

A comparison of adapalene gel 0.1% vs. tretinoin gel 0.025% in the treatment of acne vulgaris in China

P Tu,*† G-Q Li,† X-J Zhu,† J Zheng,‡ W-Z Wong§

†Department of Dermatology, First Hospital, Peking University, No. 8 Xi Shi Ku St., Beijing 100034, China, ‡Rue Jin Hospital, Shanghai Second Medical University, Shanghai, China, §First Hospital, Wu Han City, China. *Corresponding author, tel. +86 10 6617 1122 / 2350; fax +86 10 6651 8714

ABSTRACT

Aim To compare the efficacy, safety and tolerability of adapalene gel 0.1% vs. tretinoin gel 0.025% in a Chinese patient population.

Background Although acne vulgaris is a common problem among Asians and Asian-Americans, little has been published on the specific manifestations, sequelae, and treatment-responsiveness of this disorder in Asian skin types. Since Asian skin types tend to be more highly pigmented than those of white people of European descent, many Asians share the predisposition toward postinflammatory hyperpigmentation seen in Africans, African-Americans and other dark-skinned peoples. It is generally assumed that the efficacy and safety of topical retinoids is the same in Asians as in white people. Tretinoin has been available in China for decades; adapalene became available in 1998.

Methods A total of 150 patients with grade II–III acne vulgaris seen at three dermatology clinics were randomized to 8 weeks of daily treatment with either adapalene gel 0.1% or tretinoin gel 0.025%. Counts of total lesions, inflammatory lesions and non-inflammatory lesions were made at baseline and again at treatment weeks 2, 4, 6 and 8. Global assessment ratings, based on percent lesion reduction from baseline were also made. Erythema, burning, pruritus, scaling and dryness were rated on a 0–3 severity scale.

Results A total of 139 patients completed the efficacy evaluation, and 144 patients completed the safety evaluation. Both adapalene and tretinoin produce dramatic reductions in total, inflammatory and non-inflammatory lesion counts, in the range of 69–74% on average. More than 70% of patients in both groups had complete clearance or marked improvement. In general, irritation was mild, but was both more common and more severe in the tretinoin group vs. the adapalene group. No systemic side effects were seen.

Conclusions Adapalene offers comparable efficacy to tretinoin, but is less irritating. It represents a good alternative for the treatment of mild to moderate acne vulgaris in Chinese patients.

Key words: adapalene, tretinoin, acne vulgaris, Chinese patients

Introduction

In recent years, the dermatological community has begun to recognize that many Asians share important cutaneous features with Africans, African-Americans and other peoples categorized as having 'black' skin. A broader term, 'skin of colour', has recently begun appearing in the dermatological literature to reflect these commonalities.¹ Some Asian skin types, particularly those from India, Pakistan and other parts of South-east Asia, have pigmentation patterns nearly identical to those seen among sub-Saharan Africans and people of African descent. Whereas Chinese, Japanese, Koreans and others from the Far East have lighter skin than the peoples generally

considered black, they often have greater skin pigmentation than people of white, European ancestry.

To varying degrees, Asians share the general predisposition of darker-skinned people for postinflammatory hyperpigmentation. Any cutaneous condition that involves inflammation can result in postinflammatory pigment changes. Melasma, macules associated with photoaging, and acne-related hyperpigmentation are all fairly common problems in Asian populations.

Hyperpigmentation is related to a rise in tyrosinase triggered by the inflammatory cascade. The increased enzyme activity promotes conversion of tyrosine and other precursor molecules into melanin. The intensity of the postinflammatory hyperpigmentation

is somewhat related to the intensity of the initial inflammation and to the baseline level of skin pigmentation.^{1,2}

The risk of postinflammatory hyperpigmentation presents significant challenges to dermatologists treating acne in Asian patients. Pigmentary abnormalities associated with acne can be persistent and disfiguring among black people, Asians, and other dark-skinned individuals.² In clinical practice, these patients may find these secondary sequelae of acne to be even more bothersome than the primary acne lesions.

