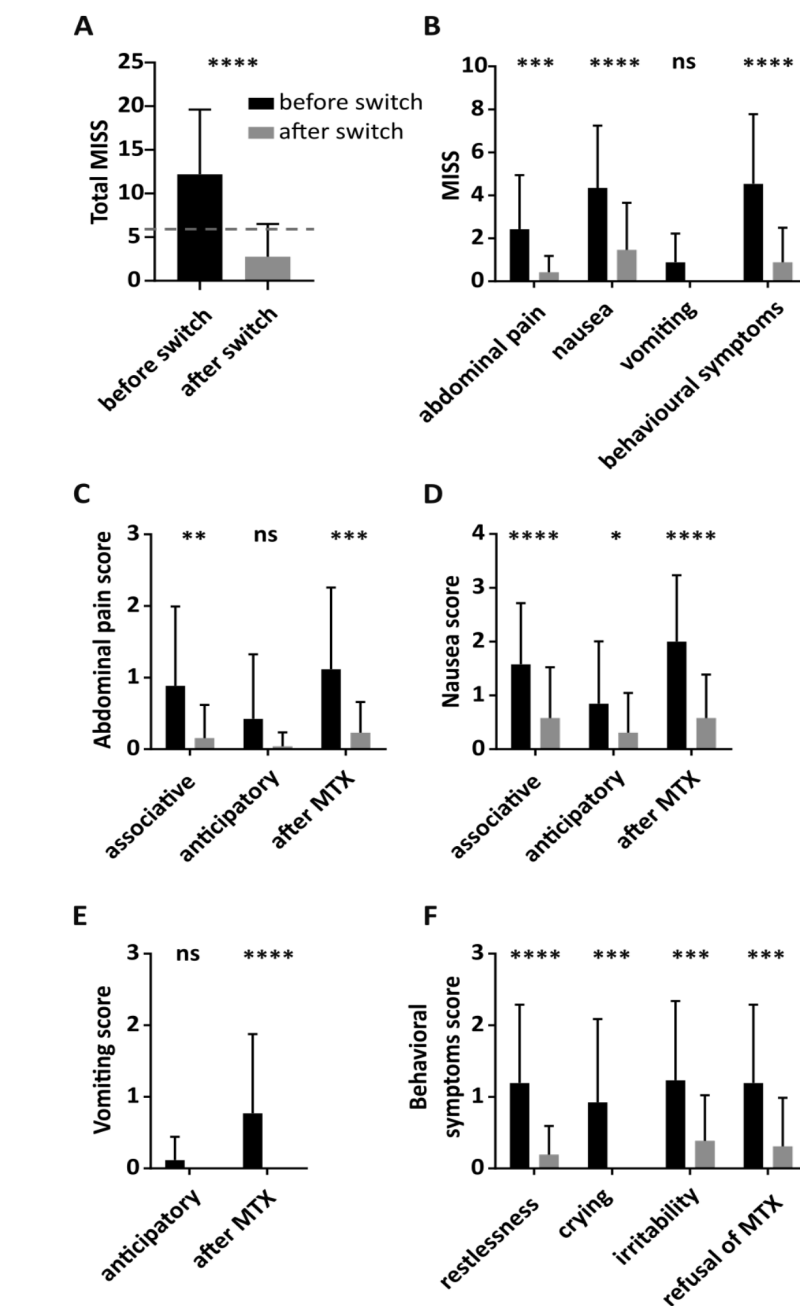


Fig. 1. MTX intolerance during once-weekly dosage and after transitioning to a LIOS MTX regimen. **A:** Overall MISS. MTX intolerance is defined as a score ≥ 6 (dashed line). **B:** Subdomains of MISS. **(C-F)** subdomains in correlation to the time of medication intake, **(C)** abdominal pain, **(D)** nausea, **(E)** vomiting, and **(F)** behavioural symptoms. $n=26$. Statistical analysis was performed with **(A)** paired t-test, and **(B-F)** two-way ANOVA with Sidak multiple comparison test. p -values are indicated.

of 26 (46%) patients were able to discontinue MTX due to a good therapy response. Four out of 26 patients (15%) could be re-treated with LIOS MTX upon experiencing a relapse after previous withdrawal. Nine out of 26 patients (35%) received continuous LIOS MTX therapy due to the severe course of the underlying rheumatic disease. This subgroup was followed during the second

observational period until 2024, with a median duration of LIOS MTX therapy of 72 months. One out of 26 patients (4%) had to discontinue LIOS MTX therapy after 4.6 years due to psychological aversion to all kinds of medication, associated with a newly diagnosed depression.

