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Drug Survival of Dupilumab, Methotrexate, and Cyclosporine A in Children With Atopic Dermatitis

in Children With Atopic Dermatitis

Lisa P. van der Rijst, MD; Esmé Kamphuis, MD; Marie L. A. Schuttelaar, MD, PhD; Rimoon Hurmuz, MD; Marieke M. B. Seyger, MD, PhD; Anouk G. M. Caron, MD; Nicolaas P. A. Zuithoff, PhD; N. Tan Nguyen, MD; Marijke Kamsteeg, MD, PhD; Marjolein S. de Bruin-Weller, MD, PhD; Suzanne G. M. A. Pasmans, MD, PhD; Maritza A. Middelkamp-Hup, MD, PhD; Marlies de Graaf, MD, PhD

IMPORTANCE Dupilumab, methotrexate (MTX), and cyclosporine A (CsA) are valuable treatment options for pediatric patients with refractory moderate to severe atopic dermatitis (AD). Yet, comparative data on these treatments in pediatric patients are scarce.

OBJECTIVE To evaluate drug survival of dupilumab, MTX, and CsA, and identify associated predictors in a multicenter daily practice cohort study of pediatric patients with AD.

DESIGN, SETTING, AND PARTICIPANTS This multicenter daily practice cohort study included patients with AD aged 2 to 17 years treated with dupilumab, MTX, and/or CsA in 5 tertiary centers in the Netherlands between 2013 and 2023. Data were extracted from the prospective BioDay and TREAT Netherlands registries and electronic medical records.

EXPOSURES Dupilumab, MTX, CsA.

MAIN OUTCOMES AND MEASURES Drug survival was analyzed using Cox proportional hazard regression models. Univariable and multivariable Cox regression analyses were conducted to identify variables associated with drug discontinuation.

RESULTS A total of 502 treatment episodes in 362 unique patients were included, comprising 192 dupilumab episodes, 94 MTX episodes, and 216 CsA episodes. Overall, the mean (SD) age at treatment initiation was 12.9 (3.8) years, and 272 treatment episodes (54.2%) in female patients. The 1-year, 2-year, and 3-year overall drug survival rates, respectively, were 84.1%, 72.3%, and 62.0% for dupilumab; 60.7%, 39.3%, and 25.3% for MTX; and 43.9%, 21.5%, and 10.4% for CsA. Ineffectiveness was the most frequent reason for drug discontinuation, accounting for 178 episodes (35.5%), mostly in patients treated with CsA, followed by adverse effects in 94 patients (18.7%). Treatment with MTX and treatment with CsA were independently associated with a higher risk for drug discontinuation due to ineffectiveness (hazard ratio [HR], 4.45 [95% CI, 2.38-8.34] and HR, 10.88 [95% CI, 6.23-19.02], respectively) and adverse effects (HR, 4.39 [95% CI, 2.05-9.39] and HR, 3.83 [95% CI, 1.85-7.92], respectively) compared to treatment with dupilumab. Patients aged 12 to 17 years starting systemic treatment were independently associated with a higher risk for drug discontinuation due to ineffectiveness (HR, 1.55 [95% CI, 1.10-2.20]) and adverse effects (HR, 2.39 [95% CI, 1.33-4.30]).

CONCLUSIONS AND RELEVANCE This multicenter daily practice cohort study demonstrated a superior 1-year, 2-year, and 3-year overall drug survival for dupilumab, followed by MTX, with the lowest rates observed for CsA in pediatric patients with AD. This study also identified characteristics associated with discontinuation. These results provide insight into drug survival resulting from the effectiveness, safety, and tolerability of these systemic treatments in pediatric patients with AD and contribute to the optimization of patient outcomes.

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Marlies de Graaf, MD, PhD, Department of Dermatology and Allergology, University Medical Center Utrecht, Heidelberglaan 100, 3584CX Utrecht, the Netherlands (m.degraaf-10@umcutrecht.nl).

Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease that affects up to 20% of children.[1-3] AD is associated with a substantial multidimensional patient burden, increasing with disease severity.[3,4] Most patients with AD have mild to moderate disease that can be adequately controlled with emollients, topical anti-inflammatory treatments, and/or UV therapy.[5,6] However, a minority of patients with refractory moderate to severe disease require systemic treatment to induce and maintain disease control.[5,7]

Conventional systemic immunosuppressants methotrexate (MTX) and cyclosporine A (CsA) are commonly prescribed off-label for the short-term or long-term treatment of moderate to severe AD in pediatric patients.[8-10] Dupilumab, a monoclonal antibody blocking the effects of both interleukin-4 and interleukin-13, has been approved for the treatment of moderate to severe AD in adolescents (aged 12-17 years), children (aged 6-11 years), and young children (aged 6 months to 5 years) in 2019, 2020, and 2023, respectively, and was thereby the first registered biological for pediatric patients with moderate to severe AD.[11-13]

Dupilumab, MTX, and CsA have demonstrated effectiveness in the treatment of pediatric patients with AD in clinical practice–based studies and clinical trials.[7,11-18] However, clinical data from daily practice studies about long-term efficacy and safety remain scarce, and clinical trials do not fully reflect daily clinical practice.[19-21] Drug survival is a proxy measure for the effectiveness, safety, adherence, and tolerability of a drug, and it helps reflect daily practice by evaluating the time from initiation to discontinuation of treatment.[19,20] To date, there are limited drug survival studies in pediatric patients, and comparative studies between drug survival of dupilumab, MTX, and CsA are lacking.[18,22-24]

Therefore, the primary objective of this study was to investigate the 1-year, 2-year, and 3-year drug survival of dupilumab, MTX, and CsA in a multicenter daily practice cohort study of pediatric patients with AD. The secondary objective was to identify characteristics associated with discontinuation of these treatments.

