SHORT COMMUNICATION

Apremilast Decreased Proinflammatory Cytokines and Subsequently Increased Inhibitory ones in Psoriasis: A Prospective Cohort Study

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Psoriasis is a chronic and systemic inflammatory skin disease characterized by erythematous papules and plaques with thick scales. Tumor necrosis factor (TNF)-α, interleukin (IL)-17, and IL-23 from various cells are thought to play an important role in the pathophysiology of psoriasis (1–5). Recently, it has been reported that vascular abnormalities are also observed in psoriasis as an indicator of systemic inflammation. This has been shown to correlate with serum cytokine levels (6, 7).

Apremilast is an oral drug that targets phosphodiesterase (PDE)-4 and exerts its therapeutic effect by increasing intracellular cAMP levels. This action reduces inflammatory cytokines produced by the cells and increases the production of suppressive cytokines (8, 9). Cytokines at very low concentrations are difficult to measure and require a large volume of blood for detection. Therefore, a system called microfluidic ELISA has been recently developed to measure cytokines in serum with high sensitivity. This system was developed through collaborative research between the fields of medicine and engineering (2, 10, 11). In this study, we treated patients with moderate to severe psoriasis using apremilast and assessed the severity of skin lesions, pruritus, and serum cytokine levels. The aim was to investigate in detail the effect of apremilast on psoriasis.

MATERIALS AND METHODS

Patients, the cytokine assay methods, antibodies used, and statistical methods are described in Appendix S1.

RESULTS

Patient characteristics

The demographic and disease characteristics of the study cohort are depicted in Tabls SI. Comorbidities included hypertension (17 cases), diabetes (5 cases), dyslipidemia (11 cases), hyperuricemia (7 cases), and fatty liver (5 cases), but all of which were mild. Therefore, no concomitant medications were used. There were no adverse events that occurred, no adverse events that appeared to be causally related, and no serious adverse events.

Changes in baseline PASI scores and serum levels of various cytokines following apremilast treatment for psoriasis. The mean rates of PASI improvement were 53 [95% confidence interval (CI): 38–68] in week 4, 75 [95%CI: 59–91] in week 16, and 86 [95%CI: 79–94] in week 24. The mean rates of pruritus VAS improvement were 56 [95%CI: 36–75] in week 4, 69 [95%CI: 49–90] in week 16, and 78 [95%CI: 63–93] in week 24. All points showed significant improvement after applying the Bonferroni correction (Fig. S1). Skin lesions and itching showed significant improvement as early as 4 weeks after starting apremilast treatment. In psoriasis, some patients experience severe skin lesions and intense itching, and apremilast significantly improved both symptoms. The speed of efficacy varied from case to case, with some patients improving early and others later. Overall, the skin lesions and itching improved steadily. The results suggest the possibility of achieving excellent therapeutic effects if the patient continues taking the drug for at least 6 months.

The rate of change and absolute difference in serum levels of IL-1β, IL-6, IL-17A, IL-17F, IL-17C, IL-21, IL-22, IL-23, IL-36γ, TGF-β1, and TNF-α decreased following apremilast treatment. Each inflammatory cytokine steadily and significantly improved as week 4, week 16, and week 24 progressed. In contrast, serum IL-10 and IL-35 levels, both of which have inhibitory functions, increased after 24 weeks of apremilast treatment (**Table I** and Table SII). The concentrations of IL-12, IL-18, and IFN-α remained unchanged during apremilast treatment. All statistical analyses were Bonferroni-corrected.

If we separate patients with a pruritus VAS score of 50 or more (itchy) and those with less than 50 (not itchy),

Table I. Absolute difference from the baseline for each serum cytokine.

	Week 4	Week 16	Week 24
IL-1β	−1.3 (0.8)*	−1.9 (1.0)*	−2.0 (1.2)*
IL-6	−1.0 (0.6)*	−1.5 (0.5)*	−1.6 (0.5)*
IL-10	−0.1 (0.4)	−0.1 (0.5)	1.0 (1.0)*
IL-12	−0.2 (0.5)	−0.2 (0.6)	0.1 (0.8)
IL-17A	−2.7 (1.7)*	−4.5 (1.4)*	−4.6 (1.4)*
IL-17F	−11.0 (7.6)*	−18.4 (5.3)*	−19.6 (4.8)*
IL-17C	−13.9 (9.0)*	−22.8 (6.4)*	−24.8 (5.8)*
IL-18	−0.5 (0.9)	−1.1 (2.0)	−0.3 (2.5)
IL-21	−1.4 (1.2)*	−1.2 (1.0)*	−1.2 (1.3)*
IL-22	−1.9 (1.3)*	−3.2 (0.9)*	−3.4 (0.8)*
IL-23	−2.6 (1.4)*	−4.1 (1.3)*	−4.4 (1.4)*
IL-35	−0.2 (0.8)	−0.1 (1.0)	1.5 (1.2)*
IL-36γ	−7.2 (5.4)*	−12.5 (3.7)*	−13.5 (3.4)*
IFN-α	−0.1 (0.1)	−0.1 (0.1)	0.0 (0.1)
TGF-β1	−0.6 (0.6)*	−0.6 (0.5)*	−0.5 (0.6)*
TNF-α	−3.0 (1.8)*	−4.6 (1.6)*	−4.9 (1.6)*

Only TGF-β1 is in ng/mL. Other cytokines are in pg/mL. The values are given in mean (SD). Asterisks show statistically significant after Bonferroni correction ($p < 0.05$).

the absolute PASI at week 24, and the levels of IL-17A, IL-17F, IL-17C, TNF-α, IL-23, IL-22, IL-1β, and IL-12 in week 0 were significantly lower in the "not itchy" group.

