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A Brief Review on the First Evaluation of a Synbiotic Food Supplement in Birch Pollen Allergic Patients in an Allergen Exposure Chamber

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Abstract

Allergic Rhinitis (AR) is a "type 2" inflammatory disease, caused by an immunoglobulin E (IgE)-mediated reaction to inhaled allergens and characterized by nasal symptoms. Pharmacologic treatment of AR mainly consists of oral/intranasal anti-histamines, intranasal glucocorticosteroids and Allergen-Specific Immunotherapy (AIT). When used correctly, these therapies are effective in most - but not in all - patients and can improve symptoms and Quality of Life (QOL); however, many patients show poor adherence to treatment, do not follow prescriptions, and coincidently experience side effects that lead to treatment cessation.

Here, we briefly review and discuss recent findings from a proof-of-concept study about a synbiotic food supplement (*Lactobacillus acidophilus* NCFM, *Bifidobacterium lactis* BL-04 and Fructo-Oligosaccharides), which was evaluated in birch pollen allergic patients with AR, in a highly standardized setting of an Allergen Exposure Chamber (AEC). The study has demonstrated significant symptom improvement after the intake of the synbiotic food supplement. Both, the median TNSS was reduced by 50% (adjusted p-value=0.025) and the median TSS by 80% (adjusted p-value=0.0097), as well as the personal well-being of the patients was increased by 50%. In addition, the synbiotic food supplement revealed an excellent safety and tolerability profile.

The present study is an excellent example that demonstrates efficacy for a specific synbiotic product and a superior tolerability and safety profile in the treatment of AR. It can be considered as an adjunct therapy for patients who do not improve with conventional medication for rhinitis, do not tolerate it or do not fit criteria for AIT. Evidence available to date guides us to consider probiotics/synbiotics as complementary treatment strategies in AR.

Keywords: Probiotic • Synbiotic • Allergy • Symptom relief • Allergen exposure chamber • Food supplement

Abbreviations: AE: Adverse Event; AEC: Allergen Exposure Chamber; AIT: Allergen-Specific Immunotherapy: AR: Allergic Rhinitis; ARC: Allergic Rhinoconjunctivitis; CFU: Colony Forming Units; EMA: European Medicines Agency; FDA: U.S. Food and Drug Administration; FOS: Fructo-Oligosaccharides; PNIF: Peak Nasal Inspiratory Flow; PEF: Peak Expiratory Flow; QOL: Quality of Life; RC: Rhino Conjunctivitis; TNSS: Total Nasal Symptom Score; TSS: Total Symptom Score; WHO: World Health Organization

Background

Allergic rhinitis (AR) is a "type 2" inflammatory disease, caused by an Immunoglobulin E (IgE)-mediated reaction to inhaled allergens and characterized by nasal symptoms (sneezing, nasal congestion, nasal itching and rhinorrhoea) [1]. Genetically predisposed (atopic) individuals can develop AR as a consequence of environmental exposure to allergens; moreover, AR is often co-morbid with conjunctivitis and asthma [1].

Different from other allergic conditions such as anaphylaxis and asthma, in which there is a risk of fatality, AR is sometimes not considered as a "severe" disease. However, even if AR is sometimes trivialized and compared to be the same like a common cold, AR actually interferes with every aspect of a patient's life (from sleep to cognitive functions) and has a large negative effect on their Quality of Life (QOL), making them feel tired, miserable and irritable [2]. It has been estimated that more than 100 million people in Europe are "trapped" by this disease, which defines AR as a major healthcare problem [2].

Pharmacologic treatment of AR mainly consists of oral/intranasal anti-histamines, intranasal glucocorticosteroids and Allergen-Specific Immunotherapy (AIT), the only causative treatment option [3]. When used correctly, these therapies are effective in most-but not in all-patients and can improve symptoms and QOL; [1,4] However many patients show poor adherence to treatment, do not follow prescriptions and coincidently experience side effects that lead to treatment cessation[1,3].

The most common drawback reported for oral anti-histamines is fatigue, while for intranasal glucocorticosteroids there is the possibility of nasal bleeding, which occurs in a minority-but not neglectable part-of the patients [3]. AIT, the only causative treatment to date, which is an allergen-specific treatment and needs to be continued for at least 3 years, is not suitable for all patients (e.g. poly-allergic patients) and it takes time until its beneficial effects have their onset and are noticeable for the patient [3]. For these reasons, other treatments which can help to further improve the current situation of AR patients are needed.

