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ORIGINAL ARTICLE

β-Glucan-based cream (containing pleuran isolated from *pleurotus ostreatus*) in supportive treatment of mild-to-moderate atopic dermatitis

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Abstract

Background: Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases with serious impact on quality of life. β-Glucans are natural substances with potent immunomodulatory and anti-inflammatory activity. *Methods*: In a multicentre open split-body study, we studied the effect of Imunoglukan P4H® cream in a group of 105 patients with AD (39 males, 37%). Evaluation of subjective (visual analogue scale, VAS) and objective (EASI score, eczema area and severity index) characteristics of AD was carried out. *Results*: In total, 80 patients (76.2%) completed the study. Topical β-glucan application resulted in the significant improvement of both objective and subjective symptoms of AD. On the application side, significant decline in the number of days with AD exacerbation and its severity was observed. Moreover, the subjects experienced decline of pruritus on the β-glucan half of the body (VAS score: 1.68 vs. 1.95, $p < 0.001$). During the study, the continual and significant decline of EASI scores on the site of β-glucan application was observed (V4: 1.57 vs. 1.85, $p < 0.001$). The preparation was in general well tolerated. *Conclusions*: This is the first study evaluating and confirming the potential use of β-glucan-based cream as a supportive complementary therapy of atopic dermatitis.

Keywords

atopic dermatitis, β-glucan, complementary medicine, pleuran, topical treatment

History

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Introduction

Atopic dermatitis (AD) is one of the most common chronic inflammatory diseases of skin, especially in children, and its prevalence is increasing gradually worldwide. Although effective topical and systemic therapies are available, absolute clinical remission especially in more severe forms is usually impossible to achieve. It has been shown in a number of studies that patients with AD frequently have recourse to complementary and alternative medicine (CAM) (1). Among the most commonly used modalities of CAM are different herbal products, polyunsaturated essential fatty acids, probiotics and prebiotics, vitamins, minerals or acupuncture (1,2). However, the true efficacy, safety and possible unwanted side effects of certain CAM therapies have not been studied appropriately and relevant studies are still lacking.

β-Glucans are a group of biologically active polysaccharides of natural origin with a proven pleiotropic immunomodulation effect. The most effective are β-glucans extracted from mushrooms and their action strongly depends on the purity of the extracted compound. From *in vitro* experiments, and also animal and human clinical studies, there is increasing evidence of the importance of β-glucans in the treatment of different allergic diseases (3). The efficacy of systemic application of β-glucans in the treatment of AD has been confirmed in both animal experiments and human studies (4,5). Topical application of β-glucans in dermatology is increasing, since their pluripotent mechanisms of action (antioxidant, anti-inflammatory and regeneration effects, immunomodulation, radioprotection, moisturization, rejuvenation) could help as complementary therapy in the management of various skin diseases (6,7). In clinical medicine, topical application of β-glucans was successfully studied in the treatment of different skin diseases and conditions such as radiation dermatitis, venous ulcers, wound healing, solar keratosis, HPV-associated vulvar lesions and contact dermatitis (8–14). Topical application of mushroom extract containing β-glucan was effective in the treatment of AD in animal models (15); however, the use of topical β-glucans in AD management in humans has not yet been investigated. In our open label, interventional split-body study, we aimed to evaluate the efficacy and tolerability of β-glucan-based cream in the supportive treatment of mild-to-moderate AD.

Materials and methods

This multicentre open split-body study was conducted across 10 dermatological centres (8 centres in Slovakia and 2 in the Czech Republic) and enrolled 105 patients in total (39 males, 37%, mean

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age 20.4 years). The study was approved by the Ethical Committee of the University Hospital of F.D. Roosevelt in Banska Bystrica and of Bulovka University Hospital, Charles University (Prague) and was conducted under Good Clinical Practise regulations. The patients of parents of the children signed consent forms. The study was performed according to the guidelines of the Declaration of Helsinki and Tokyo for humans.

