SUMMARY

It has been discovered that (in particular, dermatological) conditions involving cutaneous or connective tissue damage can be treated by inhibiting carbamylation. Specifically, it has been shown that a patient suffering from vulvar lichen sclerosus has achieved complete remission of symptoms, reduction of pain, and a dramatic improvement of skin changes after few weeks of treatment with a cream containing nucleophiles. There is a rationale that isocyanate, derived from urea, arising from associated urinary incontinence, and/or increased MPO-mediated transformation of thiocyanate due to inflammation, is a causal factor for lichen sclerosus due to destructive carbamylation of cutaneous and connective tissue (e.g. elastin, collagen). Without being bound by theory, the inventors believe that carbamylation affects the intramolecular bridges and the 3-dimensional structure of collagen, elastin and anchoring filaments, which results in the atrophy, fibrosis, fissures, and hyperkeratosis observed not only in LS patients, but also a range of other inflammatory diseases with cutaneous and connective tissue manifestations, including but not limited to, cutaneous Lupus erythematosus, localized scleroderma, lichen planus, Dupuytren's contracture, Carpal tunnel syndrome, morphea, acquired perforating dermatosis, and vulvovaginal atrophy.

Further, other recent studies have identified circulating autoantibodies against the Extracellular Matrix 1 protein (ECM1) in most patients with lichen sclerosus (Tran et.al. 2019). Within the epidermis, ECM1 has a role in the control of keratinocyte differentiation. ECM1 binds to the major heparan sulphate proteoglycan, perlecan. In this way, ECM1 may act as a 'biological glue' in the dermis, helping to regulate basement membrane and interstitial collagen fibril macro-assembly and growth factor binding. ECM1 may also have a role in other acquired skin disorders and physiological skin changes. It is conceivable that carbamylation may also lead to dysregulation of ECM1 and thereby contribute to cutaneous and connective tissue damage in lichen sclerosus and other conditions.

Another important protein for function of various tissues is filaggrin, which is particularly essential for epidermal homeostasis (Thyssen and Maibach 2014). Similarly, carbamylation of filaggrin may lead to loss of function, resulting in cutaneous and connective tissue damage.

A pharmaceutical composition is thus provided, said pharmaceutical composition comprising a nucleophilic compound capable of inhibiting carbamylation, for use in the treatment of a condition (in particular, a dermatological condition) involving cutaneous or connective tissue damage. A method for treating a dermatological condition, in particular a dermatological condition, involving cutaneous or connective tissue damage in a patient is also provided, said

method comprising administering a pharmaceutical composition comprising a nucleophilic compound capable of inhibiting carbamylation to said patient.

In an aspect, there is provided a pharmaceutical composition comprising a nucleophilic compound capable of inhibiting carbamylation, for use in the treatment of lichen sclerosus.

In another aspect, there is provided the use of a pharmaceutical composition comprising a nucleophilic compound capable of inhibiting carbamylation in the manufacture of a medicament for the treatment of lichen sclerosus.

CLAIMS

1. A pharmaceutical composition comprising a nucleophilic compound capable of inhibiting carbamylation, for use in the treatment of lichen sclerosus.

2. Use of a pharmaceutical composition comprising a nucleophilic compound capable of inhibiting carbamylation in the manufacture of a medicament for the treatment of lichen sclerosus.

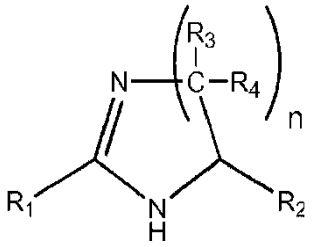
3. The pharmaceutical composition for use according to claim 1 or the use according to claim 2, wherein said composition is a topical composition.

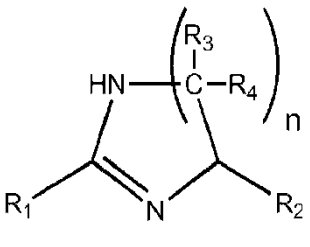
4. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein said nucleophilic compound results in a degree of BSA carbamylation of less than 80%, preferably less than 70%, more preferably less than 60%, even more preferably less than 50% as measured by the in vitro protein carbamylation assay provided herein.

5. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein the nucleophilic compound is a dipeptide, a tripeptide or a tetrapeptide, preferably a dipeptide.

6. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein the nucleophilic compound is a dipeptide or tetrapeptide selected from: Gly-Gly, Lys-Pro, Val-Pro, Ile-Pro, Tyr-Pro, Ser-Pro, Pro-Ser, Ala-Gln, Ala-Glu, Tyr-Ala, Val-Tyr, Gly-Sar, Gly-His, Gly-Gly-Gly-Gly, D-Phe-D-Phe-D-Leu-D-Lys-4-amino-piperidine-4-carboxylic acid TFA salt, or wherein the nucleophilic compound is selected from the group consisting of acetylcysteine, phenelzine and sitagliptin.

7. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein the nucleophilic compound is not a compound of formula (I) or (II):





(I) (II)

in which R1 is H or C_1-C_4 alkyl,

R2 is H, -COOH, -COO(C_1-C_4 alkyl) or -CONHR$_5$, where R_5 is H, C_1-C_4 alkyl, an amino acid radical, dipeptide radical or tripeptide radical, R3 and R4 are in each case independently of one another H or OH, n is 1, 2 or 3, or a pharmaceutically acceptable salt, stereoisomer or solvate thereof.

8. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein the lichen sclerosus is genital lichen sclerosus , preferably vulvar lichen sclerosus.

9. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein the nucleophilic compound is selected from the group of acetylcysteine, phenelzine, sitagliptin, or Ala-Gln and wherein said composition is a topical composition.

10. The pharmaceutical composition for use or the use according to any one of the preceding claims, wherein the invention is a topical cream comprising (in w/w%):

- Histidine 0.1 – 1 %
- Arginine 0.5 – 1.5 %
- Lysine 0.50 – 1.5 %
- Optionally, corticosteroid 0.01 – 1.0 %

by weight of the entire pharmaceutical composition.