Lactoferrin in Sjögren's Syndrome

Dear Editor:

Lactoferrin is a glycoprotein present in human milk and is secreted into tears by the lacrimal gland. It has several functions, including antiinflammatory effects and promotion of cell growth and DNA synthesis, and antiangiogenic and antitumoral properties.[1,2] Tear lactoferrin level has been reported to be an indicator of lacrimal secretory function.[3] Previous studies also reported that tear lactoferrin level correlated with the severity of conjunctivocorneal epithelial lesions in patients with primary, secondary, and non–Sjögren's syndrome dry eyes.[3]

We studied the alterations of the tear functions and the ocular surface disorder in 20 eyes of 10 Sjögren's syndrome patients (4 male, 6 female; mean age, 60.5 years) with dry eyes by performing corneal sensitivity measurements, tear film lipid layer interferometry, a Schirmer test, tear film breakup time (BUT) measurements, ocular surface vital staining, and conjunctival impression cytology with 1 month of peroral enteric lactoferrin treatment and with its cessation in a crossover-design prospective trial. Fourteen eyes of 7 Sjögren's syndrome patients (3 male, 4 female; mean age, 62) who did not consent to a lactoferrin trial served as the control group undergoing the same examinations as the LF treatment group throughout the study period. None of the patients had another ocular or systemic disorder or history of ocular surgery or used contact lenses. Patients without symptomatic and objective improvement despite use of nonpreserved artificial tears, autologous serum eyedrops, and upper and lower punctal occlusion for 8 weeks who did not wish to use topical cyclosporine or steroid eyedrops were included in this study. Informed consents and ethical board reviews were obtained. Patients received 270 mg/day of oral enteric lactoferrin capsules (NRL Pharma, Kawasaki, Japan) for 1 month. Examinations were performed before commencement, at 1 month, and 4 weeks after cessation of lactoferrin treatment.

The mean corneal sensitivity , BUT value, central tear film lipid layer thickness, vital staining scores, squamous metaplasia grades, and goblet cell densities were significantly worse before lactoferrin treatment, improving significantly and concomitantly with dry eye symptomatology after 1 month of treatment. These parameters worsened again 1 month after cessation of treatment. Differences were statistically significant. Schirmer test scores did not show any changes. The mean frequency of artificial tear instillations in a day decreased significantly 1 month after treatment, with a significant increase within 4 weeks after cessation of treatment. There were no significant changes in the control group, which did not receive oral lactoferrin (Figs 1–8 [available at http://aaojournal.org]). All patients reported transient loosening of stools for 3 to 7 days with treatment. No other complications were observed.

Lactoferrin receptors exist in human nervous tissues and are upregulated with neural damage.[2] Bovine lactoferrin administration has also been reported to stimulate nerve growth factor secretion and aid neural healing in mice, which might explain the improvements in corneal sensitivity.[2] Biomicroscopy revealed resolution of conjunctival inflammation with lactoferrin ingestion and reversal of the findings after cessation of lactoferrin. HLA-DR; interleukins 1α, 1β, 6, and 8; transforming growth factor β1; and tumor necrosis factor α were reported to be upregulated in the conjunctiva of Sjögren's syndrome patients.[4] Lactoferrin can directly inhibit the production of several cytokines, including tumor necrosis factor α and interleukin 1β, via receptor-mediated signaling pathways.[1,2] Lactoferrin can suppress inflammation by downregulating tumor necrosis factor α and upregulating interleukin 10 in rat adjuvant-induced artritis.[1,2] Lactoferrin can also nonselectively inhibit T-cell proliferation in human inflammatory skin disease.[2] A topical lactoferrin drop was found to suppress the loss of corneal epithelial integrity in a rabbit dry eye model.[5] We attribute the tear function and ocular surface improvements in our study to suppression of inflammatory mediators by lactoferrin. Our findings of conjunctival inflammatory resolution with lactoferrin should be substantiated with data from flow cytometry or tear enzyme-linked immunosorbent assay studies investigating the expression of inflammatory cytokines.

In summary, oral lactoferrin seemed to be an efficient treatment modality in improving tear stability and ocular surface epithelium in dry eye patients with Sjögren's syndrome. We did not detect any safety concerns regarding oral lactoferrin use in our study. We hope that the results of this trial stimulate further randomized double-blind studies involving more subjects and investigating the changes of symptoms and conjunctivocorneal epithelial integrity as primary end points. Such a future study with a minimum of 90% power to reflect statistically significant similar vital staining scores observed in the current study should have an estimated sample size of at least 22 subjects in both the active drug group and the vehicle/placebo group.[6]

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6. Chow SC, Liu JP. Sample size determination. In: Balding DJ, Noel AC, eds. Design and Analysis of Clinical Trials. Concept and Methodologies. Hoboken, NJ: Wiley Interscience; 2004:438–510.

