

Fig. 2. Mean use of hydrocortisone butyrate topical in each 2-week period.

regularly during the trial: ESR, full blood count, haematocrit, MCV, MCH, MCHC, differential white cell count, platelets, sodium, potassium, calcium, albumin, urea, creatinine, acid phosphatase, basic phosphatase, SGOT, SGPT, LDH, phosphate, urate, total lipid, bilirubin, cholesterol, iron and prothrombin time. Urine was analysed for blood and protein.

Statistical testing was conducted at the two-tail 5% level using a Mann-Whitney U-Test on differences of clinicians' scores.

RESULTS

Both groups showed nearly identical recovery during the trial and there were no statistically significant differences in the clinicians' scores for any parameter. Only in estimating the amount of hydrocortisone butyrate used, was it possible to show that the patients of the placebo group did use more cream than those in the active group (Fig. 2). However, the difference failed to reach statistical significance.

No patients had any drug-related complaints. In one patient of the active group and in 2 patients of the placebo group there were slightly, but transiently, elevated liver enzyme levels. The other laboratory tests were within normal range.

DISCUSSION

In this investigation we were not able to prove the new chromone drug to be effective in systemic treatment of atopic dermatitis. Being the first group to use this drug in a large-scale investigation, we applied the minimum dose expected to show an effect. To avoid patients in the placebo group withdrawing from the trial because of exacerbation, all the patients were allowed to use hydrocortisone butyrate topically, which might have obscured an effect of the drug. The investigation took place in

the spring and summer months when most patients with atopic dermatitis are getting better, an effect which again would tend to obscure the expression of the drug to be investigated. One patient had transient slightly elevated liver enzymes which might have been produced by the drug. There were no drug-related complaints.

New investigations with this anti-allergic drug in the treatment of atopic dermatitis are warranted.

ACKNOWLEDGEMENTS

Fisons Limited is thanked for supplying us with FLP 57787 and for statistical analyses of the results. Gist-Brocades is thanked for supplying us with locoid®.

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Peroral Aromatic Retinoid Treatment of Palmoplantar Pustulosis: Double-Blind Comparison of Ro 10-9359 and Placebo.

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Received October 3, 1978

Abstract. Nineteen patients with chronic, recalcitrant palmoplantar pustulosis took either placebo or aromatic retinoid ethyl ester (Ro 10-9359) during a 4-month therapeutic trial. The maximal dose of Ro 10-9359 varied between 25 and 100 mg per day, according to the individual patient's tolerance. An excellent or good therapeutic response was obtained in 6 out of 9 patients on the active medication and in 2 out of 10 patients on placebo. The difference in therapeutic response between the Ro 10-9359 group and the placebo group was statistically significant ($p < 0.05$). Drying and chapping of the lips

was the most common side effect of Ro 10-9359 treatment.

Key words: Aromatic retinoid; Ro 10-9359; Palmoplantar pustulosis; Double-blind study

Palmoplantar pustulosis (PPP) is a chronic, disabling eruption of the hands and feet, characterized by erythema, pustulation and scaling. Although in some patients favourable therapeutic results may be obtained with systemic methotrexate, longterm tetracycline administration, or local PUVA treatment, many cases still pose a therapeutic enigma, and the condition still awaits its ideal therapeutic regimen.

Recent preliminary data has indicated that a new retinoic acid derivate, aromatic retinoid ethyl ester (Ro 10-9359) may be effective in alleviating the symptoms of PPP (3, 11). No controlled therapeutic series, however, has yet been published. This report presents the results from a double-blind comparison of Ro 10-9359 and placebo in the treatment of PPP.

MATERIAL AND METHODS

Twenty patients, 13 of whom were female, entered the study. The age of patients varied between 19 and 72 years, mean 44 years. The duration of the dermatosis ranged from 1 to 16 years, mean 3.6 years. The diagnosis was based on a typical clinical picture and the exclusion of contact sensitivity and bacterial or fungal infections. By random allocation, either 25 mg capsules of Ro 10-9359 or lactose placebo, in identical capsules, was supplied, each preparation to 10 of the patients. The total duration of the active trial was 4 months, during which the patients were seen at 1-month intervals. In addition, a post-treatment examination was made in 14 of the cases, 2-4 months after stopping the medication. At each visit the local status was recorded according to previously fixed criteria (see Fig. 1), using a 0-4 scale for the individual symptoms and a 0-5 scale for the overall judgement (see Table). Colour photographs were taken at each visit, and the patient interviewed regarding side-effects, using a preformed record sheet.

During the first trial month, each patient took one capsule daily. At monthly intervals the daily dose was increased by one capsule. However, if moderate side effects were recorded, no further increase in the dose was made and in the case of severe intolerance, a reduced dose was utilized for the rest of the 4-month period. For the period of the study, each patient was instructed to carry on with the local treatment he had been using prior to inclusion in the study. S-krea, S-AFOS, S-ASAT, white blood cell count and sedimentation rate were checked at monthly intervals, and S-Ca, S-Pi, white cell differential count, and S-vitamin A at the start and close of the trial period.

