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**Original Research Article**

# Effectiveness and safety of a combination of sun protection and depigmentation agent in the treatment of epidermal hyperpigmentation

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## ABSTRACT

**Background:** Medication adherence is recognized as a worldwide public health problem. As a multi-modality approach with sun protection and depigmentation is quintessential in patients with epidermal hyperpigmentation, a combination of day and night cream may be prudent for long-term improvement and compliance. Aim of the current investigation was to assess treatment outcomes and medication compliance in patients with epidermal hyperpigmentation using day and night cream in a combi-kit packaging (Melaglow day and night™ combi-kit).
**Methods:** Sixty patients (18-45 years) with epidermal pigmentation were enrolled in this 12-week study. Treatment effectiveness was determined by melanin index/erythema measure (dermacatch), extent, depth and density of pigmentation (fotofinder), and clinical/dermoscopic aspects (grade-1: <25%; grade-2: 25%-50%; grade-3: 50%-75%; grade-4: >75% reduction in the amount of epidermal pigment), safety, satisfaction, and compliance were assessed.
**Results:** Out of 60 patients, 52 completed the study. The overall percentage of melanin and erythema improvement was 22.51% and 13.85%, respectively. Based on fotofinder images, 36.54% had grade-2, 34.62% had grade-3, 15.38% had grade-1, and 13.46% patients had grade-4 improvement. Based on the photographic images, 40.38% had grade-2, 32.69% had grade-3, 17.31% had a grade-1, and 9.62% had grade-4 improvement in skin color. All patients agreed that combi-kit helped in remembering and adhering to treatment. Most patients were satisfied with the treatment (84.62%), with compliance rate of 97.72%. No adverse events were reported.
**Conclusions:** Combi-kit containing day and night cream (Melaglow day and night™ combi-kit) was safe and effective in the treatment of epidermal pigmentation, ensuing treatment compliance, and patient satisfaction.

**Keywords:** Dermacatch, Epidermal pigmentation, Erythema, Fotofinder, Melanin

## INTRODUCTION

Skin pigmentation represents one of the most remarkably diverse phenotypes in humans, with symptoms manifesting in a multitude of ways. It is one of the major dermatological issues with a high prevalence reported in the Indian population.[1] While characteristic pigmentation in these patients with colored skin offers numerous benefits such as sun protection and slow signs of aging, on the other hand, it increases the susceptibility to hyperpigmentation.[2] These pigmentary anomalies are often perceived as aesthetically disparaging, resulting in significant emotional and psychosocial impairment for the patients. In general, these conditions are difficult to treat, hence the need of cosmeceuticals.

A few of the foremost prominent and effective medications for hyperpigmentation are melanogenesis inhibitors that target tyrosinase, an enzyme pivotal in the synthesis of melanin. However, despite the availability of multiple treatment options for the condition, hyperpigmentation continues to present the

dermatologists with clinical management challenges. This could be attributed to the safety concerns with long-term exposure of these agents, and overall efficacy.[3]

These concerns of the currently available topical agents have prompted research to develop alternative skin lightening agents.[4] Since solar exposures have been involved in several short and long term harmful effects on the skin including the development of pigmentary disorders, strategies for maintaining even skin tone and managing skin hyperpigmentation include exogenous protection approaches such as photo protection, along with the depigmentation. This propensity towards combinatorial therapies could be also attributed to the refractory nature and complex etiology of the disease. Such combinatory therapies of sun protecting, and depigmenting agents may include molecules to stimulate cellular turnover and reduce skin inflammation, which has been shown to be effective in improving the disease, as well as reducing melanin production.[5,6]

Data suggests that the active compounds from plants such as arbutin, aloesin, gentisic acid, flavonoids, hesperidin, licorice, niacinamide, yeast derivatives, and polyphenols are potent inhibitors of melanin formation and may not be associated with cytotoxicity or mutagenicity of melanocytes.[3, 7] Hence the objective of this study was to assess the effectiveness, safety, and patient satisfaction with a day (niacinamide, alpha arbutin, kojic acid dipalmiate, licorice extract-40%, galanga extract, scorbyl glucoiside, vitamin E, octylmethoxycinnamate, galsorb avobenzone, octylmethoxycinnamate glasorb avo-benzone, glasorb octocrylene, uvinul A plus granular, parsol Tx, tinosorb) and night cream (niacinamaide, kojic acid, glycolic acid, arbutin, kokum butter, jojoba oil, olive oil, soy isoflavones, pterowhite, licorice extract-40%, vitamin E) in a combi-kit (Melaglow day and night™, Abbott healthcare, Mumbai, India; study medication) in patients with epidermal hyper-pigmentation.

