A METHOD OF TREATING A DERMATOLOGICAL CONDITION

TECHNICAL FIELD

The present disclosure relates broadly to a method of treating a dermatological/skin condition, such as pruritus/itch and associated conditions, and related uses and agents.

BACKGROUND

There is a paucity of effective treatment options for dermatological/skin conditions such as pruritus/itch and associated conditions. In particular, chronic pruritus of unknown origin (CPUO) is defined as itch lasting for longer than six weeks, with a non-contributory diagnostic workup. A recent systematic review revealed an absence of evidence for interventions, such as topical emollients, cooling lotions, corticosteroids, antidepressants, antihistamines, anticonvulsants, and phototherapy. Consistent with the data in published literature, multiple interventions have demonstrated poor efficacies, with an absence of curative treatment.

Thus, there is a need to address or at least ameliorate one or more of the above-mentioned problems. In particular, there is a need to provide a method of treating a dermatological/skin condition, such as pruritus/itch and associated conditions, and related uses and agents that address or at least ameliorate one or more of the above-mentioned problems.

SUMMARY

In one aspect, there is provided use of an agent that is capable of reducing obstruction of a sweat duct in the manufacture of a medicament for the treatment of pruritus in a subject.

In one embodiment, the agent is capable of reducing obstruction of a sweat duct at its orifice by keratin.

In one embodiment, the agent is capable of reducing an expression of keratin.

In one embodiment, the agent is capable of binding to retinoic acid receptor (RAR) and/or retinoid X receptor (RXR).

In one embodiment, the agent comprises retinoid.

In one embodiment, the retinoid is selected from the group consisting of tretinoin, isotretinoin, alitretinoin, acitretin, etretinate, bexarotene, adapalene, tazarotene and derivatives thereof.

In one embodiment, the retinoid is selected from the group consisting of isotretinoin, acitretin and derivatives thereof.

In one embodiment, the medicament is to be administered systematically.

In one embodiment, the medicament is to be administered orally.

In one embodiment, the medicament is in a solid dosage form.

In one embodiment, the medicament is to be administered daily.

In one embodiment, the medicament is to be administered daily at a dosage of 10 mg to 20 mg.

In one embodiment, the medicament is capable of reducing an intensity of pruritus in the subject by at least about 20% as measured by a numerical rating scale (NRS).

In one embodiment, the medicament is capable of reducing an intensity of pruritus in the subject by at least about 25% as measured by a NRS.

In one embodiment, the medicament is capable of resolving pruritus in the subject.

In one embodiment, the subject has severe pruritus as measured by a NRS.

In one embodiment, the subject was previously ineffectively treated for pruritus by another medicament selected from: medicaments indicated for pruritus, topical medicaments, emollients, steroids, antihistamines and combinations thereof.

In one embodiment, the subject has sweat ducts that are at least partially obstructed at their orifices by keratin.

In one embodiment, the pruritus comprises chronic pruritus that lasted for at least 6 weeks.

In one embodiment, the chronic pruritus comprises chronic pruritus of unknown origin (CPUO).

DEFINITIONS

The term “treatment", "treat" and “therapy”, and synonyms thereof as used herein refer to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) a medical condition (such as a dermatological/skin condition), which includes but is not limited to diseases, symptoms and disorders. A medical condition also includes a body’s response to a disease or disorder, e.g. inflammation. Those in need of such treatment include those already with a medical condition as well as those prone to getting the medical condition or those in whom a medical condition is to be prevented.

The term “subject” as used herein includes patients and non-patients. The term “patient” refers to individuals suffering or are likely to suffer from a medical condition such as a dermatological/skin condition, while “non-patients” refer to individuals not suffering and are likely to not suffer from the medical condition. “Non-patients” include healthy individuals, non-diseased individuals and/or an individual free from the medical condition. The term “subject” includes humans and animals. Animals include murine

and the like. “Murine” refers to any mammal from the family Muridae, such as mouse, rat, and the like.

As used herein, the term "therapeutically effective amount" will be an amount of an active agent that is capable of preventing, reversing or at least slowing down (lessening) a medical condition, such as a dermatological/skin condition. Dosages and administration of agents, compounds, compositions and formulations of the present disclosure may be determined by one of ordinary skill in the art of clinical pharmacology or pharmacokinetics. See, for example, Mordenti and Rescigno, (1992) Pharmaceutical Research. 9:17-25; Morenti et al., (1991) Pharmaceutical Research. 8:1351-1359; and Mordenti and Chappell, "The use of interspecies scaling in toxicokinetics" in Toxicokinetics and New Drug Development, Yacobi et al. (eds) (Pergamon Press: NY, 1989), pp. 42-96. An effective amount of the active agent of the present disclosure to be employed therapeutically will depend, for example, upon the therapeutic objectives, the route of administration, and the condition of the subject. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect.

The term "micro" as used herein is to be interpreted broadly to include dimensions from about 1 micron to about 1000 microns.

The term "nano" as used herein is to be interpreted broadly to include dimensions less than about 1000 nm.

The term “particle” as used herein broadly refers to a discrete entity or a discrete body. The particle described herein can include an organic, an inorganic or a biological particle. The particle used described herein may also be a macro-particle that is formed by an aggregate of a plurality of sub-particles or a fragment of a small object. The particle of the present disclosure may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. The term “size” when used to refer to the particle broadly refers to the largest dimension of the particle. For example, when the particle is substantially spherical, the term “size” can refer to the diameter of the particle; or when the particle is substantially non-spherical, the term “size” can refer to the largest length of the particle.

The terms "coupled" or "connected" as used in this description are intended to cover both directly connected or connected through one or more intermediate means, unless otherwise stated.

The term "associated with", used herein when referring to two elements refers to a broad relationship between the two elements. The relationship includes, but is not limited to a physical, a chemical or a biological relationship. For example, when element A is associated with element B, elements A and B may be directly or indirectly attached to each other or element A may contain element B or vice versa.

The term "adjacent" used herein when referring to two elements refers to one element being in close proximity to another element and may be but is not limited to the elements contacting each other or may further include the elements being separated by one or more further elements disposed therebetween.

The term "and/or", e.g., "X and/or Y" is understood to mean either "X and Y" or "X or Y" and should be taken to provide explicit support for both meanings or for either meaning.

Further, in the description herein, the word “substantially” whenever used is understood to include, but not restricted to, "entirely" or “completely” and the like. In addition, terms such as "comprising", "comprise", and the like whenever used, are intended to be non-restricting descriptive language in that they broadly include elements/components recited after such terms, in addition to other components not explicitly recited. For example, when “comprising” is used, reference to a “one” feature is also intended to be a reference to “at least one” of that feature. Terms such as “consisting”, “consist”, and the like, may in the appropriate context, be considered as a subset of terms such as "comprising", "comprise", and the like. Therefore, in embodiments disclosed herein using the terms such as "comprising", "comprise", and the like, it will be appreciated that these embodiments provide teaching for corresponding embodiments using terms such as “consisting”, “consist”, and the like. Further, terms such as "about", "approximately" and the like whenever used, typically means a reasonable variation, for example a variation of +/- 5% of the disclosed value,

or a variance of 4% of the disclosed value, or a variance of 3% of the disclosed value, a variance of 2% of the disclosed value or a variance of 1% of the disclosed value.

