

Real-world Methotrexate Use in a Prospective Cohort of Paediatric Patients with Plaque Psoriasis: Effectiveness, Adverse Events and Folic Acid Regimen

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In paediatric psoriasis, few studies have evaluated methotrexate effectiveness, adverse events and folic acid regimen. Therefore this study prospectively assessed methotrexate adverse events and effectiveness in paediatric patients with psoriasis in a real-world setting. Furthermore, gastrointestinal adverse events and methotrexate effectiveness were compared between folic acid regimens (5 mg once weekly vs 1 mg 6 times weekly). Data for paediatric patients with psoriasis treated with methotrexate from September 2008 to October 2020 were extracted from Child-CAPTURE, a prospective, daily clinical practice registry. Effectiveness was determined by Psoriasis Area and Severity Index (PASI). Comparison of persistent gastrointestinal adverse events between folic acid regimens were assessed through Kaplan–Meier analysis. A total of 105 paediatric patients with plaque psoriasis (41.0% male, mean age 14.1 years) were included. At week 24 and 48, an absolute PASI ≤ 2.0 was achieved by approximately one-third of all patients. During follow-up, 46.7% reported ≥ 1 persistent adverse events. After 1 and 2 years, approximately one-quarter of patients achieved a PASI ≤ 2.0 without persistent adverse events. Although non-significant, a possible trend towards lower occurrence of gastrointestinal adverse events was found for folic acid 1 mg 6 times weekly ($p = 0.196$), with similar effectiveness between folic acid regimens. These findings show that a subgroup of paediatric patients with psoriasis responded well to methotrexate treatment without considerable side-effects during a 2-year follow-up.

Key words: psoriasis; paediatric; methotrexate; effectiveness; adverse events; folic acid.

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Methotrexate (MTX) is frequently prescribed as a first-line systemic treatment for paediatric patients with psoriasis (1). Although it is commonly used, evidence on the effectiveness and safety of MTX in the paediatric psoriasis population is sparse, with only a

SIGNIFICANCE

Although methotrexate is commonly prescribed as a systemic treatment for paediatric patients with psoriasis, evidence on its effectiveness and safety in this population is sparse. This study of 105 paediatric patients treated with methotrexate was therefore conducted, and showed that an absolute Psoriasis Area and Severity Index ≤ 2.0 was achieved by 30.4% and 35.3% of patients after, respectively, 1 and 2 years. Although almost half of patients reported at least 1 persistent adverse event, 26.5% and 22.5% achieved a Psoriasis Area and Severity Index ≤ 2.0 without persistent adverse events after, respectively, 1 and 2 years. Therefore, this study shows that a subgroup of paediatric patients with psoriasis responded well to methotrexate treatment without considerable side-effects during 2-year follow-up.

few retrospective studies (1–4) and 1 small ($n=25$) prospective study (5) assessing MTX effectiveness and/or safety in a real-world setting. In addition, 1 randomized clinical trial compared adalimumab with MTX ($n=37$) in paediatric patients with psoriasis (6).

Folic acid (FA) is supplemented during MTX treatment to reduce the hepatic and gastrointestinal adverse events (GI-AEs) (1, 7–9). To date, there is no consensus for FA timing and dosing in the treatment of psoriasis. Current Dutch and European consensus is to administer FA once weekly (7, 10), whereas recent American guidelines advise FA 1 mg daily or 6 days per week (8). Only 3 retrospective studies have compared these different FA regimens in patients with rheumatoid arthritis (11, 12) and in paediatric patients with psoriasis (1), which all showed a greater beneficial effect on AEs when FA was given 6 or 7 days per week compared with once weekly supplementation.

In recent years, with the approval of many biologic agents for paediatric psoriasis, the treatment landscape for paediatric patients with psoriasis is changing. In view of extracutaneous comorbidities and the potential for lifelong chronicity, the paediatric psoriasis treatment paradigm is shifting towards a potentially more aggressive management in a subset of children (13). In order to ascertain the role of MTX treatment in this changing treatment landscape, it is important to gain more prospective real-world evidence on MTX effectiveness and

safety. Given the fact that absolute treatment outcomes are currently becoming increasingly important (14–16), this study aimed to assess MTX effectiveness using both relative and absolute treatment outcomes, and safety in a large prospective, daily clinical practice cohort of paediatric patients with psoriasis. Furthermore, the occurrence of GI-AEs and MTX effectiveness were compared between FA supplemented 5 mg once weekly vs 1 mg 6 times per week.

