



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 9/00	A2	(11) International Publication Number: WO 00/06118 (43) International Publication Date: 10 February 2000 (10.02.00)
(21) International Application Number: PCT/US99/17020 (22) International Filing Date: 28 July 1999 (28.07.99) (30) Priority Data: 09/123,589 28 July 1998 (28.07.98) US 09/249,371 12 February 1999 (12.02.99) US (71) Applicant: BERSHAD, Susan [US/US]; 2 Stonebridge Road, Montclair, NJ 07042 (US). (74) Agents: LOUGHNANE, Michael, D. et al.; Kenyon & Kenyon, One Broadway, New York, NY 10004 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>Without international search report and to be republished upon receipt of that report.</i>
(54) Title: SHORT CONTACT TREATMENT OF ACNE AND PHOTOAGING WITH TOPICAL RETINOIDS (57) Abstract The present invention relates to a method of treating acne and photoaging using short-term contact with a topically-applied retinoid composition, including use of the retinoids tazarotene, tretinoin and adapalene.		

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SHORT CONTACT TREATMENT OF ACNE AND PHOTOAGING WITH TOPICAL RETINOIDS

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BACKGROUND OF THE INVENTION

The present invention is directed to the treatment of various chronic and acute skin conditions, particularly acne and photoaging using topical retinoids.

The retinoids are a family of compounds including vitamin A, retinoic acid (RA), related derivatives of these, and other compounds capable of binding to retinoic acid receptors (RAR). RA, which is a natural metabolite of vitamin A (retinol), is known as a potent modulator (i.e., an inhibitor or, to the contrary, a stimulator, depending on the nature of the cells treated) of the differentiation and proliferation of many normal or transformed cell types. All-*trans*-RA (tretinoin) acts on the differentiation and proliferation of cells by interacting with RARs contained in the cell nucleus. There are, to date, three identified subtypes of known RAR receptors, respectively termed RAR- α , - β , - γ . These receptors, after binding the RA ligand, interact with the promoter region of genes regulated by RA at specific response elements. To bind to the response elements, the RARs heterodimerize with another type of receptor designated as RXR. The natural ligand of RXRs is 9-*cis*-retinoic acid.

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Many retinoids are known and have been described to date. Generally, retinoids can be identified by their ability to bind RARs, either as all the RARs or selectively to an individual RAR class. Further, retinoids exhibit a diverse spectrum of activities. Among these is use as a topical therapeutic for treatment of skin conditions.

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There is presently in use an FDA approved treatment for acne employing tazarotene topical gel that is marketed by Allergan, Inc. under the brand name Tazorac™. Moreover, tretinoin, also known by the tradename Retin-A™, and adapalene are approved for topical use to treat skin conditions.

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The mechanism of action in the treatment of acne and photoaging with tazarotene or other retinoids is not known. The current FDA-approved therapeutic regimen requires Tazorac™ gel to be applied topically in its 0.05% or its 0.1%

formulation and left on the affected skin for long periods of time, e.g. overnight. It is generally applied in the evening and left in place until routine washing in the morning. Thus, in the treatment of acne, the Tazorac™ gel would typically be left on the skin for 8 to 12 hours.

5 Unfortunately, a major shortcoming of this course of treatment is that adverse skin reactions are experienced by a significant portion of users. To overcome these shortcomings, it has now been found that topically-applied retinoids can be used to treat acne and photoaging using a short-contact treatment regimen. For example, tazarotene has been used for short-contact therapy to treat acne and photoaging as
10 disclosed in co-pending application 09/123,589, entitled "Short Contact Treatment For Acne and Photoaging," filed July 28, 1998 and which is hereby incorporated herein by reference.

SUMMARY OF THE INVENTION

15 The present invention is directed to a method of treating acne in a human patient by topically applying an effective amount of a retinoid composition to the affected area of a patient's skin, allowing that composition to remain in contact with the skin for a period of from about thirty seconds to about 15 minutes, followed by rinsing the composition from the affected area. Generally, the short contact
20 treatment is performed once or twice a day at least three times a week. In preferred embodiments, the active retinoid in the composition is tazarotene, tretinoin or adapalene and, more preferably, is tazarotene.

