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Original Article

The efficacy of 1064-nm Q-switched Nd: YAG laser combined with tranexamic acid, glutathione, and vitamin C in the treatment of chloasma

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Abstract: Objective: To investigate the effect of 1064-nm Q-switched Nd: YAG laser combined with tranexamic acid (TXA), glutathione (GSH), and vitamin C (VC) in the treatment of chloasma and its effects on serum luteinizing hormone (LH) and estradiol (E2) levels. Methods: Sixty patients diagnosed with chloasma were enrolled. Among them, 30 patients (Group A) were treated with a 1064-nm Q-switched Nd: YAG laser, while another 30 patients (Group B) were treated with the same laser equipment combined with TXA, GSH, and VC. They were compared in terms of their baseline data and the chloasma area and chloasma color score before and after treatment. Changes in the LH and E2 levels before and after treatment in the two groups were determined by using an enzyme-linked immunosorbent assay (ELISA). Skin lesion subsidence was compared between the two groups before and after treatment using the modified Melasma Area and Severity Index (mMASI) score. The efficacy, adverse reactions, and recurrence after treatment were compared. Results: After treatment, group B showed significantly lower parameters than group A, including the chloasma area and chloasma color, serum LH and E2 levels, mMASI scores and the recurrence rate (All $P < 0.05$). Group B exhibited a significantly higher effective rate than Group A. There were no statistically significant differences between the two groups in xerosis cutis or pigmentation ($P < 0.05$). Conclusion: 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC can enhance the therapeutic effect on patients with chloasma, improve their chloasma area, chloasma color score, and skin lesion subsidence, and ensure the safety of treatment, as well as regulate their endocrine hormone levels, so it is worthy of clinical popularization.

Keywords: 1064-nm Q-switched Nd: YAG laser, tranexamic acid, glutathione, vitamin C, chloasma

Introduction

Chloasma is a common, chronic, refractory pigmented dermatitis in the Department of Dermatology [1-3], with a higher incidence in males than in females. The treatment of the disease takes a long time because its recurrence rate is extremely high, and it is difficult to cure [4, 5]. Patients with chloasma do not have subjective symptoms, so they usually neglect the disease. However, the long-term overactivation of pigment cells on the epidermis leads to skin cancer, which is harmful to the patients' physical and mental health [6, 7]. The pathogenesis of chloasma is complex, and it can be induced by endocrine dysfunction, genetic factors, drugs, ultraviolet radiation, etc. [8, 9].

Currently, chloasma is commonly treated with tranexamic acid (TXA), glutathione (GSH), vitamin C (VC), and natural vitamin E [10]. However, these drugs lead to results that are far from satisfactory, only alleviating or inhibiting pigmentation [11]. With the rapid progress in laser medicine in recent years, laser therapy has been increasingly applied to skin diseases, accelerating pigment metabolism and exhibiting the effect of freckle removal [12]. The non-exfoliative fractional laser significantly improves efficacy and safety in the treatment of chloasma [13]. In this study, the efficacy of the 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC in the treatment of chloasma and its effects on changes in serum luteinizing hormone (LH) and estradiol (E2) levels were explored.

Materials and methods

Baseline data

Sixty patients with chloasma diagnosed and treated in our hospital were enrolled in this study. Among them, 30 patients (Group A) were treated with the 1064-nm Q-switched Nd: YAG laser and had an average age of 35.12 ± 5.78 years. Another 30 patients (Group B) were treated with the 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC and had an average age of 35.66 ± 5.04 years. The inclusion criteria were as follows: patients with complete medical records; patients with chloasma [14].

The exclusion criteria were as follows: patients allergic to drugs used in this study; patients with a contraindication to lasers; pregnant and lactating women; patients with hepatic or renal dysfunction and previous coagulation disorders; patients with complications; patients with consciousness, cognitive, or other mental disorders or with communication disorders. Patients and their families were informed before this study, which was approved by the Hospital Ethics Committee.

