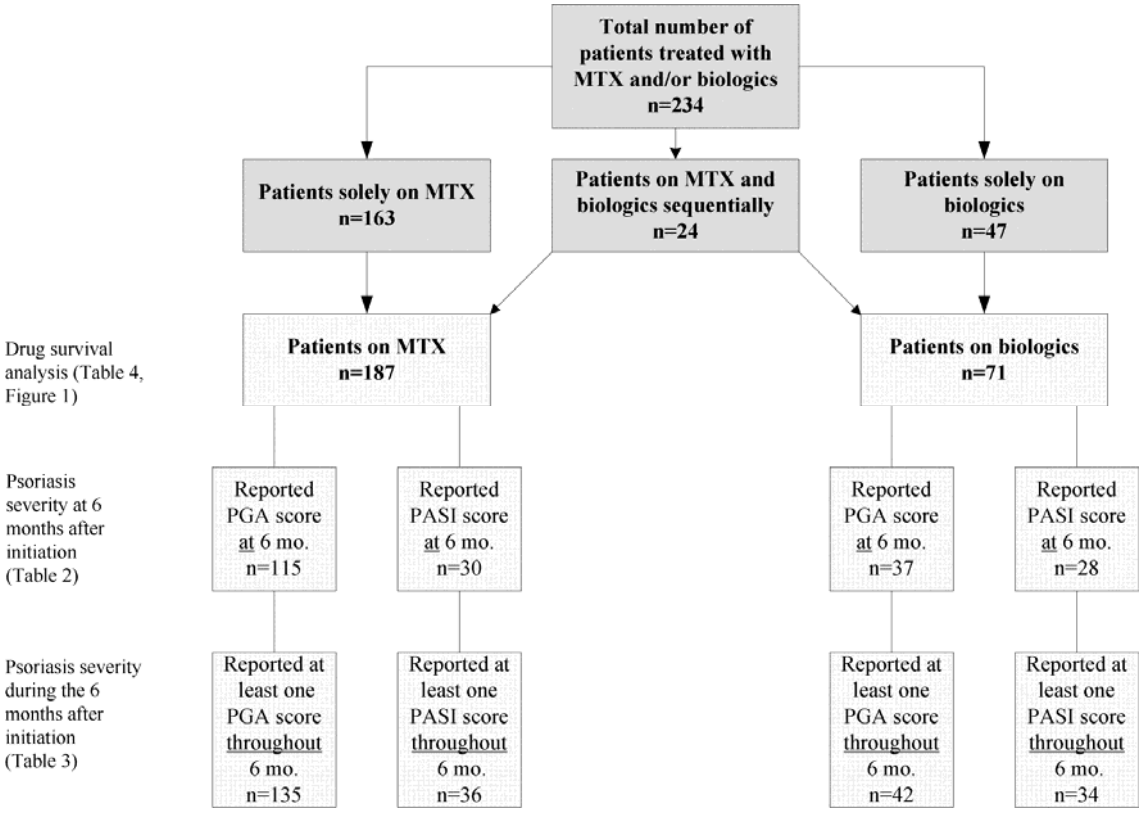
Supplementary Online Content

Bronckers IMGJ, Paller AS, West DP, et al; for the Psoriasis Investigator Group, the Pediatric Dermatology Research Alliance, and the European Working Group on Pediatric Psoriasis. A comparison of psoriasis severity in pediatric patients treated with methotrexate vs biologic agents. *JAMA Dermatol*. Published online February 5, 2020. doi:10.1001/jamadermatol.2019.4835

This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure. Flow chart of methotrexate and biologic treatment episodes available for determination of psoriasis severity (PGA and PASI) and drug survival.



