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Skin rejuvenating effects of interleukin-1 alpha: A cosmetic study on collagen deposition and elasticity in ageing skin

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ABSTRACT

Objective: The aim of this study was to test the efficacy of interleukin-1 alpha (IL-1a – trademark name Dermatopoietin) on skin renewal, in volunteers with signs of skin ageing. Method: A placebo-controlled and randomized clinical study on skin renewal was conducted in 21 healthy female volunteers (51 ±6 years) by administering a cosmetic formulation with and without IL-1a twice daily upon either the right or left forearm for eight weeks.

Results: Ultrasonograms of all 21 volunteers at baseline and after 28 and 56 days of treatment with a cosmetic formulation containing IL-1a showed improvement of skin density and the partial disappearance of SLEB in all volunteers. The verum formulation containing IL-1a increased elasticity by 20.7% and 15.2% after 28 and 56 days, respectively. Verum-treated skin showed less viscoelasticity than placebo-treated skin.

Conclusion: The results show experimental evidence for a structural (density) and functional (elasticity) improvement of skin by topical administration of a cosmetic formulation containing IL-1a.

IL-1a, a cytokine of 159 amino acids, is best known for its role in the regulation of the immune response. Due to its pleiotropic nature, it has, however, other functions. In skin, IL-1a acts as a messenger regulating skin homeostasis,[1,2] and it is highly and constitutively expressed by keratinocytes in the epidermis.[3] The epidermis, in particular the stratum corneum, is the tissue which contains by far the highest content of IL-1a in the human body.[4] The target cells of epidermal IL-1a are dermal fibroblasts.[8] IL-1a does not only stimulate their proliferation but also activates, in a concentration-dependent manner, the production of procollagen and collagenase, as well as the expression of several growth and differentiation factors for epidermal cells.[5,9,10,11,12] Only at low concentrations does IL-1a also induce the expression of the tissue inhibitor of metalloproteinase (TIMP), a potent inhibitor of collagenase, thus shifting the balance between the production and degradation of collagen towards production.[8] Therefore, only low doses of IL-1a are beneficial for collagen replenishment in skin. Furthermore, keratinocyte-derived IL-1a induces fibroblasts to express growth factors which act back on the epidermis and stimulate its regeneration.[13] The expression of IL-1a by keratinocytes[2,14] and the production of collagen[15] have been shown to decline in ageing skin. The resulting deficit of IL-1a has been hypothesised to be at least partially responsible for the signs of skin ageing. The study detailed below shows that topical administration of a cosmetic formulation containing IL-1a on ageing skin improves structure and function of ageing skin by increasing its density (collagen deposition) and improving its elasticity.

METHOD:

Skin density (collagen content) was measured by ultrasonography at 20 MHz using a DermaScan scanner. Bright pixels on ultrasonograms represent high echogenic areas rich in protein; dark pixels represent low echogenic areas composed primarily of proteoglycans, lipids and water. Skin elasticity was measured with a Cutometer SEM 575, a non-invasive suction/relaxation device to measure the kinetics of rapid and slow movements of skin deformation. Suction and relaxation periods lasted 1 s each. The parameter R2 ('gross skin elasticity', **Figure 1**) is measured during the relaxation phase. It measures the ratio of the rapidly relaxing skin deformation at the end of the 1 s-relaxation phase over the total skin extension at the end of the 1 s-suction period. It is the portion of the relaxation phase with elastic characteristics. The parameter R6 is measured during the suction period. It is the 'viscoelastic to elastic portion' of skin elasticity (**Figure 2**) and is measured by determining the fraction of the extension from 0.1 s to 1 s over the initial rapid extension during the first 0.1 s after applying suction.

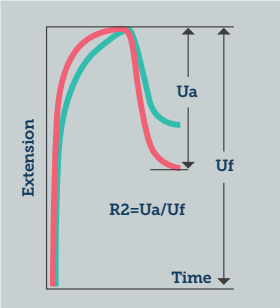


Figure 1.
Schematic representation of the cutometric measurement of 'gross skin elasticity' (parameter R2). 'Extension' is the deformation of skin upon applying suction. Upon release of suction the skin relaxes and eventually returns to the original shape by multiple processes at different velocities. The suction and relaxation phases lasted 1 s each. Uf is the extension after 1s of suction, Ua is measured after relaxation for 1s. Ua represents the elastic component of the relaxation process of skin. The larger R2 = Ua/Uf the higher the skin's elasticity. Green: aged skin; red: young skin.

