JAMA Dermatology | Original Investigation

Safety of Systemic Agents for the Treatment of Pediatric Psoriasis

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IMPORTANCE Use of systemic therapies for moderate to severe psoriasis in children is increasing, but comparative data on their use and toxicities are limited.

OBJECTIVE To assess patterns of use and relative risks of systemic agents for moderate to severe psoriasis in children.

DESIGN, SETTING, AND PARTICIPANTS A retrospective review was conducted at 20 centers in North America and Europe, and included all consecutive children with moderate to severe psoriasis who used systemic medications or phototherapy for at least 3 months from December 1, 1990, to September 16, 2014.

MAIN OUTCOMES AND MEASURES The minimal core data set included age, sex, severity of psoriasis, systemic interventions, monitoring, adverse events (AEs), and reason for discontinuation.

RESULTS For 390 children (203 girls and 187 boys; mean [SD] age at diagnosis, 8.4 [3.7] years) with psoriasis who used 1 or more systemic medications, the mean interval between diagnosis and starting systemic therapy was 3.0 years. Methotrexate was used by 270 patients (69.2%), biologic agents (primarily etanercept) by 106 (27.2%), acitretin by 57 (14.6%), cyclosporine by 30 (7.7%), fumaric acid esters by 19 (4.9%), and more than 1 medication was used by 73 (18.7%). Of 270 children taking methotrexate, 130 (48.1%) reported 1 or more AEs associated with methotrexate, primarily gastrointestinal (67 [24.8%]). Folic acid 6 days per week (odds ratio, 0.16; 95% CI, 0.06-0.41; $P < .001$) or 7 days per week (OR, 0.21; 95% CI, 0.08-0.58; $P = .003$) protected against gastrointestinal AEs more than once-weekly folic acid, regardless of the total weekly dosage. Methotrexate-associated hepatic transaminase elevations were associated with obesity (35 of 270 patients [13.0%]), but a folic acid regimen was not. Injection site reactions occurred in 20 of 106 patients (18.9%) treated with tumor necrosis factor inhibitors, but did not lead to discontinuation of treatment. Having 1 or more AEs related to medication, gastrointestinal AE, laboratory abnormality, or AE leading to discontinuation of the drug was more likely with methotrexate than tumor necrosis factor inhibitors, but having 1 or more infections related to medication (predominantly upper airway) was less likely. Six patients developed a serious treatment-related AE (methotrexate, 3; fumaric acid esters, 2; and adalimumab, 1), but methotrexate and biologic agents were taken for a mean duration that was 2-fold greater than the mean duration for cyclosporine or fumaric acid esters. No patient developed tuberculosis or a malignant neoplasm.

CONCLUSIONS AND RELEVANCE Medication-related AEs occur less often with tumor necrosis factor inhibitors than with methotrexate. Folic acid administration 6 or 7 times per week protected more against methotrexate-induced gastrointestinal AEs than did weekly administration. A prospective registry is needed to track the long-term risks of systemic agents for pediatric psoriasis.

JAMA Dermatol. doi:10.1001/jamadermatol.2017.3029
Published online September 13, 2017.

Supplemental content

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Psoriasis is a common chronic inflammatory skin disorder that affects 2% to 3% of the adult population, with approximately one-third of patients having disease onset before 18 years of age. The prevalence increases linearly throughout childhood,[1-3] and the incidence of pediatric psoriasis has more than doubled between 1970 and 2000.[4]

Although many affected children have mild disease that responds adequately to topical intervention, more severe or recalcitrant disease is not uncommon in children, may impair health-related quality of life,[5,6] and often requires systemic therapy. Phototherapy and systemic medications, particularly methotrexate, cyclosporine, fumaric acid esters (FAE), oral acitretin, and biologic agents, are used to treat moderate to severe pediatric psoriasis.[7-13] However, data are sparse on the relative use of systemic agents and their toxic effects in the pediatric population. Standardized guidelines are lacking, and few clinical trials have been conducted in children.[8,13] Randomized, vehicle-controlled trials have documented the efficacy and safety of etanercept, adalimumab, and ustekinumab in pediatric psoriasis.[14-18] Only methotrexate and adalimumab have been compared head-to-head.[18] We retrospectively assessed the adverse effects of systemic agents in a large cohort of North American and European children with moderate to severe psoriasis to provide information about the relative risk of available interventions.

Key Points

Question What are the risks of systemic medications for pediatric psoriasis?

Findings In this cohort study of 390 children with moderate to severe psoriasis, methotrexate and tumor necrosis factor inhibitors were most frequently used; compared with methotrexate, more medication-related adverse events overall and per patient-years of use occurred with cyclosporine, acitretin, and fumaric acid esters, and fewer occurred with use of tumor necrosis factor inhibitors. Folic acid administration 6 or 7 times weekly was associated with fewer methotrexate-induced gastrointestinal adverse effects compared with once-weekly administration.

Meaning Overall, tumor necrosis factor inhibitors were associated with fewer adverse events than methotrexate; folic acid administration 6 or 7 times weekly may lower the risk of methotrexate-related gastrointestinal adverse events compared with weekly administration.

Methods

Patient Selection

This international, retrospective study was conducted by a consortium of 20 centers in the United States, Canada, and Europe. Principal investigators at 10 centers were members of the Psoriasis Investigator Group of the Pediatric Dermatology Research Alliance and principal investigators at 10 centers were members of the European Working Group on Pediatric Psoriasis. All available medical records were reviewed for patients diagnosed with moderate to severe psoriasis as decided by the treating physician and who, between December 1, 1990, and September 16, 2014, used systemic medications or phototherapy prior to their 18th birthday for at least 3 months. Patients who were treated primarily for palmoplantar, scalp, or nail psoriasis did not have moderate to severe psoriasis, but were included only with respect to monitoring the occurrence of adverse events (AEs). The University of California San Diego Human Research Protections Program; Le Comité d'Ethique du Centre Hospitalier Universitaire d'Angers (Argenteuil); Commissie Voor Medische Ethiek Universitair Ziekenhuis Gent (Ghent); Ethikkommission Charite Universitatsmedizin Berlin; Saint Louis University Institutional Review Board; Hospital for Sick Children Research Ethics Board; Mayo Clinic Institutional Review Board; University of Massachusetts Medical School Institutional Review Board; Comite Etico de Investigacion Clinica Hospital de la Santa Creu i Sant Pau (Barcelona); Nottingham University Hospitals Clinical Quality, Risk, and Safety Team; Phoenix Children's Hospital Institutional Review Board; Children's Hospital of Wisconsin Institutional Review Board #2; Agia Sofia Hospital Ethics Review Board (Athens); Radboud University Nijmegen Medical Centre Research Ethics Committee; University of California San Francisco Human Research Protection Program Committee on Human Research; Ethik-Kommission UKSH Campus Kiel; Heim Pal Institutional Research Ethics Committee (Budapest); Boston Children's Hospital Committee on Clinical Investigation; Danish Committee System on Health Research Ethics Gentofte Hospital; and Northwestern University Institutional Review Board approved the protocol for this research by expedited or full review. Written informed consent for this retrospective medical record review was waived by each investigator's institutional review board.

