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Probiotics and refractory chronic spontaneous urticaria

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Summary

Background. *In chronic spontaneous urticaria (CSU) first-line therapy with an antihistamine-based regimen may not achieve satisfactory control in patients. Thus, a continuing need exists for effective and safe treatments for refractory CSU.* ***Aim.*** *To evaluate the clinical efficacy and safety of an intake of a combination of 2 probiotics (*Lactobacillus salivarius *LS01 and* Bifidobacterium breve *BR03) in patients with CSU who remain symptomatic despite concomitant H1-antihistamine therapy.* ***Methods.*** *This report analyzes the effects of therapy with two probiotic strains on the clinical progress of 52 unselected patients with difficulty to treat CSU underwent to medical examination in two Italian specialist urticaria Clinics between September 2013 and September 2014. A mixture of* Lactobacillus *LS01 and* Bifidobacterium *BR03 were administered in each patient twice daily for 8 weeks. To evaluate patients' improvement with probiotics, urticaria activity score over 7 days (UAS7) was used at baseline and at week 8 in addition to a 5-question urticaria quality of life questionnaire.* ***Results.*** *Fifty-two patients with CSU were included in this study (10 male and 42 female, age range 19-72 years). Mean disease duration was 1.5 years. Fourteen patients discontinued treatment, so evaluable population consisted of 38 patients. Nine of the 38 patients experienced mild clinical improvement during probiotic treatment (23.7%); one patient reported significant clinical improvement (2.6%) and one patient had complete remission of urticaria (2.6%). Twenty-seven patients did not have improvement in symptoms (71.1%). No side effects during the course of therapy were reported.* ***Conclusions.*** *A combination of* Lactobacillus salivarius *LS01 and* Bifidobacterium breve *BR03 administered twice daily for 8 weeks might reduce the symptoms scores and improve quality of life scores in a part of patients with CSU who remained symptomatic despite treatment with H1 antihistamine mostly in subjects with allergic rhinitis.*

Introduction

Chronic spontaneous urticaria (CSU) is classically defined as the occurrence of spontaneous wheals on most days for more than six weeks. It is a common skin condition that affects 0.1-3% of people in the USA and Europe (1).

The course and duration of CSU are highly variable and unpredictable. Spontaneous remission may often occur within 12 months, but a substantial number of patients may have symptoms lasting periodically for years, or suffer irritating symptoms such as pruritus for decades (2). CSU is frequently a disabling disease due to the persistency of clinical symptoms, the unpredictable course and negative influence on the quality of life, as it can cause sleep disruption, fatigue, social isolation, energy loss and emotional / sexual disturbances (3). The goal of treatment

in CSU is to ensure rapid and prolonged control of the symptoms and a rapid return to normal social activities.
Symptomatic treatment for CSU is the most frequently used form of management, and a step-wise approach is recommended (4). Modern second-generation H1-receptor antagonists are the primary treatment at licensed doses (5,6), and updosing is second-line treatment. First-line therapy with an antihistamine-based regimen may not achieve satisfactory control in 5% to as many as 50% of patients with CSU (7). Those with refractory CSU require treatment with H1-antihistamines increasing doses by up to 4 times; if symptoms persist, a trial of omalizumab, cyclosporine or montelukast (4,8) as add on therapy is recommended; frequent exacerbations may be treated with systemic steroid. However, the toxicities and adverse events associated with cyclosporine and long-term steroid exposure should be considered carefully (9). Thus, a continuing need exists for effective and safe treatments for refractory CSU; trials of several novel therapeutics are in progress.
It was seen that *Lactobacillus salivarius* LS01 and the combination of 2 probiotics (*Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03) have the capability to reduce the release of pro-Th-2 cytokines from THP-1 cells, favouring an improvement in T-helper cell (Th)1/Th2 (10,11).
Th2 cells play a critical role in the pathogenesis of allergic reactions and in the production of IgE antibodies.
In CSU, IgE antibodies, FcεRI, and mast cells are likely to play essential pathologic roles, although the causative factors have not been identified (12). The aim of this study was to evaluate the clinical efficacy and safety of an intake of a combination of 2 probiotics (*Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03) in patients with CSU who remain symptomatic despite concomitant H1-antihistamine therapy.

