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Quantifying patient preferences for systemic atopic dermatitis treatments using a discrete-choice experiment

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ABSTRACT

Objectives: To identify meaningful treatment attributes and quantify patient preferences for attributes of systemic atopic dermatitis (AD) treatments.

Materials and methods: Qualitative interviews were conducted with adults with moderate-to-severe AD ($N=21$) to identify AD treatment attributes that patients consider most important and inform attribute selection for an online discrete-choice experiment (DCE) survey administered to patients in the United States with moderate-to-severe AD. Participants identified probability of clear/almost clear skin at 16 weeks, time to itch relief, mode of administration, and safety risks as very important. DCE data were analyzed using a random-parameters logit model to estimate the relative importance of treatment attributes and maximum acceptable risk.

Results: A total of 320 respondents completed the DCE survey (74% female; mean age, 35 years). Annual risk of malignancy was the most important attribute, followed by mode of administration, probability of clear skin at 16 weeks, and time to onset of itch relief. Respondents preferred daily oral treatment over injectable treatment. Respondents were willing to accept increases in adverse event risks for improvements in efficacy and mode of administration.

Conclusion: The findings of this study can help inform joint patient-physician decision making in managing moderate-to-severe AD.

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KEYWORDS

Atopic dermatitis; discrete-choice experiment; maximum acceptable risk; patient preference

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease that is characterized by intense itching (pruritus), dry skin, redness, exudation, and pain (1–5). AD is common, affecting up to approximately 20% of children and adolescents and approximately 5–10% of adults (6–9), and is associated with a substantial economic and quality-of-life burden (10,11).

Treatments for AD include emollients (e.g. creams, lotions, ointments), topical corticosteroids (e.g. hydrocortisone, triamcinolone acetonide), topical calcineurin inhibitors (e.g. tacrolimus, pimecrolimus), phosphodiesterase-4 inhibitors (crisaborole), systemic oral and injectable treatments, and phototherapy (1,12–14). Despite conventional systemic immunomodulators being recommended for the management of moderate-to-severe AD, only a few are licensed for this indication (i.e. systemic corticosteroids in the United States and cyclosporine in Europe) (1,15,16). Dupilumab, an interleukin (IL)-4 receptor alpha antagonist (1), is a relatively new systemic therapy (licensed by the US Food and Drug Administration in March 2017 and the European Medicines Agency in September 2017) available as a subcutaneous injection. Several systemic treatments are currently being developed to expand the armamentarium for moderate-to-severe AD, including oral Janus kinase (JAK) inhibitors

(i.e. abrocitinib, baricitinib, and upadacitinib) and injectable anti-IL-13 antibodies (i.e. tralokinumab and lebrikizumab) that have shown promise in early phase clinical studies (17–22).

With this potential influx of additional systemic treatment options, it is important to understand how and to what degree the attributes of systemic treatments are valued by patients to improve patient-physician decision making. Unfortunately, no data exist on patient preferences for systemic AD treatments in the United States and Europe. One study was conducted in Japan, which reported that the top 3 attributes for the patients are risk of mild side effects, time until response, and efficacy of reducing itching; however, this study focused more on the differences between the top attributes for patients and physicians for injection treatments (23).

This study, the first of its kind in the United States and the United Kingdom, was designed to address this gap in the literature with 2 objectives. The first objective was to conduct qualitative interviews to identify the AD treatment attributes that patients with moderate-to-severe AD consider most important when making treatment decisions. The second objective was to quantify patient preferences for the systemic AD treatment attributes that emerged from these qualitative interviews and differentiate between systemic treatments using a discrete-choice experiment (DCE).

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Materials and methods

Survey development

Qualitative interviews

In-depth face-to-face qualitative interviews were conducted with adult (≥ 18 years) patients with AD ($N = 21$). A mix of moderate to very severe disease severity levels, as measured by the Patient-Oriented Eczema Measure (POEM) (24), was represented in the recruitment (16 moderate, 5 severe (inclusive of very severe)). Participants were identified by medical recruiters at qualitative research firms in the United States (L&E Research, Raleigh, NC) and the United Kingdom (Acumen, Manchester, England). Screening criteria for patients were as follows: (1) self-reported diagnosis of AD, (2) diagnosed ≥ 3 months prior to screening, and (3) experience with prescription or over-the-counter treatment for AD. Research materials were reviewed and approved by Research Triangle Institute's institutional review board (STUDY00020631); all patients provided informed consent prior to their participation.

All interviews were conducted using the same semistructured interview guide. To elicit a comprehensive list of treatment attributes that influence preference, participants were first asked about their experiences with AD and its treatments. Participants were then asked what they liked and did not like about current and previous treatments, as well as which factors would influence their decision to try a new treatment. Important concepts and dominant trends were identified across interviews to generate themes through a thematic analysis method (25). Results from the qualitative interviews were used to develop a set of treatment attributes that (1) reflect the priorities of adult patients with moderate-to-severe AD and (2) potentially differentiate between systemic AD treatments. During the qualitative work it emerged that the most important attributes when selecting a new treatment were, in no particular order: (1) time to onset of itch relief, (2) probability of skin clearance, (3) frequency or ease of administration (convenience), and (4) safety. These 4 attributes were among the most frequently reported and included in the top 5 attributes affecting patient preference.