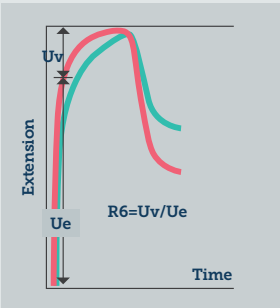
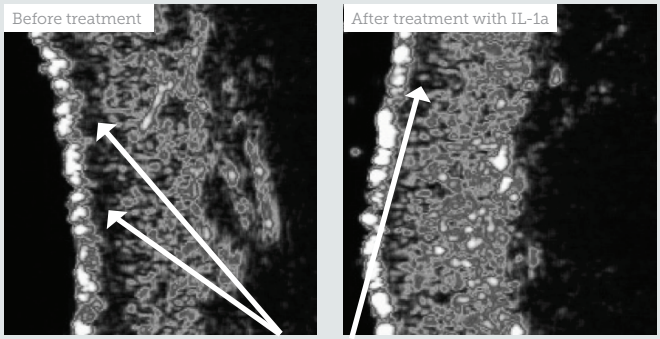


Figure 2.
Schematic representation of the cutometric measurement of the viscoelastic portion of the skin extension process (parameter R6). The application of suction lasts 1s. Ue represents the fast elastic component of skin extension that occurs during the first 0.1s. Uv is the slow viscoelastic portion between 0.1s and 1s. R6 = Uv/Ue = [extension at t = 1s – extension at t = 0.1s] / extension at t = 0.1s. Green: aged skin; red: young skin.

RESULTS:

Ultrasonography at 20 MHz frequency

Ultrasonography is a visualisation technique for skin architecture (**Figure 3**). Light pixels indicate high echogenic areas containing lots of protein, e.g. collagen, keratin and elastin. Dark pixels, on the contrary, are low echogenic due to their scarcity of proteins and abundance of proteoglycans, lipids and/or water. A typical marker of skin ageing, in particular of photoageing, is SLEB, the subepidermal low echogenic band.[16]



SLEB: subepidermal low echogenic band, a reliable marker of skin (photo-)ageing.

Figure 3.
Ultrasonography at 20 MHz is a technique to visualise skin architecture. Light pixels reflect skin proteins, dark pixels proteoglycans, lipid and/or water. The dense structure on the left side is the epidermis (keratin). Underneath the epidermis is the dermis with the main protein collagen. The SLEB, which partially disappears after treatment with IL-1a, is part of the dermis.

Figure 4 (right) shows the ultrasonograms of 20 volunteers at baseline and after 28 and 56 days of treatment with a cosmetic formulation containing IL-1a. Striking is the clear improvement of skin density and the partial disappearance of SLEB in all volunteers.

Skin elasticity

Skin elasticity is a functional parameter of skin which slowly deteriorates with ageing.[17] **Figure 5** shows that the verum formulation containing IL-1a has a skin rejuvenating effect by increasing elasticity by 26.8% and 15.2% after 28 and 56 days, compared to placebo, respectively. The placebo formulation was without effect. A related skin parameter is called R6, which denominates the ratio between the viscoelastic and the elastic deformation of skin upon applying a mechanical force (suction). The portion of viscoelastic processes in skin deformation increases with age. **Figure 6** shows that verum-treated skin exhibits 21.4% less viscoelasticity than placebo-treated skin after 28-days treatment.

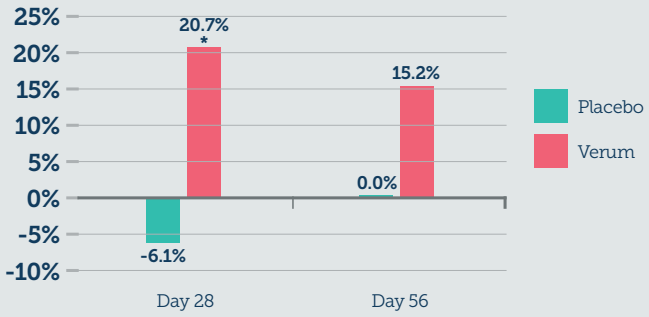


Figure 5.
Change of gross skin elasticity (R2) after 28- or 56-day treatment with either verum or placebo. R2 indicates the elastic portion of skin relaxation after its mechanical deformation. Only the formulation containing IL-1a improved skin elasticity. The difference between verum and placebo at Day 28 was significant with a p-value of 0.03.

Figure 4.