Patients treated for less than 3 months were included only if an AE led to treatment discontinuation. Exclusion criteria were having no history of systemic medication or phototherapy for psoriasis, age older than 18 years at initiation of therapy, or having psoriatic arthritis as the indication for systemic medication, but without prescriber-determined moderate to severe psoriasis as an additional indication.

Design and Data Management

A total of 54 data points were extracted for each participant; of these, a minimal core data set (dependent on the systemic agent used) was required for inclusion (**Box**). These data points included demographic information, psoriasis characteristics and severity, systemic agent(s) used, net treatment duration, efficacy, AEs and serious AEs (SAEs), and reason for discontinuation of treatment. A maximum of 3 possible treatment episodes per systemic drug was allowed, with information for each episode collected separately.

Deidentified data from each center were transmitted to a central data coordinating center at Northwestern University and organized using the Research Electronic Data Capture system, a secure web-based data management application. The first patient was reviewed on September 1, 2014, and the last on July 31, 2015, with a final data lock of December 14, 2015.

Box. Collected Data Points

Patient Characteristics
1. Date of medical record review[a]
2. Year of birth, mm/yyyy[a]
3. Sex[a]
4. Race
5. Ethnicity
6. Diagnosis at original presentation
7. Age at diagnosis, y

Family History
1. Psoriasis in parents or siblings
2. Psoriasis in extended family
3. Psoriatic arthritis in parents or siblings

Medical History
1. Weight (kg) within 3 mo of starting systemic therapy
2. Height (cm) within 3 mo of starting systemic therapy
3. Obesity or overweight status, BMI percentile[b]
4. Fatty liver disease or NAFLD
5. Psychiatric disorder
6. Psoriatic arthritis
7. Hyperlipidemia
8. Hypertension
9. Type 1 or 2 diabetes
10. Crohn disease
11. Other autoimmune disorder
12. Other skin disorder
13. Tonsillectomy
14. Other disorders

Treatment-Specific Information
1. Age at start of intervention[a]
2. Date at start of intervention[a]
3. Primary indication[a,c]
4. Type of psoriasis at start of treatment[a]
5. Location of psoriasis at start of treatment[a]
6. Severity of psoriasis at start of treatment[a]
7. Associated symptoms at start of treatment
8. Baseline laboratory screening (if appropriate)[a,d]
9. Biologic: tuberculosis screening[a]
10. Starting dosage, mg/wk[a]
11. Maximum dosage, mg/wk[a]
12. Total cumulative dose
13. Methotrexate: route of administration[a]
14. Methotrexate: folic acid prescription[a]
15. Methotrexate: folic acid administered as multivitamin vs pure folic acid
16. Methotrexate: folic acid dose, mg/wk
17. Severity of psoriasis at 1 mo
18. Severity of psoriasis at 3 mo[a,e]
19. Severity of psoriasis at 6 months
20. Still receiving treatment on September 16, 2014
21. Doses missed
22. Net duration of treatment (months)[a]
23. Reason for treatment discontinuation[a]
24. Concomitant topical therapy
25. Concurrent systemic intervention for psoriasis[a]
26. Other systemic medication used concomitantly

Adverse Events
1. Adverse event, serious adverse event[a]
2. Relation to treatment[a]
3. Time (days) from start dose to adverse event
4. Intervention for adverse event[a]

Abbreviations: BMI, body mass index; NAFLD, nonalcoholic fatty liver disease.

[a] Minimal core data set. Note that the number of required data points in the minimal core data set varied depending on intervention (eg, a patient administered methotrexate would need baseline laboratory testing, a route of administration, and information about folic acid administration, data points that were not required for a child taking a biologic) and outcome (eg, if there were no adverse event or serious adverse event, there would be no need for data regarding relation to treatment and intervention for that adverse event).

[b] Medical record reviewer was asked to provide weight, height, and calculated BMI and, if unknown, whether patient was overweight or obese before the start of systemic treatment.

[c] Only psoriasis or psoriatic arthritis plus psoriasis of at least moderate severity were acceptable indications.

[d] Medical record reviewer was asked to provide specific baseline laboratory test results, if abnormal, at any time before initiation of systemic treatment.

[e] Severity scores within 3 mo before start of the systemic intervention and during at least 1 follow-up visit were required for inclusion.

Adverse Events

Preselected AEs of interest were recorded by organ system, but additional AEs could be entered as free text for selected questions. Investigator opinion about the relation of the AE to treatment, time of AE onset, and intervention for the AE were also captured. Serious AEs, defined by US Food and Drug Administration criteria,[19] were grouped into the following categories: malignant neoplasm, hepatic disease (hepatic failure; requirement for biopsy or hospitalization), bone marrow suppression, and other (documented as free text).

Severity Scores

Participating sites provided either Psoriasis Area and Severity Index scores, body surface area, Physician Global Assessment (PGA) scores, or sufficient details about the average lesional plaque appearance using free text for a reviewer to assign a PGA score from 0 (clear) to 5 (very severe). Severity scoring had to be available within the 3 months before initiation of systemic medication and during at least 1 return visit at 0 to 2 months, 2 to 4 months, or 4 to 8 months after treatment initiation.

