METHODS FOR TREATMENT OF SCARRING FIBROTIC ALOPECIA

Scarring fibrotic alopecia of the scalp resulting from traumatic hair treatments and other exogenous causes may be treated by topically applying to affected areas of the scalp a retinoid in an amount effective to reduce chronic irritation and inflammation induced by such causes and which results in hair loss, hair thinning, hair breakage, fibrotic scars, and atrophy. The retinoid may be applied daily in a non-toxic, dermatologically acceptable vehicle, preferably an emollient vehicle, and preferably in amounts equivalent to about 0.01 to 0.25 weight percent retinoic acid in the vehicle. The treatment is particularly satisfactory for adult, particularly middle-aged, black women who have experienced years of trauma from hot combs, permanents, hair straighteners, and the like.
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METHODS FOR TREATMENT OF
SCARRING FIBROTIC ALOPECIA

Field of the Invention
The present invention relates to methods of treating disorders affecting the scalp of black women. More particularly, the present invention is directed to topical treatment of scarring fibrotic alopecia resulting from traumatic hair treatments such as hot combs and chemical insults.

Background of the Invention
Scarring fibrotic alopecia is a destructive disorder of the human scalp which occurs almost exclusively in middle-aged black women. The disorder results from traumatic hair treatments over a period of time (years or even decades) involving such agents as hot combs, permanents, straighteners, bleaches, and other exogenous damaging applications. Scarring fibrotic alopecia is characterized by chronic irritation and inflammation of the central area of the scalp resulting in hair loss, hair thinning, hair breakage, fibrotic scars, and atrophy.

This exogenous type of alopecia is not well recognized in the literature. However, the early, less severe, stages of the disorder are described at length in P. LoPresti,
C. Papa, and A. Kligman, *Hot Comb Alopecia*, 98 Arch. Derm. 234 (1968). The early stages involve a chronic inflammation around the upper portion of the hair follicle. This inflammation is characterized by a dense infiltration of lymphocytes and an increase in fibroblasts in a loose fibrous framework. In many cases, the blood vessels are dilated and surrounded by lymphocytes. The chronic inflammation causes degeneration of the upper portion of the external root sheath. The unsheathed hair attempts to reach the epidermis through a channel without an epithelial lining. Instability in the external root sheath is evidenced by nubbins and tongues of undifferentiated epithelial cells.

As the disorder progresses, the cells of the hair bulb which synthesize the proteins comprising the hair shaft undergo gradual degeneration. Remnants of the hair shaft may remain in the dermis. As the disorder progresses further, the inflammation regresses leaving thick bands of dense, eosinophilic collagen. The sclerotic bands replace the follicles. The sebaceous gland is also obliterated. In the final stages of the disorder, the scalp surface shows indurated scarring with many follicular orifices obliterated or distorted. The hard fibrotic scars are evidenced by raised lumps or ridges on the scalp, as opposed to the smoother, surface-level scars of earlier stages as in hot comb alopecia.

The prior art discusses the uses of retinoids and their derivatives in the treatment of other types of hair thinning and baldness, notably androgenic alopecias of men and women. These patterned alopecias are genetically determined and
are not accompanied by scarring of the surface. Common baldness, or androgenic alopecia, is an indigenous condition quite unlike fibrotic alopecias which result solely from chemical and physical traumas operating over many years.

Vitamin A and its derivatives, generally known as retinoids, affect the growth, differentiation, and proliferation of many different types of cells. Retinoids have been used in the treatment of severe cystic acne, psoriasis, and other keratinization disorders.


Published PCT Application No. WO 83/02558 of Bazzano discloses the use of retinoids and minoxidil to increase the rate of hair growth, prolong the anagen phase of the hair cycle and to treat specific types of alopecia, such as male pattern alopecia.

Published PCT Application No. WO 82/02833 of Bazzano discloses the use of retinoids and their derivatives to increase the rate of hair growth and prolong the anagen phase of the hair cycle in the treatment of normal hair loss. The use of retinoids to stimulate the cells of the dermal papillae and cells of the root sheath of the hair follicle is also discussed.

U.S. Patent No. 4,874,791 of K. Adachi et al. discloses a hair-growing agent comprised of an aliphatic carboxylic acid having an odd number of carbon atoms, or its derivatives. Adachi also discloses that vitamins, such as vitamin E, may assist in the prevention and improvement of common male and female baldness.

My U.S. Patents Nos. 4,603,146, 4,877,805, and 4,888,342 disclose methods of treatment using vitamin A acid and other retinoids to improve the quality and appearance of sun-damaged exposed skin, particularly human facial skin but the hair and normal scalp are not mentioned.

