Supplemental Online Content

van der Rijst LP, Kamphuis E, Schuttelaar MLA, et al. Drug survival of dupilumab, methotrexate, and cyclosporine A in children with atopic dermatitis. Published October 16, 2024.*JAMA Dermatol*. doi:10.1001/jamadermatol.2024.3717

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

eTable 1. Concomitant Medication Use During Treatment with Dupilumab, Cyclosporine A and Methotrexate

	Treatment Episodes		
	Dupilumab N = 192	**Methotrexate** N = 94	**Cyclosporine A** N = 216
Concomitant use of topical treatment, *n* (%)			
Topical corticosteroids	183 (95.3)	85 (90.4)	208 (96.3)
Topical immune modulators	50 (26.0)	47 (50.0)	37 (17.1)
Topical tar preparations	10 (5.2)	12 (12.8)	10 (4.6)
Emollients	178 (92.7)	83 (88.3)	201 (93.1)
Missing	0 (0.0)	1 (1.1)	1 (0.5)
Immunosuppressants started during treatment	7 (3.6)	4 (4.3)	7 (3.2)
Oral corticosteroids, *n* (%)	4 (2.0)[a]	4 (4.3)[b]	7 (3.2)[c]
Moment of start during treatment in weeks, median (IQR)	21.5 (13.0-102.0)	27.5 (4.5-49.0)	43.0 (21.0-87.3)[d]
Duration of oral corticosteroids in days, median (IQR)	4.0 (4.0-23.5)	14.0 (12.5-24.5)	15.0 (7.8-32.5)[d]
Missing, *n* (%)	0 (0.0)	0 (0.0)	1 (0.5)[d]
Methotrexate, *n* (%)	2 (1.0)	N/A	0 (0.0)
Moment of start during treatment in weeks, median (IQR)	46.5 (39.0-N/A)	–	–
Duration of methotrexate in days, median (IQR)	462.0 (413.0-N/A)	–	–
Cyclosporine A, *n* (%)	1 (0.5)	0 (0.0)	N/A
Moment of start during treatment in weeks, median (IQR)	80.0 (80.0-80.0)		
Duration of cyclosporine A in days, median (IQR)	148.0 (148.0-148.0)	–	–

[a] Concomitant treatment for atopic dermatitis (n=2) and asthma (n=2); [b] Concomitant treatment for atopic dermatitis (n=4); [c] Concomitant treatment for atopic dermatitis (n=6) and vernal keratoconjunctivitis (n=1); [d] Start/stop dates were missing. *Abbreviations*: IQR, interquartile range; N/A, not applicable due to low counts.

eTable 2. Adverse Effects in Patients who Discontinued Treatment with Dupilumab, Methotrexate and Cyclosporine A due to Adverse Effects

Adverse Effects Specified by Treatment	*N*
Dupilumab	
Number of treatment episodes discontinued due to adverse effects	16
Total number of adverse effects reported	23[a]
Ocular	
Conjunctivitis	7
Blepharitis	1
Skin related	
Psoriasis like dermatitis	1
Pain	1
Other	3[b]
Gastro-intestinal	
Nausea	1
Pain abdomen	1
Stomach pain/reflux	1
Infections	
Upper respiratory infection	1
Bacterial infection	1
Other	
Headache	2
Joint pain	1
Dizziness	1
Weight gain	1
Methotrexate	
Number of treatment episodes discontinued due to adverse effects	28
Total number of adverse effects reported	39[a]
Gastro-intestinal	
Nausea	15
Vomiting	1
Pain abdomen	5
Laboratory abnormalities	
Elevated liver enzymes	6
Infections	
Cystitis	1
Other	
Headache	5
Fatigue	4
Dizziness	2
Cyclosporine A	
Number of treatment episodes discontinued due to adverse effects	50
Total number of adverse effects reported	81[a]
Ocular	
Photophobia	1
Refractive errors	1
Skin related	
Hirsutism	2
Other	2[c]
Gastro-intestinal	
Nausea	14
Vomiting	1
Pain abdomen	6
Stomach pain/reflux	2

eTable 2 continues on next page.

eTable 2 *(continued).*

Adverse Effects Specified by Treatment	*N*
Cyclosporine A	
Number of treatment episodes discontinued due to adverse effects	50
Total number of adverse effects reported	81[a]
Laboratory abnormalities	
Elevated liver enzymes	1
Increased levels of creatinine	4
Hypertriglyceridemia	1
Thrombocytosis	1
Infections	
Cystitis	1
Airway infection	2
Other	
Headache	17
Fatigue	8
Myalgia	3
Dizziness	1
Hypertension	1
Paresthesia	5
Weight gain	1
General malaise/fever/flushes	4[d]
Other	1[e]
Psychiatric disorder	1
Missing	1

