

Interleukin-17 in Various Ocular Surface Inflammatory Diseases

Min Ho Kang^{1,2}, Mee Kum Kim^{2,3},
Hyun Joo Lee², Hyeon Il Lee⁴,
Won Ryang Wee^{2,3} and Jin Hak Lee^{2,3}

¹Department of Ophthalmology, Hanyang University Guri Hospital, Guri; ²Seoul Artificial Eye Center, Seoul National University Hospital Clinical Research Institute, Seoul; ³Department of Ophthalmology, Seoul National University College of Medicine, Seoul; ⁴GM Eye Clinic, Seoul, Korea

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Address for Correspondence:

Mee Kum Kim, MD

Department of Ophthalmology, Seoul National University Hospital, 101 Daehak-ro, Jongno-gu, Seoul 110-744, Korea
Tel: +82.2-2072-2438, Fax: +82.2-741-3187
E-mail: kmk9@snu.ac.kr

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Recently, the association of Th-17 cells or IL-17 with ocular inflammatory diseases such as uveitis, scleritis and dry eye syndrome was discovered. We assessed whether interleukin (IL)-17 was present in the tears of various ocular surface inflammatory diseases and the tear IL-17 concentrations were clinically correlated with various ocular surface inflammatory diseases. We measured concentrations of IL-17 in tears of normal subjects ($n = 28$) and patients ($n = 141$) with meibomian gland dysfunction (MGD), dry eye syndrome (DES), Sjögren syndrome (SS), Stevens-Johnson syndrome (SJS), graft-versus-host disease (GVHD), filamentary keratitis, and autoimmune keratitis associated with rheumatoid arthritis or systemic lupus erythematosus. Clinical epitheliopathy scores were based on the surface area of corneal and conjunctival fluorescein staining. The mean concentrations of IL-17 in tears of patients with filamentary keratitis, GVHD, autoimmune keratitis, SS, DES, MGD, SJS were significantly higher in order than that in normal subjects. Tear IL-17 concentration was significantly correlated with clinical epitheliopathy scores in the patients with systemic inflammatory disease, while tear IL-17 was not correlated with clinical severity of the cornea and conjunctiva in the dry eye patients without any systemic inflammatory disease. Tear IL-17 is likely to correlate clinically with corneal disease severity only in the patients with systemic inflammatory disease.

Key Words: Interleukin-17; Tears; Ocular Surface Inflammatory Diseases; Epitheliopathy Score

INTRODUCTION

Since a distinct T cell subset, known as T helper type 17 lymphocyte (Th-17), which is characterized by the production of interleukin (IL)-17 has been identified (1, 2), compelling evidence has accumulated that Th-17 cells are involved in a wide variety of autoimmune (3-8) and allergic diseases (9) and transplantation rejection (10). Recent studies have indicated that Th-17 cells are involved in psoriasis (3), rheumatoid arthritis (RA) (4), multiple sclerosis (MS) (5), inflammatory bowel disease (IBD) (6), systemic lupus erythematosus (SLE) (7) and asthma (9), through the IL-17/IL-23 axis.

Currently, the association of Th-17 cells or IL-17 with ocular inflammatory diseases such as uveitis (11, 12) and scleritis (12), as well as dry eye syndrome (13, 14), has also been revealed. In addition, Th-17 cells have been found to play an important role in early herpes virus-induced corneal inflammation (15).

IL-17, which is mainly produced by Th-17 cells, mediates powerful effects on stromal cells, resulting in production of inflammatory cytokines and recruitment of leukocytes, especially neutrophils, thus creating a link between innate and adaptive immunity (2). The IL-17 associated modulation of stromal cells may have an affect on conjunctival and corneal wound healing

in various ocular surface inflammatory diseases, leading to epithelial erosion, which the clinician assesses for clinical scoring and disease severity.