Therapeutic methods

Group A was treated with the 1064-nm Q-switched Nd: YAG laser. Before each operation, the doctors and patients wore goggles to avoid eye damage. The energy density of the 1064-nm Q-switched Nd: YAG laser therapeutic head was 2.12 J/cm^2-3.56 J/cm^2, 6 mm-8 mm in diameter, 5 Hz-10 Hz. The laser therapeutic head was kept about 5 cm away from skin. The energy, light spot, and frequency during the treatment is adjusted according to the subcutaneous and pinpoint-sized bleeding points or redness occurs. The laser therapy was performed every two weeks. The course of treatment was formulated based on the patients' different conditions, and 5-10 visits for laser therapy was generally considered 1 course of treatment.

On the basis of the treatment in Group A, the patients in Group B were intravenously dripped with a 5% glucose solution (200 mL) (Shijiazhuang No.4 Pharmaceutical Co., Ltd., SFDA Approval Number: H13022473), TXA (0.25 g) (Shanghai Sine Wanxiang Pharmaceutical Co., Ltd., SFDA Approval Number: H31020040), GSH (1.2 g) (Fuan Pharmaceutical Group Qingyutang Pharmaceutical Co., Ltd., SFDA Approval Number: H20163042), and VC (0.1 g) (Northeast Pharmaceutical Group Shenyang First Pharmaceutical Co., Ltd., SFDA Approval Number: H21020713). The patients were treated for 6 weeks, twice/week.

Outcome measures and evaluation standards

Group A and Group B were compared in terms of their general clinical data, the chloasma area [11], and their chloasma color scores before and after treatment. Changes in the LH and E2 levels before and after treatment in the two groups were determined by using an enzyme-linked immunosorbent assay (ELISA).

Skin lesion subsidence was compared between the two groups before and after treatment using the modified Melasma Area and Severity Index (mMASI) score [15]. The score was positively correlated with the severity of chloasma; higher scores represent more serious chloasma. The efficacy after treatment was compared with the evaluation criteria as follows [6]: Cured: indicated that the spot color basically disappeared and the pigmentation area subsided by more than 90%. Markedly effective: indicated that the spot color significantly lightened and the pigmentation area subsided by 60%-90%. Effective: indicated that the spot color lightened and the pigmentation area subsided by 30%-60%. Invalid: indicated that the spot color deepened or did not change, and the pigmentation area subsided by less than 30%. The adverse reactions (xerosis cutis and pigmentation) and recurrence after treatment were compared between the two groups.

Statistical methods

SPSS 19.0 (Asia Analytics Formerly SPSS China) was used for the statistical analysis. Count data were expressed as [n(%)], and an χ^2 test was used for the comparisons between two groups. Fisher's exact test was used for the comparison of ranked data. Measurement data were expressed as ($\bar{x}$ ± SD), and a paired *t* test was used for the comparisons before and after

Table 1. General clinical data

Groups	Group A (n = 30)	Group B (n = 30)	t/X^2	P
Age (Years)	35.12 ± 5.78	35.66 ± 5.04	0.386	0.701
Gender			0.000	1.000
Male	0 (100.00)	0 (0.00)		
Female	30 (100.00)	30 (100.00)		
BMI (Kg/m^2)	18.24 ± 2.10	18.02 ± 2.53	0.715	0.367
Typing			0.085	0.958
Dermal	10 (33.33)	9 (30.00)		
Epidermal	5 (16.67)	5 (16.67)		
Mixed	15 (50.00)	16 (53.33)		
Menstrual disorders			2.222	0.136
Yes	10 (33.33)	5 (16.67)		
No	20 (66.67)	25 (83.33)		
Long-term use of contraceptives			0.000	1.000
Yes	0 (100.00)	0 (0.00)		
No	30 (100.00)	30 (100.00)		
Chemexfoliation			3.455	0.063
Yes	15 (50.00)	8 (26.67)		
No	15 (50.00)	22 (73.33)		
Hepatic diseases			0.000	1.000
Yes	0 (100.00)	0 (0.00)		
No	30 (100.00)	30 (100.00)		

