Ocular Surface Disease in Patients With Atopic Dermatitis Treated With Dupilumab: A Prospective Case-Control Study

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Abstract

Purpose:

The aim of this study was to evaluate the variation of dry eye disease (DED) prevalence in patients with atopic dermatitis (AD) treated with dupilumab.

Methods:

This prospective case–control study included consecutive patients with moderate-to-severe AD scheduled for dupilumab between May and December 2021 and healthy subjects. DED prevalence, the Ocular Surface Disease Index, tear film breakup time test, osmolarity, Oxford staining score, and Schirmer test results were collected at baseline, 1 month, and 6 months after dupilumab therapy. The Eczema Area and Severity Index was assessed at baseline. Ocular side effects and discontinuation of dupilumab were also recorded.

Results:

Seventy-two eyes from 36 patients with AD treated with dupilumab and 36 healthy controls were included. Prevalence of DED increased from 16.7% at baseline to 33.3% at 6 months in the dupilumab group ($P = 0.001$), whereas it remained unchanged in the control group ($P = 0.110$). At 6 months, the Ocular Surface Disease Index and Oxford score increased (from 8.5 ± 9.8 to 11.0 ± 13.0, $P = 0.068$, and from 0.1 ± 0.5 to 0.3 ± 0.6, $P = 0.050$, respectively), the tear film breakup time test and Schirmer test results decreased (from 7.8 ± 2.6 s to 7.1 ± 2.7 s, $P < 0.001$, and from 15.4 ± 9.6 mm to 13.2 ± 7.9 mm, $P = 0.036$, respectively) in the dupilumab

group, whereas they remained stable in the control group (P > 0.05). Osmolarity was unchanged (dupilumab P = 0.987 and controls P = 0.073). At 6 months after dupilumab therapy, 42% of patients had conjunctivitis, 36% blepharitis, and 2.8% keratitis. No severe side effects were reported, and none of the patients discontinued dupilumab. No association between Eczema Area and Severity Index and DED prevalence was shown.

Conclusions:

DED prevalence increased in patients with AD treated with dupilumab at 6 months. However, no severe ocular side effects were found and no patient discontinued therapy.

Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting 20% of children and 3% of adults.1 Atopic keratoconjunctivitis (AKC) is the most commonly reported ocular comorbidity of AD, with a frequency from 25% to 40%.2 Dupilumab, a monoclonal antibody inhibiting interleukin (IL)-4 and IL-13 signaling, is the first biologic agent approved for the treatment of patients with moderate-to-severe AD. The drug has shown good efficacy and safety results; nevertheless, ocular adverse events with a frequency from 9% to 34% have been documented in clinical trials and real-life studies.3,4 The ocular manifestations were identified as dupilumab-associated conjunctivitis or dupilumab-induced ocular surface disease (DIOSD), and the onset of symptoms occurs from 4 to 50 weeks after treatment, with a mean of 18 weeks.5

There is not a universal consensus on the prevalence of DIOSD. This pathology has been described in the literature as having a broad spectrum of signs and symptoms including red eye, photophobia, visual disturbance, mucoid discharge, ocular pain, and erythema. In most studies, diagnosis of DIOSD was based on patient-reported symptoms to the dermatologist, without an ophthalmologic evaluation or a control with the general population.6

The Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II)7 reported that ocular surface pathologies such as AKC can present in association with dry eye disease (DED) and classified AKC as a possible risk factor for development of DED. The diagnosis and monitoring of AKC and DIOSD are clinical, qualitative, and difficult to standardize; differently, DED has a well-defined diagnosis based on quantitative and repeatable tests. The objectivity of the assessment of DED can be useful in creating a common language of approach to dupilumab-associated ocular surface disease. The purpose of our study was to evaluate the variation of DED prevalence after 6 months of therapy in patients with AD treated with dupilumab, in a prospective case–control study.

MATERIALS AND METHODS

We conducted a prospective case–control study on patients attending the Departments of Dermatology and Ophthalmology of the University of Turin, Italy. The study protocol complied with the tenets of the Declaration of Helsinki. Institutional ethics committee approval was obtained, and the study objective, methodology, duration, and associated possible consequences were explained to all patients before signing the informed consent form for participation.