End Points

The coprimary end points were percentage of patients experiencing at least 1 AE deemed treatment related at any time during use of the medication, and most frequently reported AEs for each treatment. Secondary end points included percentages of children experiencing an AE resulting in drug discontinuation, percentage of children experiencing an SAE, comparison of AEs in patients treated with the 2 most commonly used agents (methotrexate vs tumor necrosis factor inhibitor [TNF-I]), and factors contributing to the occurrence of AEs in patients receiving methotrexate.

Statistical Analysis

Demographic and safety data were summarized as means and SDs for continuous variables, and numbers and percentages

for categorical variables. Safety data were presented as number and percentage of patients developing 1 or more AEs.

Adverse events and AE subcategories in patients treated with methotrexate or with a TNF-I were studied by generalized estimating equations modeling to account for dependence of measurements with different systemic agents used by one patient. Outcome measures were corrected for sex, age at treatment start, and treatment duration. To exclude any possible influence of previously provided treatments on AEs and AE subcategories, the same analysis was performed using multivariable logistic regression modeling on patients receiving methotrexate or a TNF-I who had not received other conventional systemic agents and biologic agents. Univariable and multivariable logistic regression models were used to explore determinants for the probability of developing at least 1 AE during methotrexate treatment. The following 3 outcome measures were studied: the overall occurrence of AE(s), the occurrence of gastrointestinal (GI) AE(s), and the occurrence of abnormal laboratory test results. To assess possible outcomes, patient sex, age at treatment start, treatment duration, maximum methotrexate dose (milligram per kilogram per week) and route of administration, and folic acid dosage (milligram per week) and regimen were correlated with AE occurrence. Only patients with complete data for these factors were selected (n = 162), and factors of interest were analyzed separately using univariable logistic regression models. To further determine which factors were associated most robustly with AEs, a backward selection procedure was followed, using multivariable logistic regression, starting with all factors in the model. To amplify the assessment of folic acid regimens in methotrexate treatment, we performed an analysis of variance on the association between the change in PGA score and folic acid regimen. All analyses were performed with SPSS, version 22.0 (IBM SPSS Inc). $P < .05$ was considered statistically significant.

Results

Study Patients

Deidentified data from 509 patients, deemed by investigators to meet minimal inclusion criteria, were provided to the data coordinating center. Further review at Northwestern University and Radboud University excluded 63 children without minimal inclusion criteria and 56 who used only phototherapy. The main reasons for exclusion were failure to report severity of psoriasis at treatment start or during follow-up, treatment duration less than 3 months, and lack of documentation of starting dose, maximal dose, or reason for treatment discontinuation. The final data set included 390 children.

Patient characteristics are shown in **Table 1**. Most children were white (62.6%) and the mean (SD) body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) was 21.8 (5.7). North American children had a significantly higher mean (SD) BMI compared with European children (22.9 [6.4] vs 20.5 [4.5]; $P = .001$). Systemic treatment was initiated at a mean interval of 3.0 years after diagnosis (mean [SD] ages, 11.4 [3.7] years at initiation of therapy vs 8.4 [3.7] years at diagnosis). Overall, 274 of 283 patients (96.8%) had psoriasis of at least moderate severity based on PGA scores; the remaining 9 patients (3.2%) experienced primarily nail, scalp, or palmoplantar psoriasis. The most frequently reported associations were psoriatic arthritis (43 [11.0%]) and psychiatric disorders (25 [6.4%]). Methotrexate was the most commonly used systemic medication (270 [69.2%]; 175 of 230 [76.1%] in North America vs 95 of 160 [59.4%] in Europe; $P < .001$), followed by biologic agents (106 [27.2%]; 60 of 230 [26.1%] in North America vs 46 of 160 [28.8%] in Europe; $P = .56$) (**Table 2**). Etanercept was the most frequently prescribed biologic (80 of 106 [75.5%]). Acitretin, cyclosporine, and FAE (unavailable in North America) were more frequently prescribed in Europe.

Adverse Events

Table 2 summarizes the percentages of patients developing 1 or more treatment-related AEs or AEs leading to drug discontinuation. Almost half the patients receiving methotrexate experienced 1 or more treatment-related AEs (130 of 270 [48.1%]); nausea alone (n = 46), elevated transaminase levels (n = 13), dyspepsia (n = 19), and fatigue (n = 17) were the most frequently reported treatment-related AEs. Documented infections were primarily of the skin (5 of 270 [1.9%]) and upper respiratory tract (4 of 270 [1.5%]). Of the 106 patients treated with biologic agents, 41 (38.7%) reported 1 or more related AEs, most commonly injection site reactions (20 [18.9%]). Infections, reported in 12 patients (11.3%), were primarily airway infections and were more frequent with adalimumab (3 of 19 [15.8%]) than etanercept (7 of 80 [8.8%]) (Table 2). Adverse events led to treatment discontinuation for 33 patients receiving methotrexate (12.2%) and for 3 patients receiving a biologic (2.8%). A total of 38 of 57 patients treated with acitretin (66.7%) and 13 of 19 patients receiving FAE (68.4%) developed 1 or more treatment-related AEs, leading to discontinuation of treatment for 6 patients receiving acitretin (10.5%) and 2 patients receiving FAE (10.5%); no premature closure of the epiphysis was reported from the use of acetretin.

Seven patients reported an SAE. Of the 3 SAEs occurring in patients receiving methotrexate, 1 was considered causally associated (hepatic failure) and 2 (hypersensitivity pneumonitis and severe personality changes) were considered probably associated with methotrexate. One patient developed appendicitis 2.5 years after initiation of adalimumab therapy. Two patients receiving FAE experienced either pericarditis or bone marrow suppression. One patient receiving cyclosporine experienced a car crash with brain injury (deemed unlikely to be associated with the medication). No deaths, malignant neoplasms, or mycobacterial infections were reported.