 Another aspect of the invention provides a method of treating skin damaged by photoaging by topically applying an effective amount of a retinoid
25 composition to the affected area of a patient's skin, allowing that composition to remain in contact with the skin for a period of from about thirty seconds to about ten minutes, followed by rinsing the composition from the affected area. Generally, the short contact treatment is performed once or twice a day at least three times a week. In preferred embodiments, the active retinoid in the composition is tazarotene,
30 tretinoin or adapalene and, more preferably, is tazarotene.

DESCRIPTION OF THE INVENTION

According to the invention, it has been found that short-contact retinoid therapy yields surprisingly improved and beneficial results in the treatment of acne. It has further been found that the short-contact retinoid therapy actually reduces and even reverses the effects of sun-induced aging (photoaging).

“Short-contact retinoid therapy”, as used herein, is intended to distinguish over conventional, or extended-contact, treatment(s) wherein, the retinoid of interest is applied to a patient’s skin (typically once a day) and left on the skin indefinitely or until routine washing or showering occurs after a prolonged period of time (typically overnight).

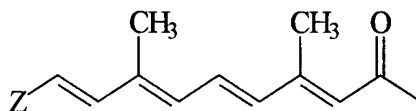
In accordance with the invention, short-contact retinoid therapy thus comprises the steps of applying a retinoid composition to an affected area of the skin for a brief time period followed by rinsing of the skin/affected area. In the case of acne, the usual contact time is from about 30 seconds to about 15 minutes, preferably for a period of from about 2 to about 5 minutes. In the case of photoaging, the usual contact time is from about 30 seconds to about 10 minutes, preferably for about 1 to about 3 minutes. Immediately following the prescribed period of time, the skin is rinsed thoroughly, typically with lukewarm water.

For both acne and photoaging therapy, the short-contact treatments are generally applied to the affected area(s) once or twice a day, preferably twice a day, and repeated at least three times a week. If desired or needed, the treatments can be repeated daily. The overall duration of therapy can be continued for as long as the conditions exist, after the conditions are treated or ameliorated to maintain the status of the patient quo, or can be used to prevent or reduce the onset of acne or photoaging symptoms and thus continued for an indefinite period of time. The duration of therapy is readily determined by the patient’s doctor consistent with the goal of the therapy.

In accordance with the invention and as used herein, a “retinoid composition” comprises therapeutically-active retinoids, or pharmaceutically-

acceptable salts thereof, in admixture with a pharmaceutically acceptable carrier. The therapeutically-active retinoids of the invention are selected from the group consisting of a retinoic acid; retinol; therapeutically-active retinoic acid derivatives; therapeutically-active carboxylic acids represented by the formula

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and retinoids which are C₂₀ or C₂₂ desmethyl vinyls of said groups, wherein Z is a substituted or unsubstituted phenyl group, a substituted or unsubstituted naphthyl group or a cyclohexenyl group, and said phenyl or naphthyl group can be substituted with from 0 to 5 substituents selected from the group consisting of halo, hydroxy, alkyl, alkoxy, amino, cyano or carbalkoxy, and wherein double bonds in the polyene chain of any of said groups can have a *cis* or *trans* configuration; acetylenic retinoids; adapalene; adapalene derivatives and any compound, natural or synthetic, which possesses the topical biological activity of retinoic acid in the skin and/or the ability to bind to one or more RARs; as well as the geometric isomers and stereoisomers of any of these compounds.

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Examples of retinoids contemplated by the invention can be found in U.S. Patent Nos. 4,476,056; 4,105,681; 4,215,215; 4,054,589 and 3,882,244.

Retinoids include both *cis* and *trans* forms having therapeutic activity. The retinoids can include a 9-*cis* double bond, a 13-*cis* double bond or a 13-*trans* double bond.