U.S. Patent No. 4,937,068 of J. Baral discloses treatment with topical tretinoin and a lotion containing ammonium lactate to give glabrous skin a sartanned appearance and to produce a softened skin texture.

U.S. Patent No. 4,895,727 of L. Allen discloses a method of inducing a reservoir effect in mucous membranes and skin to increase the penetration and residence time of other pharmaceutical active agents, such as retinoids, and discloses that vitamin A may be used as an anti-scarring agent.

The present methods of treatment fulfill a long-felt need not adequately addressed in the prior art, namely, treatment of the trauma-induced scalp disorder, scarring fibrotic alopecia in blacks.
Brief Summary of the Invention

According to the present invention, scarring fibrotic alopecia of the human scalp may be treated by topically applying to affected areas of the scalp a composition containing a therapeutically effective amount of vitamin A acid. In particular, the present invention is directed to methods of treating scarring fibrotic alopecia of the scalp of adult, particularly middle-aged, black women which results from traumatic hair treatment by applying topically to affected areas of the scalp vitamin A acid in a non-toxic, dermatologically acceptable vehicle in an amount effective to reduce the chronic irritation and inflammation, hair loss, hair thinning, hair breakage, fibrotic scars, and follicular atrophy.

Detailed Description of the Preferred Embodiments

Retinoic acid is a derivative of Vitamin A (known in the art as retinol, the alcohol form of Vitamin A). Retinoic acid is the acid metabolite of retinol where the terminal hydroxyl group of retinol is replaced with a carboxyl group. Retinol is formed in the body from beta-carotene, generally found in yellow vegetables, such as carrots.

Retinoic acid is available commercially from Johnson & Johnson, sold under the trademark "RETIN-A" (tretinoin), for treatment of acne.

Retinoids have been defined as comprising Vitamin A (retinol) and its derivatives, such as Vitamin A aldehyde (retinal) and Vitamin A acid (retinoic acid), comprising the so-called natural retinoids. However, subsequent efforts in synthetic chemistry have resulted in a much larger class of chemical compounds that are termed
retinoids due to their biological similarities to Vitamin A and its derivatives.

Compounds useful in the present invention include natural and/or synthetic analogues of Vitamin A which possess the biological activity of Vitamin A acid as described herein. Accordingly, as used herein for purposes of the present invention, the term "retinoid" will be understood to include any of the foregoing compounds.

Examples of suitable retinoids are set forth in Table I, it being understood that the present invention is not limited thereto.

**TABLE I**

<table>
<thead>
<tr>
<th>Chemical, Common and/or Commercial Name</th>
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<tr>
<td>Isotretinoin</td>
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<td>13-cis-retinoic acid</td>
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<tr>
<td>ACCUTANE</td>
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<tr>
<td>Etretinate</td>
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<tr>
<td>TEGISON</td>
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<tr>
<td>(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester</td>
</tr>
<tr>
<td>(all-E)-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid</td>
</tr>
<tr>
<td>Motretinide</td>
</tr>
<tr>
<td>N-ethyl-9-(4-methoxy-2,3,6-trimethylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraemide</td>
</tr>
<tr>
<td>(E,E)-9-(2,6-dichloro-4-methoxy-3-methylphenyl)-3,7-dimethyl-2,4,6,8-nonatetraenoic acid ethyl ester</td>
</tr>
<tr>
<td>7,8-didehydroretinoic acid</td>
</tr>
<tr>
<td>(E,E)-4-[2-methyl-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3-butadienyl] benzoic acid</td>
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</table>
(E)-4-[(4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexatrienyl) benzonic acid

(all-E)-3,7-dimethyl-9-(3-thienyl)-2,4,6,8-nonatetraenoic acid

(E,E,E)-3-methyl-7-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl)-2,4,6-octatrienoic acid

(E)-6-[2-(2,6,6-trimethyl-1-cyclohexen-1-yl) ethenyl]-2-naphthalenecarboxylic acid

(E,E,E)-7-(2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl)-3-methyl-2,4,6-octatrienoic acid

(E)-4-[2,3-dihydro-1,1,3,3-tetramethyl-1H-inden-5-yl]-1-propenyl] benzoic acid

TTNPB
(E)-4-[2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl-1-propenyl] benzoic acid

(E)-4-[2-(5,6,7,8-tetrahydro-3-methyl-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl] benzoic acid

(E)-1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-(1-methyl-2-phenylethyl) naphthalene

6-(1,2,3,4-tetrahydro-1,1,4,4-tetramethyl-6-naphthyl)-2-naphthalene-carboxylic acid

(E)-6-[2-[4-(ethylsulfonyl)phenyl-1-methylethenyl]-1,2,3,4-tetrahydro-1,1,4,4-tetramethylnaphthalene

4-[5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthalenyl]ethenyl] benzoic acid