Compliance is characterized as the degree to which the patient's conduct conforms to the physician's recommendations. Poor medication compliance may result in worsening disease severity and increased medical costs. Barriers to medication compliance are numerous, which also includes the prescription of complex medication regimens and convenience factors.[8] Hence in this study, an attempt was also made to understand the role of compliance packaging (sun protecting and depigmenting agents in a combi-kit with single packaging) in patient compliance.

## METHODS

### *Study design and patient population*

Current open label, observational, non-comparative, investigator-initiated study, with an observation period of 12 weeks, was conducted between December 2018 to May 2019 at Cutis academy of cutaneous sciences, Bangalore. Adults (between 18-45 years; inclusive) with epidermal pigmentation, agreeable to follow all the study procedures including abstinence from usage of any over-the-counter product related to face applications, and willing to sign the informed consent form and provide consent for being photographed, were enrolled in this study. Patients using other pigment reduction creams (except sunscreen and moisturizer); with other dermatological disorder of the face that may interfere with the study evaluation (acne, dermatosis papulosa nigra (DPN), melasma, seborrheic melanosis); with known hypersensitivity to any of the study drugs/constituents; expected to be exposed to the triggering factors (excessive sun exposure, UVB photo therapy etc); who have received facial procedures like dermabrasion, chemical peels or laser procedures within the last 1 month; or who were deemed unfit for participation by the investigator were excluded from the study. Pregnant or lactating women were also not included in this study. The study was conducted in accordance with the principles of declaration of Helsinki, international conference on harmonization good clinical practice (ICH-GCP) guidelines, and Indian regulatory guidelines (Indian council of medical research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.

The assessments were done at the following visits: visit 1 (baseline/day 0), visit 2, (sixth week) and visit 3 (twelth week). At baseline, all the participants were advised to use study medication on the face, once daily; day cream in the morning, 30 minutes before going out in the sun and night cream, 60-120 minutes before going to the bed at night. Each patient was given instructions on the quantity of application of cream as per the FTU (finger tip unit)[1]. Further, the patients were instructed to use a sunscreen (SPF-30) thrice daily and face wash, twice daily, for 12 weeks. They were also instructed to use a moisturizer in the day.

### *Study assessments*

The effectiveness in terms of reduction in epidermal hyperpigmentation was assessed by dermacatch, dermoscope using fotofinder and clinical photographs. The melanin and erythema index were measured at baseline, week 6 and 12 using dermacatch (dermacatch™, colorix, Neuchatel, Switzerland). The pigmentation was assessed using fotofinder (fotofinder™ systems, GmbH, Deutschland). Clinical photographs were taken at each visit. Grading (for fotofinder and clinical photographs) was done as following: grade-1: <25% reduction; grade-2: 25-50% reduction; grade-3: 51-75% reduction; grade-4: >76 % reduction. At end of week 12, patient satisfaction was measured as excellent, very good, good and not satisfied. Patient compliance was assessed based on completed patient diary during study visits. Safety was also assessed at each visit.

***Statistical analysis***

Data was summarized descriptively. Dermacatch values were analysed using repeated measures of ANOVA, with $p<0.05$ being considered as statistically significant. Clinical and fotofinder photographs were assessed subjectively and a grade was given based on percentage improvement.

## RESULTS

A total of 52 out of 60 patients with epidermal hyperpigmentation completed the study. All were women. Eight patients were lost to follow-up. The mean age of the patients was 28.36 years.

***Melanin and erythema measure: dermacatch***

There was a significant reduction in melanin and erythema values at week 12 compared to baseline for all patients ($p<0.05$) (Table 1). The overall percentage of melanin improvement was 22.51% and erythema improvement was 13.85% ($p<0.05$). The percentage of dermacatch improvement is depicted in (Figure 3-4).

