

Effects of Oral Administration of *Lactobacillus acidophilus* L-92 on the Symptoms and Serum Cytokines of Atopic Dermatitis in Japanese Adults: A Double-Blind, Randomized, Clinical Trial

Yusuke Inoue^a Takeshi Kambara^b Naoko Murata^a Junko Komori-Yamaguchi^a
Setsuko Matsukura^b Yukitoshi Takahashi^c Zenro Ikezawa^a Michiko Aihara^a

^aDepartment of Environmental Immuno-Dermatology, Yokohama City University Graduate School of Medicine, and

^bDepartment of Dermatology, Yokohama City University Medical Center, Yokohama, and ^cNational Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka, Japan

Key Words

Atopic dermatitis · *Lactobacillus acidophilus* L-92 · Cytokine levels

Abstract

Objectives: Several studies on lactobacilli have demonstrated they are effective against atopic dermatitis (AD) in children, but there are very few reports of their effects in adults. We investigated the changes in AD symptoms in adults after the ingestion of the *Lactobacillus acidophilus* strain L-92 (L-92), which has been shown to have a curative effect on AD in children. **Methods:** A double-blind, parallel-group, placebo-controlled comparison was performed on 49 AD patients aged ≥ 16 years using heat-killed L-92. Skin lesions were assessed using the SCORing AD (SCORAD) index before the start of L-92 ingestion and 4 and 8 weeks after ingestion. Serum cytokine and blood marker levels were measured 8 weeks after the start of L-92 ingestion. **Results:** The group that ingested L-92 had lower SCORAD scores than the controls ($p = 0.002$). The L-92 group also had decreased ratios of change for eosinophil count ($p = 0.03$) and increased ratios

of change for serum TGF- β ($p = 0.03$). Ratios of change for serum TGF- β rose significantly ($p = 0.04$) in patients showing mitigated symptoms with L-92 administration. **Conclusions:** Administration of heat-killed L-92 was effective for AD symptoms in adults. L-92 may contribute to the suppression of Th2-dominant inflammation. Our preliminary trial is the first to report the effects of L-92 on adult AD.

© 2015 S. Karger AG, Basel

Introduction

Atopic dermatitis (AD) is a chronically relapsing inflammatory skin disease with allergic and immunological abnormalities, including increased serum IgE levels. Various factors are involved in the onset of AD, such as a genetic predisposition that causes a poor skin barrier [1] and sustained antigen ingress through defective barriers, leading to Th2-dominant inflammation. Various environmental factors also contribute to the development of AD. Kalliomäki et al. [2] were first to show the effects of probiotics separated from enteric microflora on lowering

the incidence of AD. It has been reported that intestinal inflammatory reactions and disruptions in intestinal barrier function are involved in the pathogenesis of AD [3]. Betsi et al. [4] suggested that changing the pattern of intestinal colony formation in infants would affect the immune system and mitigate future AD symptoms; however, this has not been fully elucidated. Although there have been some clinical studies, including intervention studies on probiotics in AD patients, the curative effects remain a topic of controversy [5].

Several probiotics have been reported to have certain antiallergic effects in humans, for example, *Lactobacillus acidophilus* [6–9], *L. plantarum* [10], *L. rhamnosus* GG (LGG) [11, 12] and *L. casei* [13]. However, based on a once-yearly follow-up cohort study on children up to the age of 5 years, Loo et al. [14] found that the early use of probiotics had no significant effect on eczema, asthma, allergic rhinitis, food allergy or sensitization to dust-mite allergens.

The most studied probiotics, in terms of treating and preventing allergic diseases, belong to the genera *Lactobacillus* and *Bifidobacterium*. Effective probiotics are believed to have immunoregulatory properties and mediate immunomodulation [15]. In addition, the immunoregulatory materials produced by the probiotics, including the bacterial cells themselves, even when heat-killed, have immunoregulatory potential [6].

Several studies have indicated that *L. acidophilus* strain L-92 (L-92) has immunoregulatory properties. L-92 has been reported to mitigate the symptoms of Japanese cedar pollen allergy [16] and perennial allergic rhinitis and to improve blood test scores [17].

There have been only a few clinical studies on probiotic administration in Japanese AD patients. It has been reported that administration of L-92 to children (aged 1–12 years) ameliorated the severity of AD and decreased levels of serum thymus and activation-regulated chemokine (TARC) and Th2 cytokine in 8 weeks [12]. The effect of L-92 administration on adults with AD has not been reported, so we examined whether administration of this strain mitigates the symptoms of AD in adults and investigated how it affects serum cytokine levels.