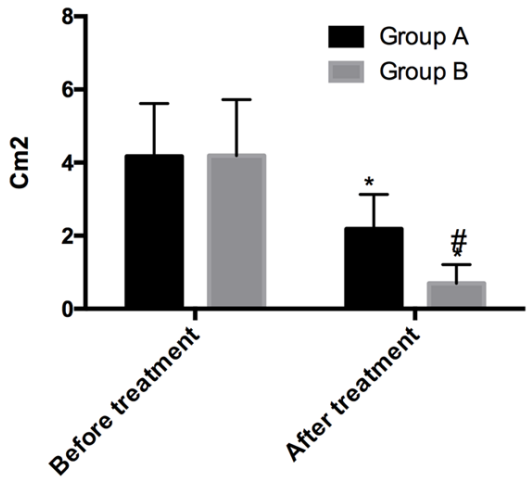

Figure 1. Comparison of chloasma area before and after treatment. *: indicated that after treatment, the chloasma areas in Group A and Group B significantly decreased (P < 0.001). #: indicated that after treatment, the chloasma area in Group B was significantly smaller than it was in Group A (P < 0.001).

treatment within the same group, and an independent samples *t* test was used for comparisons between two groups. P < 0.05 indicated a significant difference.

Results

Baseline data

No significant differences in the baseline data were found between the two groups (P > 0.05) (**Table 1**).

Comparison of the chloasma areas and chloasma color scores before and after treatment

The chloasma areas before and after treatment in Group A were (4.17 ± 1.45) cm^2 and (2.18 ± 0.95) cm^2, and the areas in Group B were (4.19 ± 1.53) cm^2 and (0.70 ± 0.51) cm^2. After treatment, the chloasma area in Group B was significantly smaller than it was in Group A (P < 0.001). More details are shown in **Figure 1**.

Comparison of the chloasma color scores before and after treatment

The chloasma color scores before and after treatment in Group A were (2.53 ± 0.92) and (1.6 ± 0.51) points, while the scores in Group B were (2.55 ± 0.88) and (0.6 ± 0.43) points. After treatment, the chloasma color scores in

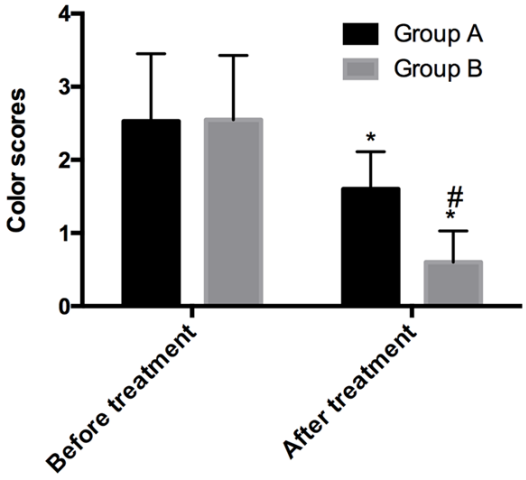

Figure 2. Comparison of the chloasma color scores before and after treatment. *: indicated that after treatment, the chloasma color scores in Group A and Group B significantly decreased (P < 0.001). #: indicated that after treatment, the chloasma color score in Group B was significantly lower than it was in Group A (P < 0.001).

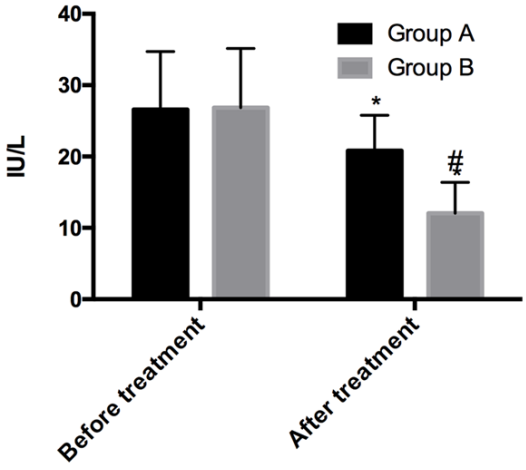

Figure 3. Comparison of the LH level changes before and after treatment. *: indicated that after treatment, the serum LH levels in Group A and Group B significantly decreased (P < 0.001). #: indicated that after treatment, the serum LH level in Group B was significantly lower than it was in Group A (P < 0.001).

Group B was significantly lower than they were in Group A (P < 0.001) (**Figure 2**).