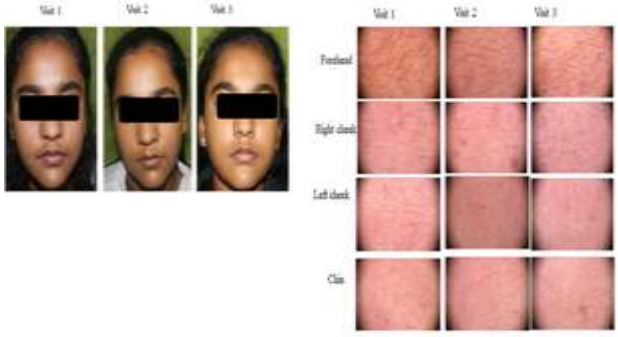

**Figure 1: Clinical photographs and foto finder images of patient one.**

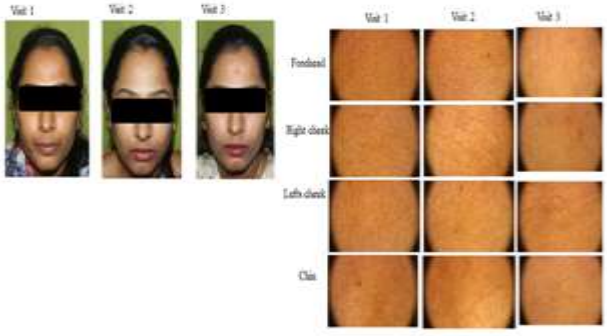

**Figure 2: Clinical photographs and fotofinder images of patient two.**

***Fotofinder pigmentation***

Based on fotofinder images, a total of 36.54% (N=19) reported grade-2, 34.62% (N=18) reported grade-3, 15.38% (N=8) grade-1, and 13.46% (N=7) patients reported grade-4 improvement (Figure 5).

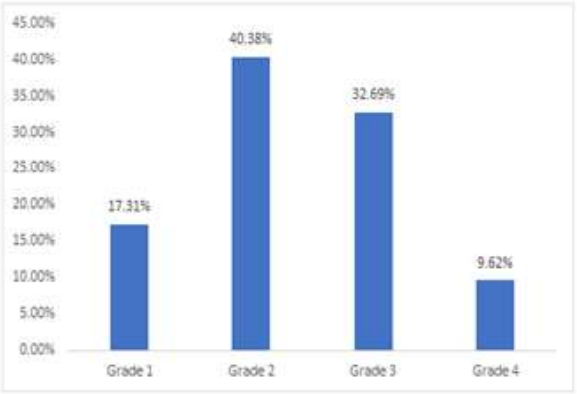


**Figure 3: Dermacatch values overall percentage of improvement observed through percentage melanin reduction.**

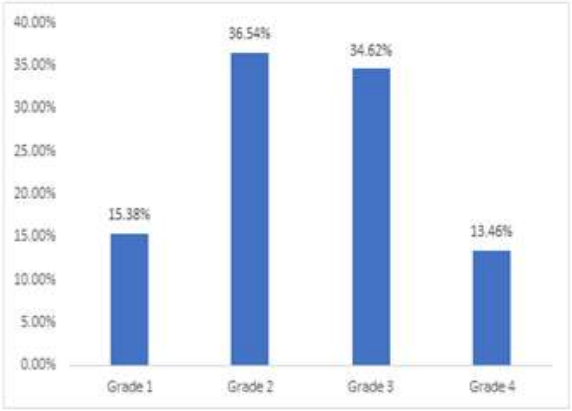


**Figure 4: Dermacatch values overall percentage of improvement observed through percentage erythema reduction.**

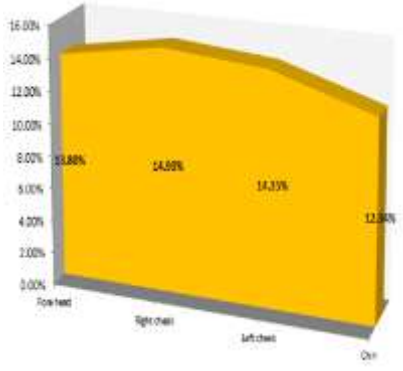

**Figure 5: Dermoscopic assessment using fotofinder.**

***Clinical photographic assessment***

Based on clinical photographs, 40.38% (N=21) patients had grade-2 improvement, 32.69% (N=17) patients had grade-3, 17.31% (N=9) patients had grade-1 and 9.62% (N=5) patients had grade-4 improvement (Figure 6).