Prevalence of acne among Asians

Surprisingly few studies in the English literature deal with acne prevalence among Asians or Asian-Americans. By far the largest such study comes from the National Skin Centre, a large referral centre in Singapore. In the 2-year period from the beginning of 1989 to the end of 1990, a total of 74 589 new patient encounters occurred at the centre.³ While the vast majority of patients (77.2%) were Chinese, there were sufficient numbers of Indians (9.9%), Malays (7.6%) and people of other ethnic groups to allow comparisons of disease prevalence according to racial and skin-type variables.

In general, acne was the second most-common new diagnosis, representing 10.9% of all new diagnoses. Dermatitis was by far the most common diagnostic category, accounting for 34.2% of all patients. There were clear age-associated variations in disease prevalence; acne was the most prevalent diagnosis among the 20–29 years olds, accounting for 52% of all new cases in this age group.

While acne was somewhat more prevalent among the Chinese subgroup compared with the total patient population, there were no significant differences in acne prevalence when the various racial/ethnic subgroups were directly compared.³ Overall, the incidence of acne seems to be on the rise in Singapore, as is the number of patients, particularly males, seeking treatment for the cosmetic sequelae of this disorder.

A retrospective analysis of case records from 199 Indo-Chinese immigrants seen at a tertiary care dermatology clinic in Australia indicated that pigmentation disorders and disorders of the sebaceous glands – including acne vulgaris – were the leading diagnoses in this population: melasma (chloasma) and acne vulgaris were the two most common presentations.⁴

There is little recent prevalence research on acne in other Asian countries. Data from studies published from the late 1950s through the late 1970s show somewhat lower prevalence rates in Japan, Hong Kong, and Korea compared with the UK, Singapore and the US. However, the relevance of this data today is questionable.

Asians in the US tend to seek dermatological care more frequently than African-Americans, Native Americans or other darker-skinned people. A survey representing an estimated 24 million patient encounters by US dermatologists in 1990, indicated clearly that after adjusting for their proportion in the

general population, Asians or Pacific Islanders were far more likely than other peoples of colour to visit dermatologists; their representation in dermatological clinics was comparable to that seen in white people. This may reflect a higher overall socioeconomic status for Asian minorities in the US compared with black people and Native Americans.⁵

Treatment of acne and its sequelae in Asian patients

As in all populations, optimal acne therapy depends on addressing as many of the key pathogenic factors as possible. When treating Asians or other darker-skinned individuals, it is particularly important to focus treatment on the inflammatory aspects of the disease, owing to the fact that Asians are more likely than white people to develop acne-associated hyperpigmentation.

To date, no published trials have appeared in the English-language literature of any of the major acne therapies in exclusively Asian populations. Many major studies have included some Asian patients, but there are no reports of specific differences in response or safety among these subjects. In routine clinical practice, topical retinoids, benzoyl peroxide, and antibiotics are all generally considered to be as safe and effective among Asian patients as they are in white patients.

Findings of small studies support the efficacy and safety of laser skin resurfacing,^{6,7} glycolic acid peels,⁸ and topical retinoid beta-glucuronide,⁹ as effective primary or adjunctive therapies for acne vulgaris in various Asian skin types. There is also at least one series of case reports in the traditional Chinese medicine literature suggesting that acupuncture in combination with traditional ‘cupping’ is effective for treatment of acne.¹⁰

While there are no published trials of topical retinoid therapy for acne-associated hyperpigmentation in Asians, topical retinoic acid combined with 2% hydroquinone has been shown to be effective in the treatment of melasma,¹¹ and two studies suggest positive benefit against melasma and hyperpigmentation associated with photoaging in specific Asian patient populations.^{12,13} Forty-five patients (23 Chinese and 22 Japanese) with photoaging-associated hyperpigmentation were randomized to 0.1% tretinoin cream or vehicle, once daily, for 40 weeks. Ninety percent of those on active treatment showed significant lightening of hyperpigmented macules compared with only 33% of patients on vehicle. Colorimetry confirmed this difference, and histological analysis showed a 41% decrease in epidermal pigmentation in response to tretinoin, as compared with a 37% increase in pigmentation in the vehicle-treated patients.¹²

