Dupilumab-associated ocular surface disease in atopic dermatitis has a distinct tear profile

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Conflict of Interest

Chia-Yu Chu

served as an investigator for AbbVie, Amgen, Dermira, Janssen, Eli Lilly, Novartis, Oneness Biotech, Pfizer, Regeneron Pharmaceuticals Inc., Roche, and Sanofi; a consultant/advisory board member for AbbVie, Amgen, Eli Lilly, Novartis, Pfizer, Roche, Sanofi, and Viatris; and has received speaker fees from AbbVie, Eli Lilly, Janssen, Mylan, Novartis, Pfizer, Roche, Sanofi, and Viatris.

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The exact mechanism of dupilumab-associated OSD (DAOSD) remains undetermined

- Atopic dermatitis (AD) is a chronic inflammatory skin disease often associated with ocular surface disease (OSD).
- Dupilumab, an IL-4Rα inhibitor, is an effective treatment for AD but it frequently induces dupilumab-associated OSD (DAOSD).
- DAOSD may result from a paucity of conjunctival goblet cells; however, the exact mechanism remains undetermined.
- A shift from mixed Th2/Th17 inflammatory markers in tear fluid to a Th1/Th17 pattern was observed in AD patients with DAOSD.

Akinlade B, et al. Br J Dermatol. 2019;181(3):459-473.
Neagu N, et al. J Eur Acad Dermatol Venereol. 2022;36(6);820-835.
Bakker DS, et al. Br J Dermatol. 2019;180(5):1248-1249.
Achten R, et al. Allergy 2023;78(8):2266-2276.
Thormann K, et al. Allergy 2024;79(4):937-948.

Aims of this study

- To further identify the characteristics of OSD in AD patients and to explore the mechanisms of DAOSD.
- A prospective, open-labeled, observational study to evaluate the eye condition, conjunctival goblet cell number, and inflammatory profile of tear fluid of moderate-to-severe AD patients before and after dupilumab treatment.
- To develop effective prevention and treatment strategies for ultimately improving the ocular health and quality of life of these patients.

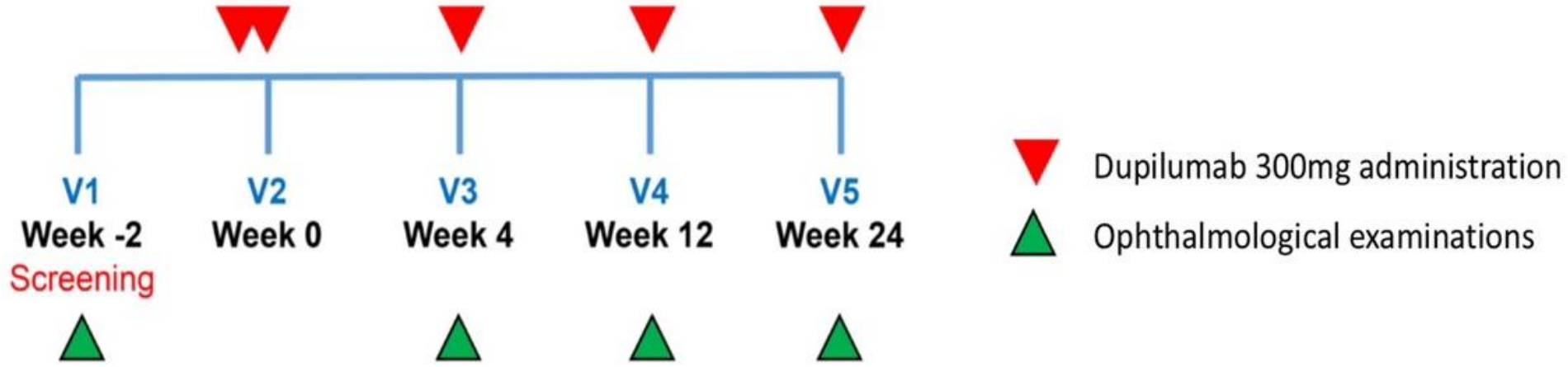
Methods

- A prospective, single-arm, open-labeled, observational study enrolling 50 adult patients with moderate-to-severe AD between November 2020 and April 2023.
- IRB approval number: 202002061RIPB.
- All participants signed an informed consent from before being screened and fulfilled the following inclusion criteria:

  (1) A diagnosis of AD for ≥6 months before screening for an inadequate response to medium-to-high potency topical corticosteroids; and

  (2) An Eczema Area and Severity Index (EASI) score of 16 or higher at screening or baseline.
- All participants received 600 mg of dupilumab at baseline followed by 300 mg every two weeks. The total treatment period for each patient was 24 weeks.
- The patients' demographic characteristics and medical records were obtained.

- All patients received questionnaires for self-reporting outcomes, dermatological evaluations for AD disease severity assessment, and ophthalmological tests for OSD at screening, baseline, weeks 4, 12, and 24.
- A diagnosis of OSD was made based on abnormal findings in clinical ophthalmological examinations, symptoms of eye discomforts, and/or prescription of eye drops.



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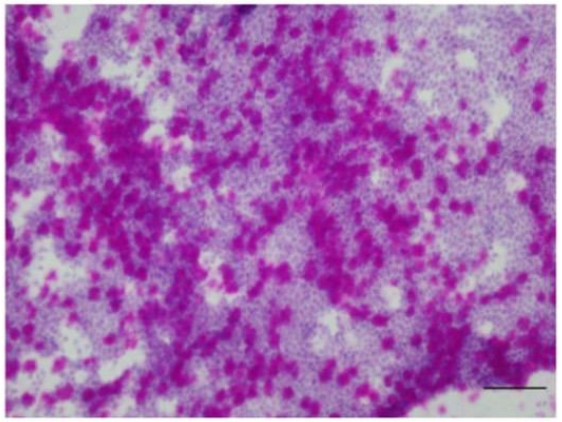
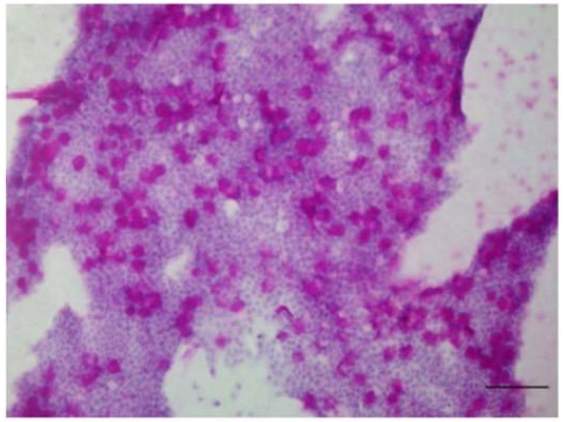


