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Dupilumab Drug Survival and Associated Predictors in Patients With Moderate to Severe Atopic Dermatitis

Long-term Results From the Daily Practice BioDay Registry

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IMPORTANCE Long-term data on dupilumab drug survival in patients with atopic dermatitis (AD) are scarce. Furthermore, little is known about the factors associated with drug survival of dupilumab in AD.

OBJECTIVE To describe the drug survival of dupilumab in patients with AD and to identify associated predictors.

DESIGN, SETTING, AND PARTICIPANTS This cohort study was based on data from the multicenter prospective daily practice BioDay registry, in which 4 university and 10 nonuniversity hospitals in the Netherlands participated. Analysis included patients (age ≥18 years) participating in the BioDay registry with a follow-up of at least 4 weeks. The first patient treated with dupilumab was recorded in the BioDay registry in October 2017; data lock took place in December 2020, and data analysis was performed from October 2017 to December 2020.

MAIN OUTCOMES AND MEASURES Drug survival was analyzed by Kaplan-Meier survival curves and associated characteristics by using univariate and multivariate Cox regression analysis.

RESULTS A total of 715 adult patients with AD (mean [SD] age, 41.8 [16.0] years; 418 [58.5%] were male) were included with a 1-year, 2-year, and 3-year overall dupilumab drug survival of 90.3%, 85.9%, and 78.6%, respectively. Characteristics associated with shorter drug survival owing to ineffectiveness were the use of immunosuppressant drugs at baseline (hazard ratio [HR], 2.64; 95% CI, 1.10-6.37) and being a nonresponder at 4 weeks (HR, 8.68; 95% CI, 2.97-25.35). Characteristics associated with shorter drug survival owing to adverse effects were the use of immunosuppressant drugs at baseline (HR, 2.69; 95% CI, 1.32-5.48), age 65 years or older (HR, 2.94; 95% CI, 1.10-7.87), and Investigator Global Assessment score of very severe AD (HR, 3.51; 95% CI, 1.20-10.28).

CONCLUSIONS AND RELEVANCE This cohort study demonstrated a good overall 1-year, 2-year, and 3-year dupilumab drug survival. Patients using immunosuppressive therapy at baseline and those with an absence of treatment effect at week 4 tended to discontinue treatment owing to ineffectiveness more frequently. Using immunosuppressant drugs at baseline, older age, and Investigator Global Assessment score of very severe AD were characteristics associated with an increased risk for discontinuation owing to adverse effects. These data provide more insight and new perspectives regarding dupilumab treatment in AD and can contribute to the optimization of patient outcomes.

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Supplemental content

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Atopic dermatitis (AD) is a multifactorial, pruritic skin disease resulting from the interaction of genetic disposition and environmental triggers with skin barrier dysfunction and a type 2–driven immune dysregulation.[1] Dupilumab is a monoclonal antibody that targets the interleukin (IL)-4 receptor subunit α (IL-4Rα). This results in the blocking of signaling of T2 cytokines, IL-4 and IL-13, and consequently the inhibition of the Th2 pathway.[2,3] Overall, the clinical efficacy and safety of dupilumab have been demonstrated in clinical trials for the treatment of patients with AD.[4-7] In these clinical trials, efficacy of dupilumab was investigated under ideal and controlled circumstances in selected patients, and therefore, results are hard to generalize to daily practice.

Drug survival is an analysis that reflects daily practice by analyzing the expected duration of time until an event, discontinuation of the drug, occurs.[8] Drug survival and associated predictors are dependent on a combination of factors such as drug effectiveness, the occurrence of adverse effects, patient factors, and the availability of other treatment options. Our previous study showed a longer drug survival of dupilumab compared with cyclosporine A and methotrexate, with only a limited number of patients discontinuing treatment owing to ineffectiveness and/or adverse effects.[9] At that time, a prediction analysis of drug survival was not feasible because of the low number of patients discontinuing dupilumab treatment. Furthermore, predictor studies regarding dupilumab drug survival are limited and not specified for the reason of discontinuation.[10] Consequently, little is known about which factors might be associated with the drug survival of dupilumab and whether certain clinical characteristics might be predictive for discontinuation owing to either ineffectiveness and/or adverse effects. The primary objective of the present study was to investigate the drug survival of dupilumab in patients with AD treated in daily practice and to identify its associated predictors.

Key Points

Question What is the drug survival of dupilumab in patients with atopic dermatitis (AD), and what are its associated predictors?