Selection of attribute levels

Both efficacy measures (time to onset of itch relief and probability of skin clearance) were included in the DCE, and published clinical data on available/investigational moderate-to-severe AD treatments were used to guide the selection of ranges for the levels of these attributes (17–19,26).

For safety, the study focused on long-term adverse events that are characteristic of systemic immunosuppressants and the overall JAK class, including the risk of serious infections, risk of venous thromboembolism, and risk of malignancy. Because the ranges for these events among a moderate-to-severe AD population using systemic therapies were not available at the time of this study, we used published data from patients with inflammatory disease states (e.g. rheumatoid arthritis) treated with similar systemic treatment options (27–29). For frequency of administration, we included the 2 most common administration options: a biweekly injection or daily oral pill.

Pretest interviews

The draft survey instrument (inclusive of the DCE) was pretested in one-on-one qualitative interviews with a convenience sample of 15 participants with AD in Raleigh, NC. The pretest interviews confirmed that the attribute descriptions included in the DCE survey instrument were easily understood, that the overall survey length was appropriate, and that participants were willing to make tradeoffs among treatment attributes and levels and accepted the hypothetical scenario used to contextualize the survey instrument. Participants in the pretest interviews expressed difficulty making tradeoffs between two adverse events (venous thromboembolism and malignancy risks) and efficacy because the levels of these risks were perceived to be too low to affect the treatment decision. To ensure that the range of levels of risk was wide enough to facilitate tradeoffs, the upper bound of the risk ranges for each of these attributes was increased from 1.0% (based on the literature (28,29)) to 1.5%. No other changes to the list of attributes or the levels of each attribute were made. The final attributes and levels are shown in Table 1, and an example of a choice question from the DCE is shown in Figure 1.

Table 1. Attributes and levels included in the discrete-choice experiment questions.

Technical attribute label	Respondent-facing attribute label	Respondent-facing attribute levels
Time to onset of itch relief	How long it takes until you will feel some improvement in itching after starting the medicine	1 day 3 days 7 days (1 week) 14 days (2 weeks)
Probability of skin clearance at 16 weeks	Chance of achieving clear or almost clear skin within 16 weeks after starting the medicine	150 people out of 1000 (15%) 350 people out of 1000 (35%) 500 people out of 1000 (50%)
Annual risk of serious infection	Annual risk of getting a serious infection while taking the medicine	1 person out of 1000 (0.1%) 10 people out of 1000 (1%) 30 people out of 1000 (3%)
Annual risk of venous thromboembolism	Annual risk of having a blood clot while taking the medicine	1 person out of 1000 (0.1%) 5 people out of 1000 (0.5%) 15 people out of 1000 (1.5%)
Annual risk of malignancy	Annual risk of developing cancer while taking the medicine	1 person out of 1000 (0.1%) 5 people out of 1000 (0.5%) 15 people out of 1000 (1.5%)
Mode of administration	How you take the medicine	1 pill every day 1 injection every 2 weeks

Medicine Feature	Medicine A	Medicine B
How long it takes until you will feel some <u>improvement in itching</u> after starting the medicine	<p>1 day</p>	<p>7 days (1 week)</p>
Chance of achieving <u>clear or almost clear skin within 16 weeks</u> after starting the medicine	<p>150 people out of 1000 (15%)</p>	<p>350 people out of 1000 (35%)</p>
Annual risk of getting a <u>serious infection</u> while taking the medicine	<p>30 people out of 1000 (3%)</p>	<p>1 person out of 1000 (0.1%)</p>
Annual risk of having a <u>blood clot</u> while taking the medicine	<p>1 person out of 1000 (0.1%)</p>	<p>5 people out of 1000 (0.5%)</p>
Annual risk of developing <u>cancer</u> while taking the medicine	<p>1 person out of 1000 (0.1%)</p>	<p>15 people out of 1000 (1.5%)</p>
How you take the medicine	<p>1 pill every day</p>	<p>1 injection every 2 weeks</p>
Which medicine would you choose?	<input type="checkbox"/>	<input type="checkbox"/>

Figure 1. Example choice task.

Final survey administration

The final survey included basic demographic and health history questions along with the DCE. The DCE methodology, which follows good research practices, is considered the most suited to quantify preferences and has been widely employed to quantify respondents’ preferences and the tradeoffs they are willing to accept between the benefits and risks of treatments (30–33). Because there is a limit to the number of choice questions each respondent can reasonably answer before becoming fatigued, the DCE experimental design was split into equally sized blocks, each with 12 unique choice questions. The survey was programmed and hosted online, and respondents were randomly assigned to 1 block of 12 choice questions randomized to avoid ordering effects.