More recently, a combination of tretinoin 0.1%, hydroquinone 5%, and hydrocortisone 1%, applied twice weekly for 4 months, produced a statistically significant decrease in epidermal pigmentation in 25 Korean women with melasma, a common form of hyperpigmentation among Asians. The effect could be detected within 4 weeks of commencing treatment.¹³

Good results were also reported when 0.05% tretinoin cream was combined with 20% azelaic acid,¹⁴ and a multicentre study

of 300 patients in Thailand and the Philippines found that 20% azelaic acid cream alone produced results substantially superior to 2% hydroquinone cream in the treatment of melasma.¹⁵

While tretinoin may have some benefit in reducing hyperpigmented macules, it is important to remember that this agent may be irritating, especially in the first 2 weeks of treatment, depending on dose, genetics and the individual tolerance of the patient. In a study of tretinoin 0.1% cream for treatment of hyperpigmentation in black people, 50% of those on active therapy had moderate to severe skin reactions, including erythema and desquamation. While none of these patients experienced residual hyperpigmentation secondary to these reactions, it is a possibility worth bearing in mind when using this topical retinoid in any darker-skinned individual.¹⁶

Adapalene in the treatment of acne in Chinese patients

Adapalene has been marketed in China since 1998 and is increasingly accepted by dermatologists there as a well-tolerated alternative to topical tretinoin. We conducted an 8-week, randomized, double-blind, head-to-head comparison between adapalene gel 0.1% and tretinoin gel 0.025% in an entirely Chinese patient population.

Materials and methods

Patient selection and treatment protocol

A total of 150 patients with grade II–III acne vulgaris were seen from December 1997 to February 1998 at three centres: First Hospital Peking University, Rajjin Hospital-Shanghai Second Medical University, and Wuhan First Hospital. After an initial baseline evaluation, including lesion counts, they were randomized to receive either adapalene gel 0.1% or tretinoin gel 0.025%, applied daily, for a total of 8 weeks.

Endpoints

The primary endpoint was reduction in total number of inflammatory and non-inflammatory acne lesions. We measured clinical efficacy according to a global assessment of improvement scale in which a total lesion reduction of 90% or greater was deemed 'cleared'; 60% or greater reduction but less than 90% was deemed 'marked improvement'; 20% or greater but less than 60% was considered 'improvement', and lesion reduction of 20% or less was considered 'unchanged.' A lesion reduction of 60% or greater indicated that the agent in question was 'effective' for the purposes of this study. Assessment of safety was based on a 0–3 gradation of five safety parameters: erythema, burning, pruritus, scaling and skin dryness. The patients were re-evaluated at treatment weeks 2, 4, 6, and 8.

Table 1 Patient population

	Adapalene gel 0.1%	Tretinoin gel 0.025%
<i>Baseline</i>		
Males/Females, <i>n</i>	28/47	33/42
Mean age years (range)	19 (14–30)	19 (14–29)
Skin phototype, <i>n</i> (%)		
I	0	1 (1)
II	5 (7)	3 (4)
III	45 (60)	44 (59)
IV	25 (33)	27 (36)
Total lesion count mean (SD)	58.5 (18.1)	59.2 (21.6)
Global grade mean (SD)	2.6 (0.5)	2.5 (0.6)
<i>Study end</i>		
Patients discontinued, <i>n</i> (%)	4 (5.3)	9 (12.0)
Patients evaluable for efficacy, <i>n</i> (%)	75 (100)	75 (100)
Patients evaluable for safety, <i>n</i> (%)	71 (94.7)	66 (88.0)

Results

A total of 139 patients (72 adapalene and 67 tretinoin) completed the efficacy evaluations, and 144 completed the safety evaluations. Table 1 summarizes the baseline characteristics, and mean lesion counts, of the 150 enrolled patients.