For this study, we hypothesized that Th-17 cells might be involved to different degrees not only in autoimmune ocular surface disease but also in nonautoimmune ocular surface disease. We also presumed that the involvement of Th-17 cells could be correlated with clinical scores of ocular surfaces, which represent disease severity. Therefore, we aimed to quantify IL-17 in the tears of various ocular surface inflammatory diseases, and to assess whether there were clinical correlations of tear IL-17 concentration with various ocular surface inflammatory diseases.

MATERIALS AND METHODS

Subjects

Patients visiting the outpatient clinic of Seoul National University Hospital between March and October 2009, and who presented with various ocular surface diseases, were enrolled ($n = 142$). Normal subjects without any ocular problems and systemic diseases voluntarily participated as controls ($n = 28$). Ocular surface disease was diagnosed by an ophthalmologist.

The included ocular surface diseases were as follows: meibomian gland dysfunction (MGD, $n = 51$), dry eye syndrome without any systemic disease and meibomian gland dysfunction (DES, $n = 38$), Sjögren syndrome (SS, $n = 33$), chronic limbal deficiency secondary to Stevens-Johnson syndrome (SJS, $n = 5$), DES with rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE, $n = 4$), graft-versus-host disease (GVHD, $n = 7$), and filamentary keratitis ($n = 3$). Patients taking oral or topical steroids or topical cyclosporine eye drops within one month before enrollment were excluded.

Patient characteristics are summarized in Table 1. There were 141 patients (23 males) included in the study, with a mean age of 52.6 yr.

The patients were divided into two groups; subjects without systemic inflammatory disease (group A) and the others with systemic inflammatory disease (group B). Group A included simple dry eye, MGD and filamentary keratitis, while group B included GVHD, SS, SJS, dry eye with RA or SLE. Tear IL-17 concentration were compared among the disease in each group, and the correlation of tear IL-17 with clinical severity of the cornea

Table 1. Demographic characteristics of study subjects

Groups	Number of patients	Sex ratio (percent female %)	Age (yr)	Clinical scores
Normal	28	75.0	38.32 ± 16.12	0
MGD	51	76.5	60.94 ± 12.39	0.19 ± 0.69
Sjögren	33	100.0	50.10 ± 12.48	1.69 ± 1.33
GVHD	7	42.8	40.70 ± 14.41	2.0 ± 1.15
Autoimmune keratitis	4	100	50.30 ± 8.85	0.5 ± 1.0
DES	38	89.5	51.10 ± 15.22	0.5 ± 0.86
Filamentary keratitis	3	66.7	56.00 ± 32.14	2.67 ± 1.15
SJS	5	60.0	47.20 ± 12.58	2.8 ± 1.09

MGD, meibomian gland dysfunction; Sjögren, Sjögren syndrome; GVHD, graft-versus host disease; Autoimmune keratitis, dry eye syndrome with Rheumatic arthritis or Systemic lupus erythematosus; DES, dry eye syndrome without systemic disease; SJS, Stevens-Johnson syndrome.

were analyzed in each group.

Measurement of tear IL-17 concentrations

A previously reported protocol was followed for sampling tears (16). Topical anesthetics was not used to avoid diluting effect before collecting tear. To avoid reflex tearing, Schirmer strip was carefully placed not to irritate conjunctival surface as possible as we could. Tears were collected for 5 min by the Schirmer I method using filter paper (Color Bar Schirmer Tear Test standardized sterile strips, Eagle Vision, Inc., Memphis, TN, USA) in the same exam room to minimize the effect of ambient humidity. After collection, each Schirmer strip was stored at -20°C until use. For evaluation, each Schirmer strip was thawed and the tear volume was calculated by converting 1 mm of tear-moistened Schirmer strip to 1 μL of tear volume (16). The strip was eluted at room temperature overnight with a final volume of 0.05 M phosphate-buffered solution (PBS, pH 7.2) containing 0.5 M NaCl, and 0.5% Tween 20, such that the tear sample was diluted to 40-fold.