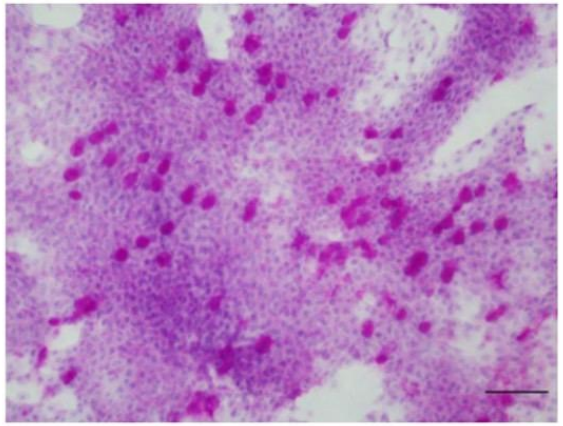
Goblet (PAS+) cells > 500 /mm2

Grade 1



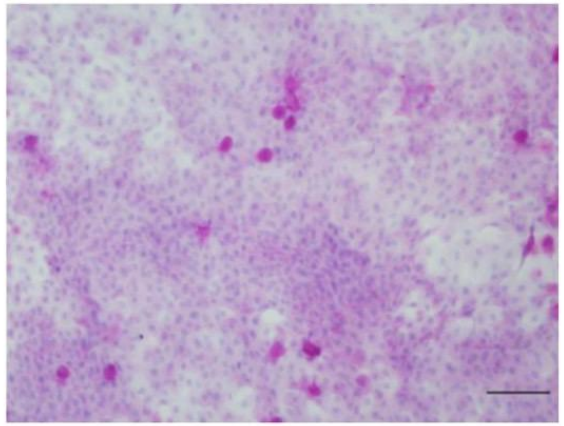
Goblet (PAS+) cells 350 - 500 /mm2

Grade 2



Goblet (PAS+) cells 100 - 350 /mm2

Grade 3



Goblet (PAS+) cells < 100 /mm2

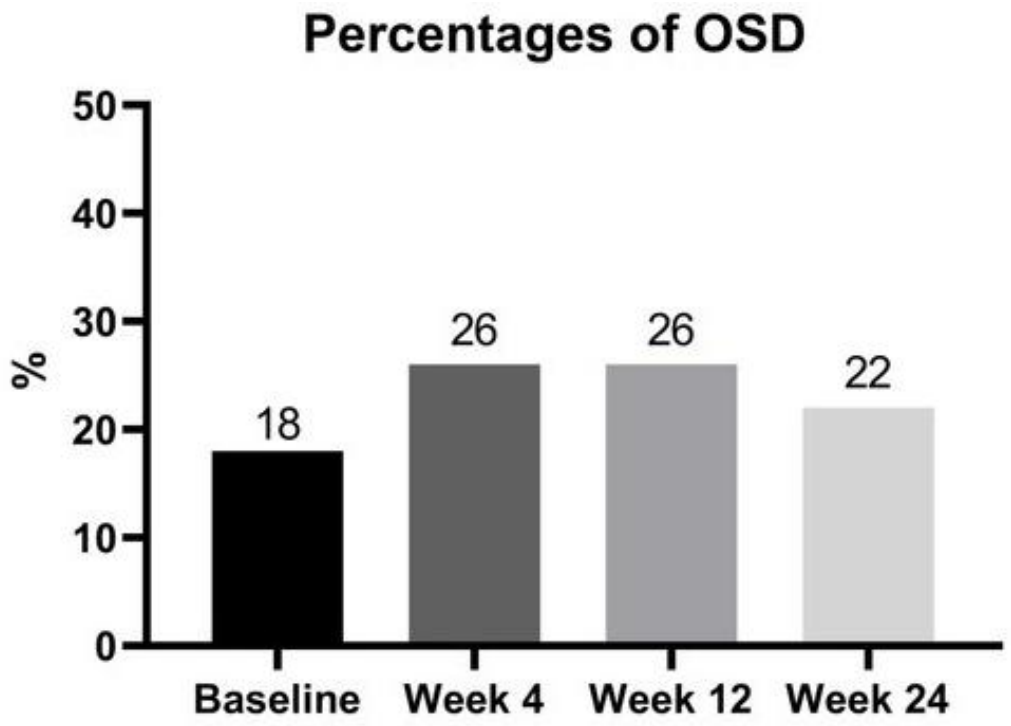
Nelson's grading for the impression cytology of conjunctival goblet cells.

Items checked by the multiplex bead-based assay

Cytokines	IL-1α, IL-1β, IL-1RA, IL-2, IL-4, IL-5, IL-6, IL-8, IL-9, IL-10, IL-13, IL-15, IL-16, IL-17A, IL-18, IL-31, IFN-α, TNF-α
Chemokines	Eotaxin, Eotaxin-2, GRO-α, IP-10, MCP-1α, MIP-1α, MIP-1β, MIP-3α, SDF-1α, RANTES
Growth factors and other mediators	BDNF, EGF, FGF-2, NGF-β, PDGF-BB, SCF, VEGF-A, VEGF-D, GM-CSF, MMP-2

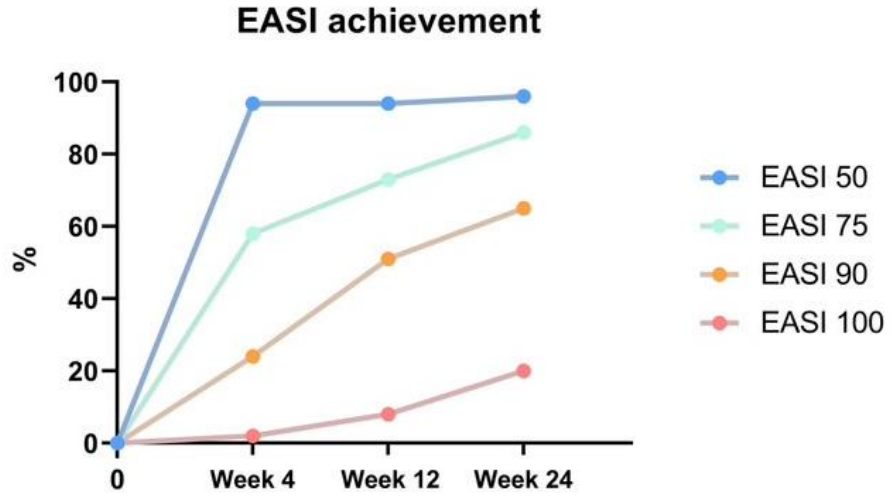
Results

- A total of 50 participants were enrolled, with a male predominance (n=31, 62%).
- The mean age was 34.9±14.7 years.
- All participants had moderate-to-severe AD
- EASI=24.3±12.6
- SCORAD=54.0±15.2
- IGA scores=3.6±0.5
- At baseline, 9 participants (18%) already presented with OSD
- These 9 patients and others who developed OSD after dupilumab treatment were considered to have DAOSD.
- The number of patients with DAOSD varied during the treatment period, ranging from 18% to 26%.
- During the entire 6-month study period, a total of 23 participants (46%) had ever been diagnosed as having DAOSD.



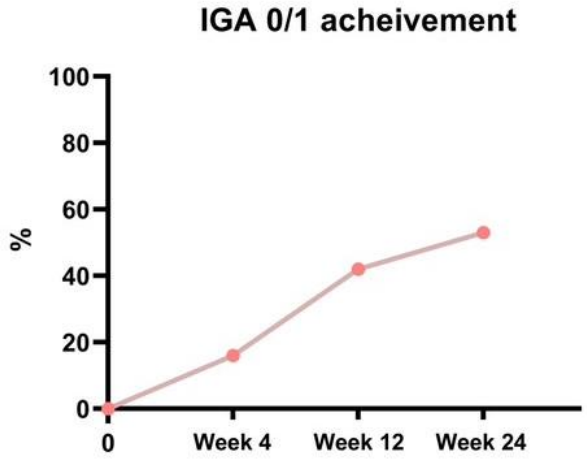
Dupilumab exhibited excellent treatment outcomes in AD patients