[a] Sum of adverse effects may exceed as treatments may have been discontinued due to more than one adverse effect; [b] Including n=1 injection skin reaction, n=1 oral lymphangioma, n=1 head-neck dermatitis; [c] Including n=1 skin infection, n=1 urticaria; [d] Including n=1 general malaise, n=1 fever, n=2 hot flushes; [e] Combination of seizures and atopic dermatitis flares.

eTable 3. Survival Rates and Specifications of the Drug Survival Analyses for Dupilumab, Cyclosporine A and Methotrexate

		Overall Survival [a]			*Survival Specified by Discontinuation Reason*								
					Ineffectiveness			**Adverse effects**			**Administration problems**		
	Number at risk	Survival (%)[c]	Censored	Events	Survival (%)[c]	Censored	Events	Survival (%)[c]	Censored	Events	Survival (%)[c]	Censored	Events
Dupilumab													
0 year	192	100.0	0	0	100.0	0	0	100.0	0	0	100.0	0	0
1.0 year	124	84.1	38	30	93.1	58	10	94.1	58	10	96.3	60	8
2.0 years	56	72.3	96	40	87.1	121	15	90.0	122	14	93.4	127	9
3.0 years	17	62.0	129	46	80.9	156	19	84.5	159	16	91.0	165	10
Methotrexate													
0 year	94	100.0	0	0	100.0	0	0	100.0	0	0	100.0	0	0
1.0 year	49	60.7	7	38	75.4	22	23	78.5	30	15	98.6	45	0
2.0 years	25	39.3	14	55	58.0	35	34	65.9	46	23	97.5	67	2
3.0 years	15	25.3	18	61	43.4	42	37	51.1	51	28	96.6	77	2[b]
Cyclosporine A													
0 year	216	100.0	0	0	100.0	0	0	100.0	0	0	100.0	0	0
1.0 year	78	43.9	25	113	54.2	57	81	79.2	98	40	92.6	128	10
2.0 years	32	21.5	34	150	30.6	75	109	66.8	138	46	87.1	171	13
3.0 years	10	10.4	41	165	16.3	84	122	52.3	156	50	82.6	192	14

[a] Censored for well-controlled disease and lost to follow-up. [b] Oral administration (n=1) and subcutaneous administration (n=1). [c] Survival rates were estimated with a Cox proportional hazards model (see methods for details).

eTable 4. Overall Survival Rates and Specifications of the Drug Survival Analyses for Methotrexate and Cyclosporine A Before and After the Introduction of Dupilumab

Treatment Episode	Overall Survival[a]							
	Before Dupilumab Introduction[b]				After Dupilumab Introduction[b]			
	Number at Risk	Survival (%)[c]	Censored	Events	Number at Risk	Survival (%)[c]	Censored	Events
Methotrexate								
0 year	49	100.0	0	0	45	100.0	0	0
1.0 year	33	70.8	2	14	16	43.8	5	24
2.0 years	22	49.6	4	23	3	18.7	10	32
3.0 years	14	37.6	7	28	1	9.6	11	33
Cyclosporine A								
0 year	135	100.0	0	0	81	100.0	0	0
1.0 year	63	52.2	13	59	15	32.5	12	54
2.0 years	27	26.7	17	91	5	10.2	17	59
3.0 years	9	13.6	23	103	1	3.2	18	62

[a] Overall survival censored for well-controlled disease and lost to follow-up. [b] Defined as European Medicines Agency's (EMA) approval of dupilumab for adolescents aged ≥12 to <18 years and children <12 years was defined on 6 August 2019 and 30 November 2020, respectively. [c] Survival rates were estimated with a Cox proportional hazards model (see methods for details).

eTable 5. Drug Discontinuation Reasons for Methotrexate and Cyclosporine A Before and After the Introduction of Dupilumab During 3 Years of Treatment

	Methotrexate		Cyclosporine A	
	Before Dupilumab Introduction[a] N = 49	After Dupilumab Introduction[a] N = 45	Before Dupilumab Introduction[a] N = 135	After Dupilumab Introduction[a] N = 81
Total episodes discontinued, *n* (%)	28 (57.1)	33 (73.3)	103 (76.3)	62 (76.5)
Reason for discontinuation, *n* (%)				
Ineffectiveness	17 (34.7)	20 (44.4)	78 (57.8)	44 (54.3)
Adverse effects	11 (22.4)	17 (37.8)	27 (20.0)	23 (28.4)
Administration problems	2 (4.1)	0 (0.0)	11 (8.1)	3 (3.7)
Unknown/patient wish	4 (8.2)	2 (4.4)	5 (3.7)	4 (4.9)
Restricted treatment duration	0 (0.0)	0 (0.0)	6 (4.4)	1 (1.2)
Well-controlled disease	3 (6.1)	3 (6.7)	18 (13.3)	4 (4.9)

