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Probiotics and allergies: myth or reality?

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Summary

During the last years, along with the growing knowledge about the role and importance of the intestinal flora, interest remarkably increased in probiotic bacteria supplementation. It has indeed been demonstrated that the intestinal microbiota is very important in the regulation of several functions of the organism, even those far from the gastro-enteric system. Among them, great interest was stimulated by the proven capability of the intestinal microbiota to regulate the immune system, in particular to rebalance the TH1/Th2 ratio. Consequence thereof is the assumption that the administration of probiotic bacteria may induce clinical benefits in allergic pathologies. Many clinical studies have been carried out that considered the possibility of preventing allergic sensitizations, and preventing and treating atopic dermatitis and allergic rhinitis. Many studies demonstrated that the administration of probiotics is able to prevent the onset of allergic sensitizations and improve the symptoms of atopic dermatitis and allergic rhinitis; however, studies were published, too, that achieved negative outcomes. The overall evaluation of results is, however, difficult, as the strains used and the study design are markedly heterogeneous. Future investigations with a better standardization will be able to better explain the role of the intestinal flora in atopy, and the role of probiotics in the treatment of allergic diseases.

Introduction

In the early 20th century, the Russian scientist Il'ja Il'ič Mečnikov, who was to be awarded with the Nobel prize for his studies about phagocytosis, first assumed that the particular longevity of some Eastern European populations was due to the wide consumption of acid milk: thus, he called *Lactobacillus bulgaricus* the bacillus he identified as responsible for the process. However, only in 1965, the term "probiotics" was mentioned in an article published in "Science" (1). At present, the interest in the use of probiotics is very high, as shown from the dizzyly increasing number of publications in Medline during the last 10 years, paralleling the investigations about the role and importance of the intestinal bacterial flora in regulating nu-

merous functions, even in organisms and systems far from the gastrointestinal tract. Indeed, probiotics:

- promote the exclusion of antigens by increasing degradation and altering their immunogenicity, thus reducing the antigen load;
- regulate the secretion of pro- and anti-inflammatory mediators, orienting the development of the immune system;
- bring the properties of an unbalanced microbiota back to normal;
- normalize increased gut permeability, that is the outcome of the inflammation of the mucosa;
- inhibit the colonization by pathogenic microorganisms via the production of anti-microbial substances (post-biotics), and/or through competition by adhesion to the mucosa (2,3).

Among these functions, the ability of the intestinal flora to modulate the activity of the immune system seems particularly interesting. The mechanisms most frequently observed are the following:

- immunomodulation (induction of T_{reg} cells, re-alignment of the Th1/Th2 ratio);
- secretion of Th1 cytokines (IL-10, IL-12, TGF- β);
- decreased IgE production;
- development of tolerogenic dendritic cells;
- activation of NK cells;
- stimulation of Toll-like receptors;
- production of secretory IgA (2,4-6).

In particular, the modulation of the Th1/Th2 ratio together with the increased number of T_{reg} cells and their functions allowed assuming the clinical efficacy of probiotics in the field of allergies.

Probiotics and allergies

Some preliminary observations are particularly interesting. First, germ-free animals are characterized by important immunologic anomalies:

- less developed Peyer plaques and mesenteric lymph nodes;
- smaller number of B and T cells;
- absence of germinal centres;
- smaller number of DC, CD4⁺T cells, IgA-specific B cells;
- small-sized spleen;
- T_H2-type immune responses;
- reduced CD4⁺CD25⁺ number and activity;
- increased inflammatory response to provocation tests.

All the above-mentioned alterations are reversible with probiotics supplementation (7). The observations about the intestinal flora of atopic children are particularly important. Epidemiologic data have shown that the bacterial flora in these children is different from that of healthy children, with higher levels of *Clostridia* and lower levels of *bifidobacteria*. Other trials pointed out that an early colonization with potentially pathogen bacteria, such as *Clostridium difficile* and *Staphylococcus aureus*, mainly occurs in children who will develop allergy. On the contrary, *Lactobacilli* and *bifidobacteria* are most commonly present in the intestinal flora of healthy children (8-11). Hence, the usefulness of submitting these patients to daily long-term probiotics supplementation was assumed, in order to modulate the immune system in the anti-atopic sense.