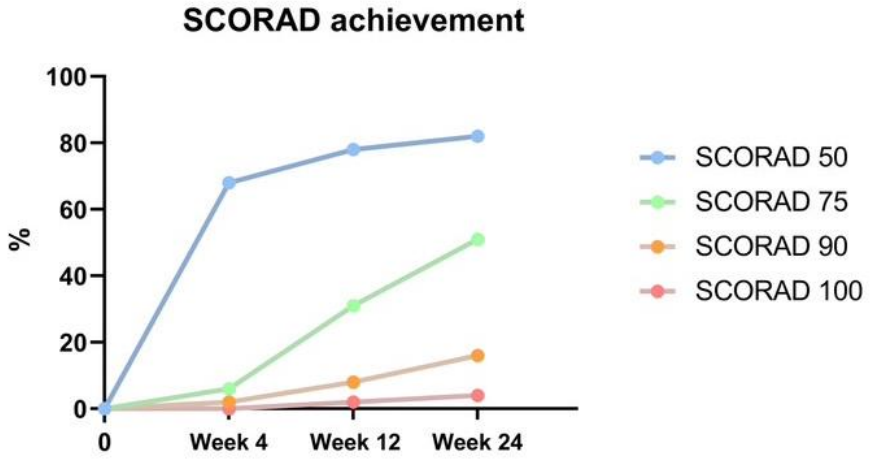
- Week 4:
  - EASI 50=94%
  - EASI 75=58%
  - EASI 90=24%
  - EASI 100=2%
- Week 24:
  - EASI 50=98%
  - EASI 75=86%
  - EASI 90=65%
  - EASI 100=20%



IGA 0/1:

- week 4=16%
- week 12=42%
- week 24=52%

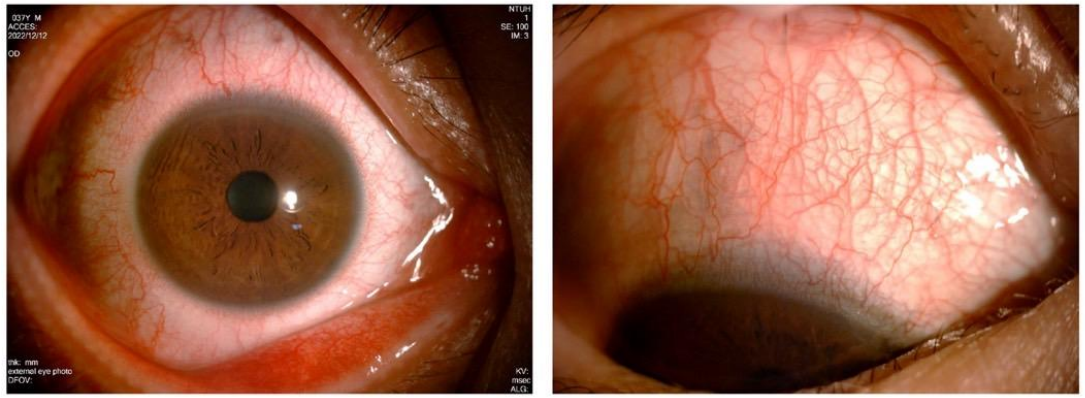




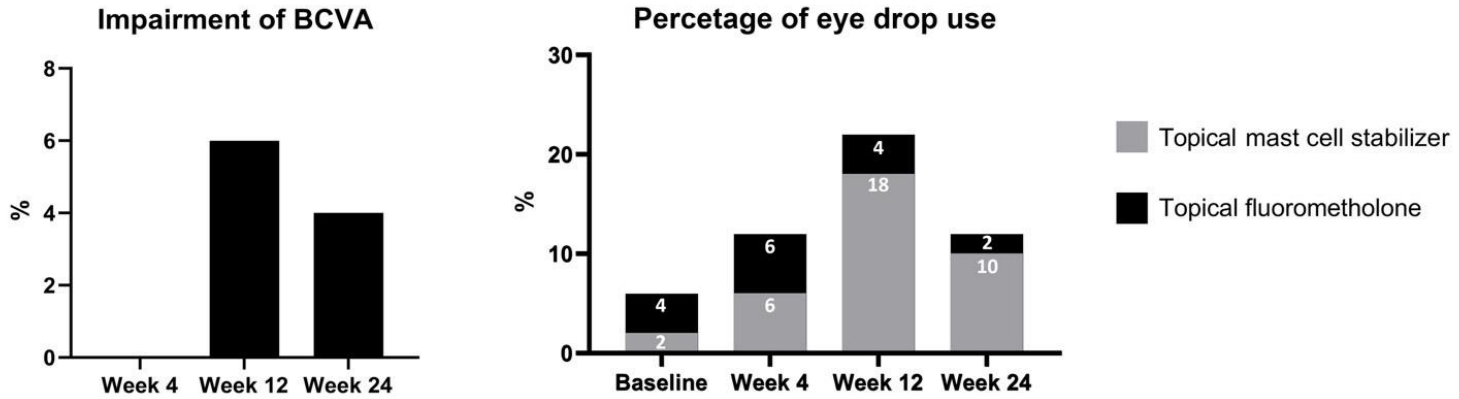
A similar trend in improvement was also observed for SCORAD

(A)

External photography of one patient with DAOSD.



(B)



- In most of these AD patients, DAOSD was mild and easily controlled with eye drops containing mast cell stabilizers or steroids.

(A) External photography of one representative patient with DAOSD was shown.
(B) The percentages of patients showing impairment in the Best Correlated Visual Acuity (BCVA) during dupilumab treatment. A drop of more than 25% of the baseline was defined as impairment. Percentages of patients using anti-inflammatory eye drops were shown here.

AD patients with DAOSD had similar clinical and laboratory characteristics at baseline compared to those without DAOSD

- The percentage of severe cases (IGA grade 4), the mean serum IgE value, and the blood eosinophil count were numerically, but not statistically, higher for patients in the DAOSD group.
- AD patients already showed high rates of subjective and objective abnormalities in eyes before starting dupilumab treatment.

Table 1. Demographic characteristics at baseline of the patients with atopic dermatitis in this study.

	Patients with DAOSD n=23	Patients without DAOSD n=27	*p*-value
Age	33.5±14.4	36.5±14.6	0.312
Gender (M/F)	15/8	16/11	0.665
EASI	24.6±11.6	22.4±10.4	0.659
SCORAD	55.3±14.0	52.9±15.9	0.927
IGA (3/4)	7/16	13/14	0.203
POEM	18.0±6.0	16.3±6.5	0.436
Pruritus VAS	5.4±2.7	5.7±3.0	0.619
Sleepless VAS	4.3±2.9	5.0±3.1	0.437
IgE (IU/ml)	24533.9±32346.5	10013.8±14868.4	0.319
Blood eosinophils (/µl)	796.4±557.3	557.0±460.2	0.142
Ophthalmological tests (number and % of patients with abnormal values)			
OSDI	9 (39.1%)	9 (33.3%)	0.670
Conjunctival score	10 (43.5%)	18 (66.7%)	0.100
Corneal score	6 (26.1%)	8 (29.6%)	0.781
Schirmer's test	3 (13.0%)	3 (11.1%)	0.834
NIKBUT	15 (65.2%)	14 (51.9%)	0.340

DAOSD: dupilumab-associated ocular surface disease; EASI: eczema area and severity index; F: female; IGA: Investigator's Global Assessment; IgE: immunoglobulin E; M: male; NIKBUT: non-invasive keratograph tear break-up time; OSDI: ocular surface disease index; POEM: patient-oriented eczema measure; SCORAD: scoring atopic dermatitis; VAS: visual analogue scale.

- We further separated patients with DAOSD into two subgroups: patients that had OSD at baseline (n=9) and patients with new-onset DAOSD during dupilumab treatment (n=14).
- Compared to the patients in the no-DAOSD group, both patients with OSD at baseline and patients with new-onset DAOSD showed similar baseline demographic characteristics.