Key Points

Question What is the drug survival of dupilumab, methotrexate, and cyclosporine A in children with atopic dermatitis, and what variables are associated with drug discontinuation?

Findings In this multicenter daily practice cohort study of 502 treatment episodes in children with atopic dermatitis, dupilumab demonstrated superior 1-year, 2-year, and 3-year overall drug survival, followed by methotrexate and cyclosporine A. The introduction of dupilumab was associated with decreased drug survival of methotrexate and cyclosporine A, and characteristics associated with discontinuation due to adverse effects and ineffectiveness were identified.

Meaning These results provide insight into drug survival based on the effectiveness, safety, and tolerability of these systemic treatments in children with atopic dermatitis, and contribute to the optimization of patient outcomes.

Methods

Study Design

This cohort study included data from patients aged 2 to 17 years who started treatment with dupilumab, MTX, and/or CsA for moderate to severe AD in 1 of 5 tertiary centers in the Netherlands (University Medical Center Utrecht; Amsterdam University Medical Center; Erasmus MC University Medical Center, Rotterdam; Radboud University Medical Center, Nijmegen; and University Medical Center Groningen between January 1, 2013, and December 31, 2022. The database was locked on July 1, 2023. There were no regulatory requirements that could have influenced the choice of treatment. Patients who received the treatment as part of a clinical trial were excluded. The study was approved by the Medical Ethics Review Committee NedMec (University Medical Center Utrecht) and was performed according to the Declaration of Helsinki.

Data Collection

Patient and treatment characteristics were extracted from the prospective BioDay registry, Treatment of Atopic Eczema (TREAT) Netherlands registry, and electronic medical records. Patient characteristics included age, sex, body weight, age of AD onset, self-reported atopy (asthma, allergic rhinitis, allergic conjunctivitis, or food allergy), medical history, treatment history, and baseline Eczema Area and Severity Index (EASI) ranging from 0 (clear) to 72 (very severe) at treatment initiation.[25] Treatment characteristics included initiation and discontinuation dates, starting dosage, maximum dosage, administration form, adverse effects, reasons for discontinuation, and concomitant medication use. Dupilumab was administered according to the US Food and Drug Administration–approved dosing schedules. National guidelines were followed for the dosing of MTX (0.2-0.4 mg/kg/wk) and CsA (3-5 mg/kg/d).[26-28] Reasons for discontinuation were stratified into ineffectiveness, adverse effects, administration problems, well-controlled disease, restricted treatment duration (due to off-label treatment with immunosuppressants), and unknown/patient wish. Multiple reasons for discontinuation were recorded if applicable (eg, ineffectiveness and adverse effects). Ineffectiveness was defined as the lack of improvement in objective clinical signs and/or subjective patient-reported symptoms. Concomitant use of systemic immunosuppressive treatment was recorded as use of prednisolone, CsA, or Janus kinase inhibitors within 1 week; MTX within 4 weeks; and biologics within 10 weeks before baseline. A treatment episode was defined as the time from treatment initiation to discontinuation. A new episode was recorded if more than 90 days had elapsed between consecutive treatments with the same drug. Treatment episodes in patients who reached 18 years of age were followed up continuously until discontinuation. The last follow-up date was recorded in patients who were lost to follow-up.

Statistical Analyses

Drug Survival

Continuous data were expressed as mean (SD), and categorical data as frequencies and percentages. Drug survival was defined as the time from drug initiation to discontinuation. This

variable was estimated using Cox proportional hazard regression models with robust standard errors to correct for multiple episodes per patient.[29] Type 3 tests (Wald tests) were used to test for differences within survival. Primarily, the 1-year, 2-year, and 3-year overall drug survival of dupilumab, MTX, and CsA was evaluated. Active treatments at database lock, patients lost to follow-up, and patients discontinuing treatment due to well-controlled disease were censored. Secondary, drug survival owing to ineffectiveness, adverse effects, and administration problems were analyzed separately. In addition, drug survival analyses of MTX and CsA were performed before and after the introduction of dupilumab, defined as its approval by the European Medicines Agency (August 6, 2019, and November 30, 2020, for patients aged 12 to 17 years and younger than 12 years, respectively).[14,15]

Determining Characteristics Associated With Drug Survival

The following variables were defined as variables that may be associated with discontinuing treatment due to ineffectiveness, adverse effects, and/or administration problems: treatment with dupilumab, treatment with MTX, treatment with CsA, gender, age (dichotomized into 2-11 years and 12-17 years), asthma, allergic rhinitis, allergic conjunctivitis, food allergy, AD in first-degree relatives, non-naive status for systemic treatments (excluding oral corticosteroids), and use of concomitant immunosuppressants at baseline.

Univariable Cox regression analysis was performed to identify the variables associated with drug discontinuation due to ineffectiveness, adverse effects, and administration problems, and discontinuation due to the combination of ineffectiveness, adverse effects, and/or administration problems for each individual treatment. A multivariable Cox regression analysis was performed for the individual reasons for discontinuation and for each treatment separately. All of the aforementioned variables were included in the multivariable analysis. To compare discriminative properties of the variables associated with discontinuation, C statistics with 95% CIs were calculated, similar to an area under the receiver operator characteristic curve for dichotomous outcomes. The validity of the proportional hazards assumption was assessed with residual analysis. *P* values of less than .05 were considered statistically significant. Data were analyzed using SPSS Statistics, version 27.0.0.0 (IBM), and SAS 9.4 (SAS Institute Inc).