Materials and Methods

Forty-nine patients with AD (28 males and 21 females), aged ≥16 years, were enrolled in the study. A randomized, double-blind, placebo-controlled comparison was performed using age- and sex-matched groups. Patients were randomly allocated to the L-92 administration group (n = 24) and the placebo group (n = 25), respectively, and the physician and patients were blinded to this al-

Table 1. Clinical characteristics of the L-92 and placebo groups

	L-92 group	Placebo group
Participants, n	24	25
Age, years (mean ± SD)	29.6±13.8	29.7±14.5
Male/female	14/10	14/11
SCORAD score	46.95 (75.5–29.5)	39.50 (74.2–12.0)
TARC, pg/ml	2,310 (14,220–160)	1,283 (2,921–226)
LDH, IU/l	239.5 (472–143)	213 (767–131)
Eosinophils, n/μl	475 (1,902–114)	425 (4,510–31)
Total IgE, IU/ml	10,060 (33,522–806)	5,977 (22,820–2)

Figures are expressed as medians with minimum and maximum values in parentheses, unless indicated otherwise.

location. Patient characteristics are listed in table 1. Distribution of age and sex were well-balanced between the 2 groups. All patients had been treated with topical corticosteroid ointment (strong/very strong-class steroids for the body including the extremities and mild-class steroids for the face and neck) with moisturizer and one or two oral antihistamines, according to the guidelines for the management of AD [18]. These treatments were continued during the entire study period (and for 2 more weeks without changes).

L-92 was administered as 20.7 mg/day in tablet form for 8 weeks. Placebo tablets contained maltose, starch, vegetable oil and fat. Heat-killed and dried L-92 powder was included in the L-92 tablets. Written informed consent was obtained from all patients.

Assessment of Clinical Conditions

All patients were evaluated by experienced dermatologists for the general severity of their AD using the SCORing AD (SCORAD) index [19] before intervention and after 4 and 8 weeks. SCORAD scores are the total of the severity and extent of eczema and subjective symptoms on pruritus and insomnia. We also evaluated the number of eosinophils in the peripheral blood and the levels of serum IgE, lactate dehydrogenase (LDH) and TARC, in order to reflect AD progression.

Cytokine Detection

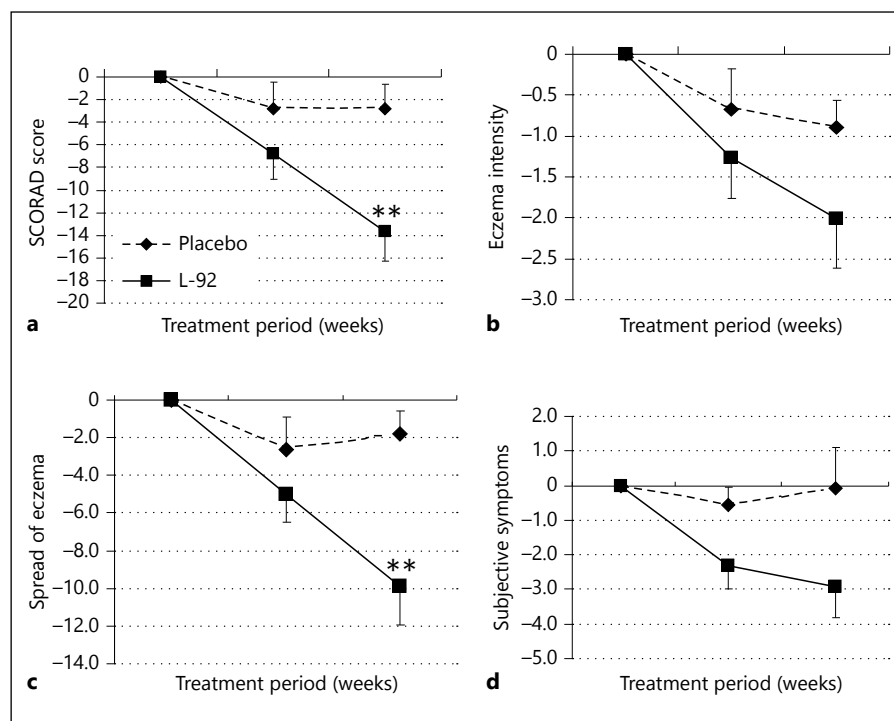
Several cytokines were also measured before and after 8 weeks of intervention, because they had been reported to relate to the pathogenesis of AD [20, 21].

Venous blood samples (5–10 ml) were taken from patients using vacutainer tubes under sterile conditions. Serum was obtained from freshly drawn, rapidly centrifuged samples. It was quickly frozen at –80°C and stored until required.