METHODS

Registry and data collection

Data for this study were extracted from the Continuous Assessment of Psoriasis Treatment Use Registry (Child-CAPTURE), a single-centre, observational, prospective, daily clinical practice cohort. This ongoing cohort includes all children (<18 years at first visit) with the diagnosis of psoriasis who attended the outpatient clinic of the Department of Dermatology at the Radboud University Medical Centre in Nijmegen, the Netherlands, between September, 2008 and October 2020 (data-lock). Patients included in the registry who reach the age of 18 years are followed as young adults. This study was reviewed by the ethics committee and was deemed to not fall within the remit of the Medical Research Involving Human Subjects Act. Written informed consent was obtained from the parents or guardians and/or from the participating patients according to applicable rules.

Patient selection

All paediatric patients with plaque psoriasis that initiated MTX treatment at some point during follow-up in the Child-CAPTURE were included in this study. Patients were excluded from the study if they received any other systemic therapy concomitant with MTX, if they were treated with MTX primarily for psoriatic arthritis or if they were previously treated with MTX (before inclusion in the Child-CAPTURE). In case of multiple MTX treatment episodes during follow-up, only the first treatment episode was included in analyses. Patients with a treatment duration <12 weeks were included only if they discontinued MTX treatment before 12 weeks due to an AE.

Patient and treatment characteristics

Baseline characteristics including sex, type of psoriasis, age and psoriasis duration were collected at first visit. Psoriasis severity was measured with the Psoriasis Area and Severity Index (PASI [range 0–72]) at baseline and at every follow-up visit. In general, visits took place every 12 weeks during the first year of treatment and every 12–24 weeks thereafter. If necessary (e.g. in case of an AE or loss of effectiveness), additional patient contacts were planned. MTX treatment characteristics were captured, including start date, dose, route of administration (oral or subcutaneous), FA regimen and, if applicable, reason for discontinuation. MTX dosage was 15 mg/m²/week or 15 mg/week if body surface area was >1 m² at treatment initiation with increase during follow-up if needed until a maximum of 20 mg/week for oral and 25 mg/week for subcutaneous administration and a taper if tolerated. Furthermore, patients could switch from oral to subcutaneous administration during follow-up if needed.

Adverse events

All AEs were documented in preselected categories according to the Common Terminology Criteria for Adverse Events (17).

Additional AEs could be entered as free text in case it did not fit within a preselected category. In addition, the date of AE onset and investigator opinion on the correlation of the AE with MTX were reported. Each AE was categorized as either transient, defined as an AE that was resolved before the next patient contact, or persistent, defined as an AE that was reported during at least 2 consecutive patient contacts. A serious AE was defined as an event that resulted in death, was life threatening, required inpatient or prolonged hospitalization or resulted in persistent or significant disability.

Folic acid regimens

At the start of the Child-CAPTURE registry in September 2008, patients being treated with MTX received FA 5 mg once weekly, according to Dutch guidelines (7). However, in reaction to our publication in which FA 6 times per week was associated with fewer MTX-induced GI-AEs compared with once weekly (1), from November 2016 onwards patients who initiated MTX were given FA 1 mg 6 times per week. Therefore we were able to compare FA regimens through a quasi-experimental design (18) with a more recent cohort (November 2016 to October 2020) using FA 6 times per week and a "historical" comparison cohort (September 2008 to November 2016) using FA once weekly from the same registry.

Statistical analysis

Patient and treatment characteristics were presented as means (SD) in case of normal distributed continuous variables or medians (IQR) in case of non-normal distributed continuous variables and numbers (percentage) for categorical variables. Safety data were summarized as the number (percentage) of patients developing

Table 1. Patient and treatment characteristics of all paediatric patients with plaque psoriasis at start of methotrexate treatment (n = 105)