Findings A total of 715 patients with AD were included with a 1-, 2-, and 3-year overall dupilumab drug survival of 90.3%, 85.9%, and 78.6%, respectively. Patients using immunosuppressive drugs at baseline and nonresponders at week 4 tended to discontinue treatment owing to ineffectiveness more frequently; using immunosuppressive drugs at baseline, older age, and very severe AD were risk factors for shorter drug survival associated with adverse effects.

Meaning These data provide more insight and new perspectives regarding dupilumab treatment in AD and can contribute to the optimization of patient outcomes.

Methods

Study Design and Patients

All patients (age ≥18 years) participating in the BioDay registry with a follow-up of at least 4 weeks were included in this study. A total of 4 university and 10 nonuniversity hospitals in the Netherlands participate in the registry. It contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both patient-reported outcomes as well as clinical parameters. The first patient treated with dupilumab was recorded in the BioDay registry in October 2017; data lock took place in December 2020 owing to the introduction of new advanced systemic treatment in 2021.

This study was approved by the local Medical Research Ethics Committee as a noninterventional study (METC 18/239) and was performed according to the Declaration of Helsinki. All patients provided written informed consent.

Protocol and Data Collection

All patients received a loading dose of dupilumab of 600 mg subcutaneously, followed by 300-mg injections every other week in the first year. In cases of well-controlled AD or severe adverse effects, tapering of dupilumab dosage was considered.

The following patient and treatment characteristics were recorded at baseline: sex, age, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), time of onset of AD, history of immunosuppressive therapy, presence of atopic comorbidities, and use of immunosuppressive therapy at the start of dupilumab treatment. Patients were recorded as using immunosuppressive therapy at the start of dupilumab treatment when prednisone or cyclosporine had been used within 1 week before starting dupilumab treatment and, in the case of methotrexate, within 4 weeks before the start of dupilumab treatment.

Disease severity was assessed by physician-measured clinical eczema scores, namely the Eczema Area and Severity Index (EASI) and the Investigator Global Assessment (IGA) score on a 6-point scale (scores range from 0 [clear AD] to 5 [very severe AD]).[11] Discontinuation owing to both ineffectiveness and adverse effects was based on patient-clinician discussions.

Statistical Analyses

Drug Survival

Drug survival was analyzed with Kaplan-Meier survival curves. Overall, 3 drug survival events were defined and analyzed separately: discontinuation in overall drug survival, discontinuation owing to ineffectiveness, and discontinuation owing to adverse effects. When patients discontinued owing to both ineffectiveness and adverse effects, they were considered to have an event in both subanalyses. Patients were censored when still using dupilumab at time of the data lock (December 2020) or when lost to follow up. When patients discontinued for other reasons (eg, pregnancy wish), they were included statistically in the overall drug survival analysis but were censored in the subanalyses. For each included patient, only the first treatment episode of dupilumab was analyzed, and treatment interruptions of less than 90 days were considered as 1 continuous episode.

Potential Predictors

We defined the following variables as potential associated predictors of dupilumab drug survival: sex, age, BMI, time of onset of AD, allergic asthma, allergic rhinitis, allergic conjunctivitis, food allergy, delta EASI (the absolute difference between

EASI score at week 4 and baseline), use of immunosuppressive therapy at the start of dupilumab treatment, IGA score (as a categorical variable), weekly average Numerical Rating Scale (NRS) pruritus score, and eosinophil and thymus- and activation-regulated chemokine levels at the start of dupilumab treatment. Because the effect of delta EASI was stronger than baseline EASI and we wanted to assess the association of early response with drug survival, we included the delta EASI instead of baseline EASI. The delta EASI was dichotomized into (1) nonresponder at 4 weeks if delta EASI was 0 or greater (representing equal or worsening of AD activity after 4 weeks of dupilumab treatment compared with baseline) and (2) responder if delta EASI was less than 0. Age at start of treatment was dichotomized into (1) younger than 65 years and (2) 65 years and older. Continuous variables with a highly skewed distribution were log transformed. To increase interpretability, BMI was categorized in 5-point intervals. Late-onset AD was defined as AD onset after age 18 years.

