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Improvements in itch and sleep following treatment with baricitinib in combination with topical corticosteroids are associated with better quality of life and productivity in adult patients with moderate-to-severe atopic dermatitis: a post hoc analysis from BREEZE-AD7

Background: Treatment with baricitinib in combination with topical corticosteroids previously showed greater improvements in itch and sleep versus placebo in adults with moderate-to-severe AD. *Objectives:* To assess whether improvements in itch and sleep translate to greater quality of life (QoL), productivity and treatment benefit in AD. *Materials & Methods:* In this post hoc analysis with data from BREEZE-AD7 (NCT03733301), itch and sleep improvements at Week 16 were defined by ≥4-point improvements in the Itch Numeric Rating Scale and ≥1.5 decreases in the number of night-time awakenings since baseline, respectively. Dermatology Life Quality Index, Work Productivity and Activity Impairment-AD and Patient Benefit Index (PBI) scores were compared in patients with and without improvements. Proportions were analysed using logistic regression with non-responder imputation. Changes from baseline were calculated using ANCOVA, with last observation carried forward. Least square mean PBI scores were assessed using ANOVA. *Results:* More patients with itch improvement versus no itch improvement reported no impact of AD on QoL (28.4% vs. 6.0%). Daily activity impairment was lower in patients with itch improvement (-39.6% vs. -15.6%). A greater proportion of patients with sleep improvement versus no sleep improvement had no AD-related impact on QoL (24.1% vs. 1.5%). Patients with sleep improvement had less daily activity impairment (-35.0% vs. -18.5%). Patients with itch and sleep improvements experienced greater treatment benefit. *Conclusion:* Patients with AD who experienced clinically meaningful improvements in itch and sleep following treatment had significantly better QoL, productivity and treatment benefit. Addressing these symptoms is important to achieving meaningful and patient-relevant improvements in well-being.

Key words: atopic dermatitis, baricitinib, itch, productivity, quality of life, sleep

Atopic dermatitis (AD) is a common, chronic, highly symptomatic, inflammatory skin disease with significant impacts on patients' quality of life (QoL). Intense itch, the hallmark symptom of AD, can be distressing and distracting, adversely affecting patients' emotional well-being, daily functioning, and productivity [1, 2]. Moreover, pruritic symptoms often intensify at night, causing patients to have trouble falling and staying asleep. Poor sleep quality can further lead to daytime fatigue, cognitive impairment, and worse overall health in patients with AD [3]. As itch and sleep disturbance have important consequences on patients' daily lives, managing these symptoms are important aspects of AD treatment [4].

Because of their potential to mediate signalling of multiple cytokines involved in AD pathogenesis, Janus kinase (JAK) inhibitors have emerged as effective therapeutics for AD. Baricitinib, an oral, selective JAK1/JAK2 inhibitor, may decrease the activity of inflammatory cytokines involved in AD pathogenesis, including IL-31, a cytokine heavily involved in pruritus and dependent on the JAK1 signalling pathway [5]. In a 16-week Phase 3 trial of adults with moderate-to-severe AD, patients treated with baricitinib in combination with topical corticosteroids (TCS) had significantly greater improvements in itch and sleep compared with placebo-treated patients [6]. Using data from this trial, the present post hoc analysis assessed whether improve-

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ments in itch and sleep are associated with greater QoL, productivity and treatment benefit in adults with AD.

Materials and methods

Study population

This is a post hoc analysis of the baricitinib randomized clinical trial BREEZE-AD7 (NCT03733301), a multicentre, double-blind, placebo-controlled, parallel-arm, 16-week, Phase 3 study evaluating the efficacy and safety of baricitinib 2 mg and 4 mg in combination with background TCS therapy in adults with moderate-to-severe AD who previously had an inadequate response to TCS therapy [6]. The study was performed in 10 countries across Asia, Australia, Europe and South America. The study was conducted in accordance with ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol and amendment were approved by the appropriate institutional review boards/ethics committees at each study site, and all patients provided written informed consent. No additional ethical approval was required to conduct the present analysis.

