

Journal Pre-proof

Conjunctivitis in patients with atopic dermatitis treated with dupilumab is associated with higher baseline serum levels of IgE and TARC but not clinical severity in a real-world setting

Hideaki Uchida, MD, Masahiro Kamata, MD, PhD, Mayumi Nagata, MD, Saki Fukaya, MD, Kotaro Hayashi, MD, PhD, Atsuko Fukuyasu, MD, Takamitsu Tanaka, MD, PhD, Takeko Ishikawa, MD, PhD, Takamitsu Ohnishi, MD, PhD, Yayoi Tada, MD, PhD

PII: S0190-9622(19)33316-X

DOI: <https://doi.org/10.1016/j.jaad.2019.12.039>

Reference: YMJD 14092

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 3 November 2019

Revised Date: 5 December 2019

Accepted Date: 19 December 2019

Please cite this article as: Uchida H, Kamata M, Nagata M, Fukaya S, Hayashi K, Fukuyasu A, Tanaka T, Ishikawa T, Ohnishi T, Tada Y, Conjunctivitis in patients with atopic dermatitis treated with dupilumab is associated with higher baseline serum levels of IgE and TARC but not clinical severity in a real-world setting, *Journal of the American Academy of Dermatology* (2020), doi: <https://doi.org/10.1016/j.jaad.2019.12.039>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier on behalf of the American Academy of Dermatology, Inc.



Conjunctivitis in patients with atopic dermatitis treated with dupilumab is associated with higher baseline serum levels of IgE and TARC but not clinical severity in a real-world setting

Hideaki Uchida, MD, Masahiro Kamata, MD, PhD, Mayumi Nagata, MD, Saki Fukaya, MD, Kotaro Hayashi, MD, PhD, Atsuko Fukuyasu, MD, Takamitsu Tanaka, MD, PhD, Takeko Ishikawa, MD, PhD, Takamitsu Ohnishi, MD, PhD, Yayoi Tada, MD, PhD

Department of Dermatology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan

Correspondence: Masahiro Kamata, MD, PhD

Department of Dermatology, Teikyo University School of Medicine, 2-11-1 Kaga, Itabashi-ku, Tokyo 173-8605, Japan

TEL +81-3-3964-2473, FAX +81-3-5375-5314

E-mail: mkamata-ty@umin.ac.jp

Short title: Parameters associated with conjunctivitis induced by dupilumab in atopic

dermatitis

Short summary: Conjunctivitis in patients with atopic dermatitis treated with dupilumab is associated with baseline serum levels of IgE and TARC but not subjective severity scores in a real-world setting. These objective parameters are useful as practical predictors of later development of conjunctivitis.

Manuscript word count; 500 figure count; 1, table count; 0

Funding sources: none.

Conflict of interest: M.K. and Y.T. received honoraria for lectures from Sanofi.

Key words: atopic dermatitis, dupilumab, conjunctivitis, IgE, thymus and activation-regulated chemokine

31 Abbreviations: atopic dermatitis, AD; thymus and activation-regulated chemokine,
32 TARC; investigator's global assessment, IGA; body surface area, BSA; eczema area and
33 severity index, EASI; topical corticosteroid, ROC; lactate dehydrogenase levels, LDH.

34

Conjunctivitis has been observed as an adverse event in atopic dermatitis (AD) patients receiving dupilumab. Its incidence rate ranges from 8.6% to 21.44% in clinical trials¹, while real-world data have shown even higher prevalence^{2,3}. We herein analyzed our data to explore practical predictors of later development of conjunctivitis in AD patients initiating dupilumab in a real-world setting.

Adult AD patients who had been treated with dupilumab in our hospital for more than three months as of October 1, 2019 were included in this study. Other inclusion criteria were the same as those described in our previous article³. Baseline clinical severity, patients' history of conjunctivitis, and results from laboratory blood tests were compared between patients who developed conjunctivitis and those who did not.

Data on 57 Japanese adult AD patients were analyzed. Forty-nine patients were male, and eight were female. The mean age at starting dupilumab was 38.1 ± 11.8 years (mean $\pm$ standard deviation). Conjunctivitis was observed in 22.8% (13/57) of patients after starting dupilumab. The mean time to develop conjunctivitis after beginning dupilumab was 5.3 ± 3.9 weeks. The frequency of having a history of conjunctivitis at baseline was higher in patients who developed conjunctivitis after starting dupilumab than in those who did not. Patients who developed conjunctivitis after starting dupilumab had significantly higher serum levels of thymus and activation-regulated chemokine

(TARC) and IgE at baseline than those who did not (Figure 1). The cut-off values of TARC and IgE levels at baseline were 3,342 pg/ml (sensitivity 69.23%, specificity 79.55%) and 11,200 IU/ml (76.92%, 69.77%), respectively, with moderate accuracy. No significant differences were observed between them in clinical severity including investigator's global assessment (IGA), affected body surface area, and the eczema area and severity index, and other results of laboratory blood tests.