The study was conducted between September 2012 and May 2013 and consisted of continuous six-month observation during the flare season. Patients were asked to apply a standard emollient all over the body and on the left side of the body they applied two or three times per day a 0.25% β-glucan-based cream (Imunoglukan P4H® cream). For statistical comparison, the differences between the left side (Imunoglukan P4H® cream and emollient) and the right side (emollient only) of the body were evaluated. The active substance within this natural product was previously isolated, identified and chemically characterized by Karacsonyi and Kuniak and is free of endotoxins (16). The testing for toxicity was performed by the Institute of Preventative and Clinical Medicine of Slovak Medical University (Final Report No. E-51/05) and the tests were performed in compliance with the criteria of the Directive of Good Laboratory Practice and Directive 2004/10/EC of the European Parliament and the Council of 11 February 2004. All adverse events were documented throughout the study. Investigators' notes of adverse events were coded according to the *Medical Dictionary for Regulatory Activities*.

Patients made four visits during the study: V0 – screening visit on recruitment, V1 – after 8 weeks of treatment, V2 – after 16 weeks of treatment and V3 – after 24 weeks of treatment. During V0, the inclusion/exclusion criteria were evaluated. Inclusion criteria included the following: (i) the diagnosis of mild-to-moderate atopic dermatitis that was defined as disease affecting $\leq$10% of body surface area and no more than four relapses per year during the last three years; (ii) age over six months; (iii) subjects in remission stage of atopic dermatitis; (iv) last application of topical corticosteroids or topical immunomodulators (pimecrolimus, tacrolimus) minimum three days before entering the study; (v) signed informed consent; (vi) the absence of any clinically significant internal or dermatologic disease that would interfere with the observation and evaluation. Exclusion criteria were defined as follows: (i) subjects with known hypersensitivity or intolerance to Imunoglukan P4H® cream and emollient base; (ii) subjects with severe forms of AD (affecting more than 10% of the body surface area, with more than four relapses per year); (iii) subjects with AD flare at the time of enrolment into the study; (iv) subjects with clinically evident bacterial, viral or parasitic skin infections; (v) application of topical corticosteroids or topical immunomodulators (pimecrolimus, tacrolimus) less than three days before entry into the observation; (vi) systemic treatment with corticosteroids, cyclosporine A, leukotriene receptor antagonists or anti-IgE monoclonal antibody; (vii) previous treatment with Imunoglukan P4H® cream less than one month before entry into the observation; (viii) the presence of clinically significant disease that would interfere with the observation evaluation; (ix) pregnancy, breastfeeding or age below six months. Those patients with observed allergy or intolerance to the studied cream, with poor adherence and compliance to the study, with missing or incomplete study documentation, or with changed therapy were withdrawn from the study.

During V1, V2 and V3, subjective parameters, such as pruritus (visual analogue scale, VAS: 1 – 10 points, 1 = absent, 10 = the most severe), intensity of flares (up to three points, 1 = mild, 2 = moderate, 3 = severe) and duration of flares were assessed by patients. At the same time points, for objective evaluation of the AD characteristics, the eczema area and severity index (EASI score) was evaluated by skilled dermatologists. The EASI score was recommended as a suitable follow-up in drug-effect studies of AD.

The results are presented as mean values. Data were analysed with the software package SPSS version 9.0 (SPSS Inc., Chicago, IL). The normality of the data was evaluated by the Shapiro–Wilk test and data were then analysed by the non-parametric paired Wilcoxon test with ties. p values lower than 0.05 were considered to be statistically significant.