Table 2. Comparisons between patients with preceding OSD and patients without DAOSD at baseline

	Patients with preceding OSD N=9	Patients without DAOSD N=27	*P* value
Age	35.2±14.1	36.5±14.6	0.836
Gender (M/F)	5/4	16/11	0.845
EASI	27.4±13.0	22.4±10.4	0.420
SCORAD	61.6±13.6	52.9±15.9	0.383
IGA (3/4)	3/6	13/14	0.439
POEM	17.7±7.3	16.3±6.5	0.713
Pruritus VAS	5.8±2.9	5.7±3.0	0.920
Sleepless VAS	5.0±3.3	5.0±3.1	0.993
IgE (IU/ml)	33813.8±50046.1	10013.8±14868.4	0.836
Blood eosinophils (/μl)	899.6±632.8	557.0±460.2	0.371
Ophthalmologic tests (number and % of patients with abnormal values)			
OSDI	4 (44.4%)	9 (33.3%)	0.548
Conjunctival score	3 (33.3%)	18 (66.7%)	0.079
Corneal score	5 (55.6%)	8 (29.6%)	0.161
Schirmer's test	1 (11.1%)	3 (11.1%)	1.000
NIKBUT	6 (66.7%)	14 (51.9%)	0.439

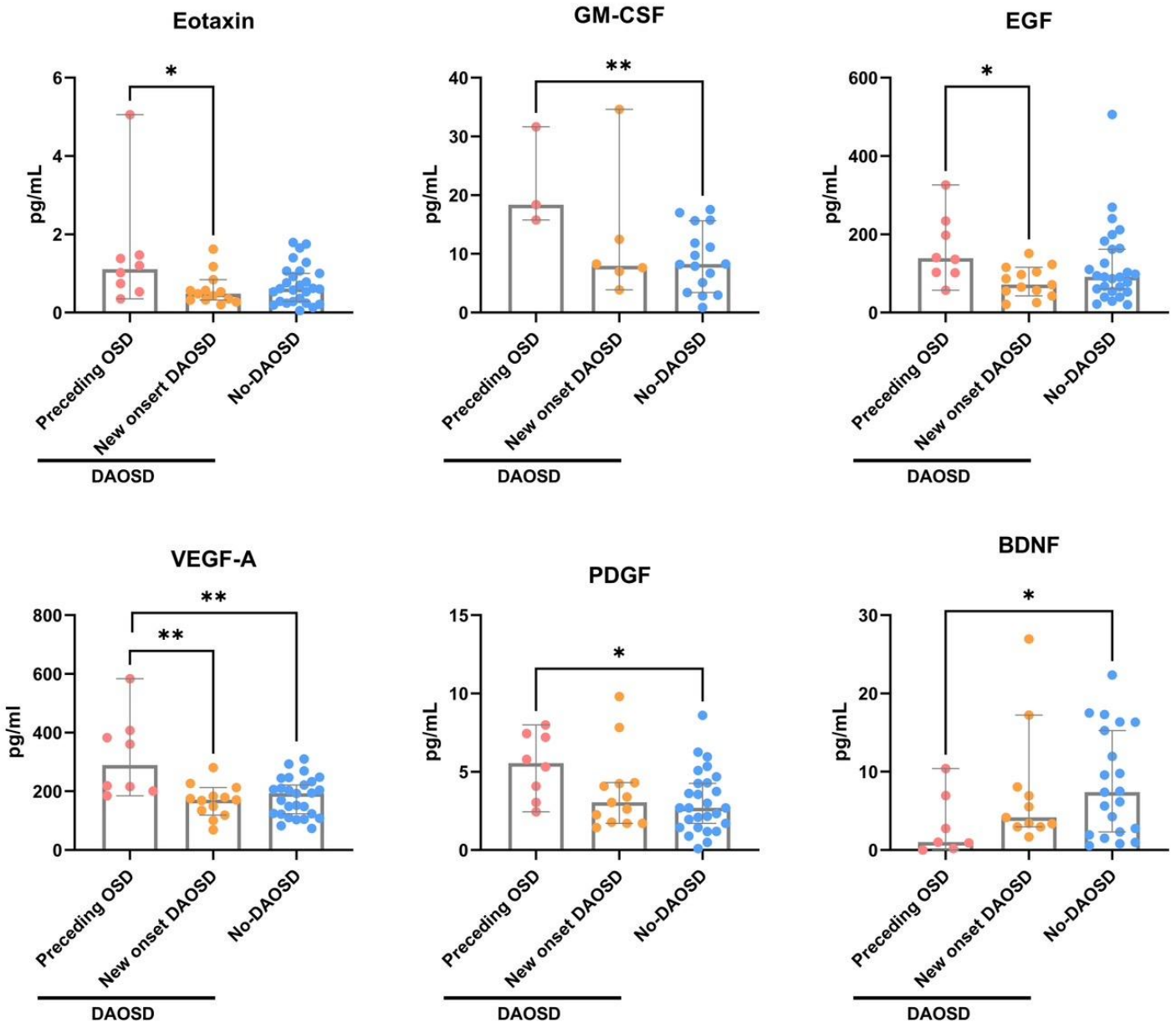
DAOSD: dupilumab-associated ocular surface disease; EASI: eczema area and severity index; F: female; IGA: investigator global assessment; IgE: immunoglobulin E; M: male; NIKBUT: non-invasive keratography tear break up time; OSDI: ocular surface disease index; POEM: patient oriented eczema measure; SCORAD: scoring atopic dermatitis; VAS: visual analogue scale.

Table 3. Comparisons between patients with new onset DAOSD and patients without DAOSD at baseline

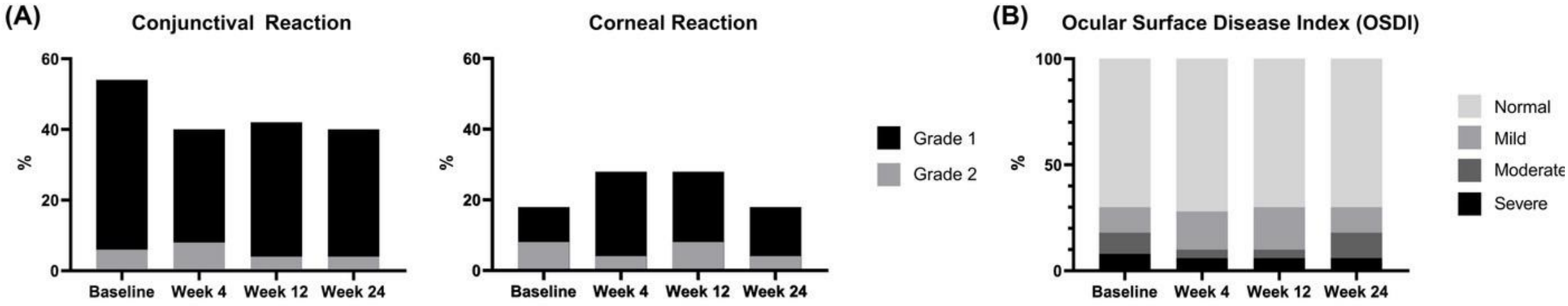
	Patients with new onset DAOSD N=14	Patients without DAOSD N=27	*P* value
Age	32.4±14.5	36.5±14.6	0.205
Gender (M/F)	10/4	16/11	0.443
EASI	22.8±10.2	22.4±10.4	0.994
SCORAD	51.2±12.6	52.9±15.9	0.601
IGA (3/4)	4/10	13/14	0.228
POEM	18.2±6.8	16.3±6.5	0.417
Pruritus VAS	5.1±2.4	5.7±3.0	0.434
Sleepless VAS	3.8±2.5	5.0±3.1	0.278
IgE (IU/ml)	20822.0±20365.4	10013.8±14868.4	0.265
Blood eosinophils (/μl)	749.5±512.6	557.0±460.2	0.186
Ophthalmologic tests (number and % of patients with abnormal values)			
OSDI	5 (35.7%)	9 (33.3%)	0.879
Conjunctival score	8 (57.1%)	18 (66.7%)	0.548
Corneal score	1 (7.1%)	8 (29.6%)	0.099
Schirmer's test	2 (14.3%)	3 (11.1%)	0.768
NIKBUT	9 (64.3%)	14 (51.9%)	0.447