Prediction of Discontinuation Owing to Ineffectiveness and/or Adverse Effects

The analysis was performed in 2 steps. First, a univariate Cox regression analysis was performed for each variable separately. Second, a multivariate analysis, including all potential predictors (ie, without univariate preselection), was performed to assess interactions between all variables. As the number of discontinuations owing to ineffectiveness and/or adverse effects was relatively low for the number of predictors to be evaluated, we applied the Firth correction in estimation of the multivariate Cox model. The predictive performance of the model was assessed with the C statistic, which is similar to an area under the receiver operator characteristic curve for dichotomous outcomes. Validity of the proportional hazards assumption was assessed with residual analysis.[12] The assumption of a linearity of continuous predictors and the outcome was assessed with restrictive cubic spline analyses.

Prior to analyzing the data, we noted missing values on several predictors. As a complete case analysis, only analyzing patients without missing values may have resulted in bias and loss of statistical power, so we decided to use multiple imputation. Missing data were imputed with a fully conditional specification and included all potential predictors as well as the outcome. Based on the percentage of patients, we constructed 50 imputed data sets.[13,14] The analysis was performed on each imputed data set, and the results were subsequently pooled with Rubin rules.[12] *P* values were 2-sided and significant at $P < .05$. All data were analyzed using SPSS Statistics, version 26.0.0.1 (IBM), and SAS, version 9.4 (SAS Institute Inc).

Results

Patient and Treatment Characteristics

A total of 715 patients (mean [SD] age, 41.8 [16.0] years) were included at start of dupilumab treatment. A total of 418 patients (58.5%) were male, and 183 patients (25.6%) used immunosuppressive drugs at the start of treatment. The median (IQR) EASI score at baseline was 15.6 (10.1-24.9). Forty-eight patients (6.7%) showed no improvement or worsening of EASI score at week 4 (mean EASI score increase of 57.9%) compared with baseline and were defined as nonresponders at week 4. Responders at week 4 (582 of 715) had a mean EASI score decrease of 55.3%. The IGA score was very severe AD in 8.3% (n = 58) of the patients. Furthermore, patients reported a mean (SD) NRS pruritus score of 6.8 (2.3) (**Table 1**). During dupilumab treatment, 7 patients (1.0%) started or continued concomitant immunosuppressive therapy owing to ineffectiveness, of which 3 patients discontinued treatment owing to ineffectiveness.

Reasons for Discontinuation

At the moment of data lock, December 2020, 614 patients (85.9%) were still using dupilumab, 90 patients (12.6%) had discontinued dupilumab treatment, and 11 patients (1.5%) were lost to follow-up (**Table 2**). Eighteen patients (2.5%) discontinued treatment owing to ineffectiveness. As shown in Table 2, 30 patients (4.2%) terminated dupilumab owing to adverse effects, with dupilumab-associated ocular surface disease (DAOSD) being the largest group (n = 17 [2.4%]). The majority of these patients (n = 6) who discontinued treatment owing to DAOSD had an IGA score of very severe AD at the start of dupilumab treatment. The second largest group of adverse effects were cutaneous adverse effects (n = 10); these skin lesions developed over a longer time period with a median (IQR) dupilumab treatment duration of 63 (46-83) weeks before discontinuation (Table 2). Six patients (0.8%) discontinued treatment owing to a combination of both adverse effects and ineffectiveness. Eleven patients (1.5%) discontinued treatment owing to wish for pregnancy and 25 patients owing to other reasons (3.5%) (Table 2; eTable 1 in the Supplement).

Drug Survival Analysis

The 1-year, 2-year, and 3-year overall drug survival of dupilumab was 90.3%, 85.9%, and 78.6%, respectively, and was mostly associated with adverse effects. The drug survival with adverse effects as an event were 96.3%, 93.2%, and 92.6% after 1, 2, and 3 years, respectively (**Figure 1**). The drug survival with ineffectiveness as an event was 96.5%, 95.7%, and 95.7% after 1 year, 2 years, and 3 years, respectively. This indicates that after 2 years of dupilumab treatment, no additional patients discontinued dupilumab treatment owing to ineffectiveness.

Predictors for Discontinuation Owing to Ineffectiveness

Results from the univariate analyses showed that the use of immunosuppressive drugs at the start of dupilumab treatment (hazard ratio [HR], 2.47; 95% CI, 1.09-5.60), being a nonresponder at week 4 (HR, 7.95; 95% CI, 3.32-19.07), and IGA score of very severe AD (HR, 3.95; 95% CI, 1.20-12.95) were associated with an increased hazard to discontinue treatment owing to ineffectiveness, while presence of a food allergy (HR, 0.31; 95% CI, 0.12-0.84) was associated with a lower probability to discontinue treatment owing to ineffectiveness (**Table 3**).