eTable 1. Treatment episode characteristics (N=258)[a]			
Characteristic	**MTX treatment episodes, No. (%)[b]** (N=187, 72.5%)	**Biologic treatment, No. (%)[b,c]** (N=71, 27.5%)	**P- value[d]**
Continent			0.118
North America	115 (61.5)	37 (52.1)	
Europe	72 (38.5)	34 (47.9)	
Sex			0.595
Male	86 (46.0)	35 (49.3)	
Female	101 (54.0)	36 (50.7)	
Race			0.632
White	116 (62.0)	52 (73.2)	
Black or African American	7 (3.7)	1 (1.4)	
Asian	5 (2.7)	2 (2.8)	
Unknown or not reported	59 (31.6)	16 (22.5)	
Ethnicity			0.640
Not Hispanic or Latino	83 (44.4)	34 (47.9)	
Hispanic or Latino	18 (9.6)	10 (14.1)	
Unknown or not reported	86 (46.0)	27 (38.0)	
BMI category (N=119)	*N=86*	*N=30*	0.449
Underweight	6 (7.0)	0 (0.0)	
Normal weight	43 (50.0)	15 (50.0)	
Overweight	11 (12.8)	7 (23.3)	
Obesity	26 (30.2)	8 (26.7)	
BMI percentile, mean (SD)	66.4 (32.1)	72.8 (28.1)	0.262
BMI, mean (SD)	21.5 (6.2)	23.6 (7.4)	0.062
Age at diagnosis, mean (SD), y	8.6 (3.7)	8.7 (3.8)	0.724
Age at start of systemic therapy, mean (SD), y	11.7 (3.6)	13.3 (2.9)	**0.000**
Disease duration, mean (SD), y	3.3 (3.4)	4.6 (3.3)	**0.003**
Treatment duration, mean (SD), y	1.5 (1.3)	1.7 (1.5)	0.547
Naive for systemic medication/ Previously used systemic medication	179 (95.7)	46 (64.8)	**0.000**
Naive for biologic agents/ Previously used biologic agents[d]	186 (99.5)	NA	
Naive for methotrexate/ Previously used MTX[e]	NA	48 (67.6)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); MTX, methotrexate; NA, not applicable.
[a] All MTX and biologic treatment episodes were included (MTX n=163; biologics n=.47, MTX and biologics; n=24). MTX treatment could have been preceded by other conventional systemics or biological agents. Treatment with biologics could have been preceded by conventional systemics (including MTX) or other biological agents. However, patients were treated at any one time with single systemic medication.
[b] Data are presented as number (percentage) of patients unless otherwise indicated.
[c] Etanercept was the most frequently prescribed biologic (n=52; 73.2%) followed by adalimumab (n=14; 19.7%), ustekinumab (n=4; 5.6%) and infliximab (n=1; 1.4%)
[d] Continuous and categorical data are compared by Generalized Estimating Equations to account for dependence of measurements with different systemics used by one patient. The probability of MTX/biologic is estimated as function of the characteristic of interest. Data are presented as No. (%) and mean (SD).
[d] Of 187 patients on MTX, 29 switched to a biologic agent (23 of 29 treatment episodes were included in the biologic group of this study) and 1 had previously used a biologic.
[e] Of 71 patients on biologics, 23 previously used MTX (23 treatment episodes were included in the MTX group of this study) and 2 switched to MTX (1 of 2 treatment episodes was included in the MTX group of this study).

eTable 2. Prescription of MTX and/or biologics in patients with plaque psoriasis in North America vs. Europe (N=234)[a]

Timeframe of prescription	No. (%) of patients solely on MTX (N=163, 69.7%)		No. (%) of patients solely on biologic agent[b] (N=47, 20.1%)		No. (%) of patients treated sequentially with MTX and biologic agent or vice versa (N=24, 10.2%)			
					MTX		Biologic agents[c]	
	North America (N=111)	Europe (N=52)	North America (N=33)	Europe (N=14)	North America (N=4)	Europe (N=20)	North America (N=4)	Europe (N=20)
12.1990 – etanercept trial[d]	3 (2.7)	5 (9.6)	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Inclusion etanercept trial – EMA approval etanercept[e]	23 (20.7)	5 (9.6)	9 (27.3)	1 (7.1)	0 (0.0)	6 (30.0)	1 (25.0)	1 (5.0)
EMA approval etanercept – 09.2014	85 (76.6)	42 (80.8)	23 (69.7)	13 (92.9)	4 (100.0)	14 (70.0)	3 (75.0)	19 (95.0)

Abbreviations: MTX, methotrexate; EMA, European Medicines Agency.

