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Mahonia aquifolium in patients with Psoriasis vulgaris – an intraindividual study

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Summary

Psoriasis vulgaris is a skin disease with a multi-factorial genesis where no causal treatment is known. Based on our own pilot studies, we set up a randomized, placebo-controlled clinical trial to evaluate the efficacy and safety of *Mahonia aquifolium* bark extract in psoriasis patients. From autumn 1990 to spring 1992 we treated 82 patients of all severity gradings, recruited by 22 family physicians. Patients were told to apply two types of ointment (verum/placebo) one to the left side of their body the other to the right. After an average treatment period of four weeks, patients as well as physicians assessed the therapy's success on a three-level ordinal rating scale. Statistically significant differences (α = 5%) could be found for patients' but not for physicians' assessments. Additional analyses show that treatment differences are not significantly masked by parallel antipsoriatic therapies. Adverse drug reactions, such as itching and burning sensations and 'allergic reactions,' occured in four patients. Therefore, we regard *Mahonia aquifolium* bark extract as a potent and safe therapy of moderately severe cases of psoriasis vulgaris.

Key words: *Mahonia aquifolium*, Psoriasis vulgaris, clinical trial, efficacy, phytotherapy.

Introduction

Psoriasis vulgaris is a hereditary disease with a multi-factorial genesis, appearing in 1–3% of the European population (Lampi, 1983). Typical changes in the skin include hyperkeratosis, parakeratosis and akantosis. They are attributed to an increased mitosis rate in the basal regions of the epidermis and disorders of the maturing and differentiation of keratinocytes. These farreaching and infectious changes of dermis and epidermis cause the typical desquamation of the stratum corneum. Mechanic-, infectious- and psychosomatic factors are adequately researched as triggers of Psoriasis vulgaris. Nonetheless, the ethiology and pathogenesis of psoriasis are for the most part unexplored (Jung, 1995).

To this day, there is only a symptomatic treatment with the aim of alleviating or, if possible, eliminating the skin manifestation. A secondary aim is to keep the patient relapse-free as long as possible. Numerous therapeutic substances exist, some being very fast-acting, but their applications often strain the patient, demand a high compliance and in some cases can be classified as risky (Braun-Falco 1987). These include keratolysis with salicylic acid- or urea ointments, especially anti-psoriatric local therapy using dithranol, calcipotriol, tar ointments or steroids and systemic treatments with retinoids and steroids. The same is true for ultraviolet-photo-therapy (SOP) and the photo-chemo-therapy after the application of 8-Methoxypsoralen (PUVA). According to present knowledge, none of the therapeutic methods named above offer a safe and practicable long-term therapy.

A topical long-term treatment is for the most part unavoidable, since most psoriasis patients have to deal with their disease all life long. Therefore, it seems reasonable to look for new treatment strategies that would reduce the amount of risky medication.

Mahonia aquifolium (Fam. nat.: Berberidaceae) is an ornamental shrub found in Pacific Coast of North America. American folk medicine mentions Mahonia bark extract to treat various dermatological diseases. Although *Mahonia*

does not play any part in phytotherapy, in homeopathy it does; presumably, it is because of this that the American as well as the German HAB have a prescription producing Mahonia bark extract.

On the other hand it is surprising to see that the phytotherapeutical use of *Mahonia* tincture is suggested in literature (Bommer 1943, Stiegele 1950). The majority of a great number of screened case reports had long observation periods. They resulted in a uniform positive impression as well as our own unpublished preliminary studies did.

The therapeutic-empirical knowledge was supported by the fact that the active substances in the extract – Berberin, Berbamin and Oxyacanthin – are members of the relatively large and heterogeneous chemical group of (vegeto-) alkaloids that have revealed an antiphlogistic effect in experimental examinations (Akhter et al. 1977, Kostalova et al. 1986).

We felt this background was sufficient to conduct a double blind, placebo-controlled clinical trial with an intraindividual comparison of body sides to assess the efficacy of *Mahonia* bark extract when applied to treat psoriasis.