Evaluation based on subcategories of side effects revealed a significant posi-

tive impact in all four MISS categories, concerning stomachache, nausea, vomiting, and behavioural complaints (Fig. 1B-F). Sub-analyses of MTX intolerance, in correlation with the time of medication intake, revealed significant positive effects on associative abdominal pain and nausea (when thinking of taking MTX), anticipatory nausea (immediately before MTX intake) and post-MTX abdominal pain, nausea and vomiting (Fig. 1B-F). No vomiting was observed in any of the 26 patients on the LIOS MTX regimen. Additionally, there was a significant decline from 92% to 8% of patients who needed countermeasures (antiemetic treatment or covert dosing) against MTX intolerance (Fig. 2).

As the perception of MTX intake became more positive, there was a highly significant improvement in long pre-administration discussions (>5 minutes) between parents and patients. Two additional questions assessed whether the overall burden on parents and patients had decreased and whether long-term MTX therapy was considered feasible following the switch to the LIOS MTX regimen. The vast majority of parents and patients (92%) responded affirmatively to both. Further questions answered by the patients and parents about potential side effects of the LIOS MTX regimen revealed no significant change in general psychological support, tiredness, hair loss, or susceptibility to infections (Fig. 2). For information on the additional questionnaire for patients/parents, see Appendix 1 in the online Supplementary file.

The effect of LIOS MTX regimen on laboratory parameters and disease activity

We checked for laboratory side-effects (complete blood count, liver function enzymes, lipase, renal function test), inflammation (CRP, ESR) and immunological parameters (differential blood count, IgG) three and six months before and after the switch to the LIOS MTX regimen, respectively (see Appendix 2 in the online Supplementary file). Overall, there was no significant change in the side effect profile, inflammation, or immunological parameters after

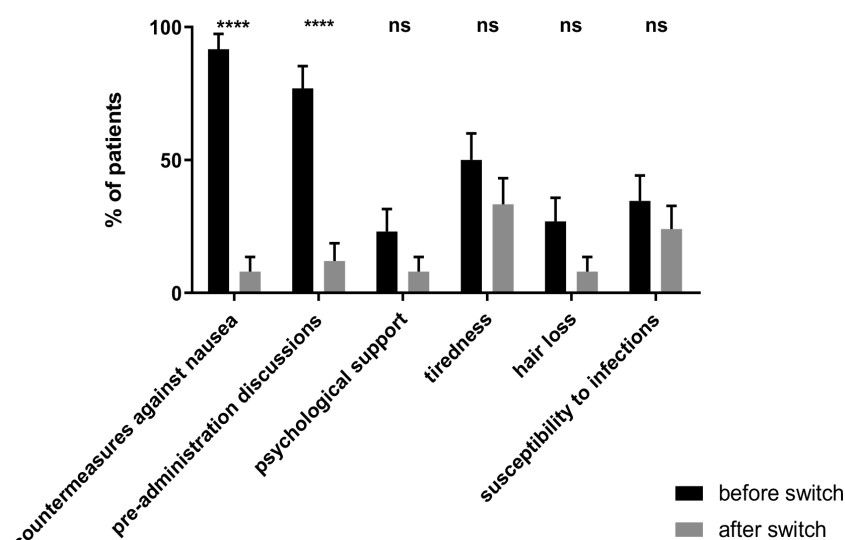


Fig. 2. Symptoms and mental stressors exceeding those inquired with MISS. Use of countermeasures against nausea, pre-administration discussions, need for psychological support, unspecific and not directly related to MTX intolerance, tiredness, hair loss, and susceptibility to infections were evaluated before and after the switch to the LIOS MTX regimen. n=26, but data points are not complete for all patients. Statistical analysis was performed with mixed-effects model and Sidak multiple comparison test. *p*-values are indicated.

switching to the LIOS MTX therapy regimen (Fig. 3).

All patients on ongoing LIOS MTX therapy remained in remission of the underlying rheumatic disease at the end of the first observation period (8–39 months after switching to LIOS MTX regimen), as assessed by physician global evaluation and disease-specific validated disease activity scores (including cJADAS, CMAS, and SLE-DAI, as applicable).