The Bio-Plex Pro Human Cytokine 27-plex assay (M50-0KCAF0Y; Bio-Rad, Hercules, Calif., USA) was used according to the manufacturer's instructions to evaluate the concentrations of IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p70, IL-13, IL-17, eotaxin/CCL1 and interferon-γ (IFN-γ).

IL-18 levels were measured using the human IL-18 ELISA kit (MBL, Nagoya, Japan). Transforming growth factor-β (TGF-β)

Fig. 1. Comparison of changes in SCORAD (a), intensity of eczema (b), spread of eczema (c) and subjective symptoms (d) between the L-92-administered group and the placebo group before treatment and at 4 and 8 weeks after treatment. Data was analyzed using the Mann-Whitney U test. * $p < 0.05$ and ** $p < 0.01$ were statistically significant.



levels were measured using the LEGEND Free Active TGF- β 1 kit (BioLegend, San Diego, Calif., USA). These assays detected only human cytokines.

Statistics

Statistical significance was determined using the Mann-Whitney U test and accepted as $p < 0.05$. Statistical analysis was performed using SPSS version 17.0 (SPSS Inc., Chicago, Ill., USA).

Results

Comparison of Changes in SCORAD Score and Blood Marker Levels between the L-92 and Placebo Groups

We compared the changes in SCORAD scores between the L-92 and placebo groups. Seventeen patients (70.8%) showed an improvement in the L-92 group and 11 patients (44%) showed an improvement in the placebo group. The SCORAD scores were significantly reduced in the L-92 group compared with the placebo group ($p < 0.01$; fig. 1a). Each component of SCORAD was significantly decreased in the L-92 group in comparison with the placebo group ($p < 0.01$; fig. 1c).

Changes in blood marker levels were also compared: the eosinophil count was significantly lower in the L-92 group than in the placebo group whereas for serum IgE,

LDH and TARC levels, there were no significant differences between the groups (fig. 2).

No abnormal clinical changes were noted in any of the patients during the study.

Comparison of Changes in Serum Cytokine Levels between the L-92 and Placebo Groups

Serum cytokine levels before intervention in each group are shown in table 2. To clarify the change in cytokine levels in each patient, we calculated the ratio of changes in serum cytokine levels after 8 weeks intervention, and then compared these ratios between the L-92 and placebo groups. TGF- β was significantly increased in the L-92 group compared with the placebo group ($p = 0.03$) and IL-12p70 also tended to be increased ($p = 0.06$), but no other cytokines showed significant differences (fig. 3).

Comparison of Changes in Serum Cytokine Levels between Improved and Nonimproved Patients with L-92 Administration

To clarify the effects of L-92 on mitigated symptoms relating to cytokine production, serum cytokine levels were compared between the improved patients and non-improved patients in the L-92 group, i.e. 17 vs. 7 patients. Significantly greater changes were found in the TGF- β of

Fig. 2. Comparison of changes in laboratory parameters between the L-92-administered group and the placebo group. Ratios of change are shown for blood eosinophil counts (a) and levels of serum IgE (b), LDH (c) and TARC (d) in both groups. Data were analyzed using the Mann-Whitney U test. * $p < 0.05$ was statistically significant.

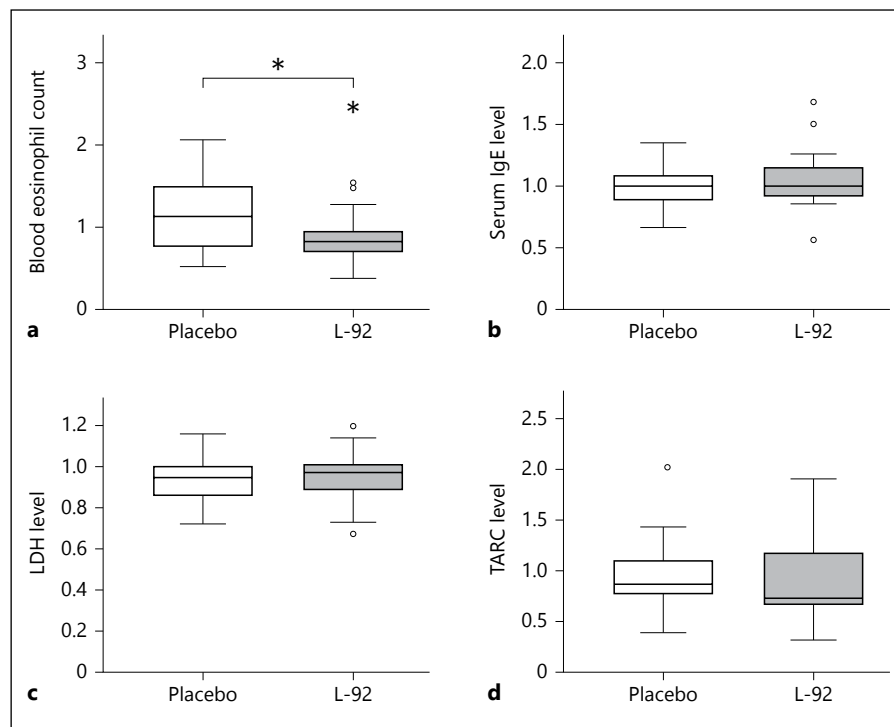


Table 2. Serum cytokine levels (pg/ml) before the administration of L-92 and placebo