Most patients received monotherapy with methotrexate (n = 253) or TNF-I (etanercept, adalimumab, or infliximab; n = 84), allowing comparison of AE risk and odds ratios (ORs) of occurrence. Patients treated with more than 1 drug concurrently were not analyzed. Having 1 or more associated AEs (OR, 1.76; 95% CI, 1.06-2.92; $P = .03$), GI AEs (OR, 11.49; 95% CI, 3.31-39.88; $P < .001$), or abnormal laboratory test results (OR, 5.87; 95% CI, 1.81-18.99; $P = .003$) or discontinuation of treatment from an associated AE (OR, 5.69; 95% CI, 1.31-24.82; $P = .02$)

Table 1. Characteristics of 390 Patients

Characteristic	Patients, No. (%)[a]
Continent	
North America	230 (59.0)
Europe	160 (41.0)
Sex	
Male	187 (47.9)
Female	203 (52.1)
Race	
White	244 (62.6)
Black or African American	15 (3.8)
Asian	14 (3.6)
Unknown or not reported	117 (30.0)
Ethnicity	
Not Hispanic or Latino	175 (44.9)
Hispanic or Latino	47 (12.1)
Unknown or not reported	168 (43.1)
Family history	
Psoriasis in parents or siblings (n = 340)	119 (35.0)
Psoriatic arthritis in parents or siblings (n = 250)	15 (6.0)
Comorbidity	
Psoriatic arthritis	43 (11.0)
Psychiatric disorder[b]	25 (6.4)
Hyperlipidemia	8 (2.1)
Hypertension	4 (1.0)
Type 1 or 2 diabetes	3 (0.8)
Crohn disease	3 (0.8)
BMI category (n = 189)	
Underweight (<5th percentile)	6 (3.2)
Healthy weight (5th to <85th percentile)	96 (50.8)
Overweight (≥85th to <95th percentile)	36 (19.0)
Obese (≥95th percentile)	51 (27.0)
BMI percentile, mean (SD) (n = 189)	70.6 (29.0)
BMI mean (SD) (n = 192)	21.8 (5.7)
North America (n = 105)	22.9 (6.4)
Europe (n = 87)	20.5 (4.5)
Psoriasis severity at onset of therapy	
PGA score (n = 283)[c,d]	
Minimal	1 (0.4)
Mild	8 (2.8)
Moderate	110 (38.9)
Severe	140 (49.5)
Very severe	24 (8.5)
BSA, mean (SD), % (n = 169)	27.2 (21.5)
PASI score, mean (SD) (n = 90)	13.9 (8.7)
Age at diagnosis, mean (SD), y	8.4 (3.7)
Age at start of systemic therapy, mean (SD), y	11.4 (3.7)
Duration of treatment, mean (SD), mo	
Biologic agents	20.0 (17.5)
Methotrexate	18.7 (16.8)
Acitretin	18.4 (25.0)
Fumaric acid esters	9.4 (5.4)
Cyclosporine	8.4 (5.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); BSA Body Surface Area; PGA, Physician's Global Assessment; PASI, Psoriasis Area and Severity Index.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Psychiatric disorders included attention-deficit/hyperactivity disorder, depression, and anxiety.

[c] The PGA scores range from 0 (clear) to 5 (very severe).

[d] If psoriasis severity score was not clearly stated (<5% of children), PGA scores were assigned by a central reviewer from a detailed description of extent and characteristics of the lesions.

Table 2. AEs Attributed to a Systemic Medication

Systemic Agent, No. (%) (N = 390)[a]	Patients Developing ≥1 AEs, No. (%)[b]	Patients Developing ≥1 Medication-Related AEs, No. (%)[c,d]	Mean No. of AEs per Treatment Year	Patients Developing ≥1 AEs Leading to Treatment Discontinuation, No. (%)[e]
Methotrexate (270 [69.2%])	144 (53.3)	Total, 130 (48.1); nausea, 46 (17.0); elevated transaminase levels, 36 (13.3); dyspepsia, 19 (7.0); fatigue, 17 (6.3); infections, 12 (4.4)[f]; abnormal WBC count, 10 (3.7)	0.96	Total, 33 (12.2); nausea, 11 (4.1); elevated transaminase levels, 8 (3.0); fatigue, 6 (2.2); infections, 2 (0.7); abnormal WBC count, 2 (0.7)
Biologic agents (106 [27.2%])	47 (44.3)	Total, 41 (38.7); injection site reactions, 20 (18.9); infections, 12 (11.3)[g]; fatigue, 2 (1.9); headache, 2 (1.9); diarrhea, 2 (1.9)	0.60	Total, 3 (2.8); infections, 1 (0.9); fatigue, 1 (0.9); vomiting or nausea, 1 (0.9); abdominal pain, 1 (0.9)
Etanercept (80 [20.5%])	37 (46.3)	Total, 31 (38.8); injection site reactions, 19 (23.8); infections, 7 (8.8)[h]; gastrointestinal, 4 (5.0)[i]; laboratory, 3 (3.8)[j]		Total, 2 (2.5); gastrointestinal, 2 (2.5)
Adalimumab (19 [4.9%])	7 (36.8)	Total, 7 (36.8); infections, 3 (15.8)[k]; laboratory test results, 2 (10.5)[l]; injection site reactions, 1 (5.3); headache, 1 (5.3)		Total, 0
Ustekinumab (5 [1.3%])	3 (60.0)	Total, 3 (60.0); infections, 2 (40.0)[m]; fatigue, 2 (40.0); diarrhea, 1 (20.0)		Total, 1 (20.0); fatigue, 1 (20.0); infection, 1 (20.0)
Infliximab (2 [0.5%])	0	Total, 0		Total, 0
Acitretin (57 [14.6%])	38 (66.7)	Total, 38 (66.7); cheilitis, 17 (29.8); xerosis, 15 (26.3); hyperlipidemia, 8 (14.0); elevated transaminase levels, 4 (7.0); epistaxis, 3 (5.3)	1.92	Total, 6 (10.5); xerosis, 2 (3.5); hyperlipidemia, 2 (3.5); cheilitis, 1 (1.8); mild leukopenia, 1 (1.8); headache, 1 (1.8)
Cyclosporine (30 [7.7%])	13 (43.3)	Total, 11 (36.7); gingival hyperplasia, 4 (13.3); hypertrichosis, 4 (13.3); headache, 3 (10.0); hypertension, 2 (6.7); loss of appetite, 1 (3.3)	1.32	Total, 3 (10.0); gingival hyperplasia, 1 (3.3); hypertrichosis, 1 (3.3); headache, 1 (3.3); hypertension, 1 (3.3)
Fumaric acid esters (19 [4.9%])	13 (68.4)	Total, 13 (68.4); flushing, 8 (42.1); diarrhea, 6 (31.6); abdominal pain, 5 (26.3); abnormal WBC count, 4 (21.1); headache, 2 (10.5)	1.68	Total, 2 (10.5); flushing, 1 (5.3); abdominal pain, 1 (5.3); lymphocytopenia, 1 (5.3)

Abbreviations: AEs, adverse events; WBC, white blood cell.

