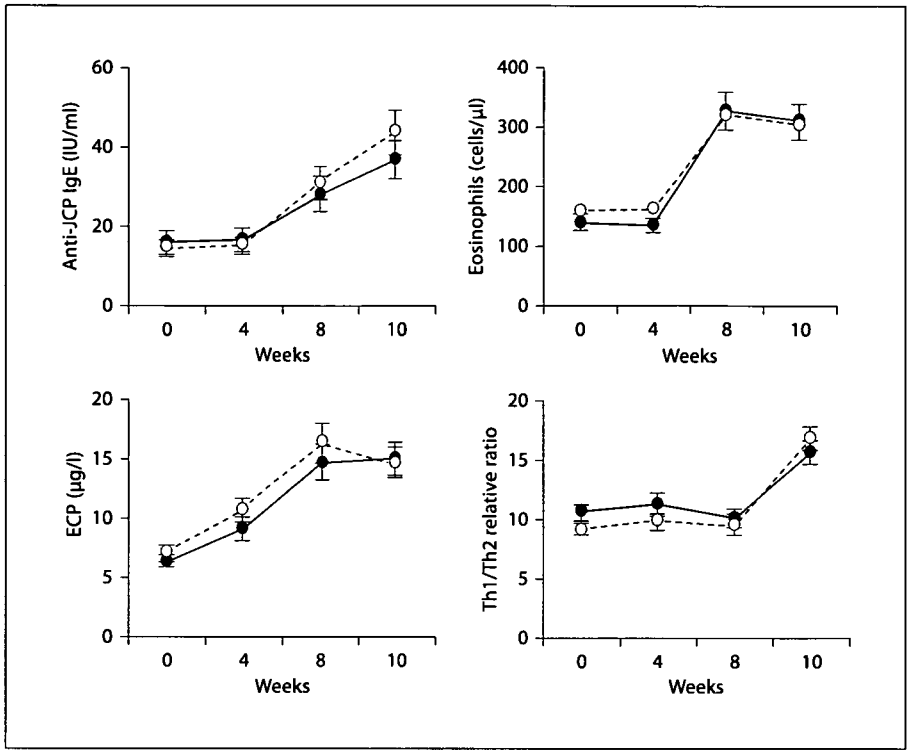

Fig. 4. Immunological parameters throughout the study period. Data are presented as means ± SE. ● = LcS group; ○ = placebo group.

Nasal and ocular SMS were not different between the LcS group and the placebo group. These results show that supplementation with fermented milk containing LcS during the JCP season does not prevent the exacerbation of seasonal allergic rhinitis. When the subjects were divided into two subgroups based on the severity of nasal symptom score before the start of ingestion, nasal SMS of the participants with moderate-to-severe nasal symptom scores was lower in the LcS group than in the placebo group at 4 weeks and 5 weeks, indicating that LcS may delay the onset of allergic symptoms in patients with a moderate-to-severe condition. In previous studies, we found that a daily drink of 80 ml of fermented milk containing LcS caused recovery of natural killer cell activity in humans [17–19]. Therefore, we considered that 80 ml of fermented milk containing LcS could be sufficient for modulating human immune function. However, it remains to be elucidated whether more than 80 ml may improve the results in placebo-controlled trials using participants with moderate-to-severe nasal symptoms in future investigations.

The clinical effects of probiotics on allergic rhinitis have been examined in several studies. Fermented milk containing *L. paracasei* LP-33 reduced the subjective symptoms in patients with perennial allergic rhinitis more efficiently than fermented milk containing *Streptococcus thermophilus* and *L. bulgaricus* [6]. Fermented milk containing *L. acidophilus* L-92 improved the subjective symptoms in not only perennial allergic rhinitis, but also Japanese cedar pollinosis, compared with heat-treated milk, although the immunological parameters were not different between the L-92 group and the placebo group [7, 8]. Furthermore, the clinical symptoms in Japanese cedar pollinosis were relieved in patients ingesting yogurt fermented with *B. longum* BB536, *S. thermophilus*, and *L. delbrueckii* compared with those ingesting yogurt fermented with *S. thermophilus* and *L. delbrueckii*, and the immunological parameters were modulated by *B. longum*-BB536-fermented yogurt [9]. These results suggest that some probiotic strains and/or their fermentation products are responsible for improvement of allergic rhinitis. In contrast, supplementation with capsules containing *L. rhamnosus* GG did not improve the clinical symptoms of birch-pollen-allergic patients [20]. Therefore, further investigation is required to elucidate the antiallergic effects of probiotics on allergic rhinitis. Viljanen et al. [21] have reported that administration of *L. rhamnosus* GG did not improve the clinical scores in infants with food allergy, but this probiotic was considered effective for the improvement of symptoms in the IgE-sensi-

tized subgroup. Our results also suggest that supplementation with LcS might delay the onset of allergic symptoms in subjects with moderate-to-severe symptom scores. Altogether, the effect of probiotics on allergic rhinitis may vary dependent on the disease condition.