Results

Patient Characteristics

A total of 502 treatment episodes in 362 unique patients were included, comprising 192 dupilumab episodes, 94 MTX episodes, and 216 CsA episodes. The data from 209 treatment episodes (41.6%) were extracted from the BioDay or TREAT Netherlands registry, of which 151 episodes (72.2%) involved dupilumab. The data from 293 treatment episodes (58.4%) were extracted from the electronic medical records, of which 252 episodes (86.0%) involved MTX and CsA. Overall, the mean (SD) age at treatment initiation was 12.9 (3.8) years, and 272 treatment episodes (54.2%) in female patients. The overall mean (SD) baseline EASI score was 20.0 (11.6), indicating moderate to severe disease. **Table 1** shows the baseline characteristics of patients specified by the individual treatments. Notably, the proportion of patients using concomitant immunosuppressants at baseline varied within the treatment groups (dupilumab: 38 treatment episodes [19.8%]; MTX: 16 treatment episodes [17.0%]; CsA: 6 treatment episodes [2.8%]) (Table 1). The use of concomitant immunosuppressants during treatment was comparable between treatments (eTable 1 in Supplement 1).

Treatment Patterns

CsA was most frequently administered as first-line treatment in 195 patients (54.6%), followed by dupilumab in 96 patients (26.9%), and MTX in 59 patients (16.5%) (eFigure 1 in Supplement 1). Collectively, 79 patients switched to treatment with dupilumab as second-line treatment, 30 to MTX, and 11 to CsA. A subset of 25 patients discontinued treatment due to well-controlled disease after first-line treatment with CsA (n = 21) or MTX (n = 4). A smaller number of patients discontinued treatment due to well-controlled disease in subsequent lines of treatment (8 after second-line treatment and 1 after third-line treatment).

Reasons for Discontinuing Treatment

At database lock, 52 dupilumab treatment episodes (27.1%), 67 MTX treatment episodes (71.3%), and 187 CsA treatment episodes (86.6%) were discontinued (**Table 2**). Overall, ineffectiveness was the most common reason for discontinuation in 178 treatment episodes (35.5%), followed by 94 (18.7%) for adverse effects (18.7%). Discontinuation due to ineffectiveness was most common in treatment episodes with CsA (56.5%), while discontinuation due to adverse effects was more common in treatment episodes with MTX (29.8%). In patients discontinuing treatment due to adverse effects, conjunctivitis was the most common adverse effect in discontinuing dupilumab treatment, nausea in patients discontinuing MTX, and headache in patients discontinuing CsA (eTable 2 in Supplement 1). Discontinuation due to administration problems was observed in 14 CsA treatment episodes (6.5%), compared to 2 MTX treatment episodes (2.1%; 1 oral administration and 1 subcutaneous administration) and 10 dupilumab episodes (5.2%). Discontinuation due to well-controlled disease occurred in 22 CsA treatment episodes (10.2%), followed by 6 MTX treatment episodes (6.4%) and 6 dupilumab treatment episodes (3.1%).

Drug Survival Rates

Dupilumab showed superior overall survival rates compared to MTX and CsA. In addition, MTX showed superior overall survival rates compared to CsA. The 1-year, 2-year, and 3-year overall drug survival events and rates were as follows: 30 events (84.1%), 40 events (72.3%), and 46 events (62.0%) for dupilumab, respectively; 38 events (60.7%), 55 events (39.3%), and 61 events (25.3%) for MTX, respectively; and 113 events (43.9%), 150 events (21.5%), and 165 events (10.4%) for CsA, respectively (**Figure 1**A; eTable 3 in Supplement 1). Ineffectiveness was the most frequent reason for drug discontinuation in all

Table 1. Baseline Patient Characteristics Specified by Treatment Episode

Characteristic	Treatment episodes, No. (%)		
	Dupilumab (n = 192)	Methotrexate (n = 94)	Cyclosporine A (n = 216)
Age, mean (SD), y	13.1 (3.6)	12.2 (3.8)	12.9 (3.9)
Age group, y			
2-5	5 (2.6)	7 (7.4)	16 (7.4)
6-11	49 (25.5)	27 (28.7)	48 (22.2)
12-17	138 (71.9)	60 (63.8)	152 (70.4)
Sex			
Female	98 (51.0)	54 (57.4)	120 (55.6)
Male	94 (49.0)	40 (42.6)	96 (44.4)
Weight, mean (SD), kg[a]	52.0 (21.3)	46.1 (18.6)	50.7 (20.9)
Unknown	15 (7.8)	23 (24.5)	51 (23.6)
AD onset age			
Infancy (0-1 y)	143 (74.5)	66 (70.2)	143 (66.2)
Childhood (2-11 y)	43 (22.4)	23 (24.5)	60 (27.8)
Adolescence (12-17 y)	2 (1.0)	1 (1.1)	3 (1.4)
Unknown	4 (2.1)	4 (4.3)	10 (4.6)
Atopy in first-degree relatives[b]	159 (82.8)	71 (75.5)	183 (84.7)
Atopic dermatitis	121 (63.0)	49 (52.1)	132 (61.1)
Allergic rhinitis	95 (49.5)	36 (38.3)	102 (47.2)
Asthma	85 (44.3)	31 (33.0)	77 (35.6)
Food allergy	20 (10.4)	4 (4.3)	20 (9.3)
Unknown	5 (2.6)	4 (4.3)	11 (5.1)
Atopic comorbidities[b]			
Allergic rhinitis	148 (77.1)	66 (70.2)	147 (68.1)
Unknown	0	0	3 (1.4)
Asthma	113 (58.9)	42 (44.7)	108 (50.0)
Unknown	0	1 (1.1)	3 (1.4)
Allergic conjunctivitis	93 (48.4)	27 (28.7)	111 (51.4)
Unknown	11 (5.7)	15 (16.0)	24 (11.1)
Food allergy	105 (54.7)	57 (60.6)	100 (46.3)
Unknown	1 (0.5)	1 (1.1)	5 (2.3)
EASI, mean (SD)[c]	19.8 (11.6)	20.7 (11.8)	20.0 (11.6)
Unknown	22 (11.5)	36 (38.3)	109 (50.5)
Concomitant immunomodulator use	38 (19.8)	16 (17.0)	6 (2.8)
Oral corticosteroids	3 (1.6)	7 (7.5)	4 (1.9)
Cyclosporine A	21 (10.9)	8 (8.5)	NA
Methotrexate	13 (6.8)	NA	2 (0.9)
Dupilumab	NA	1 (1.1)	0
Other immunosuppressive drugs	1 (0.5)[d]	0	0
Unknown	0	1 (1.1)	1 (0.5)
Prior immunomodulator use			
≥1 AD systemic treatment(s)	117 (60.9)	54 (57.4)	85 (39.4)
Cyclosporine A	78 (40.6)	34 (36.2)	14 (6.5)
Methotrexate	24 (12.5)	2 (2.1)	8 (3.7)
Dupilumab	2 (1.0)	2 (2.1)	3 (1.4)
Systemic corticosteroids	56 (29.2)	32 (34.0)	74 (34.3)
Other AD systemic treatment[e]	12 (6.3)	1 (1.1)	5 (2.3)

