include pain, erythema, swelling, edema, burning, itching, exfoliation, hyperpigmentation and prolonged irritation and hypersensitivity after treatment. Such side-effects are particularly undesirable when the treatment site is the face, scalp or neck. This is frequently the case when the PDT is for the treatment of lesions (e.g. actinic keratosis, acne, basal cell carcinoma, warts, psoriasis, rosacea, wound healing, squamous cell carcinoma *in situ* or other hyperproliferating or infectious disorders) and when PDT is performed using short-term illumination with high-power light sources. In particular the often substantive pain experienced by the patients in these circumstances results in poor acceptance of this treatment, in particular if PDT has to be applied more than once or on extended skin regions.

An alternative treatment is daylight PDT, which uses sun light with increased exposure time to activate the photosensitizer instead of the high-power light sources used in conventional PDT. The side effects of daylight PDT, in particular the pain, are significantly reduced (Dirschka et al., J Eur Acad Dermatol Venereol. 2018 Jul 19). While the efficacy of daylight PDT seems comparable to conventional PDT, the recurrene rate is significantly higher in daylight PDT.

The present invention teaches the use of photosensitizers in an improved PDT comprising two different light exposures. The present invention therefore provides inter alia the advantages of reduced side effects, in particular reduced pain, and a low recurrence rate.

Summary

In one aspect, the present disclosure provides use of a composition comprising a photosensitizer in the manufacture of a medicament for preventing or treating dermatological disease in a patient, wherein the composition is to be used in the following order of steps: (a) said composition is to be topically applied or subcutaneously injected to an area of the skin of said patient, (b) exposure of at least said area of the skin to light with a wavelength spectrum and preferably also irradiance similar or identical to sun light for a duration of 30 min to 5 hours, preferably 1 to 3 hours, more preferably 1 to 2 hours, and (c) exposure of at least said area of the skin to light of a narrower wavelength spectrum compared to step (b), preferably comprising only one maximum in the absorbance spectrum of said photosensitizer.

In another aspect, the present disclosure provides kit of parts comprising a light source capable of emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light and/or yellow-red or violet-blue light and an instruction manual for carrying out steps (b) and (c) of the use as described herein. In yet another aspect, the present disclosure provides a light source capable of emitting light with a wavelength spectrum and

preferably also irradiance similar or identical to sun light and yellow-red or violet-blue light and a controller, wherein the controller is programmed for carrying out steps (b) and (c) of the use as described herein.

In a first example, the present disclosure provides a composition comprising a photosensitizer for use in prevention or treatment of dermatological disease in a patient, wherein the composition is used in the following order of steps:

(a) application of said composition to an area of the skin of said patient,

(b) exposure of at least said area of the skin to light with a wavelength spectrum similar or identical to sun light for a duration of 30 min to 5 hours, preferably 1 to 3 hours, more preferably 1 to 2 hours, and

(c) exposure of at least said area of the skin to light of a narrower wavelength spectrum compared to step (b), preferably comprising only one maximum in the absorbance spectrum of said photosensitizer.

In a second example, the present disclosure provides a method of treating or preventing a dermatological disease in a patient in need thereof in which a photosensitizer is applied to an area of the skin of the patient as indicated in the first example of the disclosure.

In a third example, the present disclosure provides a kit of parts comprising a light source capable of emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light and/or yellow-red or violet-blue light and an instruction manual for carrying out steps (b) and (c) of the method of the second example of the disclosure.

In a fourth example, the present disclosure provides a light source capable of emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light and yellow-red or violet-blue light and a controller, wherein the controller is programmed for carrying out steps (b) and (c) of the method of the second example of the disclosure.

List of Figures

In the following, the content of the figures comprised in this specification is described. In this context please also refer to the detailed description of the invention above and/or below.

Figure 1: Side effect of PDT (pain score) refers to a comparison of the pain experienced by photodynamic therapy using a 5-ALA photosensitizer followed by illumination with a commonly used PDT red light source, as compared to using 5-ALA in combination with the PDT of the present invention using a combination of initially artificial daylight followed by the identical red light illumination. The pain was scored with a visual analog scale for pain (VAS). The area of treatment had an influence on the pain experienced in both treatments.

Surprisingly the pain experienced was significantly reduced when using a combination of daylight and red light after application of the photosensitizer as opposed to only red light illumination after application of the photosensitizer.

Figure 2: Absorbance spectrum of protoporphyrin IX (PpIX) refers to the absorbance spectrum in the range of 350 nm to 700 nm. The highest absorption maximum is located at 405 nm. A much smaller but, due to the greatly better tissue penetration of longer-wave light, clinically nevertheless significant absorption maximum is located at 635 nm. In between three additional maxima are located in the range of 500 nm to 550 nm.