Characteristics	
<i>Patient characteristics</i>	
Sex (male), n (%)	43 (41.0)
Age, years, mean (SD) [range]	14.1 (3.1) [5.7–17.9]
BMI ^a , n (%)	
Underweight	9 (8.6)
Normal weight	74 (70.5)
Overweight/obesity	22 (21.0)
Psoriasis location ^b , n (%)	
Scalp	104 (99.0)
Inverse	47 (44.8)
Unguiform	17 (16.2)
Psoriasis duration, median (IQR) [range]	4.1 (4.8) [0.3–14.7]
PASI (0–72), mean (SD) [range]	10.2 (6.2) [3.0–42.4]
Body surface area (0–100), mean (SD) [range]	14.7 (13.2) [2.5–76.0]
PGA (0–5), mean (SD) [range]	3.3 (1.0) [1.0–5.0]
CDLQI (0–30), mean (SD) [range]	10.2 (5.0) [1.0–24.0]
<i>Treatment characteristics</i>	
Dose, mg/kg/week ^c , mean (SD) [range]	0.27 (0.09) [0.02–0.51]
Administration route, n (%)	
Oral	103 (98.1)
Subcutaneous	2 (1.9)
Folic acid regimen, n (%)	
5 mg once weekly	48 (45.7)
1 mg 6 times per week	53 (50.5)
Both	4 (3.8)

^aCut-offs for overweight/obesity were based on the extended International Obesity Taskforce (IOTF) body mass index (BMI) cut-offs for thinness, overweight and obesity by Cole et al. ^bTotal number of patients does not equal sum of patients reporting different locations of psoriasis because more than 1 location of psoriasis can be reported in the same patient. ^cFour patients initiated MTX at the start of the Child-CAPTURE with a test dose (<0.1 mg/kg/week), which was increased after several weeks if treatment was tolerated. All other patients initiated treatment with a dose of 15 mg/m²/week or 15 mg/week if BSA >1 m². CDLQI: Children's Dermatology Life Quality Index; IQR: interquartile range; PASI: Psoriasis Area and Severity Index; PGA: Physician Global Assessment; SD: standard deviation.

≥ 1 treatment-related AE and the number (percentage) of patients developing ≥ 1 persistent treatment-related AE (i.e. not including transient AEs).

To evaluate MTX effectiveness, the percentage of patients achieving (i) at least a 75% PASI reduction (PASI 75), (ii) at least a 90% PASI reduction (PASI 90), (iii) an absolute score of PASI ≤ 3.0 and (iv) an absolute score of PASI ≤ 2.0 were determined every 12 weeks up to 96 weeks. PASI scores at exact time-points were obtained with interpolation using the 2 PASI scores closest before and after these time-points. Since the inclusion of patients in the Child-CAPTURE and MTX initiation is continuously ongoing, some patients might only have a short follow-up time at time of data-lock, although still being actively treated with MTX. Hence, patients had different follow-up times at data-lock, with patients who discontinued MTX or were lost to follow-up, but also patients who were active on treatment at data-lock (Fig. S1). Therefore, 2 methods were applied to assess effectiveness: (i) as treated analysis and (ii) last observation carried forward (LOCF) analysis. Clopper-Pearson confidence interval was used to calculate the exact confidence intervals for the presented proportions.

Comparison of GI-AEs occurrence between FA regimens was assessed through Kaplan–Meier survival analysis, since this analysis allows for varying follow-up times of patients in both regimens. One-minus-survival curves of the FA regimens were compared with a Cox regression analysis with correction for possible confounders. To compare effectiveness between FA regimens, the percentage of patients achieving an absolute PASI ≤ 3.0 and ≤ 2.0 in both FA groups was assessed at weeks 12, 24, 36 and 48. Logistic regression analysis was performed to compare effectiveness between FA regimens. For both the Cox regression analysis and logistic regression analysis the following possible confounders at start of MTX were included: sex, age, body mass index, and MTX dose in mg/kg. Only confounders that altered the unadjusted exposure-outcome effect by 10% or more were retained in the models. For all statistical analyses a *p*-value < 0.05 was considered significant. Analyses were conducted with SPSS, version 25.0 (IBM SPSS Inc., Armonk, NY, USA) and SAS, version 9.2 (SAS Institute Inc., Cary, NC, USA). All analyses were supervised by a senior statistician (HMMG).

RESULTS

Patient and treatment characteristics

Patient and treatment characteristics of 105 paediatric patients with plaque psoriasis are shown in **Table I**. The mean and median follow-up time were 1.8 (1.6) and 1.3 (1.6) (0.1–8.0) years, respectively. Fig. S1 shows the treatment status of patients during follow-up. At time of data-lock, 66 (62.8%) patients had discontinued MTX treatment: 19 (18.1%) due to ineffectiveness, 28 (26.7%) due to AEs, 10 (9.5%) due to both ineffectiveness and AEs, and 9 (8.6%) due to other reasons including remission of psoriasis (*n* = 5), patients' own decision (*n* = 2) and desire to consume alcohol (*n* = 2). The mean MTX dose at start of treatment was 0.27 mg/kg/week. Only 2 patients initiated MTX subcutaneously, but

during follow-up 34 switched from oral to subcutaneous administration.