Cytokine	Median		Range	
	placebo	L-92	placebo	L-92
IL-4	5.55	4.87	3.87–8.88	3.30–7.65
IL-5	3.01	3.02	1.33–6.60	1.13–5.85
IL-6	9.73	7.53	5.11–144.22	4.54–19.11
IL-10	8.63	8.76	0.76–37.79	3.01–19.74
IL-12p70	29.04	29.49	10.61–221.25	11.39–75.81
IL-13	9.14	8.56	4.82–33.32	4.59–15.52
IL-17	91.15	87.81	0.99–183.93	3.03–269.62
IL-18	108.57	141.69	63.10–178.56	77.18–278.78
Eotaxin	80.45	67.18	14.38–235.62	25.37–158.37
IFN- γ	155.76	140.39	107.76–299.34	109.76–262.93
TNF- α	34.82	28.93	18.88–99.10	13.31–87.20
TGF- β	210.48	178.10	30.77–345.71	9.47–465.91

improved patients compared with nonimproved patients ($p = 0.04$; fig. 4).

Other cytokines measured showed no significant differences between these groups. In addition, a comparison between improved and nonimproved patients in the placebo group showed no significant differences in any of the cytokines (data not shown).

Discussion

In this study, we investigated the supportive effects of L-92 on the symptoms of AD in adults by means of a double-blind, parallel-group, placebo-controlled study using heat-killed L-92 tablets and a placebo. Serum cytokine levels were measured in both groups to study the mechanism of effectiveness of L-92 administration. Administration of L-92 improved cutaneous symptoms and decreased eosinophil count (fig. 1, 2) in association with changes in the cytokine profile (fig. 3, 4). In our study, L-92 did not adversely affect the health of any patients.

In another parallel-group, placebo-controlled comparison, the administration of sterilized milk fermented with L-92 significantly improved the nasal symptoms of Japanese cedar pollinosis patients in 6–10 weeks [16]. In another such comparison of 49 allergic rhinitis patients, 8-week administration of sterilized milk fermented with L-92 significantly improved the scores for rhinitis symptoms (sneezing, runny nose, stuffy nose, itchy eyes and watery eyes) and blood marker levels (total IgE, mite-specific IgE, house dust IgE, Th1/Th2 ratio and eosinophil count) [17]. Various studies on the effects of probiotics on AD in children have been reported. Torii et al. [7] investigated the effects of 8 weeks of