In our study, the participants comprised subjects with moderate-to-severe AD scheduled for dupilumab treatment and healthy volunteers as controls. All consecutive patients diagnosed with moderate-to-severe AD scheduled for dupilumab treatment between May 2021 and December 2021 were assessed for eligibility in the dupilumab group. Dupilumab was injected subcutaneously, as labeled, starting with a loading dose of 600 mg, followed by 300 mg every other week. Healthy subjects were defined as having no suspicious dermatologic or ophthalmic pathologies.

Included patients were aged ≥18 years and had a follow-up of at least 6 months. Exclusion criteria were (1) systemic pathologies other than AD (diabetes, autoimmune disorders, and allergies), (2) ocular pathologies that could affect ocular surface assessments (pathological corneal ectasia such as keratoconus, pterygium, or glaucoma), (3) use of any topical ocular therapy or lubrication, (4) use of contact lenses, (5) previous corneal surgery or refractive laser surgery, and (6) history of ocular trauma and unexplained visual loss.

Demographic data such as age, sex, and medical history were collected. After inclusion, all enrolled patients received dermatologic assessment at baseline before administering dupilumab treatment and disease severity was assessed by the Eczema Area and Severity Index (EASI) score. Details of atopic family history, allergies, disease age at onset were also collected. Patients who reached 6 months of follow-up were assessed by EASI.

Baseline ophthalmologic examination included best-corrected visual acuity, slit-lamp examination, Goldmann tonometry, and fundus examination. A systematic ophthalmologic evaluation was performed by the same ophthalmologist before the first injection of dupilumab, 1 month and 6 months after, and at any time patients developed an ocular adverse event. No treatment was adopted if minor ocular side effects (ie, conjunctivitis, blepharitis, or superficial punctate keratitis) were recorded throughout the follow-up, whereas topical lubricants and corticosteroid drops were allowed if the patient developed major ocular side effects (ie, cicatricial conjunctivitis, cicatricial ectropion, or visual acuity loss). For each study participant, both eyes were tested and the data of the worse eye were used for analysis.

Diagnosis of DED was assessed according to the TFOS DEWS II Diagnostic Methodology Report,7 and the recommended order of noninvasive tests performed was as follows: symptom questionnaire, tear film breakup time test (TBUT), osmolarity, ocular surface staining, and Schirmer test with at least 30-minute intervals between each examination. Symptoms and at least 1positive result of the markers of homeostasis listed below constituted the diagnosis of DED. DED assessment and recommended tests were performed at baseline and 1 month and 6 months of follow-up.

The Ocular Surface Disease Index (OSDI) symptomatology questionnaire was administered to patients by an ophthalmologist at any time of follow-up before the ophthalmic examination in order not to influence the patients' responses and the total score was calculated as previously described.8 The OSDI scores defined the ocular surface as normal (0–12 points) or having mild (13–22 points), moderate (23–32 points), or severe (33–100 points) ocular surface disease. Tear turnover was evaluated by measuring TBUT in seconds (s).9 TBUT cutoff for dry eye diagnosis was <10 seconds. Moderate dry eye was defined if TBUT was between 5 and 10 seconds, severe dry eye was defined if TBUT was = or <5 seconds, and very severe dry eye was defined if tear film breakup happened immediately after blinking.9

The TearLab Osmolarity Test (San Diego, CA) was used to evaluate tear composition.10 A test card was put in contact with the inferior tear meniscus to collect about 50 nL of tear fluid by passive capillary action. TFOS DEWS11 recommendations supporting the 308 mOsm/L cutoff were applied to distinguish mild from moderate disease and the 316 mOsm/L cutoff to distinguish moderate from severe disease. Ocular surface integrity was evaluated by grading fluorescein staining on the cornea and conjunctiva following the Oxford grading scale.12 The examiner compared the overall appearance of the patient's corneal staining with a reference figure and selected the appropriate grade (from 0, absent to 5, severe) that best represented the state of corneal staining. Aqueous tear deficiency was assessed with the Schirmer I test (without anesthesia).9 Moderate dry eye was defined if the Schirmer score (mm/5 minutes) was between 5 and 10, severe dry eye if the Schirmer score was equal or <5, and very severe dry eye if the Schirmer score was equal or <2.9

Any other ocular manifestation was recorded as well. Minor ocular side effects (if any) collected were conjunctivitis, blepharitis, and superficial punctate keratitis, whereas major ocular side effects (if any) were cicatricial conjunctivitis, cicatricial ectropion, and visual acuity loss. Moreover, discontinuation of dupilumab because of ocular side effects was listed.