Tear concentrations of IL-17A were measured using a commercially-available enzyme-linked immunosorbent assay (ELISA) kit (Human IL-17 DuoSet; R&D Systems, Minneapolis, MN, USA) according to manufacturer instructions. ELISAs were performed in triplicate to ensure the reproducibility of the data. According to the manufacturer, the assay's lower limit of detection was 15 pg/mL.

Clinical scoring of ocular surface epitheliopathy

Clinical scoring was based on the area of corneal and conjunctival fluorescein staining (17), and was modified according to the protocol of the study clinic. One drop of 2% sterile fluorescein was instilled into each conjunctival sac, and after the patient blinked several times, corneal and conjunctival staining were scored as quickly as possible. There were 3 corneal regions (upper, middle, and lower) and 4 conjunctival regions (superi-

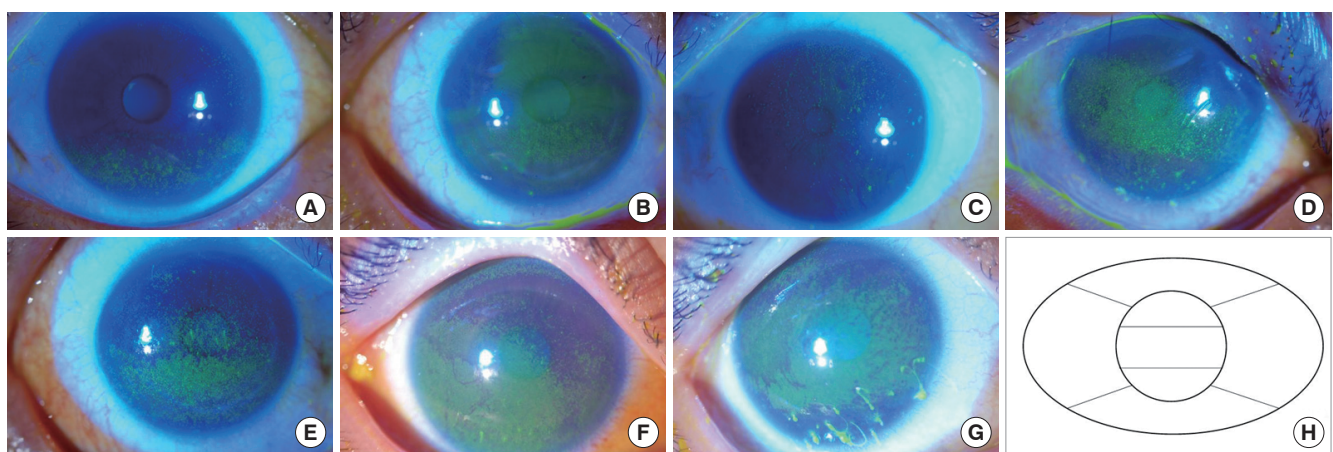


Fig. 1. Photograph standards and diagram for clinical scoring of corneal and conjunctival staining, with fewer modifications. Corneal staining standards; (A, B) and (C) each are 1 point; (D) and (E) each are 2 points; (F) and (G) each are 3 points. (H) Diagram: fluorescein staining was recorded in upper, middle and lower corneal regions; and superior, inferior, nasal, and temporal conjunctival regions.

or, inferior, nasal, and temporal) evaluated (Fig. 1). A maximum of 3 points was used for corneal fluorescein staining as follows: 0 point for no punctuate staining of the cornea; 1 point for corneal epithelial staining in 1 region or less, 2 points for 2 regions or less, but more than 1 region, 3 points for more than 2 regions (Fig. 1).

A maximum of 3 points was also used for conjunctival fluorescein staining as follows: 0 point for no punctuate staining of the conjunctiva; 1 point for conjunctival staining in 1 quadrant or less, 2 points for 2 quadrants, and 3 points for 3 or more quadrants of conjunctival staining. Clinical scores were calculated by adding the corneal and conjunctival scores, with a maximum score of 6 points (18).