Discussion

MTX intolerance in children with rheumatic diseases represents a major obstacle to successful and sustainable anti-rheumatic treatment and leads to significant loss of quality of life in the affected children. The conventional once-weekly regimen of MTX used globally in children with rheumatic diseases leads to MTX intolerance in up to 73% of paediatric patients (13). Currently, the most frequently used countermeasures, in addition to folic acid, include antiemetics, covert dosing and changing the route of administration (subcutaneous *vs.* oral). There is little evidence to support that these countermeasures reduce MTX intolerance in the long term (12, 13). In our cohort, patients were included if at least two of

the mentioned countermeasures against MTX intolerance were not successful and patients and parents refused further treatment.

To our knowledge, this study is the first to explore the influence of large interval oral split-dose (LIOS) MTX regimen on pre-existing MTX intolerance in paediatric patients with rheumatic diseases, by dividing the current once-weekly MTX dose into two reduced oral doses of approximately 50% each (maximum 10 mg) at three- and four-day intervals.

Based on earlier pharmacokinetic studies, circulating plasma concentrations of MTX and its primary metabolite, 7-hydroxymethotrexate (7-OH-MTX), decline substantially within the first 48 hours after administration, suggesting that toxicity is significantly reduced after three days (20–22). This observed decline in plasma levels provides a rationale for our extended-interval dosing strategy. Accordingly, longer intervals between reduced single doses were implemented to minimise accumulation and potentially improve tolerability by lowering peak plasma concentrations. This therapeutic approach is also consistent with the general clinical experience that post-MTX side effects in children with rheumatic disease usually