The main outcome of the study was to determine the changes in prevalence of DED between baseline and 6 months in patients with AD receiving dupilumab after baseline assessment and in healthy subjects not receiving therapy. Secondary outcomes were (1) to evaluate the

effect of dupilumab on the ocular surface by collecting the mean values and variation of each TFOS DEWS II recommended test in cases and controls at baseline and 1 month and 6 months of follow-up; (2) to assess the rate of ocular side effects in the dupilumab group; (3) to determine the number of patients who had to discontinue dupilumab throughout the follow-up because of adverse ocular side effects; and (4) to establish the association between EASI and prevalence of DED at each time point.

Statistical Analysis

Descriptive statistics were reported as mean and standard deviation for continuous variables or frequency and percentage for qualitative variables. Statistical significance was defined with a Pvalue ≤0.05.

To evaluate the association between 2 qualitative variables the Pearson $\chi 2$ test was adopted. When needed (>20% of values ≤5 and/or presence of values <1), and to have an easier interpretation of the data, the Cramer V test was used to verify association between variables. Given the number of eyes examined, nonparametric tests were used. The Wilcoxon test was performed to evaluate differences in the scores of 2 nonparametric quantitative variables in the same group at different time points (paired samples). The Gamma test was used to evaluate the association between 2 ordinal variables. The Mann–Whitney U test was used to evaluate the difference in the scores of a nonparametric quantitative variable in 2 groups.

A subgroup analysis of patients who developed DED was performed by evaluating factors at baseline that may potentially influence the development of the disease at 6 months. The $\chi 2$ test was used for categorical variables with correction by the Fisher test when necessary. Given the number of 30 subjects, nonparametric tests were performed and the Mann–Whitney U test was used for quantitative variables. Univariate binary logistic regression analysis was performed to test the impact of factors on the development of DED at 6 months. Factors that were significant in the univariate analysis were included in the multivariate binary logistic regression. We further investigated the prognostic ability of the variables with receiver operating characteristic curves and their area under the curve. The receiver operating characteristic curves were compared using the DeLong test. The Youden index was used to find the optimal cutoff values, defined as the maximum value of sensitivity + specificity −1. All statistical analyses were performed using SPSS Statistics software (IBM SPSS Statistics for Windows, version 28.0; IBM Corp., Armonk, NY).

RESULTS

A total of 72 patients (72 eyes) were included in the study, 36 patients with AD treated with dupilumab and 36 healthy controls. The mean follow-up was 30 ± 5 weeks. The 2 groups were comparable by demographical, dermatological, and ocular features (no significant difference

between groups, P > 0.05), except for TBUT values (P < 0.001). Patients' characteristics are summarized in Table 1.

The prevalence of DED (Fig. 1) significantly increased from 16.7% at baseline to 33.3% at 6 months in the dupilumab group (Pearson test, P = 0.001), with 23.3% of the eyes (n = 7) developing DED after administering dupilumab, while it remained the same (5.6%) in the control group (Pearson test, P = 0.110). In the dupilumab group, the mean OSDI questionnaire scores were 8.5 ± 9.8 at baseline, 10.6 ± 11.9 at 1 month, and 11.0 ± 13.0 at 6 months, with a mean increase (Wilcoxon test, P = 0.068) of 2.6 ± 1.5 at the final visit. In the control group, there were no differences between baseline and the last follow-up OSDI assessments (Wilcoxon test, P = 0.183), which were 5.6 ± 4.6 at baseline, 5.8 ± 4.9 at 1 month, and 6.7 ± 7.0 at 6 months (Fig. 2A).

The mean TBUT had a mean decrease of 0.7 ± 1.8 seconds (Wilcoxon test, P < 0.001) at the last follow-up in the dupilumab group, whereas there were no differences between baseline and 6 months of follow-up in the control group (Wilcoxon test, P = 0.100). The mean TBUT values at baseline, 1 month, and 6 months were 7.8 ± 2.6, 8.0 ± 2.8, and 7.1 ± 2.7 seconds in the dupilumab group and 11.8 ± 2.5, 10 ± 2.7, and 10 ± 3.2 seconds in the control group, respectively (Fig. 2B).