[a] Patients treated with phototherapy alone (n = 56) were excluded from analysis.

[b] Specific AEs refer to most frequently reported AEs for each systemic treatment.

[c] Total number of patients experiencing 1 or more AEs does not equal the sum of patients experiencing 1 or more specific AEs because more than 1 AE can be reported in the same patient.

[d] Related AEs included possibly, probably, and definitely related AEs.

[e] Some reasons for discontinuation of treatment were not considered to be related AEs by the investigator.

[f] Infections were primarily of the skin (5 of 12 children) and upper airway (4 of 12 children).

[g] Infections were primarily upper airway (7 of 12 children), bronchitis (2 of 12 children), and skin (2 of 12 children).

[h] Infections were primarily of the upper airway (4 of 7 children).

[i] Gastrointestinal AEs were vomiting, abdominal pain, and nausea. The former 2 led to treatment discontinuation.

[j] Laboratory abnormalities were elevated transaminase levels.

[k] Infections were of the upper airway (2 of 3 children) and skin (1 of 3 children).

[l] Laboratory abnormalities were antidrug antibodies to adalimumab and abnormal complement test results (elevated C3, and C4 complement).

[m] Infections were toxoplasmosis and upper airway infection. The former led to treatment discontinuation.

was more likely with methotrexate than TNF-I, but having 1 or more associated infections was less likely with methotrexate (OR, 0.36; 95% CI, 0.15-0.88; P = .03) (**Table 3**). Subset analysis of patients who had not taken other conventional systemic agents and biologic agents yielded similar results (236 receiving methotrexate vs 48 receiving TNF-I), with significant differences in the risk of development of 1 or more associated GIs or laboratory AEs (eTable 1 in the Supplement).

Methotrexate Dosing and Folic Acid Regimen and the Risk of AEs

Methotrexate was administered orally for 207 children (76.7%), subcutaneously for 28 (10.4%), and both orally and subcutaneously or intramuscularly at different times for 35 (13.0%). Further information on temporal sequence was not captured. The mean (SD) methotrexate treatment duration was 18.7 (16.8) months, the mean (SD) initial dosage was 0.27 (0.13) mg/kg/wk, and the mean (SD) maximal dose was 0.36 (0.16) mg/kg/wk (eTable 2 in the Supplement). The most frequently reported AEs from methotrexate were GI (nausea, 46 of 270 [17.0%] and dyspepsia, 19 of 270 [7.0%]) and elevated hepatic transaminases (36 of 270 [13.3%]). Univariable and multivariable logistic regression analyses were performed to determine the potential association of patient and treatment characteristics with the occurrence of AEs for the 162 patients for whom all data were available (**Table 4**). Older age at the onset of treatment and higher maximal methotrexate dosage independently increased the probability of developing an AE (older age: OR, 1.14; 95% CI, 1.01-1.27; dosage, OR 26.14; 95% CI, 1.64-417.77) but not of a GI AE (Table 4 and eFigure 1A and B in the Supplement). Longer treatment duration also increased the risk of GI AE (OR, 1.04; 95% CI, 1.02-1.07; P = .003) (Table 4 and eFigure 1B in the Supplement). Weight and height information for the BMI calculation was available for 94 of the patients taking methotrexate; of the various AEs, only 1 or more related elevated hepatic transaminase levels correlated with

Table 3. Association Between the Occurrence of Overall AEs, Gastrointestinal AEs, Laboratory Abnormalities, and Infections and Systemic Treatment[a]

Event	Methotrexate vs TNF-I[b]	
	OR (95% CI)	*P* Value
≥1 AEs	1.56 (0.94-2.58)	.08
≥1 Related AEs	1.76 (1.06-2.92)	.03
≥1 AEs leading to treatment discontinuation	5.69 (1.31-24.82)	.02
≥1 GI AEs	12.27 (3.56-42.29)	<.001
≥1 Related GI AEs	11.49 (3.31-39.88)	<.001
≥1 GI AEs leading to treatment discontinuation	2.20 (0.45-10.58)	.33
≥1 Laboratory abnormalities	3.42 (1.41-8.29)	.01
≥1 Related laboratory abnormalities	5.87 (1.81-18.99)	.003
≥1 Laboratory abnormalities leading to treatment discontinuation[c]	Not computed	
≥1 Infections	0.35 (0.17-0.75)	.01
≥1 Related infections	0.36 (0.15-0.88)	.03
≥1 Infections leading to treatment discontinuation[c]	Not computed	

Abbreviations: AEs, adverse events; GEE, General estimating equation; GI, gastrointestinal; OR, odds ratio; TNF-I, tumor necrosis factor inhibitor.

[a] The relation between medication and AE(s) was studied by GEE modeling. Patients who used methotrexate and biologic agents at different times were included in both treatment groups, although related AEs were based on temporal relationships. Outcome measures were corrected for sex, age at treatment start, and treatment duration.

[b] Patients included in the methotrexate group (N = 253) could have been previously treated with other conventional systemics and biologic agents. Patients included in the TNF-I group (N = 84) could have been previously treated with conventional systemics and other biologic agents. At the time of occurrence of the AE, however, any patient included in this assessment was solely receiving methotrexate or a TNF-I.

[c] Could not be computed for this outcome variable.

obesity (OR, 4.52; 95% CI, 1.30-15.72; *P* = .02), possibly associated with hepatic steatosis (eTable 3 in the Supplement).