Results from the multivariate model are shown in **Figure 2**. Patients using immunosuppressive therapy at the start of dupilumab treatment showed shorter drug survival (HR, 2.64;

Table 1. Patient Characteristics for the Total Cohort and Differentiated for Reason of Discontinuation

Characteristic	No. (%)		
	Total	Ineffectiveness	Adverse effects
No. (%)	715 (100)	24 (100)	36 (100)
Sex			
Female	297 (41.5)	11 (45.8)	14 (38.9)
Male	418 (58.5)	13 (54.2)	22 (61.1)
Age, mean (SD), y	41.8 (16.0)	38.7 (20.2)	46.2 (16.4)
BMI, mean (SD)	25.6 (4.5)	25.3 (3.8)	26.1 (4.8)
Age at AD onset			
Childhood	586 (82.0)	19 (79.2)	28 (77.8)
Adolescence	43 (6.0)	3 (12.5)	4 (11.1)
Adulthood	72 (10.0)	2 (8.3)	3 (8.3)
Missing	14 (2.0)	0	1 (2.8)
Immunosuppressive drugs history			
Naive for immunosuppressive drugs	27 (3.8)	0	1 (2.9)
1 Prior immunosuppressive drug	351 (49.1)	8 (33.3)	10 (28.6)
2 Prior immunosuppressive drugs	207 (29.0)	9 (37.5)	13 (37.1)
≥3 Prior immunosuppressive drugs	130 (18.2)	7 (29.2)	11 (32.4)
Use of immunosuppressive therapy at BL	183 (25.6)	11 (45.8)	16 (44.4)
Missing	13 (1.8)	1 (4.2)	0
Atopic comorbidity			
Allergic asthma	396 (55.3)	10 (41.7)	21 (58.3)
Missing	15 (2.1)	0	0
Allergic rhinitis	469 (65.5)	13 (54.2)	25 (69.4)
Missing	37 (5.2)	0	0
Allergic conjunctivitis	408 (57.1)	9 (37.5)	21 (58.3)
Missing	24 (3.4)	4 (16.7)	2 (5.6)
Food allergy	313 (43.8)	5 (20.8)	11 (30.6)
Missing	19 (2.7)	0	1 (2.8)
EASI score, median (IQR)	15.6 (10.1-24.9)	20.0 (11.0-36.8)	19.8 (12.0-32.1)
Missing	10	0	0
IGA score at BL			
0 Clear AD	0	0	0
1 Almost clear AD	12 (1.7)	0	1 (2.8)
2 Mild AD	104 (14.5)	5 (20.8)	6 (16.7)
3 Moderate AD	289 (40.4)	6 (25.0)	10 (27.8)
4 Severe AD	233 (32.6)	8 (33.3)	11 (30.6)
5 Very severe AD	58 (8.1)	5 (20.8)	8 (22.2)
Missing	19 (2.7)	0	0
Weekly average pruritus NRS score at BL, mean (SD)	6.8 (2.3)	7.1 (2.8)	6.8 (2.8)
Missing	78	5	3
Eosinophil levels at BL, median (IQR), $\times 10^9$/L	0.3 (0.2-0.5)	0.4 (0.2-0.8)	0.4 (0.2-0.7)
Missing	46	3	2
Serum TARC levels at BL, median (IQR), pg/mL	1884 (829-3840)	2911 (940-5699)	2887 (957-5140)
Missing	147	9	7
Response at wk 4			
Nonresponder at wk 4	48 (6.7)	8 (33.3)	5 (13.9)
ΔEASI wk 4 vs BL, %	−46.6	−15.7	−40.9
Clear AD (EASI = 0) at wk 4	2 (0.3)	0	0
Almost clear AD (EASI ≤ 1.1) at wk 4	24 (3.4)	0	3 (8.3)
Mild AD (EASI ≤ 7) at wk 4	318 (44.5)	3 (12.5)	14 (38.9)
Missing	85 (11.9)	4 (16.7)	4 (11.1)

Abbreviations: AD, atopic dermatitis; BL, baseline; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment Scale; NRS, Numerical Rating Scale; TARC, thymus- and activation-regulated chemokine.

95% CI, 1.10-6.37). Furthermore, being a nonresponder at week 4 (HR, 8.68; 95% CI, 2.97-25.35) was also associated with shorter drug survival. The C statistic was 0.85, indicating reasonably good discriminative properties of the model to predict discontinuation of dupilumab due to ineffectiveness (Figure 2; eTable 2 in the Supplement).