Patients were ≥18 years and had a diagnosis of AD, as defined by the American Academy of Dermatology, at least 12 months prior to screening, and a documented history of an inadequate response to topical therapies within six months before screening. Patients had moderate-to-severe disease at screening and baseline, as defined by an Eczema Area and Severity Index (EASI) score ≥16, a vIGA-AD™ score ≥3, and ≥10% body surface area (BSA) involvement. All patients received moderate- and/or low-potency TCS for active lesions. In countries where approved, topical calcineurin inhibitors and/or crisaborole could be used in areas considered inadvisable for TCS. Rescue therapy with high- or ultrahigh-potency TCS or systemic therapies was available for patients with worsening and unacceptable AD symptoms after two weeks of treatment. The current post hoc analysis was conducted on the intent-to-treat population.

Measures

Itch severity

Itch was measured with the Itch Numeric Rating Scale (NRS), in which patients rated itch severity over the past 24 hours from 0 ("no itch") to 10 ("worst itch imaginable"). This information was entered into an electronic diary at the end of each patient's day, and weekly mean scores were assessed. Patients with baseline Itch NRS ≥4 were categorized as having improvement in itch if they experienced a ≥4-point improvement in the Itch NRS at Week 16. This cut-off was derived from the scale's minimal clinically important difference (MCID) [7].

Sleep disturbance

Sleep disturbance was measured using the Atopic Dermatitis Sleep Scale (ADSS) Item 2, which captures the self-reported number of night-time awakenings due to itch. Patients recorded the number of times they woke during the previous night, ranging from 0 to 29 times, in the electronic daily diary, and weekly mean scores were assessed. Patients with baseline ADSS Item 2 ≥1.5 were classified as having sleep improvement at Week 16 if they experienced a ≥1.5 decrease in the number of night-time awakenings from baseline (the ADSS Item 2 MCID) [8].

Quality of life

The Dermatology Life Quality Index (DLQI) was used to assess patients' QoL [9] with scores spanning from 0 to 30, with higher scores indicating greater impairment on QoL. The following DLQI endpoints were assessed: the proportion of patients with a DLQI total score of 0 or 1 (no impact of AD on QoL) at Week 16 and the proportion of patients who had ≥4-point improvement in DLQI from baseline, the MCID threshold [10, 11].

Work productivity and daily living

The Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis (WPAI-AD) measures impairment due to AD from four domains. The following were determined for employed patients: absenteeism (work time missed), presenteeism (work time spent impaired), and overall work impairment (total productivity loss associated with absenteeism and presenteeism); daily activity impairment was calculated for all patients. Scores are calculated as percentages, with higher scores indicating more impairment and less productivity [12].

Patient-relevant treatment benefit

The Patient Benefit Index (PBI) consists of two questionnaires [13]. The Patient Needs Questionnaire is completed before therapy and indicates individual importance of objectives. In the Patient Benefit Questionnaire, completed during the study, patients rate the extent to which treatment objectives have been met. Responses include 0 ('not at all'), 1 ('somewhat'), 2 ('moderately'), 3 ('quite'), 4 ('very'), and 5 ('does/did not apply'). Individual global scores are calculated by weighing achievement values by their importance to the individual. The PBI is further supplemented by scales evaluating physical well-being, emotional well-being, performance capacity on the job and in everyday living, social contacts, leisure activities, and QoL. Patients with PBI ≥1 are considered to have at least minimum patient-relevant treatment benefit.

Statistical analysis

The Itch NRS and ADSS Item 2 data were collected in patient electronic daily diaries. The weekly mean scores were calculated using data from the previous seven days, if at least four of the seven diary values were not missing.

This post hoc analysis consisted of two analysis sets. The first analysis set was composed of patients with baseline Itch NRS ≥4. We compared the proportion of patients with ≥4-point improvement in the Itch NRS by treatment arms, and then compared DLQI, WPAI-AD, and PBI in those who achieved 4-point improvement in itch vs those who did not. The second analysis set was composed of patients with baseline ADSS Item 2 ≥1.5 and we compared the proportions of patients with ≥1.5-point improvement in the ADSS Item 2 by treatment arms, and then compared DLQI, WPAI-AD, and PBI in those who achieved 1.5-point improvement in ADSS Item 2 vs those who did not.