Lesion clearance

Figure 1 summarizes the therapeutic response in terms of percent reductions in non-inflammatory lesion counts. A measurable effect was evident for both agents by the end of treatment week 2: adapalene produced a 21.8% reduction, tretinoin 27.1%. Lesion reductions continued steadily throughout the treatment course. By week 8, adapalene and tretinoin were essentially equivalent, both producing 70% reductions in the total number of non-inflammatory lesions from baseline.

We saw a similar pattern when looking at inflammatory lesion counts (fig. 2). Significant reductions were already apparent after 2 weeks of treatment, with adapalene effecting a 29.8% reduction and tretinoin 33.1%. By the end of the treatment course, adapalene had produced a 74.8% reduction in inflammatory lesions as compared with 72.2% for tretinoin.

Total lesion count followed the same trend (fig. 3). By week 2, adapalene produced a 24.9% reduction in total lesion number, tretinoin 29.4%. At the close of the 8-week treatment period, adapalene provided 72.1% lesion clearance as compared with 70.8% for tretinoin.

Global improvements

In terms of overall global efficacy, the two agents were essentially equivalent (fig. 4). None of the patients remained unchanged, and more than 70% of patients in both treatment arms had complete clearances or marked improvement.

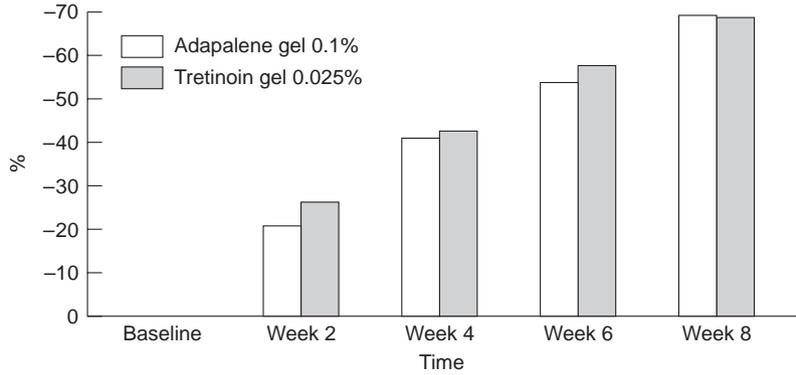


fig. 1 Percentage reduction in non-inflammatory lesion counts.

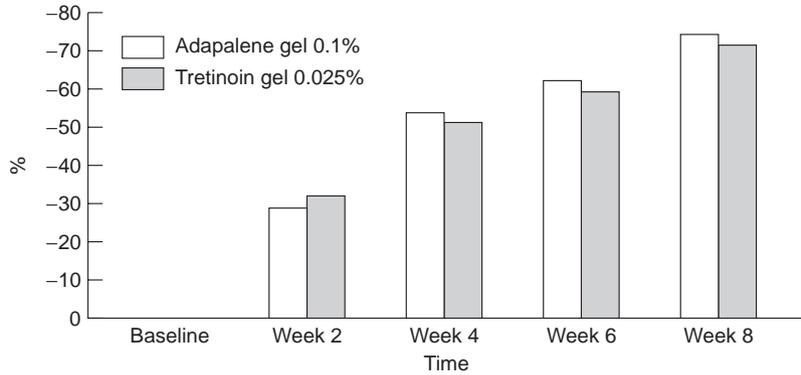


fig. 2 Percentage reduction in inflammatory lesion counts.

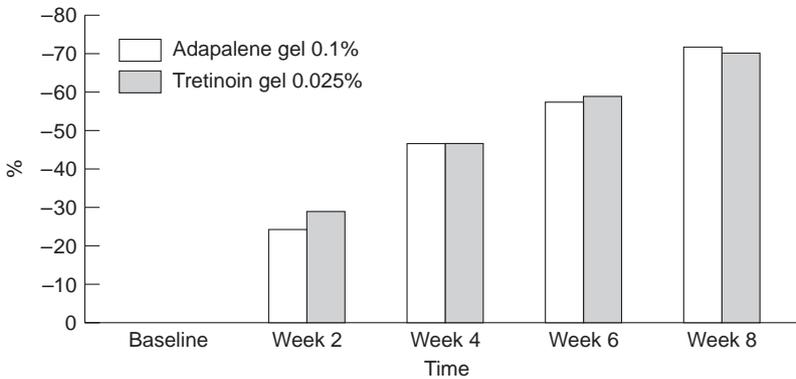


fig. 3 Percentage reduction in total lesion counts.

