IALUSET VITAL® Cream Improves Adults Atopic Dermatitis

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Atopic dermatitis (AD) is a chronic relapsing skin disease, associated with impaired skin barrier function and characterized by poorly defined pruritic, erythematous lesions. In this study, the efficacy of a new topical cream (IALUSET VITAL®), containing hyaluronic acid and the extract of Salvia haenkei, in reducing symptoms of moderate AD in adults was investigated. This study was a randomized, double blind, vehicle-controlled clinical study. Treatment efficacy was evaluated considering both objective parameters (Scoring Atopic Dermatitis, SCORAD) and subjective pa-rameters (Patient Oriented Eczema Measure, POEM, and an itching sensation) and through non-invasive bioengineering techniques to measure skin moisturization and Trans Epidermal Water Loss (TEWL).

Keywords: atopic dermatitis ; hyaluronic acid ; cream ; SCORAD

1. Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disease, affecting up to 20% of children and up to 3% of adults [1], characterized by erythematous skin lesions with intense pruritus, a very disabling symptom that considerably impairs a patient's quality of life. It is widely recognized that AD is a multifactorial disease, involving immune disorders, impaired skin barrier function and environmental factors. Nevertheless, a major debate exists as to whether AD is primarily driven by immune dysregulation (inside-out theory) or epidermal barrier dysfunction (outside-in theory) [2][3]. Common tracts of 10–40% of AD patients are the loss-of-function mutation of the *FLG* gene, encoding the structural epidermal protein filaggrin, contributing to epidermal barrier dysfunction [4][5] and a reduced content of ceramides, important water-holding molecules in the extracellular space in the horny layer [6]. These events lead to trans-epidermal water loss, a component of a physiological process known as *perspiratio insensibilis*, and increased permeability to allergens and pathogens and promotes inflammation stimulating the activation of the innate immune response. Cutaneous sensory nerves transmit the increased itch signal to the brain, which leads to further scratching and impairing of skin integrity with the establishment of a self-feeding vicious circle [2][7]. With regard to the treatment of AD, current therapies aim to clear inflamed lesions and reduce itch in order to improve patient's everyday life. Topical therapies with emollients and anti-inflammatory drugs are the mainstay for mild-to-moderate AD; phototherapy and systemic immunomodulatory drugs can be effective in more-severe AD [8].

Hyaluronic acid (HA), a polysaccharide composed of alternating glucuronic acid and N-acetylglucosamine residues, is one of the main components of the extracellular matrix [9], especially in the skin that accounts for about 50% of the total content of HA in the body [10]. HA is a key factor in wound healing and tissue repair processes, being involved in proliferation, differentiation, and migration of keratinocytes [11][12][13], as well as in skin aging owing to its ability to retain water and moisturize skin [9]. In addition, evidence from animal studies have shown that HA is also involved in the establishment and homeostasis of epidermal skin barrier, regulating both epidermal differentiation and lipid synthesis/secretion through the interaction with its receptor CD44 [13][14]. In addition, clinical studies support the safety and the efficacy of hyaluronic acid-based emollient foam in treating patients with moderate AD [15][16].

Herbal extracts have been used for the treatment of skin diseases, among which AD, for centuries [17]. Recently, both in vitro and clinical studies have shown the efficacy of the extract of *Salvia haenkei*, a plant native of Bolivia largely used in traditional medicine [18], as an anti-aging agent [19][20]. In addition, an extract of *Salvia haenkei* has been patented both as re-epithelizing and cicatrizing agent [21] and as an active agent in the treatment of dermatological diseases [22].

2. Evaluation of the Efficacy of IALUSET VITAL® Cream in Helping the Improvement of the Atopic Dermatitis Symptoms in Adults

Atopic dermatitis is mainly characterized by dysfunctions of the skin barrier and an uncontrolled inflammatory response. HA has been shown to play an important role in regulating homeostasis of the skin, especially in maintaining selective permeability of the epidermis and controlling inflammatory response. Moreover, because of its hygroscopic property, HA provides a hydrated microenvironment which facilitates the transport of nutrients through the tissue [23]. Finally, HA directly affects the function of skin cells by mediating signaling events that control the proliferation/differentiation of keratinocytes and lamellar bodies production, important mechanisms for maintaining selective permeability and repair of the skin [11][13]. It was also demonstrated that topical application of HA induces keratinocyte proliferation/differentiation and increases epidermal thickness and skin barrier repair [14].