Data collected after rescue or treatment discontinuation were considered missing. Logistic regression models with baseline disease severity (vIGA-AD), baseline value, region, and treatment group as independent variables were applied for comparing 4-point improvement in itch or ≥1.5-point improvement in the ADSS item 2 between treatment arms. Non-responder imputation was used.

For DLQI, WPAI, and PBI improvement at Week 16, we considered a treatment-by-itch or sleep improvement interaction in the model and evaluated its significance at the α level of 0.1. When the *p* value for the interaction was greater than 0.1, we conducted treatment-agnostic analyses for DLQI, WPAI, or PBI improvement.

The DLQI responder comparisons were limited to patients with baseline DLQI scores ≥4 or ≥1, depending on the outcome assessed, and logistic regression models were used for these analyses. Mean changes, from baseline at Week 16, in DLQI and WPAI-AD scores were analysed in separate ANCOVA models, with missing data imputed by last observation carried forward, using the last observation prior to rescue or discontinuation. PBI scores at Week 16 were analysed using ANOVA.

Results

Patient characteristics

Baseline characteristics of the study population by itch and sleep improvement subgroups are listed in *table 1*.

Improvement in itch

After the 16-week treatment period, overall, 33.9% (102/301) patients achieved a ≥4-point improvement in the itch severity score. As reported previously, the proportions of patients who achieved itch improvement by treatment group were 20.2% (21/104) with placebo, 44.0% (44/100; $p < 0.001$ versus placebo) with baricitinib 4 mg, and 38.1% with baricitinib 2 mg (37/97, $p = 0.002$ versus placebo) [6].

Table 1. Baseline demographic and clinical characteristics by itch and sleep improvement subgroups*.

	Itch improvement at Week 16[a] (*n* = 301)		Sleep improvement at Week 16[b] (*n* = 148)	
	Yes (*n* = 102)	**No (*n* = 199)**	**Yes (*n* = 83)**	**No (*n* = 65)**
Treatment group, *n* (%)				
Placebo + TCS	21 (20.6)	83 (41.7)	19 (22.9)	30 (46.2)
Baricitinib 2 mg + TCS	37 (36.3)	60 (30.2)	30 (36.1)	20 (30.8)
Baricitinib 4 mg + TCS	44 (43.1)	56 (28.1)	34 (41.0)	15 (23.1)
Age, years	33.8 (12.8)	33.5 (12.3)	35.8 (12.3)	37.6 (12.7)
Female, *n* (%)	47 (46.1)	57 (28.6)	31 (37.3)	24 (36.9)
Race, *n*[c] (%)				
White	54 (52.9)	80 (40.2)	43 (51.8)	33 (50.8)
Asian	43 (42.2)	113 (56.8)	39 (47.0)	28 (43.1)
Multiple	5 (4.9)	6 (3.0)	1 (1.2)	4 (6.2)
Region, *n* (%)				
Europe	42 (41.2)	62 (31.2)	30 (36.1)	25 (38.5)
Japan	10 (9.8)	49 (24.6)	10 (12.0)	10 (15.4)
Rest of world	50 (49.0)	88 (44.2)	43 (51.8)	30 (46.2)
Duration since AD diagnosis, years	25.4 (13.4)	22.9 (13.2)	26.8 (14.0)	26.4 (14.1)
Age at time of AD diagnosis	8.7 (12.8)	10.8 (13.0)	9.4 (12.2)	11.5 (15.8)
BSA (%)	49.7 (23.9)	51.5 (22.6)	54.7 (23.5)	53.5 (21.2)
Itch NRS	8.0 (1.4)	7.2 (1.6)	7.9 (1.7)	7.8 (1.8)
ADSS Item 2	2.2 (2.2)	1.8 (2.2)	3.6 (2.5)	3.0 (2.4)
DLQI	17.3 (7.5)	14.6 (7.6)	18.2 (7.9)	18.9 (6.5)
WPAI-AD				
Absenteeism[d]	11.7 (24.5)	9.4 (22.7)	12.7 (25.8)	19.4 (30.5)
Presenteeism[d]	51.4 (24.5)	46.2 (25.4)	52.8 (25.0)	60.5 (20.2)
Overall work impairment[d]	54.5 (25.2)	48.4 (26.7)	55.1 (25.5)	65.7 (21.3)
Daily activity impairment	59.8 (24.0)	54.4 (26.0)	62.1 (23.8)	62.0 (25.6)