Subjects and Methods

Subjects

From autumn 1990 to spring 1992, 82 patients with clinically diagnosed Psoriasis vulgaris of all degrees of severity took part in this study. The recruitment and treatment involved 22 family physicians and dermatologists throughout Germany. Due to their participation in earlier studies, all the physicians were known to the study coordinators, so their reliability and compliance was guaranteed. The inclusion and exclusion criteria (Table 1) were kept relatively unspecific in order to avoid the well-known logistical problems that accompany a multi-center trial with family physicians. Moreover, these precautions were taken to obtain unselected and representative patients.

Table 1. Inclusion criteria.

Criterion
clinically verified Psoriasis vulgaris
age > 16 years
symmetrical manifestation in both body sides (i.e. test and contralateral control area)
no actual application of systemic remedies potentially influencing the course of disease (e.g. corticoids)
expected compliance based on the physicians judgement
no application of local dermatological therapies
no inclusion in any other clinical trial
informed consent

Medication

Verum consisted of an ointment with a 10% content of *Mahonia* bark extract. The ointment base was used as a placebo. It contained anhydrous lanolin, paraffine, wool wax alcohols, cetylstearyl alcohol and white vaseline. Standardised *Mahonia* bark extract and ointment base were prepared according to the German Homeopathic Pharmacopoeia (HAB1). The addition of the bark extract to the ointment caused a slight shift in colour, but this was only visible if the two ointments were directly compared to each other. They were then put into special tubes, all identical and each containing 100 g of the ointments.

Patients recieved one of each of the tubes. They were told to apply one type to the right side of their body, the other to the left. Body sides had been randomly allocated to verum or placebo. Apart from the study name and the manufacturer, only the words specifying which side the ointment was to be applied were visible. Since the tubes were delivered in unopened packages, the physician was unable to tell which ointment was assigned to which body side.

The patients were asked to massage the ointments into their afflicted areas two or three times a day and to wear bandages smeared with the ointments at night. The total therapy length was individually assigned by the treating physician. The trial coordinators suggested a length of eight weeks.

Measurements

At study entry the physicians documented relevant anamnestic data such as age of manifestation and severity of affection. After the therapy had ended the patients were asked to return and have the treatment's success assessed for each body side, using a three-step scale:

1. Symptoms unchanged
2. Symptoms improved
3. Symptoms disappeared completely

The efficacy was assessed independently by the patient and the treating physician. Both assessments were regarded as main outcome parameters. Neither clinical improvement nor the severity of the disease were further operationalised. The treating physicians checked whether the prescribed ointments had been used on a regular basis. This was done by having the patients bring both tubes with them to the final appointment. Moreover, additional antipsoriatic treatments (self-medication, use of ointments prescribed before the study, artificial insolation, etc.) were documented according to precise and standardised questioning. Adverse events or adverse drug effects were documented freely.

Statistics

All analyses were conducted according to the intention-to-treat principle. The hypothesis that verum- and placebo therapy differed in their efficacy was analysed via an exact

Table 2. Patients' characteristics

Parameter	
sex (n = 82)	
male	43 (52.4%)
female	39 (47.6%)
severity (n = 74)	
light	7 (9.5%)
medium	27 (36.5%)
severe	40 (54.1%)
age (n = 80)	
mean ± std. dev.	48±17 years
median	48 years
quartiles	35–59 years
range	16–85 years
duration of disease (n = 67)	
mean ± std. dev.	18±14 years
median	12 years
quartiles	7–27 years
range	0–57 years
age of manifestation (n = 65)	
mean ± std. dev.	29±19 years
median	23 years
quartiles	14–40 years
range	0–79 years

Table 3. Agreement of physician's and patient's assessment (verum and placebo combined).

Physician (n = 80)	Patient (n = 80)		
	unchanged	improved	disappeared
unchanged	106	7	0
improved	4	39	0
disappeared	0	4	0

Table 4. Assessment of efficacy by patient and physician.

			verum		
			unchanged	improved	disappeared
patient (n = 80)	placebo	unchanged	46	15	0
		improved	3	16	0
		disappeared	0	0	0
physician (n = 80)	placebo	unchanged	48	14	0
		improved	3	12	0
		disappeared	0	2	1

Table 5. Odds-Ratios for a better result for verum.