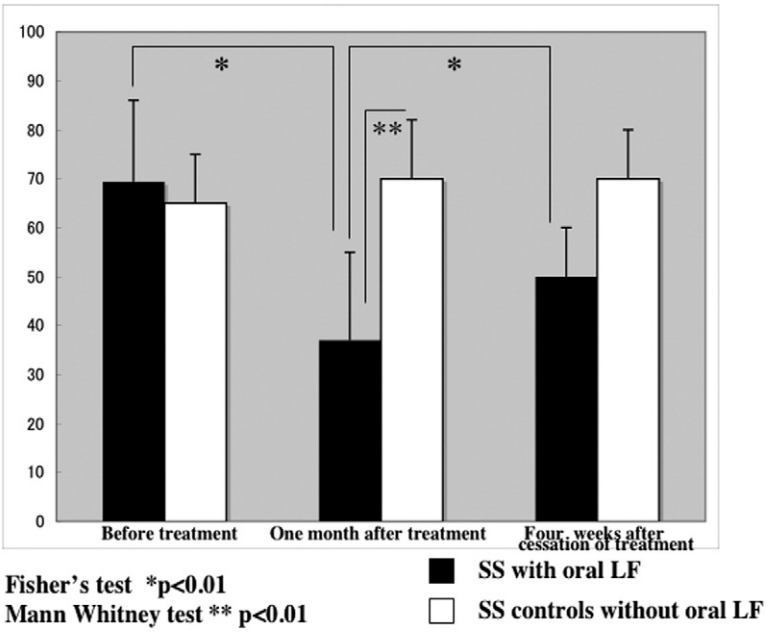

Figure 1. Change in mean visual analog ocular symptom (VAS) score with lactoferrin (LF) treatment. Note the significant decrease in the mean VAS score with 1 month of lactoferrin use and the reincrease in the mean score 4 weeks after cessation of treatment. SS = Sjögren's syndrome.

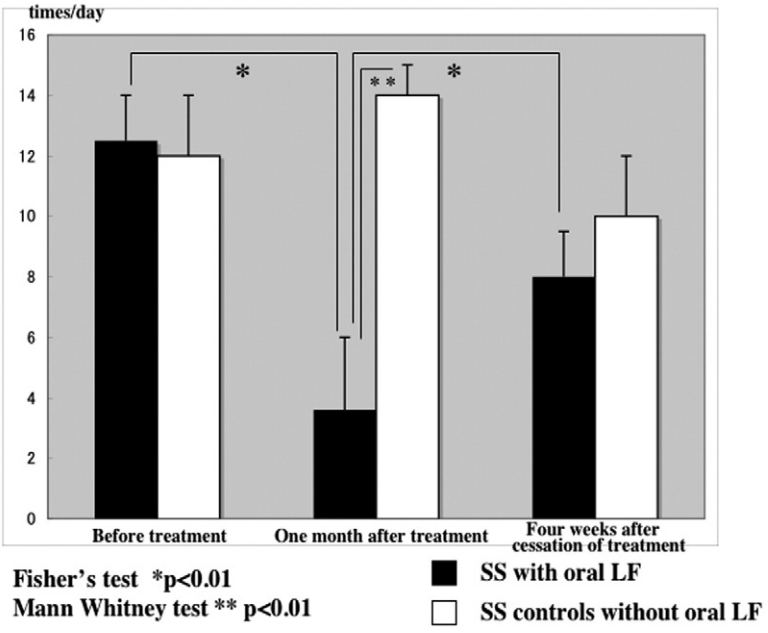

Figure 2. Change in frequency of artificial tear drop instillations per day with lactoferrin (LF) treatment. Note the significant decrease in the mean number of artificial tear drop instillations with 1 month of lactoferrin use and the reincrease in the frequency of instillations 4 weeks after cessation of treatment. SS = Sjögren's syndrome.

