

PROSPECTIVE, RANDOMIZED PLACEBO-CONTROLLED DOUBLE-BLIND STUDY ON THE EFFICACY AND SAFETY OF A SERIES OF HERBAL SKIN-CARE PRODUCTS FOR STABLE CHRONIC PLAQUE PSORIASIS

Harald Maier, Peter Donath, Michael Tirant, Dragana Relic, Shahla Farokhnia, Herbert Hönigsmann, Adrian Tanew

Division of Special and Environmental Dermatology, Department of Dermatology, University of Vienna Medical School

INTRODUCTION

At present, topical cortisone is still the mainstay of therapy for stable chronic plaque psoriasis as long as the affected skin area is not too extensive. However, there is growing concern among patients about possible side effects of steroid therapy. A recent study showed that overall, 42 % patients were unsatisfied with the current management of their skin disease. This is the reason why, like in other medical specialities¹ patients with psoriasis more and more, turn to complementary treatment options such as magnetic field resonance therapy, traditional Chinese medicine (TCM) and herbal medicine.² It is the young, the well-educated, patients with higher income, women and patients with chronic disease who are most open-minded to complementary methods.² Actually, a flourishing market for complementary health products has developed.³ Unfortunately, most providers refuse to have their products tested according to international scientific standards.^{4,5} Advertising is merely based on anecdotal reports and the single opinions of (mostly prominent) persons.³ At the very best, uncontrolled clinical observations are presented.

STUDY OBJECTIVE

We assessed the efficacy and safety of an Australian series of herbal skin-care products (Dr. Michaels[®] skin-care products for psoriasis) for the management of stable chronic plaque psoriasis. The producer claims that the skin disease improves significantly within a 6 to 8 weeks treatment course.

MATERIALS AND METHODS

We chose a prospective, randomized, placebo-controlled, double-blind design. After obtaining written consent, 34 (15 female/ 19 male) patients with mild to moderate stable chronic plaque psoriasis were randomly assigned to either *verum* or *control* group. Exclusion criteria were: severe psoriasis, arthropathic psoriasis, intertriginous psoriasis, palmoplantar psoriasis, use of any antipsoriatic treatment modality, any medication which may influence or interfere with the course of the disease. Both *verum* and *control* series consisted of a cleansing gel, an ointment and an oil blend (skin conditioner). The products were packed in neutral bottles. The products had to be used twice daily and in the same manner. All skin lesions except the scalp were treated. The cleansing gel was distributed generously on the lesions and washed off after three to five minutes with warm water. Afterwards the lesion was covered with the ointment. After the ointment had dried up the plaques were covered with a thin layer of oil. Except for a small amount of coal tar (0.8 %) in the cleansing gel only, the *verum* products contained only herbal oils and waxes plus the normal emulsifiers, stabilisers and preservatives.⁶ As *control* products we used compositions of well-known neutral ointments and a medicinal bathing oil. The study period was eight weeks. Assessment, using the Psoriasis Activity Severity Index (PASI) scores, was done before treatment, after 2, 4, 6 and 8 weeks by a blind observer (dermatologist). The values of scalp involvement were not included. For each patient, photographs of typical lesions were taken at the beginning, 4 weeks and 8 weeks follow-up. Patient improvement was determined by the percentage reduction of the PASI scores. Statistical analysis was carried out using the Mann-Whitney-U Test with SPSS for Windows.

⁷ Dermal toxicology and safety tests were also undertaken on 20 patients including children to evaluate any hypersensitivity that may result from the application of the product family.

RESULTS

The data presented here are the results of a group of 24 patients (14 *verum* / 10 *control*) with a mean age of 48.2 years who had completed the 8 weeks treatment course. Two patients (1 *verum* / 1 *control*) could only be followed for 6 weeks. The data of these patients were not included in the statistical analysis. Another six patients (2 *verum* / 4 *control*) dropped out. Another two *verum* patients had to be excluded because of non-compliance. For two of the drop-outs assigned to the *placebo* group it was too obvious that they had been given the control products and therefore refused further participation. The other two *control* patients stopped the treatment because of side effects.