Furthermore, in the description herein, certain values may be disclosed in a range. The values showing the end points of a range are intended to illustrate a preferred range. Whenever a range has been described, it is intended that the range covers and teaches all possible sub-ranges as well as individual numerical values within that range. That is, the end points of a range should not be interpreted as inflexible limitations. For example, a description of a range of 1% to 5% is intended to have specifically disclosed sub-ranges 1% to 2%, 1% to 3%, 1% to 4%, 2% to 3% etc., as well as individually, values within that range such as 1%, 2%, 3%, 4% and 5%. It is to be appreciated that the individual numerical values within the range also include integers, fractions and decimals. Furthermore, whenever a range has been described, it is also intended that the range covers and teaches values of up to 2 additional decimal places or significant figures (where appropriate) from the shown numerical end points. For example, a description of a range of 1% to 5% is intended to have specifically disclosed the ranges 1.00% to 5.00% and also 1.0% to 5.0% and all their intermediate values (such as 1.01%, 1.02% … 4.98%, 4.99%, 5.00% and 1.1%, 1.2% ... 4.8%, 4.9%, 5.0% etc.,) spanning the ranges. The intention of the above specific disclosure is applicable to any depth/breadth of a range.

Additionally, when describing some embodiments, the disclosure may have disclosed a method and/or process as a particular sequence of steps. However, unless otherwise required, it will be appreciated that the method or process should not be limited to the particular sequence of steps disclosed. Other sequences of steps may be possible. The particular order of the steps disclosed herein should not be construed as undue limitations. Unless otherwise required, a method and/or process disclosed herein should not be limited to the steps being carried out in the order written. The sequence of steps may be varied and still remain within the scope of the disclosure.

Furthermore, it will be appreciated that while the present disclosure provides embodiments having one or more of the features/characteristics discussed herein, one or more of these features/characteristics may also be disclaimed in other alternative

embodiments and the present disclosure provides support for such disclaimers and these associated alternative embodiments.

DESCRIPTION OF EMBODIMENTS

Exemplary, non-limiting embodiments of a method of treating a dermatological/skin condition, such as pruritus/itch and associated conditions, and related uses and agents are disclosed hereinafter.

In various embodiments, there is provided a method of treating a dermatological/skin condition in a subject. In various embodiments, the dermatological/skin condition comprises pruritus/itch and related conditions.

In one example, dilation of the sweat ducts and exudation of fluid to the surroundings were observed in patients suffering from a dermatological/skin condition such as pruritus/itch and related conditions. This suggests an obstruction of sweat orifice at the stratum corneum, which comprises keratin, in these patients. Unlike patients with hypohidrosis or complete sweat duct obstruction, however, these patients were generally able to sweat. Skin biopsies of itchy versus non-itchy skin areas in these patients demonstrated leakage of sweat components into the dermis. Without being bound by theory, it is believed that partial sweat duct obstruction contribute to dermatological/skin condition such as pruritus/itch and related conditions in a subject. Without being bound by theory, it is believed that sweat which leaks into the epidermis irritates intraepidermal nerve fibers to result in itch, and sweat which leaks into the dermis irritates nociceptive nerve fibers to result in a prickly sensation.

In various embodiments therefore, the method comprises reducing obstruction of sweat ducts in the subject, optionally reducing obstruction of sweat ducts at their orifice by keratin. The obstruction may be partial or complete. In some embodiments, the obstruction is a partial obstruction. In various embodiments, the method comprises reducing keratinization/hyperkeratinization in the subject. In various embodiments, the method comprises regulating/modulating an expression/level/amount of keratin in the subject. In various embodiments, the method comprises reducing an expression/level/amount of keratin in the subject. An “expression” includes genotypic

expression and phenotypic expression. Without being bound by theory, it is believed that nuclear hormone receptors such as retinoid receptor is involved in the regulation of keratin is expression/level/amount. In various embodiments therefore, the method comprises activating a nuclear hormone receptor, optionally a retinoid receptor. In various embodiments, the method comprises activating a retinoic acid receptor (RAR) and/or a retinoid X receptor (RXR). The RAR and RXR may be of subtypes α, β and/or γ. In various embodiments, the method comprises activating a retinoid signalling pathway.

In various embodiments, the method comprises administering to the subject an agent that is capable of reducing obstruction of sweat ducts, optionally reducing obstruction of sweat ducts at their orifices by keratin. In various embodiments, the method comprises administering to the subject an agent that is capable of reducing hyperkeratinization. In various embodiments, the method comprises administering to the subject an agent that is capable of regulating/modulating an expression/level/amount of keratin in a subject. In various embodiments, regulating/modulating an expression/level/amount of keratin in a subject comprises reducing an expression/level/amount of keratin in the subject. In various embodiments, the method comprises administering to the subject an agent that is capable of activating a nuclear hormone receptor, optionally a retinoid receptor. In various embodiments, the method comprises administering to the subject an agent that is capable of activating a retinoic acid receptor (RAR) and/or a retinoid X receptor (RXR). In various embodiments, the method comprises administering to the subject an agent that is capable of activating a retinoid signalling pathway.

An “agent” may be anything (physical, chemical, biological etc.) that a subject may be exposed to or administered with e.g., in order to reduce obstruction of sweat ducts. Non-limiting examples of an “agent” include chemicals, compounds, compositions, molecules, small molecules, nucleic acid sequences, nucleic acid analogs, proteins, peptides, aptamers, antigen-binding proteins, antibodies, or fragments or derivatives thereof. The term “agent” in no way excludes the use of two or more such agents. Accordingly, the term “agent” also contemplates mixtures, fusions, combinations, compositions and conjugates, for example, mixtures, fusions, combinations, compositions and conjugates of any chemicals, compounds,

compositions, molecules, small molecules, nucleic acid sequences, nucleic acid analogs, proteins, peptides, aptamers, antigen-binding proteins, antibodies, or fragments or derivatives thereof etc. In various embodiments, the agent comprises a therapeutic agent.