The sum of the columns exceed the total number of patients as patients could have multiple reasons for discontinuation.
[a] Defined as European Medicines Agency's (EMA) approval of dupilumab for adolescents aged ≥12 to <18 years and children <12 years was defined on 6 August 2019 and 30 November 2020, respectively.

eTable 6. Predictors of Drug Discontinuation Owing to Ineffectiveness, Adverse Effects and/or Administration Problems Determined by Univariable Cox Regression Analysis

	Ineffectiveness		Adverse effects		Administration problems	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Treatment characteristics						
Treatment with dupilumab	Reference	NA	Reference	NA	Reference	NA
Treatment with methotrexate	**3.94 (2.28-6.81)**	**<.001**	**3.98 (2.16-7.32)**	**<.001**	0.37 (0.08-1.73)	.205
Treatment with cyclosporine A	**8.56 (5.34-13.72)**	**<.001**	**3.84 (2.18-6.75)**	**<.001**	2.02 (0.91-4.47)	.084
Patient characteristics						
Sex (female)	1.00 (0.75-1.33)	.981	1.06 (0.71-1.58)	.797	0.46 (0.21-1.01)	.052
Age start treatment 2-11 years	Reference	NA	Reference	NA	Reference	NA
Age start treatment 12-17 years	1.25 (0.91-1.72)	.165	**1.84 (1.12-3.01)**	**.015**	0.60 (0.28-1.26)	.176
AD in first degree relatives	1.23 (0.91-1.67)	.176	**0.54 (0.36-0.81)**	**.003**	1.18 (0.55-2.56)	.672
Comorbid asthma	0.80 (0.60-1.07)	.134	0.97 (0.65-1.46)	.896	0.98 (0.47-2.06)	.959
Comorbid allergic rhinitis	0.99 (0.72-1.36)	.946	0.94 (0.60-1.45)	.765	1.05 (0.46-2.40)	.911
Comorbid allergic conjunctivitis	1.05 (0.77-1.41)	.777	1.06 (0.69-1.63)	.798	1.01 (0.46-2.26)	.973
Comorbid food allergy	0.88 (0.66-1.18)	.386	1.10 (0.72-1.65)	.664	1.05 (0.49-2.2)	.906
Systemic naïve[a]	**1.75 (1.24-2.46)**	**.001**	**1.96 (1.20-3.22)**	**.007**	1.50 (0.64-3.55)	.352
Use of immunosuppressants at baseline[b]	**0.57 (0.35-0.94)**	**.026**	**0.36 (0.16-0.83)**	**.016**	0.67 (0.20-2.22)	.509

[a] Excluding oral corticosteroids. [b] Patients with baseline use of immunosuppressants had a median baseline EASI of 21.2 (IQR 17.2-31.3), and patients without baseline use of immunosuppressants had a median baseline EASI of 18.4 (IQR 11.6-28.1).
Abbreviations: AD, atopic dermatitis; CI, confidence interval; HR, hazard ratio, NA, not applicable.