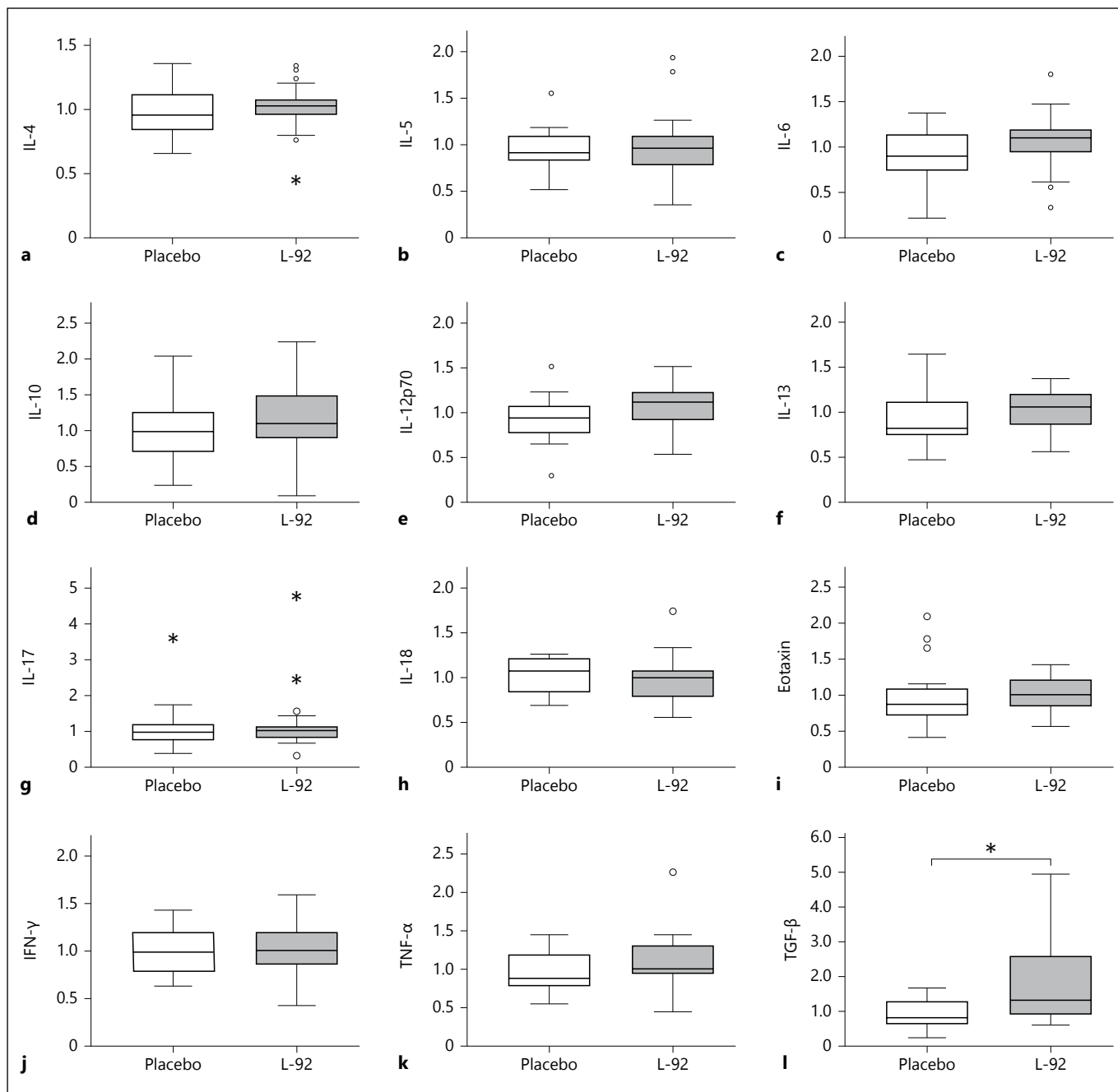


Fig. 3. Comparison of changes in serum cytokine levels between the L-92-administered group and the placebo group. Rates of change are shown for IL-4 (a), IL-5 (b), IL-6 (c), IL-10 (d), IL-12p70 (e),

IL-13 (f), IL-17 (g), IL-18 (h), eotaxin (i), IFN-γ (j), TNF-α (k) and TGF-β levels (l) in both groups. Data were analyzed using the Mann-Whitney U test. * p < 0.05 was statistically significant.

administration of L-92 to Japanese children. One study reported that 8-week administration of LGG to 102 infants with AD showed no significant lowering of SCORAD scores [22] and 6-month administration of *L. acidophilus* to 231 babies whose mothers had allergic

symptoms resulted in no significant difference in the onset of AD when compared to a placebo group [23]. In addition, administration of LGG to 59 infants over a period of 12 weeks did not lower the SCORAD scores significantly when compared to the placebo group, al-

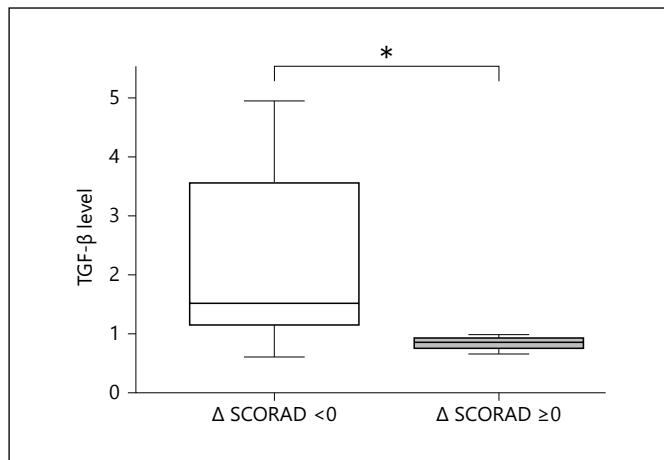


Fig. 4. Comparison of changes in serum cytokine levels between patients with improved and nonimproved SCORAD scores in the L-92-administered group. Ratios of change are shown for TGF- β levels. Data were analyzed using the Mann-Whitney U test. * $p < 0.05$ was statistically significant.

though it did improve the scores in those with food allergies [11].