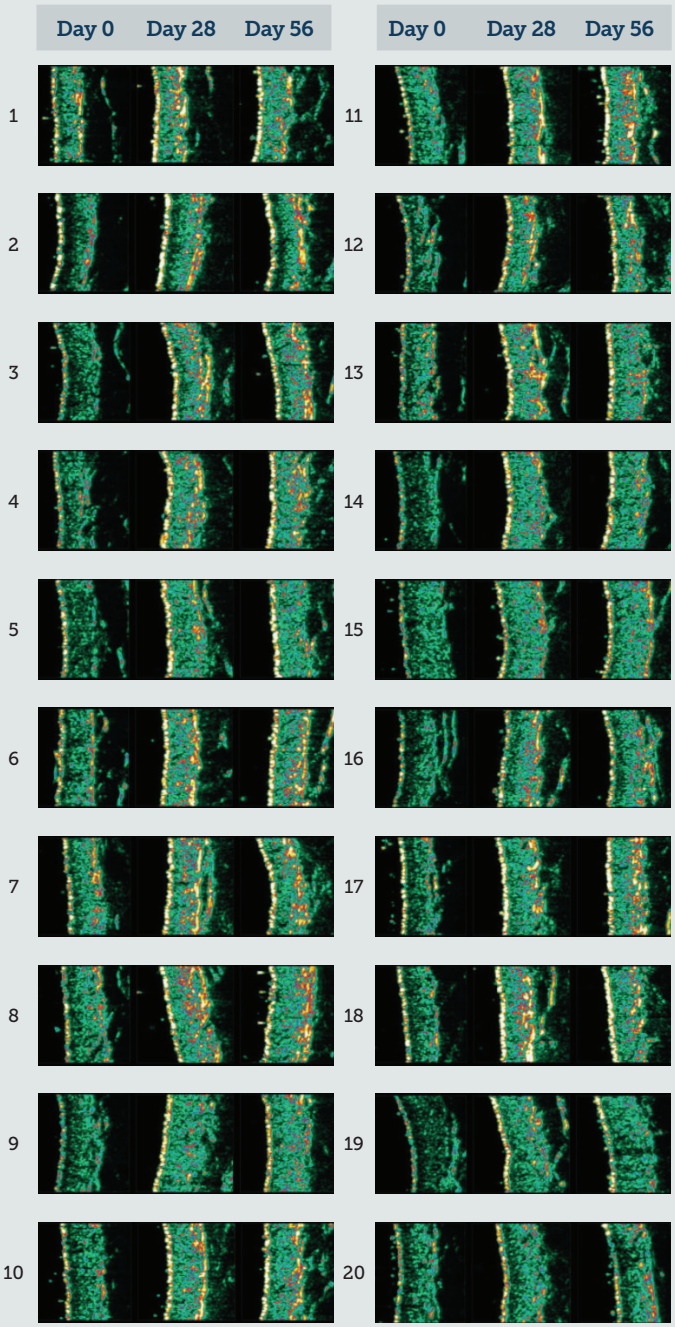


Figure 4.
Ultrasonograms of the forearm skin of 20 subjects out of the 21 volunteers participating in the study at baseline and after 28 and 56 days of treatment with a formulation containing IL-1a, respectively. All subjects showed clear improvement of skin structure.

CONCLUSION:

IL-1a is shown to be an innovative active ingredient for cosmetic products with skin rejuvenating (anti-ageing) properties. It acts on the surface of skin by stimulating keratinocytes, the main cells of the epidermis, to produce and release endogenous IL-1a. The physiological function of this cytokine is to stimulate the fibroblasts in the dermis to increase the expression of collagen and elastin which leads to denser and tighter skin, and eventually to an improved skin elasticity and reduced wrinkles (not shown). Topical IL-1a thus affects deep skin structures without penetrating skin by triggering a cascade of

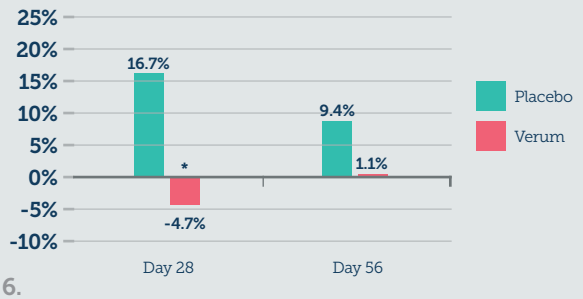


Figure 6.
Change of viscoelasticity (R6) of skin after a 28- or 56-day treatment with verum or placebo, respectively. The difference between verum and placebo at Day 28 was significant with a p-value of 0.0008.

reactions, which propagate from the surface to the depth of skin. In the present paper we show experimental evidence for a structural (density) and functional (elasticity) improvement of skin by topical administration of a cosmetic formulation containing IL-1a.

This study was conducted by the Skin Test Institute, Neuchâtel, Switzerland, under the guidance of Dr Alain Béguin.

Dr Igor Pomytkin created Dermatopoietin and is the owner of numerous other patents. He has a PhD in chemistry and is the current science director of Buddha Biopharma Oy, Helsinki, Finland. Dr Pomytkin previously worked as a senior research scientist at the Institute of Chemical Physics, Moscow.

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