Statistical analysis

To compare the mean IL-17 concentration in tears of normal subjects with the mean concentrations in tears of the disease groups, a nonparametric statistical test (Mann-Whitney U test) was used. The Pearson correlation analysis test was used to assess the relationship between clinical scores and IL-17 concentrations in tears. For all tests, $P < 0.05$ was considered to be significant.

Ethics statement

This study was approved by the institutional review board of Seoul National University Hospital (H-0803-029-238). All subjects signed informed consent forms for participation in this study.

RESULTS

The demographics of the patients were shown in Table 1. The score in corneal severity were higher in SJS, filamentary keratitis, GVHD and SS in order (Table 1).

An aim of this study was to evaluate whether IL-17 is involved in various ocular surface inflammations. Surprisingly, most ocular surface diseases, including not only autoimmune-associated keratitis but also non-autoimmune surface inflammation, showed increased tear IL-17 concentrations, suggesting possible involvement of Th-17 cells. The mean concentrations of tear IL-17A in patients with GVHD, SS, autoimmune keratitis, MGD, DES, and filamentary keratitis were significantly higher than the mean concentration of IL-17A in normal subjects (Table 2 and Fig. 2, $P < 0.05$, Mann-Whitney U test). The mean concentration of tear IL-17A was highest in filamentary keratitis, followed in

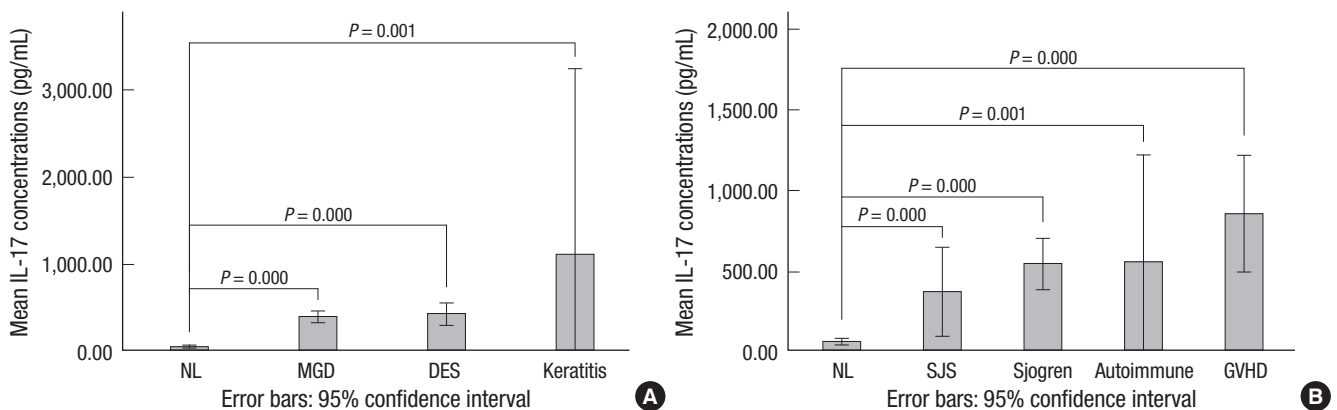


Fig. 2. Mean values of IL-17 concentrations in tears of each patient group compared to the normal control group. The patients were divided into two groups; subjects without systemic inflammatory disease (A, group A) and the others with systemic inflammatory disease (B, group B). In all groups, the mean concentrations of IL-17 were significantly higher than that of the normal group (Mann-Whitney U test). NL, normal control; MGD, meibomian gland dysfunction; Sjogren, Sjögren syndrome; GVHD, graft-versus host disease; Autoimmune, dry eye syndrome associated with rheumatoid arthritis or systemic lupus erythematosus; DES, dry eye syndrome without systemic disease; SJS, Stevens-Johnson syndrome; Keratitis, filamentary keratitis.