DAOSD: dupilumab-associated ocular surface disease; EASI: eczema area and severity index; F: female; IGA: investigator global assessment; IgE: immunoglobulin E; M: male; NIKBUT: non-invasive keratogrph tear break up time; OSDI: ocular surface disease index; POEM: patient oriented eczema measure; SCORAD: scoring atopic dermatitis; VAS: visual analogue scale

In the tear analysis, patients with OSD at baseline had higher levels of eotaxin, granulocyte monocyte–colony stimulating factor (GM-CSF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF)-A, and platelet-derived growth factor (PDGF)-BB, but had a significantly lower level of brain-derived growth factor (BDNF)



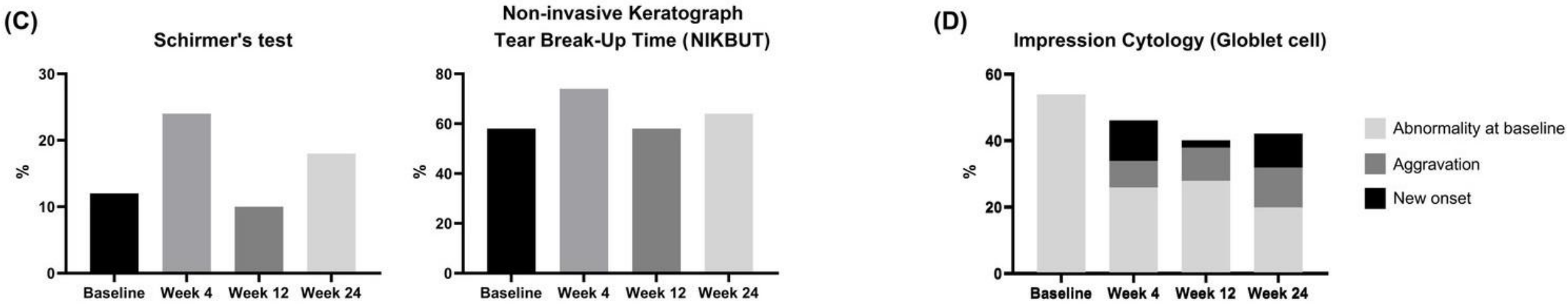
The rates of abnormal findings in ophthalmological examinations did not deteriorate during dupilumab treatment



Abnormal findings of conjunctival and corneal reactions at baseline were 54% and 18%, respectively

The overall rates of impairment were steady and were between 28% and 32% during the study period

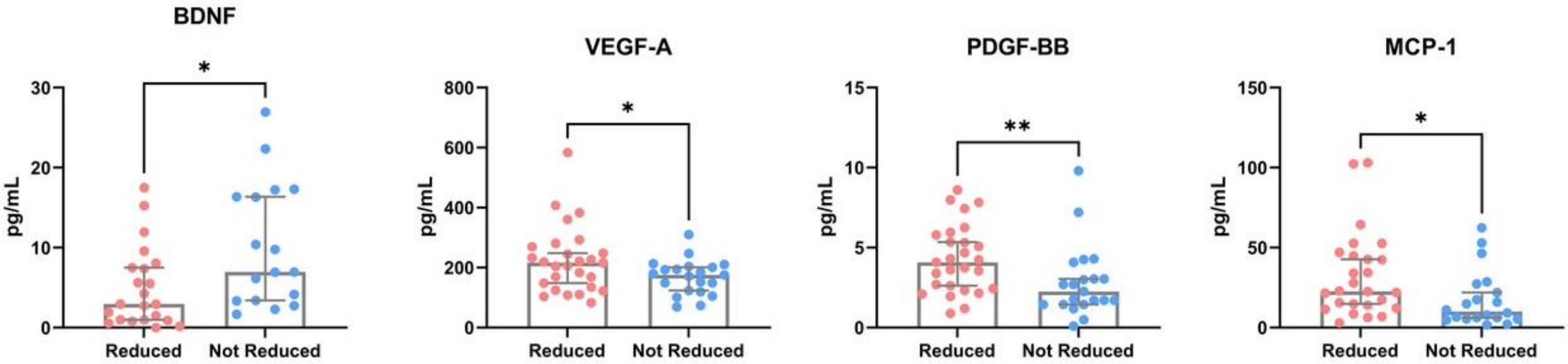
The rates of abnormal findings in ophthalmological examinations and the numbers of conjunctival goblet cells did not deteriorate during dupilumab treatment



At baseline, a high rate of abnormal NIKBUT was observed, while the rates of abnormal findings in Schirmer's test were much lower

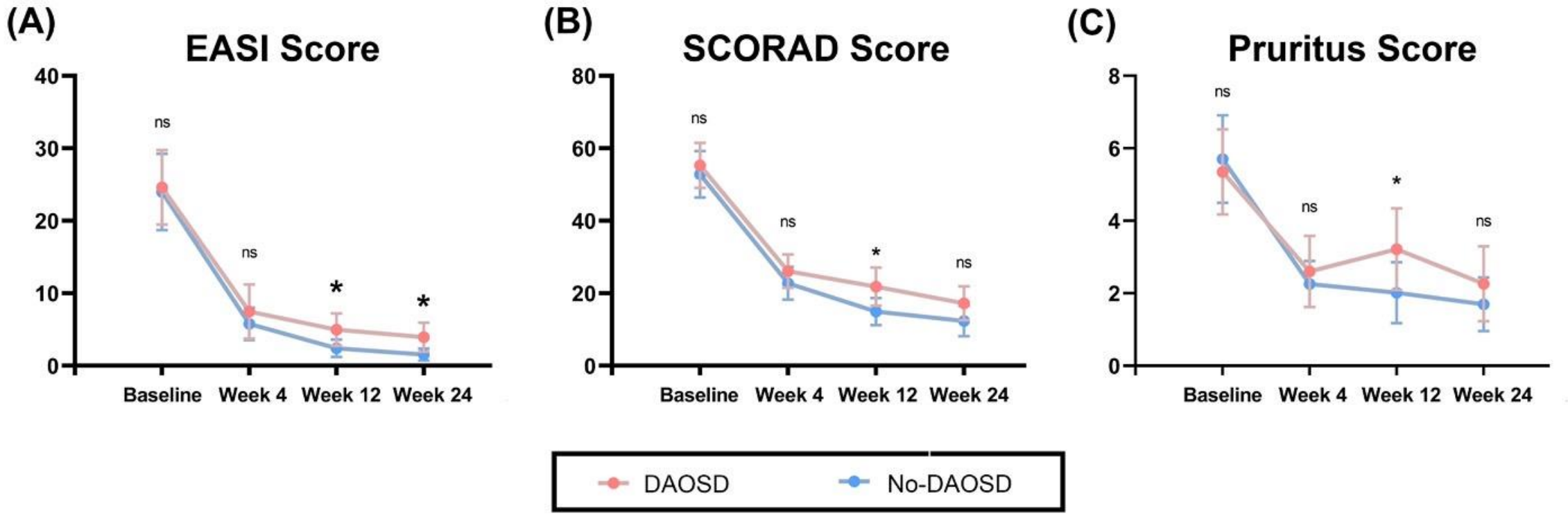
The numbers of conjunctival goblet cells determined by impression cytology were markedly reduced (≥ grade 2) in more than half of the AD patients at baseline. Overall, the percentage of AD patients with abnormal number of conjunctival goblet cells became smaller during and after dupilumab treatment.