The mean osmolarity scores did not show significant differences between baseline and 6 months in both dupilumab and control groups (Wilcoxon test, P = 0.987 and P = 0.073, respectively). The mean osmolarity scores were 301.2 ± 13.9, 295.3 ± 35.8, and 301.3 ± 13.7 mOsm/L in the dupilumab group and 303.6 ± 15.0, 301.2 ± 13.9, and 298.2 ± 11.2 mOsm/L in the control group at baseline, 1 month, and 6 months, respectively (Fig. 2C).

The mean Oxford staining score showed an increase at the last follow-up visit in the dupilumab group (Gamma test, P = 0.050), whereas it did not show significant differences between baseline and 6 months in the control group (Gamma test, P = 0.289). The mean Oxford scores were 0.1 ± 0.5 points and 0.1 ± 0.4 points at baseline, 0.2 ± 0.5 points and 0.1 ± 0.3 points at 1 month, and 0.3 ± 0.6 points and 0.1 ± 0.2 at 6 months in the dupilumab and control groups, respectively.

In the dupilumab group, the mean Schirmer test scores were 15.4 ± 9.6 mm at baseline, 14.0 ± 9.4 mm at 1 month, and 13.2 ± 7.9 mm at 6 months, with a mean increase (Wilcoxon test, P = 0.036) of 2.2 ± 1.2 mm at the final visit. In the control group, there were no differences between baseline and the last follow-up Schirmer assessments (Wilcoxon test, P = 0.193), which were 13.8 ± 5.5 mm at baseline, 14.1 ± 5.8 mm at 1 month, and 14.8 ± 5.7 mm at 6 months (Fig. 2D).

Table 2 shows the occurrence of ocular side effects in the dupilumab group. The most frequent ocular side effects at 1 month and 6 months were conjunctivitis and blepharitis. One patient was diagnosed with keratitis, intended as superficial punctate keratitis, at 1 month and 6 months. None of the patients required topical therapy due to severe ocular side effects throughout the follow-up and 100% of patients diagnosed with DED presented with at least one of the ocular side effects described. No major ocular side effects were noted and none of the patients required topical therapy or discontinued dupilumab throughout the follow-up. No association between prevalence of DED and EASI in the dupilumab group was shown between the ophthalmologic and dermatologic parameters at the 3 time points (Whitney U test, P = 0.777 at baseline, P = 0.761 at 1 month, P = 0.767 at 6 months).

Subgroup Analysis

The results of the univariate analysis of patients who developed DED are reported in Table 3. Multivariate logistic regression showed that the only factor at baseline that was significantly associated with the development of DED at 6 months was OSDI. The mean OSDI score at baseline was higher in the group of patients who developed DED at 6 months compared with the group who did not: 10.86 ± 6.84 points versus 3.57 ± 3.49 points, respectively (Whitney U test, P = 0.002). The probability of developing DED at 6 months increased by 75.9% (Whitney U test, P = 0.039) with an increase of 1 point of OSDI. The goodness of fit of the data to the real model was 69.8% (Nagelkerke R2). A baseline OSDI score <5 reduced the probability of developing DED at 6 months by 17-fold.

DISCUSSION

In this study, we observed an increase in the prevalence of DED in patients with AD treated with dupilumab after 6 months of therapy, whereas the prevalence of DED remained unchanged in healthy subjects. In the literature published to date, studies reported cases of DIOSD diagnosed by various specialists, most of them being retrospective chart reviews based on patient-reported symptoms.13–15 In most cases, an ophthalmologic evaluation was not performed and a preexisting underlying ocular surface disease was not investigated.5 DIOSD has been described with a wide range of clinical definitions and its pathogenesis is still poorly understood.6 Some hypotheses concern its immunological action which inhibits IL-4 and IL-13 signaling with a consequent reduction of goblet cells, a reduced production of mucin and tear film instability with conjunctival inflammation. However, this effect seems to be reversible with discontinuation of dupilumab.16,17

Diagnosis of DIOSD is difficult to standardize, and the distinction between the worsening of an underlying ocular surface disease and the onset of a new dupilumab-related ocular pathology is challenging and operator-dependent. This could explain the heterogeneity in the reported prevalence of DIOSD, ranging from 9% to 34%.3,4

TFOS DEWS II proved that DED is involved in most ocular surface disorders, as well as being directly related to AKC.7 Therefore, in the absence of a uniform definition of DIOSD, we used the validated diagnosis of DED to assess the effect of dupilumab on the ocular surface of patients with AD.