Table 2. The concentrations of the tear IL-17 in the various ocular surface diseases (pg/mL)

Groups	Mean	Standard deviation	Minimum	Maximum	Median
Normal	45.35	57.46	15.00	200.20	15.00
MGD	389.98	244.92	35.71	969.06	336.65
Sjögren	530.43	446.32	35.44	2,162.27	418.27
GVHD	845.23	391.11	222.08	1,455.10	908.22
Autoimmune keratitis	542.31	421.24	124.05	1,122.14	525.32
DES	422.98	389.77	39.76	1,740.43	279.78
Filamentary keratitis	1,102.04	859.71	232.78	1,998.70	1,022.63
SJS	356.79	223.74	141.99	728.16	328.89

MGD, meibomian gland dysfunction; Sjögren, Sjögren syndrome; GVHD, graft-versus host disease; Autoimmune keratitis, dry eye syndrome with Rheumatic arthritis or Systemic lupus erythematosus; DES, dry eye syndrome without systemic disease; SJS, Stevens-Johnson syndrome.

order of decreasing concentrations by GVHD, autoimmune keratitis, SS, DES, MGD and SJS. Interestingly, the mean concentration of IL-17A in GVHD patients was higher than in DES, SJS and SS patients ($P = 0.007$, 0.032 , and 0.031 , Mann-Whitney U test, Fig. 3).

While, correlates tear IL-17 concentrations with clinical scores of ocular surface inflammation, it could provide clinically relevant information. As shown in Fig. 4, tear IL-17 concentrations significantly correlated with clinical scores in patients with systemic inflammatory disease, (Pearson correlation coefficient [r] = 0.364 , $P = 0.022$, Pearson correlation analysis test) on the contrary, tear IL-17 did not correlate with the clinical severity in the dry eye patients without any systemic inflammatory disease (Pearson correlation coefficient [r] = 0.012 , $P = 0.901$, Pearson correlation analysis test) although high tear IL-17 was shown in these patients. To rule out age as a confounding factor, age was analyzed in relation to tear IL-17 concentrations, and there was no

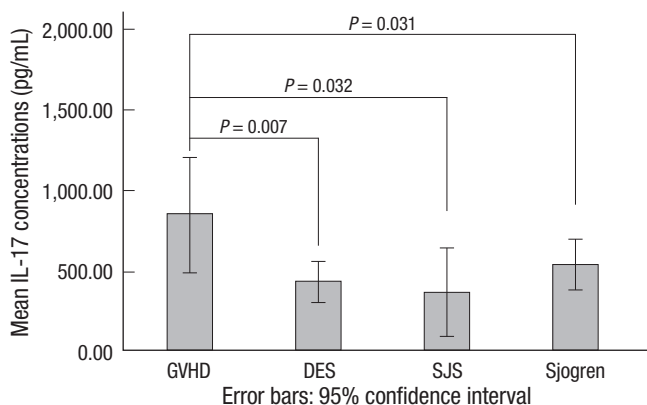


Fig. 3. Mean values of IL-17 concentrations in tears of each patient group compared to the Graft-versus-host disease patients. The mean IL-17 concentration of graft-versus-host disease patients was significantly higher than those of dry eye syndrome without systemic disease patients, Stevens-Johnson syndrome and Sjögren syndrome patients (Mann-Whitney U test). GVHD, graft-versus-host disease; DES, dry eye syndrome without systemic disease; SJS, Stevens-Johnson syndrome; Sjogren, Sjögren syndrome.

