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BRIEF REPORT

Patient-Reported Ocular Disorders and Symptoms in Adults with Moderate-to-Severe Atopic Dermatitis: Screening and Baseline Survey Data from a Clinical Trial

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ABSTRACT

Introduction: Patients with atopic dermatitis (AD) have a greater risk of conjunctivitis and other ocular surface disorders than the general population. We evaluated the burden of ocular surface disorders and related symptoms prior to treatment initiation in adults with moderate-to-severe AD.

Methods: Patients were enrolled in a randomized, placebo-controlled, double-blinded, phase 3 trial of dupilumab administered with concomitant topical corticosteroids. At the beginning of the screening period, all enrolled patients completed a survey of ocular disorder diagnoses received in the past year; at baseline, patients completed a survey of frequency and severity of ocular symptoms (discomfort, itching, redness, and tearing) experienced in the past month.

Results: A total of 712 of 740 patients enrolled in the trial provided responses to the survey. At screening, 286 of 740 patients (38.6%) reported having at least one ocular disorder in the past year. At baseline, 499 of 712 respondents (70.1%) reported having at least one symptom within the past month. Of these patients, 4.4%, 6.0%, 5.5%, and 4.4%, respectively, reported having discomfort, itching, redness, and tearing all of the time. Mild discomfort, itching, redness, and tearing were reported by 26.1%, 33.7%, 30.8%, and 31.6% of patients, respectively, while 7.3%, 7.7%, 6.2%, and 4.2%, reported severe discomfort, itching, redness, and tearing, respectively.

Conclusions: These data demonstrate a high burden of ocular surface disorders and related symptoms in a population of adults with moderate-to-severe AD. Dermatologists should be aware of increased incidence of these disorders in AD and query their patients for signs and symptoms of eye disease.

ClinicalTrials.gov Registration Number: NCT02260986.

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Keywords: Atopic dermatitis; Burden; Ocular disorders; Symptoms; Survey

Key Summary Points
Why carry out this study?
Patients with atopic dermatitis (AD) have a greater risk of conjunctivitis and other ocular surface disorders than the general population.
We evaluated the burden of ocular surface disorders and related symptoms prior to treatment initiation with dupilumab in adults with moderate-to-severe AD enrolled in a randomized, placebo-controlled, double-blinded phase 3 trial of dupilumab administered with concomitant topical corticosteroids.
What was learned from the study?
These data demonstrate a high burden of ocular surface disorders and related symptoms in a population of adults with moderate-to-severe AD.
Dermatologists should be aware of increased incidence of these disorders in AD and query their patients for signs and symptoms of eye disease.

DIGITAL FEATURES

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INTRODUCTION

Patients with atopic dermatitis (AD) have a greater risk of conjunctivitis and other ocular surface disorders (e.g., atopic keratoconjunctivitis [AKC], keratoconus, herpetic eye disease, and dry eye) than the general population [1–12]. The prevalence rates of ocular surface disorders in patients with AD are high, with studies showing up to 32–42% of patients with AD reporting eye disease or prescriptions for eye disorders in the past 12 months [1, 5, 6]. Some of these disorders, such as AKC, may lead to serious eye problems, impaired vision, or even vision loss [3, 4, 9]. Incidence of ocular surface disorders increases with AD severity and factors related to AD severity, including elevated circulating levels of IgE, thymus and activation-regulated chemokine, and eosinophils [1, 6, 13].

To provide further information on the prevalence and severity of these disorders, particularly in patients with moderate-to-severe AD, we evaluated the burden of ocular surface disorders and related symptoms prior to treatment initiation in adults with moderate-to-severe AD enrolled in a phase 3 trial of dupilumab.

METHODS

LIBERTY AD CHRONOS (NCT02260986) was a randomized, placebo-controlled, double-blinded, phase 3 trial of dupilumab administered with concomitant topical corticosteroids [14]. Detailed patient eligibility criteria were previously published [14]. In brief, patients were eligible to enroll in CHRONOS if they were at least 18 years of age, and had chronic moderate-to-severe AD, inadequate response to medium- to high-potency topical corticosteroids (with or without concomitant topical calcineurin inhibitors) within 6 months before screening, an Investigator's Global Assessment Score of at least 3 (on a scale of 0–4, where 3 was moderate and 4 was severe), and an Eczema Area and Severity Index score of at least 16 at screening and baseline.

At the beginning of the 35-day screening period, patients completed a survey of ocular disorder diagnoses received in the past year. At baseline, they completed a survey of frequency and severity of ocular symptoms (itching,

Table 1 Screening: ocular surface disorders during the past year

Screening question	Yes	No	I don't know	Missing
Responded to survey, *n*/*N* (%)	712/740 (96.2)	28/740 (3.8)	–	–
Reported ≥ 1 eye disorder in the past year	286/740 (38.6)	–	–	–
Do you have or have you had, *n1* (%)[a]				
AKC	87 (12.2)	523 (73.5)	101 (14.2)	1 (0.1)
Dry eye	146 (20.5)	533 (74.9)	33 (4.6)	0
HSV of the eye	30 (4.2)	650 (91.3)	32 (4.5)	0
Keratoconus	15 (2.1)	609 (85.5)	87 (12.2)	1 (0.1)
Perennial allergic conjunctivitis	107 (15.0)	524 (73.6)	81 (11.4)	0
Rosacea of the eye	19 (2.7)	650 (91.3)	43 (6.0)	0

AKC atopic keratoconjunctivitis, *HSV* herpes simplex virus infection, *N* number of patients enrolled in the study, *n* number of patients who responded to the survey, *n1* number of patients with given response

[a] The percentage is the number of patients with a given response divided by the total number of patients who responded to the survey; patients may have had more than one ocular disorder diagnosed in the past year

tearing, redness, and discomfort) experienced in the past month.