Clinical studies about probiotics and allergies

The first DBPC trial about the use of probiotics in allergies dates back to 2001, only (12). Since then, most studies on

probiotics were performed mainly in the following three allergy situations:

1. prevention of the onset of allergic sensitization;
2. prevention and treatment of atopic dermatitis;
3. prevention and treatment of allergic rhinitis.

Prevention of the onset of allergic sensitization

An important meta-analysis has recently been published on this topic: it considered 25 studies and as many as 4031 patients (13). This study observed a significant IgE decrease as well as allergic sensitization in treated subjects after the administration after and before birth, i.e. to pregnant women. Outcomes about clinical symptoms were conflictual. However, some Authors do not share this observation.

Prevention and treatment of atopic dermatitis

As for this pathology, contrasting outcomes have been observed as for the possibility of *preventing* its onset: the most favorable evidence was observed in IgE sensitized children. Several studies show that the major benefits are achieved when probiotics are administered *before* and *after* birth. The long-term persistence (5-7 years) of prevention effects was further observed, together with the significant decrease of positive results at prick-tests for ubiquitous allergens. Better results were observed in some studies about the treatment of atopic dermatitis, as for both symptoms and SCORAD levels (14-17). Moreover, it is interesting to observe that a recent wide review of the various nutrient supplements identified in probiotics the most effective substances in the prevention and reduction of atopic dermatitis (18).

Prevention and treatment of allergic rhinitis

Allergic rhinitis seems to be the atopic pathology in which the best clinical results were achieved using probiotics supplementation. Most studies show beneficial effects on seasonal and perennial allergic rhinitis as for symptoms, drug consumption and QoL (15,19,20).

The administration of probiotics showed to alleviate the symptoms of rhinitis and to interfere with inflammation markers, decreasing the eosinophilic inflammation of the mucosa (21) and the production of IL-5 (22). On the contrary, an increased IL-10 and IL-12 production was observed (23). **Table 1** summarizes the characteristics of the main DBPC studies carried out with probiotics in allergic rhinitis. As it can be seen, the pattern of these studies is characterized from marked heterogeneity, as for population, strain used, duration and outcomes. A very recent large study performed by GA₂LEN (24) has to be mentioned: it involved 425 adult patients suffering from grass pollen allergy (215 active, 210 placebo patients) who were treat-

ed for 7 weeks with *Lactobacillus paracasei* (LP-33®) 2×10^9 CFU/die. The study was carried out during the pollen season. It provided for a 10 days' run-in period with Loratadine, followed from the randomization of patients to treatment with LP-33 + Loratadine or Placebo + Loratadine for 5 weeks, and finally a further two weeks' treatment after the discontinuation of antihistamine. Patients treated with the probiotic strain showed a very significant RQOL improvement (mod. from Juniper, JACI 2008) in comparison with baseline and the Placebo group. This wide DBPC study demonstrates that the combination of a probiotic strain and the traditional anti-allergy therapy significantly improves the quality of life of patients suffering from grass pollen-induced allergic rhinitis.

Finally, the possible interactions between probiotics and allergen-specific Immunotherapy (AIT) should be mentioned. The

immunomodulatory characteristics of some probiotic strains suggest that they can be used together with AIT to strengthen its effect. Some strains specifically selected because of their ability to induce a marked production of IL-10 and IL-12, such as *Lactobacillus plantarum* or *Bifidobacterium bifidum*, were shown to increase tolerance after SLIT in OVA-sensitized mice, at least partially strengthening the Th1 and T_{Reg} response (25-27). No study of this sort was carried out in allergic patients.

Comments

Studies about the use of probiotics in allergic pathologies often achieve contrasting outcomes. It is indeed not a clear field and the interpretation of results is subject to numerous biases. The most relevant are the following:

Table 1 - DBPC studies of probiotics in allergic rhinitis.