Table 2. Treatment Characteristics and Reasons for Discontinuation of Dupilumab

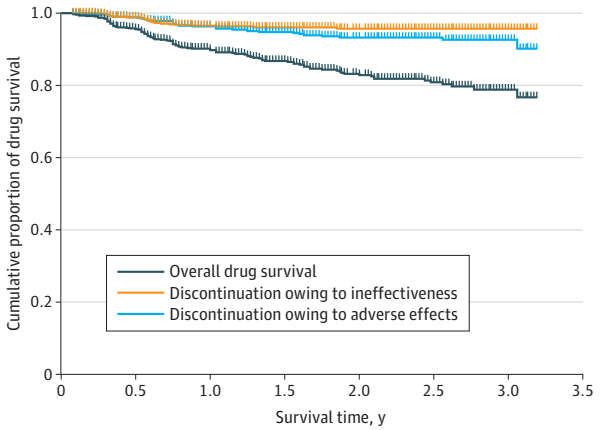
Status of dupilumab treatment by data lock	No. (%)	Duration of dupilumab treatment, median (IQR), wk
Active	614 (85.9)	84 (43-131)
Discontinued	90 (12.6)	36 (18-66)
Lost to follow-up	11 (1.5)	71 (30-87)
Reasons for discontinuation[a]		
Ineffectiveness	18 (2.5)	28 (17-33)
Adverse effects	30 (4.2)	40 (24-69)
Both ineffectiveness and adverse effects	6 (0.8)	36 (30-46)
Pregnancy wish	11 (1.5)	70 (19-108)
Other	25 (3.5)	32 (18-66)
Adverse effects as reason for discontinuation		
Ocular-related complaints	20 (2.8)	32 (17-41)
Conjunctivitis (DAOSD)	14 (2.0)	31 (18-41)
Uveitis	3 (0.4)	28 (4-97)
Limbitis (DAOSD)	2 (0.3)	39 (39-39)
Cornea perforation (DAOSD)	1 (0.1)	4 (4-4)
Skin-related complaints	10 (1.4)	63 (46-83)
Atypical lymphomatoid reaction	3 (0.4)	54 (27-85)
Worsening of MF[b]	1 (0.1)	60 (60-60)
Psoriasiform lesions	3 (0.4)	65 (16-83)
Rosacea	3 (0.4)	81 (46-91)
Muscle and joint pain	2 (0.3)	47 (39-54)
Eosinophilia	1 (0.1)	40 (40-40)
Combination of headache/chest pain/tiredness	1 (0.1)	30 (30-30)
Systemic T-cell lymphoma	1 (0.1)	159 (159-159)
Agitation	1 (0.1)	133 (133-133)

Abbreviations: DAOSD, dupilumab-associated ocular surface disease; MF, mycosis fungoides.

[a] None of the patients discontinued treatment owing to controlled disease.

[b] In retrospect, 1 patient was misdiagnosed and appeared to have MF prior to start of dupilumab therapy that worsened after dupilumab therapy.

Figure 1. Dupilumab Drug Survival and Split for Reasons for Discontinuation



Predictors for Discontinuation Owing to Adverse Effects

The association of an increased risk for discontinuation owing to adverse effects from univariate analysis was using immunosuppressive therapy at baseline (HR, 2.16; 95% CI, 1.11-4.17) and an IGA score of very severe AD (HR, 3.76; 95% CI, 1.48-9.53) (Table 3).

Multivariate analysis showed the presence of immunosuppressive therapy at baseline (HR, 2.69; 95% CI, 1.32-5.48), older age (≥65 years) (HR, 2.94; 95% CI, 1.10-7.87), and an IGA score of very severe AD (HR, 3.51; 95% CI, 1.20-10.28) were independent associated characteristics with an increased risk for discontinuation of dupilumab owing to adverse effects. The C statistic was 0.72, which indicates reasonable discriminative properties of the model to predict discontinuation of dupilumab owing to adverse effects (Figure 2; eTable 2 in the Supplement).

Discussion

Overall, dupilumab showed a good drug survival of 90.3%, 85.9%, and 78.6% after 1 year, 2 years, and 3 years of treatment, respectively, and was predominantly associated with adverse effects. Use of immunosuppressive therapy at baseline, older age (≥65 years), and an IGA score of very severe AD were independent risk factors for shorter drug survival associated with adverse effects. Use of immunosuppressive therapy at baseline and no response after 4 weeks of dupilumab treatment were independent risk factors for shorter drug survival associated with ineffectiveness.