Distinct tear cytokine profiles at baseline in patients with a reduced conjunctival goblet cell number



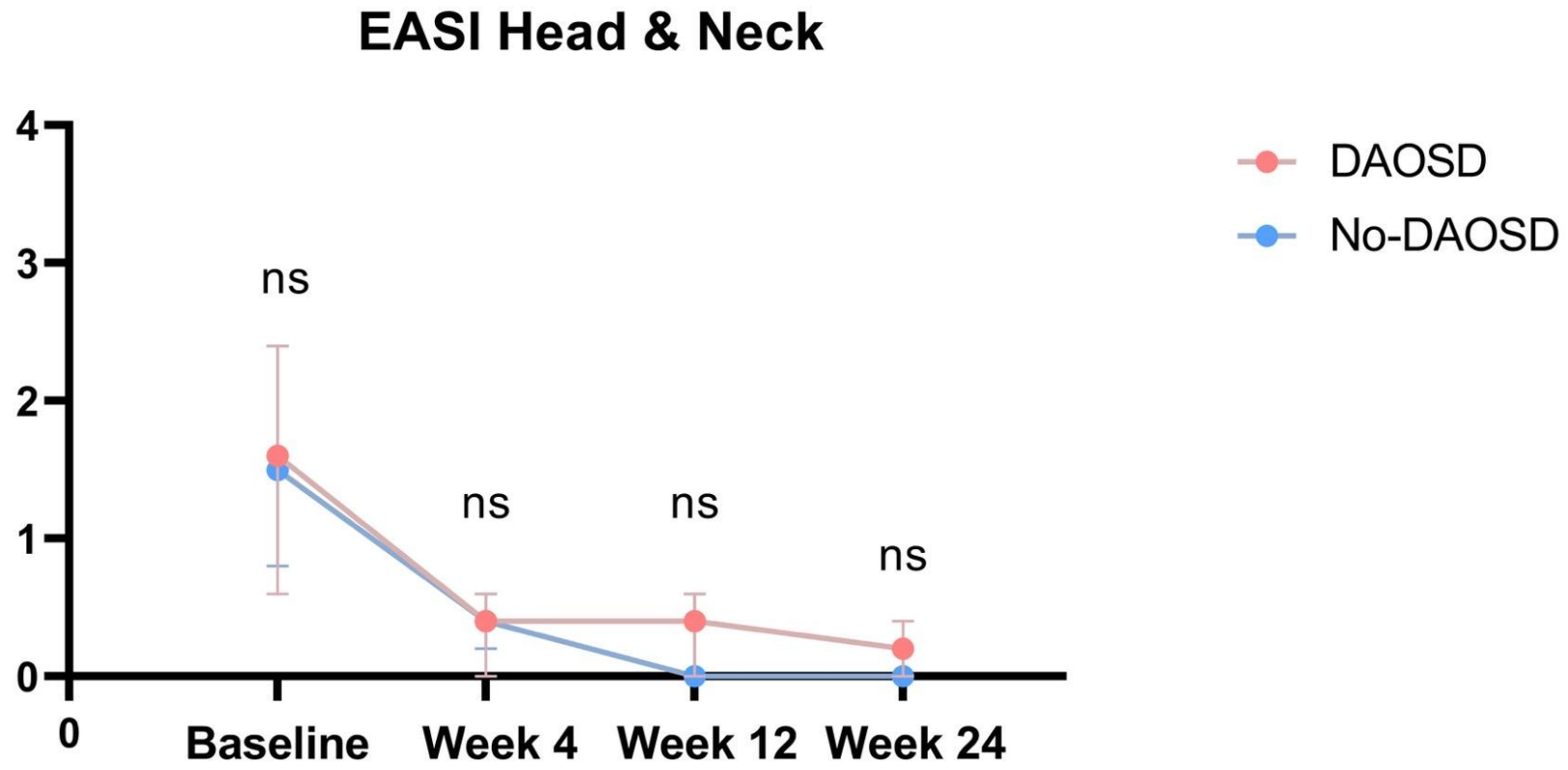
The levels of tear BDNF, VEGF-A, PDGF-BB, and MCP-1 showed significant differences in patients with a reduced conjunctival goblet cell number at baseline.

AD patients without DAOSD showed better clinical improvement than those with DAOSD



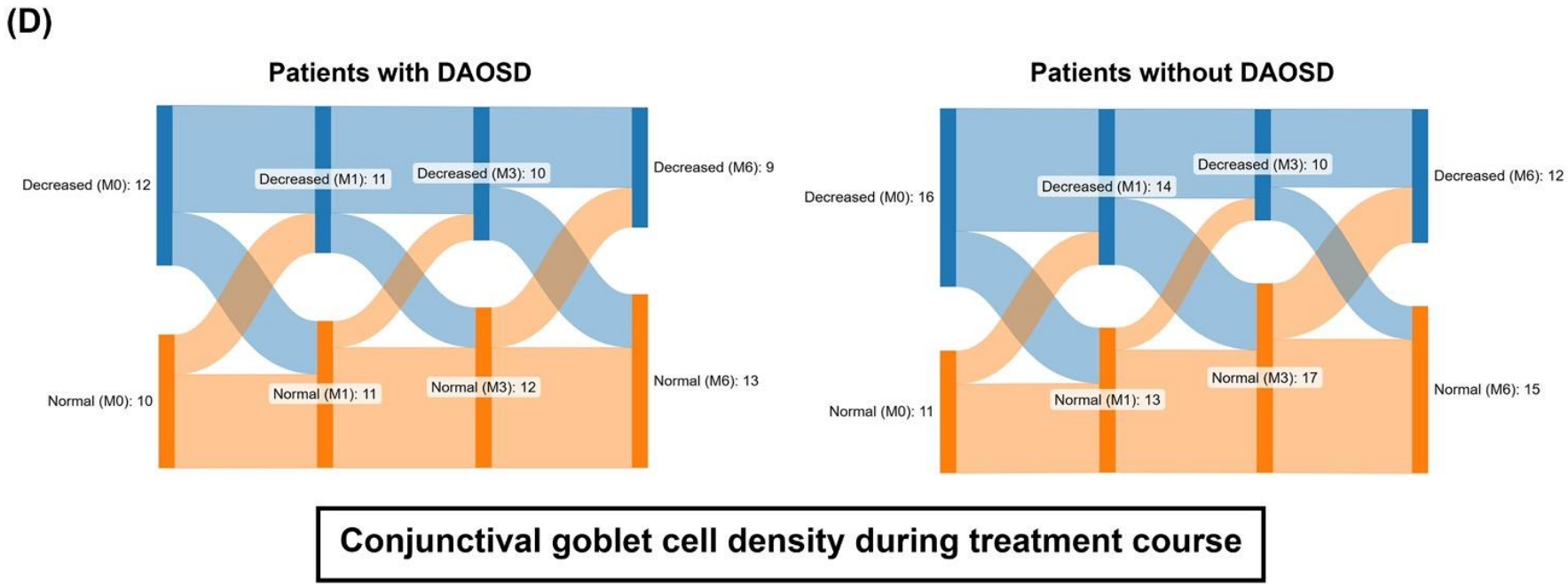
- AD patients with DAOSD showed higher EASI (a mean value of 5.0 vs. 2.4, *p*=0.039), SCORAD (a mean value of 21.8 vs. 15.0, *p*=0.036), and pruritus VAS (a mean value of 3.2 vs. 2.0, *p*=0.028) scores at week 12 compared to those without DAOSD.
- At week 24, the EASI score was still significantly different between the groups (4.0 for AD with DAOSD vs. 1.5 for AD without DAOSD, *p*=0.036).