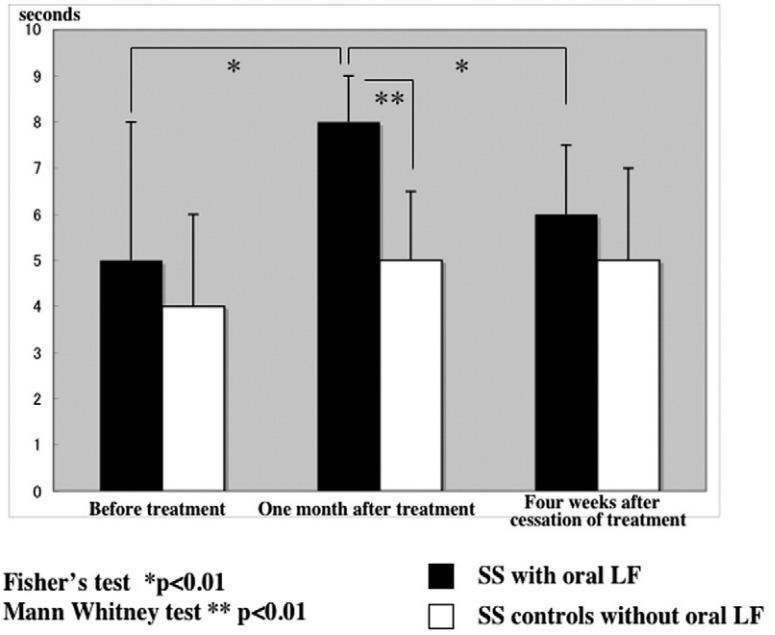

Figure 3. Change in mean tear film breakup time (BUT) values with lactoferrin (LF) treatment. Note the improvement of the tear film BUT with 1 month of lactoferrin use and the deterioration of tear stability 4 weeks after cessation of treatment. SS = Sjögren's syndrome.

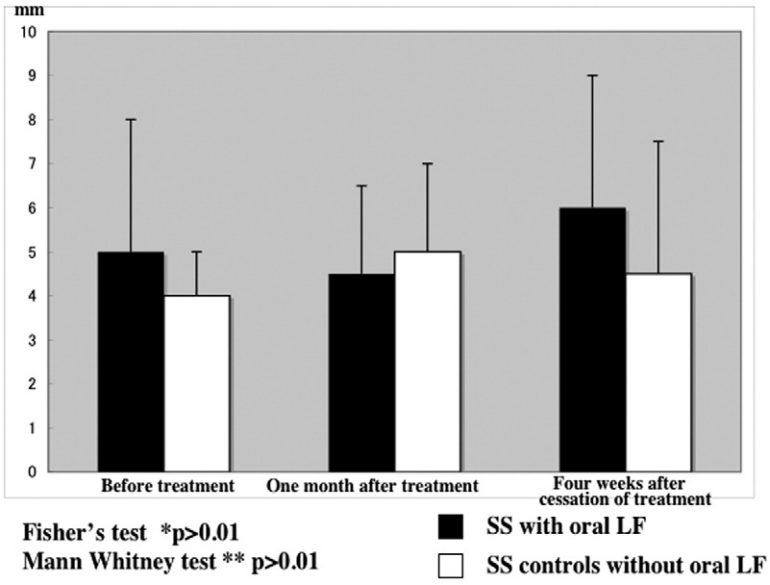

Figure 4. Change in mean Schirmer test scores with lactoferrin (LF) treatment. Note the absence of statistically significant changes in tear quantity with lactoferrin use or its withdrawal. SS = Sjögren's syndrome.

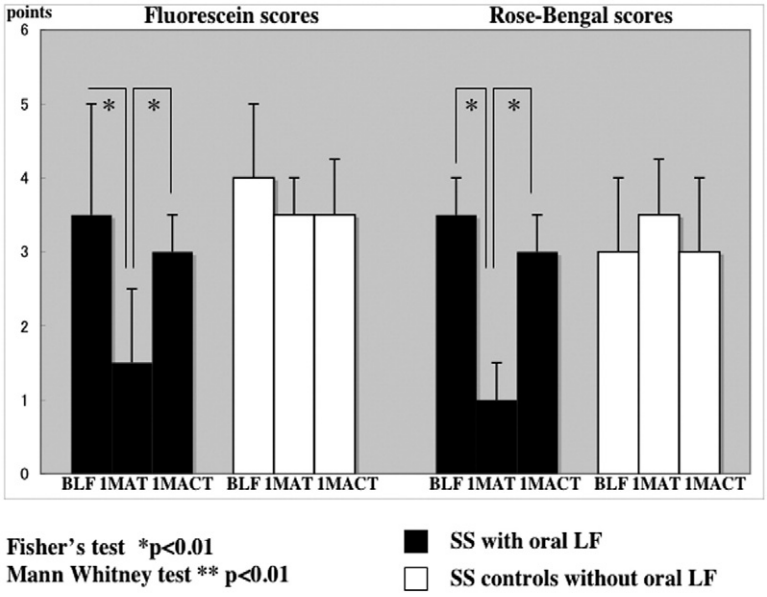

Figure 5. Change in mean vital staining scores with lactoferrin (LF) treatment. Note the significant improvements of the ocular surface vital staining scores with 1 month of lactoferrin use and the deterioration with cessation of lactoferrin. 1MACT = 1 month after cessation of treatment; 1MAT = 1 month after treatment; BLF = before lactoferrin treatment; SS = Sjögren's syndrome.