Folic acid was prescribed for 239 of the 253 patients for whom this information was available (94.5%), with a mean (SD) folic acid dosage of 7.5 (5.8) mg/wk. The other 14 patients received folic acid in a multivitamin (no further information available). Three folic acid regimens were used: once weekly (71 [29.7%]; the most common regimen in Europe), 6 days per week, avoiding the methotrexate day (85 [35.6%]), or 7 days per week (83 [34.7%]). Folic acid given 6 days per week (OR, 0.16; 95% CI, 0.06-0.41; *P* < .001) or 7 days per week (OR, 0.21; 95% CI, 0.08-0.58; *P* = .003) was associated with a lower probability of developing a GI AE compared with folic acid once weekly, independent of treatment duration (eFigure 1C in the Supplement). Maximal dose of methotrexate had no influence on the occurrence of GI AEs. Mean improvement in PGA score after 6 months of methotrexate treatment was not different among the 3 folic acid regimens, although there was a trend toward decreased efficacy with daily folic acid (mean [SD] PGA score: weekly, 1.58 [1.20]; 6 days per week, 1.52 [1.25]; 7 days per week, 1.41 [1.04]; *P* = .81) (eFigure 2 in the Supplement). Within the group of children taking methotrexate and pure folic acid, we did not find any significant difference between oral only vs subcutaneous only administration in the percentage of 1 or more related AEs, 1 or more related GI AEs, or 1 or more related elevated hepatic transaminase AEs (eTable 4 in the Supplement). However, interpretation of these data is limited by the small numbers of patients given methotrexate subcutaneously and relatively greater tendency in Europe to administer methotrexate subcutaneously and to administer folic acid once weekly, which could have masked a lower GI risk from the subcutaneous administration. In addition, patients given both oral and subcutaneous methotrexate were excluded, because the order of use, reason for a switch (GI toxic effects vs need for greater efficacy), and temporal association between AE occurrence and form of administration was not uniformly captured.

Discussion

This international, multicenter, retrospective study focused on the tolerability and observed AEs of systemic treatment in moderate to severe psoriasis in children. Standard guidelines for treatment choice in pediatric psoriasis are lacking. Few trials have examined the short- and long-term AEs of systemic agents, contributing to clinicians' concerns about use of these systemic agents[20] and, possibly, the 3-year mean interval between psoriasis diagnosis and initiation of treatment. Prior retrospective studies of children with psoriasis treated with acitretin or FAE also showed a latency of approximately 3 years from diagnosis to initiation of treatment.[9,21]

Methotrexate was the most commonly used systemic treatment for moderate to severe psoriasis in children in both North America and Europe (69.2%). In addition, the percentage of patients receiving biologic agents was similar for the 2 continents (27.2%), despite being off-label treatment in North America during the study period. Etanercept was approved to treat severe plaque psoriasis in children 8 years of age or older by the European Medicines Agency in 2009 (and subsequently approved for those ≥6 years of age).[22-24] In our study, 1 or more associated AEs was more likely to occur in patients receiving methotrexate, acitretin, or FAE, compared with those receiving biologic agents. In addition, fewer patients receiving biologic agents (2.8%) than other systemic agents developed AEs leading to discontinuation of treatment.

A 2-fold increased risk of transaminase elevation, but not hepatic cirrhosis, fibrosis, or failure, was associated with

Table 4. Association Between Patient Characteristics and the Occurrence of AEs in Patients Receiving Methotrexate Who Were Taking Folic Acid

Variable	Range	≥1 Related AEs		≥1 Related Gastrointestinal AEs		≥1 Related Elevated Hepatic Transaminase Levels[a]	
		OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Univariable Logistic Regression							
Sex							
Male		1 [Reference]		1 [Reference]		1 [Reference]	
Female		1.35 (0.73-2.51)	.34	1.03 (0.51-2.11)	.93	0.94 (0.40-2.20)	.88
Route of methotrexate administration			.20		.48		.51
Oral		1 [Reference]		1 [Reference]		1 [Reference]	
Subcutaneous		1.31 (0.49-3.48)	.59	1.16 (0.38-3.49)	.80	0.26 (0.03-2.01)	.20
Oral and subcutaneous		2.86 (0.74-11.06)	.13	2.32 (0.68-7.85)	.18	0.42 (0.05-3.40)	.41
Oral and intramuscular		0.32 (0.06-1.64)	.17	0.46 (0.06-3.92)	.48	0.66 (0.08-5.61)	.70
Pure folic acid regimen		1 [Reference]	.37	1 [Reference]	<.001	1 [Reference]	.60
Once weekly		1 [Reference]		1 [Reference]		1 [Reference]	
Daily 6 d/wk (avoiding methotrexate day)		0.62 (0.30-1.29)	.26	0.17 (0.07-0.43)	<.001	1.63 (0.56-4.74)	.37
Daily 7 d/wk		0.63 (0.28-1.40)	.26	0.26 (0.10-0.66)	.005	1.69 (0.54-5.31)	.37
Age at start, y	2.00-17.00	1.05 (0.96-1.15)	.34	1.05 (0.94-1.16)	.42	0.96 (0.85-1.08)	.48
Treatment duration, mo	0.72-80.26	1.02 (1.00-1.05)	.08	1.04 (1.01-1.07)	.006	1.00 (0.96-1.03)	.77
methotrexate maximum dose, mg/kg	0.11-1.47	5.11 (0.60-43.27)	.13	2.00 (0.26-15.02)	.52	0.59 (0.04-9.85)	.71
Pure folic acid dose, mg/wk	1.00-30.00	1.00 (0.96-1.05)	.93	1.01 (0.96-1.06)	.77	1.01 (0.94-1.07)	.88
Logistic Regression Modeling Estimating the Probability of AEs Based on ≥1 Predictor Variables[b]							
Pure folic acid regimen		NI[c]	NI[c]	NI[c]	<.001	NI[c]	NI[c]
Once weekly		NI[c]	NI[c]	NI[c]	NI[c]	NI[c]	NI[c]
Daily 6 d/wk (avoiding methotrexate day)		NI[c]	NI[c]	0.16 (0.06-0.41)	<.001	NI[c]	NI[c]
Daily 7 d/wk		NI[c]	NI[c]	0.21 (0.08-0.58)	.003	NI[c]	NI[c]
Age at start, y	2.00-17.00	1.14 (1.01-1.27)	.03	NI[c]	NI[c]	NI[c]	NI[c]
Treatment duration, mo[d]	0.72-80.26	NI[c]	NI[c]	1.04 (1.01-1.04)	.003	NI[c]	NI[c]
Methotrexate maximum dose, mg/kg	0.11-1.47	26.14 (1.64-417.77)	.03	NI[c]	NI[c]	NI[c]	NI[c]
Pure folic acid dose, mg/wk	1.00-30.00						

Abbreviations: AEs, adverse events; NI, no influence; OR, odds ratio.