Comparison of the LH level changes before and after treatment

The serum LH levels before and after treatment in Group A were (26.57 ± 8.15) IU/L and (20.82 ± 4.95) IU/L, and the levels in Group B were (26.86 ± 8.28) IU/L and (12.04 ± 4.33) IU/L. After treatment, the LH levels in Group B was significantly lower than they were in Group A (P < 0.001) (**Figure 3**).

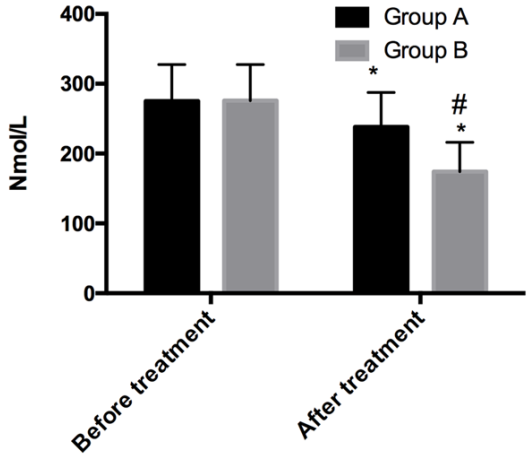

Figure 4. Comparison of E2 level changes before and after treatment. *: indicated that after treatment, the serum E2 levels in Group A and Group B significantly decreased (P < 0.001). #: indicated that after treatment, the serum E2 level in Group B was significantly lower than it was in Group A (P < 0.001).

Comparison of the E2 level changes before and after treatment

The serum E2 levels before and after treatment in Group A were (275.20 ± 52.41) nmol/L and (238.11 ± 49.38) nmol/L, and the levels in Group B were (275.76 ± 51.84) nmol/L and (174.04 ± 42.22) nmol/L. After treatment, the E2 levels in Group B was significantly lower than they were in Group A (P < 0.001). More details are shown in **Figure 4**.

Comparison of skin lesion subsidence before and after treatment

The mMASI scores before and after treatment in Group A were (11.28 ± 2.19) and (6.23 ± 2.05) points, and the scores in Group B were (11.47 ± 2.21) and (2.74 ± 1.36) points. After treatment, the mMASI scores in Group B was significantly lower than that in Group A (P < 0.001). More details are shown in **Table 2**.

Comparison of efficacy after treatment

Group A showed significantly lower efficacy than Group B (90.00%) (P < 0.001) (**Table 3**).

Table 2. mMASI scores before and after treatment

Groups	Group A (n = 30)	Group B (n = 30)	t	P
Before treatment	11.28 ± 2.19	11.47 ± 2.21	0.335	0.739
After treatment	6.23 ± 2.05	2.74 ± 1.36	7.770	< 0.001
t	6.103	8.344		
P	< 0.001	< 0.001		

Table 3. Efficacy after treatment

Groups	Group A (n = 30)	Group B (n = 30)	X^2	P
Cured	10 (33.33)	16 (53.33)	-	-
Markedly effective	7 (23.33)	11 (36.67)	-	-
Effective	7 (23.33)	2 (6.67)	-	-
Invalid	6 (20.00)	1 (3.33)	-	-
Total effective rate	17 (56.67)	27 (90.00)	8.523	0.004

Table 4. Adverse reactions and recurrence after treatment

Groups	Group A (n = 30)	Group B (n = 30)	X^2	P
Xerosis cutis	4 (13.33)	4 (13.33)	0.000	1.000
Pigmentation	4 (13.33)	4 (13.33)	0.000	1.000
Recurrence	7 (23.33)	1 (3.33)	5.192	0.023

Comparison of adverse reactions and recurrence after treatment

After treatment, Group A had 4 cases of xerosis cutis, 4 cases of pigmentation, and 7 cases of recurrence, and Group B had 4 cases of xerosis cutis, 4 cases of pigmentation, and 1 case of recurrence. There were no statistically significant differences between the two groups in xerosis cutis or pigmentation ($P < 0.05$). The recurrence rate in Group A was significantly higher than it was in Group B ($P > 0.05$). More details are shown in **Table 4**.