Materials and Methods

This report is an analysis of the effects of therapy with two probiotic strains on the clinical progress of 52 unselected patients with difficult to treat CSU, who previously underwent medical examination in two Italian specialist urticaria Clinics (Unit of Study on Urticaria / Angioedema, Policlinico, Bari, and Allergology Unit, Miulli Hospital, Acquaviva delle Fonti) between September 2013 and September 2014. To be started on probiotic therapy, patients had to have shown to be unresponsive after almost one month of H1-anthistamines treatment.
In all enrolled patients, a diagnosis of CSU was made by a careful history and detailed physical examination, submitting them to clinical, laboratory and instrumental investigations according to individual clinical history and findings in each patient. Tests included: urinalysis, routine laboratory evaluation (including complement C3, C4 and C1 inhibitor antigenic level, thyroid function test, antithyroid autoantibodies, antinuclear antibodies, rheumatoid factor, serum immunoglobulins, circulating immune complexes, cryoglobulins, stool screening for blood, parasites and yeast, serology for viral, bacterial and parasite antibodies, serum electrophoresis, gastroscopy, biopsy and enzyme-linked immunosorbent assay for specific anti-Helicobacter pylori IgG antibodies), X-ray studies (including dental series, sinus series and chest X-ray) and sonography of the upper abdomen. Skin prick tests were performed with common available foods and inhalants (Stallergenes, Milan, Italy). In some cases, a "prick-prick test" with fresh raw food was made. Measurement of total IgE level was made (UniCAP, Thermofisher, Milan, Italy) and specific serum IgE according to patients' anamnesis (UniCAP, Thermofisher, Milan, Italy).
Drug-related etiology was established on the basis of the criteria laid down by the protocols in literature (13). Briefly, the methods used to evaluate patients with suspected drug-induced urticaria were a detailed history, withdrawal of the suspected drug, and in some cases in vivo and in vitro testing. In order to evaluate the role of foods and additives, single blind placebo-controlled in vivo provocation tests with foods and additives were performed when necessary. Autologous serum skin tests, were performed as previously reported (14). So, in these patients inducible urticarial alone, urticaria caused by medications, insect bites, food or other known causes were excluded. In addition, patients with significant concomitant illness (e.g. malignancies or psychiatric, hepatic, endocrine or other major systemic diseases) were also excluded.
After the CSU diagnosis, all patients had received second generation H1-antihistamines at up to twofold higher than the licensed dose in an attempt to control their condition. Some patients had even received three or more different antihistamines. Eighteen and nine patients had previously required corticosteroids and montelukast, respectively, to control symptoms.
Patients were administered twice daily for 8 weeks a marketed oral probiotic (Bifiderm®, Bayer S.p.A, which is a mixture of *Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03 at a dose ≥ 1x109 colony-forming units (CFU)/g each in maltodextrin).
Throughout the treatment period, participants were required to maintain stable doses of the previous therapy with H1-antihistamines.
Each patient was examined by the physician 3 times over the 8-week period: this included (apart from the initial screening visits), a 1st visit at the start of treatment with the probiotic state; a 2nd visit after 4 weeks of treatment; and a final visit after 8 weeks (end of treatment).
Throughout the study and one week before starting the probiotic state, all patients recorded their symptoms in a daily diary (pruritus and number of wheals). At each clinical visit the patient's diary was reviewed, the patient was interviewed as to the

event/s occurring in the previous week/s, and a physical examination was performed.

Baseline severity was determined by urticaria activity score over 7 days (UAS7) 1 week before probiotic treatment. UAS7 is a simple patient-reported scoring system that captures the severity of pruritus and number of hives during 1 week (15). Intensity of pruritus (range, 0 [none] to 3 [severe]) and the number of hives ratings (range, 0 [none] to 3 [> 12 hives]) were recorded daily (maximum, 6 points per day). Scores were then summed for 1 week to represent the UAS7 (scale, 0-42). All patients had a UAS7 of 6 or greater despite antihistamine therapy. The primary end point was the change from baseline to week 8 in the UAS7. The responses to the probiotic state were described as follows: "complete response" was defined as a reduction of 90% or more in the UAS7, "significant improvement" as a reduction in the UAS7 of 90%-30%, "mild improvement" as a reduction in the UAS7 of 30%-10% and "no significant improvement" as less than 10% reduction in the UAS7.

A 5-question urticaria quality of life questionnaire was administered at each clinical visit, evaluating the following domains: cutaneous symptoms, emotions, practical problems. The questions were: "Over the last week, how itchy, sore, painful or stinging has your skin been? Over the last week, how embarrassed or self-conscious have you been because of your skin? Over the last week, how much has your skin influenced the clothes you wear? Over the last week, how much has your skin affected any social or leisure activities? Over the last week, has your skin prevented you from working or studying? If "No", over the last week how much has your skin been a problem at work or studying?". These are part of the Dermatology QualityLife Index (16).

Patients scored their response to each question on a 4-point scale ranging from 0 (no problems) to 3 (severe problems).

Safety and tolerability were assessed on the basis of the adverse events referred or changes in vital signs, and physical examination findings.

Approval from the Ethics Committee of the hospital was not necessary, because the analyses were performed on data recorded during the routine treatment of patients. Patients provided oral informed consent to have their data included for analysis.