Table 1. Overall therapeutical results obtained in the 4-month trial period

The following rating was used: Exa=exacerbation, 0=no effect, 1=insufficient effect, 2=moderate effect, 3=good effect, 4=excellent effect

Treatment	Therapeutical result					
	Exa	0	1	2	3	4
Placebo (N=10)	0	2	3	3	1	1
Ro 10-9359 (N=9)	0	0	2	1	3	3

RESULTS

Nineteen patients completed the study. Table 1 shows the overall therapeutic results obtained. An excellent or good response was recorded in 6 out of 9 patients on Ro 10-9359 and in 2 out of 10 patients on placebo. The difference between the Ro 10-9359 and placebo groups is statistically significant by the χ^2 test (<0.05). Fig. 1 shows the relative efficiency of Ro 10-9359 treatment in alleviating the various skin symptoms of PPP. Vesiculation and pustulation were reduced more effectively than desquamation or erythema. Accordingly, many patients referred to the therapeutic effect as one of "drying up" the lesions.

Due to side effects, only one of the patients taking Ro 10-9359 reached the maximum dosage, i.e. 100 mg daily. Three patients took a personal maximum of 75 mg, 4 patients 50 mg, and one patient 25 mg per day. With these dosages, the most common side effect was drying of the lips (8 patients), of the nasal mucous membrane (8 patients), or of the mucous membrane of the mouth (5 patients). All of these side effects were mild, except for a marked or severe lip dryness recorded in 2 and 1 patient respectively. Oral mucous membrane erosions were seen in 4 patients, mild conjunctivitis in 3 patients, and a mild to marked paronychia reaction in 3 patients. Three patients reported chilling and 5 increased sweating during the therapy. Moderate, diffuse hair loss was seen in 2 patients. Blood tests revealed no abnormalities. The one drop-out case in the Ro 10-9359 series was a woman aged 72, who had a transient ischemic attack (TIA) with mild, reversible signs of hemiplegia.

Prior to opening of the code for the trial, 6 of the actively medicated and 8 of the placebo-treated patients were subjected to a post-treatment examination, 2-4 months after stopping the medication. The

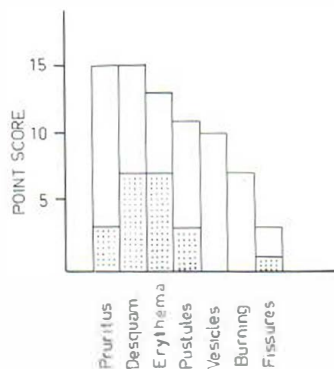


Fig. 1. Alleviation of skin symptoms by Ro 10-9359 treatment. White bars indicate symptom scores before treatment, stippled parts of bars refer to symptom scores at last treatment examination. In the individual patient, each symptom was scored 0-4. In the figure, the scores of 9 Ro 10-9359-treated patients have been combined.

status of all of the placebo patients had remained unaltered during the follow-up period. The 6 Ro 10-9359 patients included 4 who had responded with a good or excellent clearing of their dermatosis during the period of medication. Two of these continued to show a remission, while the 2 other patients deteriorated during the follow-up period. In the latter 2 cases, a re-institution of the Ro 10-9359 treatment on an open trial basis led in both cases to a new remission of the dermatosis within a few weeks.

DISCUSSION

The first report on the systemic use of retinoid acid (RA) in dermatology dates back to 1971 (8), and a number of therapeutical trials with RA or its derivatives have been put on record since then. These therapeutic endeavours have, however, been hampered by severe side effects (7, 10). The lately introduced retinoid acid ester, Ro 10-9359, has been shown to present a better therapeutic index than RA or any of its earlier derivatives (5). Several reports have documented a favourable therapeutic effect of Ro 10-9359 in the treatment of psoriasis (1, 3, 5, 6, 9, 11).

The present study corroborates and extends previous preliminary observations that Ro 10-9359 is also effective in alleviating the symptoms of palmo-plantar pustulosis (3, 11). The mechanism of action of Ro 10-9359 in PPP is at present completely unknown, but interestingly enough, favourable results

have been obtained in other pustular dermatoses such as pustular psoriasis (5, 6) and subcorneal pustular dermatosis (2, 4).

The frequent side effects, even though not of a serious nature, restrict the usage of Ro 10-9359, and in a proportion of the patients a therapeutically effective dosage cannot be reached. Nevertheless, Ro 10-9359 may be considered a useful alternative in our very limited therapeutic armoury for the treatment of PPP. The observation that PPP may stay quiescent for some time after an interruption of the retinoid treatment may be of practical importance, and points toward the possible benefit of alternating treatment regimens.

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