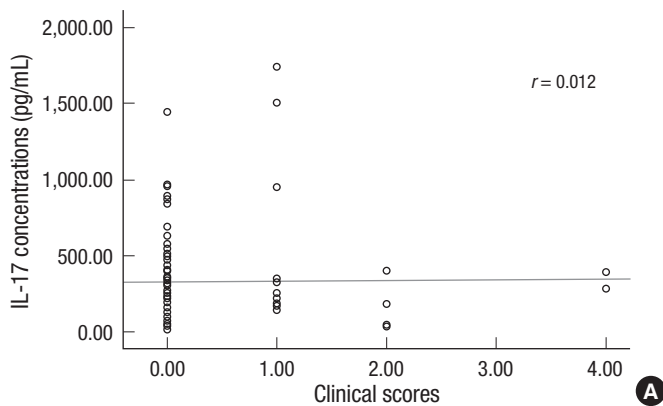


Fig. 4. Correlation of tear IL-17 concentrations with clinical scores. There was no correlation of tear IL-17 with clinical scores in subjects the dry eye patients without systemic disease (group A; **A**) Pearson correlation coefficient [r] = 0.012 , $P = 0.901$) while, tear IL-17 did correlate a statistically significantly positive correlation with clinical severity in the patients with systemic diseases (group B; **B**) Pearson correlation coefficient [r] = 0.364 , $P = 0.002$).

significant correlation (Pearson correlation coefficient [r] = -0.037 , $P = 0.637$, Pearson correlation analysis test, Fig. 5). It suggested that tear IL-17 is likely to be clinically involved in corneal inflammation in the patients with systemic inflammatory disease.

DISCUSSION

The demonstration of IL-17 involvement in various ocular surface diseases is supporting evidence for recent reports (13, 19) showing that Th-17 cells are important in the pathogenesis of ocular surface diseases. We demonstrated in this study that elevated tear IL-17 levels were seen in not only autoimmune-associated but also non-autoimmune-associated ocular surface diseases, including meibomian gland disease and dry eye syndrome. However, the concentrations of IL-17 correlated well with clinical scoring of epitheliopathy only in the patients with systemic inflammatory disease, indicating that tear IL-17 expression levels can provide clinically-relevant information on corneal disease severity in the patients with systemic autoimmune disease and systemic inflammatory disease like GVHD.

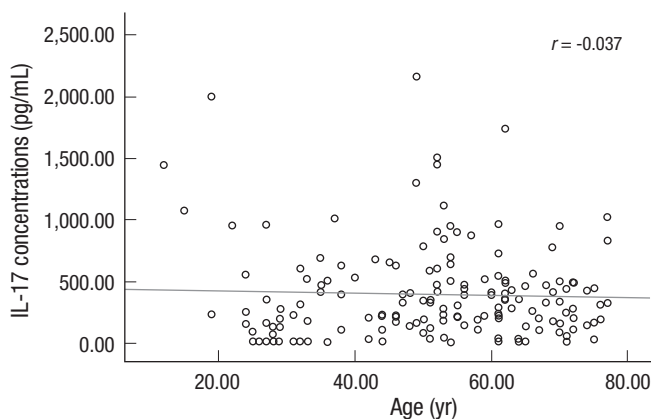
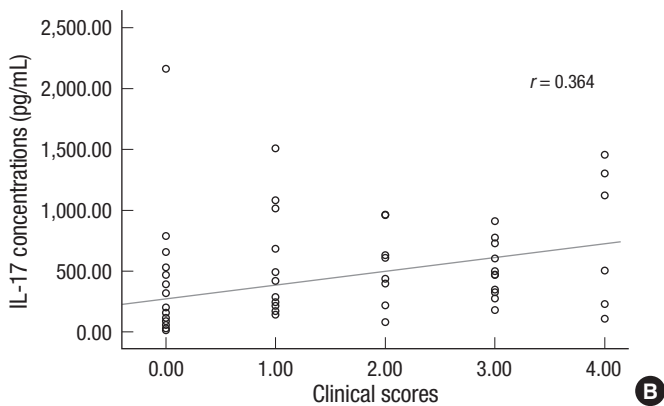


Fig. 5. Simple scatter graph of ages and IL-17 concentrations. There was no correlation between age and IL-17 concentrations ($P = 0.637$, r = Pearson correlation coefficient).