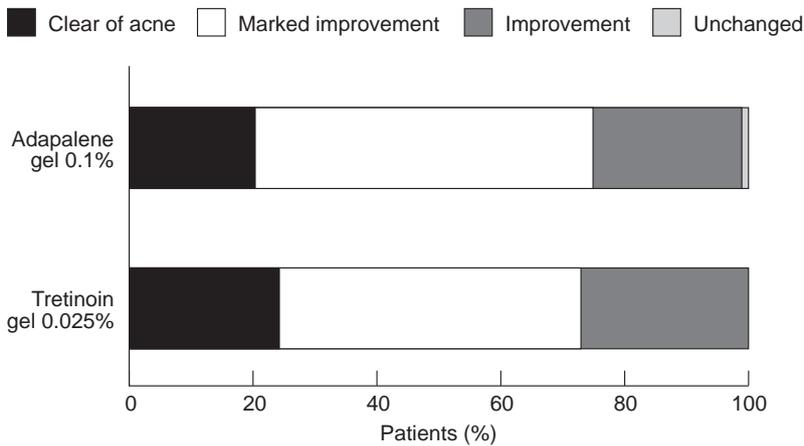


fig. 4 Efficacy: global improvement.

fig. 5 Comparison of incidence of local irritation between adapalene and tretinoin groups. NS = Not significant.

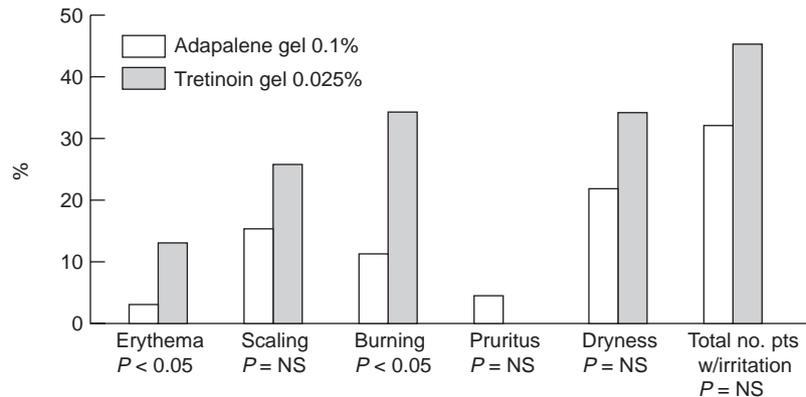
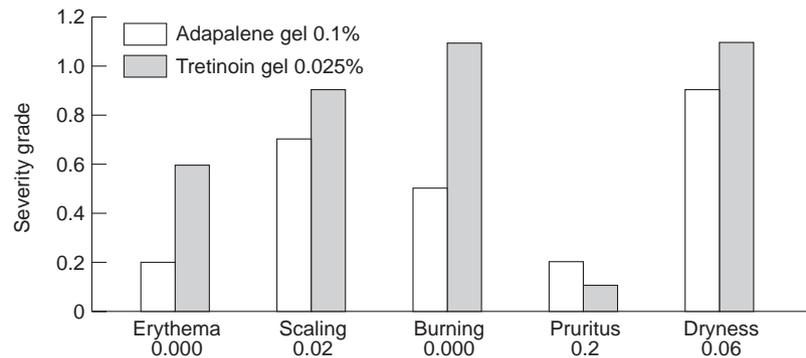


fig. 6 Comparison of severity grade in local irritation between adapalene and tretinoin groups.