Before therapy, the mean PASI score of the *verum* group was 6.8 ± 2.4 SD, and 5.5 ± 2.0 SD in the *control* group, respectively. After the 8 weeks treatment course, the mean PASI score in the *verum* group was 1.02 ± 1.01 SD, which is equivalent to a PASI score reduction of $89\% \pm 14.9\%$. The respective values in the control group at the 8 weeks follow-up were 4.1 ± 1.7 SD for the PASI and $22 \pm 28.7\%$ for the PASI score reduction. **Figure 1** shows the mean values of the PASI score for the different follow-up dates which are given in Table 1 in detail.

The difference of the PASI score reduction at 8 weeks follow-up between the two groups was statistically significant ($p < 0.001$). **Figure 2 a** shows the indicator plaque of a patient with complete remission after 6 weeks treatment with Dr. Michaels[®] skin-care products for psoriasis and **Figure 2 b** a patient with partial remission after 8 weeks treatment.

The *verum* patient who could be followed-up only for 6 weeks showed a PASI score reduction of 70%. The respective data of the *control* patient with the shorter follow-up period was 4.8%. Three patients in the *verum* and three patients in the *control* group reported mild side effects (*verum* group: 1 irritation, 2 folliculitis / *control* group: 3 irritation). In the dermal toxicology and safety test group, one (1) patient showed a minor irritation to the cleansing gel. The remainder of the test cases results fell well within the acceptable parameter range provided by EADV and EU.

DISCUSSION

This study shows that the herbal skin-care products tested improves mild to moderate stable chronic plaque psoriasis significantly. One strength of this study is the clear study design which is regarded as the gold standard of clinical tests. The left and right sides comparison was not undertaken to avoid any potential mistakes of mixing up the sides or the use of the more effective product only on both sides. In addition to the personal instructions given on how to use the products, a very simple structured leaflet was also handed out. The patients were informed not to give the blind observer (Assessor) any information on the products used. Furthermore, they did not apply the products on the days of the follow-ups in order to prevent the observer from identifying the *verum* products by their characteristic odour. The blind observer is a consultant of dermatology and is very experienced in clinical scoring. As is well known, the PASI is a standardized internationally accepted evaluation score which in the hands of an experienced clinician is a reliable assessment tool. Additionally, photographs were taken with standardized focussing. Images, however, lack the third dimension which represents the infiltration of a psoriatic plaque and contributes to the clinical picture of a lesion essentially.

It was so obvious in the study course that the *verum* products were superior to the *placebo* preparations. Except for coal tar which is present in only the cleansing gel, none of the listed herbal ingredients is a known antipsoriatic remedy. Therefore, an analysis for undeclared

drugs (cortisone, calcipotriol, macrolides) was undertaken⁸ although the producer (who is one of the authors, M.T.) gave a statement of innocuousness and provided the complete list of constituents and the respective material safety data sheets. Two samples of different batches of each product were analysed. None of the products contained any of the compounds mentioned above.

Some aspects of this study have to be addressed in detail. Dr. Michaels[®] skin-care products are a complex mixture of botanical ingredients. There is a lack of information on the active pharmacologic principle(s) which is (are) responsible for the effectiveness. Coal tar is the only (known) antipsoriatic ingredient. However, the surprising improvement is inconsistent with our clinical experience with standard compositions containing coal tar. It is speculated here that the products contain other antiproliferative and anti-inflammatory compound (s) which is (are) not known at present. Therefore, it was not possible to compose a “true” placebo (formulation of the verum minus active ingredient). The management of the patients of the placebo group was challenging. Several patients had been treated with different topical antipsoriatics and skin-care products previously. They could therefore compare the effect of the present treatment with previous responses. The follow-up visits at two weeks interval were close enough to give them the “love and tender care” and to encourage them to continue. Actually, only two “very experienced” patients with a long history of psoriasis and a lot of different treatment modalities dropped out. All compliant *placebo* patients showed an improvement of the condition which could be expected by the use of greasy skin-care products only.