[a] Patients could have been previously treated with conventional systemic agents (except for MTX). However, patients were treated at any one time with a single systemic medication.

[b] Etanercept was the most frequently prescribed biologic (n=32; 68.1%) followed by adalimumab (n=11; 23.4%), ustekinumab (n=3; 6.4%) and infliximab (n=1, 2.1%).

[e] Etanercept was the most frequently prescribed biologic (n=20; 83.3%) followed by adalimumab (n=3; 12.5%) and ustekinumab (n=1; 4.2%).

[d] The etanercept trial started in August, 2004.

[e] The original approval of etanercept in pediatric plaque psoriasis by the EMA was in December 2008 and the first publication reporting etanercept for pediatric psoriasis appeared in the January, 2008.[16]

eTable 3. The odds ratio of achieving PGA 0-1 (left) and PASI75 (right) with biologics vs. MTX at some point during the 6-month follow-up.[a,b,c]

	PGA 0/1 (N=177)				**PASI75** (N=70)		
Systemic treatment	**OR**	**[CI]**	**p-value**	**Systemic treatment**	**OR**	**[CI]**	**p-value**
Overall odds				Overall odds			
MTX (N=135)	1 [reference]			MTX (N=36)	1 [reference]		
Biologic (N=42)[d]	2.00	[0.98-4.00]	**0.056**	Biologic (N=34)[e]	4.56	[2.02-10.27]	**0.000**
Odds at time points (mo)[f]				Follow-up (mo)[f]			
1 mo	1 [reference]			1 mo	1 [reference]		
3 mo	2.90	[1.49-5.62]	0.002	3 mo	4.49	[1.87-10.74]	0.001
6 mo	7.20	[3.81-13.61]	0.000	6 mo	11.58	[4.17-32.21]	0.000
Severity score at start[g]				Severity score at start			
PGA	0.45	[0.29-0.70]	0.000	PGA			
PASI				PASI	1.03	[0.98-1.07]	0.260

Abbreviations: CI, confidence interval; GEE, General estimating equation; MTX, methotrexate; OR, odds ratio; PASI, psoriasis area and severity index; PGA, physician global assessment.

[a] The relation between medication and severity scores during follow up was studied by GEE modeling. Patients who used MTX and biologics at different times were included in both treatment groups. **Sex, age at treatment start and disease duration** did not influence results and were therefore not included in the model. There was no interaction between follow-up duration and medication.

[b] MTX treatment could have been preceded by other conventional systemics or biological agents. Treatment with biologics could have been preceded by conventional systemics (including MTX) or other biological agents. However, patients were treated at any one time with single systemic medication.

[c] Participating sites provided PASI and/or PGA scores at medication initiation and during at least one follow-up visit. Patient numbers are therefore not identical in both groups. The percentage of missing data is <10% at each specific timepoint.

[d] Etanercept was the most frequently prescribed biologic (n=29; 69.0%) followed by adalimumab (n=10; 23.8%), ustekinumab (n=2; 4.8%) and infliximab (n=1; 2.4%).

[e] Etanercept was the most frequently prescribed biologic (n=25; 73.5%) followed by adalimumab (n=5; 14.7%), ustekinumab (n=4; 11.8%).

[f] Severity scoring had to be available within the 3 months before systemic medication initiation and during at least one follow-up visit at 0-2 months (defined as 1 month follow-up), 2-4 months (defined as 3 month follow-up) or 4-8 months (defined as 6 month follow-up) after treatment initiation.