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Derivatives of retinoic acid include, but are not limited to, esters, amides, other biologically active forms of retinoic acid such as those with a chemical modification or substitution of a substituent of the molecule, and the like. Derivatives of adapalene include, but are not limited to, esters and amides of the naphthoic acid moiety, other biologically active forms of adapalene such as those having a chemical modification or substitution on some part of the molecule while retaining activity, and the like.

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A pharmaceutically acceptable salt may be prepared for any compound of this invention having a functionality capable of forming such salt, for example an

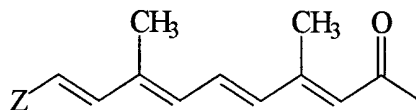
acid or amine functionality. A pharmaceutically acceptable salt may be any salt which retains the activity of the parent compound and does not impart any deleterious or untoward effect on the subject to which it is administered and in the context in which it is administered.

5 The preferred compounds of the invention include, but are not limited to, retinoic acid including tretinoin, 13-*cis* retinoic acid, 9-*cis*-retinoic acid, acetylenic retinoids including tazarotene and adapalene.

10 As used herein a "therapeutically-active retinoid" is a compound which, when applied topically, exhibits or possesses a biological action similar to retinoic acid (i.e., similar to vitamin A acid). Hence, these retinoids include those compounds, synthetic or natural, which have one or more of the therapeutic activities known for retinoic acid. Such activities include but are not limited to binding to and activating RARs, treating and preventing cancer and other proliferative disorders, acting as differentiating agents or anti-proliferatives agents and anti-tumor activity.

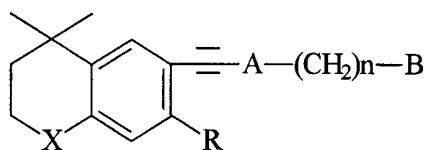
15 As used herein "vinylogs" are desmethyl retinoyl groups having 1 or 2 additional vinyl groups relative to retinoic acid. For example such compounds include 2,6,6-trimethyl-1-(10'-carboxy-deca-1',3',5',7',9'-pentaenyl)cyclohex-1-ene and 2,6,6-trimethyl-1-(12'-carboxy-dodeca-1',3',5',7',9',11'-hexaenyl)cyclohex-1-ene. These groups are also referred to as C20 and C22 vinylogs of desmethyl retinoic acid and are described in U.S. Patent No. 3,882,244. The vinylogs of this invention can be prepared from a retinoyl group, any therapeutically active retinoid carboxyl group, or any group of the formula

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wherein Z is as defined herein.

25 The acetylenic retinoids of the invention are the compounds of the formula represented by



wherein X is S, O, or NR' where R' is hydrogen or lower alkyl; R is hydrogen or lower alkyl; A is pyridinyl, thienyl, furyl, pyridazinyl, pyrimidinyl or pyrazinyl; n is 0-2; and B is H, —COOH or a pharmaceutically acceptable salt, ester or amide thereof, —CH₂OH or an ether or ester derivative, or —CHO or an acetal derivative, or —COR₁,
 5 —(CH₂)_mCH₃ where m is 0-4.

The term "ester" as used here refers to and covers any compound falling within the definition of that term as classically used in organic chemistry. Where A is —COOH, this term covers the products derived from treatment of this
 10 function with alcohols. Where the ester is derived from compounds where A is —CH₂OH, this term covers compounds of the formula —CH₂OOCR where R is any substituted or unsubstituted aliphatic, aromatic or aliphatic-aromatic group.

Preferred esters are derived from the saturated aliphatic alcohols or acids of ten or fewer carbon atoms or the cyclic or saturated aliphatic cyclic alcohols
 15 and acids of 5 to 10 carbon atoms. Particularly preferred aliphatic esters are those derived from lower alkyl acids and alcohols. Here, and where ever else used, lower alkyl means having 1-6 carbon atoms. Also preferred are the phenyl or lower alkylphenyl esters.