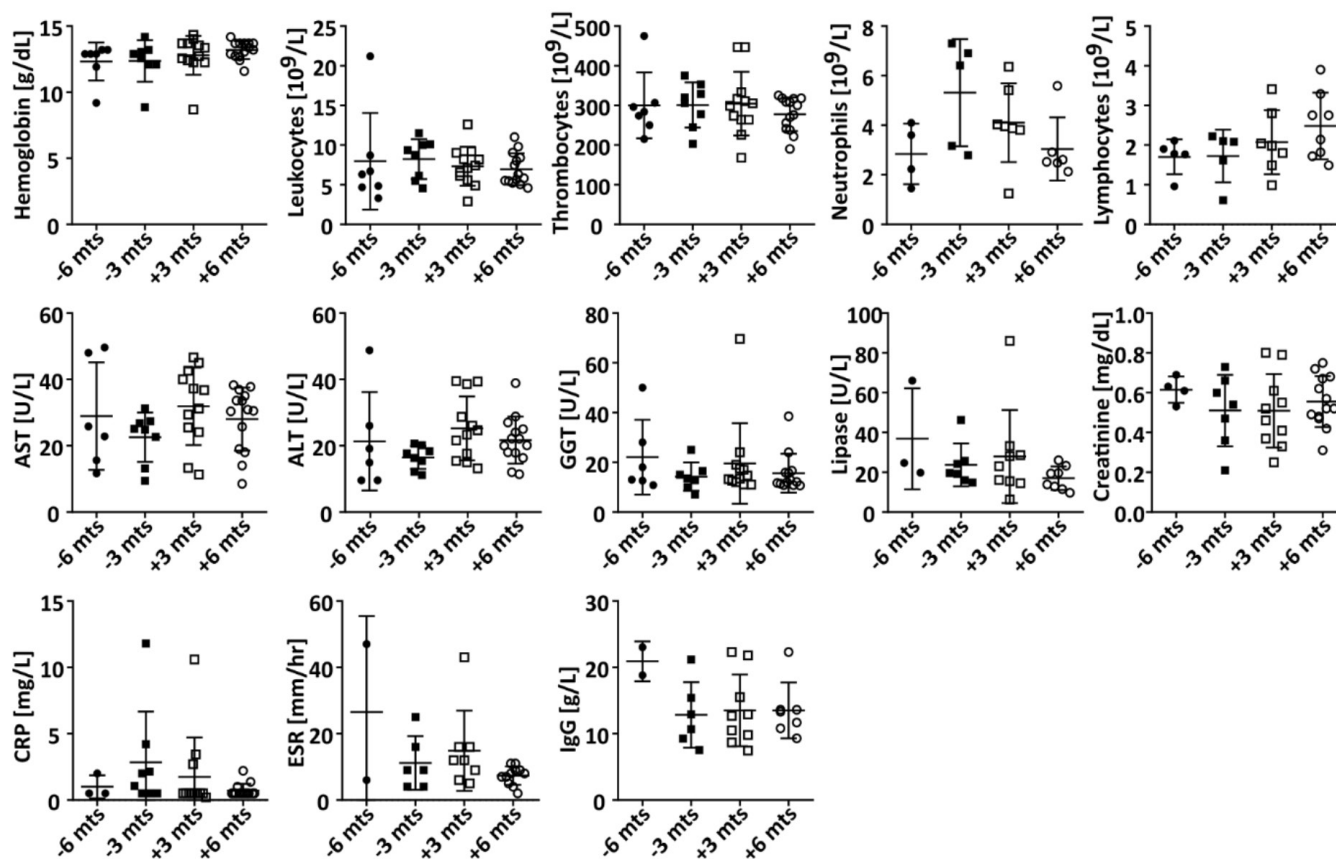


Fig. 3. Laboratory parameters three and six months before and after the switch to LIOS MTX regimen.

n=26, but data points are not complete for all patients at all time points. Statistical analysis was performed with one-way ANOVA and Turkey test for multiple comparisons. No statistically significant differences were found.

resolve within 48(–72) hours and that lower MTX doses up to a maximum of (5–)7.5 mg/m² (e.g. in periods of MTX tapering or co-medication for biological therapies) are often better tolerated than higher MTX single doses. In addition, previous use of MTX split-dose regimens in small case series in adults showed a reduction of subjective MTX side effects, superiority in terms of bioavailability, and non-inferiority in terms of efficacy (14–17).

We used the MISS questionnaire to quantify MTX intolerance before and after the change in therapy regimen. MTX intolerance was diagnosed if the total score was ≥ 6 points, along with a score ≥ 1 for associative, anticipatory and/or behavioural components (18). Six months after switching to the LIOS MTX regimen, average MISS values decreased from 12.3 to 2.8, and thus below the threshold that defines MTX intolerance. In particular, the complete absence of pre-MTX and post-MTX vomiting, along with the highly signifi-

cant reduction in distressing post-MTX nausea, likely played a key role in the long-term restoration of general MTX tolerance and compliance with the LIOS regimen. This interpretation was informally supported by patient and parent feedback obtained during routine outpatient visits. Consistent with these findings, there was a significant decrease in all four measured behavioural complaints of the MISS questionnaire including restlessness, irritability, refusal and crying when taking MTX. The additional questions that go beyond the MISS also showed a positive impact on the daily lives of parents and children after switching to the LIOS MTX regimen. There was a highly significant improvement in the duration and nature of pre-administration discussions between parents and patients. In addition, the majority of parents and patients (92%) stated that they felt relief from the LIOS MTX regimen and that they could now imagine long-term MTX therapy again. The need for countermeasures like anti-

emetic treatment or covert dosing of MTX decreased significantly.

In line with this, all 26 patients with pre-existing MTX intolerance were able to continue LIOS MTX therapy for at least eight months. Approximately half of the patients were able to discontinue MTX during further follow-up. The other half had to continue their treatment for a longer period of time, due to severe or relapsing rheumatic disease and tolerated LIOS MTX therapy up to 7 years. One patient had to stop LIOS MTX after 5 years due to subjective intolerance to all medications in the context of newly diagnosed depression. This case is a reminder of the psychological burden of chronic diseases. Although dysfunctional coping mechanisms in dealing with stressors such as medication side effects may play a role in the development of MTX intolerance, targeted psychological interventions such as behavioural therapy or eye movement desensitisation and reprocessing (EMDR) could only partially and temporarily (on

average for 4 months) reduce MTX intolerance in children with JIA who all continued to receive a conventional once-weekly dose of MTX (13, 23, 24). At the time of the switch to the LIOS MTX regimen, none of our patients was receiving targeted psychotherapy for MTX intolerance.