To make sure that a herbal product does not contain intended or unintended adulterants and / or contaminants, is part of the quality control.^{4,5} Dr. Michaels[®] skin-care products are manufactured according to Good Manufacturing Practice (GMP) certified by the Therapeutic Goods Administration of the Australian Health and Family Services. In contrast to synthetic drugs, herbal remedies may show a considerable variation in the composition (e.g., genetic variability of the plants, variable growing conditions, differences in harvesting procedures and processing of extracts).^{4,5} Chromatographic analysis and marker compounds do not ensure consistency and stability.⁵ These methods can only define a range within which product quality is acceptable.

The third requirement is dermal toxicology and safety.^{4,5} Before to the start of the clinical trial, a dermal toxicology and tolerability test⁹ was done on a group of 20 healthy volunteers with good results. Among the population of the study presented one patient developed a mild irritative dermatitis. That patient stopped using the cleaning gel as the irritation was attributed to the tar in the cleansing gel. The improvement of the disease in that patient was in agreement with the general course of the verum group. We are aware that the excellent (short-term) tolerability of Dr. Michaels[®] skin-care products does not necessarily exclude long-term side effects.⁴ Coal tar and solar radiation may be a problem. However, serious side effects are unlikely due to the toxicologic profile of the constituents.⁶ In order to assess all the allergic potency, the products should undergo a field test.

CONCLUSIONS

The products tested already fulfill a lot of aspects addressed by the European Parliament in the proposal for a directive on traditional herbal medicinal products.¹⁰ As long as the products are composed of a mixture of various plant extracts a range of variation should be defined. The next step, however, should be the attempt to identify the active pharmacologic principle.

Our investigation demonstrates that complementary methods may play a role in dermatologic therapy as far as they undergo standardised clinical trials and fulfill the basic requirements such as product safety and quality assurance. Dr Michaels skin-care products can be used successfully in the treatment of stable chronic plaque psoriasis.

ACKNOWLEDGEMENT

We gratefully acknowledge Dr. Michals RICA GmbH, Traiskirchen, Austria, for providing the study products, Eva Hofbauer, Pharmacovigilance Unit, Federal Ministry of Health and Women, for initiating undeclared constituents testing and Andreas Mayrhofer PhD, Bundesinstitut für Arzneimittel (BfA), Vienna, for conducting the analysis for undeclared constituents.

REFERENCES

1. Straus S. E. Perspective: Herbal medicines-what´s in the bottle? *N Engl J Med* 2002; 347: 1997-8.
2. Ben Arye E, Ziv M, Frenkel M, Lavi I, Rosenman D. Complementary medicine and psoriasis: Linking the patient´s outlook with evidence-based medicine. *Dermatology* 2003; 207: 302-7.
3. Federspiel K & Herbst V. Die Andere Medizin. Nutzen und Risiken sanfter Heilmethoden. Stiftung Warentest-Berlin, Verein für Konsumenteninformation-Wien, eds. Stuttgart, Germany: Zenit-Presservertrieb, 1996.
4. De Smet P A G M. Drug therapy : Herbal remedies. *N Engl J Med* 2002 ; 347 : 2046-56.
5. Marcus D M & Grollman A P. Botanic medicines- the need for new regulations. *N Engl J Med* 2002; 347: 2073-7.
6. Kosmetika – Inhaltsstoffe - Funktionen. Industrieverband Körperpflege- und Waschmittel e.V. (IKW)-Frankfurt a Main, Fachverband der chemischen Industrie Österreichs (FCIO) Berufsgruppe Körperpflegemittel-Wien, eds. Garching, Germany: Heichlinger Druckerei GmbH, 1998.
7. SPSS Inc.- Chicago, Illinois, USA
8. Mayrhofer A, Wieser M, Wollein G. Entwicklung eines Screening-Systems für die Untersuchung corticoidverdächtiger Proben mittels HPLC-UV und HPLC-PB-MS. *Sci Pharm* 1996; 64: 225-44.
9. Frosch P J & Kligman A M. The soap chamber test: a new method for assessing the irritancy of soaps. *J Am Acad Dermatol* 1, 35, 1979.
10. Proposal for a directive of the European parliament and the council amending the directive 2001/83/EC as regards traditional herbal medicinal products. *Official Journal of the European Communities*. C126 E/May 28, 2002; pp 263-7.