The mechanism of the apparent anti-inflammatory impact of probiotic organisms is unclear: some studies suggest that they act on human intestinal epithelial cells, affecting intracellular signal transduction and promoting the secretion of TGF- β , IL-8 and prostaglandin E2 [24]. Studies using humans and mice indicated that probiotics and their products are engulfed by M cells in Peyer's patches, the major immunoregulatory tissue in the intestinal epithelium, and are presented to immunocompetent cells. Dendrocytes receive the presented information and induce the differentiation and maturation of undifferentiated and immature T cells. Macrophages also receive information from the M cells and can regulate IFN- γ , IL-4 and IL-5 production as well as affect the functional differentiation of Th cells [19]. It is likely that IFN- γ , TGF- β and IL-10 signals induced by probiotics induce T cells to differentiate and mature properly, prevent allergic inflammation and lead to oral desensitization to foods [19].

L-92 induces apoptosis in mice Th1 and Th2 cells upon antigen stimulation in vitro. L-92 regulates B7-H1 and B7-H2 production by dendrocytes and induces apoptosis of these cells [21]. Oral administration of L-92 to ovalbumin (OVA)-sensitized DO11.10 mice, i.e. transgenic mice overexpressing T cells that react specifically to OVA, increased the CD4+T cell apoptosis of Th2 cells [25]. Consecutive administration of heat-killed

L-92 to OVA-sensitized mice lowered IgE levels and reduced IFN- γ , IL-4, IL-10 and IgE production in the splenocytes and Peyer's patches. Induced production of TGF- β and IgA was observed in the Peyer's patches, suggesting that L-92 induces the differentiation of naive T cells into regulatory T (Treg) cells via TGF- β [6]. Oral administration of L-92 to mice that developed contact dermatitis on the ears after application of dinitrofluorobenzene was found to increase the ratio of Foxp3+CD4+CD25+ cells in the cervical lymph nodes and spleen, and was reported to increase Foxp3, IL-10 and TGF- β mRNA expression in the ear tissue [26]. It has been reported that TGF- β induces Foxp3+ Treg cells in peripheral blood mononuclear cells (PBMCs) [27]. Recently, oral administration of a mixture of 5 probiotic strains (*L. acidophilus*, *L. casei*, *L. reuteri*, *Bifidobacterium bifidum* and *Streptococcus thermophilus*) was reported to increase levels of IL-10 and TGF- β , suppress the differentiation of Th2 and Th17 cells and promote the differentiation of CD4+Foxp3+Treg cells in mice [28]. Furthermore, when milk fermented by various species and strains of lactic acid bacteria was administered to OVA-sensitized mice, L-92 was found to strongly suppress IgE production [29]. It was also reported that mice treated by oral administration of heat-killed L-92 exhibited lower levels of mast cells, eosinophil infiltration and Th1/Th2 cytokine expression and the L-92 acted as an antiallergic agent in vivo [30]. L-92 also showed a higher enteron recovery rate than other species and strains and became more strongly established [27]. These results indicate that oral administration of L-92 might clinically be more useful than other species and strains of lactic acid bacteria.

In humans, it has been reported that the administration of *L. acidophilus* induces Foxp3+ Treg cells in PBMCs [24, 25]. These findings strongly suggest that some *Lactobacillus* species also stimulate Treg induction in humans. It is also suggested that, in humans, this induction by some species of *Lactobacillus* is via a signaling pathway mediated by dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN) [31]. Studies on both mice and humans suggest that L-92 may induce Treg cells via TGF- β to induce Th1 predominant conditions in vivo.

In this study on adult AD patients, the increases in TGF- β were significantly higher in the L-92 group and IL-12p70 also tended to increase when compared with the placebo group (fig. 3). Our results are consistent with a recent report that L-92 acts on human intestinal cells via protein A and promotes the release of IL-12 [32].

When L-92 cells were cultured at a low pH, the release of IL-12, IFN- γ and IL-10 was increased, but IL-4 release was decreased from splenocytes in mice [33].

The results of L-92 administration on adult AD suggest an activation of Th1 or/and Treg cells. The improvement in AD patients by ingestion of L-92 might be, at least partly, due to the promoted differentiation of PBMCs into Th1 and/or Treg cells, and the resulting suppression of Th2 differentiation.

In conclusion, our preliminary trial is the first report demonstrating that L-92 is effective against AD in adults. No serious side effects were observed in any of the patients. We suggest that L-92 could be used as a food supplement to reduce the dose of steroidal anti-inflammatory

ointments required for atopic treatment. However, further studies with different strains of *Lactobacillus* are necessary to confirm its beneficial role in AD and to clarify the immunological mechanisms.