**Interactions between the treatment arms (placebo, baricitinib 2 mg, or baricitinib 4 mg) with either the itch improvement or sleep improvement were not significant at the α level of 0.1 for DLQI, WPAI-AD, and PBI measures. Therefore, comparisons between patients with and without itch or sleep improvement were assessed across treatment arms. AD: atopic dermatitis; ADSS: Atopic Dermatitis Sleep Scale; BSA: body surface area; DLQI: Dermatology Life Quality Index; ITT: intent-to-treat; NRS: Numeric Rating Scale; PBO: placebo; TCS: topical corticosteroids; WPAI-AD: Work Productivity and Activity Impairment Questionnaire-Atopic Dermatitis. Data are expressed as mean (standard deviation) unless stated otherwise.*

[a] *Itch improvement is defined as a ≥4-point decrease in Itch NRS score at Week 16.*

[b] *Sleep improvement is defined as a ≥1.5-point decrease in ADSS Item 2 score at Week 16.*

[c] *Number of patients with complete data.*

[d] *Calculated in employed patients only (n = 210 in ITT).*

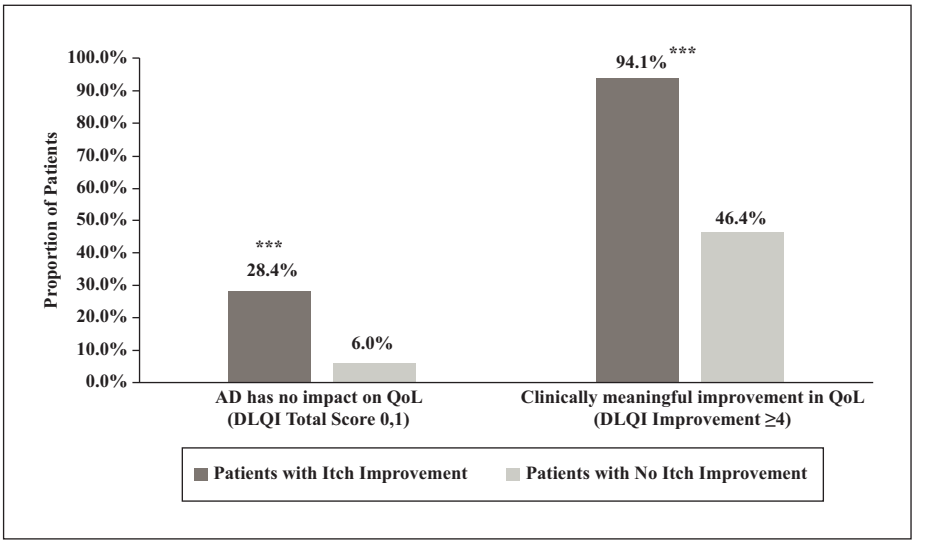

Figure 1. Proportion of patients with and without itch improvement achieving DLQI endpoints at Week 16. AD: atopic dermatitis; DLQI: Dermatology Life Quality Index. ***$p < 0.001$. Itch improvement is defined as a ≥4-point decrease in the Itch Numeric Rating Scale at Week 16. Analysis included patients with baseline DLQI scores ≥4 or ≥1, depending on the outcome assessed. Logistic regression models were used with terms for baseline disease severity (vIGA-AD), baseline value, region, treatment group, itch/sleep improvement (yes or no), and the interaction of treatment and itch/sleep response; non-responder imputation was applied for missing data.

The interactions between the treatment arms with itch improvement were not significant at the α level of 0.1 for DLQI, WPAI-AD, or PBI measures. Therefore, comparisons between patients with and without itch improvement were assessed across treatment arms.

