

Supplementary material

Appendix 1. Questionnaire. Further questions to evaluate MTX tolerance/intolerance (The questionnaire was given to the families in German).

Further questions

Total duration of MTX treatment before and after adjustment

- **Previous** MTX once a week: for a total of _____ months / years (please circle)
- **New** MTX twice a week: for a total of _____ months / years (please circle)

Type of MTX therapy before adjustment

- **Previously**, I had MTX as a ☐ injection ☐ tablet ☐ liquid for oral intake

Dosage of MTX therapy before and after adjustment

- **Previous** MTX: _____ mg once a week + folic acid _____ mg
- **New** MTX: _____ mg twice a week + folic acid _____ mg

Tricks we tried earlier to counteract nausea:

- Switching from injection to tablet or liquid for oral intake
- “Hidden” administration
- Anti-nausea medication: ☐ Zofran/Ondansetron ☐ Vomex
- MediCoat swallowing aid (☐ before adjustment ☐ after adjustment)

Are these tricks to counteract nausea still needed after the adjustment?

- Yes
- No

After switching to two smaller doses of MTX per week, would a long-term MTX therapy (*e.g.* for one more year) be feasible for you again?

- Yes
- No

	<u>Before the switch</u> MTX once a week	<u>After the switch</u> MTX twice a week
Fatigue	☐ yes ☐ no	☐ yes ☐ no
Hair loss	☐ yes ☐ no	☐ yes ☐ no
Susceptibility to infections or frequent MTX breaks due to infections (>3 per year)	☐ yes ☐ no	☐ yes ☐ no
Long discussions about taking MTX (>5 minutes)	☐ yes ☐ no	☐ yes ☐ no
Psychological support needed	☐ yes ☐ no	☐ yes ☐ no

Has the burden on you as parents or the patient decreased after switching to two smaller doses of MTX per week?

- Yes, as parents we feel a relief, which is (please circle) very strong / strong / moderate / only slight
- No (burden remains the same)

Appendix 2. Documentation by the physician

Physician documentation

Name: _____ First name: _____
 Date of birth: _____ Weight: _____ Height: _____
 BSA: _____ m² Sex: w/m
 Date of MTX split-dose start: _____ ≥ Age at start: _____
 Duration of MTX split-dose: _____
 Rheumatology diagnosis: _____
 ANA positive ☐ negative ☐ **HLAB27** positive ☐ negative ☐ **RF** positive ☐ negative ☐

Secondary diagnoses:

1. _____
2. _____
3. _____

Co-medications:

1. _____
2. _____
3. _____

Disease activity:

1. Before the adjustment, all patients were in remission
2. After the adjustment: ☐ Inactive disease ☐ CR ☐ physician's global score of <1 ☐ Relapse

- Joint infiltrations despite baseline therapy: yes/no: before/after
- MTX dose before:mg/week; absolute dose =mg/m²/week;
and aftermg/week; absolute dose =mg/m²/week.
- Folic acid dose: absolute dose in mg/week: _____ mg before/after
- Therapy discontinuation due to side effects before/after
- Abdominal ultrasound: Liver parenchyma abnormalities? yes / no

Lab values: Measurements before (6–12 months, contact general paediatrician if necessary) and after (at least 3 months), document all findings with dates ≥ intervals from the switch to split-dose must be calculable (attach printouts of lab sheets)

Parameter	Before adjustment	After adjustment
Leukocytes		
Neutrophils		
Lymphocytes		
Haemoglobin		
MCV		
MCH		
Platelets		
CRP		
ESR		
Transaminitis with MTX pauses known in patient yes/no: before/after		
ASAT		
ALAT		
GGT		
Lipase		
Creatinine		
IgG		
IgM		

Supplementary Table S1. Methotrexate intolerance severity score (MISS).

	No complaints	Complaints (score 1-3 points)		
	0	Mild 1	Moderate 2	Severe 3
Stomachache				
My child has a stomachache after taking MTX	☐	☐	☐	☐
My child has a stomachache several hours to one day before taking MTX	☐	☐	☐	☐
My child has a stomachache when thinking of MTX	☐	☐	☐	☐
Nausea				
My child is nauseous after taking MTX	☐	☐	☐	☐
My child is nauseous several hours to one day before taking MTX	☐	☐	☐	☐
My child is nauseous when thinking of MTX	☐	☐	☐	☐
Vomiting				
My child vomits after taking MTX	☐	☐	☐	☐
My child vomits hours to one day before taking MTX	☐	☐	☐	☐
Behavioural complaints				
My child is restless when taking MTX	☐	☐	☐	☐
My child cries when taking MTX	☐	☐	☐	☐
My child is irritable when taking MTX	☐	☐	☐	☐
My child refuses to take MTX	☐	☐	☐	☐