EASI scores of head and neck region have a similar but not significant trend of differences between the groups



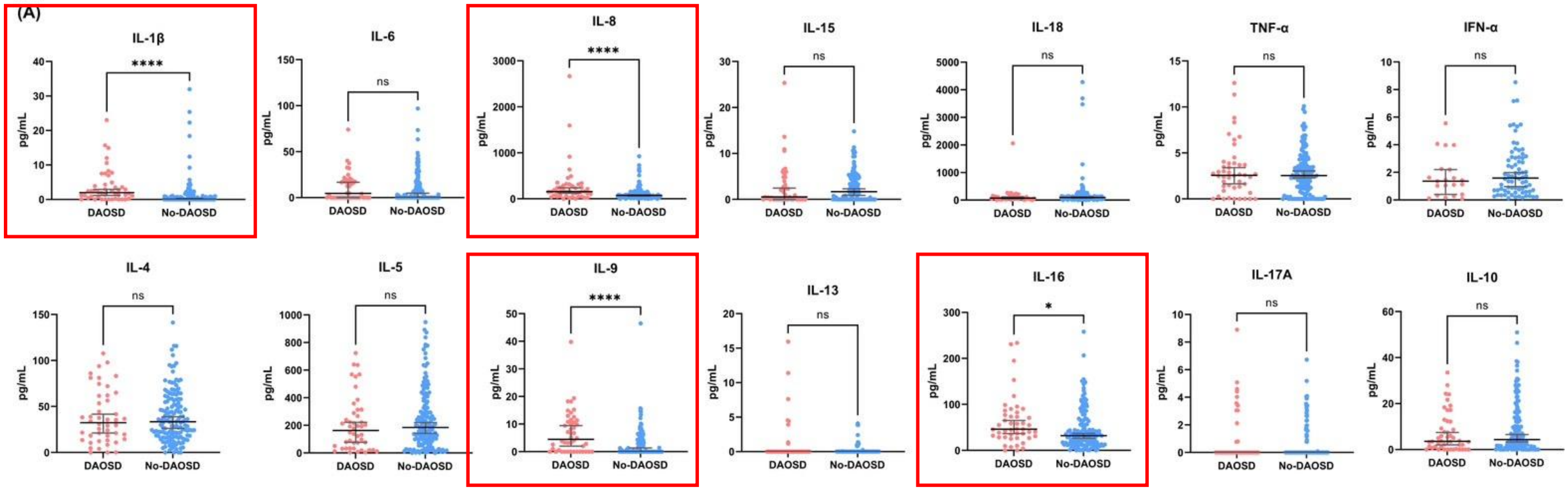
Comparisons of the EASI score of head and neck region between patients with DAOSD and those without DAOSD.

The number of patients showing a reduction in conjunctival goblet cells was similar and became fewer in both groups during dupilumab treatment



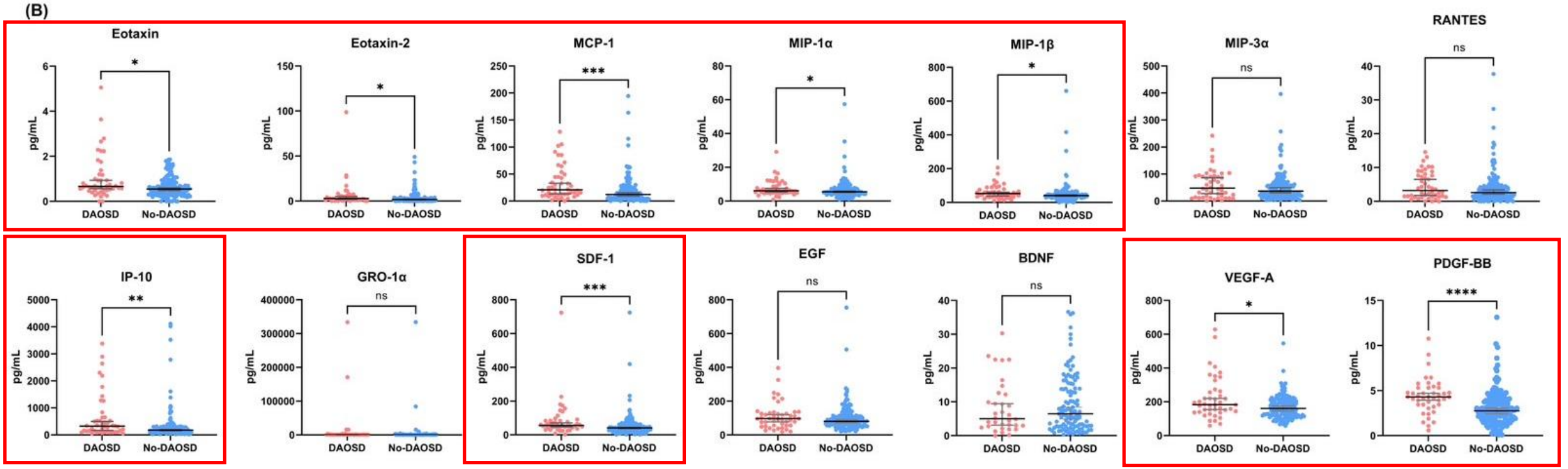
The percentages of AD patients with a reduced number of conjunctival goblet cells decreased after dupilumab treatment in both groups of patients with DAOSD and those without DAOSD .

Tear fluid inflammatory profiles of AD patients with DAOSD were different from those without DAOSD



- we compared the cytokine and chemokine expression in tear fluid from patients during DAOSD episodes (tear fluid n=46) and that from patients not during DAOSD events (tear fluid n=148).
- Several proinflammatory cytokines in tear fluid were significantly elevated in patients during DAOSD episodes: IL-1β, IL-8, IL-9, and IL-16.
- Other Th2 cytokines and IL-17A were similar.

Tear fluid inflammatory profiles of AD patients with DAOSD were different from those without DAOSD (Cont'd)



- Many chemokines including eotaxin, eotaxin-2, MCP-1, macrophage inflammatory protein-1α (MIP-1α), MIP-1β, interferon γ-induced protein-10 (IP-10), and stromal cell-derived factor-1 (SDF-1), were significantly elevated in patients during DAOSD episodes.
- Regarding to growth factors, VEGF-A and PDGF-BB levels were significantly elevated in patients during DAOSD episodes.

Discussion

- Many of our AD patients showed subjective eye discomfort or objective eye abnormalities: abnormal conjunctival and corneal reactions, reduced tear production, or a reduced number of conjunctival goblet cells before the use of dupilumab.
- Despite almost half of our patients developing DAOSD at some point during the dupilumab treatment, the overall abnormalities found in eye examinations remained unchanged or even improved.
- DAOSD in most of these AD patients was mild and could be well controlled by topical anti-inflammatory eye drops.
- None of the patients stopped the dupilumab treatment due to DAOSD.