Forty-eight (45.7%) patients used FA 5 mg once weekly, 53 (50.5%) used FA 1 mg 6 times per week and 4 (3.8%) patients switched from FA once weekly to 6 times per week or vice versa during follow-up. A comparison of patient and treatment characteristics between FA regimens is shown in Table SI. Only the mean follow-up time differed significantly, with a shorter mean treatment duration for patients with FA 6 times per week (1.1 [SD 0.8] years) vs once weekly (2.4 [SD 2.0] years, *p* < 0.001).

Adverse events

Table II summarizes the percentage of patients experiencing ≥ 1 treatment-related AE and ≥ 1 persistent treatment-related AE. Overall, 90 (86.7%) patients experienced ≥ 1 AE and 49 (46.7%) experienced ≥ 1 persistent AE. GI-AEs were reported most frequently, with

Table II. Adverse events (AEs) in paediatric patients with plaque psoriasis treated with methotrexate (*n* = 105)

	Number of patients developing ≥ 1 AE, <i>n</i> (%)		≥ 1 persistent AE, <i>n</i> (%)	
	All patients (<i>n</i> = 105)	All patients (<i>n</i> = 105)	Patients with FA once weekly (<i>n</i> = 48)	Patients with FA 6 times weekly (<i>n</i> = 53)
Total AEs	90 (86.7)	49 (46.7)	29 (60.4)	17 (32.1)
Gastrointestinal AEs, total	75 (71.4)	41 (39.0)	23 (47.9)	15 (28.3)
Nausea	64 (61.0)	37 (35.2)	22 (45.8)	12 (22.6)
Abdominal pain	24 (22.9)	15 (14.3)	10 (20.8)	5 (9.4)
Vomiting	15 (14.3)	7 (6.7)	5 (10.4)	1 (1.9)
Loss of appetite	15 (14.3)	10 (9.5)	4 (8.3)	6 (11.3)
Diarrhoea	10 (9.5)	2 (1.9)	0	2 (3.8)
Dyspepsia	11 (10.5)	2 (1.9)	2 (4.2)	0
Oral ulcers	6 (5.7)	0	0	0
Dysphagia	2 (1.9)	1 (1.0)	1 (2.1)	0
Constipation	1 (1.0)	0	0	0
General AEs	49 (46.7)	25 (23.8)	14 (29.2)	10 (18.9)
Fatigue	15 (14.3)	4 (3.8)	2 (4.2)	1 (1.9)
Dizziness	7 (6.7)	3 (2.9)	2 (4.2)	1 (1.9)
Weight loss	2 (1.9)	0	0	0
Investigations	19 (18.1)	2 (1.9)	1 (2.1)	1 (1.9)
Increased transaminase levels	3 (2.9)	0	0	0
Increased bilirubin	8 (7.6)	0	0	0
Abnormal WBC count	2 (1.9)	1 (1.0)	1 (2.1)	0
Anaemia				
Infections	30 (28.6)	0	0	0
Flu-like symptoms	27 (25.7)	0	0	0
Upper respiratory infections	1 (1.0)	0	0	0
Pneumonia ^a	5 (4.8)	0	0	0
Abdominal infections	4 (3.8)	0	0	0
Skin infections	4 (3.8)	0	0	0
Middle ear inflammation	1 (1.0)	0	0	0
Conjunctivitis (infective)	1 (1.0)	0	0	0
Urinary tract infections	1 (1.0)	0	0	0
Skin disorders	5 (4.8)	2 (1.9)	2 (4.2)	0
Acneiform rash	6 (5.7)	2 (1.9)	0	2 (3.8)
Diffuse hair loss				
Psychological AEs	2 (1.9)	0	0	0
Agitation	2 (1.9)	2 (1.9)	1 (2.1)	1 (1.9)
Depressive symptoms	1 (1.0)	0	0	0
Suicide attempt				

^aPneumonia was recorded as a serious AE. Other AEs reported include: epistaxis (*n* = 1), hyperhidrosis (*n* = 1), hyperventilation (*n* = 1), injection site reaction (*n* = 1), anal fissure (*n* = 1), herpes labialis (*n* = 1), perforation of tympanic membrane (*n* = 1).