Probiotics, which are defined as living microorganisms by the WHO which, when ingested in adequate amounts, may have a beneficial effect on the host [5], have been considered for this indication in the last years, as well as synbiotics (similar used to the term symbiotic), which are defined as combination of probiotics and prebiotics (a selectively fermented ingredient that allows specific changes, both in the composition and/or activity in the gastrointestinal microbiota that confers benefits upon host wellbeing and health) [6].

Probiotics and synbiotics, consisting of living microorganisms which can interact with the innate immune system of the host, can induce an immunomodulatory effect, and have been evaluated in several studies in patients with AR [7-12] with promising results both in patients with allergic sensitization to pollens or house dust mites.

However, it has to be noted that as probiotics/synbiotics are generally considered as a food supplement, a variety of different commercially available or experimental products have been evaluated, and by acknowledging that their effects are species-specific, the results obtained with a specific product

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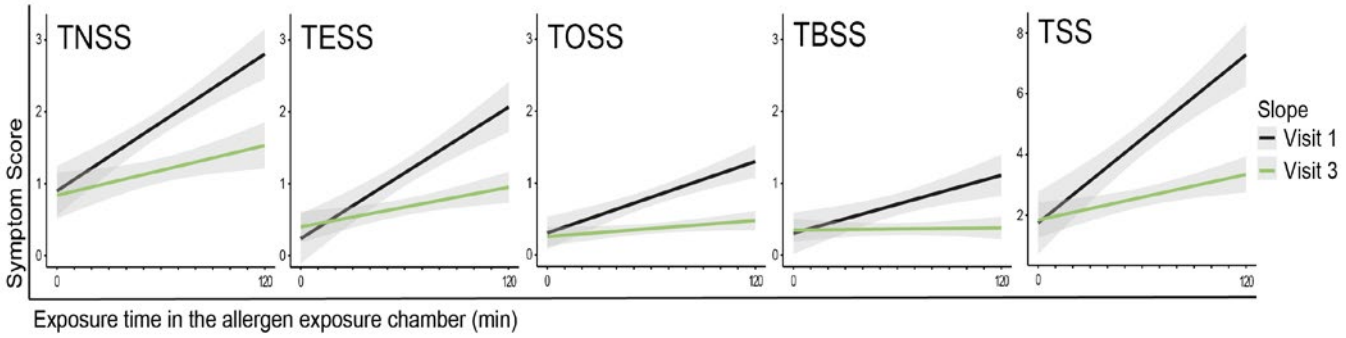

Figure 1. Depicted is the slope of symptom increase of all symptom scores during both exposures (Visit 1=black, Visit 3=green). Total Nasal Symptom Score (TNSS), Total Eye Symptom Score (TESS), Total Bronchial Symptom Score (TBSS), Total Other Symptom Score (TOSS), and the resulting sum of all symptoms=Total Symptom Score (TSS) were analysed for their linear evolution over time during the birch pollen exposure in the allergen exposure chamber (baseline=V1, and after synbiotic supplementation=V3). All symptom scores improved to a relevant extent, in this case visible by a weaker symptom-increase over time, in other words a smaller slope increase during V3 compared to V1.

cannot be attributed to a different probiotic/synbiotic. In this regard, no class-effect can be assumed.

Another pitfall regarding the evaluation of probiotics/synbiotics in AR-and also more general in prevention and treatment of allergic diseases-is, that most of the studies carried out so far do present a lack of quality, or have a weak design (are not randomized controlled trials),or are influenced by external variables (e.g. pollen season) [10].

In this regard, both the European Medicines Agency (EMA) and the Food and Drugs Administration (FDA), promote the use of Allergen Exposure Chambers (AEC) as a highly reliable tool to assess the efficacy of treatments for allergic diseases, and even for allergen immunotherapy in particular [13-15].