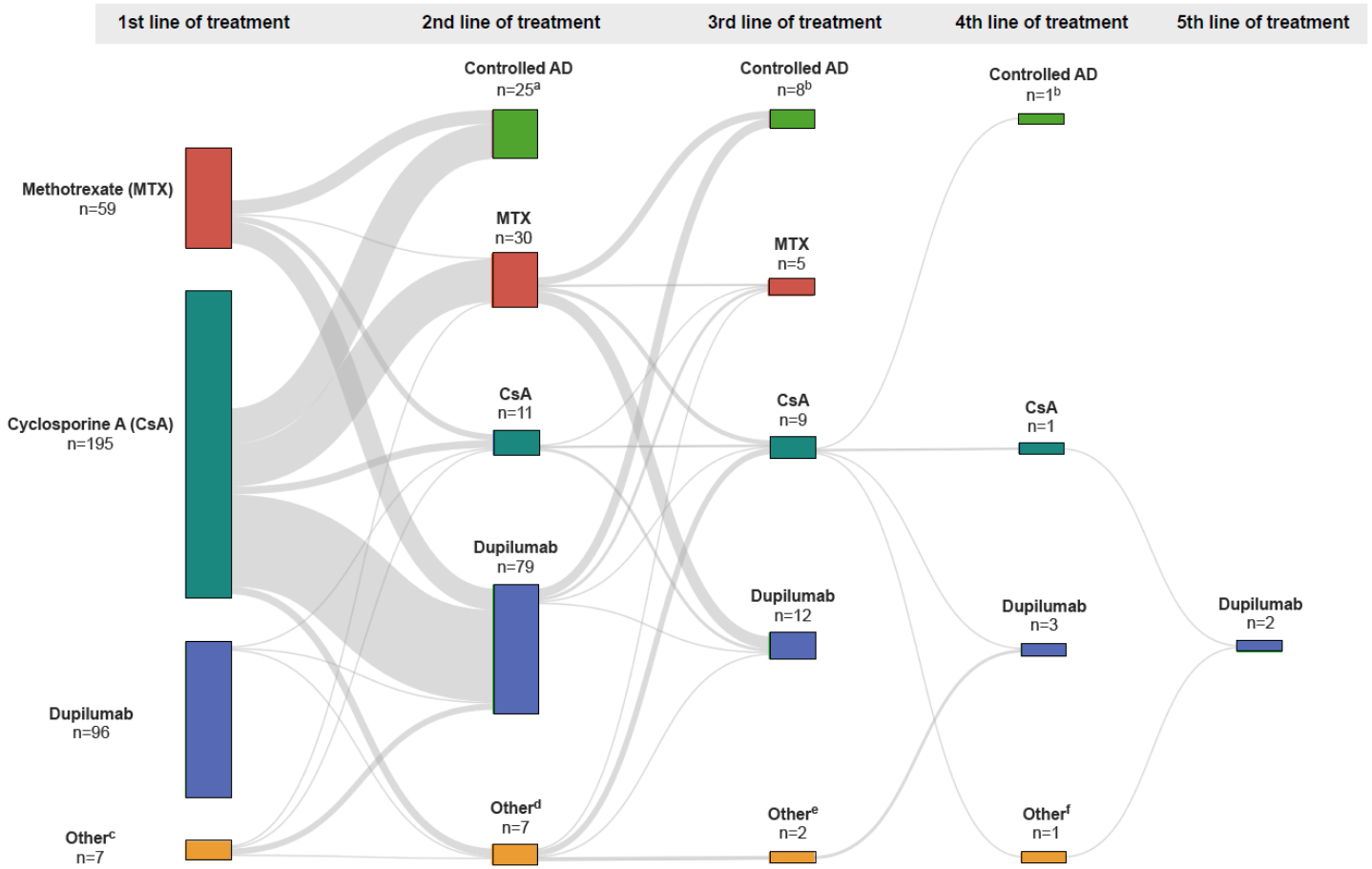
eTable 7. Predictors of Discontinuation Stratified by Treatment Determined by Univariable Cox Regression Analysis

	Dupilumab		Methotrexate		Cyclosporine A	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Sex (female)	0.91 (0.50-1.67)	.765	0.81 (0.49-1.35)	.414	1.01 (0.74-1.38)	.932
Age start treatment 2-11 years	Reference	NA	Reference	NA	Reference	NA
Age start treatment 12-17 years	1.36 (0.62-2.98)	.440	**2.66 (1.51-4.67)**	**<.001**	1.10 (0.78-1.54)	.588
AD in first degree relatives	0.75 (0.41-1.37)	.349	1.16 (0.70-1.93)	.568	0.87 (0.63-1.19)	.371
Comorbid asthma	1.01 (0.55-1.88)	.955	1.07 (0.65-1.78)	.783	0.78 (0.57-1.06)	.108
Comorbid allergic rhinitis	0.98 (0.49-1.97)	.953	1.63 (0.90-2.92)	.105	0.85 (0.61-1.19)	.348
Comorbid allergic conjunctivitis	0.84 (0.44-1.61)	.604	1.16 (0.65-2.06)	.615	0.82 (0.59-1.13)	.222
Comorbid food allergy	1.06 (0.57-1.98)	.854	0.90 (0.53-1.54)	.697	1.04 (0.76-1.41)	.824
Systemic naïve[a]	1.20 (0.63-2.27)	.582	0.62 (0.37-1.04)	.070	0.87 (0.51-1.49)	.616
Use of immunosuppressants at baseline	1.28 (0.65-2.53)	.472	0.99 (0.51-1.94)	.977	1.04 (0.38-2.80)	.943

[a] Excluding oral corticosteroids.