Quality of life

At Week 16, 28.4% of patients with itch improvement versus 6.0% of patients without improvement reported a DLQI total score of 0 or 1 ($p < 0.0001$) (*figure 1*). A greater proportion of patients with itch improvement reported a clinically meaningful ≥4-point change in DLQI score (94.1%) compared with patients without itch improvement (46.4%, $p < 0.0001$).

Work productivity and daily living

Among the employed ($n = 191$), patients who experienced itch improvement saw notably larger reductions in presenteeism (-31.4% versus -13.7%, $p < 0.0001$) and in total work impairment (-33.5% versus -15.0%, $p < 0.0001$) than those without itch improvement (*figure 2*). The decreases in absenteeism between the two groups were not significantly different (-8.8% versus -4.9%, $p = 0.1402$). Among all patients, those with itch improvement reported significantly less daily activity impairment than those without itch improvement (-39.6% versus -15.6%, $p < 0.0001$).

Patient-relevant treatment benefit

Patients with itch improvement at Week 16 had significantly higher PBI scores than those without itch improvement (2.8 vs. 2.2, $p < 0.0001$). Similarly, a greater proportion of patients with itch improvement had PBI ≥1, indicating at least minimum patient-relevant treatment benefit (91.2% vs. 61.8%, $p < 0.0001$).

Improvement in sleep

After the 16-week treatment period, for patients with ≥1.5-point decrease in the number of night-time awakenings due to itch since baseline, 56.1% (83/148) of patients experienced sleep improvement. As reported previously, these proportions by treatment group, were 38.8% (19/49) with placebo, 69.4% (34/49; $p = 0.004$ versus placebo) with baricitinib 4 mg, and 60.0% (30/50; $p = 0.048$ versus placebo) for baricitinib 2 mg [6].

The interactions between the treatment arms with sleep improvement were not significant at the α level of 0.1 for DLQI, WPAI-AD, or PBI measures. Therefore, comparisons between patients with and without improvement were assessed across treatment arms.

Patients with sleep improvement reported similar trends in DLQI, WPAI-AD, and PBI as those patients who reported itch improvement (*figures 3, 4*). One exception was noted; among employed patients, those with sleep improvement had greater reduction in absenteeism (*figure 4*).

Discussion

In this post hoc analysis of adults with moderate-to-severe AD treated with baricitinib or placebo in combination with TCS, patients who experienced clinically meaningful improvements in itch and sleep were more likely to see large and significant increases in QoL, productivity, and treatment benefit than patients without itch or sleep improvements. Notably, more than twice as many patients with itch or sleep improvements achieved the MCID for DLQI compared with those who did not report itch or sleep improvements. Likewise, patients with itch or sleep improvements tended to report that AD did not impact their QoL. In addition, patients with improved itch and sleep expe-