The term "amide" has the meaning generally accorded that term in
 20 organic chemistry. In this instance it includes the unsubstituted amides and all aliphatic and aromatic mono- and di-substituted amides. Preferred amides are the mono- and di-substituted amides derived from the saturated aliphatic radicals of ten or fewer carbon atoms or the cyclic or saturated aliphatic-cyclic radicals of 5 to 10 carbon atoms. Particularly preferred amides are those derived from lower alkyl
 25 amines. Also preferred are mono- and di-substituted amides derived from the phenyl or lower alkylphenyl amines. Unsubstituted amides are also preferred.

Acetals and ketals includes the radicals of the formula —CK where K is (—OR)₂. Here, R is lower alkyl. Also, K may be —OR₁O— where R₁ is lower alkyl of 2-5 carbon atoms, straight chain or branched.

The preferred acetylenic retinoid compounds of this invention are those
5 where the ethynyl group and the B group are attached to the 2 and 5 positions respectively of a pyridine ring (the 6 and 3 positions in the nicotinic acid nomenclature being equivalent to the 2/5 designation in the pyridine nomenclature) or the 5 and 2 positions respectively of a thiophene group respectively; n is 0; and B is —COOH, an alkali metal salt or organic amine salt, or a lower alkyl ester, or
10 —CH₂OH and the lower alkyl esters and ethers thereof, or —CHO and acetal derivatives thereof.

The preferred acetylenic retinoid compounds include:
ethyl 6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)-nicotinate (i.e., tazarotene);
6-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)nicotinic acid;
15 ethyl 6-(2-(4,4-dimethylchroman-6-yl)ethynyl)nicotinate;
ethyl 6-(2-(4,4,7-trimethylthiochroman-6-yl)ethynyl)-nicotinate;
ethyl 6-(2-(4,4-dimethyl-1,2,3,4-tetrahydroquinolin-6-yl)ethynyl)nicotinate;
ethyl 5-(2-(4,4-dimethylthiochroman-6-yl)ethynyl)thiophene-2-carboxylate;
6-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-3-pyridylmethanol; and
20 2-(2-(4,4-dimethylthiochroman-6-yl)-ethynyl)-5-pyridinecarboxaldehyde.

The compounds of the invention can be purchased or made by methods known in the art. One means to make the acetylenic compounds of the invention is provided in U.S. Patent No. 5,089,509 which is incorporated herein by reference.

The "retinoid composition" contains the retinoid compounds of the
25 invention in amounts suitable for topical use on humans. Such compositions may be in the form of a gel, cream, lotion, ointment, cleanser or solution and include a variety of preservatives, carriers and other inactive or active ingredients.

As used herein, "therapeutically-effective amount" refers to that
amount of a therapeutically-active retinoid necessary to administer to a human patient
30 to treat acne or photoaging. Such amounts depend on the retinoid and its

bioavailability but can range from about 0.01% to about 10% by weight, or preferably from about 0.025% to about 1-5 % by weight. For tazarotene, commercially available preparations of 0.05% and 0.1% are effective. Therapeutically-effective amounts can be readily determined by one of ordinary skill in the art.

5 As demonstrated by the following examples, surprisingly good results are obtainable using short-contact retinoid therapy. Not only does it appear that there is no loss of effectiveness of the active retinoid ingredient (as compared with conventional extended-contact therapy), but also that the effectiveness may be enhanced in some instances. Even more important, the adverse reactions are
10 substantially reduced to tolerable or even negligible levels, thereby resulting in the ability and willingness of the user to adhere to the novel regimen. This combination of effects, i.e., equal or enhanced effectiveness, reduction in adverse reactions, and regimen adherence, yields surprisingly improved therapeutic efficacy.