[a] Laboratory abnormalities (n = 35) were primarily elevated hepatic transaminase levels (25 [71.4%]). White blood cell count abnormalities (6 [17.1%]) and other nonspecific laboratory test result abnormalities (4 [11.4%]) were excluded from analysis.

[b] Variables were defined as predictor factors in case statistical significance ($P < .05$) was reached in the multivariable logistic regression model. No predicting factors were found for the occurrence of elevated hepatic transaminase levels.

[c] No substantial influence of this variable on outcome measure.

[d] Treatment duration was a confounding variable, affecting the association between maximum methotrexate dose and the occurrence of overall AEs, and was kept in the logistic regression model.

methotrexate use for adults with psoriasis in 2 recent meta-analyses.[25,26] In addition, the risks of GI AEs, transaminitis, and subsequent treatment discontinuation were higher for methotrexate than adalimumab for adults with psoriasis participating in a large, randomized, prospective comparative trial (CHAMPION [CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients]).[27] Similarly, GI AEs and transaminitis are frequently described in children with psoriasis and juvenile idiopathic arthritis treated with methotrexate,[7,28] but not with biologic agents. Given that most children in our study were treated with methotrexate (n = 253) or TNF-I (n = 84) monotherapy, we were able to compare treatment-related AEs and confirm the greater risk of methotrexate-related GI AEs and laboratory-related AEs. These AEs did not lead to a greater risk of treatment discontinuation, but inadequate power or failure to control for AE severity and medication dosage could have explained the lack of significance. Injection site reactions were the predominant AE for children receiving biologic agents. Related infections, primarily airway, were also more frequently reported by patients receiving biologic agents compared to methotrexate, which is consistent with results of studies of psoriasis in adults.[29,30] Reported infections with both drug classes were not serious. Older age at the start of treatment, but not BMI percentile, was associated with more AEs overall, which may reflect more frequent reporting by older teens or an increased risk of AEs related to behaviors, such as alcohol intake despite warning.[31]

Folic acid supplementation during methotrexate treatment is thought to reduce the incidence of GI AEs, but, to date, there are no consensus guidelines for dosage and timing of folic acid administration.[32,33] We found that the risk of GI AEs

correlated with the folic acid regimen, not the total weekly folic acid or methotrexate dosage. Our findings of more GI AEs with once-weekly folic acid dosing than with dosing 6 or 7 days per week parallel those in patients with rheumatoid arthritis taking 10 mg/week vs 1 mg/d of folic acid (adjusted between-group hazard ratio, 4.22; 95% CI, 1.19-14.98).[34] Additional testing is needed to determine if the folic acid regimen affects efficacy of methotrexate in children with psoriasis.

Limitations

Our retrospective analysis was limited by the quality of medical records and lack of standardization in the clinical approach (eg, dosages, treatment schedule, and disease severity assessments driving systemic treatment). Our requirement for a minimal core data set for patient inclusion reduced the number of eligible children from thousands to 390 meeting all criteria and having used a systemic medication, introducing possible reporting bias. In addition, there is the potential for reporting bias across drug classes, as the predefined dropdown boxes for AE subcategories were not identical (eg, in the section for methotrexate, infections could only be reported as free text, while the section for biologic agents had a dropdown option).

To date, no guidelines exist for laboratory evaluations for pediatric patients taking biologic agents beyond an annual tuberculosis assessment. Only 60% of pediatric dermatologists in the United States performed laboratory testing beyond tuberculosis testing (A.S.P., unpublished data, 2013), while clinicians in Europe probably tended to follow the European S3 guidelines for monitoring systemic treatment of psoriasis in adults.[35] Only abnormal laboratory values were collected in our study. As such, the total number of laboratory tests was likely far less for biologic agents than for methotrexate, potentially increasing the likelihood of finding an abnormal laboratory test result for patients receiving methotrexate. Even when checked at least 72 hours after methotrexate dosing, transient elevations in hepatic transaminase levels are common in children, likely related to viral infection,[36] and often resolve without dose adjustment or discontinuation of treatment. Finally, SAEs were only gathered through 3 months after treatment discontinuation, preventing inclusion of delayed SAEs.

Conclusions

Patients with pediatric psoriasis treated with methotrexate had a greater risk of having 1 or more AEs than those treated with TNF-I, although fewer AEs occurred with methotrexate or TNF-I than with other drug classes. Gastrointestinal AEs were the most frequently reported subcategory of AEs with methotrexate and the cause of AE-related treatment discontinuation. Our data suggest that a weekly administration of folic acid could be replaced with a daily or 6 times weekly administration to reduce GI AEs, although the potential efficacy of 6 vs 7 times weekly dosing deserves further investigation.

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Accepted for Publication: June 22, 2017.

Published Online: September 13, 2017. doi:10.1001/jamadermatol.2017.3029

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Obtained funding: Seyger, Paller.
Administrative, technical, or material support: Bronckers, Seyger, West, Tom, Hogeling, Mahé, Siegfried, Vleugels, Lambert.
Study supervision: Seyger, Tollefson, Siegfried, Szalai, Cordoro, Lambert, Paller.