The survey was administered to adults in the US recruited through an online patient panel (Kantar; New York, NY).

Inclusion criteria were as follows: (1) age ≥ 18 years, (2) self-reported physician diagnosis of AD, and (3) moderate-to-severe AD based on either self-reported treatment history (i.e. currently taking an immunosuppressant or a biologic for AD) or a POEM total score ≥ 8 .

Statistical analyses

Demographic and health history variables were reported descriptively. Choice data from the DCE exercise were analyzed using a random-parameters logit (RPL) model. The RPL model relates treatment choices from each respondent to the attribute levels of each treatment profile in the sequence of choice questions. Using an RPL model is consistent with good research practices and prior precedence for regulatory decision making (31); it accommodates unobserved preference heterogeneity, avoiding

estimation bias from unobserved variation in preferences across the sample and within-sample correlation in the series of choices of each respondent. All variables were effects-coded; hence, the mean effect for each attribute was normalized at zero.

The RPL model results in a preference weight for each attribute level. The conditional relative importance of each attribute was calculated as the difference between the attribute level with the highest preference weight and the one with the lowest preference weight, to allow for comparisons across attributes. Preference weights were used to calculate the maximum acceptable percentage-point increase in the risks of adverse events respondents would trade off for each of the changes in each of the remaining attributes. In other words, this analysis was used to determine the increase in risk that exactly offsets an improvement in a specific benefit, all else being equal between alternative treatments. This was computed as the negative ratio of the difference in utility for the positive change in two levels of an attribute to the disutility generated by a unit change in the risk. Since risk was coded as categorical, the disutility between two levels was assumed to be linear between each pair of risk levels included in the survey instrument.

RPL subgroup models were used to assess whether preferences varied as a function of prespecified subgroups (i.e. eczema severity, treatment experience, itch severity, serious infection history, blood clot history, blood thinner use, years since first AD diagnoses, sex, and ethnicity). For each subgroup model, a subgroup-specific, binary variable was interacted with the variables in the main RPL model. A statistically significant *p*-value from a chi-square test of the joint significance of the interaction terms indicates whether preferences between subgroup pairs are statistically significantly different (34).

Results

Respondent characteristics

A total of 325 respondents completed the online survey; however, 5 respondents were excluded from the analyses because their choices did not show any variability (i.e. they always selected either 'Medicine A' or 'Medicine B'). The final sample of 320 was young (mean age, 35 years), predominantly female (73.8%), and predominantly white (74.7%) (Table 2). The median age at diagnosis of AD was 17 years.

Preference weights

Parameter estimates from the RPL model are presented in Table 3 (35) and graphically depicted in Figure 2 to facilitate the interpretation of the preference weights. Preference weights for efficacy and risk attributes were ordered as expected, with better outcomes being preferred to worse outcomes. On average, respondents preferred faster time to onset of itch relief; a higher probability of skin clearance at 16 weeks; and lower annual risks of serious infection, venous thromboembolism, and malignancy. Respondents also preferred a daily pill to an injection every 2 weeks.

The annual risk of malignancy was the most important attribute given the ranges of attribute levels included in the study; indeed, a change in the levels of this attribute from the lowest (0.1%) to the highest risk (1.5%) yielded the largest change in utility. The next most important changes (moving from an injection every 2 weeks to 1 pill every day and improving the

Table 2. Demographic characteristics of the sample.

	Total sample (N = 320)
Age, years	
Mean (SD)	35 (12.2)
Median	34
Female, n (%)	236 (73.8)
Race, n (%)	
White or Caucasian	239 (74.7)
Black or African American	49 (15.3)
Asian	11 (3.4)
American Indian or Alaska Native	10 (3.1)
Native Hawaiian or other Pacific Islander	2 (0.6)
Other	7 (2.2)
Hispanic or Latino (of any race), n (%)	27 (8.4)
Currently employed, n (%)	218 (68.1)
Highest level of education, n (%)	
Less than associate degree	177 (55.3)
Associate degree or higher	142 (44.4)
Prefer not to say	1 (0.3)
Married/living as married/domestic partnership, n (%)	176 (55.0)
Age when diagnosed with AD, years	
Mean (SD)	20 (14.5)
Median	17

AD: atopic dermatitis; SD: standard deviation.

probability of clear skin at 16 weeks from 15 to 50%) were approximately equally important, as the confidence intervals indicated that the estimated differences are not statistically different from each other. Reducing the time to onset of itch relief from 14 days to 1 day and reducing the annual risks of serious infection and venous thromboembolism were also approximately equally important given the ranges of onset of action and risks included in the study. It is important to highlight that these measurements of importance are conditional on the ranges of levels included in the DCE (e.g. smaller ranges across levels of a particular attribute would likely lead that attribute to be viewed as less important relative to others).