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; NA, not applicable.

[a] Weight was assessed 90 days before to 90 days after treatment initiation.

[b] Atopy in first-degree relatives and atopic comorbidities were self-reported.

[c] EASI was assessed 90 days before to 7 days after treatment initiation.

[d] Other immunosuppressive treatments included 1 patient treated with azathioprine, indicated for Crohn disease.

[e] Other AD systemic treatment distribution was as follows: for dupilumab, 2 mycophenolic acid, 5 Janus kinase inhibitors, 2 azathioprine, and 3 tralokinumab; for methotrexate, 1 mycophenolic acid; for cyclosporine A, 2 azathioprine, 2 mycophenolic acid, and 1 Janus kinase inhibitors.

treatment groups (Figure 1B; eTable 3 in Supplement 1). Dupilumab demonstrated the highest survival rates in analyses stratified by discontinuation due to adverse effects, and comparable rates were found for MTX and CsA (Figure 1C; eTable 3 in Supplement 1). Survival analyses stratified by discontinuation due to administration problems showed the highest survival rates for MTX and the lowest for CsA (Figure 1D; eTable 3 in Supplement 1).

Table 2. Treatment Characteristics

Characteristic	Treatment episodes, No. (%)		
	Dupilumab (n = 192)	Methotrexate (n = 94)	Cyclosporine A (n = 216)
Use status			
Active	134 (69.8)	23 (24.5)	23 (10.6)
Discontinued	52 (27.1)	67 (71.3)	187 (86.6)
Lost to follow-up	6 (3.1)	4 (4.3)	6 (2.8)
Reason for discontinuation			
Ineffectiveness	19 (9.9)	37 (39.4)	122 (56.5)
Adverse effects	16 (8.3)	28 (29.8)	50 (23.1)
Administration problems	10 (5.2)	2 (2.1)[a]	14 (6.5)
Unknown/patient wish	7 (3.6)	6 (6.4)	9 (4.2)
Restricted treatment duration	0	0	7 (3.2)
Well-controlled disease	6 (3.1)	6 (6.4)	22 (10.2)
Starting dose, No. (%) or mean (SD)[b]	200 mg/2 wk: 61 (31.8) 300 mg/2 wk: 85 (44.3) 300 mg/4 wk: 46 (24.0)	11.9 (2.9) mg/wk 0.3 (0.1) mg/kg/wk	4.0 (0.8) mg/kg/d
Unknown	0	2 (2.1)	21 (9.7)
Maximum dose, No. (%) or mean (SD)[b]	200 mg/2 wk: 62 (32.3) 300 mg/4 wk: 36 (18.8) 300 mg/2 wk: 85 (44.3) Other: 9 (4.7)[c]	14.6 (3.6) mg/wk 0.4 (0.2) mg/kg/wk	4.2 (0.8) mg/kg/d
Unknown	0	0	28 (13.0)

Abbreviation: AD, atopic dermatitis.

[a] Administration route distribution was 77 oral, 8 subcutaneous, and 9 unknown; at discontinuation, administration route distribution was 1 oral and 1 subcutaneous.

[b] The variables in the maximum dose row are No. (%) for dupilumab. The variables in the maximum dose row are mean (SD) for methotrexate and cyclosporine A.

[c] Other dosage distribution for dupilumab was as follows: 300 mg/3 wk, 4 (2.1%); 300 mg/10 d, 2 (1.0%); 300 mg/wk, 3 (1.6%).

Drug survival rates for CsA and MTX were significantly higher before the European Medicines Agency approval of dupilumab vs after approval (**Figure 2**; eTable 4 in Supplement 1). For both CsA and MTX, ineffectiveness was the most frequent reason for discontinuing treatment before and after the introduction of dupilumab (eTable 5 in Supplement 1).