In various embodiments, the method comprises administering to the subject an agent comprising retinoid. Examples of retinoid include, but are not limited to, tretinoin (all-trans retinoic acid; e.g., Vesanoid), isotretinoin (e.g., Accutane), alitretinoin (9-cis-retinoic acid; e.g., Toctino), acitretin (e.g., Soriatane), etretinate (e.g., Tegison), bexarotene (e.g., Tagretin), adapalene (e.g., Differin, Epiduo) and tazarotene (e.g., Tazorac). In some embodiments, the retinoid comprises retinoic acid. In various embodiments, the method comprises administering to the subject a first retinoid, optionally stopping the administration of the first retinoid and administering to the subject a second retinoid. In various embodiments, the method comprises administering to the subject a first retinoid at a first timepoint and a second retinoid at a second timepoint. In various embodiments, the first and second retinoids are different. In various embodiments, the first and second timepoints are different and/or do not overlap. In various embodiments, the first and second retinoids are selected from acitretin and isotretinoin. In some examples, the subject responded to treatment after switching from one retinoid to another retinoid.

Embodiments of the method may be non-invasive. The methods may be in vivo, ex vivo or in-vitro methods.

In various embodiments, there is provided an agent as described herein for use in therapy e.g., an agent that is capable of one or more of the following: reducing obstruction of sweat ducts, reducing obstruction of sweat ducts at their orifices by keratin, reducing hyperkeratinization, regulating/modulating/reducing an expression/level/amount of keratin in a subject, activating a nuclear hormone receptor/retinoid receptor/RAR/RXR, activating a retinoid signalling pathway, and/or an agent that is a ligand or an agonist of one of or both RAR and RXR and/or an agent that comprises retinoid.

In various embodiments, there is provided an agent as described herein for use in treating a dermatological/skin condition, optionally wherein the dermatological/skin condition comprises pruritus/itch and related conditions.

In various embodiments, there is provided an agent as described herein in the manufacture of a medicament for the treatment of a dermatological/skin condition, optionally wherein the dermatological/skin condition comprises pruritus/itch and related conditions. In various embodiments therefore, there is provided use of an agent that is capable of reducing obstruction of a sweat duct in the manufacture of a medicament for the treatment of pruritus in a subject. In various embodiments, there is provided use of retinoid in the manufacture of a medicament for the treatment of pruritus in a subject.

In various embodiments, the agent comprises retinoid. In various embodiments, the retinoid is selected from the group consisting of tretinoin, isotretinoin, alitretinoin, acitretin, etretinate, bexarotene, adapalene, tazarotene, derivatives, analogs, precursors, metabolites, prodrugs, mixtures and combinations thereof. In various embodiments, the retinoid is selected from the group consisting of tretinoin, isotretinoin, alitretinoin, acitretin, etretinate, bexarotene, adapalene, tazarotene and derivatives thereof. In various embodiments, the retinoid is selected from the group consisting of isotretinoin, acitretin and derivatives thereof. A derivative of a compound (e.g., retinoid) is not limited to one produced or obtained from the compound although it may be one produced or obtained from the compound. In some embodiments, the derivative is derivable, at least theoretically, from the compound through modification of the compound. In some embodiments, a derivative of a compound shares or at least retains to a certain extent a function, chemical property, biological property, chemical activity and/or biological activity associated with the compound. A skilled person will be able to identify, on a case-by-case basis and upon reading of the disclosure, the common structural feature, fundamental structure and/or underlying chemical basis of the compound that have to be maintained in the derivative to retain the function, chemical property, biological property, chemical activity, and/or biological activity. A skilled person will also be able to identify assays that can prove the retention of the function, chemical property, biological property, chemical activity, and/or biological activity. For example, in vivo/skin imaging (e.g., using high-definition optical coherence

tomography (HD-OCT)) may be performed on a subject before and after administration of a retinoid to determine whether the retinoid is capable of reducing obstruction of sweat ducts. For example, skin biopsies may be taken from the subject before and after administration of a retinoid to determine whether the retinoid is capable of reducing obstruction of sweat ducts e.g., using immunofluorescence analysis. The term “derivative” as used herein in relation to a compound may include analogs, prodrugs, precursors and metabolites of the compound. In various embodiments, the retinoids comprises systemic retinoids, optionally oral retinoids.

In various embodiments, the retinoid is capable of binding to/activating either one of or both of retinoic acid receptor (RAR) and a retinoid X receptor (RXR). In some embodiments, the retinoid is capable of binding to/activating RAR selectively but not RXR. In some embodiments, the retinoid is capable of binding to/activating RXR selectively but not RAR. In some embodiments, the retinoid is capable of binding to both RAR and RXR. In some embodiments, the retinoid binds preferentially to RAR over RXR. In some embodiments, the retinoid binds preferentially to RXR over RAR. In some embodiments, the retinoid is a ligand of one of or both of RAR and RXR. In some embodiments, the retinoid is an agonist of one of or both of RAR and a retinoid X receptor RXR.

In various embodiments, the agent/medicament comprise or is in the form of a composition, optionally a pharmaceutical composition. The pharmaceutical composition may further comprise a pharmaceutically acceptable carrier and/or pharmaceutically active compound. In one embodiment, there is provided a pharmaceutical composition comprising an agent as described herein and a pharmaceutically acceptable carrier for use in therapy or for use in treating a dermatological/skin condition such as pruritus/itch and related conditions.

Advantageously, embodiments of the agent/medicament/composition as described herein are effective in treating a dermatological/skin condition such as pruritus/itch and related conditions. In various embodiments, the agent/medicament/composition is capable of achieving a Minimal Clinically Important Difference (MCID) in numerical rating of the severity/intensity of the dermatological/skin condition such as pruritus/itch (including chronic pruritus/itch) and

related conditions. In some examples, the MCID may be about 2 points on a numerical rating scale of 1-10, in accordance with previously determined MCID in numerical ratings of chronic itch and/or in accordance with the internationally recognised way of evaluating itch. In various embodiments, the agent/medicament is capable of reducing a severity/intensity of the dermatological/skin condition such as pruritus/itch and related conditions in the subject by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or at least about 100% as measured by a scale. The scale may be unidimensional or multidimensional. Examples of unidimensional scales for a dermatological/skin condition such as pruritus/itch include, but are not limited to, the numerical rating scale (NRS) and the visual analogue scale (VAS). In NRS and VAS, subjects may self-report their severity/intensity of pruritus/itch. For example, in NRS, subjects may self-report their severity/intensity of pruritus/itch or peak pruritus/itch based on the question: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch overall (on average) during the previous 24 hours?', or the question: 'On a scale of 0 to 10, with 0 being "no itch" and 10 being "worst itch imaginable", how would you rate your itch at the worst moment during the previous 24 hours?'. In NRS, the severity/intensity of pruritus/itch can be categorized into no (0 point), mild (1–3 points), moderate (4–6 points), severe (7–8 points), and very severe pruritus (≥9 points). For example, in VAS, the scale may consist of a 10 cm long line with the question: 'On a scale of "no itch" (left) to "worst itch imaginable" (right), how was your itch, on average, in the past 24 hours?', or the question: 'On a scale of "no itch" (left) to "worst itch imaginable" (right), how was your worst itch in the past 24 hours?'. Subjects may mark a position on the line between 0 (left) and 10 (right) that best represents their pruritus/itch. In VAS, the severity/intensity of pruritus/itch can be categorized as follows: $0 = \text{no pruritus}$, $> 0 – < 4$ points = mild pruritus, $\geqslant 4 – < 7$ points = moderate pruritus, $\geqslant 7 – < 9$ points = severe pruritus, and $\geqslant 9$ points = very severe. Examples of multidimensional scales for a dermatological/skin condition such as pruritus/itch include the pruritus grading system (Szepietowski JC, Schwartz RA. Uremic pruritus. Int J Dermatol. 1998;37(4):247–53), the 5-D itch scale (Elman S,