Results

Fifty-two patients with CSU were included in this study (10 male and 42 female, age range 19-72 years). Mean disease duration was 1.5 years (range 0.3-9.4 years). Twenty-four of these subjects had a history of angioedema. Twelve of the 52 patients had to have a documented history of seasonal or perennial allergic rhinitis related to positive skin prick test and/or laboratory tests.

Fourteen patients discontinued treatment. The reasons for discontinuation were: non-compliance (n = 3); and lack of desire to continue because of no improvement in symptoms (n = 11).

The evaluable population thus consisted of 38 patients. A total of 18 patients (44%) were classified as having a suspected chronic autoreactive urticaria demonstrated by a positive autologous serum skin test.

Nine of the 38 patients experienced mild clinical improvement during probiotic treatment (23.7%). One of the 38 patients experienced significant clinical improvement (2.6%). One patient had complete remission of urticaria (2.6%). This female patient had a UAS7 of 8 despite antihistamine therapy, and the duration of urticaria was 6 months. Then, a total of 11 subjects (28.9%) showed improvement on Probiotic therapy (**table 1**).

In this group, at week 8, mean 5-question urticaria quality of life questionnaire score decreased from baseline (1 week before probiotic treatment) by 2.46 points. Twenty-seven patients did not have improvement in symptoms (71.1%) and eleven of them required short courses of prednisone for symptom relief.

We compared the characteristics of 11 patients with improvement in symptoms with those of 27 patients without improvement in symptoms.

In subjects with improvement in symptoms emerged only a high prevalence of allergic rhinitis (8 of 11) than in the group of patients without improvement of symptoms (2 of 27).

No patient reported any side effects during the course of therapy in all study groups.

Discussion

CSU, one of the most frequent skin allergy diseases, is a heterogeneous condition, and prognostic factors for each treatment are not well known. CSU is a disease that is particularly difficult to treat. Although non-sedating antihistamines are recommended as first-line agents, a substantial proportion of patients remain poorly responsive to these agents even if H2-receptor antagonists and/or leukotriene pathway inhibitors are added (17). Such patients are often treated with corticosteroids or cyclosporine or omalizumab (4), and alternatives to these agents would be a welcome addition if efficacy could be shown with an acceptable tolerability profile. Thus, a continuing need exists for effective and safe treatments for refractory CSU.

In this study we evaluated the clinical efficacy and safety of an intake of a combination of 2 probiotics (*Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03) in patients with CSU who were refractory to conventional treatment.

In a group of 11 subjects, after Probiotics intake, a reduction of disease activity and improvement of patients' health-related quality of life were observed. From a questionnaire administered to urticarial patients, O'Donnell et al. (3) established that the disability described by patients is comparable to that of patients with ischemic heart disease. Successively, Finlay et al. (16) developed the Dermatology Life Quality Index (DLQI). They used it to measure and compare the disability induced by a variety of

common dermatological conditions and suggest that the questionnaire can be administered before and after treatment interventions, to serve as an indicator of treatment efficacy.

Because of the relatively small patient population in our study, it was difficult to determine any patient characteristics that were predictors of response to Probiotic supplement. The presence of thyroid autoantibodies, angioedema, positive ASST, and age did not appear to predict response. The presence of allergic rhinitis in CSU patients seemed to be a possible predictor of response to Probiotics.

The role of probiotics in regulating intestinal health has been widely studied for over a century. Modulation of the intestinal microbiota is one of the important functions of probiotics, which is deeply associated with the modulation of the intestinal immune system, improving bowel movement and decreasing allergy (18,19). However, in recent years, several lines of evidence suggest that some bacterial probiotics can modulate the skin immune system (20). In human clinical trials, probiotic supplementation showed potential in the relief of atopic dermatitis and dry skin (21).

There is evidence suggesting that alteration of the composition and/or size of the gut microflora may modulate the IgE response to allergens (22). Because modern lifestyles have contributed to changes in the composition of the intestinal microflora, diet supplementation with probiotics may counterbalance the Th-2 activity by promoting Th-1 cytokines production and downregulate IgE production via inhibition of IL-4 and IL-5 production (23). Additionally, it was showed that *L. paracasei* NC 2461 induced development of a population of CD4+ T cells that produced TGF-β and IL-10 (24), which could downregulate IgE production (25).

It was seen that *Lactobacillus salivarius* LS01 and the combination of 2 probiotics (*Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03) reduced the release of type 2 cytokines [interleukin (IL)-4 and IL-13] and induced an improvement in the T-helper cell (Th)1/Th2 ratio. This probiotic formulation upregulates Th1 functions and down regulates Th2 and Th17 activity, improving Th1/Th2 and Th17/Treg ratios (10,11).