A few retrospective studies previously mentioned DED in these patients; however, the disease was diagnosed by dermatologists,18 referred by the patient,15 or referred to generically as “dryness.”19 In our study the prevalence of DED in the healthy controls was comparable to the overall prevalence of DED in the general population,20 whereas it was higher in patients with AD. This finding can be motivated by the fact that patients with AD might already have an

underlying ocular surface disorder and even present with AKC before administering dupilumab treatment.2 Interestingly, no difference between the prevalence of DED in the 2 groups was recorded at baseline. The 2 groups were comparable for rate of conjunctivitis, with a small percentage of patients with AD affected by mild conjunctivitis not requiring therapy. Considering the TFOS DEWS II tests, cases and controls did not differ except for TBUT values at baseline evaluation, with a lower mean TBUT in the group of patients with AD. As already stated, patients with AD can present with subclinical ocular surface disorders and the TBUT test is highly sensitive to tear film instability even in the absence of a significant reduction in tear production and with an apparently normal ocular surface.21

The increase of DED prevalence in the group of patients treated with dupilumab and concomitant stability of DED prevalence in the healthy group suggest that dupilumab may interact with the ocular surface pathogenetic mechanisms leading to the development of dry eye. Dupilumab probably interferes with a predisposition to the development of ocular surface disorders already existing in subjects with AD.

Regarding the recommended TFOS DEWS II tests, the results changed significantly at 6 months except for osmolarity that remained stable in the group of patients treated with dupilumab. Despite the worsening of the mentioned tests, mean OSDI and Schirmer remained in the normal ranges after 6 months of treatment and mean TBUT decreased by only 0.7 seconds, with a poor clinical significance.

All variations were consistent with the increased prevalence of DED at 6 months and the significance in reduction of TBUT seems to corroborate the concept regarding the high diagnostic sensitivity of the test. On the contrary, in the control group, TBUT remained unchanged. Touhouche et al22 previously reported TBUT and Schirmer values in patients treated with dupilumab, with TBUT values comparable to ours, but lower values of Schirmer tests. This may be motivated by the fact that the study did not analyze all treated eyes but only the eyes (16/46) reporting dupilumab-associated ocular adverse events.

Most cases of DIOSD have been reported as mild to moderate.3 In our study, the reported occurrences of conjunctivitis and blepharitis are slightly higher than those reported by clinical trials (from 8.6% to 28%)23 and comparable to real-life experiences.14,15 All were mild not leading to treatment discontinuation. Despite an increased prevalence of DED, and an overall worsening of TFOS DEWS recommended tests, in our study, no patient presented with severe ocular side effects such as conjunctivitis associated with cicatrization, reported in 0% to 1% of clinical trials5 and in greater percentages in real-life studies.13,15 Thus, dupilumab showed to modify the ocular surface balance without causing a serious pathology and with a good tolerability profile.

In our study, we did not find an association between the prevalence of DED and AD disease severity assessed with the EASI score. We can explain this finding if we think of DED as a prelude to the development of full-blown DIOSD. Our result was in contrast with previous studies, in which the AD severity score was evaluated by applying the Investigator Global Assessment scale, a score that is commonly used for clinical trials, although seldomly in clinical practice,24 and with a reliability below the normal limits.25 However, additional studies focusing on the association between dermatologic parameters of AD assessment and DIOSD should help shed further light on this aspect.

The subgroup analysis proved that the only variable associated with the presence of DED at 6 months was the presence of a higher OSDI score at baseline. This result should be interpreted in the light of the other mentioned tests.

The main limitation of our study is the control group, composed of healthy patients instead of patients with AD not receiving therapy. However, we had no other option of comparison because dupilumab at the time of the study was the only available therapeutic choice for moderate-to-severe AD in clinical practice. Our study also has strengths, including its prospective design, the use of standardized and repeatable methods, and the presence of a control group.

In conclusion, this study demonstrated that dupilumab therapy has an influence on the ocular surface of patients with AD, determining an increase of DED

prevalence and a worsening of almost all TFOS DEWS II test results over a 6-month follow-up. However, the drug showed an overall good ocular safety profile and no patient had to discontinue therapy nor required treatment due to severe ocular side effects. Evaluation of DED and standardized test performance could help to objectively assess the diagnosis of DIOSD and its monitoring, thus its optimal management. However, further studies are needed to confirm our findings.