(E)-2-(1,1,4,4-tetramethyl-1,2,3,4-tetrahydronaphth-7-yl-[4-tetrazol-5-yl] phenyl]-1-propene

(E)-4-[2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthalenyl)-1-propenyl] benzyl alcohol
AM-80
2-(4-Carboxybenzamido)-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene

AM-580
2-[N-(4-Carboxyphenyl)carbamoyl]-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene

CH-55
1-[3,5-(Di-tert-butyl)benzoyl]-2-(4-Carboxyphenyl) ethene

TTNT
2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-6-benzo(b) thiophene carboxylic acid

TTNF
2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-6-benzo(b) furancarboxylic acid

TTNI
2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-6-indolecarboxylic acid

TTNN
2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-6-naphthalene carboxylic acid

p-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-anthracenyl) benzoic acid

Esters or amides of 13-trans retinoic acid or 13-cis retinoic acid wherein the -OH group of the carboxylic acid (-COOH) group is substituted by -OR₁ or NR₁R₂, wherein R₁, R₂ and R₃ are such that these esters or amides can be converted to 13-trans retinoic acid or 13-cis retinoic acid through hydrolysis, metabolism, cleavage, etc.

Also encompassed within the term "retinoid" are geometric and stereoisomers of the retinoids.

While the methods below describe treatment with vitamin A acid (tretinoin), one skilled in the art would understand that any retinoid having biological similarity to vitamin A
acid may be used in accordance with the present invention.

Tretinoin (Vitamin A acid) is available commercially from Ortho Pharmaceutical Corporation under the trademark "RETIN-A". RETIN-A Cream contains tretinoin in three different strengths, namely 0.025%, 0.05% and 0.1% by weight. The cream also contains stearic acid, isopropyl myristate, polyoxyl 40 stearate, stearyl alcohol, xanthan gum, sorbic acid, butylated hydroxytoluene, and purified water. Ortho also produces gels having 0.01% and 0.025% tretinoin by weight and a solution containing 0.05% tretinoin by weight. One of ordinary skill in the art will understand from the present disclosure that vitamin A acid, as used in the present treatments, may also be provided in any other suitable non-toxic, dermatologically acceptable vehicle, such as in an emollient vehicle, ointment, solution or aerosol.

According to the present invention, the composition containing vitamin A acid is applied topically to affected areas of the scalp daily. In one embodiment of the present invention, the vitamin A acid is topically applied in a non-toxic, dermatologically acceptable vehicle. Preferably, this vehicle is an emollient vehicle. In the presently preferred embodiment, therapeutically effective amounts of vitamin A acid are applied to the scalp by use of the commercially available

RETIN-A (tretinoin) creams.

Therapeutically effective amounts of vitamin A acid are preferably applied daily to the scalp. One of ordinary skill in the art will understand that the frequency of the dosages for treatment of an individual patient may be increased
or decreased in accordance with the present invention, based upon such factors as age, sensitivity of the scalp, and stage and severity of the disease. It is desirable, however, to limit the dosage to that which is therapeutically effective but which avoids the irritation sometimes associated with an excess dosage of vitamin A acid.

In accordance with the present invention, a "therapeutically effective amount" is the amount of vitamin A acid which will reduce the chronic irritation and inflammation and other symptoms set forth above which are associated with trauma-induced scarring fibrotic alopecia. Based on retinoic acid as the retinoid, concentrations equivalent to about 0.01 to 0.25 weight percent retinoic acid in the vehicle, and preferably about 0.025 to 0.1 weight percent, may be used.

The prior art fails to adequately address treatment of scarring fibrotic alopecia. Indeed this condition is not recognized in textbooks of dermatology. More specifically, the prior art fails to recognize the value of vitamin A acid for treatment of these trauma-induced scalp disorders which predominately affect adult or middle-aged black women and which manifest themselves by embarrassing and painful chronic irritation and inflammation.

The present vitamin A acid treatments result in a lessening of the chronic irritation and inflammation associated with trauma-induced scarring fibrotic alopecia. Treatment with vitamin A acid also reduces the debilitating effects of hair loss, hair thinning, hair breakage, fibrotic scars, and atrophy of the follicles.
Although studies have not progressed long enough to be certain, it is believed that treatment can be stopped, without relapse, after about one year, provided that the treated subject discontinues traumatic treatments such as hot combs and chemical injuries.

While the inventor does not wish to be bound by any particular theory, it is believed that retinoids (1) facilitate removal of inflammatory infiltrates; (2) moderate scarring; and (3) promote scalp healing by restructuring of the dermal matrix.

The invention will now be described with reference to the following specific, non-limiting example.