Acknowledgments

We thank the participating patients for their understanding and acceptance of the purpose of this study, the dermatologists for their assistance with assessments of the clinical condition of the AD patients and Assistant Prof. Mari Oba, PhD (Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan) for assistance with the statistical analysis.

References

- ▶ 1 Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, Goudie DR, Sandilands A, Campbell LE, Smith FJ, O'Regan GM, Watson RM, Cecil JE, Bale SJ, Compton JG, DiGiovanna JJ, Fleckman P, Lewis-Jones S, Arseculeratne G, Sergeant A, Munro CS, El Houate B, McElreavey K, Halkjaer LB, Bisgaard H, Mukhopadhyay S, McLean WH: Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006;38:441–446.
- ▶ 2 Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E: Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. *Lancet* 2001;357:1076–1079.
- ▶ 3 Caffarelli C, Cavagni G, Deriu FM, Zanotti P, Atherton DJ: Gastrointestinal symptoms in atopic eczema. *Arch Dis Child* 1998;78:230.
- ▶ 4 Betsi GI, Papadavid E, Falagas ME: Probiotics for the treatment or prevention of atopic dermatitis: a review of the evidence from randomized controlled trials. *Am J Clin Dermatol* 2008;9:93–103.
- ▶ 5 Brouwer ML, Wolt-Plompen SA, Dubois AE, van der Heide S, Jansen DF, Hoijer MA, Kauffman HF, Duiverman EJ: No effects of probiotics on atopic dermatitis in infancy: a randomized placebo-controlled trial. *Clin Exp Allergy* 2006;36:899–906.
- ▶ 6 Torii A, Torii S, Fujiwara S, Tanaka H, Inagaki N, Nagai H: *Lactobacillus acidophilus* strain L-92 regulates the production of Th1 cytokine as well as Th2 cytokines. *Allergol Int* 2007;56:293–301.
- ▶ 7 Torii S, Torii A, Itoh K, Urisu A, Terada A, Fujisawa T, Yamada K, Suzuki H, Ishida Y, Nakamura F, Kanzato H, Sawada D, Nonaka A, Hatanaka M, Fujiwara S: Effects of oral administration of *Lactobacillus acidophilus* L-92 on the symptoms and serum markers of atopic dermatitis in children. *Int Arch Allergy Immunol* 2011;154:236–245.
- ▶ 8 de Roock S, van Elk M, van Dijk ME, Timmerman HM, Rijkers GT, Prakken BJ, Hoekstra MO, de Kleer IM: Lactic acid bacteria differ in their ability to induce functional regulatory T cells in humans. *Clin Exp Allergy* 2010;40:103–110.
- ▶ 9 Sudo N, Yu XN, Aiba Y, Oyama N, Sonoda J, Koga Y, Kubo C: An oral introduction of intestinal bacteria prevents the development of a long-term Th2-skewed immunological memory induced by neonatal antibiotic treatment in mice. *Clin Exp Allergy* 2002;32:1112–1116.
- ▶ 10 Yoshida T, Fujiwara W, Enomoto M, Nakayama S, Matsuda H, Sugiyama H, Shimojoh M, Okada S, Hattori M: An increased number of CD4+ CD25+ cells induced by an oral administration of *Lactobacillus plantarum* NRIC 0380 are involved in antiallergic activity. *Int Arch Allergy Immunol* 2013;162:283–289.
- ▶ 11 Sistik D, Kelly R, Wickens K, Stanley T, Fitzharris P, Crane J: Is the effect of probiotics on atopic dermatitis confined to food sensitized children? *Clin Exp Allergy* 2006;36:629–633.
- ▶ 12 Ou CY, Kuo HC, Wang L, Hsu TY, Chuang H, Liu CA, Chang JC, Yu HR, Yang KD: Prenatal and postnatal probiotics reduces maternal but not childhood allergic diseases: a randomized, double-blind, placebo-controlled trial. *Clin Exp Allergy* 2012;42:1386–1396.
- ▶ 13 Chiba Y, Shida K, Nagata S, Wada M, Bian L, Wang C, Shimizu T, Yamashiro Y, Kiyoshima-Shibata J, Nanno M, Nomoto K: Well-controlled proinflammatory cytokine responses of Peyer's patch cells to probiotic *Lactobacillus casei*. *Immunology* 2010;130:352–362.
- ▶ 14 Loo EX, Llanora GV, Lu Q, Aw MM, Lee BW, Shek LP: Supplementation with probiotics in the first 6 months of life did not protect against eczema and allergy in at-risk Asian infants: a 5-year follow-up. *Int Arch Allergy Immunol* 2014;163:25–28.
- ▶ 15 Yan F, Polk DB: Probiotics and immune health. *Curr Opin Gastroenterol* 2011;27:496–501.
- ▶ 16 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.
- ▶ 17 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.
- ▶ 18 Saeki H, Furue M, Furukawa F, et al: Guidelines for management of atopic dermatitis. *J Dermatol* 2009;36:563–577.
- ▶ 19 Kunz B, Oranje AP, Labre'ze L, et al: Clinical validation and guidelines for the SCORAD index: consensus report of the European Task Force on atopic dermatitis. *Dermatology* 1997;195:10–19.
- ▶ 20 Schäkel K, Döbel T, Bosselmann I: Future treatment options for atopic dermatitis – small molecules and beyond. *J Dermatol Sci* 2014;73:91–100.
- ▶ 21 Mjösberg J, Eidsmo L: Update on innate lymphoid cells in atopic and non-atopic inflammation in the airways and skin. *Clin Exp Allergy* 2014;44:1033–1043.
- ▶ 22 Taylor AL, Dunstan JA, Prescott SL: Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007;119:184–191.