Results

This multicentre open split-body study enrolled 105 patients (39 men, 37%, 66 women, 63%; mean age 20.4 years). Thirty-nine patients (37%) were younger than 15 (13 younger than 2). Full six-month observation was completed by 80 patients (76%; 27 men, 34% and 53 women, 66%, mean age 19.71 years) and 31 (39%) of them were younger than 15. Regular application of β-glucan-based cream resulted in a significant shortening of flare duration in days at the end of the study (left side vs. right side: 10.00 days vs. 11.20 days, $p = 0.038$). A few days after the beginning of the application of β-glucan-based cream, the weekly score of pruritus and intensity of flares evaluated by patients significantly decreased on the β-glucan side of the body and this attenuation remained significant across the whole study (Table 1). When patients younger than 15 were analysed, the duration of flares in days did not differ between the left and right sides of the body; however, the weekly score for itching was reduced at V2 and V3, and also, the intensity of flares was significantly reduced at the end of the study (Table 2). The eczema area and severity index was evaluated four times by a skilled dermatologist. At the beginning of the study, EASI scores on both sides of the body did not differ. Regular application of β-glucan-based cream led to the significant decline of this objective parameter of the intensity and severity of AD in all the visits (V1, V2, V3). The differences were observed at the level of the whole population and in the subgroup of patients younger than 15 (Table 3).

Of the 105 patients recruited, 80 (76%) completed the study. Nine patients (8.6%) were withdrawn for β-glucan-based cream non-related reasons (patient's decision, absence from study visits). In 13 subjects (12.4%), mild local side effects were observed, but they were not considered to be a reason for withdrawal from the study as they were only transient and disappeared during regular application of β-glucan-based cream. Sixteen patients (15.2%) did not complete the study because of intolerance of the cream and three of them suffered contact dermatitis. None of these side

Table 1. Parameters evaluated by patients and their changes during the study in the whole population.

	Treatment period		
	Week 1–8 (left/right side)	Week 9–16 (left/right side)	Week 14–24 (left/right side)
Duration of flares in days	14.02/14.03	12.89/12.80	10.00/11.20[a]
Weekly score of pruritus (VAS: 1–10 points)	2.28/2.40[b]	2.07/2.27[b]	1.68/1.95[c]
Intensity of flares (1 – mild, 2 – moderate, 3 – severe)	0.95/1.04[a]	1.01/1.06[b]	0.80/0.96[c]

VAS – visual analogue scale, left side – β-glucan-based cream + standard emollient, right side – standard emollient.
[a] $p < 0.05$,
[b] $p < 0.01$,
[c] $p < 0.001$.

Table 2. Parameters evaluated by patients and changes in patients younger than 15 during the study.

	Treatment period		
	Week 1–8 (left/right side)	Week 9–16 (left/right side)	Week 14–24 (left/right side)
Duration of flares in days	16.11/17.06	13.75/13.78	11.93/12.63
Weekly score of pruritus (VAS: 1–10 points)	2.04/2.04	1.82/1/90[a]	1.56/1.83[b]
Intensity of flares (1 – mild, 2 – moderate, 3 – severe)	1.05/1.17	0.87/0.91	0.73/0.90[c]

VAS – visual analogue scale, left side – β-glucan-based cream + standard emollient, right side – standard emollient.
[a]$p < 0.05$,
[b]$p < 0.01$,
[c]$p < 0.001$.

Table 3. EASI score evaluated by dermatologists during the study.

	Visit			
	V0 (left/right side)	V1 (left/right side)	V2 (left/right side)	V3 (left/right side)
EASI score (whole population)	2.47/2.55	1.31/1.75[c]	1.52/1.59[b]	1.57/1.85[c]
EASI score (patients ≤ 15 ys)	2.29/2.39	0.86/1.72[b]	1.16/1.19[a]	1.31/1.77[b]

EASI – eczema area and severity index; left side – β-glucan-based cream + standard emollient, right side – standard emollient.
[a]$p < 0.05$,
[b]$p < 0.01$,
[c]$p < 0.001$.

effects were severe. In general, the β-glucan-based cream was well tolerated and did not exhibit any serious adverse effects.

Discussion

This is the first study evaluating the efficacy and tolerability of β-glucan-based cream (Imunoglukan P4H® cream) in the treatment and remission maintenance of AD in humans. We demonstrated that the regular application of β-glucan-based cream decreased the duration and intensity of AD flares and attenuated the pruritus intensity within a few days of regular application. The treatment resulted in a significant and persistent reduction of objective features of AD (EASI score) across the whole study. The treatment was in general well tolerated and no serious adverse events were recorded.