Maximum acceptable increases in risk

The results from the RPL model were also used to assess the respondents' maximum acceptable increases in the risk of serious infection, venous thromboembolism, and malignancy for improvements in each of the efficacy attributes and preferred mode of administration (Table 4). On average, respondents were willing to accept more than the largest possible percentage-point increase in risk of serious infection presented in the DCE (2.9 percentage-points; i.e. the difference between the lower bound risk of 0.1% and the upper bound risk of 3%) to reduce the time to onset of itch relief from 14 days to 1 day, improve the probability of skin clearance at 16 weeks from 15% to 35% or 50%, or use a daily pill instead of an injectable medication.

Additionally, on average, respondents were willing to accept more than the largest possible percentage-point increase in risk of venous thromboembolism presented in the DCE (1.4 percentage-points; i.e. the difference between the lower bound risk of 0.1% and the upper bound risk of 1.5%) for either reducing the time to onset of itch relief from 14 days to 1 day, improving the probability of skin clearance at 16 weeks from 15 to 50%, or using a daily pill over an injectable medication (Table 4). On the other hand, respondents demonstrated a smaller risk tolerance for malignancy. Respondents were willing to accept increases in risk of malignancy of 0.38, 0.65, and 0.78 percentage points for reducing the time to onset of itch relief from 14 days to 1 day, improving the probability of skin clearance at 16 weeks from

Table 3. Random-parameters logit model estimates: preference weights ($N = 320$).

Attribute	Level	Mean PW			Significant SD ^b
		Coefficient estimate	95% CI	<i>p</i> value from previous level	
Time to onset of itch relief	1 day	0.468	0.284 to 0.653	–	Yes
	3 days	0.160	–0.010 to 0.329	.029	Yes
	7 days	–0.163	–0.314 to –0.012	.013	Yes
	14 days ^a	–0.464	–0.678 to –0.251	.047	Yes
Probability of skin clearance at 16 weeks	15%	–0.743	–0.918 to –0.568	–	Yes
	35%	0.101	–0.011 to 0.213	<.001	No
	50% ^a	0.642	0.471 to 0.812	<.001	Yes
Annual risk of serious infection	0.1%	0.391	0.260 to 0.521	–	No
	1%	0.045	–0.084 to 0.173	.002	No
	3% ^a	–0.435	–0.566 to –0.305	<.001	No
Annual risk of venous thromboembolism	0.1%	0.354	0.216 to 0.492	–	Yes
	0.5%	0.133	0.011 to 0.255	.048	Yes
	1.5% ^a	–0.487	–0.630 to –0.345	<.001	No
Annual risk of malignancy	0.1%	1.193	0.958 to 1.427	–	Yes
	0.5%	0.211	0.082 to 0.340	<.001	Yes
	1.5% ^a	–1.404	–1.661 to –1.146	<.001	Yes
Mode of administration	1 pill every day	0.796	0.609 to 0.984	–	Yes
	1 injection every 2 weeks ^a	–0.796	–0.984 to –0.609	<.001	Yes
K	24	–	–	–	–
LL	–1773.29	–	–	–	–
BIC	3761.26	–	–	–	–

Because all attribute levels are effects-coded, the sum of the mean coefficient estimates for a given attribute equals zero (unless rounding affected presentation in the table). The LL and the BIC are included for completeness in the table, but they are relative values and can only be used to compare goodness of fit across models and do not have a meaning in absolute terms. The column labeled '*p* value from previous level' shows the results of a one-sample *t* test of the statistical significance of differences between each level and the level immediately preceding it in the table. SDs are based on the normal distribution assumed for each attribute level in the random-parameters logit model.

All levels within each attribute were statistically different from each other ($p < .05$). For example, the PW for 3 days to itch relief is 0.16, which is not statistically significantly different from zero (the 95% CI includes 0); however, the PW for 3 days is statistically significantly different from the PW for 1 day to itch relief ($p = .026$). The SD estimate of the normal distribution assumed for 3 days to itch relief is statistically significant, indicating that preferences for this level varied systematically among respondents (i.e. preference heterogeneity exists in this attribute level).

BIC: Bayesian information criterion; CI: confidence interval; K: number of parameters in the model; LL: log-likelihood; PW: preference weight;

SD: standard deviation.

^aThese levels are omitted in the effects-coded model and have been recovered after estimation using the delta method to retrieve standard errors and thus CIs [35].

15% to 50%, and using a daily pill over an injectable, respectively (Table 4).

Subgroup analyses

The standard deviations of the normal distribution associated with each attribute level in the RPL indicated that preferences varied among respondents. A subgroup analysis measured the differences in patient preferences between prespecified groups, and among 9 subgroups tested, those based on prior serious infection and current blood thinner use showed differences in preferences (Table 5). Reducing the risk of malignancy was more important among those without a history of serious infections ($n = 215$) compared with respondents with prior serious infections ($n = 105$) (Figure 3(A)). There were no notable differences in preferences between the two groups for annual risk of serious infections; furthermore, respondents with prior serious infections did not differentiate between 7 and 14 days for onset of itch relief, 35 and 50% for probability of skin clearance at 16 weeks, 0.1 and 1% for risk of serious infection, and 0.1 and 0.5% for risk of venous thromboembolism (Figure 3(A)). The preferences of respondents who reported using blood thinners ($n = 33$) were also different compared with those who do not ($n = 287$), although caution should be applied given the small sample size,

large confidence intervals, and disordering of the preference weights (Table 5; Figure 3(B)).