FA: folic acid; WBC: white blood cell.

39.0% reporting ≥ 1 persistent GI-AE during follow-up. Overall, nausea (61.0%), fatigue (46.7%), abdominal pain (22.9%) and increased transaminase levels (18.1%) were noted most often. Infections regarded primarily flu-like symptoms (28.6%) and upper respiratory infections (25.7%). Only 1 patient experienced a serious AE (pneumonia).

Effectiveness

Three patients who discontinued MTX due to an AE before 12 weeks of follow-up were excluded from effectiveness evaluation, since their follow-up PASI scores were unavailable. **Fig. 1** summarizes MTX effectiveness with both absolute and relative PASI improvement every 12 weeks up to 2 years' follow-up by as treated and LOCF analyses. Both analyses showed that effectiveness tended to increase up until week 24. At week 24, the PASI 75 rate was 29.4% (95% confidence interval (95% CI) 20.8–39.9%), PASI 90 rate was 12.7% (95% CI 7.0–20.8%), an absolute PASI ≤ 3.0 was reached in 44.1% (95% CI 34.3–54.3%) and PASI ≤ 2.0 in 30.4% (95% CI 21.7–40.3%) by LOCF analyses (Fig. 1a–d). These rates increased at week 48 and 96, with, respectively, 37.3% (95% CI 27.9–47.4%) and 33.3% (95% CI 24.3–43.4%) achieving PASI 75, 12.7% (95% CI 7.0–20.8%) and 11.8% (95% CI 6.2–19.6%) PASI 90, 53.9% (95% CI 43.8–63.8%) and 46.1% (95% CI 36.2–56.2%) PASI ≤ 3.0 , and 35.3% (95% CI 26.1–45.4%) and 30.4% (95% CI 21.7–40.3%) achieving PASI ≤ 2.0 (Fig. 1a–d).

Overall, as treated analyses showed slightly higher rates (Fig. 1e–h). Furthermore, to gain more insight in MTX effectiveness, while also taking safety into account, effectiveness was evaluated with an additional distinction between patients with and without persistent AEs. This evaluation showed that, after 1 and 2 years, respectively, 39.2% (95% CI 29.7–49.4%) and 33.3% (95% CI 24.3–43.4%) of all patients achieved a PASI ≤ 3.0 without experiencing a persistent AE and, respectively, 26.5% (95% CI 18.2–36.1%) and 22.5% (95% CI 14.9–31.9%) achieved a PASI ≤ 2.0 without a persistent AE by LOCF analyses (**Fig. 2**).

Comparison of folic acid regimens

An overview of treatment-related persistent AEs split per FA regimen is described in Table II. Although a higher number of patients using FA once weekly experienced ≥ 1 persistent GI-AEs vs FA 6 times per week (23 [47.9%] vs 15 [28.3%]), a direct comparison of these numbers was not possible due to the difference in follow-up time between regimens. Therefore, Kaplan–Meier survival analysis was performed to compare FA regimens (**Fig. 3**). A trend towards lower occurrence of persistent GI-AEs over time was seen for patients with FA 6 times per week vs once weekly after 1 year (31.8% vs 41.7%) and 2 years (31.8% vs 51.3%), although this difference was not statistically significant (hazard ratio 0.656, 95% CI 0.346–1.243, $p=0.196$) (Table SII). Furthermore, effectiveness between FA regimens was compared. The