Hynan LS, Gabriel V, Mayo MJ. The 5-D itch scale: a new measure of pruritus. Br J Dermatol. 2010;162(3):587–93), and the itch severity scale (Majeski CJ, Johnson JA, Davison SN, Lauzon CJ. Itch severity scale: a self-report instrument for the measurement of pruritus severity. Br J Dermatol. 2007;156(4):667–73).

In various embodiments, the agent/medicament/composition is capable of reducing a severity/intensity of the dermatological/skin condition such as pruritus/itch and related conditions in the subject by at least about 5%, at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95% or at least about 100%, e.g., as measured by a numerical rating scale (NRS). In various embodiments, the agent/medicament/composition is capable of reducing a severity/intensity of the dermatological/skin condition such as pruritus/itch and related conditions in the subject by at least about 1 point, at least about 2 points, at least about 3 points, at least about 4 points, at least about 5 points, at least about 6 points, at least about 7 points, at least about 8 points, at least about 9 points, at least about 10 points e.g., as measured by a NRS. In various embodiments, the NRS comprises a rating of 0-10, wherein 0 represents no itch and 10 represents worst itch imaginable. In various embodiments, such improvement is measured/detected/identified after about 1 month, about 2 months, about 3 months, about 4 months or about 5 months from the administration of the agent/medicament/composition. In various embodiments, such improvement is maintained for about at least about 1 month, at least about 2 months, at least about 3 months, at least about 4 months, at least about 5 months, at least about 6 months, at least about 7 months, at least about 8 months, at least about 9 months, at least about 10 months, at least about 11 months or at least about 12 months.

In various embodiments, the agent/medicament/composition is capable of resolving of the dermatological/skin condition such as pruritus/itch and related conditions in the subject. In various embodiments, the agent/medicament/composition is capable of achieving curative treatment of the dermatological/skin condition such as pruritus/itch and related conditions. In one example, subjects achieved an itch score

of 0 or 1 after being administered the agent/medicament/composition. In one example, sustained resolution of the dermatological/skin condition such as pruritus/itch and related conditions in the subject is achieved after administration of the agent/medicament/composition. In one example, sustained resolution of the dermatological/skin condition such as pruritus/itch and related conditions of at least about 200 days, about 250 days or about 300 days is achieved. In one example, subjects exhibit a durable disease-free period after stopping treatment.

In various embodiments, the dermatological/skin condition comprises pruritus/itch. In various embodiments, the pruritus/itch comprises pruritus/itch lasting for or that lasted for more than about 1 week, more than about 2 weeks, more than about 3 weeks, more than about 4 weeks, more than about 5 weeks, more than about 6 weeks, more than about 7 weeks, more than about 8 weeks, more than about 9 weeks, more than about 10 weeks, more than about 11 weeks, more than about 12 weeks, more than about 13 weeks, more than about 14 weeks, more than about 15 weeks, more than about 16 weeks, more than about 17 weeks or more than about 18 weeks. In various embodiments, the pruritus/itch comprises chronic pruritus/itch. In various embodiments, the pruritus/itch comprises chronic pruritus/itch lasting for or that lasted for more than about 6 weeks, more than about 7 weeks, more than about 8 weeks, more than about 9 weeks, more than about 10 weeks, more than about 11 weeks, more than about 12 weeks, more than about 13 weeks, more than about 14 weeks, more than about 15 weeks, more than about 16 weeks, more than about 17 weeks or more than about 18 weeks. In one embodiments, the pruritus/itch comprises chronic pruritus/itch lasting for or that lasted for more than about 6 weeks. In various embodiments, the chronic pruritus/itch comprises chronic pruritus of unknown origin (CPUO). In various embodiments, the chronic pruritus of unknown origin does not have a known etiology e.g., based on diagnostic workup.

The route of administration of the medicament/agent/composition is not particularly limited and may include administration by the systemic, oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intrasternal and intradermal). The suitable route of administration may vary with the condition and age of the subject. In various embodiments, administration is by the systemic route. In various embodiments,

administration is by the oral route. In various embodiments therefore, the medicament/agent/composition is to be administered systematically. In various embodiments, the medicament/agent/composition is to be administered orally.

The frequency and duration of administration/treatment may vary with the route of the administration and the condition of the subject. In some embodiments, the medicament/agent/composition is to be administered daily. In some embodiments, the medicament/agent/composition is to be administered e.g., daily until the dermatological/skin condition such as pruritus/itch and related conditions are substantially resolved. In various embodiments, the duration of treatment is no more than about 3 months, no more than about 5 months, no more than about 10 months, no more than about 20 months, no more than about 30 months, no more than about 40 months, no more than about 50 months, no more than about 60 months, no more than about 70 months, no more than about 80 months, no more than about 90 months, no more than about 100 months, no more than about 110 months, no more than about 120 months, no more than about 130 months, no more than about 140 months, no more than about 150 months, no more than about 160 months, no more than about 170 months, no more than about 180 months, no more than about 190 months, no more than about 200 months, no more than about 210 months, no more than about 220 months, no more than about 230 months, no more than about 240 months, no more than about 250 months, no more than about 260 months, no more than about 270 months, no more than about 280 months, no more than about 290 months, no more than about 300 months, no more than about 310 months, no more than about 320 months, no more than about 330 months, no more than about 340 months, no more than about 350 months or no more than about 360 months.

In various embodiments, a predetermined amount/ therapeutically effective amount of the agent/medicament/composition is administered to the subject. In various embodiments, the amount/dosage of the agent/medicament/composition administered to the subject at any one time is from about 5 mg to about 50 mg, from about 5 mg to about 30 mg or from about 10 mg to about 20 mg. In various embodiments, the amount/dosage of the agent/medicament/composition administered to the subject at any one time is about 5 mg, about 10 mg, about 15 mg, about 20 mg, about 25 mg, about 30 mg, about 35 mg, about 40 mg, about 45 mg or about 50 mg.