Characteristics Associated With Discontinuation Stratified by Reason

Multivariable Cox regression analyses demonstrated that treatment with MTX and treatment with CsA were independently associated with a higher risk for drug discontinuation due to ineffectiveness (hazard ratio [HR], 4.45 [95% CI, 2.38-8.34] and HR, 10.88 [95% CI, 6.23-19.02], respectively) and adverse effects (HR, 4.39 [95% CI, 2.05-9.39] and HR, 3.83 [95% CI, 1.85-7.92], respectively) compared to treatment with dupilumab (**Figure 3**). In addition, patients aged 12 to 17 years at baseline were independently associated with a higher risk for discontinuation due to ineffectiveness (HR, 1.55 [95% CI 1.10-2.20]) and adverse effects (HR, 2.39 [95% CI 1.33-4.30]), compared to younger patients aged 2 to 11 years. (Figure 3) Moreover, patients with AD in first-degree relatives were independently associated with a lower risk of discontinuing treatment due to adverse effects (HR, 0.55 [95% CI, 0.34-0.88]) (Figure 3B). The C statistics of multivariable models for discontinuation due to ineffectiveness, adverse effects, and administration problems were 0.75, 0.74, and 0.68, respectively.

Notably, the univariable analysis showed that patients naive to systemic therapy had a significantly higher risk for discontinuation due to ineffectiveness and adverse effects, and baseline immunosuppressant use was associated with a significantly lower risk for discontinuation (eTable 6 in Supplement 1). However, these characteristics were not statistically significant in multivariable analyses.

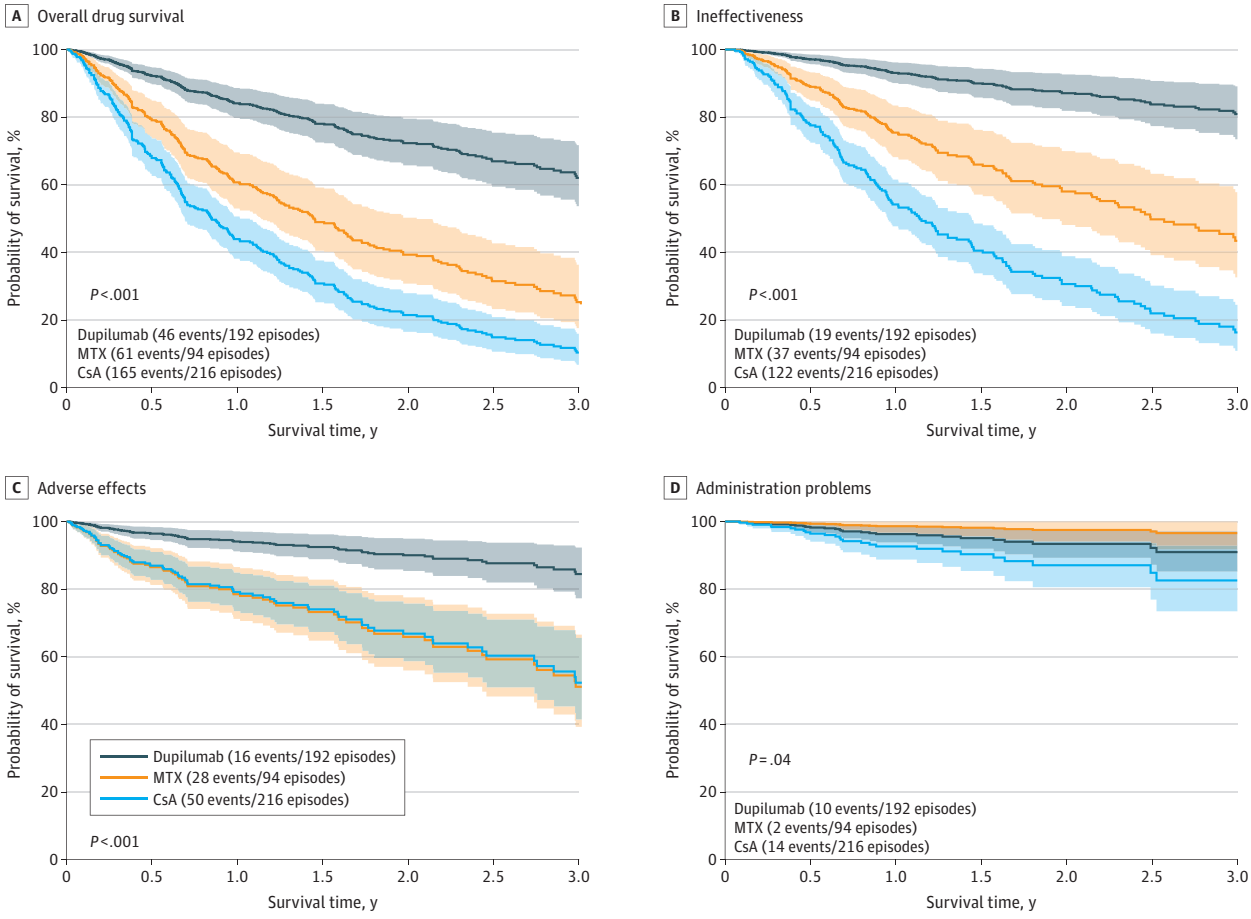
Characteristics Associated With Discontinuation Stratified by Treatment

Univariable and multivariable Cox regression analyses of characteristics associated with the discontinuation of individual treatments are shown in eTable 7 and eFigure 2 in Supplement 1. Patients aged 12 to 17 years were found to be independently associated with a higher risk of discontinuing treatment with MTX (HR, 2.92 [95% CI, 1.49-5.73]; *P* = .002), compared to younger patients aged 2 to 11 years (C statistic = 0.70). Patients with comorbid asthma were independently associated with a lower risk of discontinuing treatment when treated with CsA. However, the concordance between the model-based estimate and observed rates of discontinuing CsA and dupilumab was weak (C statistics = 0.57 and 0.59, respectively). Identification of characteristics associated with discontinuation stratified by individual treatment and by reason for discontinuation was not possible due to the low amount of discontinuation events, especially in patients treated with dupilumab.