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TABLE 1. Baseline Characteristics of Eyes Included in the Study

Characteristic	Dupilumab (n = 36)	Controls (n = 36)	*P**
Age (yrs), mean (±SD)	35.8 (±14.7)	35.8 (±14.7)	0.49
Sex, n (%)			
Male	22 (61.1)	21 (58.3)	0.81
Female	14 (38.9)	14 (38.9)	
AD age onset (yrs), mean (±SD)	8.3 (±16.1)	N/A	N/A
EASI, mean (±SD)	26.2 (±9.1)	N/A	N/A
BCVA (logMAR), mean (±SD)	0.04 (±0.2)	0.05 (±0.2)	0.85
IOP (mm Hg), mean (±SD)	12.3 (±4.2)	13.4 (±3.9)	0.56
OSDI, mean (±SD)	8.5 (±9.8)	5.6 (±4.6)	0.11
TBUT (mm), mean (±SD)	7.8 (±2.6)	11.8 (±2.5)	<0.001
Osmolarity (mOsm/L), mean (±SD)	301.2 (±13.9)	303.6 (±15.0)	0.29
Oxford grading, mean (±SD)	0.1 (±0.5)	0.1 (±0.4)	0.60
Schirmer I (mm), mean (±SD)	15.4 (±9.6)	13.8 (±5.4)	0.41
DED, n (%)	6 (16.7)	2 (5.6)	0.52
Conjunctivitis, n (%)	5 (13.9)	0 (0)	0.63

*$P \leq 0.05$ were considered significant.

BCVA, best-corrected visual acuity; IOP, intraocular pressure; logMAR, logarithm of the minimum angle of resolution; N/A, not applicable.

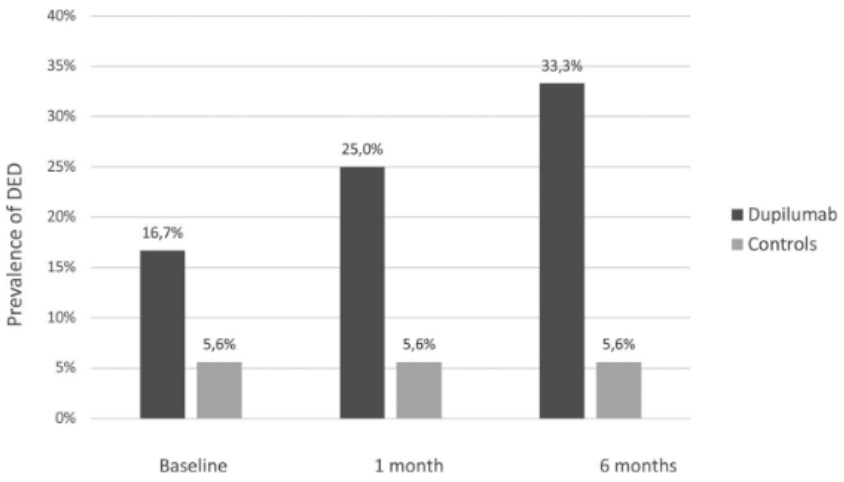

FIGURE 1. Prevalence of DED in patients treated with dupilumab and in healthy controls at baseline, 1 month, and 6 months.