Cai SC, et al. J Dermatolog Treat. 2016;27(6):531–7

A reduction in goblet cells may impair the protective effects of tear fluid

- Tear fluid consists of three layers:
  Lipid layer: formed by the products of meibomian glands
  Aqueous layer: formed by lacrimal glands
  Mucous layer: secreted by goblet cells
- A reduction in goblet cells→ change in the composition of tear fluid; impair the protective effects of tear fluid.
- Higher percentage of patients with abnormal NIKBUT findings and only a small proportion of patients with abnormal Schirmer's test results
- A relatively normal Schirmer's test result: the aqueous layer is adequate
- A short NIKBUT: tear fluid composition might be altered, especially the lipid layer or the mucous layer→ reduced tear film stability.

Koh S, et al. Acta Ophthalmol. 2015;93(2):e135-139
Mantelli F, et al. Curr Opin Allergy Clin Immunol. 2013;13(5):563-568

Distinct inflammatory profiles in eye diseases

- Patients with a reduced number of conjunctival goblet cells at baseline had significantly different levels of BDNF, VEGF-A, and PDGF-BB in tear fluid.
- BDNF could increase cultured goblet cell secretion in a dose-dependent manner.
- VEGF concentration in tears was significantly higher in individuals with a history of atopy than in those without such a history. VEGF plays a role in corneal neovascularization
- Patients with dry eye disease treated with anti-VEGF eye drops→ significant improvement in tear film stability, corneal staining, and symptoms→ Anti-VEGF treatment might be a potential therapy in treating dry eye disease.
- PDGF may involve in the corneal fibrosis response to epithelial-stromal injury.
- An elevated PDGF-BB level in the tear fluid of patients with a reduced number of goblet cells may reflect a response to repeated inflammation in these patients.
- DAOSD development may result from heightened impairment of conjunctival goblet cells by dupilumab in patients already with a reduced number or dampened function of goblet cells.

Ríos JD, et al. Invest Ophthalmol Vis Sci. 2007;48(4):1543-1551
Chan J, et al. Int J Mol Sci. 2024;25(3):1369
Kasetsuwan N, et al. PLos One 2020;15(6):e0234186
Torricelli AM, et al. Exp Eye Res. 2016;142:110-118

Distinct inflammatory profiles in DAOSD

- Proinflammatory cytokines and chemokines were significantly elevated during the DAOSD event.
- These elevated cytokines (IL-1β, IL-8, IL-9, and IL-16) and chemokines (MCP-1, MIP-1α, MIP-1β, eotaxin, eotaxin-2, IP-10, and SDF-1) showed a distinct pattern→ potential involvement of innate immune cells (neutrophils, eosinophils, and macrophages/monocytes) and Th1-dominant immune responses in the pathogenesis of DAOSD.
- The elevated levels of VEGF-A and PDGF-BB during the DAOSD event may also support the potential repeated occurrence of injuries, repairs, and fibrosis in eyes.
- The higher residual disease activity and cutaneous inflammation as well as the higher residual pruritus after dupilumab treatment in these patients may partly contribute to the development of DAOSD.
- This is supported by the higher levels of Th2-related chemokines (eotaxin and eotaxin-2) in the tear fluid of patients with DAOSD.

Ríos JD, et al. Invest Ophthalmol Vis Sci. 2007;48(4):1543-1551

Limitations of the study

- A single medical center study→ The heterogeneity of AD patients might be insufficient.
- Only enrolled 50 patients and only 23 had DAOSD→ Whether the findings of our study could be generalized to all DAOSD patients requires further confirmation.
- We did not directly examine the tear fluid composition→ A more detailed evaluation of tear fluid composition, especially the mucous or lipid components, may provide deeper insights into the pathogenesis of DAOSD.

Conclusion

Study design

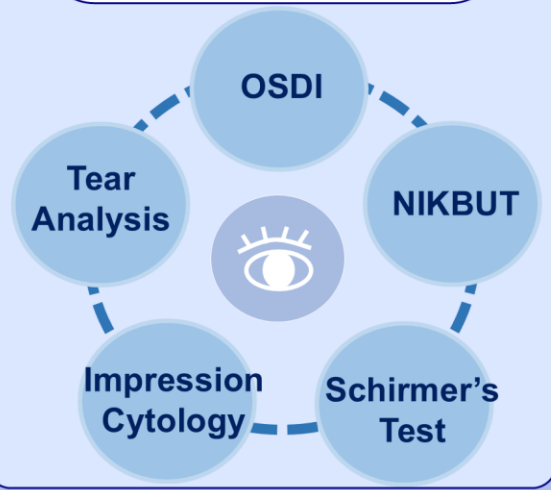
Dupilumab

Moderate-to-Severe Atopic Dermatitis

Baseline — Week 4 — Week 12 — Week 24

Dupilumab-associated Ocular Surface Disease (**DAOSD**)

Key Evaluations



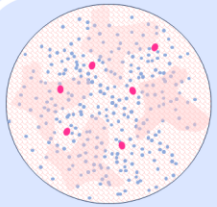
High Rates of Eye Abnormality At Baseline

18%

Ocular Surface Disease Before Dupilumab

↑ Eotaxin
↑ GM-CSF
↑ VEGF-A
↑ EGF
↑ PDGF-BB
↓ BDGF

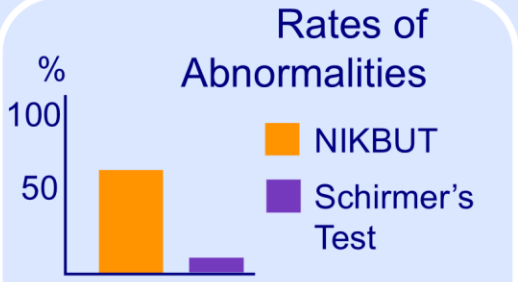
Tear Fluid Analysis

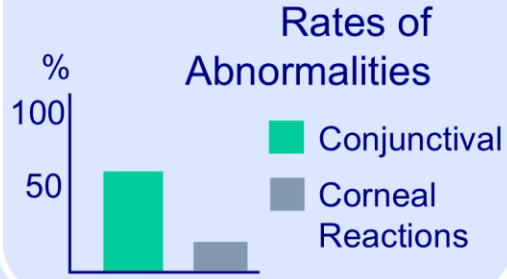


54%

Reduced Conjunctival Goblet Cells

↑ MCP-1
↑ VEGF-A
↑ PDGF-BB
↓ BDGF





Tear Fluid During DAOSD

Th1 / Innate Immunity Predominant

↑ **Cytokines**
IL-1β, IL-8
IL-9, IL-16

↑ **Chemokines**
Eotaxin, Eotaxin-2
MCP-1, MIP-1α, MIP-1β
IP-10, SDF-1

↑ **Growth Factors**
VEGF-A, PDGF-BB

Thank You for Your Attention

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Conclusion

- Eye abnormalities were prevalent in patients with moderate-to-severe AD.
- A reduced number of conjunctival goblet cell and abnormal growth factor levels in tear fluid were common even before dupilumab treatment.
- Dupilumab elicited good treatment responses without significant exaggeration of eye abnormalities.
- DAOSD usually lasted for a short duration and was easily controlled by topical anti-inflammatory eye drops.
- Our results highlighted that tear fluid has a distinct inflammatory profile, involving innate immunity and Th1 responses, during the DAOSD event.
- The inflammation might be caused by AD per se or aggravated by the anti-IL-4/IL-13 effect of dupilumab.
- Our results suggest that certain prophylactic measures, for example, topical eye products with lubricating or anti-VEGF effects, may be helpful for reducing OSD and DAOSD events.