Discussion

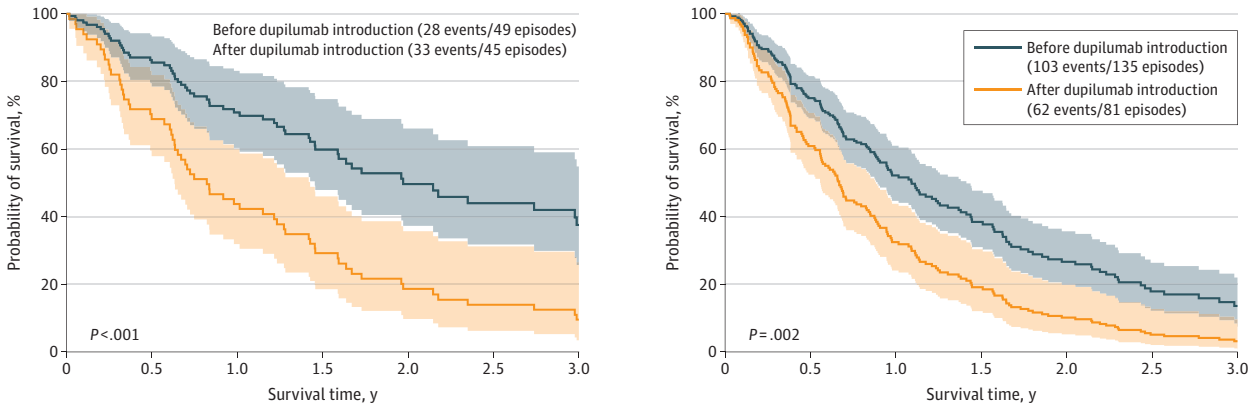
This multicenter daily practice cohort study demonstrated superior 1-year, 2-year, and 3-year overall survival rates for dupilumab followed by MTX and CsA in a large cohort of pediatric patients with AD. Drug discontinuation was predominantly associated with ineffectiveness in all treatment groups. Treatment with MTX, CsA, and age of 12 to 17 years at

Figure 1. Overall Drug Survival and Survival by Reason for Discontinuation for Dupilumab, Cyclosporine A (CsA), and Methotrexate (MTX) Over 3 Years



In addition to overall drug survival (A), the drug survival curves were stratified by discontinuation due to ineffectiveness (B), adverse effects (C), and administration problems (D). The data from patients who discontinued treatment due to well-controlled disease and those lost to follow-up were censored in the overall drug survival analysis. The shaded areas represent 95% CIs.

Figure 2. Overall Drug Survival of Methotrexate and Cyclosporine A Before and After the Introduction of Dupilumab

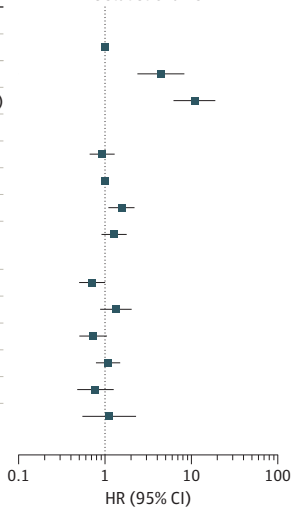


Dupilumab introduction was defined as the European Medicines Agency approval of dupilumab for adolescents aged 12 to 17 years on August 6, 2019, and for children younger than 12 years on November 30, 2020. The data from patients who discontinued treatment due to well-controlled disease and those lost to follow-up were censored. The shaded areas represent 95% CIs.

Figure 3. Variables Associated With Drug Discontinuation Due to Ineffectiveness, Adverse Effects, and Administration Problems

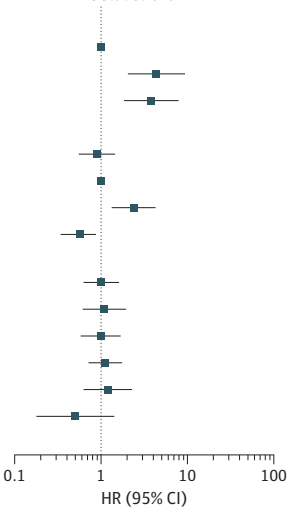
A Ineffectiveness

Study	HR (95% CI)	P value
Treatment characteristics		
Dupilumab	1 [Reference]	NA
Methotrexate	4.45 (2.38-8.34)	<.001
Cyclosporine A	10.88 (6.23-19.02)	<.001
Patient characteristics (BL)		
Sex (female)	0.93 (0.67-1.30)	.67
Age ≥2 to <12 y	1 [Reference]	NA
Age ≥12 to <18 y	1.55 (1.10-2.20)	.01
AD in first-degree relatives	1.28 (0.91-1.79)	.15
Asthma	0.71 (0.50-1.01)	.05
Allergic rhinitis	1.34 (0.88-2.04)	.17
Allergic conjunctivitis	0.73 (0.51-1.06)	.10
Food allergy	1.09 (0.79-1.50)	.61
Systemic naive[a]	0.77 (0.48-1.26)	.31
Use of immunosuppressants	1.12 (0.55-2.29)	.75