The discovery of specific cells and cytokines with pivotal roles in inflammation can lead to the development of targeted therapy to selectively inhibit critical steps, with minimal side effects. Chauhan et al. (13) showed that *in vivo* blockade of IL-17 significantly reduced the severity and progression of disease. Fortunately, eyes can be treated topically, thereby avoiding systemic toxicity. Because of this, recent excellent work on the role of Th-17 cells in ocular surface disease could in the near future lead to the development of topical IL-17-targeted therapy that acts by interfering with local Th-17 cell activity.

Actually, the ocular surface has a Th-17 cell differentiation-friendly environment enriched with cytokines, including TGF- β 1, IL-6, IL-23, and IL-1 β induced by certain stimuli (14, 19, 20). Zheng et al. (19) showed that corneal epithelial cells that are exposed to hyperosmotic, microbial, and inflammatory stimuli secreted cytokines promoting Th-17 cell differentiation. Our clinical data also suggest that Th-17 cells may be crucial in various ocular surface inflammations, especially in systemic inflammatory disease. The *in vivo* correlation of IL-17 with clinical scores of epithelial cell injury in the patients with systemic inflammatory disease strongly supports the results of Zheng's *in vitro* experiments that damaged epithelial cells might enhance Th-17 cell differentiation (19). In addition, IL-17 is known to induce epithelial, stromal and immune cells to secrete proinflammatory cytokines such as IL-6, TNF- α , IL-1, and IL-8 (21) and disruptive enzymes such as metalloproteinase-9 (14). A vicious cycle may develop in which a high IL-17 concentration is maintained in an ocular environment with damaged epithelial cells that have already produced proinflammatory cytokines.

As mentioned in the introduction, autoimmune diseases such as Sjögren syndrome, rheumatoid arthritis, and systemic lupus erythematosus, which often involve the ocular surface, are related to Th-17 cells. In fact, serum levels of IL-17 have been reported to correlate with both the activity and severity of these autoimmune diseases (22, 23). Subsequently, ocular involvement of IL-17 in these diseases may well be expected, which was clearly seen in the results of our study. Moreover, we found that serum IL-17 was also elevated in patients with GVHD, Sjögren syndrome- and rheumatoid arthritis-associated dry eye (24). In that previous study, the serum IL-17 level correlated significantly with the fluorescein staining score in these patients with systemic inflammatory disease, which corresponded well with this study showing correlation of tear IL-17 with clinical severity of the cornea. Therefore, on top of this previous evidence, the fact that correlation of the tear IL-17 with clinical severity strongly suggested that IL-17 might be involved in corneal surface inflammation in systemically autoimmune disease patients. Therefore, taking into consideration these previous reports including our study (22, 23), clinical correlation of tear IL-17 concentrations with ocular surface damage scores may be a valuable approach for assessing disease severity, providing the chance of bypass of

lacrimal biopsy in Sjögren's syndrome.

Another interesting finding in this study was that chronic ocular GVHD showed a markedly high concentration of tear IL-17 compared with autoimmune and nonautoimmune ocular surface disorders. To the best of our knowledge, this is the first finding of IL-17 in ocular GVHD. Th-17 cells are known to mediate systemic GVHD (25, 26) although the exact role of Th-17 is still debated (27). The reason why ocular GVHD presented with high IL-17 values is still unclear. It can be presumed that it may be caused by direct invasion of host Th-17 cells as well as by damaged ocular epithelial cells inducing Th-17 cell differentiation from recruited naïve T cells. Further investigation is needed to elucidate the exact mechanisms for GVHD ocular IL-17.