- ▶ 23 Fölster-Holst R, Müller F, Schnopp N, Abeck D, Kreiselmaier I, Lenz T, von Rügen U, Schrezenmeir J, Christophers E, Weichenthal M: Prospective, randomized controlled trial on *Lactobacillus rhamnosus* in infants with moderate to severe atopic dermatitis. *Br J Dermatol* 2006;155:1256–1261.
- ▶ 24 Corthésy B, Gaskins HR, Mercenier A: Cross-talk between probiotic bacteria and the host immune system. *J Nutr* 2007;137(3 suppl 2): 781S–790S.
- ▶ 25 Kanzato H, Fujiwara S, Ise W, Kaminogawa S, Sato R, Hachimura S: *Lactobacillus acidophilus* strain L-92 induces apoptosis of antigen-stimulated T cells by modulating dendritic cell function. *Immunobiology* 2008;213:399–408.
- ▶ 26 Shah MM, Saio M, Yamashita H, Tanaka H, Takami T, Ezaki T, Inagaki N: *Lactobacillus acidophilus* strain L-92 induces CD4(+) CD25(+)Foxp3(+) regulatory T cells and suppresses allergic contact dermatitis. *Biol Pharm Bull* 2012;35:612–616.
- ▶ 27 Chen W, Jin W, Hardegen N, Lei KJ, Li L, Marinos N, McGrady G, Wahl SM: Conversion of peripheral CD4+CD25– naive T cells to CD4+CD25+ regulatory T cells by TGF-beta induction of transcription factor Foxp3. *J Exp Med* 2003;198:1875–1886.
- ▶ 28 Kwon HK, Lee CG, So JS, Chae CS, Hwang JS, Sahoo A, Nam JH, Rhee JH, Hwang KC, Im SH: Generation of regulatory dendritic cells and CD4+Foxp3+ T cells by probiotics administration suppresses immune disorders. *Proc Natl Acad Sci U S A* 2010;107:2159–2164.
- ▶ 29 Ishida Y, Bandou I, Kanzato H, Yamamoto N: Decrease in ovalbumin specific IgE of mice serum after oral uptake of lactic acid bacteria. *Biosci Biotechnol Biochem* 2003;67:951–957.
- ▶ 30 Shah MM, Miyamoto Y, Yamada Y, Yamashita H, Tanaka H, Ezaki T, Nagai H, Inagaki N: Orally supplemented *Lactobacillus acidophilus* strain L-92 inhibits passive and active cutaneous anaphylaxis as well as 2,4-dinitrofluorobenzene and mite fecal antigen induced atopic dermatitis-like skin lesions in mice. *Microbiol Immunol* 2010;54:523–533.
- ▶ 31 Smits HH, Engering A, van der Kleij D, de Jong EC, Schipper K, van Capel TM, Zaat BA, Yazdanbakhsh M, Wierenga EA, van Kooyk Y, Kapsenberg ML: Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intracellular adhesion molecule 3-grabbing nonintegrin. *J Allergy Clin Immunol* 2005; 115:1260–1267.
- ▶ 32 Ashida N, Yanagihara S, Shinoda T, Yamamoto N: Characterization of adhesive molecule with affinity to Caco-2 cells in *Lactobacillus acidophilus* by proteome analysis. *J Biosci Bioeng* 2011;112:333–337.
- ▶ 33 Kuwana R, Yamamoto N: Increases in GroES and GroEL from *Lactobacillus acidophilus* L-92 in response to a decrease in medium pH, and changes in cytokine release from splenocytes: transcriptome and proteome analyses. *J Biosci Bioeng* 2012;114:9–16.