	Odds-Ratio	p-value	95% confidence interval
patient's assessment			
medium vs. light grading	3.95	0.2107	0.51–∞
severe vs. light grading	1.41	0.7822	0.17–∞
parallel antipsoriatic medication	1.00	0.3329	0.99–1.01
physician's assessment			
medium vs. light grading	2.77	0.6820	0.26–146
severe vs. light grading	1.01	1.0000	0.09–55.8
parallel antipsoriatic medication	1.00	0.3409	0.99-1.01

Marginal Homogeneity Test in 3x3 contingency tables (Kuritz et al. 1988). A Bonferoni-Holm-Procedure (Holm, 1979), was used to maintain the multiple test niveau (α = 5%).

In a secondary analysis we attempted to answer the following questions:

- Are basic variables discernable that modify the efficacy of the *Mahonia* treatment?
- Do protocol violations change the results?

Multiple logistic regression models were fitted to the data. Here the response variable was binary: Either the verum- was superior to the placebo therapy or not. Sex, age, age of manifestation, severity of the symptoms and the application of accompanying antipsoriatric treatments were counted as potential influential factors. The hypothesis whether an influential factor modified the difference in treatment efficacy was proven by Wald's two-sided asymptotic test (Breslow and Day, 1980).

Results

Basic Data

Only one of the 82 randomised patients violated the in- and exclusion criteria choosing to apply corticoids in addition to *Mahonia* during the entire observation period.

The distribution of the most important sampled basic parameters is given in Table 2. It shows the length of infection as well as the patients' age when psoriasis was first diagnosed. It also documents the great variation in the samples included (very old patients with a long history of psoriasis as well as young adults were included in the trial). Generally the disease manifested itself in patients when they were children (Type 1), but in some cases not until they were relatively old (Type 2).

Compliance and Protocol Violations

All 82 patients were treated on both body sides. During the follow-up-phase, 13 patients violated the protocol by occasionally having parallel antipsoriatric treatment. In these cases one patient used a dermatologicum containing corticoids, four used dermatotherapeuthic medication without corticoids and eight patients used assorted other types of medication (for example, homeopathic therapies). As a result, 17% of the patients violated the protocol. Information was missing whether another 12 patients had violated any protocol guidelines.

All except two patients came to the final check-up. The median treatment period prior to this examination was four weeks (interquartile range 21–49, range: 13–185).

Four days after the end of the individual therapy 50% of the case record forms had been filled out and returned. The time it took to return these forms seldomly exceeded the limit of one month (25%), indicating the physicians' high degree of compliance.

Efficacy

The assessment of both types of ointments by physicians and patients usually corresponded well. There were only small deviations concerning placebo and verum (Table 3).

As visible in Table 4, more than half the patients (61.3%, CI: 49.7%–71.9%) and physicians (63.8%, CI: 52.2%–74.2%) assessed the verum ointment as useless. Nonetheless, the difference when compared to the placebo is obvious and significantly proven in the patients' assessment ($p = 0.008$, physicians' assessment: $p = 0.064$).

A dichotomisation of the outcome variable in the categories 'unchanged' 'improved or disappeared' resulted in statistically confirmable differences. This was true for the efficacy assessment by the patients and the physicians (patients' assessment: $p = 0.008$, physicians' assessment: $p = 0.013$).

For none of the influential factors taken into account the logistic regression could prove a significant modification of the therapy efficacy. Results concerning the severity of psoriasis or additional medication are listed in Table 5. Note, that these were not the estimations from the univariate models, but those after adjustment for the effects of all possible covariates. Additional anti-psoriatric treatment did not show any relevant effect, so that no interaction can be proven with the *Mahonia* treatment.