Literature Review

First evaluation of a synbiotic food supplement in birch pollen allergic patients in an AEC

As the scientific community is constantly and legitimately requesting solid clinical data about the effects of probiotics, we would like to briefly review and discuss recent findings about a synbiotic food supplement, consisting of *Lactobacillus acidophilus* NCFM, *Bifidobacterium lactis* BL-04 and fructo-oligosaccharides. This synbiotic product has been recently evaluated for the treatment of allergic rhinitis in a group of birch pollen-allergic patients by using an Allergen Exposure Chamber (AEC) and the results were published in the world allergy organization journal [16]. The same probiotic strains had already been evaluated in other previous studies, demonstrating promising results [17,18].

The recent study by Bergmann et al. [16] was the first evaluation of a synbiotic food supplement in birch pollen allergic patients in an allergen exposure chamber. It was a proof-of-concept study, investigating the effects of the daily intake of a synbiotic food supplement for four months on the symptoms of birch-pollen-induced allergic rhinoconjunctivitis. One of the major advantages of this study was the highly-standardized and robust read-out *via* a controlled provocation in an allergen exposure chamber before the intake of the synbiotic food supplement compared to after the intake period. An AEC enables the investigator to handle the pitfalls of varying pollen exposures during different seasons, because it permits a standardized clinical setting and reliably generates reproducible allergic symptoms during the controlled exposures in the chamber. In brief, 30 rhinoconjunctivitis patients (with or without asthma) with proven history of clinically relevant birch pollen allergy (positive skin prick test, Allergic Rhinoconjunctivitis Symptoms (ARC) for at least 2 years according to the ARIA criteria) were exposed to birch pollen in an allergen exposure chamber twice. The two exposures were performed 4 months apart and the patients took a daily dose of a marketed synbiotic food supplement (Polagen-available in Spain; Pollagen available in Italy, Austria, and Germany) consisting of *Lactobacillus acidophilus* NCFM (1×10^9 CFU), *Bifidobacterium lactis* BL-04 (3×10^9 CFU), and Fructo-Oligosaccharides (FOS), between the two exposures [16]. The patients recorded their nasal, conjunctival, bronchial and other symptoms every 10 min during the exposure, and also measured Peak Nasal Inspiratory Flow (PNIF), Peak Expiratory Flow (PEF), and recorded their personal well-being every 30 min. Spirometry was assessed before and after the exposure. In addition, adverse events related to the exposure were recorded in a safety call (24 h after the exposures) and AEs related to the synbiotic food supplement were collected during the entire study period. Both co-primary endpoints of the study (TNSS-Total Nasal Symptom Score and TSS-Total Symptom Score at 120 min of exposure) revealed a significant symptom improvement for the patients after the intake of the synbiotic food supplement. The median TNSS was reduced by 50% (adjusted p-value=0.025) and the median TSS by 80% (adjusted p-value=0.0097). Interestingly, the authors also evaluated the temporal evolution of all symptom scores during the whole exposure time in the chamber as an exploratory endpoint by employing linear mixed effects models. They could show a remarkable improvement for all symptom scores after the synbiotic supplementation, visible by a weaker symptom-increase over time (Figure 1). A tendency for a slightly improved PEF was reported, but no relevant differences for PNIF and spirometry. However, the personal well-being of the patients was increased by 50% at the end of the exposure after the intake of the synbiotic food supplement. The safety assessment showed an improved tolerability of the patients to the birch pollen exposure after supplementation, because far less late phase reactions were recorded. Since no AEs related to the synbiotic food supplement were reported, the authors rated the safety and tolerability of the product as excellent.

Although the highlighted study was not placebo-controlled, a limitation clearly acknowledged and discussed by the authors [16], we also acknowledge the authors' conclusion that the synbiotic food supplement induced clinically relevant symptom improvement, reported as 50%, respectively 80% improvement in the co-primary endpoints TNSS and TSS.

Discussion

Since the end of the 19th century with the industrial revolution, and specifically since the middle of the 20th century, the environment in which our species is living has changed dramatically: A very rapid change for organisms like humans, whose biological systems do not adapt so quickly. Along the way, we have lost "Our old friends" [19], the biodiversity and richness [20] of microorganisms and macro organisms that have colonized our bodies from the first steps of our species onwards and have shaped the evolution of our immune systems. This is the basis of many of the modern diseases, especially those of immunological origin, as it is the case for autoimmune diseases as well as allergic diseases.