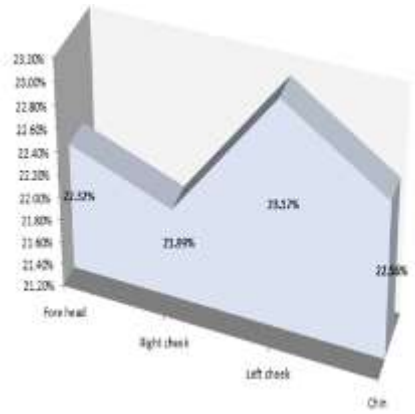

**Figure 6: Clinical photographic assessment.**

***Patient satisfaction***

Patient satisfaction with respect to the improvement in skin color was also assessed at the third visit. Based on the outcome, 23.08% patients rated the product as excellent, 42.31% patients rated the product as very good, 19.23% patients rated the product as good and 15.38% patients were not satisfied with the product.

***Compliance***

Compliance with day cream was reported by 97.73%; 97.71% reported compliance with night cream. Further, all patients agreed that comb-kit with single packaging is more convenient to use than two separately packaged creams, facilitated in remembering and adhering to treatment (Table 2). Safety wise no adverse events were reported.

## DISCUSSION

Hyperpigmentation is one of the major dermatological concerns for populations with pigmented skin phototypes, with a high prevalence within the Indian populace. With the recent safety concerns regarding the use of hydroquinone, various botanicals are being explored in commercial preparations due to the lack of any side-effects.[9]

**Table 1: Melanin and erythema measure at baseline, week 6 and week 12 post treatment.**

| Dermacatch values | Forehead | | Right face | | Left face | | Chin | |
|---|---|---|---|---|---|---|---|---|
| | Melanin | Erythema | Melanin | Erythema | Melanin | Erythema | Melanin | Erythema |
| **Visit 1** | 696.33 | 437.37 | 667.58 | 425.71 | 663.77 | 426.04 | 686.48 | 434.60 |
| **Visit 2** | 647.65 | 403.56 | 619.90 | 388.54 | 615.12 | 390.81 | 636.81 | 399.62 |
| **Visit 3** | 610.56 | 377.00 | 587.56 | 362.27 | 576.33 | 364.90 | 596.06 | 372.27 |

**Table 2: Treatment compliance with combi kit.**

| Questions | Completely agree (%) | Somewhat agree (%) | Neither agree nor disagree (%) | Somewhat disagree (%) | Completely disagree (%) |
|---|---|---|---|---|---|
| **Combi kit with single packaging is more convenient to use than 2 separately packaged creams** | 57.69 | 42.31 | 0.00 | 0.00 | 0.00 |
| **Combi kit has helped me remembering the treatment regimen** | 36.54 | 63.46 | 0.00 | 0.00 | 0.00 |
| **Combi kit packaging helps adhering to regimen in treatments of longer duration** | 48.08 | 51.92 | 0.00 | 0.00 | 0.00 |

Most of the hyperpigmentation disorders among Indians can be attributed to or exacerbated by solar exposure. Since solar exposures may result in numerous adverse effects on the skin, a combinatorial, multi-modality treatment approach with photoprotection and depigmentation agent would be imperative in Indian patients.

Photoprotective agents play a critical role in reducing and minimizing the incidence of human skin disorders induced by ultraviolet (UV) rays. Studies indicate that UVA radiation may result in nuclear and mitochondrial DNA damage, gene mutations and skin cancer, dysregulation of enzymatic chain reactions, immune suppression, lipid peroxidation (membrane damage), and photoallergic and phototoxic effects.[10,11] UVB radiation, on the other hand, may result in pigmentation, sunburn, immune-suppression, and photo carcinogenesis. Photoprotective agents such as sunscreens prevent and minimize the negative effects of UV light based on its ability to absorb, reflect, and scatter solar rays.[12,13] A depigmenting agent, on the other hand, suppresses melanocyte metabolic processes of the skin; inhibits the enzymatic oxidation of tyrosine to DOPA (3, 4-dihydroxyphenylalanine), stimulate cellular turnover, and provide anti-inflammatory and antioxidant benefits.