β-Glucans are one of the most studied and frequently used natural immunomodulators in the management of various diseases resulting from changed immune functions. The efficacy of systemic application of β-glucans in the treatment of AD was studied in animal models and also in humans. Dietary β-glucan significantly reduced signs of canine atopic dermatitis and was well tolerated (17). In an animal model of AD, application of paramylon (β-glucan from *Euglena gracilis*) caused responses of both T_H1 and T_H2 to be blocked. The effect of paramylon was also documented by a significant decline in symptom score (5). In another animal model, the topical application of water-soluble extract from the mushroom *Phellinus linteus*, which contained β-glucan, reduced clinical symptoms of experimentally induced AD with the decrease in lymphocyte recruitment in the inflamed site. On a laboratory level, this preparation reduced IgE production and down-regulated the levels of pro-allergic cytokines (15). IgE is an important allergic mediator and is involved in the pathogenesis of AD. Therefore, its blockage could be of potential therapeutic interest for AD. The inhibition of IgE production by β-glucan application was described also in human studies (18). In a multicentre clinical study with superfine β-glucan (lentinan), the effect on AD was studied. The treatment resulted in a significant improvement in objective markers of AD severity and intensity. After three months of treatment, both total and specific IgE levels were reduced significantly. No undesirable changes in haematological and biochemical tests and no clinical adverse events were observed (4).

In our study, 16 patients did not complete the study because of skin side effects of the applied cream and three of them suffered from contact dermatitis. With regard to cutaneous reactions, there are several reports of dermatitis, systemic allergic contact dermatitis or contact dermatitis induced by ingestion of raw or undercooked shiitake mushrooms or after skin contact with medicinal mushrooms which are the source of β-glucans (19,20). However, these reactions are very rare and, in general, systemic or topical application of β-glucans is safe and well tolerated (4,9,18). Moreover, local adverse events could also result from the other components presented in the cream and cannot be attributed only to the contained β-glucan.

The positive therapeutic effect of β-glucan in the treatment of AD and other skin conditions could be explained by several mechanisms aimed at different cellular and mediating aspects of AD pathogenesis. Majtan et al. observed the concentration-dependent increase of pro-metalloproteinase 9, which is involved in tissue remodelling and wound healing, from human keratinocytes after pleuran application (21). Moreover, β-glucans are able to stimulate human dermal fibroblast collagen biosynthesis (22). Depending on the route of application, β-glucan enhanced wound healing by increasing macrophage infiltration and collagen deposition by stimulation of tissue granulation and promoting re-epithelialization (23). Topical application of β-glucans accelerated venous ulcer healing and burns (10,24).

β-Glucans also possess anti-infective properties. The novel coladerm-beta glucan membrane exhibited potential antibacterial activity against a broad spectrum of Gram-positive and Gram-negative bacteria (25). β-Glucans showed potent antioxidant and radioprotective activities and possessed moisturizing and rejuvenation characteristics (7,26). The regular topical administration of β-glucan led to increase in skin firmness and stratum corneum hydration and improved skin barrier functions (6). Carboxymethyl-glucan in topical application was able to protect the skin against UV-A irradiation and enhanced the renewal rate of the stratum corneum in the skin (23). The effect of topical β-glucan in the treatment of solar keratosis was confirmed by a randomized double-blind placebo-controlled prospective study (14). Several authors studied the possible use of β-glucans in the prevention and treatment of radiation dermatitis (9,13).

Conclusions

Imunoglukan P4H® cream is effective in the treatment and maintenance of disease remission in children and adults with AD. It decreases the duration and intensity of flares and the intensity of pruritus and attenuates objective scores of AD with good tolerability and low frequency of unwanted adverse effects. The preparation can be used as a supportive complementary therapy for atopic dermatitis thanks to its pluripotent biological effect. This β-glucan-based cream could expand the current range of AD therapeutic modalities and is suitable for regular long-term therapeutic and preventative application. Further studies are

needed for the establishment of its potential effect on other skin diseases.

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Declaration of interests

Authors declare that there are no conflicts of interest. The study was supported by Pleuran Ltd. and the project Center of Experimental and Clinical Respirology (ITMS 26220120004).

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