Author	Year	Strain s	Target	Weeks	Endpoints	Outcomes
Singh	2013	Bif. lactis NCC2818	Seasonal rhinitis	8	Symptoms and cytokines	Improvement
Lin	2013	Lact. salivarius	Perennial rhinitis; children	12	SMS	Reduction
Koyama	2010	<i>Lactobacillus rhamnosus</i> GR-1; <i>Bif. adolescens</i>	Seasonal rhinitis	2 seasons	Symptoms and cytokines	Improvement of cytokines
Chen	2010	<i>Lactobacillus gasseri</i> A5	Pediatric asthma	8	Symptoms, cytokines and PEF	Improvement
Nagata	2010	<i>Lactobacillus plantarum</i> No.14	Seasonal rhinitis	6	Symptoms, cytokines and eosinophils	Improvement
Ouwehand	2009	<i>L. acidophilus</i> ; <i>B. lactis</i>	Birch rhinitis	16	Score cytokines	Trend far improvement
Kawase	2009	<i>Lactobacillus</i> GG (LGG) <i>L. gasseri</i> TM C0356	Cypress rhinitis	10	Symptoms and cytokines	Improvement
Xiao	2007	<i>Bif. longum</i>	Cypress rhinitis	4 + 4 cross over EEC	Symptoms	Reduction ocular symptoms
Tamura	2007	<i>Lact. casei</i> Shirota	Cypress rhinitis	8	Symptoms	Poor results
Giovannini	2007	<i>Lactobacillus casei</i>	Asthma and rhinitis; children	54	Free interval from exacerbations	Rhinitis improvement
Ishida	2005	<i>Lactobacillus acidophilus</i> ceppo L-92	Perennial rhinitis	8	Symptoms	Improvement
Helin	2002	<i>Lactobacillus rhamnosus</i>	Birch asthma and rhinitis; children	5,5 months	SMS	negative

- type of probiotic (alive/dead, different strains);
- time of administration (before birth, after birth, before and after birth);
- duration and dosage of administration;
- probiotic mix or other combinations;
- **not comparability of studies carried out using different strains: the results observed with a given strain cannot be extrapolated to other strains, though of the same genre or species;**
- subject-related factors (genetics, atopy);
- environmental factors (microbial load, microbiota, nutrition, pharmacological treatments, country of origin).

In view of these discrepancies, a recent WAO document about the use of probiotics in pediatric allergology stated: “Probiotics do not have an established role in the prevention or treatment of allergy” (28). This is, however, not a failure, as the Authors themselves write in their Take Home Messages: “This is not to say that “probiotic hypothesis” is a dead end. On the contrary, there is tantalizing evidence in vitro and in animal models that the future lies in this direction”. After all, the FAO and WHO are recognizing the existence of adequate scientific proofs demonstrating that the consumption of probiotics-containing food may beneficially affect health. They also explain that these effects concern gastro-intestinal infections, some intestinal diseases, urogenital diseases, allergies and infections, they all being disorders affecting large part of the world population (Food and Agriculture Organization and World Health Organization expert consultation: Joint FAO/WHO Expert Consultation on Evaluation of Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria. Cordoba, Argentina. http://www.fao.org/documents/pub_dett.asp?lang=en&pub_id=61756).

Final Messages

- Intestinal flora plays a fundamental role in several physiopathological processes even far from the gut.
- Numerous evidences show that restoring the activity of the flora through the administration of probiotics is associated with clinical benefits in various pathological situations.
- In particular, several evidences exist that relate intestinal flora with immunity levels and with allergy.
- Furthermore, evidences are available showing that the administration of some probiotic strains interferes with the natural history of allergy and with existing symptoms.
- Evidences and conflicting positions are mainly due to the different characteristics of each individual strain, and to problems linked with the methodology of the studies carried out and evaluated.

Conflict of interest

Dr. Madonini is Scientific Director of Allergopharma S.p.A

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