Last observation carried forward (LOCF) analyses

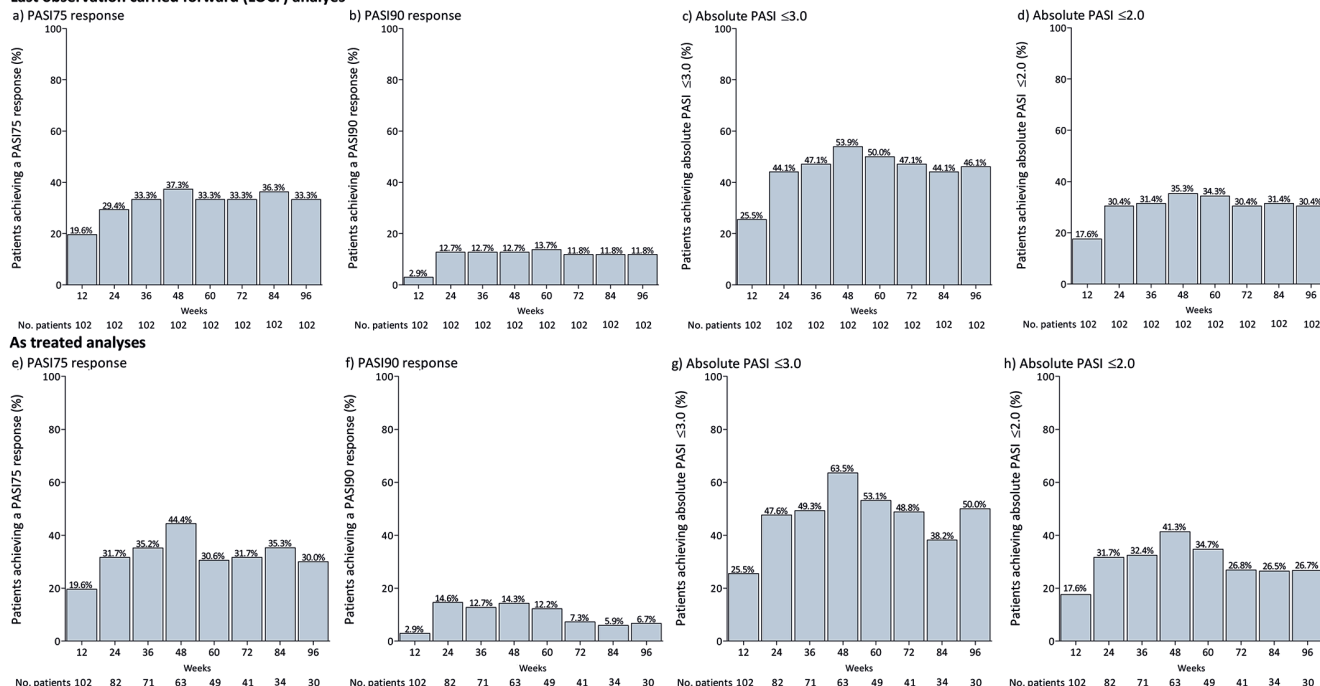


Fig. 1. Percentage of paediatric patients treated with methotrexate achieving PASI 75 response, PASI 90 response, absolute PASI ≤ 3.0 and absolute PASI ≤ 2.0 by last observation carried forward (LOCF) analyses (a, b, c, d) and as treated analyses (e, f, g, h). Clopper–Pearson confidence interval was used to calculate the exact confidence intervals for the presented proportions. PASI: Psoriasis Area and Severity Index; PASI 75: at least 75% reduction in PASI; PASI 90: at least 90% reduction in PASI.

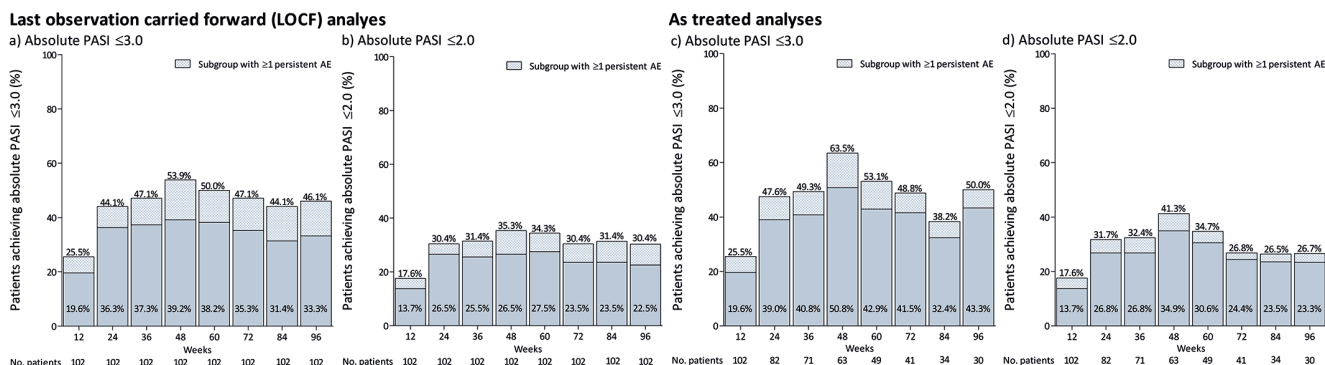


Fig. 2. Percentage of paediatric patients treated with methotrexate achieving an absolute Psoriasis Area and Severity Index (PASI) ≤ 3.0 and PASI ≤ 2.0 without and with persistent adverse events (AEs) (a, b) by last observation carried forward (LOCF) analysis and (c, d) as treated analysis. An additional distinction was made between patients with and without persistent adverse events at all time-points. NS: not significant.