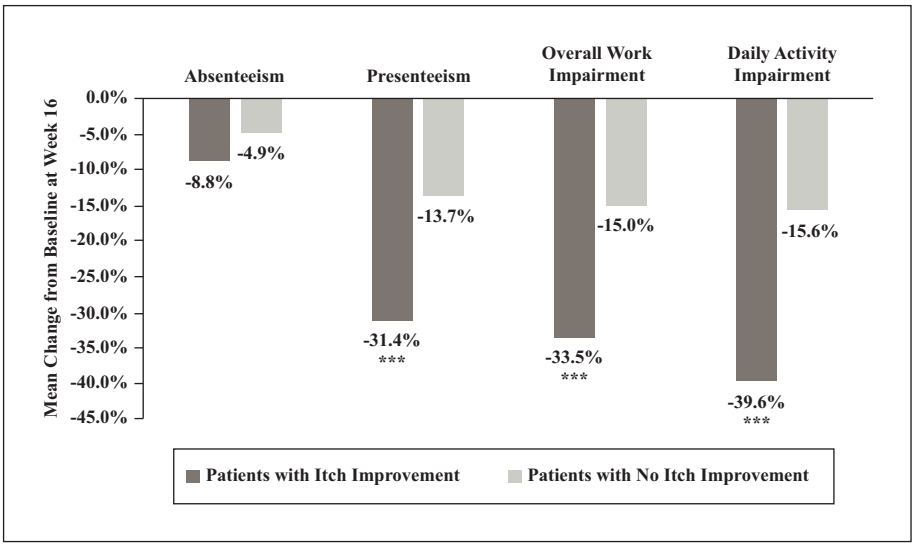

Figure 2. Mean change from baseline in work productivity and daily activity impairment in patients with and without itch improvement. Scores are based on Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis. ***$p < 0.001$. Itch improvement is defined as a ≥4-point decrease in the Itch Numeric Rating Scale at Week 16. Absenteeism, presenteeism, and overall work impairment were measured in employed patients only ($n = 191$).

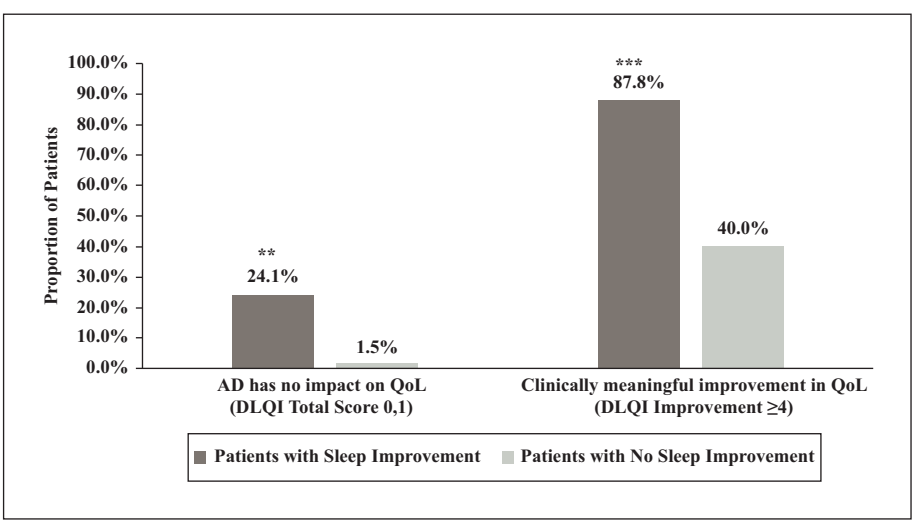

Figure 3. Proportion of patients with and without sleep improvement achieving DLQI endpoints at Week 16. AD: atopic dermatitis; DLQI: Dermatology Life Quality Index. **$p < 0.01$, ***$p < 0.001$. Sleep improvement is defined as a ≥1.5-point decrease in Atopic Dermatitis Sleep Scale Item 2 score at Week 16. Analysis included patients with baseline DLQI scores ≥4, or ≥1, depending on the outcome assessed. Logistic regression models were used with terms for baseline disease severity (vIGA-AD), baseline value, region, treatment group, itch/sleep improvement (yes or no), and the interaction of treatment and itch/sleep response; non-responder imputation was applied for missing data.

rienced less impairment at work and in daily activities. Moreover, these patients were significantly more likely to report relevant treatment benefit. These findings demonstrate how addressing itch and related sleep disturbance are key to improving well-being for patients with AD.

Patients with AD have identified addressing skin-related QoL impairment as an important therapeutic need [4]. Specifically, the management of itch and sleep, two of the most burdensome symptoms of AD [14], may be key to mitigating the impact of the disease on patient QoL [15, 16]. In this study, as reported previously, patients treated with baricitinib 4 mg or 2 mg in combination with TCS were more likely to see improvement in itch and sleep disturbance due to itch than patients treated with placebo plus TCS [6]. The originating study also revealed a positive impact of baricitinib treatment on QoL and productivity measures [6]. The present post hoc analysis indicates that these increases in QoL and productivity were more pronounced in those with clinically meaningful improvements in itch and sleep, suggesting that these symptoms are core to patient well-being. Furthermore, patients who experienced itch or sleep improvement also reported greater treatment

