

Editorial

Probiotics against allergy: data, doubts, and perspectives

P. M. Matricardi

CNR – IneMM, Section of Immunology, Viale Marx 15/
43–00137 Rome, Italy

Strategies for a primary prevention of atopy

The epidemic of allergic diseases has made their prevention in at-risk infants a public health priority. Allergen-specific approaches have been proposed, including avoidance of the offending food and of indoor allergens (1, 2) or, more recently, active immunoprophylaxis (3), which is generating great expectations (4). The complementary concept of prevention based on allergen-nonspecific approaches arose from data linking the allergy epidemic to hygiene (5, 6) and suggesting that exposure to certain infections can prevent IgE sensitization to allergens (7) and inflammation triggered by allergen–IgE interactions (8). Properly conditioned by microbial antigens typical of a traditional lifestyle, the innate immune system would progressively ‘teach’ the adaptive immune system to interact safely with nonmicrobial antigens that possess allergenic properties (‘immunoeducation’) (9). Consequently, IgE sensitization might be prevented by the administration of appropriate microbes or their substances rather than by forsaking a hygienic lifestyle (10). Unfortunately, this wishful concept is not simple to apply. Indeed, a scientific approach to the use of microbes in the prevention of IgE sensitization requires profound knowledge of how the newborn’s immune response to allergens matures during exposure to an extremely complex microbial world (9). To this end, carefully designed, longitudinal studies in humans are needed to gain more insight into the role of commensals and pathogens in the development of IgE sensitization (11). Prevention or therapy of allergy by administration of microbial products originally licensed with other indications may be considered just an empiric shortcut.

Trials of probiotics in allergy prevention and therapy

The meaning of the term “probiotic” changes over time (12), but a widely accepted definition is ‘a live microbial feed supplement which beneficially affects the host

(animal) by improving its microbial balance’ (13). Classic examples are the lactic acid bacteria *Lactobacilli* and *Bifidobacteria*, which are also normal components of human intestinal microflora (13). Probiotics have been so far proposed as treatments for an astonishingly long and diversified list of diseases, including diarrheal disorders, constipation, inflammatory bowel diseases, respiratory disease, colon cancer, lactase deficiency, atherosclerosis, and osteoporosis; they were also reported to stimulate the immune system, increase absorption of minerals and vitamins, reduce catabolic products eliminated by kidney and liver, improve growth and well-being (13–15).

Last, probiotic preparations have also been proposed to treat allergic diseases (16). A rationale for such use was identified, *a posteriori*, in epidemiological data suggesting that changes in the gut microbial flora might underlay the epidemic trend of allergy (11, 17, 18) and in several *in vitro* and *in vivo* studies reporting that probiotics can exert a wide array of immune effects, some of them potentially contrasting those characteristic of the atopic constitution (14, 19). The first double-blind placebo-controlled (DBPC) trial appeared in 1997 (20). *Lactobacillus GG* (LGG) was administered to breastfeeding mothers of 10 infants with atopic eczema/dermatitis syndrome [AEDS (21)] due to allergy to milk, and hydrolyzed milk-formula containing LGG was given to 15 bottle-fed infants with AEDS; 16 controls received placebo. After one month of treatment eczema had improved significantly and indirect markers of intestinal inflammation were reduced in treated infants compared with children who did not receive LGG. It was concluded that probiotic bacteria may be effective in the treatment of food allergy, possibly by promoting endogenous barrier mechanisms and by alleviating intestinal inflammation (20). However, no evidence was shown that LGG given *per os* to mothers or to infants really created differences in the intestinal concentration of *Lactobacillus* spp. of treated infants compared with control infants: actually, data on *Lactobacillus* spp. in

stool samples before treatment were omitted, and those at the end of the study period were given only in 'treated' infants but not in controls (20). Finally, the median SCORAD value was similar (15 in treated infants, 19 in controls) after one month of treatment, and was even slightly higher in treated than in controls (16 vs 14) one month after the end of treatment (20).