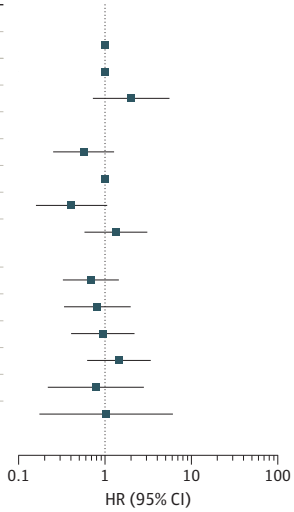
B Adverse effects

HR (95% CI)	P value
1 [Reference]	NA
4.39 (2.05-9.39)	<.001
3.83 (1.85-7.92)	<.001
0.90 (0.55-1.46)	.66
1 [Reference]	NA
2.39 (1.33-4.30)	.004
0.55 (0.34-0.88)	.12
1.01 (0.63-1.63)	.97
1.10 (0.61-1.96)	.76
0.99 (0.58-1.69)	.98
1.12 (0.72-1.78)	.61
1.20 (0.63-2.29)	.58
0.51 (0.18-1.43)	.20



C Administration problems

Study	HR (95% CI)	P value
Treatment characteristics		
Dupilumab	1 [Reference]	NA
Methotrexate	Not applicable[b]	NA
Cyclosporine A	2.01 (0.72-5.60)	.18
Patient characteristics (BL)		
Sex (female)	0.57 (0.25-1.27)	.17
Age ≥2 to <12 y	1 [Reference]	NA
Age ≥12 to <18 y	0.41 (0.16-1.06)	.07
AD in first-degree relatives	1.34 (0.58-3.10)	.49
Asthma	0.69 (0.33-1.45)	.33
Allergic rhinitis	0.82 (0.34-1.99)	.66
Allergic conjunctivitis	0.95 (0.41-2.20)	.90
Food allergy	1.45 (0.62-3.39)	.39
Systemic naive[a]	0.78 (0.22-2.83)	.71
Use of immunosuppressants	1.03 (0.17-6.13)	.97



The results in this figure were determined by multivariable Cox regression analysis. AD indicates atopic dermatitis; BL, baseline; HR, hazard ratio; NA, not applicable.

[a]Excluding oral corticosteroids.

[b]Not applicable as this characteristic was excluded from the model to avoid convergence problems and spurious results with only 2 events.

baseline were independently associated with a higher risk for drug discontinuation due to ineffectiveness and adverse effects.

Few studies thus far have reported drug survival rates of MTX and CsA in pediatric patients with AD.[22-24] Elsgaard et al[22] reported higher 1-year survival rates for MTX (69%) and CsA (50%) compared with our study, but the 1-year survival rates for MTX and CsA before the introduction of dupilumab were comparable. The date of database lock for this study was established before the introduction of dupilumab for children aged 6 to 11 years (March 2020), which may explain these higher rates, as there were limited alternative treatment options available for this age group.[22] Before the introduction of dupilumab, Law Ping Man et al[24] observed a longer median survival with MTX (23 months) compared to CsA (8 months), which is comparable with our results. Daguzé et al[23] found lower 1-year drug survival rates for CsA (34.1%) before the introduction of dupilumab in pediatric (n = 12) and adult (n = 76) patients with AD compared to our study. However, patients discontinuing treatment due to disease remission

were not censored, possibly contributing to these lower survival rates.[23] Although not reporting survival rates, the randomized clinical trial in pediatric patients by Flohr et al[18] demonstrated a more sustained response with MTX compared to CsA during 36 weeks of treatment, which aligns with our study's results.

Consistent with our study's results, previous drug survival studies in adult patients with AD showed superior drug survival of dupilumab compared to MTX and CsA.[30-35] The 1-year drug survival rate of dupilumab varied between 83% and 95% in adults, which is relatively high compared to the survival rate in our study (83.6%).[32,33,36,37] Administration problems (eg, needle phobia) may contribute to the relatively lower rates in pediatric patients, as this was more common in our study compared to studies in adult patients.[32,33,36,37] The 1-year drug survival rates for MTX and CsA in adult patients varied widely, ranging from 41% to 76% for MTX and from 34% to 44% for CsA, which aligns with our results.[24,32,34,38-40]

Comparable with findings in adult patients with AD, our study shows that drug discontinuation was predominantly associated with ineffectiveness.[32,34] However, studies in pediatric patients, with smaller numbers of patients included, have reported varying results with ineffectiveness and adverse effects as the main reasons for discontinuing MTX and/or CsA.[22-24] Interestingly, our study shows that discontinuation due to administration problems was most common in patients treated with CsA. The administration form of CsA, which comes in a bitter-tasting solution or relatively large capsules, and twice-daily dosing frequency may contribute to higher discontinuation rates compared to weekly oral/subcutaneous administration for MTX and biweekly/monthly subcutaneous administration for dupilumab. In addition, all patients were treated at a tertiary hospital with access to inpatient facilities and trauma-free medical care programs to manage administration problems with injections.[21] This may have resulted in relatively fewer administration problems in patients treated with dupilumab and MTX. Finally, few patients discontinued treatment due to well-controlled disease, which may reflect high disease severity or reluctance of patients/parents or physicians to discontinue treatment when the disease is controlled (eg, for dupilumab). Consistent with AD studies in adults, discontinuation due to well-controlled disease was most common in patients treated with CsA.[31,32,40] Because well-controlled disease is an event that favors the effectiveness of treatment, this discontinuation event was censored in our overall drug survival analyses.