On average, a history of serious infections did not appear to influence the importance of avoiding the risk of future serious infection. Similarly, current usage of blood thinners did not appear to influence the importance of avoiding the risk of venous thromboembolism.

Discussion

This was one of the first studies (first in the United States and the United Kingdom) to our knowledge to assess patient preferences for systemic treatment options for moderate-to-severe AD. A study conducted in Japan, which assessed preferences among patients with moderate-to-severe AD focused more on differences between preferences of patients and physicians, specifically regarding attributes of injection treatments (23). Qualitative interviews from our study indicated that for systematic treatments, respondents value probability of skin clearance, time to onset of itch relief, convenient dosing/administration schedule, and avoidance of safety risks.

The results of the DCE indicated that for efficacy, probability of skin clearance at 16 weeks was the most important attribute, followed closely by time to onset of itch relief. Respondents preferred daily oral treatments to biweekly injections. From a safety

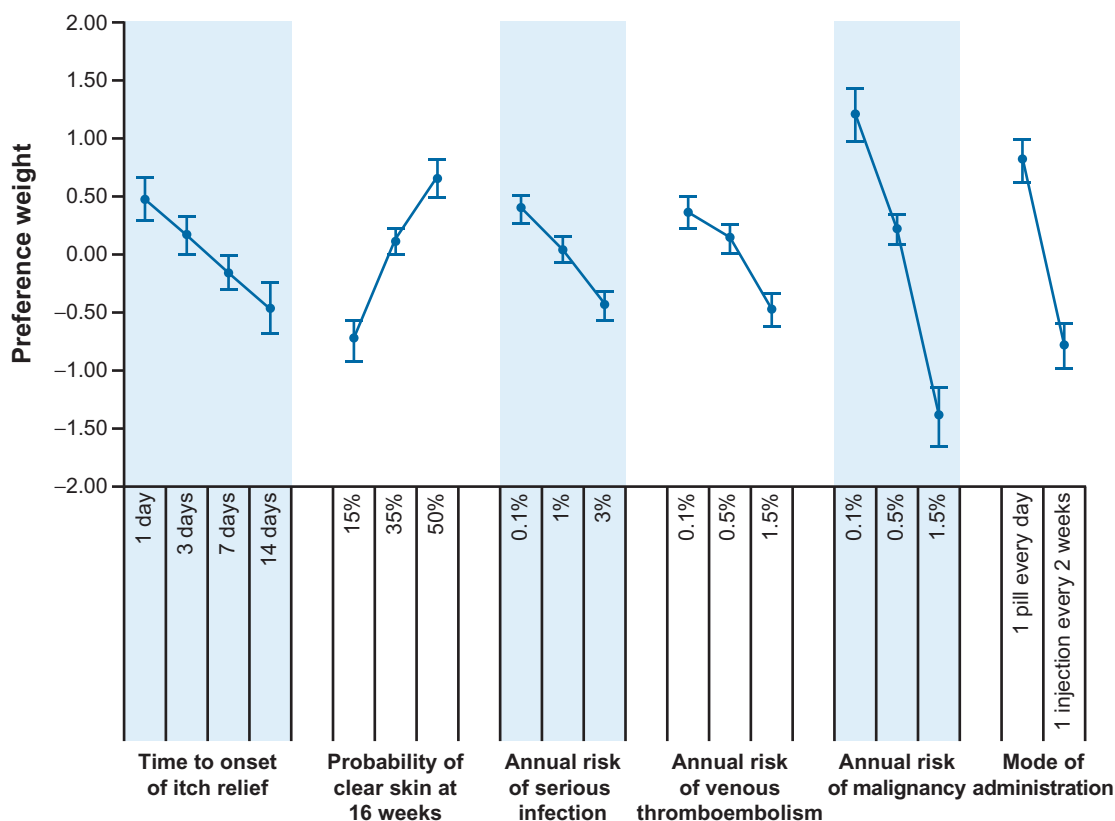


Figure 2. Random-parameters logit model estimates: preference weights ($N = 320$). Attributes are presented in the order in which they appeared in the discrete-choice experiment questions. The vertical bars around each mean preference weight (PW) represent the 95% confidence interval around the point estimate. Within each attribute, a higher PW indicates that a level is more preferred. For example, on average, respondents preferred a 50% probability of skin clearance at 16 weeks ($PW = 0.642$) more than a 35% probability ($PW = 0.101$). The change in utility associated with a change in the levels of each attribute is represented by the vertical distance between the PWs for any 2 levels of that attribute. Larger differences between PWs indicate that respondents viewed the change as having a relatively greater effect on overall utility. For example, reducing the time to onset of itch relief from 7 days to 1 day is preferable to reducing the probability of a serious infection from 1% to 0.1% because it has nearly 2 times ($0.63/0.35$) more impact on utility, all else being constant. Within each attribute, the sum of the PW equals 0.

perspective, the avoidance of annual risk of malignancy was most important followed by avoidance of annual risk of serious infections and venous thromboembolism, which were equally important. Higher risks, such as a 1.5% annual risk of malignancy, were significantly associated with reduced preference.