Adverse effects

We measured the incidence and severity of five adverse effects characteristic of treatment with retinoids: erythema, scaling, burning, pruritus, and skin dryness. All of these, with the exception of pruritus, were significantly higher in both incidence and severity among patients in the tretinoin group (figs 5, 6).

Burning was the most common unwanted effect in the tretinoin-treated patients, occurring in 34.2%, as compared with 10.8% in the adapalene group. Figure 7 shows the incidence of burning over the 8-week course of treatment. Dryness was also common among tretinoin patients, occurring in 34.2% vs. 21.6% in the adapalene group. Scaling occurred in 25.7% of the tretinoin group and in 14.8% of the adapalene group, and erythema occurred in 25.7% of the tretinoin patients vs. 2.7% of those treated with adapalene. Pruritus was the only adverse effect experienced exclusively by adapalene patients, occurring in fewer than 4%. Overall, 45.7% of the tretinoin patients experienced some form of irritation, compared with 32.4% of those treated with adapalene.

Severity was rated on a 0–3 scale, with 0 representing absence of effect, 1 being mild, 2 being moderate, and 3 being severe. Generally, the irritation experienced by patients in both groups was mild, with the highest mean score being just over 1 (mild). But there was a consistent pattern of higher severity scores among tretinoin-treated patients (fig. 6). Those in the ada-

palene group had significantly less erythema, scaling and burning. No systemic side effects occurred in either group.

Discussion

Relatively little has been published about the specific manifestations and sequelae of acne vulgaris among Asians and people of Asian descent. It is known that this is a common condition in Asian populations, one that can present special problems owing to the propensity for development of postinflammatory hyperpigmentation. This is particularly problematic for darker-skinned Asians, and it is a problem they share with Africans, African-Americans, Native Americans and other people of colour.

Given the tendency toward hyperpigmentation, it is critical when treating acne in Asian patients to minimize the inflammatory component as much as possible. Topical retinoids are a logical choice in this regard. There are no previously published trials in English for any of the retinoids in an exclusively Asian population, and it is generally assumed that they are equally effective and safe in Asian patients as in whites of European descent.

Topical retinoids have been available in China in recent decades. Adapalene, the novel naphthoic-acid derivative with retinoid activity, became available in 1998, and is rapidly becoming accepted by Chinese dermatologists as an alternative to tretinoin.

We conducted a direct, randomized comparison between adapalene gel 0.1% and tretinoin gel 0.025% in 150 patients

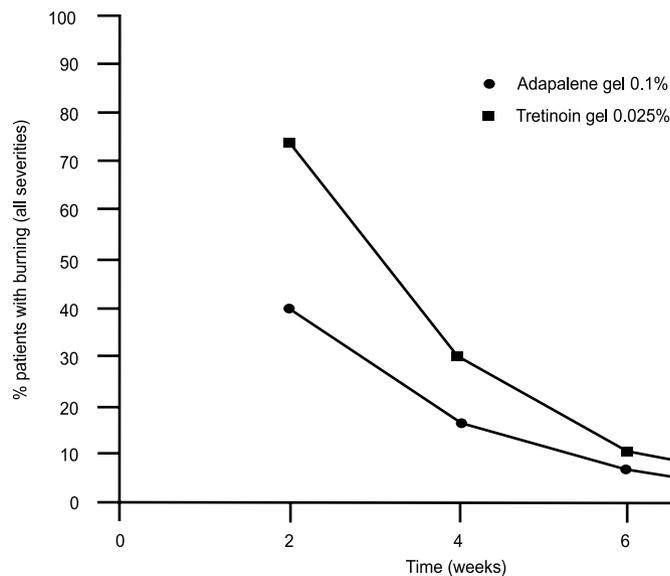


fig. 7 Incidence of burning.

treated for a total of 8 weeks. Both medications produced dramatic reductions in inflammatory, non-inflammatory, and total lesion counts, in the range of 69–74% by the end of the study. In terms of global improvement, both agents gave complete clearance rates in the range of 20%, and more than 70% of each treatment group had either complete clearances or marked improvements.