A typical dosage may be in the range of from about 10 mg to about 20 mg. Higher dosages e.g., about 30 mg, may be administered to certain subjects with a more severe condition. However, the dosage cannot be too high as subjects may not be able to tolerate the side effects associated with high dosages of certain agent/medicament/composition comprising retinoid. In various embodiments, the agent/medicament/composition is to be administered daily at a dosage of 10 mg to 20 mg. In various embodiments, the doses of the medicament/composition are escalated over time. For example, a low initial dose may be administered to the subject and then increased subsequently. For example, an increment of about 5 mg to about 10 mg may be made every few months, e.g., every 2-4 months. The dosage, initial dosage and subsequent dosage may be individualized to each subject. Advantageously, in various examples, the dosages as disclosed herein are found to be effective for treating dermatological/skin condition such as pruritus/itch and related conditions while having minimal adverse effects.

The medicament/agent/composition may be in a solid dosage form. They may further be presented as discrete units such as capsules, sachets or tablets. They may comprise a predetermined amount/ therapeutically effective amount of the active agent, e.g., an agent as described herein.

In various embodiments, the subject has severe pruritus e.g., as measured by a NRS prior to treatment. In various embodiments, the self-reported severity/intensity of pruritus/itch by the subject is at least about 7 points or at least about 8 points in a NRS having a rating of 0-10, wherein 0 represents no itch and 10 represents worst itch imaginable.

In various embodiments, the subject does not have hypohidrosis. In various embodiments, the subject does not have complete obstruction of sweat ducts e.g., at the orifices. In various embodiments, the subject has sweat ducts that are at least partially obstructed e.g., at their orifices by e.g., keratin. Partial obstruction of sweat orifices may be present in the subject. In various embodiments, keratinaceous partial obstruction of sweat orifices is present in the subject. In various embodiments, the subject has leakage of sweat into dermis and/or epidermis or both. In various embodiments, the subject does not have dermatological abnormalities e.g., clinically

evident primary dermatological abnormalities (except for scratch-induced skin lesions) and/or no major serum biochemical abnormalities. In various embodiments, the subject does not have/is not diagnosed with other dermatosis or a primary dermatosis. In various embodiments, the subject does not have a dermatological/skin condition such as pruritus/itch and related conditions that result from heterogeneous pathophysiological processes, other than sweat orificial keratinization abnormality. In various embodiments, the subject does not have pemphigoid e.g., non-bullous pemphigoid. In various embodiments, the subject has eosinophilia e.g., peripheral eosinophilia. In various embodiments, the site of the dermatological/skin condition such as pruritus/itch and related conditions is at a lower limb. In various embodiments therefore, the method further comprises a step of determining whether one or more of the above-mentioned is present in the subject prior to the administering step.

In various embodiments, the subject comprises a human subject. In various embodiments, the subject comprises an elderly subject. In various embodiments, where the subject is pregnant and/or is a female of childbearing age, retinoids/agents which are contraindicated for pregnancy (e.g., acritretin) is not administered to the subject. For such subjects, other agents/retinoids such as isotretinoin may be administered instead.

In various embodiment, the subject experienced pruritus/itch for at least about at least about 5 months, at least about 10 months, at least about 15 months, at least about 20 months, at least about 25 months, at least about 30 months, at least about 35 months, at least about 40 months, at least about 45 months, at least about 50 months, at least about 55 months, at least about 60 months, at least about 65 months, at least about 70 months, at least about 75 months, at least about 80 months, at least about 85 months, at least about 90 months, at least about 95 months, at least about 100 months, at least about 105 months, at least about 110 months, at least about 115 months or at least about 120 months.

In various embodiments, the subject was previously ineffectively treated by a conventional agent/medicament/composition/intervention for the dermatological/skin condition such as pruritus/itch and related conditions. In various embodiments, the subject was previously ineffectively treated by one or more of a different

agent/medicament/composition/intervention such as but not limited to agents/medicaments/compositions/interventions indicated for the dermatological/skin condition such as pruritus/itch and related conditions, topical medicaments/agents/compositions, emollients/topical emollients, steroids, cooling lotions, corticosteroids, antidepressants, antihistamines (e.g., systemic antihistamines), anticonvulsants and phototherapy. In various embodiments, the subject was previously ineffectively treated for the dermatological/skin condition such as pruritus/itch and related conditions by another medicament selected from: medicaments indicated for pruritus, topical medicaments, emollients, steroids, antihistamines and combinations thereof. In one example, subjects were previously ineffectively treated by at least three types of antihistamines from different generations at three to four times the recommended daily dosage.

In various embodiments, there is provided a method, a use or a product as described herein.

BRIEF DESCRIPTION OF FIGURES

FIG. 1. High-definition optical coherence tomography (HD-OCT). (a) Slice image revealing a curved tubular structures in the epidermis. Scale bar; 100 μm. (b) In the corresponding en face image, tubular structures with thickened walls (one in crosshair), with a surrounding hypo-refractive bordering region indicative of fluid collection can be observed. Scale bar; 200 μm. (c) A spiraling sweat duct within the epidermis, or acrosyringium, which is normally not visible in OCT in non-acral skin of healthy individuals. The acrosyringium is dilated in this patient with CPUO. Scale bar; 100 μm. (d) These dilated sweat ducts may present as subcorneal fluid collections, and the dilated sweat duct here is seen to extend into the dermis. Scale bar; 100 μm. (e) Three-dimensional rendering demonstrating a dilated and tortuous acrosyringium (see structure in circle) in the epidermis. Scale bar; 30 μm.

FIG. 2. Immunofluorescence staining of a biopsy of an itchy skin region in a patient with CPUO. Dermcidin, an antimicrobial peptide present in sweat, can be found outside the secretory sweat glands (arrowheads), indicating leakage of sweat into the dermis. The skin biopsies were cryosectioned to 10 μm thickness, fixed with

paraformaldehyde and immunolabelled for nucleus (DAPI; grey), sweat glands (cytokeratin-14; light grey) and dermcidin (light grey). Scale bar; 50 μm.

FIG. 3. Change in itch scores after systemic retinoid therapy (graphical representation).

EXAMPLES

Example embodiments of the disclosure will be better understood and readily apparent to one of ordinary skill in the art from the following discussions and if applicable, in conjunction with the figures. It will be appreciated that the example embodiments are illustrative, and that various modifications may be made without deviating from the scope of the invention. Example embodiments are not necessarily mutually exclusive as some may be combined with one or more embodiments to form new exemplary embodiments.

Overview

Importance: Pathogenesis of chronic pruritus of unknown origin (CPUO) is poorly understood, and effective treatment is lacking. Using *in vivo* imaging and immunofluorescence studies, features of sweat duct obstruction in affected individuals were identified.