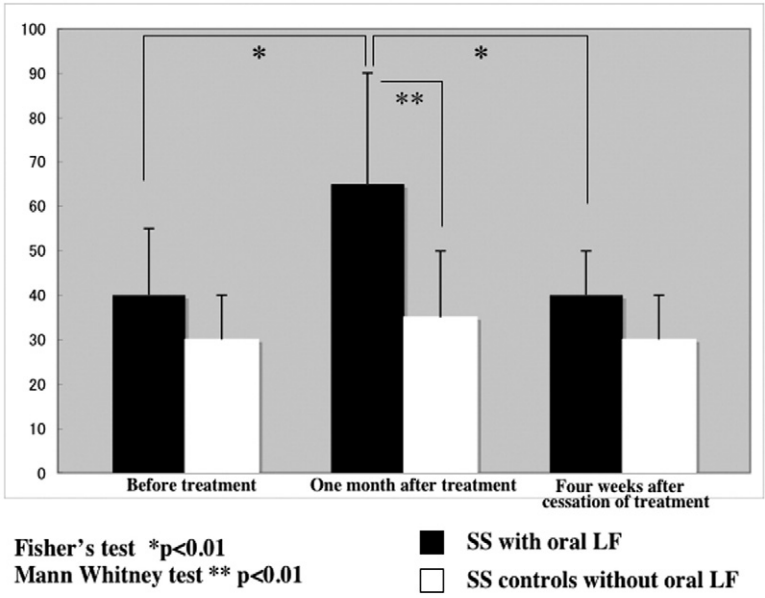

Figure 6. Change in mean tear film lipid layer thickness with lactoferrin (LF) treatment. Note the significant improvement of the mean tear film lipid layer thickness with 1 month of lactoferrin use and the deterioration with cessation of lactoferrin. SS = Sjögren's syndrome.

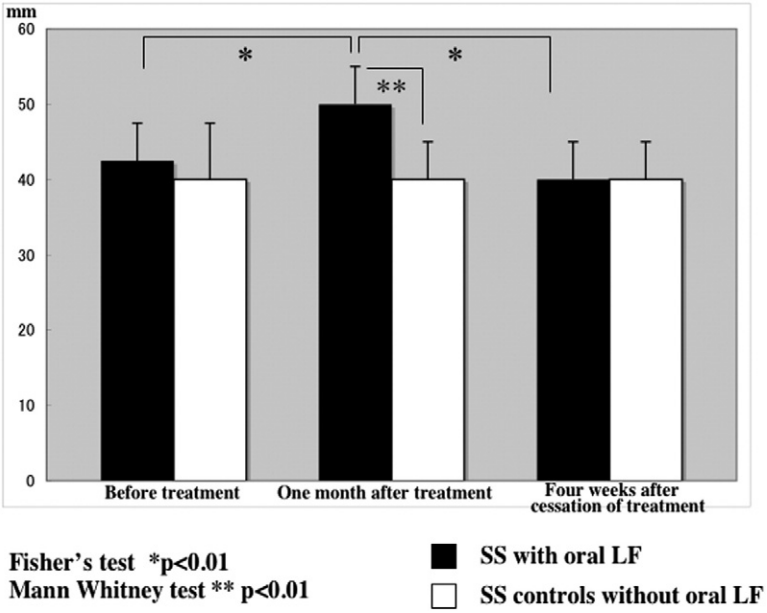

Figure 7. Change of mean corneal sensitivity with lactoferrin (LF) treatment. Note the significant improvement of the mean corneal sensitivity with 1 month of lactoferrin use and its significant deterioration with cessation of lactoferrin. SS = Sjögren's syndrome.

Impression cytology parameters	Before LF treatment	One month after LF treatment	Four weeks after cessation of treatment
Squamous Metaplasia (Nelson's Grade)	2.0±0.5	1.00±0.64 *	1.75±0.25 *
Goblet cell density (cells/mm²)	385±100	912±50 *	426±180 *

Figure 8. Impression cytology parameters. Note the significant improvements of the mean squamous metaplasia grade and goblet cell density with 1 month of lactoferrin (LF) use and the deterioration with cessation of lactoferrin. *$P<0.01$, Fisher exact test.