In a small number of cases (4 of 26) displaying fear of split-dose MTX, modifications in framing or communication, for example referring to MTX as a 'new drug' after switching to the LIOS regimen, temporally coincided with improved tolerance. These anecdotal observations should be interpreted cautiously and are not intended to imply a therapeutic effect, but merely highlight the potential role of cognitive and contextual factors in MTX intolerance. In contrast, under the previous conventional once-weekly regimen, intolerance symptoms such as post-dose nausea were reported despite attempts at covert administration.

Although many patients reported no side effects after the change to the LIOS MTX regimen, some continued to experience residual, albeit attenuated, symptoms. We would therefore suggest that future studies explore whether an earlier change in therapy, at the first signs of uncontrollable post-MTX nausea, may prevent the development of associative and anticipatory symptoms. In the context of significantly reduced post-MTX side effects with the LIOS MTX regimen, additive psychotherapy in individual cases with residual associative and anticipatory pre-MTX symptoms might prove more effective and warrants prospective evaluation in future studies.

After switching to the LIOS regimen, MTX continued to show its good overall safety profile which, however, is known to include transient mild cytopenias and elevation of transaminases in individual cases, but without significant or permanent changes in laboratory parameters after a total of six months of follow-up. There were no serious adverse events and no discontinuation of treatment due to laboratory side effects over the entire follow-up period. A recent study investigating short 12 hour interval oral split-dose MTX regimen in adults reported a slight increase

in the frequency of transaminitis (25). In our study, all patients received folic acid the day after MTX administration during conventional once-weekly MTX dosage. After changing to LIOS MTX regimen, a subgroup of the patients decided on their own authority to take folic acid also divided into two doses per week, each 24 hours after MTX. This decision was preventive in nature, rather than a response to documented side effects. The mean dose of folic acid increased from 5.4 mg to 6.8 mg per week, in parallel MTX increased from 12.9 mg to 13.6 mg per week, neither was statistically significant. There is little evidence that increasing the already high pre-existing folic acid intake reduces MTX intolerance (13), but we cannot rule out a certain supportive effect. During the initial observational period, all patients maintained inactive disease.

Limitations of this study include its retrospective nature, small sample size, and the heterogeneity of the rheumatic diseases included. Hence, it is beyond the scope of this study to investigate whether starting therapy with LIOS MTX regimen could prevent the development of MTX intolerance while maintaining effectiveness compared to conventional once-weekly MTX dosage. In addition, potential sources of bias inherent to the retrospective and uncontrolled design must be considered. Selection bias cannot be excluded, as only patients with pronounced MTX intolerance who refused continuation of conventional once-weekly MTX therapy despite standard countermeasures were included. Furthermore, expectation and placebo effects related to the introduction of a perceived 'new' treatment strategy, as well as increased clinical attention during the treatment switch, may have contributed to the observed improvement in subjective MTX intolerance. Therefore, the magnitude of the observed effects should be interpreted with caution, and causality cannot be inferred with certainty.

The cohort included patients with different rheumatic diseases and varying treatment durations, as well as patients in sustained clinical remission at the time of switching to the LIOS MTX

regimen. While this heterogeneity reflects real-world clinical practice in paediatric rheumatology, it may limit disease-specific conclusions. In particular, remission at baseline may have positively influenced treatment adherence and subjective tolerability, independent of the administration regimen. Accordingly, the present findings primarily support the feasibility and tolerability of the LIOS MTX regimen across a heterogeneous paediatric rheumatology population, rather than allowing conclusions regarding disease-specific efficacy or comparative effectiveness between disease entities.

Nevertheless, within these limitations, the consistent and sustained improvement in MTX tolerability observed across the cohort suggests potential clinical relevance of the LIOS MTX regimen in routine care. Further implications of an improved subjective tolerability of the MTX LIOS regimen combined with highly favourable cost-efficacy-toxicity ratios of MTX could even lead to a new discussion about the duration of MTX treatment in children with rheumatic diseases. In our centre, this discussion has already been initiated by patients and parents with an individual willingness to opt for a longer term LIOS MTX therapy in severe or relapsing disease courses.

In conclusion, switching children with rheumatic diseases and pre-existing MTX intolerance to the LIOS MTX regimen enables long-term continuation of treatment with significantly reduced side effects and without affecting individual disease activity or laboratory parameters. The easy implementation of the LIOS MTX regimen could become a valuable tool for children with rheumatic diseases worldwide, particularly in regions where access to biologic or targeted synthetic DMARDs is limited.

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