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E X A M P L E 1

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Twenty (20) acne patients were treated with Tazorac™ (0.05% or 0.1%). They applied the gel to the facial skin once or twice daily for two to five minutes. Immediately following treatment, the treated skin was thoroughly washed with lukewarm water (the use of washcloth was not recommended, both because of its
20 abrasiveness and tendency to retain the gel). The results following four weeks of therapy were as follows;

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1. Signs of retinization (slight reddening, peeling, and irritation) occurred in 11 of 20 patients during the first 2 weeks of short-contact tazarotene therapy. 10 of these 11 reported only minor discomfort, but one reported marked redness and irritation.

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2. Subjective improvement of acne occurred in 18 of 20 patients, usually by 2 to 3 weeks of therapy. One patient with recalcitrant acne of ten years duration had an 80% reduction in lesion counts within 3 weeks. 8 of 20 patients had greater than 75% reduction in lesion counts, 6 of 20 had greater than 50% reduction in lesion counts, and 4 of 20 had

greater than 25% reduction in lesion counts after 4 weeks or more of short-contact tazarotene therapy.

3. One patient with adult acne and photoaging noted subjective improvement in skin texture and pigmentation after 4 weeks of therapy.
4. 19 of 20 patients viewed the short-contact tazarotene therapy as pleasant and convenient.

EXAMPLE 2

As noted in Example 1, at least one of the patients noticed the improvement of skin damaged by the effects of photoaging. Similar effects are observed in other patients following the short-contact tazarotene therapy. The contact period is from 30-seconds to ten minutes, preferably one to three minutes, followed immediately by rinsing. Once or, preferably, twice per day treatment is recommended.

In addition to the patient noted in Example 1, two other patients have been treated with short-contact tazarotene therapy for photoaging, for a period of six weeks or longer. All three patients were examined and photographed at several intervals, and were found to have noticeable improvement in skin texture and pigmentation, a reduction in fine wrinkling and apparent diminution of solar keratoses, which are believed to be precancerous lesions.

CLAIMS

1. A method of treating acne in a human patient comprising the steps of (1) topically applying an effective amount of a retinoid composition to the affected area of a patient's skin; (2) allowing said composition to remain in contact with the skin for a period of from about thirty seconds to about 15 minutes; and (3) rinsing said retinoid composition from said affected area.

2. The method according to Claim 1 wherein said composition remains in contact with the skin for a period of from about two to about five minutes.

3. The method according to Claim 1 or 2 wherein said retinoid composition comprises a therapeutically-active retinoid selected from the group consisting of tretinoin, tazarotene and adapalene.

4. The method according to Claim 3 wherein said retinoid is tazarotene.

5. The method according to any one of Claims 1-4 wherein said therapeutically-active retinoid is present in an amount of about 0.01% to about 10% by weight.

6. The method according to any one of Claims 1-5, wherein steps (1) to (3) are carried out at least 3 times per week.

7. The method according to any one of Claims 1-6 wherein steps (1) to (3) are carried out repeatedly during a period of at least about four (4) weeks.

8. A method of treating skin damaged by photoaging, comprising the steps of (1) topically applying an effective amount of a retinoid composition to the affected area of a patient's skin; (2) allowing said composition to remain in contact with the skin for a period of from about thirty seconds to about ten minutes; and (3) rinsing said retinoid composition from said affected area.

9. The method according to Claim 8, wherein said composition remains in contact with the skin for a period of from about one to about three minutes.

10. The method according to Claim 8 or 9, wherein said retinoid composition, comprises a therapeutically-active retinoid selected from the group consisting of tretinoin, tazarotene and adapalene.

11. The method according to Claim 10, wherein said retinoids is tazarotene.

12. The method according to any one of Claims 8-11, wherein said therapeutically-active retinoid is present in an amount of about 0.01% to about 10% by weight.

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13. The method according to any one of Claims 8-12 wherein steps (1) to (3) are carried out at least 3 times per week.

14. The method according to anyone of Claims 8-13, wherein steps (1) to (3) are carried out repeatedly during a period of at least about 4 weeks.

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