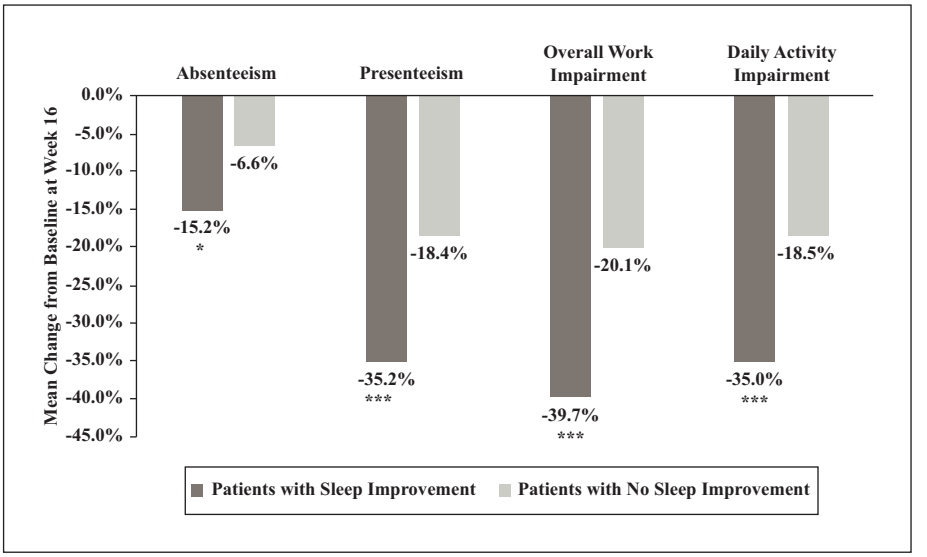

Figure 4. Mean change from baseline in work productivity and daily activity impairment in patients with and without sleep improvement. Scores are based on Work Productivity and Activity Impairment Questionnaire–Atopic Dermatitis. *$p < 0.05$, ***$p < 0.001$. Sleep improvement is defined as a ≥1.5-point decrease in Atopic Dermatitis Sleep Scale Item 2 score at Week 16. Absenteeism, presenteeism, and overall work impairment were measured in employed patients only ($n = 93$).

benefit. Together, these findings highlight the importance of the patient perspective and how therapy targeting symptoms important to patients is essential to achieving meaningful, patient-relevant improvements in QoL and productivity.

Previous studies have established the considerable economic and humanistic burden of AD [4, 17]. Consistent with other studies [18, 19], the present analysis indicates that total workplace productivity loss in patients with AD largely reflects the effects of presenteeism. Though there was significantly less absenteeism in patients with sleep improvement compared to those without, the amount of work time missed did not significantly differ between those with and without itch improvement. Rather, changes in itch and sleep appeared to have a much greater impact on work time spent impaired, suggesting presenteeism may be more clinically relevant to the AD population than absenteeism, as recently observed by Stingeni *et al*. [20]. Patients experiencing itch or sleep improvement also saw notable decreases in daily activity impairment. Estimates for MCIDs in presenteeism, work productivity loss, and activity impairment in patients with psoriasis and psoriatic arthritis range from about 15-20% [21, 22]. Though these thresholds are not yet defined for AD, patients with itch or sleep improvements in this study reported changes in these productivity measures exceeding 30% after 16 weeks of treatment.

There are important limitations to this study. Given the post hoc nature of the analysis, the results should be interpreted with caution. The data are from a clinical trial of adult patients with moderate-to-severe AD and may not be generalizable to real-world settings and the overall population of patients with AD. As only the first 16 weeks of treatment were assessed, long-term outcome assessments were not available. This study did not evaluate direct and indirect effects on QoL, correlations of itch and sleep response, or correlations with active treatment. Future studies may consider evaluating differences in itch- and sleep-related improvement by demographic or clinical characteristics, including sex, disease duration, and disease onset.

Conclusion

In this post hoc analysis of adults with moderate-to-severe AD, patients who experienced clinically meaningful improvements in itch and sleep had significantly better QoL, work productivity, daily activity performance, and treatment benefit. The findings from this study suggest that therapy targeting these important symptoms is key to improving QoL and productivity in patients with AD. ■

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