Reasons for discontinuation of dupilumab in this study (90 of 715 [12.6%]) were ineffectiveness (18 of 715 [2.5%]), adverse effects (30 of 715 [4.2%]), combination of ineffectiveness and adverse effects (6 of 715 [0.8%]), other reasons (25 of 715 [3.5%]), and pregnancy wish (11 of 715 [1.5%]). Khosravi et al[15] showed, in 2017 to 2019, an overall drug survival of dupilumab in 112 adult patients with AD after 2.2 years of 89%. A total of 9 patients (8.0%) discontinued dupilumab: 5 (4.5%) owing to AD flare, 3 (2.7%) owing to adverse effects (conjunctivitis), and 1 (0.9%) owing to ineffectiveness. Overall, the number of patients who discontinued dupilumab treatment was consistent with our results. Georgakopoulos et al[16] assessed the 2-year drug survival of dupilumab in a clinical population of patients with AD. Drug survival of dupilumab was 83% and 80% after 1 year and 2 years of treatment. Of 139 patients, treatment was discontinued in 14 patients (10.1%) owing to ineffectiveness and in 14 patients (10.1%) owing to adverse effects, and among those in whom treatment failed, the median time to discontinuation was 20 weeks. Overall, higher discontinuation rates and shorter treatment duration was observed compared with results of the current study. One explanation for this difference could be that this study was conducted when another new advanced targeted therapy for AD (eg, baricitinib) was already available, which might have led to higher discontinuation rates for dupilumab because of availability of an alternative treatment. In the current study, the data lock was set before the introduction of other new advanced systemic treatment; in this way, dupilumab drug survival could be assessed without the interference of other new advanced systemic treatments. Considering that drug survival is a comprehensive outcome covering efficacy, safety, and patients' and

Table 3. Predictors of Discontinuation Owing to Ineffectiveness and Adverse Effects Determined by Univariate Cox Regression Analysis

	Ineffectiveness		Adverse effects	
Characteristic	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Female sex	1.32 (0.59-2.95)	.49	1.02 (0.52-2.00)	.95
Age at start of treatment ≥65 y[a]	1.97 (0.67-5.76)	.22	2.07 (0.86-4.97)	.11
BMI[b]	0.94 (0.54-1.62)	.82	1.14 (0.77-1.68)	.51
Late-onset AD[c]	0.76 (0.18-3.23)	.71	0.85 (0.26-2.77)	.78
Allergic asthma	0.52 (0.23-1.17)	.11	0.99 (0.51-1.92)	.97
Allergic rhinitis	0.59 (0.26-1.31)	.19	1.08 (0.53-2.19)	.84
Allergic conjunctivitis	0.59 (0.25-1.36)	.21	1.16 (0.58-2.31)	.67
Food allergy	0.31 (0.12-0.84)	.02	0.52 (0.25-1.05)	.07
Use of immunosuppressive therapy at BL	2.47 (1.09-5.60)	.03	2.16 (1.11-4.17)	.02
Nonresponder at wk 4[d]	7.95 (3.32-19.07)	.00	2.44 (0.94-6.34)	.07
IGA 1 or 2	2.16 (0.66-7.00)	.20	1.95 (0.74-5.13)	.18
IGA 3[e]	[Reference]	NA	[Reference]	NA
IGA 4	1.78 (0.62-5.12)	.29	1.42 (0.60-3.36)	.42
IGA 5	3.95 (1.20-12.95)	.02	3.76 (1.48-9.53)	.01
Weekly average pruritus NRS score	1.06 (0.86-1.30)	.59	0.99 (0.85-1.15)	.90
Eosinophil levels	1.12 (0.68-1.84)	.64	1.18 (0.80-1.72)	.40
Serum TARC levels	1.24 (0.87-1.78)	.24	1.03 (0.77-1.39)	.83

Abbreviations: AD, atopic dermatitis; BL, baseline; BMI, body mass index; IGA, Investigator Global Assessment Scale; NA, not applicable; NRS, Numerical Rating Scale; TARC, thymus- and activation-regulated chemokine.

[a] Reference category: younger than 65 years.

[b] BMI 5-point intervals.

[c] Late-onset AD was defined as AD onset at age older than 18 years.

[d] Nonresponder at week 4 was defined as no EASI improved at week 4 compared with BL.