Discussion

The results showed that the chloasma area and chloasma color scores in the two groups significantly decreased after treatment; those in Group B were significantly lower than those in Group A. Patients with chloasma have excessive melanin deposition on the epidermis and their mast cells on the corresponding dermis also increase, which expands the chloasma area and deepens the chloasma color [16]. According to relevant studies, TXA inhibits the binding of enzymes to tyrosine to inactivate enzymes, reduces tyrosine metabolites, and blocks the synthesis of melanin proteins, thus inhibiting the occurrence of pigment and treating chloasma [17]. GSH inhibits melanin pigmentation by scavenging free radicals and superoxide ions [18]. As a dopadecarboxylase inhibitor that gradually reduces dark oxidized melanin to light reduced pigments, VC inhibits the oxidation rate of dopa [19]. TXA, GSH, and VC are commonly used to treat chloasma [20]. With the development of laser therapy in recent years, a large number of clinical studies have shown that laser combined with TXA, GSH, and VC is better than laser alone in improving chloasma areas and color during the treatment of chloasma [21]. In this study, skin lesion subsidence was objectively recorded based on the mMASI scores before and after treatment in Group A and Group B. The results showed that, after treatment, the mMASI score in the two groups significantly decreased; and it was lower in Group B than in Group A. In a similar study, the mMASI scores of patients with chloasma who were treated with laser combined with drugs were greatly reduced [22]. According to the ELISA results, before treatment, there were no statistically significant differences between the two groups in serum LH and E2 levels. After treatment, the levels in the two groups significantly decreased; the levels in Group B were significantly lower than those in Group A. Serum LH and E2 levels are important detection indices for endocrine hormones. A lot of studies have shown that the imbalance of serum LH and E2 levels accelerates the deposition of chloasma on the epidermis [23], and the levels in patients with chloasma are higher than those in healthy people [24]. Therefore, 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC can improve the hormone levels and inhibit the chloasma regeneration of patients with chloasma. Finally, Group B showed a higher total effective rate and a lower recurrence rate than Group A.

Therefore, 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC has a high degree of safety in the treatment of chloasma and can reduce the recurrence rate, with adverse symptoms similar to those after treat-

ment with a laser alone. According to a relevant study, the 1064-nm Q-switched Nd: YAG laser, which is effective for treating chloasma and promoting melanin metabolism, is an advanced technology. It uses laser energy to pulverize melanin particles through the principle of subcellular selective photothermolysis, so as to accelerate the metabolism of melanin particles [25]. The 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC is safe and enhances efficacy in the treatment of chloasma [26].

In summary, the 1064-nm Q-switched Nd: YAG laser combined with TXA, GSH, and VC can enhance the therapeutic effect on patients with chloasma, improve their chloasma areas, chloasma color scores, and skin lesion subsidence, and ensure the safety of treatment, as well as regulate their endocrine hormone levels, so it is worthy of clinical popularization.

Disclosure of conflict of interest

None.

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References

[1] Gauri M, Ahmed T, Khan MS and Ali SJJJoSS. Therapeutic evaluation of unani herbal medicine for topical application (Zimad of Tukhme Turb, Tukhme Karafs and Sirka) in melasma (Kalaf) - a single blind randomized controlled study. J Sep Sci 2015; 35: 2122-2130.

[2] Tong YU, Feng Y, Huanhuan WU, Shuiying HE, Zhang D, Yang J, Yin H and Yin Q. Therapeutic efficacy and safety of compound muni ziqi granules in the adjuvant treatment of chloasma: a systematic review. China Pharmacy 2018.

[3] Coyle ME, Liang H, Wang K, Zhang AL, Guo X, Lu C and Xue CC. Acupuncture plus moxibustion for herpes zoster: a systematic review and meta-analysis of randomized controlled trials. Dermatol Ther 2017; 30.

[4] Omoti AE, Waziri-Erameh JM and Okeigbemen VW. A review of the changes in the ophthalmic and visual system in pregnancy. Afr J Reprod Health 2008; 12: 185-196.

[5] Rivas S and Pandya AG. Treatment of melasma with topical agents, peels and lasers: an evidence-based review. Am J Clin Dermatol 2013; 14: 359-76.

[6] Zhang S, He H and Liu Y. Electroacupuncture at facial acupoints combined with electrical stimulation on the auricular vagus nerve points for 60 cases of chloasma. World J Acupunct Moxibustion 2018.