The effects of probiotics to modulate immunological parameters associated with allergic symptoms should be elucidated. It was reported that LcS suppressed IgE production in vitro and reduced the antiovalbumin IgE level in wild-type mice and transgenic mice expressing ovalbumin-specific T-cell receptor [10–12]. However, no difference was detected in immunological parameters between the LcS group and the placebo group in this clinical trial. Probiotics may possibly improve subjective symptoms even if immunological parameters such as the allergen-specific IgE level or Th1/Th2 imbalance are not normalized. In that sense, it is of great interest that supplementation with *L. rhamnosus* 19070–2 and *L. reuteri* DSM stabilized the intestinal barrier function and decreased gastrointestinal symptoms in children with atopic dermatitis [22]. Moreover, involvement of natural killer T cells and regulatory T cells in the induction and control of allergic responses has been proposed [23, 24]. Therefore, other mechanisms besides suppression of IgE production or normalization of Th1/Th2 imbalance could be involved in the antiallergic activity exerted by probiotics in humans.

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References

1 Okuda M: Clinical Guidelines for Allergic Rhinitis in Japan, ed 4 (in Japanese). Establishment Committee of the Clinical Guidelines for Allergic Rhinitis. Tokyo, Life Science, 2002, pp 24–27.

2 Aldinucci C, Bellussi L, Monciatti G, Passali GC, Salerni L, Passali D, Bocci V: Effects of dietary yoghurt on immunological and clinical parameters of rhinopathic patients. Eur J Clin Nutr 2002;56:1155–1161.

3 Suzuki M, Yoshino K, Maeda-Yamamoto M, Miyase T, Sano M: Inhibitory effects of tea catechins and O-methylated derivatives of (–)-epigallocatechin-3-O-gallate on mouse type IV allergy. J Agric Food Chem 2000;48:5649–5653.

4 Osakabe N, Takano H, Sanbongi C, Yasuda A, Yanagisawa R, Inoue K, Yoshikawa T: Anti-inflammatory and anti-allergic effect of rosmarinic acid (RA): inhibition of seasonal allergic rhinoconjunctivitis (SAR) and its mechanism. Biofactors 2004;21:127–131.

5 Latchman Y, Banerjee P, Poulter LW, Rustin M, Brostoff J: Association of immunological changes with clinical efficacy in atopic eczema patients treated with traditional Chinese herbal therapy (Zemaphyte). Int Arch Allergy Immunol 1996;109:243–249.

6 Wang MF, Lin HC, Wang YY, Hsu CH: Treatment of perennial allergic rhinitis with lactic acid bacteria. Pediatr Allergy Immunol 2004;15:152–158.

7 Ishida Y, Nakamura F, Kanzato H, Sawada D, Hirata H, Nishimura A, Kajimoto O, Fujiwara S: Clinical effects of *Lactobacillus acidophilus* strain L-92 on perennial allergic rhinitis: a double-blind, placebo-controlled study. J Dairy Sci 2005;88:527–533.

8 Ishida Y, Nakamura F, Kanzato H, Sawada D, Yamamoto N, Kagata H, Oh-ida M, Takeuchi H, Fujiwara S: Effect of milk fermented with *Lactobacillus acidophilus* strain L-92 on symptoms of Japanese cedar pollen allergy: a randomized placebo-controlled trial. Biosci Biotechnol Biochem 2005;69:1652–1660.

9 Xiao JZ, Kondo S, Yanagisawa N, Takahashi N, Odamaki T, Iwabuchi N, Iwatsuki K, Kokubo S, Togashi H, Enomoto K, Enomoto T: Effect of probiotic *Bifidobacterium longum* BBS36 in relieving clinical symptoms and modulating plasma cytokine levels of Japanese cedar pollinosis during the pollen season: a randomized double-blind, placebo-controlled trial. J Invest Allergol Clin Immunol 2006;16:86–93.