The same group recently tested the hypothesis that LGG may be useful in preventing allergic diseases if administered at birth and to pregnant mothers (22). A DBPC trial was conducted in 132 Finnish children at high risk of what is referred to as 'atopic eczema'; LGG was given daily prenatally to all the mothers of treated infants ($n=64$) in the 2–4 weeks before the expected delivery. The treated group was constituted by 36 bottle-fed infants receiving LGG *per os* during the first six months of life and 28 breast-fed infants who received LGG only prenatally. Controls and their mothers ($n=68$) assumed placebo with the same procedure. 'Atopic eczema' was diagnosed at 12 months of age in 15/64 (23%) treated children vs 31/68 (46%) controls. The authors concluded that *Lactobacillus* GG was effective in preventing early 'atopic disease' in children at high risk (22). A crucial point is that comparative data on colonization by *Lactobacilli* in 'treated' or control infants were neither given in this study, nor in the reference provided (i.e., the study already discussed (20)). Interestingly, treated and control infants had similar total and specific IgE levels and skin test responses, so the reduced rate of eczema among treated infants can be hardly explained on the basis of the TH1/TH2 paradigm, and it was proposed to arise from stimulation of the anti-inflammatory network through TH3 and T regulator 1 cells (23).

Only a few other groups have examined the effects of probiotics on allergic diseases. In a large survey, adults consumed yoghurt, inactivated yoghurt, or no yoghurt for a year (24). The symptoms of nasal allergies were less, and the total serum IgE levels were lower among volunteers who consumed yoghurt than in the control group. In this study, randomization did not include controls so selection biases could not be excluded. In a

double-blind cross-over study (25), 15 adults with moderate asthma received yoghurt with live *Lactobacilli* for one month and then by yoghurt without *Lactobacilli* for another month: no differences in spirometric functions were related to the consumption of *Lactobacilli*.

In this issue of *Allergy*, Helin T et al. (26) describe the first DBPC study examining whether treatment with *L. rhamnosus* improves symptoms and decreases medication in teenagers and adults. Treatment did not prevent sensitization to birch pollen and apple food, and no beneficial clinical effect was recorded in the 18 patients treated with *L. rhamnosus* compared with 18 controls. As in previous studies (20, 22), no demonstration was given that *L. rhamnosus* had induced any changes of intestinal microflora from baseline values in treated patients compared to controls (26).

Perspectives

Evidence supporting the use of probiotics against allergy come from trials not convincing from a methodological standpoint. Studies about probiotics in gastrointestinal disorders started long before those concerning allergic diseases (27) and with time have become more rigorous, used fixed and higher bacterial doses, multiple strain composition, and included often regular monitoring of efficient colonization, as well as the extensive use of animal models (27–29). These approaches may thus be useful in future studies on probiotics in allergy, but safety remains a major concern, especially when the use of living bacteria is promoted as prophylactic treatment in a consistent proportion of infants from the general population (30). This stated, initial trials on bacterial products in allergy moved sooner than expected the hygiene hypothesis to a level of clinical implications. Nevertheless, until an effect is convincingly demonstrated, the use of probiotics in allergy will remain not only an empiric, but also a very doubtful practice.

References

1. ARSHAD SH. Food allergen avoidance in primary prevention of food allergy. *Allergy* 2001;**56**:113–116.
2. CUSTOVIC A, WOODCOCK A. Clinical effects of allergen avoidance. *Clin Rev Allergy Immunol* 2000 June;**18**:397–419.
3. HOLT PG. A potential vaccine strategy for asthma and allied atopic diseases during early childhood. *Lancet* 1994;**344**:456–458.
4. HOLT PG. Immunoprophylaxis of atopy: light at the end of the tunnel? *Immunol Today* 1994;**15**:484–489.
5. STRACHAN DP. Hay fever, hygiene and household size. *Br Med J* 1989;**299**:1259–1260.
6. MATRICARDI PM, ROSMINI F, FERRIGNO L et al. Cross-sectional retrospective study of prevalence of atopy among Italian military students with antibodies against hepatitis A virus. *BMJ* 1997;**314**:999–1003.
7. MARTINEZ FD, HOLT PG. Role of microbial burden in aetiology of allergy and asthma. *Lancet* 1999;**354**(sII):12–15.
8. YAZDANBAKHSH M, VAN DEN BIGGELAAR A, MAIZELS RM. Th2 responses without atopy: immunoregulation in chronic helminth infections and reduced allergic disease. *Trends Immunol* 2001;**22**:372–377.
9. MATRICARDI PM, BONINI S. High bacterial turnover rate preventing atopy: a solution to inconsistencies impinging on the hygiene hypothesis? *Clin Exp Allergy* 2000;**30**:1506–1510.