Clinical trials demonstrated that baseline disease-related factors, including AD severity, prior conjunctivitis history and certain biomarkers (TARC, IgE, eosinophils), were associated with increased incidence of conjunctivitis¹. It is reasonable since levels of certain biomarkers such as TARC, IgE, and eosinophils increase with AD severity⁴⁻⁶. However, our real-world data revealed that only baseline serum TARC and IgE levels were significantly higher in patients who developed conjunctivitis, and that history of conjunctivitis and eosinophils showed its tendency, whereas baseline clinical severity did not demonstrate any association with incidence of conjunctivitis. Even in clinical trials' data, the difference in the incidence of conjunctivitis between AD patients with baseline IGA=3 and those with baseline IGA=4 was quite small in CHRONOS (0.06 vs. 0.09 per 100 patient-years) and in CAFÉ (0.22 vs. 0.23)¹. It is difficult for physicians to distinguish the subtle differences in disease severity of AD among patients with

moderate to severe AD (not including mild AD). Our study underscores that among those parameters, serum levels of TARC and IgE could reflect subtle differences in predisposition for conjunctivitis more accurately than the disease severity of AD evaluated by physicians especially among moderate-to-severe AD patients, indicating that these objective parameters are useful as practical predictors of later development of conjunctivitis.

References

1. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ et al. Conjunctivitis in dupilumab clinical trials. *Br J Dermatol* 2019;181:459-73.
2. Faiz S, Giovannelli J, Podevin C, Jachiet M, Bouaziz JD, Reguiat Z et al. Effectiveness and safety of dupilumab for the treatment of atopic dermatitis in a real-life French multicenter adult cohort. *J Am Acad Dermatol* 2019;81:143-51.
3. Uchida H, Kamata M, Mizukawa I, Watanabe A, Agematsu A, Nagata M et al. Real-world effectiveness and safety of dupilumab for the treatment of atopic dermatitis in Japanese patients: a single-centre retrospective study. *Br J Dermatol* 2019.
4. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014;371:130-9.
5. Hamilton JD, Suarez-Farinas M, Dhingra N, Cardinale I, Li X, Kostic A et al. Dupilumab improves the molecular signature in skin of patients with moderate-to-severe atopic dermatitis. *J Allergy Clin Immunol* 2014;134:1293-300.
6. Guttman-Yassky E, Bissonnette R, Ungar B, Suarez-Farinas M, Ardeleanu M, Esaki H et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2019;143:155-72.

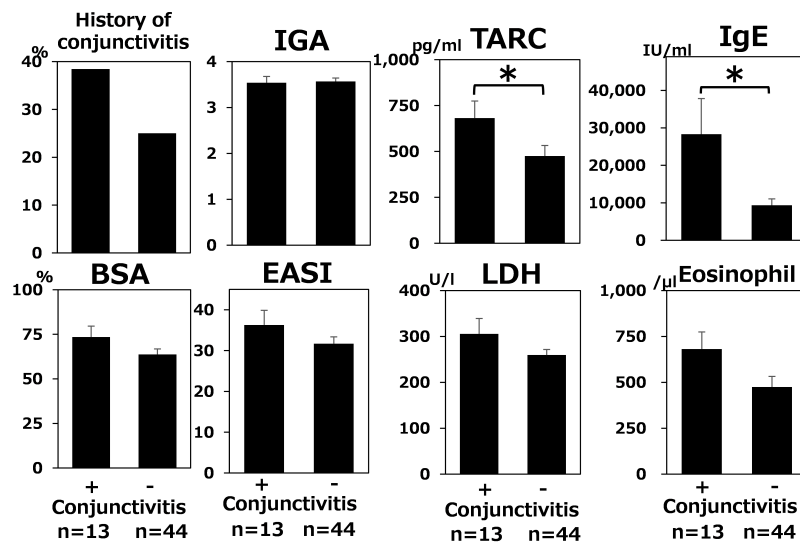
95

96

Journal Pre-proof

Figure legends**Figure 1**

Comparison of the presence of previous history of conjunctivitis, baseline atopic dermatitis (AD) severity, and certain biomarkers between AD patients who developed conjunctivitis after starting dupilumab and those who did not, and receiver operating characteristic (ROC) curves of serum thymus and activation-regulated chemokine levels (TARC) and serum IgE levels (IgE). IGA, investigator's global assessment; BSA, affected body surface area; EASI, eczema area and severity index; LDH, serum lactate dehydrogenase level; eosinophil, the number of circulating eosinophils; AUC, area under the ROC curve. Data are shown as mean with error bar representing standard error. * $p < 0.01$ between the two groups using the T-test.



	TARC	IgE
ROC curve		
AUC	0.76399	0.76118
Cut-off value	3342	11200
Youden index	0.4878	0.4669
Sensitivity (%)	69.23	76.92
Specificity (%)	79.55	69.77

Figure 1
Uchida et al.