[e] Reference category: IGA moderate.

physicians' preferences, new advanced targeted therapies will influence dupilumab drug survival. In the coming years, it will be interesting to compare the drug survival of dupilumab with other advanced systemic treatment options when they have been on the market longer.

Prior to this study, to our knowledge only 1 study regarding predictors for dupilumab drug survival had been conducted. Dal Bello et al[10] investigated drug survival of dupilumab, reasons for discontinuation, and predictive parameters of drug survival in daily practice (n = 149). Sixteen months (1.3 years) from baseline, 82.0% of patients receiving dupilumab were still receiving treatment.[10] Reasons for discontinuing dupilumab were ineffectiveness (4.7%), remission (7.4%), and cutaneous adverse effects (2.0%). Older age at diagnosis and shorter AD duration predicted shorter overall dupilumab survival. A direct comparison with the present study was not possible as we used categories for onset of AD and differentiated for reason of discontinuation. However, in the present study, late-onset AD (age >18 years) was not a significant determinant in the Cox regression analysis for the prediction of discontinuation.

To our knowledge, no other prediction studies of dupilumab drug survival that differentiated the reason of discontinuation are available in literature yet. Use of immunosuppressive therapy at baseline, older age (≥65 years), and IGA score of very severe AD at baseline were independent risk factors for shorter drug survival associated with adverse effects. Older patients were often excluded from previous clinical studies; therefore, limited data are available for this specific age group. Our results suggest that older patients are more susceptible to developing adverse effects compared with younger patients. The effect of an IGA score of very severe AD as a risk factor for discontinuation owing to adverse effects might be explained by the higher risk of developing DAOSD in these patients. Of the 36 patients who discontinued treatment owing to adverse effects, 8 (22.2%) had an IGA score of very severe AD, with the majority of these patients (6 of 8) discontinuing treatment owing to DAOSD, which is a frequently reported adverse effect of dupilumab treatment[6] and is associated with higher disease activity at baseline.[17,18] Additionally, use of immunosuppressive therapy at baseline and the absence of response after 4 weeks of dupilumab treatment were found as independent risk factors for shorter drug survival associated with ineffectiveness. Interestingly, patients who did not respond at week 4 (EASI week 4 ≥ EASI baseline, observed in 48 of 715 patients [6.7%]) had an approximately 8.7-fold increased tendency to discontinue treatment owing to ineffectiveness compared with patients who did respond to dupilumab in the first 4 weeks of treatment. Blauvelt et al[4] showed that after 4 months of dupilumab treatment, a steady state is achieved, and therefore, 16 weeks of treatment is considered as an important time point to evaluate treatment response. This study showed for the first time that no response/worsening of AD at week 4 is highly predictive for discontinuation of dupilumab owing to ineffectiveness in the longer term. Because of this new finding, additional analysis was performed by using Spearman correlation. A strong correlation of 0.74 was found between EASI score at week 4 and 16 for nonresponders at week 4, indicating that the EASI score after 4 weeks of treatment will likely result in a similar EASI score at week 16. As the availability of more new advanced systemic treatments grows, it would be beneficial for clinical practice if decision-making regarding discontinuation of a drug could be set earlier than after 4 months of treatment.

An important strength of this study is the large volume of patient data sourced from the prospective BioDay registry. We applied very few exclusion criteria to ensure the data were representative of current clinical practice and reflects a real-life situation.

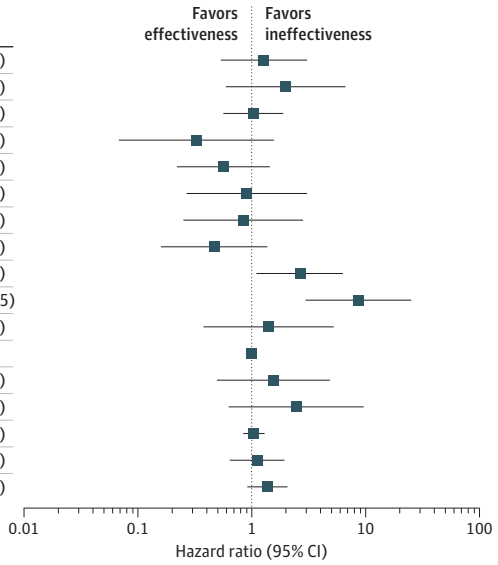
Limitations

Some limitations of this study need to be addressed. First, the predictive analysis for ineffectiveness and adverse effects was