Adverse Events

It was documented that one patient had an 'allergic reaction' to the verum and a second reported a strong itching sensation. Furthermore, two patients complained about a 'burning' sensation and an irritation of the skin after applicating the verum. Adverse irritations of the skin when using the verum were reported in several cases. No direct temporal connection between the application of the ointment and the appearance of the irritations could be made. In any case, these must be assumed as side effects of the medication.

Discussion

The trial design of the intraindividual comparison chosen by the authors is standard in dermatology. The necessary symmetrical affection of both body sides is especially fitting for the formulation of the questions in this paper, for psoriasis is generally spread disseminated over the integument. The design demands a local therapy, where the application- and target organ are identical. The question concerning a systemic efficacy by percutaneous resorption must be reserved for a separate study. In this case, the therapeutic differences would be obscured in an intraindividual comparison. The results in this paper should be regarded as conservative assessments. Note, that according to previous results, a minor systemic efficacy can be assumed (Wiesenauer, 1992).

Psoriasis demonstrates a great variation in its degree of severity, appearance and progression. This is possibly the reason for the various responses of psoriasis patients to all types of treatment. These individual differences are also apparent in treatment with *Mahonia* aquifolium. In our study this resulted in good to very good results in some cases. On the other hand, quite a few patients experienced little or no allevation of their symptoms although they were treated under the same circumstances.

The trial design could have had an additional effect on the assessed treatment efficacy: since the inclusion criteria were unspecific, the physicians involved were also allowed to include especially severe cases of psoriasis (over 50%, of surface skin afflicted). According to previous experience, these patients can hardly be treated with phytogenic dermatotherapeutic medication (Gieler et al. 1995). This would explain the high number of non-responders. It is also possible that an obscurement of the therapeutic differences took place in the intraindividual comparisons due to the incorrect treatment of body sides: First, patients did not precisely follow the assignment of ointment/body side. Second, they did not adequately wash their hands between the treatment of both body sides, making it possible to contaminate the verum/placebo ointments while massaging them in.

Regarding to above it seems likely that the treatment of Psoriasis vulgaris with *Mahonia* is superior to treatment with the placebo. Even if the difference is only found to be significant in the assessment by patients, the paper's additional analysis after dichotomisation supports this effect. *Mahonia* seems to alleviate symptoms especially effectively in moderately severe cases. Although not significant, the chances of improvement appear to be three to four times as high as in light cases of psoriasis. An interaction between *Mahonia* and other parallel methods of anti-psoriatric treatment can not be proven. Even if it is assumed that the applied parallel methods of treatment worked systemically or were simultaneously applicated to both body sides, the true therapeutic difference is not masked.

Our results are in accordance to in vitro experiments conducted by Creasy (1979) and Davidson et al. (1977). They were able to prove that Berberin interacts with DNA, altering the spatial structure of double helix, thus exerting an influence on the DNA-, RNA- and proteinsynthesis. The therapeutic effect could, therefore, be attributed to a regulation of the cell proliferation and the infectious processes in the psoriatric epidermis (Galle et al. 1994, Müller and Ziereis 1994).

Personal pilot studies support or efficacy hypothesis about *Mahonia aquifolium*. Aiming for a long-term observation, 15 Psoriasis vulgaris patients were treated an average of 100 days in a structured observational study. Although the trial took place in the disadvantageous seasons of autumn and winter, 11 of 15 patients showed an alleviation of their symptoms. Furthermore, all patients referred to the Mahonia ointment as pleasant and well tolerated. Adverse medical effects were not reported (Wiesenauer, 1992).

Although there was no systematic monitoring, we are sure that the quality of the data in this study is adequate. This is due to the fact that the physicians seemed highly motivated, for the majority of the case record forms reached the trial center in such a short time.

Exactly when Mahonia starts to work is a question that must remain unanswered. During the trial the patients were requested to report when they first felt the effects of *Mahonia*. The data was inconsistent: Two patients reported at their final examination that they had noticed no effect during the entire trial from either the verum or the placebo. Simultaneously they assessed the efficacy of the two therapies differently. On the other hand, 46 patients declared that the verum as well as the placebo left the psoriasis symptoms unchanged, but reported a point in time when differences in efficacy were first noticed (mostly in favor of verum). The reason for this apparent paradox could be the relatively rough and insensitive scale used to assess treatment efficacy. Moreover, lacking patients' compliance or habituation to the verum are possibly the cause for such effects. Only further studies with more intensive screening and a more intricate measurement scale will be able to answer these questions.