Objective: It was hypothesized that systemic retinoids would be effective in treating CPUO, through reducing hyperkeratinization and sweat duct obstruction. The study aims to evaluate the efficacy and safety of systemic retinoids.

Design: This was a retrospective descriptive analysis over a 6.5-year period from May 2014 to November 2020.

Setting: Itch subspecialty clinic of a single tertiary referral center.

Participants: Of 68 consecutive patients with CPUO who failed conventional treatments and were treated with systemic retinoids, 56 who could provide a

numerical itch score, not later diagnosed with a primary dermatosis, and returned for at least one follow-up were eventually included.

Exposure: Treatment with systemic retinoids (acitretin, isotretinoin, or both).

Main Outcomes and Measures: Treatment response was defined as a decrease in itch score of ≥2/10, sustained over the treatment course. Safety was assessed by the number of patients who stopped either or both retinoids due to side effects.

Results: Of 56 patients (mean [SD] age 55.2 [17.5] years, 69.6% male, 85.7% Chinese), the mean (SD) duration of itch was 116.3 (140.4) months and mean (SD) itch score was 8.2 (1.8). Four (7.1%) verbalized suicidal ideation due to itch.
Forty-one (73.2%) were initially treated with isotretinoin, and 15 (26.8%) with acitretin. At three months, mean decrease in itch score was 2.38 (95% CI -3.2 to -1.6, p <0.0001). Thirty-eight (67.9%) had a sustained response to treatment. Eight (14.81%) achieved an itch score of 0 or 1, with four stopping treatment for a mean (SD) of 318.5 (291.2) days with sustained resolution.

Twenty-six (46.4%) switched retinoid due to inefficacy, of which 13 eventually responded. Eight (14.3%) stopped treatment or switched retinoid due to adverse effects, the most common being dryness in five. Incidences of adverse effects were similar between isotretinoin (10.6%) and acitretin (8.11%).

Conclusions and Relevance: Based on our imaging studies implicating partial keratinaceous sweat duct obstruction with sweat leakage as the pathology in CPUO, we instituted treatment with systemic retinoids, which appear effective and safe for CPUO patients who failed conventional treatments.

Introduction

A common trigger of itch is the exposure to heat or initiation of sweating, during which there is stimulation of the autonomic nervous system. Non-invasive *in vivo* imaging was performed on individuals with chronic pruritus of unknown origin (CPUO) using high definition optical coherence tomography (HD-OCT, Skintell,

Agfa, Belgium) and features of sweat duct obstruction were identified (FIG. 1), akin to those observed in patients suffering from hypohidrosis. These abnormalities, not found in healthy individuals, were more easily perceived and accentuated after the patients were induced to sweat through exercise. HD-OCT revealed dilation of the lumen and wall of the acrosyringium (FIG. 1A, 1C, 1E), which is the spiraling intra-epidermal portion of the sweat duct. Manual image segmentation of the lumen of the dilated acrosyringium was carried out on individual image slices to obtain a 3D rendering of the dilated acrosyringium in epidermis (not shown). In other parts of the skin and in other patients, the dilation may form a collection of fluid under the stratum corneum (FIG. 1D). The surrounding epidermis is hyper-refractile (bright), which likely represents maceration of keratin. On the *en face* views, a surrounding hypo-refractive bordering region indicative of fluid accumulation can be observed (FIG. 1B). The dilation of the sweat ducts (FIG. 1D) and exudation of fluid to the surroundings point to an obstruction of the sweat orifice at the stratum corneum, which comprises keratin. Starch-iodine sweat testing, as previously described (Lim JH, Choo W, Chang JH, Tey HL, Chong WS. Application of iodinated starch powder using an atomizer spray gun - a new and effective tool to evaluate hypohidrosis. *Skin Res Technol.* 2016;22(3):370-374), was performed for patients with CPUO and it was found that they were generally able to sweat, unlike patients with hypohidrosis. It was therefore posited that partial, instead of complete, sweat duct obstruction occurs in patients with CPUO. When some of the patients with CPUO were treated with retinoids (as described below), the abovementioned abnormalities were observed to improve and subsequently resolve.

Observations from the immunostaining studies of skin biopsies of itchy versus non-itchy skin areas in CPUO patients demonstrated leakage of sweat components into the dermis (FIG. 2). Together with the HD-OCT findings above, it is theorized that sweat which leaks into the epidermis irritates intraepidermal nerve fibers to result in itch, and sweat which leaks into the dermis irritates nociceptive nerve fibers to result in the prickly sensation experienced by patients.

Based on these findings indicating keratinaceous partial obstruction of sweat orifices, patients with CPUO were treated with oral retinoids, which primarily act by reducing hyperkeratinization. As the initial results appeared promising, systemic

retinoids were given as off-label treatment for patients with CPUO who have failed treatments with multiple topical agents and systemic antihistamines.

Methods

This was a retrospective analysis of all patients with a diagnosis of CPUO, seen at the Itch Clinic, treated with systemic retinoids over a 6.5-year period between 16 May 2014 and 6 November 2020. Only patients with at least six weeks of itch, no clinically evident primary dermatological abnormalities (except for scratch-induced skin lesions), and no major serum biochemical abnormalities were included. All the patients had failed treatment with topical emollients and steroids, and at least three types of antihistamines from different generations at three to four times the recommended daily dosage. The patients had been treated with isotretinoin and/or acitretin off-label for their itch. Patients who were unable to provide a numerical itch score, those who were diagnosed with a primary dermatosis accounting for their pruritus, and those who did not return for at least one follow-up visit after starting systemic retinoids were excluded.

Patient demographics, disease characteristics, verbalization of suicidal ideation, retinoid treatment doses and duration, and adverse effects due to itch were collected. To assess the efficacy of retinoid treatment, the itch score of each patient was evaluated at each follow-up visit. The itch score reflects the patient's average intensity of itch over the prior one day on a 0-10 numerical rating scale. Treatment response is defined as a decrease in itch score of two points or more, which is sustained during the treatment course. The itch score value of two was selected in accordance with the previously determined Minimal Clinically Important Difference in numerical rating of chronic itch (Reich A, Riepe C, Anastasiadou Z, et al. Itch Assessment with Visual Analogue Scale and Numerical Rating Scale: Determination of Minimal Clinically Important Difference in Chronic Itch. *Acta Derm Venereol.* 2016;96(7):978-980). Safety was assessed by the number of patients who stopped either or both retinoids due to side effects.

All variables were summarized descriptively using counts and percentages for categorical variables and mean with standard deviation and median with

range/interquartile range for continuous variables. Two sample t-test for continuous data and Fisher's exact test for categorical data were used to assess the difference. To evaluate how itch scores changed over time after retinoid treatment, a linear mixed effects model was employed. The model for itch scores included time (t), number of retinoids used, baseline itch score, sex, race, and age when retinoid started as fixed effects, whereas a random intercept for subjects was included to account for within-subject correlations. A p-value less than 0.05 was considered statistically significant. Statistics were generated using R version. 3.5.3.