[7] Chen CY. Observations on the efficacy of pricking-cupping bloodletting in treating cervical spondylotic radiculopathy. Shanghai Journal of Acupuncture & Moxibustion 2016.

[8] Wu YH, Li QL and Yang XW. Effects of Chinese herbal medicine combined with He-Ne laser on lipoperoxide and superoxide dismutase in chloasma patients. J Tradit Chin Med 2009; 29: 163-166.

[9] Zhong XS and Zheng LL. Clinical effect observation on treatment of chloasma with acupuncture. Journal of Acupuncture and Tuina Science 2004; 2: 29-31.

[10] Feng C and Yan M. Clinical observation on tranexamic acid combined with reduced glutathione for the treatment of chloasma. Pak J Pharm Sci 2018; 31: 2823-2826.

[11] Juhasz MLW and Levin MK. The role of systemic treatments for skin lightening. J Cosmet Dermatol 2018; 17: 1144-1157.

[12] Zhang Y, Zheng X, Chen Z and Lu L. Laser and laser compound therapy for melasma: a meta-analysis. J Dermatolog Treat 2019; 1-7; [Epub ahead of print].

[13] Sünkel S. Gütegeschalteter (Quality-switched) rubin-laser. 2005.

[14] Borodic GE, Caruso P, Acquadro M and Chick S. Parry-Romberg syndrome vasculopathy and its treatment with botulinum toxin. Ophthalmic Plast Reconstr Surg 2014; 30: 22-25.

[15] Vachiramon V, Suchonwanit P and Thadanipon K. Melasma in men. J Cosmet Dermatol 2012; 11: 151-157.

[16] Zhang L, Tan WQ, Fang QQ, Zhao WY, Zhao QM, Gao J and Wang XW. Tranexamic acid for adults with melasma: a systematic review and meta-analysis. Biomed Res Int 2018; 2018: 1683414.

[17] Song W, Qin ST, Fang FX, Gao ZJ, Liang DD, Liu LL, Tian HT and Yang HB. Isolation and purification of condensed tannin from the leaves and branches of prunus cerasifera and its structure and bioactivities. Appl Biochem Biotechnol 2018; 185: 464-475.

[18] Ikeda M, Ishima Y, Kinoshita R, Chuang VTG, Tasaka N, Matsuo N, Watanabe H, Shimizu T, Ishida T, Otagiri M and Maruyama T. A novel S-sulfhydrated human serum albumin preparation suppresses melanin synthesis. Redox Biol 2018; 14: 354-360.

[19] Miao F, Su MY, Jiang S, Luo LF, Shi Y and Lei TC. Intramelanocytic acidification plays a role in

the antimelanogenic and antioxidative properties of vitamin c and its derivatives. Oxid Med Cell Longev 2019; 2019: 2084805.
[20] Wu YH, Li QL and Yang XW. Effects of Chinese herbal medicine combined with he-ne laser on lipoperoxide and superoxide dismutase in chloasma patients. J Tradit Chin Med 2009; 29: 163-166.
[21] Eshghi G, Khezrian L and Esna Ashari F. Comparison between intralesional triamcinolone and Kligman's formula in treatment of melasma. Acta Med Iran 2016; 54: 67-71.
[22] Galappatthy P and Rathnayake D. Depigmenting agents. 2018.
[23] Sevilla M, Sanchís C, Valdés-Solís T, Morallón E and Fuertes AB. Direct synthesis of graphitic carbon nanostructures from saccharides and their use as electrocatalytic supports. Carbon 2008; 46: 931-939.
[24] Sarkar R, Ailawadi P and Garg S. Melasma in Men: a review of clinical, etiological, and management issues. J Clin Aesthet Dermatol 2018; 11: 53-59.
[25] Lieberei B and Linden M. Adverse effects, side effects and medical malpractice in psychotherapy. Z Evid Fortbild Qual Gesundhwes 2008; 102: 558-562.
[26] Kim JY, Lee TR and Lee AY. Reduced WIF-1 expression stimulates skin hyperpigmentation in patients with melasma. J Invest Dermatol 2013; 133: 191-200.