The number and proportion of patients at screening who reported ocular disorder diagnoses in the past year, and the number and proportion of patients at baseline reporting frequency and severity of symptoms, were analyzed using descriptive statistics, based on the number of patients who provided responses to the survey.

The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. The protocol was reviewed and approved by institutional review boards/ethics committees at all study sites. An independent data monitoring committee monitored patient safety. All patients provided signed written informed consent.

RESULTS

Of the 740 patients enrolled in CHRONOS, 712 provided responses to the survey. At screening, 286 of 740 patients (38.6%) reported having at least one ocular disorder in the past year. Among the 712 respondents to the survey, the most common ocular disorder reported in the past year was dry eye (20.5% of patients), while the least common disorder reported was keratoconus (2.1% of patients) (Table 1). Eighty-seven patients (12.2%) reported AKC, a potentially serious ocular disorder, in the past year (Table 1).

Of the 712 respondents to the survey, 499 patients (70.1%; comprising 67.4% of all enrolled patients) reported having at least one symptom within the past month at baseline. A total of 47.9%, 65.0%, 53.8%, and 49.9% of survey respondents, respectively, reported symptoms of discomfort, itching, redness, and tearing in the past month (Table 2). Of these patients, few reported having symptoms all of the time (4.4% [discomfort], 6.0% [itching], 5.5% [redness], and 4.4% [tearing]) (Table 2). Mild symptoms of discomfort, itching, redness, and tearing were reported by 26.1%, 33.7%, 30.8%, and 31.6% of patients, respectively (Table 2). Fewer patients (15.0%, 22.6%, 15.3%, and 12.5%, respectively) reported moderate

Table 2 Baseline: frequency and severity of ocular symptoms during the past month

Baseline question, *n* (%)[a]	Discomfort *N* = 712	Itching *N* = 712	Redness *N* = 712	Tearing *N* = 712
Frequency of symptom				
None of the time	371 (52.1)	249 (35.0)	329 (46.2)	357 (50.1)
Some of the time	186 (26.1)	248 (34.8)	216 (30.3)	219 (30.8)
Half of the time	61 (8.6)	80 (11.2)	57 (8.0)	55 (7.7)
Most of the time	63 (8.8)	92 (12.9)	71 (10.0)	50 (7.0)
All of the time	31 (4.4)	43 (6.0)	39 (5.5)	31 (4.4)
Any of the time[b]	341 (47.9)	463 (65.0)	383 (53.8)	355 (49.9)
Severity of symptom				
None	367 (51.5)	256 (36.0)	340 (47.8)	368 (51.7)
Mild	186 (26.1)	240 (33.7)	219 (30.8)	225 (31.6)
Moderate	107 (15.0)	161 (22.6)	109 (15.3)	89 (12.5)
Severe	52 (7.3)	55 (7.7)	44 (6.2)	30 (4.2)

N number of patients who responded to the survey

[a] The percentage is the number of patients with a given response divided by the total number of patients who responded to the survey; patients may have had more than one symptom in the past month

[b] Any of the time comprises some, half, most, or all of the time for a particular symptom; patients may have had more than one symptom at the same time

symptoms of discomfort, itching, redness, and tearing; and only 7.3%, 7.7%, 6.2%, and 4.2%, respectively, reported severe symptoms (Table 2).

DISCUSSION

This survey demonstrated a substantial burden of ocular surface disorders within the past year in patients with moderate-to-severe AD that was inadequately controlled with topical medications. Most patients reported having at least one ocular symptom within the past month at baseline, and a substantial proportion of symptoms were moderate to severe. The burden of ocular surface disorders in this patient population is consistent with other studies demonstrating a substantially greater incidence of ocular surface disorders among patients with type 2 inflammatory disorders, such as AD, asthma, and rhinosinusitis, compared with the general population [1–12].

Previous studies have demonstrated an association of AD severity with increased risk of ocular disorders [1, 6, 13]. Although the burden of ocular disorders has been demonstrated to be high in patients with AD compared with the general population [1–12], there is also an association of AD with other type 2 inflammatory comorbidities such as allergies, asthma, and rhinitis, and in turn these type 2 inflammatory diseases are also associated with increased incidence of ocular disorders [15, 16]. Therefore, it is difficult to identify the relative contributions of AD and other associated type 2 inflammatory disorders to comorbid ocular diseases.

Some ocular disorders associated with AD, such as AKC, are potentially serious and may have an impact on vision, and, therefore, require ophthalmic assessment and treatment [1, 3, 4, 9]. Given the demonstrated association of ocular diseases with AD, it is important to increase awareness of the burden, signs and

symptoms, and management guidelines for ocular disease associated with AD among dermatologists [17, 18].

Limitations of this survey include a population comprised of patients who were screened and enrolled in a clinical trial, which may not be representative of all patients with moderate-to-severe AD; however, this is a limitation of all randomized clinical trials. The survey is a non-validated instrument, and it is possible that some patients may not have understood the medical terms of the questionnaire. Survey data for diagnoses are subject to recall bias; symptom data may be more reliable, as they reflect patient experience within the previous month.

CONCLUSION

These data demonstrate a high burden of ocular surface disorders and related symptoms in a population of adults with moderate-to-severe AD. Dermatologists should be aware of increased incidence of these disorders in patients with AD and query their patients for signs and symptoms of eye disease.

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Compliance with Ethics Guidelines. The study was conducted in accordance with the provisions of the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. The protocol was reviewed and approved by institutional review boards/ethics committees at all study sites. An independent data monitoring committee monitored patient safety. All patients provided signed written informed consent.

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Data Availability. Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.

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