Results

Sixty-eight patients were treated with systemic retinoids for CPUO between 16 May 2014 and 6 November 2020. Eight patients were excluded as they were not able to provide an objective itch score. Four patients did not return for at least one visit after initiation of retinoid therapy. Thus, a total of 56 patients were eventually included in the final analysis.

The baseline characteristics of the study population are as outlined in Table 1 below.

Table 1: Baseline Characteristics

Characteristics	**Value**
Age at first visit, years	
Mean (SD)	55.2 (17.5)
Minimum, maximum	16, 84
Age when systemic retinoid first started, years	
Mean (SD)	58.0 (18.2)
Minimum, maximum	19, 87
Sex	
Male, n (%)	39 (69.6)
Female, n (%)	17 (30.4)

Race	
Chinese, n (%)	48 (85.7)
Malay, n (%)	2 (3.6)
Indian, n (%)	6 (10.7)
Duration of itch before first visit, months	
Mean (SD)	116.3 (140.4)
Median (Q1, Q3)	48 (24, 180)
Minimum, maximum	1, 528
Baseline itch scores	
Mean (SD)	8.2 (1.8)
Minimum, maximum	3, 10
Areas affected, n (%)	
Face and scalp	32 (57.1)
Trunk	46 (82.1)
Upper limbs	49 (87.5)
Lower limbs	51 (91.1)
Verbalized suicidal ideation due to itch, n (%)	4 (7.1)
Eosinophilia, n (%)	13 (23.2)

SD, standard deviation.

Most of the patients were older, male, and Chinese. The mean duration of itch before their first visit at the Itch Clinic was 116.3 months, and mean itch score at presentation was severe at 8.2. The lower limbs were the most common areas affected. Four (7.1%) patients voluntarily verbalized suicidal ideation due to itch. Thirteen (23.2%) patients had peripheral eosinophilia.

Nine patients were treated only with acitretin, 19 only with isotretinoin, and 28 were treated with both retinoids over the course of their follow-up. FIG. 3 and Table 2 below show the changes in itch scores after starting retinoids.

Table 2: Change in itch scores after systemic retinoid initiation

Time after starting retinoids, months	Change in itch score, mean (95% CI)	P-value
0	0 (0, 0)	NA
3	-2.38 (-3.2, -1.6)	< 0.0001
6	-3.05 (-4, -2.15)	< 0.0001
9	-2.94 (-3.9, -2.02)	< 0.0001
12	-3.21 (-4.4, -2.04)	< 0.0001
15	-3.17 (-4.6, -1.78)	0.0002
18	-3.35 (-4.6, -2.08)	< 0.0001
21	-3.59 (-5, -2.18)	0.0005
24	-5.02 (-7.2, -2.87)	0.0059

CI, confidence interval; NA, not applicable

There was a significant decrease in itch score over time, noticeable at three months of treatment, during which there was a mean decrease in itch score of 2.38 points ($p < 0.0001$), with the effect being sustained throughout treatment. Thirty-eight patients (67.9%) responded to treatment, defined as having an itch score two points or more lower than baseline, sustained during treatment. A total of eight patients (14.81%) achieved an itch score of 0 or 1 (Table 3).

Table 3: Characteristics of patients who achieved no or almost no itch (itch score 0 or 1)

Statistics	All (n = 8)
Starting retinoid dose Mean, daily dose in mg (SD)	15.0 (7.1)
Maximum retinoid dose Mean, daily dose in mg (SD)	16.9 (7.5)
Cumulative dose Mean, dose in mg (SD)	8347.9 (7334.4)
Duration of onset of response Mean, days (SD)	141.0 (119.2)

Duration of treatment Mean, days (SD)	646.4 (375.6)
Duration disease-free off treatment* Mean, days (SD)	318.5 (291.2)

SD, standard deviation

*4 patients stopped treatment and had an itch score of 0 or 1 at their latest visit.

Of these, four patients had stopped treatment for a mean of 318.5 days with sustained resolution of itch.

Table 4 below shows the characteristics of patients who switched or stopped retinoids due to inefficacy or side effects.

Table 4: Treatment Data

Statistics	**Value**
Patients initially given acitretin, n (%)	15 (26.8)
Patients initially given isotretinoin, n (%)	41 (73.2)
Patients given acitretin during the course of treatment, n (%)	37 (66.1)
Patients given isotretinoin during the course of treatment, n (%)	47 (83.9)
Patients who responded to retinoids, n (%)	38 (67.9)
Patients who switched retinoids due to inefficacy, n (%)	**26 (48.2)[a]**
Eventually responded to retinoids, n (%)	13 (50.0)
Acitretin to isotretinoin, n (%)	**3 (5.36)**
Responded to isotretinoin, n (%)	1 (33.3)[b]
Isotretinoin to acitretin, n (%)	**19 (33.9)**
Responded to acitretin, n (%)	10 (52.6)[c]
Acitretin to isotretinoin and back to acitretin, n (%)	**2 (3.57)**

Responded to third retinoid, n (%)	1 (50.0)
Isotretinoin to acitretin and back to isotretinoin, n (%)	**1 (1.79)**
Responded to third retinoid, n (%)	0 (0.00)
Isotretinoin to acitretin to isotretinoin to acitretin, n (%)	**1 (1.79)**
Responded to fourth retinoid, n (%)	1 (100)
Patients who stopped or changed retinoids due to side effects, n (%)	**8 (14.3)**
Acitretin, n (%)	**3 (8.11)**
Stopped retinoid therapy, n (%)	2 (66.7)
Changed to isotretinoin, n (%)	1 (33.3)
Side effects experienced	
Dryness, n (%)	2 (66.7)
Worsening of itch, n (%)	1 (33.3)
Isotretinoin, n (%)	**5 (10.6)**
Stopped retinoid therapy, n (%)	2 (40.0)
Changed to acitretin, n (%)	3 (60.0)
Side effects experienced	
Dryness, n (%)	3 (60.0)
Abdominal pain, n (%)	1 (20.0)
Mood swings, n (%)	1 (20.0)

[a]Includes four patients who also switched retinoids due to side effects.

[b]Of the three patients who switched from acitretin to isotretinoin due to inefficacy, one defaulted follow-up and another did not respond.

[c]Of the 19 patients who switched from isotretinoin to acitretin due to inefficacy, one stopped treatment because of xerosis and eight have not returned for follow-up since.

Forty-one patients (73.2%) were initially treated with isotretinoin, while 15 (26.8%) were initially treated with acitretin. Twenty-six patients (46.4%) switched retinoid due to lack of efficacy. Five of 15 patients (33.3%) initially given acitretin switched to isotretinoin due to inefficacy. Of these patients, one eventually responded to isotretinoin, and another was switched back to acitretin with response.