10 Shida K, Makino K, Morishita A, Takamizawa K, Hachimura S, Ametani A, Sato T, Kumagai Y, Habu S, Kaminogawa S: *Lactobacillus casei* inhibits antigen-induced IgE secretion through regulation of cytokine production in murine splenocyte cultures. Int Arch Allergy Immunol 1998;115:278–287.

11 Matsuzaki T, Yamazaki R, Hashimoto S, Yokokura T: The effect of oral feeding of *Lactobacillus casei* strain Shirota on immunoglobulin E production in mice. J Dairy Sci 1998;81:48–53.

12 Shida K, Takahashi R, Iwadate E, Takamizawa K, Yasui H, Sato T, Habu S, Hachimura S, Kaminogawa S: *Lactobacillus casei* strain Shirota suppresses serum immunoglobulin E and immunoglobulin G1 responses and systemic anaphylaxis in a food allergy model. Clin Exp Allergy 2002;32:563–570.

13 Tanaka R: The effects of the ingestion of fermented milk with *Lactobacillus casei* Shirota on the gastrointestinal microbial ecology in healthy volunteers; in Leeds AR, Rowland IR (ed): Gut Flora and Health – Past, Present and Future. International Congress and Symposium Series No 219. London, Royal Society of Medicine Press, 1996, pp 37–45.

14 Spanhaak S, Havenaar R, Schaafsma G: The effect of consumption of milk fermented by *Lactobacillus casei* strain Shirota on the intestinal microflora and immune parameters in humans. Eur J Clin Nutr 1998;52:899–907.

15 Yuki N, Watanabe K, Mike A, Tagami Y, Tanaka R, Ohwaki M, Morotomi M: Survival of a probiotic, *Lactobacillus casei* strain Shirota, in the gastrointestinal tract: selective isolation from faeces and identification using monoclonal antibodies. Int J Food Microbiol 1999;48:51–57.

16 Okuda M: Grading the severity of allergic rhinitis for treatment strategy and drug study purposes. Curr Allergy Asthma Rep 2001;1:235–241

17 Nagao F, Nakayama M, Muto T, Okumura K: Effects of a fermented milk drink containing *Lactobacillus casei* strain Shirota on the immune system in healthy human subjects. Biosci Biotechnol Biochem 2000;64:2706–2708.

18 Morimoto K, Takeshita T, Nanno M, Tokudome S, Nakayama K: Modulation of natural killer cell activity by supplementation of fermented milk containing *Lactobacillus casei* in habitual smokers. Prev Med 2005;40:589–594.

19 Matsuzaki T, Saito M, Usuku K, Nose H, Izumo S, Arimura K, Osame M: A prospective uncontrolled trial of fermented milk drink containing viable *Lactobacillus casei* strain Shirota in the treatment of HTLV-1 associated myelopathy/tropical spastic paraparesis. J Neurol Sci 2005;237:75–81.
20 Helin T, Haahtela S, Haahtela T: No effect of oral treatment with an intestinal bacterial strain, *Lactobacillus rhamnosus* (ATCC 53103), on birch-pollen allergy: a placebo-controlled double-blind study. Allergy 2002; 57:243–246.
21 Viljanen M, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Kuitunen M: Probiotics in the treatment of atopic eczema/dermatitis syndrome in infants: a double-blind placebo-controlled trial. Allergy 2005;60:494–500.
22 Rosenfeldt V, Benfeldt E, Valerius NH, Paerregaard A, Michaelsen KF: Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. J Pediatr 2004;145:612–616.
23 Lisbonne M, Diem S, de Castro Keller A, Lefort J, Araujo LM, Hachem P, Fourneau JM, Sidobre S, Kronenberg M, Taniguchi M, Van Endert P, Dy M, Askenase P, Russo M, Vargaftig BB, Herbelin A, Leite-de-Moraes MC: Invariant V alpha 14 NKT cells are required for allergen-induced airway inflammation and hyperreactivity in an experimental asthma model. J Immunol 2003;171: 1637–1641.
24 Ling EM, Smith T, Nguyen XD, Pridgeon C, Dallman M, Arbery J, Carr VA, Robinson DS: Relation of CD4+CD25+ regulatory T-cell suppression of allergen-driven T-cell activation to atopic status and expression of allergic disease. Lancet 2004;363:608–615.