Figure 2. Predictors of Drug Survival for Discontinuation Owing to Ineffectiveness and Adverse Effects (Hazard Ratios) Determined by Multivariate Cox Regression Analysis

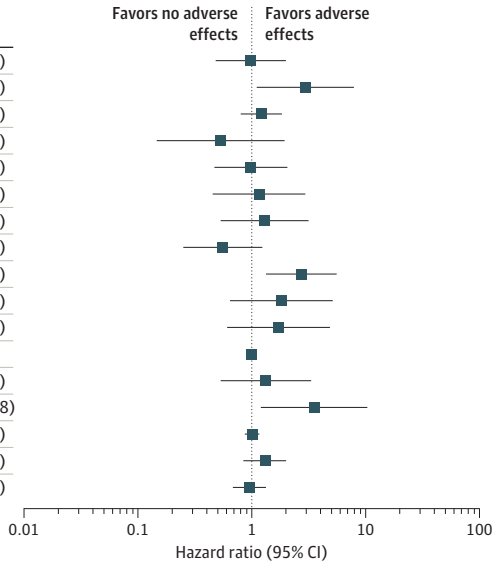
A Ineffectiveness

Characteristic	Hazard ratio (95% CI)
Sex (female)	1.28 (0.53-3.07)
Age at start of treatment (≥65 y)	1.99 (0.59-6.74)
BMI	1.04 (0.57-1.91)
Late-onset AD	0.33 (0.07-1.56)
Allergic asthma	0.56 (0.22-1.44)
Allergic rhinitis	0.90 (0.27-3.04)
Allergic conjunctivitis	0.85 (0.25-2.81)
Food allergy	0.47 (0.16-1.37)
Use of immunosuppressive at BL[a]	2.64 (1.10-6.37)
Nonresponder at week 4[b]	8.68 (2.97-25.35)
IGA 1 or 2	1.41 (0.38-5.26)
IGA 3 (reference)	NA
IGA 4	1.55 (0.50-4.83)
IGA 5	2.46 (0.63-9.60)
NRS pruritus	1.05 (0.85-1.29)
Eosinophil levels	1.12 (0.64-1.96)
Serum TARC levels	1.37 (0.91-2.06)



B Adverse effects

Characteristic	Hazard ratio (95% CI)
Sex (female)	0.97 (0.48-1.99)
Age at start of treatment (≥65 y)[a]	2.94 (1.10-7.87)
BMI	1.21 (0.80-1.83)
Late-onset AD	0.53 (0.14-1.95)
Allergic asthma	0.98 (0.47-2.05)
Allergic rhinitis	1.15 (0.45-2.93)
Allergic conjunctivitis	1.28 (0.53-3.11)
Food allergy	0.56 (0.28-1.23)
Use of immunosuppressive at BL[c]	2.69 (1.32-5.48)
Nonresponder at week 4	1.81 (0.64-5.11)
IGA 1 or 2	1.71 (0.61-4.81)
IGA 3 (reference)	NA
IGA 4	1.33 (0.54-3.32)
IGA 5[d]	3.51 (1.20-10.28)
NRS pruritus	0.99 (0.86-1.16)
Eosinophil levels	1.30 (0.84-2.00)
Serum TARC levels	0.94 (0.67-1.32)



AD indicates atopic dermatitis; BL, baseline; BMI, body mass index; IGA, Investigator Global Assessment Scale; NA, not applicable; NRS, Numerical Rating Scale; TARC, thymus- and activation-regulated chemokine.

[a] $P = .03$.

[b] $P < .001$.

[c] $P = .01$.

[d] $P = .02$.

performed with a limited number of discontinuations. We applied the Firth correction to obtain bias-corrected estimates of HRs; nevertheless, statistical power was limited, particularly in the multivariate analyses. Consequently, potential useful predictors may have shown insignificant *P* values, and such predictors need to be evaluated in future drug survival studies.

Conclusions

In this daily practice cohort study, results demonstrate a good overall 1-year, 2-year, and 3-year drug survival of dupilumab. Predictors for dupilumab drug survival showed that patients using immunosuppressive therapy at baseline and the absence of treatment effect at week 4 tended to discontinue treatment owing to ineffectiveness more frequently. In addition, using immunosuppressive therapy at baseline, older age (≥65 years), and an IGA score of very severe AD were predictors of an increased risk for discontinuation owing to adverse effects. In the coming years, daily practice registry data will provide longer follow-up data of new advanced systemic treatments, which will give information on dupilumab drug survival compared with these new systemic treatments.

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