Detailed Descriptions of the Invention

Before the present invention is described in detail below, it is to be understood that this invention is not limited to the particular methodology, protocols and reagents described herein as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims. Unless defined otherwise, all

Claims

1. Use of a composition comprising a photosensitizer in the manufacture of a medicament for preventing or treating dermatological disease in a patient, wherein the composition is to be used in the following order of steps:
   (a) said composition is to be topically applied or subcutaneously injected to an area of the skin of said patient,
   (b) exposure of at least said area of the skin to light with a wavelength spectrum and preferably also irradiance similar or identical to sun light for a duration of 30 min to 5 hours, preferably 1 to 3 hours, more preferably 1 to 2 hours, and
   (c) exposure of at least said area of the skin to light of a narrower wavelength spectrum compared to step (b), preferably comprising only one maximum in the absorbance spectrum of said photosensitizer.

2. The use according to claim 1, wherein the light used in step (c) is red light or violet light.

3. The use according to claim 1 or 2, wherein the area of the skin comprises skin effected by the disease or skin prone to be effected by the disease.

4. The use according to any one of the preceding claims, wherein there is a residence time interval subsequent to step (a) and prior to step (b) of 1 to 90 min, in particular of 15 to 30 min, preferably in the absence of light exposure.

5. The use according to any one of the preceding claims, wherein the light used in step (b) has an irradiance that is similar to that of average sunlight, preferably in locations where the patient can stay pleasantly, depending on the weather either in the shade or the sun.

6. The use according to any one of the preceding claims, wherein the light of step (b) has a wavelength spectrum of 380 nm to 780 nm, preferably with equal irradiance throughout or irradiance peak(s) at around 405 and/or 505 and/or 635 nm.

7. The use according to any one of the preceding claims, wherein:
   - the light of step (c) has a wavelength in the range of 570 nm to 750 nm, preferably of 570 nm to 670 nm, more preferably of about 635 nm; or

- the light of step (c) has a wavelength in the range of 360 nm to 495 nm, preferably 360 nm to 460 nm, more preferably of about 410 nm.

8. The use according to any one of the claims 2 to 7, wherein:
   - the red light of step (c) results in a radiant exposure of 10-75 J/cm^2, preferably of 25-45 J/cm^2;
   - the violet light of step (c) results in a radiant exposure of 1-30 J/cm^2, preferably 5 to 15 J/cm^2.

9. The use according to any one of the preceding claims, wherein the light used in step (b) has a lower irradiance than the light used in step (c), preferably the irradiance is 2- to 15-times lower than step (c).

10. The use according to any one of the preceding claims, wherein the exposure of step (c) has a duration of at least 5 minutes, preferably of 5-60 minutes, more preferably 10-30 minutes.

11. The use according to any one of the preceding claims, wherein the photosensitizer is selected from 5-aminolevulinic acid (ALA), ALA-esters, in particular methyl-5-amino-4-oxopentanoat, or hexyl-5-amino-4-oxopentanoat or their derivatives.

12. The use according to any one of the preceding claims, wherein the composition is formulated as a nanoemulsion additionally comprising:
   (a) at least one aqueous component, and
   (b) a carrier, which comprises:
      (i) at least one lipophilic component,
      (ii) at least one surfactant and
      (iii) at least one alcohol.

13. The use according to claim 12, wherein
   - the carrier is present in the aqueous component and/or
   - the surfactant is present in an amount of from 1 % by weight to 30% by weight and the alcohol is present in an amount of from 0.1 % by weight to 10% by weight, based on the total weight of the nanoemulsion.

14. The use according to any one of claims 12 or 13, wherein the aqueous component is present in an amount of from 50% by weight to 98% by weight, based on the total weight of the nanoemulsion.

15. The use according to any one of claims 12 to 14, wherein:
    - the at least one alcohol is isopropylalcohol and/or 1-propylalcohol and/or
    - the at least one lipophilic component are triglycerides and/or a mixture thereof and/or
    - the at least one surfactant is lecithin and/or a polyoxyethylene-type surfactant and/or
    - the mean diameter of the emulsified particles ranges from 10 to 100 nm.

16. The use according to any one of the preceding claims, wherein the dermatological disease is a hyperproliferative disease, preferably keratosis, more preferably actinic keratosis; basal carcinoma, squamous cell carcinoma in situ, warts, acne, rosacea or an inflammatory or infectious dermatological condition.

17. Kit of parts comprising a light source capable of emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light and/or yellow-red or violet-blue light and an instruction manual for carrying out steps (b) and (c) of the use of claim 1.

18. A light source capable of emitting light with a wavelength spectrum and preferably also irradiance similar or identical to sun light and yellow-red or violet-blue light and a controller, wherein the controller is programmed for carrying out steps (b) and (c) of the use of claim 1.