Although malignancy risk was considered the most important across all attributes (followed by probability of skin clearance at 16 weeks, mode of administration, time to onset of itch relief, serious infection risk, and venous thromboembolism risk, in that order), it is necessary to note that this result is conditional on the ranges assessed by the design of this DCE. Because data on the rates of adverse events among the moderate-to-severe AD population are lacking, the ranges were largely derived from published data for patients with other the immunological conditions, such as rheumatoid arthritis (27–29), who have a presumably higher background risk for malignancy, serious infection, and venous thromboembolism. Assuming that the different patient groups have the same preferences, if background risks of these adverse events among patients with AD are indeed lower, and smaller ranges of these risks were used in the DCE, then the degree of importance respondents placed on these events may have also been lower.

The results suggest that differences in preferences across respondents in the sample were not explained by common

demographic and clinical characteristics including sex, ethnicity, and disease severity. Patient preferences did vary by history of serious infection and potentially by prior blood thinner use, suggesting that prior experience with specific events may influence patient preferences. However, on average preferences regarding the attributes for a risk of serious infection or a risk of venous thromboembolism did not vary between their respective subgroups (i.e. history of serious infection and current use of blood thinners). Other preferences did vary across these groups but in generally subtle ways; if anything, patients with these experiences were less risk averse, but further research is needed to confirm this.

Although the intent of this study was not to establish a preference for a particular treatment over another, the results could be viewed in the context of the various profiles of systemic treatment options. In general, oral treatments (e.g. systemic immunosuppressant agents and JAK inhibitors in development) may be preferred over injectable biologics (e.g. dupilumab and other cytokine inhibitors in development) by most patients, all else being equal. Janus kinase 1 (JAK1) selective inhibitors, including abrocitinib and upadacitinib, in particular, have been associated with a particularly rapid reduction in itch as well as generally high probability of skin clearance at weeks 12 and 16 of treatment, respectively (17,19), which suggests these products would be preferred on those grounds.

Table 4. Maximum acceptable risk of serious infection, venous thromboembolism, and malignancy (N = 320).

Serious infection				
Attribute	From level	To level	Mean, %	95% CI
Time to onset of itch relief	14 days	7 days	0.78	-0.08 to 1.64
	14 days	3 days	2.06	0.59 to 3.52
	14 days	1 day	>2.90	-
	7 days	3 days	0.84	-0.06 to 1.74
	7 days	1 day	2.09	0.82 to 3.36
	3 days	1 day	0.80	0.01 to 1.60
Probability of skin clearance at 16 weeks	15%	35%	>2.90	-
	35%	50%	1.71	0.53 to 2.89
	15%	50%	>2.90	-
Mode of administration	1 injection every 2 weeks	1 pill every day	>2.90	-
Venous thromboembolism				
Attribute	From level	To level	Mean, %	95% CI
Time to onset of itch relief	14 days	7 days	0.53	-0.06 to 1.12
	14 days	3 days	1.05	0.44 to 1.66
	14 days	1 day	>1.40	-
	7 days	3 days	0.56	0.03 to 1.10
	7 days	1 day	1.06	0.55 to 1.57
	3 days	1 day	0.54	0.00 to 1.08
Probability of skin clearance at 16 weeks	15%	35%	1.40	0.88 to 1.93
	35%	50%	0.92	0.45 to 1.38
	15%	50%	>1.40	-
Mode of administration	1 injection every 2 weeks	1 pill every day	>1.40	-
Malignancy				
Attribute	From level	To level	Mean, %	95% CI
Time to onset of itch relief	14 days	7 days	0.12	0.00 to 0.25
	14 days	3 days	0.25	0.11 to 0.40
	14 days	1 day	0.38	0.22 to 0.54
	7 days	3 days	0.13	0.02 to 0.24
	7 days	1 day	0.26	0.14 to 0.38
	3 days	1 day	0.13	0.01 to 0.24
Probability of skin clearance at 16 weeks	15%	35%	0.34	0.21 to 0.47
	35%	50%	0.22	0.11 to 0.33
	15%	50%	0.65	0.40 to 0.90
Mode of administration	1 injection every 2 weeks	1 pill every day	0.78	0.51 to 1.05

The maximum acceptable risk increase for each risk relative to each improvement in the levels of all other attributes provides the average percentage increase in treatment-related risk that yields a level of disutility equal to the utility generated by improving a treatment from one level to the other level included in the table. For example, respondents were willing to accept an increase in the risk of serious infection of approximately 2 percentage points to reduce the time to onset of itch relief from 14 days to 3 days, all else being constant. '—' denotes that 95% CI was not estimable. CI: confidence interval.