Many studies have shown the effectiveness of botanical combinations in treating hyperpigmentation.[9, 14] Arbutin is a naturally occurring glucopyranoside that causes decreased tyrosinase activity without affecting messenger ribonucleic acid expression, while also inhibiting melanosome maturation at non-cytotoxic concentrations.[15,16] Studies show that arbutin is just as effective as hydroquinone, but less toxic.[17] As per the scientific committee on consumer safety report, the use of α-arbutin in cosmetic products in a concentration up to 2% in face creams and up to 0.5% in body lotions and of beta arbutin (in concentration greater than 7% in facial creams) is considered as safe.[18] Although controlled clinical trials are lacking, in vitro experiments have demonstrated its safety and effectiveness as an ingredient for skin-lightening.[19] Kojic acid, a tyrosinase inhibitor, is indicated for hyperpigmentation as the enzyme that catalyzes the development of melanin and other pigments. Data indicate that kojic acid is effective in treating hyperpigmentation when used in combination with other agents.[20,21] Results are comparable to hydroquinone cream, which is the standard treatment for hyperpigmentation. Kojic acid is typically found in concentrations of 1-4% and is tolerated well.[22] Licorice extract is one of the most widely used agents in cosmeceuticals for skin brightening owing to its benign profile. Licorice extract obtained from the root of glycyrrhia glabra linnera has been shown to improve hyperpigmentation by inhibiting the melanin biosynthesis and cyclooxygenase activity, thereby decreasing free radical production.[23] Vitamin C is a water-soluble compound, with ascorbic acid being the most common derivative, is used commonly in cosmeceuticals. They act by interrupting melanogenesis via interactions with copper ions. As ascorbic acid or vitamin C is readily degraded by oxidation, especially in aqueous media, more stable derivatives such as ascorbyl palmitate and magnesium-L-ascorbyl-2-phosphate are commonly used. Although less effective than hydroquinone, ascorbic acid does not have the harmful effects of the latter.[24] Furthermore, L-ascorbic acid has strong clinical evidence supporting efficacy in fighting UV-induced generation of free radicals and improving discoloration and pigmentation.[25,26] Vitamin E is a lipophilic antioxidant whose biologically active form is a-tocopherol. Depigmentation may be the resultant of the interaction with lipid peroxidation of melanocyte membranes, increased intracellular glutathione content and tyrosinase inhibition.[27] Hayakawa et al in their multi-clinical double-blind study showed a significant improvement of melasma and pigmented contact dermatitis lesions using topical vitamins E and C, with the combination showing better results compared to the single-vitamin treatment groups.[28] Considering the minimal side-effects such as allergic or irritant reactions with topical vitamin E, it is commonly preferred in cosmeceuticals preparations. Soy is considered to be the most commonly used skin-lightening agent in cosmetic moisturizers. Soya bean trypsin inhibitor inhibits the protease-activated receptor-2 pathway required to control melanosomal phagocytosis of keratinocytes and melanosomal transition. Soymilk's de-pigmenting effect is reversible, and 7-month routine topical treatment has resulted in no adverse effect.[29] Niacinamide reduces pigmentation by reversibly preventing the transfer of melanosomes from melanocytes to the keratinocytes, inhibiting melanogenesis. Niacinamide is a vitamin B3 derivative that is believed to reverse UV-induced photoaging. Niacinamide was found to decrease hyperpigmentation compared with placebo alone after 4 weeks of use in a study to assess the melanogenesis in vitro and facial hyperpigmentation and skin color in vivo in Japanese women.[30] There is strong clinical evidence supporting glycolic acid to treat acne, fine lines, roughness, and pigmentation. Over-the-counter products generally contain up to 10% glycolic acid, and this concentration has been demonstrated to be effective.[31,32] Plant extracts from grape seed, orchids, aloe vera, marine algae, flavonoids, green tea, licorice, soy, umbelliferone, and boswellia are also useful.[9]