It is difficult to return to an anthropophosical lifestyle [21], which has already been shown in various studies to act as a protective factor for the development of allergic diseases. One of the emerging strategies is to try to enrich our intestinal microbiota with specific beneficial bacteria, in order to restore the microbiota-immune system cross-talk [22].

In recent years, publications of clinical trials, systematic reviews and meta-analyses [23] reflecting on the use of probiotics/synbiotics in the prevention and treatment of allergic diseases, have increased. Specifically, in allergic rhinitis, the only causative treatment so far is allergen immunotherapy. Beneath this, there is also symptomatic medication (antihistamines, topical nasal corticosteroids). However, in the case of multiallergic or poly-sensitised patients, AIT is often not indicated or is less effective. On the other hand, some patients suffer from adverse reactions to AIT and others do not tolerate symptomatic medication or have corticophobia. Another aspect which should also not be neglected is, that patients under symptomatic treatment (even combinations of symptomatic treatment options), still suffer from remaining symptoms (poor symptom control), which demonstrates the need for additional therapeutic options to relief their symptoms. In these cases, probiotics/synbiotics are a good adjunct option due to their immunomodulatory effect, their safety and their good tolerability.

In 2015, Zajac et al. [24] published a systematic review and meta-analysis on the use of probiotics in the treatment of allergic rhinitis, they included 21 randomized, double-blind, placebo-controlled studies. They conclude that probiotics are beneficial as treatment for allergic rhinitis, improving symptoms and QOL. Regarding the strains used, the largest body of evidence in allergic rhinitis is found with *Lactobacillus paracasei*-33 [25], but other strains have also shown efficacy, such as those present in the discussed synbiotic food supplement, consisting of *Lactobacillus acidophilus* and *Bifidobacterium lactis*, both in seasonal allergic rhinitis due to birch pollen [18] and in non-allergic rhinitis [26].

Furthermore, this effect does not seem to be allergen specific, since similar effects have been obtained in a study published in 2013 by Singh et al. [27] a double-blind, placebo-controlled study using the same probiotic species *Bifidobacterium lactis* (but strain NCC2818) in patients allergic to grass pollen. In the active group, they observed an improvement in TNSS score and changes in immunological parameters. Regarding *Lactobacillus acidophilus*, another species of the ones present in the discussed synbiotic food supplement, has also shown to be effective compared to placebo in patients with perennial allergic rhinitis due to house dust mites [28]. In other words, the effects of probiotics do not seem to be allergen-specific. Therefore it is an interesting adjunct therapeutic option to reduce the use of symptomatic treatment or in some cases as an alternative option to AIT in poly-sensitised patients or in patients with poor tolerance to AIT.

The innovative and herein discussed proof-of-concept study carried out by Bergmann et al. [16] using an AEC in patients allergic to birch pollen before and 4 months after treatment with Pollagen/Polagen (*Lactobacillus acidophilus* NCFM, *Bifidobacterium lactis* BL-04 and fructo-oligosaccharides), has obtained very promising results in improving symptom scores, as well as safety of and tolerability to the food supplement. It is an interesting starting point for future studies with a larger sample size of patients and potentially with placebo control. In the meantime, it is a therapeutic or adjunct option for those patients who do not fit well with standard therapies for allergic rhinitis. The great additional advantage is the safety and the perfect tolerance of this synbiotic food supplement.

Conclusion

In conclusion, the microbiome plays a crucial role in the maintenance of our health and it is a potential therapeutic target. Dysbiosis, related to the loss of microbial biodiversity, is being recognized by the scientific community as one of the causes of many chronic immune-based diseases, such as allergic diseases.

Probiotics/synbiotics, aiming to balance dysbiosis, can contribute positively to reduce inflammation and re-establish mechanisms of immune tolerance or immune resilience. The present study is an excellent example that demonstrates for a specific synbiotic product its efficacy and superior tolerability and safety profile in the treatment of allergic rhinitis.

Evidence available to date guides us to consider probiotics/synbiotics as complementary treatment strategies in allergic rhinitis.

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Conflict of Interest

OJ and FF have no conflict of interest related to this article.

Author's Contribution

IO and FF conceived and wrote the manuscript, both equally contributed to the review and approved the submitted version.

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