Treatment for a period of 6 to 8 months by topical application of corticosteroids had no effect in ameliorating the condition. Twice daily massage with Chesebrough-Ponds' Vaseline (White Petrolatum U.S.P.) over a period of 2 to 4 months likewise had no beneficial effect.

In accordance with the present methods, approximately twelve middle-aged black women showing moderate expressions of scarring fibrotic alopecia, accompanied by thinning of hair over the crown of the scalp, were treated at the Center for Skin Research in Washington, D.C. and at the University of Pennsylvania in Philadelphia, Pennsylvania. In an uncontrolled experiment, a RETIN-A (tretinoin) cream containing a predetermined amount of vitamin A acid (namely, 0.025%, 0.05%, and 0.1% by weight vitamin A acid) was applied daily to the scalps of the women. Initially, patients were treated with 0.025% tretinoin. When it was observed that this level of
tretinoin produced no irritation, 0.05% and then 0.1% tretinoin creams were used. Enhanced results were observed at the higher concentrations. Preferably, a 0.1% by weight RETIN-A (tretinoin) cream is used in this particular treatment.

A substantial improvement was recorded after about six months of treatment. In particular, treatment with vitamin A acid was observed to reduce the chronic irritation and inflammation associated with scarring fibrotic alopecia. More specifically, prior to such treatment, the scalp surface of the women exhibited fibrotic, hard scarring. The chronic irritation and inflammation associated with the disease produced a fibrotic strangulation of the individual hairs. Hair loss and thinning were evident in the crown area, where remaining hairs were of poor quality and tended to break easily.

As a result of treatment using vitamin A acid, a softening of the scars and an increase in hair growth was evident in most subjects. Biopsies taken from subjects before and after such treatment showed an increase in the width and length of follicles after treatment. After 7 months of treatment, diffuse inflammatory changes were no longer evident. Hair growth was denser with longer, thicker hairs observed. Histologically, the use of tretinoin in accordance with the present treatments moderated inflammation and stimulated the hair matrix. The reduction in fibrosis allows the hair matrix to produce thicker hairs.

However, the present methods of treatment using tretinoin were not found to be particularly effective in advanced stages of the disorder in older women. The scalps of these women
exhibit major hair loss with hard, fibrotic
scarring and almost complete destruction of the
hair follicles.

The present invention may be embodied in
other specific forms without departing from the
spirit or essential attributes thereof and,
accordingly, reference should be made to the
appended claims, rather than the specification, as
indicating the scope of the invention.
CLAIMS

1. A method for treating scarring fibrotic alopecia of the human scalp comprising applying topically to affected areas of the scalp a composition comprising a therapeutically effective amount of a retinoid.

2. A method according to claim 1, wherein said human is an adult, middle-aged black woman.

3. A method according to claim 1, wherein the scarring fibrotic alopecia results from traumatic hair treatments.

4. A method according to claim 3, wherein the traumatic hair treatment comprises use of an agent selected from the group consisting of hot combs, permanents, and straighteners.

5. A method according to claim 1, wherein the scarring fibrotic alopecia is characterized by chronic irritation and inflammation resulting in hair loss, hair thinning, hair breakage, fibrotic scars, and atrophy.

6. A method according to claim 1, wherein the retinoid is present in the composition in a concentration equivalent to about 0.01 to 0.25 percent by weight retinoic acid.

7. A method according to claim 1, wherein the composition comprises the retinoid in a non-toxic, dermatologically acceptable vehicle.

8. A method according to claim 7, wherein said vehicle is an emollient vehicle.

9. A method according to claim 1, wherein said retinoid is retinoic acid.

10. A method for treating scarring fibrotic alopecia of the scalp of a middle-aged black woman resulting from a traumatic hair
treatment comprising applying topically to affected areas of the scalp vitamin A acid in a non-toxic, dermatologically acceptable vehicle in an amount effective to reduce chronic irritation and inflammation resulting in hair loss, hair thinning, hair breakage, fibrotic scars, and atrophy.
## INTERNATIONAL SEARCH REPORT

### I. CLASSIFICATION OF SUBJECT MATTER

According to international Patent Classification (IPC) or to both National Classification and IPC

| IPC (5): | A61K 31/07, 7/06, 9/107 |
| U.S. CL. | 514/725, 880 |

### II. FIELDS SEARCHED

Minimum Documentation Searched

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### III. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO, A, 82/02833 (BAZZANO) 02 SEPTEMBER 1982 See entire document.</td>
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* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

*"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"A" document member of the same patent family

### IV. CERTIFICATION

Date of the Actual Completion of the International Search: 13 May 1992

Date of Mailing of this International Search Report: 22 JUN 1992

International Searching Authority: ISA/US

Signature of Authorized Officer: David J. Colucci

Form PCT/ISA/210 (second sheet) (May 1986)