Immune response in subjects with AD is dysfunctional, characterized by the release of many pro-inflammatory cytokines, such as tumor necrosis factor (TNF) and interleukins [24]. Several authors have shown that HA reduces inflammatory response by downregulating the expression of pro-inflammatory and upregulating anti-inflammatory molecules [25][26][27][28][29]. Indeed, Kim et al. observed that HA decreases skin lesions in an atopic dermatitis model of DNFB-treated Nc/Nga mice [26].

In patients with AD, claudins' expression levels are reduced [30][31]. These proteins together with the occludin form a family of proteins that are the most important components of the tight junctions (TJs). In turn, TJs are critical in the functioning of the skin barrier because defective TJs increase paracellular permeability, resulting in an enhanced flux of environmental factors such as irritants, microbial products, toxins, and allergens, which, crossing the skin surface, trigger the immune response [32]. Recently, the extract of *Salvia haenkei* was shown to increase occludin expression as well as to control the expression and localization of filaggrin, a key marker of keratinocytes' differentiation. Thus, the extract of *Salvia haenkei* reinforces the adhesion between the cells and favors the maintenance of the barrier integrity [22].

Considering the mentioned observations, we performed this clinical study in order to assess on AD patients the efficacy of IALUSET VITAL® cream, a cosmetic containing two molecular weights of hyaluronic acid (300 kDa and 800 kDa) and the extract of *Salvia haenkei*.

This study clearly showed that the regular use of IALUSET VITAL® progressively and significantly reduces AD severity and improves SCORAD, POEM, itch, and stratum corneum moisturization scores. After one week of treatment, a significant decrease of the SCORAD index was already observed in the active group compared to the control group. Interestingly, IALUSET VITAL® treatment improved AD severity from moderate to a mild degree, in a time-dependent manner as shown by the progressive reduction of the mean change of SCORAD index from baseline by 42% compared with 25% induced by vehicles in the control group at week 4.

At the end of treatment, 70% and 65% of the patients in the active and control group, respectively, reported a reduction of the POEM score less than the median value at T0. In particular, only the active group showed 10% of patients with total remission of symptoms.

As concerns the evaluation of itching sensation, immediately after treatment, 80% and 65% of the patients in the active and control group, respectively, showed a reduction of itch score less than the median value at T0. Moreover, 60 min after the treatment, a reduction of itch score lower than the median value at T0, was recorded in 100% and 95% of the patients in the active and control group, respectively.

However, both for POEM and itch score, the differences between the two treatment groups did not appear to be statistically significant.

The treatment with IALUSET VITAL® led to a significant increase of skin hydration throughout the treatment period while the vehicle induced a more variable effect in the control group. Paradoxically, although the TEWL analysis showed a positive trend of IALUSET VITAL®, in terms of effectiveness compared to vehicles, no statistically significant difference has been shown. Similar findings have been reported in other studies on moisturizers [33][34][35]. Our results may not be consistent for several reasons. Firstly, the relationship between skin dryness and TEWL is complex, whereby changes in dryness may not necessarily reflect simultaneous changes in TEWL [36]. Then, standardization of TEWL measurements can be technically difficult, while corneometer is an effective and sensitive tool to determine skin moisturization [37]. Therefore, the latter method is more sensitive to measure the skin barrier function than TEWL in AD patients and a larger sample size may be necessary to clarify this discrepancy and achieve a statistically significant trend in TEWL changes.

The vehicle used in this study was an emollient base cream, with the same composition of IALUSET VITAL® except for the key ingredients hyaluronic acid and extract of *Salvia haenkei*. Due to the presence in the formulation of some humectant and emollient agents such as xylitylglucoside, anhydroxylitol, xylitol, isononyl isononanoate, coco caprylate/caprate, and l-arginine, the vehicle cream exhibits some beneficial moisturizing effects that should be taken into consideration when statistically significant differences in effectiveness between the active and control group have not been noted. Indeed, it is well known that emollients make the epidermis softer and more pliable, and they are effective in increasing skin hydration, improving barrier function, and reducing itching in AD [38].

Thus, the efficacy of IALUSET VITAL® is guaranteed by the good emollient properties resulting from a well-designed basic formulation and, above all, the addition of active ingredients hyaluronic acid and extract of *Salvia haenkei* that greatly increase its effectiveness. In addition, IALUSET VITAL® cream was well-tolerated by patients. Overall, this entry clearly shows that IALUSET VITAL® has a good safety profile and promotes the relief of the most common signs and symptoms of moderate AD, rapidly suppressing itch and reducing eczema severity.

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