This cohort study shows that patients treated with MTX and CsA had a higher risk of discontinuing treatment due to both ineffectiveness and adverse effects. Law Ping Man et al[24] reported that treatment with CsA was independently associated with shorter overall survival rates compared to treatment with MTX in pediatric patients (HR, 7.44 [95% CI, 1.97-28.13]. Elsgaard et al[22] found no variables that were significantly associated with the discontinuation of CsA or MTX. In addition, our study shows that being 12 to 17 years of age at baseline was independently associated with a higher risk of discontinuing treatment due to ineffectiveness and adverse effects compared to being 2 to 11 years of age. Adolescents are more likely to express adverse effects and their preferences than young children, which could have been associated with discontinuing treatment. However, these associations were not found to be significant in previous studies.[22,24] Finally, our study shows that patients with AD in first-degree relatives were independently associated with a lower risk for discontinuation due to adverse effects, possibly related to parents' more extensive knowledge of the disease and/or treatment.

Univariable analyses showed that the use of concomitant immunosuppressants at the start of treatment (baseline) was associated with a lower risk for drug discontinuation. Despite the use of concomitant immunosuppressants at baseline, patients had higher EASI scores compared to those not using immunosuppressants. Consequently, patients with more severe AD may be more satisfied with improvement and more likely to tolerate adverse effects, which could explain the lower risk for drug discontinuation. Multivariable models investigating the variables associated with discontinuation stratified by treatment type had a weak (dupilumab and CsA) to reasonable (MTX) concordance level between model-based and observed results for drug discontinuation. Due to a limited number of discontinuation events (especially for dupilumab), performing specific analyses to identify variables associated with discontinuation reasons for each treatment was not possible with this dataset. Future studies with longer follow-up time (ie, with more discontinuation events) will be needed to improve understanding of variables associated with individual drug discontinuation and reasons for discontinuation.

CsA was found to be the preferred first-line systemic treatment in our study, consistent with the predominant conventional systemic treatments prescribed for children in Europe.[9,10] The rapid effects of CsA, along with its low cost and wide availability, may explain the choice of CsA as first-line treatment. However, this study included patients treated with MTX and CsA before the introduction of dupilumab, which means that dupilumab could not yet be prescribed as a first-line treatment. In addition, we observed shorter overall drug survival rates for both MTX and CsA after the introduction of dupilumab. Patients and physicians may be less willing to tolerate suboptimal effectiveness and/or mild adverse effects when alternative treatment options are available, resulting in more rapid treatment switching. These results are consistent with the findings in adult patients with AD and with studies evaluating the drug survival of conventional immunosuppressants and biologics in psoriasis and psoriatic arthritis.[32,41]

Strengths and Limitations

The main strength of this study is the large multicenter daily practice cohort that provides data on commonly used treatments for pediatric patients with moderate to severe AD. The main limitation of this study was the partially retrospective data collection, which mainly included episodes of conventional immunosuppressants and may have introduced information bias. Second, the inclusion of multiple episodes per patient may have resulted in a slight bias as patients with multiple episodes may modify survival rates. Hence, these results should be validated in future studies. Third, due to the small number of pa-

tients treated with concomitant immunosuppressants, their effects could not be evaluated.

Conclusions

This multicenter daily practice cohort study showed superior 1-year, 2-year, and 3-year overall drug survival rates for dupilumab, followed by MTX and CsA, in pediatric patients with AD. The introduction of dupilumab has changed the therapeutic landscape for pediatric AD, which was associated with lower drug survival for CsA and MTX. These results have provided new insight into drug survival resulting from the effectiveness, safety, and tolerability of these systemic treatments, contributing to the optimization of patient outcomes in pediatric patients with AD.

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Author Affiliations: Department of Dermatology and Allergology, National Expertise Center for Atopic Dermatitis, University Medical Center Utrecht, Utrecht, the Netherlands (van der Rijst, Hurmuz, de Bruin-Weller, de Graaf); Department of Dermatology and Allergology, University Medical Center Utrecht, Wilhelmina Children's Hospital, Utrecht, the Netherlands (van der Rijst, Hurmuz, de Graaf); Department of Dermatology, University Medical Center Groningen, Groningen, the Netherlands (Kamphuis, Schuttelaar); Department of Dermatology, Radboud Medical Center, Nijmegen, the Netherlands (Seyger, Kamsteeg); Department of Dermatology, Amsterdam University Medical Center, Amsterdam, the Netherlands (Caron, Middelkamp-Hup); Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands (Zuithoff); Department of Dermatology, Centre of Pediatric Dermatology, Erasmus MC University Medical Centre Rotterdam-Sophia Children's Hospital, Rotterdam, the Netherlands (Nguyen, Pasmans); Department of Dermatology, Erasmus University Medical Center Rotterdam, Rotterdam, the Netherlands (Nguyen, Pasmans).

Author Contributions: Ms van der Rijst and Dr de Graaf had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Dr van der Rijst and Ms Kamphuis share first authorship. Dr Middelkamp-Hup and Dr de Graaf share last authorship.
Concept and design: van der Rijst, Kamphuis, Schuttelaar, Hurmuz, de Bruin-Weller, de Graaf.
Acquisition, analysis, or interpretation of data: van der Rijst, Kamphuis, Schuttelaar, Hurmuz, Seyger, Caron, Zuithoff, Nguyen, Kamsteeg, Pasmans, Middelkamp-Hup.
Drafting of the manuscript: van der Rijst, Kamphuis, Hurmuz, Middelkamp-Hup, de Graaf.
Critical review of the manuscript for important intellectual content: van der Rijst, Kamphuis, Schuttelaar, Seyger, Caron, Zuithoff, Nguyen, Kamsteeg, de Bruin-Weller, Pasmans, Middelkamp-Hup, de Graaf.
Statistical analysis: van der Rijst, Kamphuis, Hurmuz, Zuithoff.
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