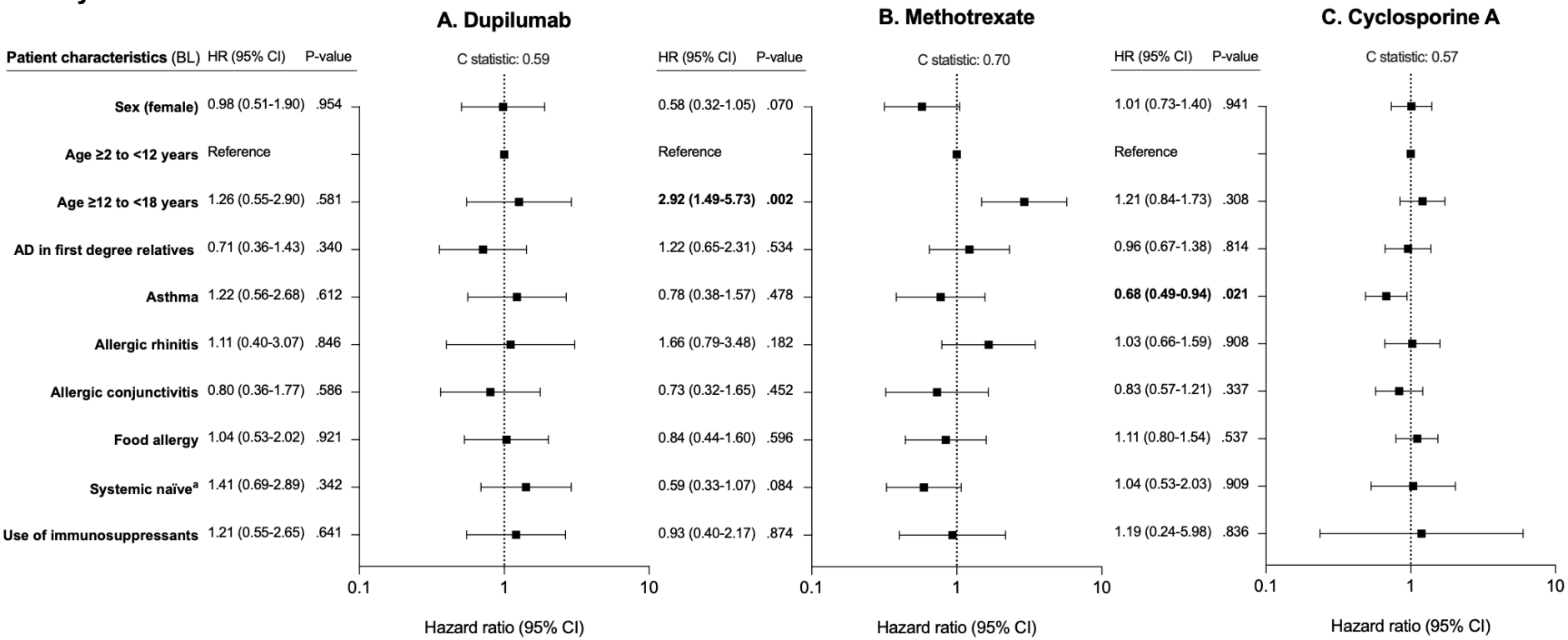
Abbreviations: AD, atopic dermatitis; CI, confidence interval; HR, hazard ratio, NA, not applicable.

eFigure 1. Sankey Diagram Illustrating the Lines of Treatment and Switching Patterns of Systemic Treatments in Patients With Atopic Dermatitis



The columns of treatment boxes represent the first, second, third, fourth, and fifth line of treatment excluding oral corticosteroids. The size of the box and width of the lines are proportional to the number of patients. [a] Well-controlled disease until data lock or lost-to-follow-up, except for n=6 patients who switched to other systemic treatments after a median duration of 119 weeks (interquartile range, 20-234). [b] Well-controlled disease until data lock or lost-to-follow-up. [c] Other treatment episodes were not included in the drug survival analyses, but were included in this Sankey diagram to enhance the visualization of the treatment switching patterns. Other treatments comprised: [d] Azathioprine (n=1), cyclosporine A (<2013) (n=2), tralokinumab (n=2), upadacitinib (n=2); [e] Azathioprine (n=1), advagraf (n=1), mycophenolate mofetil (n=3), upadacitinib (n=3); [f] Abrocitinib (n=2); [g] Tralokinumab (n=1). Figure made with SankeyMATIC.

eFigure 2. Predictors of Drug Discontinuation Stratified by Treatment Determined by Multivariable Cox Regression Analysis



Discontinuation due to ineffectiveness, adverse effects and/or administration problems for (A) Dupilumab; (B) Methotrexate; (C) Cyclosporine A.
[a] Excluding oral corticosteroids. *Abbreviations*: AD, atopic dermatitis; BL, baseline; CI, confidence interval; HR, hazard ratio.