Table 5. Discrete-choice experiment subgroup analysis: Subgroup description and results of the test of joint significance of the interaction terms (N = 320).

Subgroup pair	Subgroup description	Sample size	Chi-square <i>p</i> value
Eczema severity ^a	POEM total score of 8–16 (moderate)	207	.149
	POEM total score of 17–28 (severe)	105	
Treatment experience	Currently taking an immunosuppressant or biologic	51	.096
	Not currently taking an immunosuppressant or biologic	269	
Itch severity ^b	Itch severity score > median	154	.968
	Itch severity score ≤ median	166	
Serious infection history	Have had a serious infection	105	.011
	Have <u>not</u> had a serious infection ^c	215	
Blood clot history	Have had a blood clot	41	.181
	Have <u>not</u> had a blood clot ^d	279	
Blood thinner use	Currently taking a blood thinner	33	.014
	Not currently taking a blood thinner ^e	287	
Years since first AD diagnosis ^f	Diagnosis time > median	159	.623
	Diagnosis time ≤ median	161	
Sex	Male	84	.413
	Female	236	
Ethnicity	White	220	.424
	Other	100	

AD: atopic dermatitis; POEM: Patient-Oriented Eczema Measure.

^aEight respondents who had a POEM total score <8 who also reported taking an immunosuppressant or biologic are excluded from this subgroup.

^bRespondents were asked 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch" imaginable, how would you rate your itch at its most severe point during the last 24 h?' The median itch severity for the sample was 6.

^cThis subgroup includes 19 respondents who answered 'Don't know or not sure' to whether they had ever had a serious infection.

^dThis subgroup includes 4 respondents who answered 'Don't know or not sure' to whether they had ever been told by a doctor that they had had a blood clot.

^eThis subgroup includes 4 respondents who answered 'Don't know or not sure' to whether they were currently taking a blood thinner.

^fThe median time since diagnosis with eczema was 13 years.