Conflict of Interest Disclosures: Dr Cordoro reported serving as a consultant for and receiving honoraria from Celgene and Pfizer. Dr Holland reported serving as a consultant for and receiving honoraria from Amgen, and serving as a consultant for and receiving honoraria from Pfizer.
Dr Lara-Corrales reported serving as a consultant and investigator for and receiving honoraria from AbbVie, Janssen, and Eli Lilly. Dr Mahé reported serving as a consultant for and receiving honoraria from AbbVie, Janssen-Cilag, Novartis, and Pfizer, and serving as an investigator for AbbVie, Amgen, AstraZeneca, Boehringer, Novartis, and Pfizer.
Dr Mrowietz reported serving as a consultant and investigator for and receiving honoraria from AbbVie, Almirall Hermal GmbH, Amgen, Boehringer-Ingelheim, Celgene, Janssen, Eli Lilly, Merck, Novartis, and Pfizer. Dr Paller reported serving as a consultant for and receiving honoraria

from AbbVie, and serving as a consultant and investigator for Amgen, Eli Lilly, Janssen, Novartis, and Pfizer. Dr Philipp reported receiving travel grants or honoraria or serving as a consultant member of the advisory board and speaker's bureau for AbbVie Deutschland GmbH & Co. KG, Almirall Hermal GmbH, Amgen GmbH, Biogen IDEC GmbH, BMS GmbH, Boehringer Ingelheim Pharma GmbH & Co. KG, Celgene GmbH, Charité Research Organisation GmbH, Janssen-Cilag GmbH, Leo Pharma GmbH, Lilly Deutschland GmbH, MSD Sharp & Dohme GmbH, Novartis Pharma GmbH, and Pfizer Deutschland GmbH. Dr Seyger reported serving as a consultant for and receiving honoraria from AbbVie, Almirall, Boehringer Ingelheim, Lilly, and Pfizer; serving as a speaker for AbbVie, Lilly, and Pfizer; traveling to meetings with AbbVie, Lilly, Pfizer, and Leo Pharma; and serving as an investigator (with funds paid directly to the institution) for AbbVie, Almirall, Astellas, Leo Pharma, and Pfizer. Dr Siegfried reported serving as a consultant for and receiving honoraria from Boehringer-Ingelheim, Eli Lilly, and Novartis, and serving as an investigator for Amgen, Eli Lilly, and Janssen. Dr Tom reported serving as an investigator for Amgen, Celgene, and Janssen. Dr Zachariae reported serving as a consultant for and receiving honoraria from AbbVie, Janssen-Cilag, Eli Lilly, Merck, and Novartis, and serving as an investigator for Amgen and AbbVie. Dr Cordoro reported serving as a consultant for and receiving honoraria from Valeant. Dr Lara-Corrales reported serving as a consultant for Johnson & Johnson, Valeant, and Pierre-Fabre, and serving as an investigator for Galderma. Dr Mahé reported serving as an investigator for Leo Pharma. Dr Mrowietz reported serving as an advisor for, receiving speakers honoraria from, receiving grants from, and/or participating in clinical trials with Biogen, Celgene, Centocor, Dr Reddy's, Foamix, Forward Pharma, Leo Pharma, Medac, Miltenyi Biotech, UCB, VBL, and Xenoport. Dr Paller reported serving as a consultant and investigator for and receiving honoraria from Amicus, Celgene, and Leo, and serving as a consultant and receiving honoraria from Dermira, Galderma, Genentech, GSK, Krystal Biotech, Pierre-Fabre, Puricore, Procter & Gamble, Roivant, Sanofi-Regeneron, and Valeant. Dr Philipp reported serving as a consultant member of advisory boards and speaker's bureaus for Biogen IDEC GmbH, BMS GmbH, Celgene GmbH, Charité Research Organisation GmbH, Dermira Inc, Forward Pharma, GlaxoSmithKline GmbH & Co KG, Leo Pharma GmbH, Maruho Europe Ltd, MSD Sharp & Dohme GmbH, Mundipharma, VBL Therapeutics, and UCB Pharma. Dr Siegfried reported serving as a consultant for and receiving honoraria from Boehringer-Ingelheim, Novartis, Pierre Fabre, Verrica, Regeneron, Sanofi, Stiefel, Glaxo, and Pfizer. Dr Zachariae reported serving as a consultant for and receiving honoraria from Takeda, and serving as an investigator for Leo Pharma, Regeneron, MSD, and Takeda. No other conflicts were reported.

Funding/Support: This study was supported by a grant from the International Psoriasis Council. Dr Tom's salary related to psoriasis research is supported, in part, by Career Development Award K23AR060274 from the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases.

Role of the Funder/Sponsor: The funding sources were not involved in the design and conduct of the study; collection, management, analysis or interpretation of data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

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Additional Contributions: We thank the Psoriasis Investigator Group of the Pediatric Dermatology Research Alliance and the European Working Group on Pediatric Psoriasis for their involvement and, in particular, Luis Puig, MD, PhD, Department of Dermatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, and Ulrike Blume-Peytavi, MD, PhD, Clinical Research Center for Hair and Skin Science, Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Berlin, Germany, for their careful review of the manuscript. We thank our colleagues, the many students, fellows, research assistants, and faculty who helped to gather data for this study: Nicholas Celano, MD, University of California, San Diego; Jennifer Day, MD, Department of Dermatology, Northwestern University; Scott Elman, MD, Children's Hospital of Boston; Hanna Fadzeyeva, MD, Hospital for Sick Children, Toronto; Rivka Friedland, MD, Department of Dermatology, Northwestern University; Supriya Immaneni, BS, Department of Dermatology, Northwestern University; Tina Kiguradze, BS, Department of Dermatology, Northwestern University; Doris Greczycho, Charité-Universitäts-Medizin, Berlin, Germany; Maria Hitraya-Low, BS, University of California, San Francisco; Michael Johnson, BS, Phoenix Children's Hospital; Adam Kinzel, BS, Medical College of Wisconsin, Milwaukee; Georgios Kokolakis, MD, Charité-Universitäts-Medizin, Berlin, Germany; Eszter Pap, MD, Heim Pál Children's Hospital, Budapest, Hungary; Stephanie Rangel, PhD, Department of Dermatology, Northwestern University; Sofie De Schepper, MD, PhD, Ghent University Hospital, Ghent, Belgium; Kaspar Torz, MD, University Medical Center Schleswig-Holstein, Kiel, Germany; Klara Veres, MD, Heim Pál Children's Hospital, Budapest, Hungary; and Amanda Winkler, BS, University of Massachusetts, Worcester. We appreciate calculation of the BMI percentiles by Jonathan Silverberg, MD, PhD, MPH, Department of Dermatology, Northwestern University. None of the acknowledged contributors received compensation for these services.

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