10. MATRICARDI PM, BONINI S. Mimicking 'microbial education' of the immune system. a strategy to revert safely the epidemic trend of allergy and asthma? *Respiratory Res* 2000;**1**:129–132.
11. WOLD AE. The hygiene hypothesis revised: is the rising frequency of allergy due to changes in the intestinal flora? *Allergy* 1998;**53**:20–25.
12. SCHREZENMEIER J, DE VRESE M. Probiotics, prebiotics, and synbiotics – approaching a definition. *Am J Clin Nutr* 2001;**73**:361S–4S.
13. FULLER R. Probiotics in human medicine. *Gut* 1991;**32**:439–442.
14. DUGAS B, MERCEINER A, LENOIR-WIJKOOP I, ARNAUD C, DUGAS N, POSTAIRE E. Immunity and probiotics. *Immunol Today* 1999;**20**:387–390.
15. MARCHAND J, VANDENPLAS Y. Micro-organisms administered in the benefit of the host: myths and facts. *Eur J Gastroenterol Hepatol* 2000;**12**:1077–1088.
16. KIRJAVAINEN PV, APOSTOLOU E, SALMINEN SJ, ISOLAURI E. New aspects of probiotics – a novel approach in the management of food allergy. *Allergy* 1999;**54**:909–915.
17. BJORKSTEN B. The gastrointestinal flora and the skin – is there a link? *Pediatric Allergy Immunol* 2001;**12**:51–55.
18. MATRICARDI PM, ROSMINI F, RIONDINO S et al. Exposure to foodborne and orofecal microbes versus airborne viruses in relation to atopy and allergic asthma: epidemiological study. *Br Med J* 2000;**320**:412–417.
19. HESSLE C, HANSON LA, WOLD AE. Lactobacilli from human gastrointestinal mucosa are strong stimulators of IL-12 production. *Clin Exp Immunol* 1999;**116**:276–282.
20. MAJAMAA H, ISOLAURI E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997;**99**:179–185.
21. JOHANSSON SGO, HOURIHANE J, BOUSQUET J et al. A revised nomenclature for allergy. *Allergy* 2001;**56**:813–824.
22. KALLIOMAKI M, SALMINEN S, ARVILOMMI H, KERO P, KOSKINEN P, ISOLAURI E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;**357**:1076–1079.
23. MURCH SH. Toll of allergy reduced by probiotics. *Lancet* 2001;**357**:1057–1058.
24. TRAPP CL, CHANG CC, HALPERN GM, KEEN CL, GERSHWIN ME. The influence of chronic yoghurt consumption on populations of young and elderly adults. *Int J Immunother* 1993;**9**:53–64.
25. WHEELER JG, SHEMA SJ, BOGLE ML et al. Immune and clinical impact of *Lactobacillus acidophilus* on asthma. *Ann Allergy Asthma Immunol* 1997;**79**:229–233.
26. 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;**56**:243–246.
27. DAVIDSON GP, BUTLER RN. Probiotics in pediatric gastrointestinal disorders. *Curr Opin Pediatr* 2000;**12**:477–481.
28. GIONCHETTI P, RIZZELLO F, VENTURI A et al. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double blind, placebo controlled trial. *Gastroenterology* 2000;**119**:305–309.
29. MADSEN KL, DOYLE JS, JEWELL LD, TAVERNINI MM, FEDORAK RN. *Lactobacillus* species prevents colitis in Interleukin 10 gene-deficient mice. *Gastroenterology* 1999;**116**:1107–1114.
30. MCFARLAND LV. Beneficial microbes: health or hazard? *Eur J Gastroenterol Hepatol* 2000;**12**:1069–1071.