Though studies have been conducted to assess the role of many of the afore-mentioned depigmenting products, these have evaluated the effectiveness of individual compounds while combinations are available for use. Hence the objective of the present study was to assess the effectiveness, safety, and satisfaction with the study medication containing a combination of niacinamide 4%, alpha arbutin 2%, kojic acid dipalmiate 2%, licorice 40% ca-0.1%, galanga extract 98%, ascorbyl glucoiside 1%, vitamin eacetate 0.25%, octylmethoxycinnamate 7%, galsorb avobenzone 3%, octylmethoxycinnamate 7%, glassorb avobenzone 3%, glasorb octocrylene 3%, uvinul a plus granular 1%, parsol Tx 2%, tinosorb M 2% in the day cream and niacinamaide 4%, cetyl alcohol 3%, kojic acid 2%, glycolic acid 2%, arbutin, kokum butter 1%, jojoba oil 1%, olive oil 1%, soy isoflavones 0.5%, ptero white 0.12%, licorice extract 40%, CA 0.12%, vitamin E 0.1% in the night cream in the treatment of epidermal pigmentation.

A total of 82 potential patients were screened as per the inclusion and exclusion criteria. Only after obtaining written informed consent and photo consent from the patient, 60 patients were enrolled in the study. After a detailed history and clinical examination, the patients were handed over the topical application kit containing the study medication (in a combo kit), sunscreen, face wash, and moisturizer. The patients were followed up for a duration of 12 weeks with a total of three visits.

In these patients, the reduction in melanin (22.51%) and erythema values (13.85%) assessed using the dermacatch was statistically significant ($p< 0.05$). That is, the change in percentage of melanin and erythema before and after applying the above mentioned treatment protocol for epidermal hyperpigmentation was significant. After applying the study medication, the percentage of pigmentation was reduced in the study area.

Based on the blinded assessment by two independent dermatologists of the clinical photographs and fotofinder images, the patients were graded as grade-1: <25% reduction; grade-2: 25-50% reduction; grade-3: 51-75% reduction; grade-4: >76% reduction. Based on dermoscopic assessment using fotofinder 13.46% had grade-4 improvement, 34.62% had a grade-3 improvement, 36.54% had grade-2 improvement and 15.38% patients had grade-1 improvement with respect to reduction in pigmentation. Based on clinical photographic images, 9.26% had >grade-4 improvement, 40.38% had grade-3 improvement, 32.69% patients had grade-2 improvement and 17.31% patients had less than grade-1 improvement in the epidermal hyperpigmentation. Furthermore, the majority of the patients were satisfied with the treatment (84.62%).

Patient non-adherence to prescribed medication limits the effectiveness of any treatment. As the treatment for hyperpigmentation may require a persistent course, compliance would be a limiting factor in the management. However, evidence indicates that that reminder in any variation and reminder packaging has a positive impact on medication adherence and often also on clinical results.[8] Hence in this study, an attempt was also done to understand the role of compliance packaging (a comprehensive pack of sun protecting and depigmenting agents in a combi-kit) in patient compliance. All patients agreed that comb-kit helped in remembering and adhering to treatment and rated it 'convenient', with a compliance rate of 97.72%. All the patients agreed that comb-kit with single packaging is more convenient to use than two separately packaged creams, in turn facilitating in remembering and adhering to treatment.

### *Limitations*

Limitations of current study are; the lack of a comparator or control group and a short follow-up period.

## CONCLUSION

Current study suggests that the combi-kit containing a combination of Melaglow day (niacinamide 4%, alpha arbutin 2%, kojic acid dipalmiate 2%, licorice 40% ca - 0.1%, galanga extract 98%, ascorbyl glucoiside 1%, vitamin E acetate 0.25%, octylmethoxycinnamate 7%, galsorb avobenzone 3%, octylmethoxycinnamate 7%, glassorb avobenzone 3%, glasorb octocrylene 3%, uvinul a plus granular 1%, parsol Tx 2%, tinosorb M 2%) and night cream (niacinamaide 4%, cetyl alcohol 3%, kojic acid 2%, glycolic acid 2%, arbutin, kokum butter 1%, jojoba oil 1%, olive oil 1%, soy isoflavones 0.5%, ptero-white 0.12%, licorice extract 40% CA 0.12%, vitamin E 0.1%) is safe and efficacious in the treatment of epidermal hyperpigmentation, ensuing treatment compliance and patient satisfaction. This combination can be a preferred alternative to hydroquinone-based and triple combination cream containing hydroquinone, steroid, and tretinoin; given the efficacy and low incidence of adverse effects. Providing medications in a combi-kit package can improve treatment regimen adherence and treatment outcomes in these patients.

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