Recent evidence suggests that helper T cells (Th2) play a triggering role in the activation / recruitment of IgE antibody producing B cells, mast cells and eosinophils (26).

In cases of CSU, in which autoreactive IgG antibodies against FcεRI, IgE, or both or autoreactive IgE antibodies against autoallergens are found, these autoantibodies are causative factors, and IgE, FcεRI, and mast cells are unambiguously at the centre of the pathologic process. For the remaining cases of CSU, IgE, FcεRI, and mast cells are also likely to play essential pathologic roles, although the causative factors have not been identified.

Autoimmune processes might be the primary cause of most cases of CSU. Thus, for those cases with a clear autoimmune

Table 1 *- Characteristics of 11 patients who showed improvement in symptoms.*

No	Sex	Age, y	Duration of urticaria	Angioedema	Anti thyroid Antibody	Previous Treatment	ASST	Allergies (Rhinitis)	Effect
1	F	41	2 y	Yes	+	H1 Pred Mont	+	Parietaria	↑
2	F	36	1 y	No	-	H1	-	Grass, Olive	↑
3	F	27	5 mo	No	-	H1	-	Cypress	↑
4	F	35	3 y	Yes	+	H1 Pred	+	Grass, Olive	↑
5	F	39	7 mo	No	-	H1	-	No	↑
6	M	57	1 y	No	-	H1	-	No	↑
7	F	21	2 y	Yes	+	H1 Mont	-	Grass, House dust mite	↑
8	F	46	4 mo	No	n.d.	H1	-	No	↑
9	M	44	6 y	Yes	n.d.	H1 Pred Mont	+	Grass, Olive, Cypress	↑
10	F	39	1 y	No	-	H1 Pred	+	House dust mite, Grass	↑↑
11	F	47	6 mo	Yes	+	H1	+	House dust mite	↑↑↑

F = female; M = male; y = years; mo = months; H1 = H1-antihistamines; Pred = prednisone; Mont = montelukast; ASST = autologous serum skin test; Effect = over change in clinical symptoms after Probiotics treatment; mild clinical improvement (↑), significant clinical improvement (↑↑), complete remission of urticarial (↑↑↑); n.d. = not done

cause, the reduction of the IgE by the action of Probiotics yields the observed therapeutic efficacy. Even for those cases that involve autoimmune response and autoreactive IgE antibodies subtly, they still involve the central pathologic axis of IgE-FcεRI-mast cells, and Probiotics similarly render therapeutic effects (27,28).

The inflammatory response in the nasal mucosa in subjects with allergic rhinitis challenged intranasally with an allergen includes an immediate IgE-mediated mast cell response as well as a late-phase response characterized by recruitment of eosinophils, basophils, and T cells expressing Th2 cytokines including IL-4, a switch factor for IgE synthesis, and IL-5, an eosinophil growth factor. Recent advances have suggested that additional pathways may contribute to the pathophysiology of allergic rhinitis including local synthesis of IgE in the nasal mucosa (29).

Several studies demonstrated that Probiotics may alleviate the symptoms caused by allergic rhinitis. A meta-analysis described the results of 12 randomized clinical trials with probiotics in AR: in nine of the 12 trials, there were some improvements in clinical outcomes including nasal or ocular symptoms (30).

These data suggest that Probiotic therapy might be more effective in those patients with IgE-mediated allergic rhinitis associated with CSU.

The safety profile for the probiotic strain over 8 weeks of treatment in our patients was consistent with previous observations in patients treated with probiotic supplement (31).

Future studies should include a larger number of patients and have a double blind placebo-controlled design. The allergic setting is linked to the disruption of the Th1/Th2 balance with a Th2 profile; as a consequence, the production of IL-4, Il-5, or IL-13 by Th2 lymphocytes contributes to the development and maintenance of the allergic response. Probiotic strains, like *Bifidobacterium breve* BR03 and *Lactobacillus salivarius* LS01, able to induce massive secretion of IL-10 by human PBMCs of subjects with allergic asthma and to down-regulate the secretion of TGF-β, IL-13, and IL-17 in asthmatic subjects, may lead to the rebalancing of Th1/Th2 ratio and to the improvement of allergic symptoms and could limit the proinflammatory response, simultaneously improving the process of maintaining the state of tolerance to external antigens (32).

In addition, further studies are needed to help better identify clinical and laboratory predictors of response.

In conclusion, our study suggests that a combination of 2 probiotics (*Lactobacillus salivarius* LS01 and *Bifidobacterium breve* BR03) administered twice daily for 8 weeks might reduce the symptom scores and quality of life scores in a part of patients with CSU who remained symptomatic despite treatment with H1 antihistamine, mostly in subjects with allergic rhinitis. The probiotic approach might represent a new well tolerated option in the treatment of CSU.

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