Main effect measurement was very crude. A three point scale may not be sensitive to small changes in disease course. On the contrary, as this study was conducted in surgeries of family physicians, more detailled measurements would have required more organisational structures than we could provide. Due to the greater amount of work involved, it seems unlikely whether such a study, based on the customary patients of established family physicians, is possible. Note, that in this study the documentation was carried out free of charge by the treating physicians.

Nevertheless, clinical trials are necessary in general medical practice in order to reach a accurate assessment of a specific therapy. Thus, some methodological shortcomings are programmed. We have to keep them as small as possible. Examinations dealing only with hospitalised patients would pose the threat that the study's subjects would not be representative for the general (outpatient) population. Decisive knowledge concerning therapeutic use as well as toxicological relevance would be lost. This seems to be especially true for phytotherapeutic medication.

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References

Akhter, M., Sabir, M., Bhide, N.: Antiinflammatory effect of berberine in rats injected locally with choleratoxin. *Indian J. Med. Res.* 1977; 65: 133–141.

Braun-Falco, O., Galosi, A., Ruzicka, T.: Was ist gesichert in der Behandlung der Psoriasis? *Internist* 1987; 28: 58–64.

Bommer, S.: Biologische Therapie von Hautkrankheiten. *Dtsch. Med. Wschr.* 1943; 68: 511–515.

Breslow, N. E., Day, N. E.: Statistical Methods in Cancer Research. Vol. 1 – The Analysis of Case-Control Studies. Lyon: IARC, 1980.

Creasy, W. A.: Biochemical effects of berberine. *Biochem. Pharm.* 1979; 28: 1981–1984.

Davidson, M., Lopp, I., Alexander, S., Wilson, W.: The interaction of plant alkaloids with DNA. *Nucleic. Acid. Res.* 1977; 4: 2697–2712.

Galle, K., Müller-Jakic, B., Proebstle, K., Bladt, S., Wagner, H.: Analytical and pharmacological studies on Mahonia aquifolium. *Phytomedicine* 1994; 1: 59–62.

Gieler, U., von der Weth, A., Heger, M.: Mahonia aquifolium – a new outlook on topic treatment of psoriasis. *J. Dermatol. Treat.* 1995: 6: 31–34.

Holm, S.: A simple sequentially rejective multiple test procedure. *Scand. J. Statist.* 1979; 6: 65–70.

Jung, E. G. (Hrsg.): Dermatologie. Stuttgart: Hippokrates, 1995.

Kostalova, D., Hrochova, V., Tomio, J.: Tertiary alkaloids of Mahonia aquifolium (pursh.). *Nutt. Chem. Papers* 1986; 40: 389–394.

Kuritz, S. J., Landis, J. R., Koch, G. G.: A general overview of Mantel-Haenszel methods: applications and recent developments. *Ann. Rev. Pub. Health* 1988; 9: 123–60.

Lampi, L. A.: Dermatologie – ein Kompendium. München: Mediscript, 1983.

Müller, K., Ziereis, K.: The antipsoriatic Mahonia aquifolium and its active constituents. Pro and antioxidant properties and inhibition of 5-lipoxygenase. *Planta Med* 1994; 60: 421–424.

Stiegele, A.: Beitrag zur Behandlung der Psoriasis. *Dtsch. Zschr. Hom.* 1950; 1: 511–515.

Wiesenauer, M.: Wirksamkeit und Verträglichkeit von Mahonia aquifolium bei Psoriasis vulgaris. *Extracta Dermatol.* 1992; 16: 23–31.

Wiesenauer, M.: Mahonia aquifolium-Salbe bei Psoriasis vulgaris. *Z. Allg. Med.* 1992; 68: 670–674.

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