percentage of patients achieving an absolute PASI ≤ 3.0 and ≤ 2.0 split per FA regimen, with an additional distinction between patients with and without GI-AEs, is presented in Fig. S2. No statistical significant differences were found in effectiveness between FA regimens in both LOCF and as treated analyses at week 12 up to week 48 (Table SIII).

DISCUSSION

This prospective, single-centre, cohort study of 105 paediatric patients with plaque psoriasis focused on the safety and effectiveness of MTX in a real-world setting. At 24 weeks, 29.4% of patients achieved a PASI 75 response and 44.1% and 30.4% achieved an absolute PASI ≤ 3.0 and PASI ≤ 2.0 , respectively. Approximately one-third of all patients maintained a PASI ≤ 2.0 up to 2

years. Persistent AEs were common, with 46.7% patients experiencing at least 1 persistent AE during follow-up. Still, after 1 and 2 years of treatment, respectively, 26.5% and 22.5% of all patients achieved a PASI ≤ 2.0 without any persistent adverse events.

Previous studies in a real-world setting have shown comparable results regarding effectiveness, with PASI 75 response rates of 32.0% (prospective study, $n=25$) to 40.0% (retrospective study, $n=30$) after 24 weeks (1, 5). A randomized clinical trial comparing adalimumab with MTX found a PASI 75 rate of 32.4% at week 16 ($n=37$) (6). The current results go further to show that approximately one-third of all patients maintained a PASI 75 response up to 2 years. Furthermore, the current study assessed the number of patients achieving an absolute PASI ≤ 3.0 and ≤ 2.0 . Previous studies have shown that the use of relative PASI responses, although commonly used in randomized clinical trials, seem to be less suitable in daily clinical practice studies, probably due to lower baseline PASI scores in real-life studies, which challenges the achievement of a high relative PASI response (14–16). Indeed, the current results show a higher percentage of patients achieving an absolute PASI ≤ 3.0 and ≤ 2.0 compared with a PASI 90 response.

The most frequently reported AEs in the current study were nausea, abdominal pain, fatigue and increased transaminase levels. Overall, GI-AEs were common, as has been described previously in other studies regarding children treated with MTX (1, 4, 5, 19). Infections were frequently reported, especially flu-like symptoms (28.6%) and upper respiratory infections (25.7%); however, interpretation of the correlation with MTX treatment was difficult, as a control group is lacking.

Although FA is supplemented during MTX treatment to reduce GI-AEs, consensus on timing and dosing of FA is lacking. In line with 2 previous studies in paediatric psoriasis and rheumatoid arthritis (1, 11), the current results suggest a possible trend towards lower occurrence of GI-AEs with FA 6 times per week vs once weekly (Fig. 2); however, this difference did not reach statistical significance ($p=0.196$). MTX effectiveness

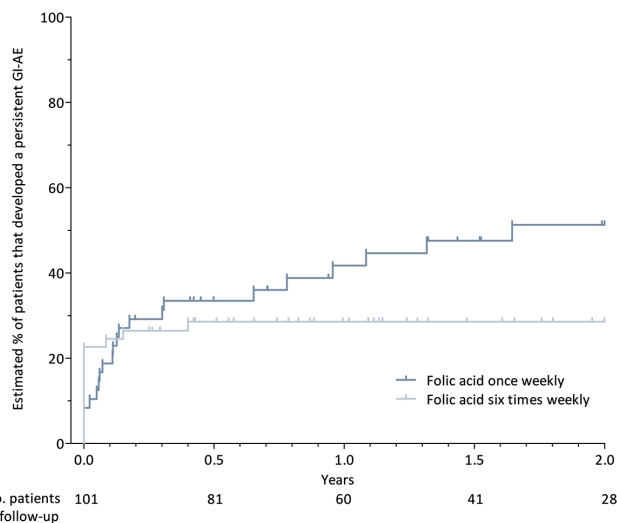


Fig. 3. Rate of occurrence of persistent gastrointestinal adverse events (GI-AE) in paediatric psoriasis patients treated with methotrexate: folic acid once weekly vs 6 times per week. Kaplan-Meier curves displaying the occurrence rates of GI-AE showed lower rates for patients with folic acid 6 times per week compared with patients with folic acid once weekly after 1 year (31.8% vs 41.7%) and 2 years (31.8% vs 51.3%), although this difference was not significant ($p=0.196$).

did not differ significantly between FA regimens during 1-year follow-up. Therefore, the current results suggest there might be a possible advantage of using FA 6 times per week vs once weekly in reducing GI-AEs without compromising on MTX effectiveness.