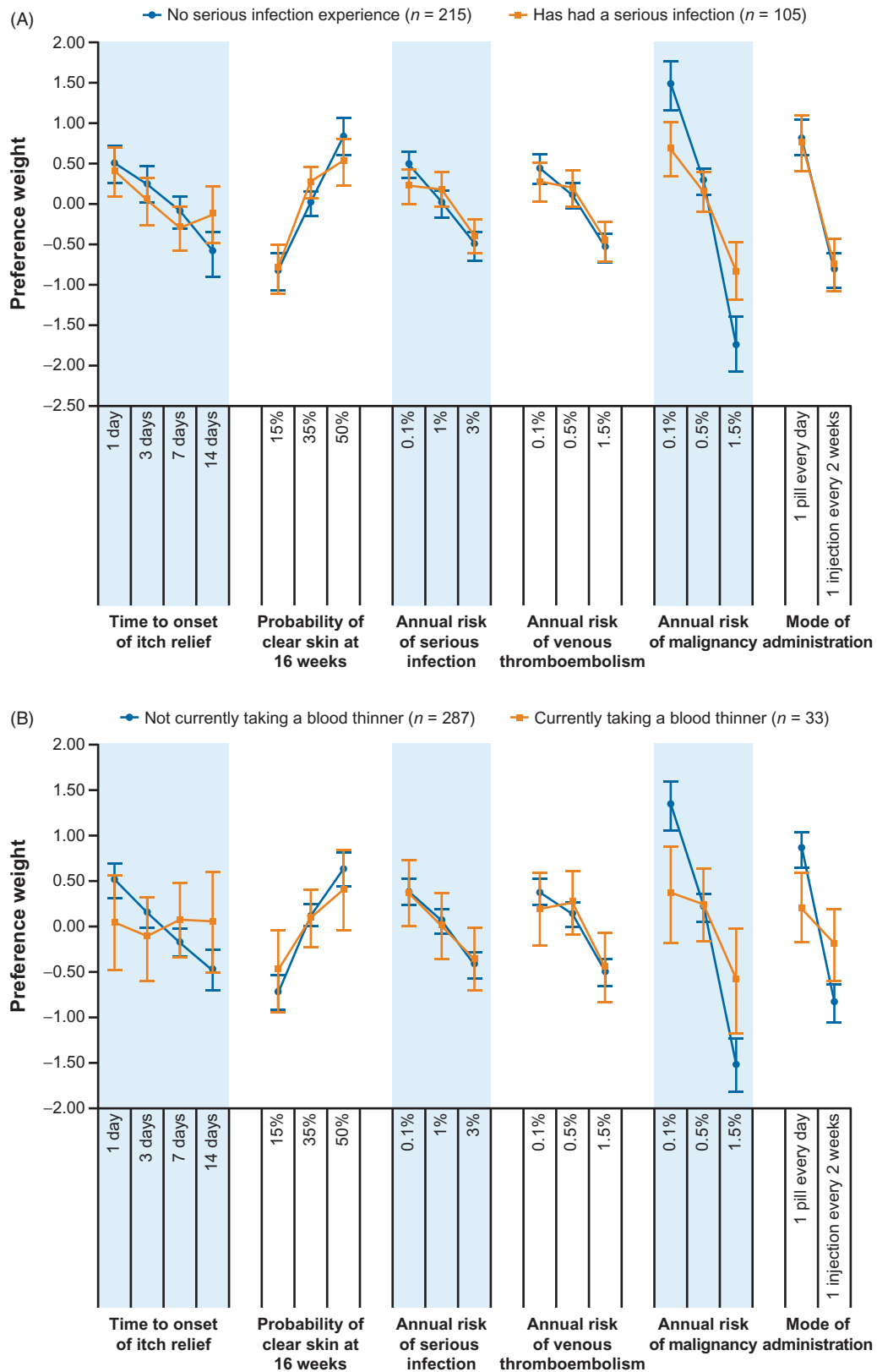


Figure 3. Random-parameters logit model estimates for the (A) serious infection subgroup and (B) blood thinner subgroup ($N = 320$). (A) Attributes are presented in the order in which they appeared in the discrete-choice experiment questions. The vertical bars around each mean preference weight (PW) represent the 95% confidence interval around the point estimate. Within each attribute, a higher PW indicates that a level is more preferred. For example, on average, respondents without serious infection experience preferred a 50% probability of skin clearance at 16 weeks ($PW = 0.837$) more than a 35% probability ($PW = 0.008$). The change in utility associated with a change in the levels of each attribute is represented by the vertical distance between the PW for any 2 levels of that attribute. Larger differences between PWs indicate that respondents viewed the change as having a relatively greater effect on overall utility. For example, among those without serious infection experience, reducing the annual risk of malignancy from 1.5% to 0.1% (change in $PW = \Delta PW = 1.47 - [-1.746] = 3.216$) is preferable to reducing the annual risk of venous thromboembolism from 1.5% to 0.1% ($\Delta PW = 0.431 - [-0.541] = 0.972$) because it has approximately 3 times (3.216/

0.972) more impact on utility, all else being constant. (B) Within each attribute, a higher PW indicates that a level is more preferred. For example, on average, respondents not currently taking a blood thinner preferred a 0.1% annual risk of malignancy ($PW = 1.330$) more than a 1.5% annual risk of malignancy ($PW = -1.529$). The change in utility associated with a change in the levels of each attribute is represented by the vertical distance between the PWs for any 2 levels of that attribute. Larger differences between PWs indicate that respondents viewed the change as having a relatively greater effect on overall utility. For example, among those not currently taking a blood thinner, reducing the annual risk of malignancy from 1.5% to 0.1% ($\Delta PW = 1.33 - [-1.529] = 2.859$) is preferable to reducing the annual risk of venous thromboembolism from 1.5% to 0.1% ($\Delta PW = 0.364 - [-0.502] = 0.866$) because it has approximately 3 times ($2.859/0.866$) more impact on utility, all else being constant.

Dupilumab has not demonstrated increased risks for the long-term safety issues assessed in this study and, therefore, may be preferred over currently available systemic immunosuppressants (e.g. methotrexate, azathioprine) that have established increased malignancy risks (13). There are potential safety concerns with the JAK inhibitor class including serious infections, venous thromboembolism, and malignancy (36). However, the specific frequencies of these risks are still under evaluation in AD. This study showed that the risk of malignancy was highly relevant for patients, but they placed more value on efficacy and convenience (i.e. ease of administration) attributes relative to the risks of serious infection and venous thromboembolism.

The results should be interpreted within the context of common limitations for this type of study. The sample of respondents is a convenience sample recruited through panels of individuals who self-reported a diagnosis with AD. Patient characteristics and preferences may not reflect the preferences and characteristics of the broader population of patients with AD. Additionally, the treatment profiles and choice pairs presented in the survey are hypothetical and, although attributes and levels were defined on existing or potential future systemic AD treatments, the study was not designed to predict actual choices or present real treatment options in real healthcare settings. DCEs, however, are a well-established method for eliciting patient preferences for treatment features, and this study followed the applicable good practices for such study designs (30,31,33).

Adults with moderate-to-severe AD preferred a higher probability of skin clearance at 16 weeks, faster time to onset of itch relief, oral administration, and lower long-term safety risks. Respondents were willing to accept higher risks of serious infections, venous thromboembolisms, and malignancies to have a once-daily oral medicine over a twice-monthly injectable and to improve the time to onset of itch relief and probability of skin clearance at 16 weeks. This research highlights the patient perspective surrounding the relevant benefits and risks of different AD systemic treatments, which can help inform joint patient-physician decision making.

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