While, the simple dry eye and MGD did not present significant correlation between the tear IL-17 and clinical severity, although high concentration of tear IL-17 was observed compared with control. The reason why this disparity happened might be condensing effect of tear as tear evaporated. That is, the condensed concentration of tear might include condensed concentration of IL-17. To clarify condensing effect of tear IL-17 due to tear evaporation, additional analysis for the abundant tear keeping protein like lactoferrin in normal condition as a control. The change of tear IL-17 would be analyzed after adjustment of lactoferrin to exclude condensing effect. Although this study was limited that additional protein data could not be analyzed to adjust condensing effect due to small volume of the tear, our study is still worthy of notice to understand role of IL-17 in not only simple dry eye but also keratitis with systemic autoimmune disease. That is, our data suggested that tear IL-17 might be clinically relevant in systemic autoimmune disease patients to assess disease severity, while tear IL-17 might not be clinically relevant in simple evaporated type of dry eye.

On the other hand, the simple dry eye and MGD did not show severe clinical scores, in contrast dry eye with systemic disease presented wide range of clinical scores from mild type to very severe type. Simple dry eye or MGD seemed not to accompany severe corneal epithelial lesion. Considering that there is a certain possibility that damaged cells per se would enhance IL-17 production by CD4 T cells (28), the explanation the other way around would be plausible. That is, the more cells are injured, the production of IL-17 appeared to be the more affected. That might be a reason why simple dry eye with rather low clinical scores did not show any relation with IL-17.

A limitation of this study is the relatively small number of patients in the autoimmune-associated ocular surface disease groups. Another limitation is that we did not identify the cells secreting IL-17. Although the main source of IL-17 is Th-17 cells, in minor amounts it can also be produced by CD8⁺ T cells, $\gamma\delta$ T cells, natural killer T (NKT) cells, neutrophils, eosinophils, and macrophages (8, 29, 30). IL-17A is the prototypical member of the IL-17 family, which consists of six related proteins, from IL-

17A to IL-17F. Th-17 cells are the major source of IL-17A and F, while other cell populations express IL-17A to a lesser extent. As a result, assessment of IL-17A indicates that Th-17 cells are more likely to be the source cells than other cell populations. Consequently, our measurement of IL-17A can to some extent justify our assumption that Th-17 cells were the source cells but this correlation certainly needs further investigation. Another limitation was that we could not control unseen microscopic reflex tearing completely during the examination. However, when the gross reflex tearing was observed, we removed Schirmer strip, wait 10-20 min, and then re-applied it to exclude most gross reflex tearing as possible as we could. In fact, one of the other limitation was that age was significantly younger in volunteering control group than the diseased group. Although we confirmed that age was not a confounding factor of IL-17 level using Pearson correlation test, it could still act a little bit as a bias factor. Nonetheless, we still believe our findings may contribute to the further understanding of ocular surface disease pathogenesis regarding involvement of IL-17.

In conclusion, tear IL-17 is likely to be associated with the dry eye in the patients with systemic autoimmune diseases or systemic inflammatory disease by showing concentrations of IL-17 correlated well with clinical severity of the cornea. This suggests that Th-17 cells may be involved in the pathogenesis of ocular surface inflammatory disease. Clinically, the measurement of the concentration of IL-17 in tear may be applied as a valuable option to evaluate the ocular surface inflammatory severity quantitatively in the patients with systemic inflammatory disease.

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AUTHOR SUMMARY

Interleukin-17 in Various Ocular Surface Inflammatory Diseases

Min Ho Kang, Mee Kum Kim, Hyun Joo Lee, Hyeon Il Lee, Won Ryang Wee and Jin Hak Lee

We measured concentration of interleukin (IL)-17 in patients' tears and found that the tear IL-17 is increased in various ocular surface diseases. Interestingly, in the patients with systemic autoimmune diseases or with systemic inflammatory disease, concentrations of IL-17 are positively correlated with clinical severity of the cornea. Our results suggest that Th-17 cells are involved in the pathogenesis of ocular surface inflammatory disease. Clinically, the measurement of tear IL-17 could be applied as a parameter for quantitative evaluation of ocular surface inflammation.