The current study was limited by the use of a quasi-experimental design with a "historical" FA regimen comparison group, which might pose a risk for time trends bias. However, since we used outcome measures that were independent of confounding due to different time-periods (e.g. PASI response, occurrence of AEs) rather than measures possibly influenced by time trends (e.g. treatment discontinuation), the different time-periods probably did not affect the results. Comparison of FA regimens was limited by relatively small subgroup numbers, possibly leading to limited power to detect differences between subgroups, with varying follow-up times. Nonetheless, the use of Kaplan–Meier analysis allowed for comparison of GI-AEs, while taking the different follow-up times into account. Although the categorization of AEs into either transient or persistent may seem arbitrary, we chose our definition of a transient AE to resolve before the next patient contact based on our clinical practice, in which we have regular patient contacts with the possibility of extra contact if necessary. Due to the single-centre design it is uncertain if the current results are fully representative of the general paediatric psoriasis population; however, our daily clinical practice study was strengthened by the prospective design, the inclusion of a relatively large number of paediatric patients ($n=105$) and long follow-up time (mean 1.8 [1.6] years), which allowed us to assess MTX effectiveness up to 2 years. Furthermore, in addition to relative PASI improvement, the current study also assessed absolute PASI improvement.

The treatment landscape for paediatric psoriasis is changing, with increasing, more effective, biologic treatment options. Indeed, although MTX is the first choice of systemic treatment in our practice according to Dutch guidelines (7), in recent years, our daily practice experience is that a switch to biologics is initiated sooner if a (persistent) AE occurs during MTX treatment. Ideally, stratification of patients with a high probability of MTX effectiveness and low probability of development of AEs would be carried out before MTX initiation, but biomarkers to assist this stratification are still lacking. The current study showed that, after 24 weeks of MTX treatment, approximately 25% of paediatric patients with plaque psoriasis achieved a PASI ≤ 2.0 without any persistent AEs, with 22.5% maintaining this outcome up to 2 years. These data show that a subgroup of patients responds well to MTX without considerable side-effects. Therefore, also considering the oral administration, low costs and the possibility to stop and retreat without risk of anti-drug development, MTX might still be a good alternative to biologics for a subgroup of patients in which a delayed response (24 weeks) is clinically acceptable.

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Author's Institutional Review board or its equivalent (CMO)

The study has been reviewed by the ethics committee on the basis of the Dutch Code of conduct for health research, the Dutch Code of conduct for responsible use, the Dutch Personal Data Protection Act and the Medical Treatment Agreement Act and does not fall within the remit of the Medical Research Involving Human Subjects Act (WMO). File number CMO: 2012/383.

Conflict of interest: FMB has carried out clinical trials for Abbvie, Janssen, Leo Pharma, Lilly, Pfizer and Celgene. IMGJB has carried out clinical trials for Abbvie, Leo Pharma and Pfizer. EMGJDJ has received research grants for the independent research fund of the Department of Dermatology of Radboud University Medical Centre Nijmegen, the Netherlands from AbbVie, Novartis, Janssen Pharmaceutica and Leo Pharma. She has acted as consultant and/or paid speaker for and/or participated in research sponsored by companies that manufacture drugs used for the treatment of psoriasis including AbbVie, Janssen Pharmaceutica, Novartis, Lilly, Celgene, Leo Pharma, UCB and Almirall. All funding is not personal, but goes to the independent research fund of the Department of Dermatology of Radboud University Medical Centre Nijmegen, the Netherlands. MMBS received grants from/was involved in clinical trials from Abbvie, Amgen, Celgene, Eli Lilly, Janssen, Leo Pharma and Pfizer. She served as a consultant for Abbvie, Eli Lilly, Janssen, Leo Pharma, Novartis, Pfizer and UCB; fees were paid directly to the institution. MRvA and JMMG have no conflicts of interest to declare.

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