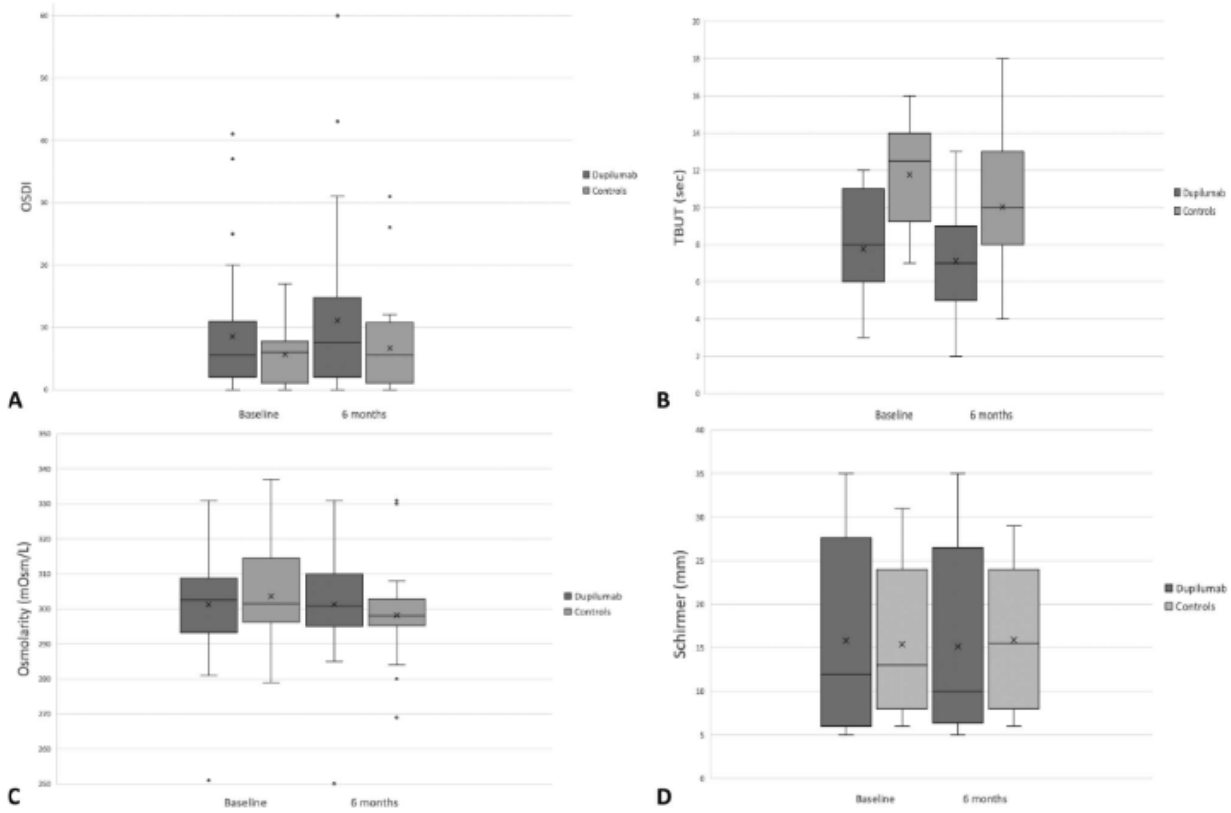

FIGURE 2. Boxplots for differences between baseline and 6 months of follow-up in patients treated with dupilumab and in healthy controls: (A) OSDI, (B) TBUT, (C) osmolarity, and(D) Schirmer I.

TABLE 2. Ocular Side Effects in the Dupilumab Group

Side Effect	1 mo	6 mo
Conjunctivitis, n (%)	11 (30.6)	15 (42)
Blepharitis, n (%)	10 (27.8)	13 (36)
Keratitis, n (%)	1 (2.8)	1 (2.8)
Cicatricial conjunctivitis, n (%)	0 (0)	0 (0)
Cicatricial ectropion, n (%)	0 (0)	0 (0)
Visual acuity loss, n (%)	0 (0)	0 (0)

TABLE 3. Univariate Analysis of Factors at Baseline in Eyes That Developed DED at 6 Months and in Eyes That Did Not Develop DED at 6 months

Factors at Baseline	Eyes Developing DED (n = 7)	Eyes Not Developing DED (n = 29)	*P**
Age (yrs), mean (±SD)	34.29 (±13.14)	37.04 (±16.57)	0.886
Male sex, n (%)	3 (42.86)	16 (55.17)	0.372
EASI, mean (±SD)	28.17 (±9.30)	25.72 (±9.43)	0.737
OSDI, mean (±SD)	10.86 (±6.84)	3.57 (±3.49)	0.002
TBUT (mm), mean (±SD)	7.29 (±1.90)	8.30 (±2.70)	0.245
Osmolarity (mOsm/L), mean (±SD)	293.71 (±6.97)	304.13 (±11.85)	0.059
Oxford grading, mean (±SD)	0.29 (±0.76)	0.00 (±0.00)	0.233
Schirmer I (mm), mean (±SD)	15.86 (±11.96)	16.00 (±9.50)	0.774

*$P \leq 0.05$ were considered significant.
BCVA, best-corrected visual acuity; OSDI, Ocular Surface Disease Index; .