[g] Severity score at start refers to the corresponding PASI and/or PGA score at medication initiation.

eTable 4. The mean reduction in PGA (left) and PASI (right) scores with biologics vs. MTX at some point during the 6-month follow-up. [a,b,c]

	PGA score (N=177)				**PASI score** (N=70)		
	Effect	**SD**	**p-value**		**Effect**	**SD**	**p-value**
Systemic treatment				**Systemic treatment**			
MTX (N=135)	0 [reference]			MTX (N=36)	0 [reference]		
Biologic (N=42)[d]	-0.31	-0.56; -0.06	**0.015**	Biologic (N=34)[e]	-3.13	[-4.33; -1.94]	**0.000**
Follow-up (mo)[f]				Follow-up (mo)[f]			
1 mo	0 [reference]			1 mo	0 [reference]		
3 mo	-0.45	-0.63; -0.27	0.000	3 mo	-2.71	[-3.99; -1.44]	0.000
6 mo	-0.98	-1.16;-0.80	0.000	6 mo	-3.49	[-4.75;-2.22]	0.000
Severity score at start[g]				Severity score at start			
BSA				BSA			
PASI				PASI	0.35	[0.26;0.44]	0.000
PGA	0.54	0.37;0.71	0.000	PGA			

Abbreviations: CI, confidence interval; MTX, methotrexate; PASI, psoriasis area and severity index; PGA, physician global assessment.

[a] The relation between medication and severity scores during follow up was studied by linear mixed modeling. Patients who used MTX and biologics at different times were included in both treatment groups. **Sex, age at treatment start and disease duration** did not influence results and were therefore not included in the model. There was no interaction between follow-up duration and medication.

[b] MTX treatment could have been preceded by other conventional systemics or biological agents. Treatment with biologics could have been preceded by conventional systemics (including MTX) or other biological agents. However, patients were treated at any one time with single systemic medication.

[c] Participating sites provided PASI and/or PGA scores at medication initiation and during at least one follow-up visit. Patient numbers are therefore not identical in both groups. The percentage of missing data is <10% at each specific timepoint.

[d] Etanercept was the most frequently prescribed biologic (n=29; 69.0%) followed by adalimumab (n=10; 23.8%), ustekinumab (n=2; 4.8%) and infliximab (n=1; 2.4%)

[e] Etanercept was the most frequently prescribed biologic (n=25; 73.5%) followed by adalimumab (n=5; 14.7%), ustekinumab (n=4; 11.8%).

[f] Severity scoring had to be available within the 3 months before systemic medication initiation and during at least one return visit at 0-2 months (defined as 1 month follow-up), 2-4 months (defined as 3 month follow-up) or 4-8 months (defined as 6 month follow-up) after treatment initiation.

[g] Severity score at start refers to the corresponding PASI and/or PGA score at medication initiation.

eTable 5. Drug survival in patients treated with MTX vs. biologics corrected for variables that explained differences in drug survival between groups[a,b,c]

	Event= discontinuation			Event= discontinuation due to ineffectiveness of systemic agent			Event= discontinuation due to AE		
Characteristics	**Hazard ratio**	**[95% CI]**	**p-value**	**Hazard ratio**	**[95% CI]**	**p-value**	**Hazard ratio**	**[95% CI]**	**p-value**
Systemic agent									
MTX vs. biologic	2.23	[1.21-4.10]	**0.010**	1.64	[0.80-3.36]	0.182	4.67	[1.08-20.26]	**0.039**
Sex									
Male vs. female	1.55	[0.97-2.49]	0.067	1.57	[0.85-2.91]	0.152	1.78	[0.75-4.21]	0.192
Older age at treatment start, yrs[d]	1.09	[1.00-1.19]	**0.041**	1.16	[1.03-1.31]	**0.013**	1.01	[0.87-1.17]	0.916
Longer disease duration, yrs[d]	1.04	[0.96-1.11]	0.364	1.02	[0.93-1.12]	0.712	1.05	[0.92-1.17]	0.458

Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; MTX, methotrexate.

Data are presented as HR with corresponding 95% CI.

[a] All MTX (N=187) and biologic (N=71) treatment episodes were included.

[b] Hazard ratios were corrected for variables that explained differences in drug survival between MTX and biologic treated patients.

[c] MTX treatment could have been preceded by other conventional systemics or biological agents. Treatment with biologics could have been preceded by conventional systemics (including MTX) or other biological agents. However, to be included, patients were treated at any one time with single systemic medication.

[d] Age in 1-year intervals, disease duration in 1-year intervals.