Correlations between serum cytokine levels and the PASI score at each time point. Correlations between disease severity and serum cytokine levels are presented in Table SIII. In week 4, serum levels of IL-1β, IL-17A, IL-17F, IL-17C, IL-18, IL-22, IL-23, IL-36γ, and TNF-α were positively correlated with the PASI score. In week 16, IL-6, IL-12, IL-17A, IL-17F, IL-17C, IL-18, IL-22, IL-23, IL-36γ, IFN-α, TGF-β1, and TNF-α were positively correlated with the PASI score (Table SIII). In week 24, IL-12, IL-17A, IL-18, IL-21, IL-36γ, IFN-α, and TGF-β1 were positively correlated with the PASI score. However, there was no significant correlation between PASI score and the concentration of each serum cytokine at week 0. One possible explanation for this is that the clinical study included individuals with severe psoriasis, defined as having a PASI score of 10 or higher. Since the serum cytokine concentrations also decreased in those whose skin lesions improved with treatment, it was considered that a correlation between serum cytokine concentrations and skin lesions was established. All statistical analyses were Bonferroni-corrected. There was no significant correlation between the change in PASI score and the change in each cytokine level in week 4. In week 16, IL-6, IL-12, IL-17C, IL-21, IL-22, and TGF-β1 showed significant correlations. In week 24, IL-10, IL-12, IL-17F, IL-17C, IL-22, IL-36γ, and TGF-β1 were found to be significant. However, the correlations were not significant after Bonferroni correction due to the multiple comparisons in this analysis.

Correlations between serum cytokine levels and pruritus VAS scores at each time point. Correlations between the pruritus VAS score and serum cytokine levels are presented in Table SIV. In week 4, serum levels of IL-1β, IL-12, IL-17A, IL-18, IL-21, IFN-α, and TGF-β1 were positively correlated with the pruritus VAS score. In week 16, IL-17F, IL-17C, IL-22, and IL-36γ were positively correlated with the pruritus VAS score (Table SIV). In week 24, IL-6, IL-17A, IL-17F, IL-17C, IL-22, IL-23, and TNF-α were positively correlated with the pruritus VAS score. IL-35 was negatively correlated with the pruritus VAS score in week 24. However, there was no significant correlation between pruritus VAS and each serum cytokine concentration in week 0. One reason for this may be that this clinical study included individuals with severe psoriasis experiencing intense itching. Since the serum cytokine concentrations also decreased in those whose itch improved with treatment, it was considered that a correlation between serum cytokine concentrations and itch was established. All statistical analyses were Bonferroni-corrected. The IFN-α exhibited a significant correlation between the change in Pruritus VAS and the change in each cytokine in week 4. The only significant correlation in Week 16 was with IL-35. In week 24, no cytokines showed a significant correlation. However, the correlations were not significant after the Bonferroni correction because of the multiple comparisons in this analysis.

DISCUSSION

Several studies have analyzed serum cytokine levels before and after apremilast treatment. Garcet et al conducted pharmacodynamic substudies of ESTEEM 2 and PSOR-011 to analyze cytokine levels and investigate whether cytokine synergies may be used to predict the response to apremilast after 16 weeks in psoriasis patients (12). They concluded that reductions in IL-17A, IL-17F, IL-22, and TNF-α at week 4 are synergistic and predictive of the extent of PASI improvement at week 16. Similar results were obtained in the present study, showing a decrease in inflammatory cytokines and a delayed increase in suppressive cytokines after treatment with apremilast. Thus, apremilast might exert its effect by balancing the immune system.

It is widely known that psoriasis causes pruritus (13,14), and several studies have investigated cytokines associated with itching in psoriatic skin lesions. Nattkemper et al examined paired biopsies (non-itchy, non-lesional skin versus itchy, lesional skin) from individuals with atopic dermatitis, psoriasis, and healthy controls. Cytokines such as CCL4, CCL7, CCL8, CCL20, IL-19, IL-20, IL-26, IL-36A, IL-36γ, and TNF-α were found to be unique to psoriatic skin with pruritus (15). In the results of this study, pruritus was also significantly improved before and after apremilast treatment. IL-1β, IL-6, IL-17, IL-21, IL-36γ, and TNF-α, cytokines known to cause itch in psoriasis, were significantly improved shortly after treatment. It was suggested that apremilast may improve itching by decreasing these cytokines.

Although there have been many papers measuring serum cytokine concentrations in psoriasis patients, no studies have measured multiple cytokines simultaneously and longitudinally. This study is the first to track serum cytokine concentrations over time in psoriasis patients before and after apremilast treatment. The study revealed that apremilast reduced the concentrations of several serum inflammatory cytokines and increased levels of inhibitory cytokines. The limitation of this study is the small number of patients, all of whom were Japanese. Future studies are expected to be conducted in various ethnic groups and on a larger scale. We also hope that through this research, collaboration between medical and engineering fields will advance not only in Japan but also worldwide. We aim for the resolution of clinical, measurement, and research issues that are currently emerging.

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Ethics approval. This study complies with the Declaration of Helsinki. The whole study was approved by the ethics committee of the University of Tokyo Graduate School of Medicine. Written informed consent was obtained from all participants.

Data Availability Statement. The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author upon reasonable request.

Conflict of interest. TF and AY belong to the Social Cooperation Program, Department of Clinical Cannabinoid Research, supported by Japan Cosmetic Association and Japan Federation of Medium & Small Enterprise Organizations. Other authors have declared that no conflict of interest exists.

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