While both medications produced some degree of mild local irritation including erythema, burning, scaling and dryness, adapalene showed a consistently lower side effect profile in terms of both incidence and severity.

We conclude that adapalene gel 0.1% has efficacy comparable to that of tretinoin gel 0.025%, but is less irritating. It appears to be a safe and effective treatment for acne vulgaris in Chinese patients and by extension, those of Chinese descent.

This study was not designed to assess the impact of retinoids on acne-associated postinflammatory hyperpigmentation. Generally, Chinese people have lighter skin pigmentation than other Asian populations, and so are at relatively lower risk for this problem. Nevertheless, it is worth bearing in mind when treating Asians with acne and warrants attention in a future retinoid trial.

References

- 1 Taylor SC. Cosmetic problems in skin of color. *Skin Pharmacol Appl Skin Physiol* 1999; **12**: 139–143.
- 2 Kenney JA. Dermatoses common in blacks. *Postgrad Med* 1977; **81**(6): 122–127.
- 3 Chua-Ty G, Goh CL, Koh SL. Patterns of skin diseases at the national skin centre (Singapore) from 1989 to 1990 *Int J Dermatol* 1992; **31**(8): 555–559.
- 4 McDonald RR, Georgouras KE. Skin disorders in Indo-Chinese immigrants. *Med J Aust* 1992; **156**(12): 847–853.
- 5 Fleischer AB Jr, Feldman SR, Bradham DD. Office-based physician services provided by dermatologists in the United States in 1990. *J Invest Dermatol* 1994; **102**(1): 93–97.
- 6 Kim JW, Lee JO. Skin resurfacing with laser in Asians. *Aesthetic Plast Surg* 1997; **21**(2): 115–117.
- 7 Ho C, Nguyen Q, Lowe NJ, Griffin ME, Lask G. Laser resurfacing in pigmented skin. *Dermatol Surg* 1995; **21**(12): 1035–1037.
- 8 Wang CM, Huang CL, Hu CT, Chan HL. The effect of glycolic acid on treatment of acne in Asian skin. *Dermatol Surg* 1997; **23**(1): 23–29.
- 9 Goswami BC, Baishya B, Barua AB, et al. Topical retinoyl beta-glucuronide is an effective treatment of mild to moderate acne vulgaris in Asian-Indian patients. *Skin Pharmacol Appl Skin Physiol* 1999; **12**(4): 167–173.
- 10 Ding LN. 50 cases of acne treated by puncturing acupoint dashui in combination with cupping. *J Tradit Chin Med* 1985; **5**(2): 128.
- 11 Pathak MA, Fitzpatrick TB, Kraus EW. Usefulness of retinoic acid in the treatment of melasma. *J Am Acad Dermatol* 1986; **15**(4) (2): 894–899.
- 12 Griffiths CE, Goldfarb MT, Finkel LJ, et al. Topical tretinoin (retinoic acid) treatment of hyperpigmented lesions associated with photoaging in Chinese and Japanese patients: a vehicle-controlled trial. *J Am Acad Dermatol* 1994; **30**(1): 76–84.
- 13 Kang WH, Chun SC, Lee S. Intermittent therapy for melasma in Asian patients with combined topical agents (retinoic acid, hydroquinone and hydrocortisone): clinical and histological studies. *J Dermatol* 1998; **25**(9): 587–596.
- 14 Graupe K, Verallo-Rowell VM, Verallo V, Zaumseil RP Combined use of 20% azelaic acid cream and 0.05% tretinoin cream in topical treatment of melasma. *J Dermatol Treatment* 1996; **7**: 235–239.
- 15 Sivayathorn A, Verallo-Rowell V, Graupe K. 20% azelaic acid cream in the topical treatment of melasma: a double-blind comparison with 2% hydroquinone. *Eur J Dermatol* 1995; **5**: 680–684.
- 16 Halder RM. The role of retinoids in the management of cutaneous conditions in blacks. *J Am Acad Dermatol* 1998; **39**: S98–S103.