Twenty-one of 47 patients (44.7%) initially given isotretinoin switched to acitretin due to inefficacy. Of these patients, eleven eventually responded to acitretin.

Eight patients (14.3%) - three on acitretin (8.11%) and five on isotretinoin (10.6%) - stopped or changed retinoids due to adverse effects. Of the three who stopped acitretin, two reported dryness and one had worsened itch. Of the five who stopped isotretinoin, three reported dryness, one had abdominal pain and one had mood swings.

Of the four patients who changed retinoids due to adverse effects, two (one from isotretinoin to acitretin, and one from acitretin to isotretinoin) responded to the second retinoid without any treatment-limiting adverse effects, while another two patients who changed from isotretinoin to acitretin have not returned for a follow-up visit within the study period.

Discussion

The point prevalence of chronic pruritus is estimated to be 13.5% in the general adult population. In 8% to 15% of affected patients, no causation or known associations are found and these patients are diagnosed to have CPUO. CPUO accounts for 3.6% to 44.5% of the cases presenting with generalized pruritus, with the highest prevalence amongst the elderly. The medical and psychosocial morbidity of this disease cannot be over-emphasized. A recent prospective cross-sectional study found that 18.5% of patients with chronic itch reported suicidal ideations due to pruritus in the course of their disease. In the study population of this disclosure, 7.1% of patients voluntarily verbalized suicidal ideation due to itch. Expression of suicidal ideation has been associated with a four-fold increased risk for subsequent completed suicides, highlighting the importance of managing pruritus in this group of patients.

The proportion of patients with eosinophilia in the study (23.2%) is in keeping with a recent retrospective cross-sectional study of patients with chronic pruritus, in which eosinophilia was present in 17.9% of patients with non-diseased skin and 39.7% of patients presenting with severe chronic secondary scratch lesions. Eosinophils are involved in host defense against pathogens and external antigens,

and their role in stimulating nerve cells and contributing to pruritus has been demonstrated in several studies. It is postulated that eosinophilia in CPUO may represent an innate immunity response to leakage of sweat components into the skin, and may result in the persistence of itch after the initial direct irritation of the nerve fibers from the leakage of sweat.

Management of CPUO remains challenging, and at present, there exists no effective treatment in the literature. In the study population, there was a mean decrease in itch score of 2.38 points ($p < 0.0001$) at three months after starting treatment, and the effect was sustained throughout treatment. Eight patients (14.3%) achieved no or almost no itch, with four (7.1%) exhibiting a durable disease-free period after stopping treatment. The results suggest that retinoids are an effective therapeutic option for CPUO who have failed conventional treatment, and can be curative in a subgroup of patients. An initial low retinoid dose of 10 to 20 mg daily should be considered.

Isotretinoin and acitretin appear similar in terms of side effect profile, with a higher proportion of patients on isotretinoin switching to acitretin due to inefficacy. Of note, pregnancy is contraindicated for three years after taking acitretin, limiting its use in females of childbearing age, which made up a small minority of the patients (8.93%) in the study population. The use of isotretinoin would thus be preferred in this subpopulation.

In the patient cohort with recalcitrant CPUO disease, 32.1% did not respond to either acitretin or isotretinoin. One possible explanation is that these retinoids having limited efficacy in reversing the keratinization abnormality present in CPUO. Another explanation may be that CPUO results from heterogeneous pathophysiological processes, other than sweat orificial keratinization abnormality. One possible alternative etiology is non-bullous pemphigoid, a still-to-be-defined entity which may present with intense pruritus without primary skin lesions, and requires immunosuppressive treatment.

In conclusion, based on the preliminary studies implicating partial keratinaceous sweat duct obstruction with leakage of sweat as the pathology in

CPUO, treatment with oral isotretinoin and/or acitretin was instituted. Systemic retinoids appear to be an effective and safe treatment option for patients with CPUO who have failed conventional treatment.

It will be appreciated by a person skilled in the art that other variations and/or modifications may be made to the embodiments disclosed herein without departing from the spirit or scope of the disclosure as broadly described. For example, in the description herein, features of different exemplary embodiments may be mixed, combined, interchanged, incorporated, adopted, modified, included etc. or the like across different exemplary embodiments. The present embodiments are, therefore, to be considered in all respects to be illustrative and not restrictive.

CLAIMS

1. Use of an agent that is capable of reducing obstruction of a sweat duct in the manufacture of a medicament for the treatment of pruritus in a subject.

2. The use according to claim 1, wherein the agent is capable of reducing obstruction of a sweat duct at its orifice by keratin.

3. The use according to claim 1 or claim 2, wherein the agent is capable of reducing an expression of keratin.

4. The use according to any one of claims 1-3, wherein the agent is capable of binding to retinoic acid receptor (RAR) and/or retinoid X receptor (RXR).

5. The use according to any one of claims 1-4, wherein the agent comprises retinoid.

6. The use according to claim 5, wherein the retinoid is selected from the group consisting of tretinoin, isotretinoin, alitretinoin, acitretin, etretinate, bexarotene, adapalene, tazarotene and derivatives thereof.

7. The use according to claim 6, wherein the retinoid is selected from the group consisting of isotretinoin, acitretin and derivatives thereof.

8. The use according to any one of claims 1-7, wherein the medicament is to be administered systematically.

9. The use according to claim 8, wherein the medicament is to be administered orally.

10. The use according to claim 9, wherein the medicament is in a solid dosage form.

11. The use according to any one of claims 1-10, wherein the medicament is to be administered daily.

12. The use according to claim 11, wherein the medicament is to be administered daily at a dosage of 10 mg to 20 mg.

13. The use according to any one of claims 1-12, wherein the medicament is capable of reducing an intensity of pruritus in the subject by at least about 20% as measured by a numerical rating scale (NRS).

14. The use according to claim 13, wherein the medicament is capable of reducing an intensity of pruritus in the subject by at least about 25% as measured by a NRS.

15. The use according to any one of claims 1-14, wherein the medicament is capable of resolving pruritus in the subject.

16. The use according to any one of claims 1-15, wherein the subject has severe pruritus as measured by a NRS.

17. The use according to any one of claims 1-16, wherein the subject was previously ineffectively treated for pruritus by another medicament selected from: medicaments indicated for pruritus, topical medicaments, emollients, steroids, antihistamines and combinations thereof.

18. The use according to any one of claims 1-17, wherein the subject has sweat ducts that are at least partially obstructed at their orifices by keratin.

19. The use according to any one of claims 1-18, wherein the pruritus comprises chronic pruritus that lasted for at least 6 weeks.

20. The use according to claim 19, wherein the chronic pruritus comprises chronic pruritus of unknown origin (CPUO).