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REPORTS

Ro 20-1724: An Agent that Significantly Improves Psoriatic Lesions in Double-Blind Clinical Trials

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Two double-blind studies comparing the effectiveness of the cyclic nucleotide-altering agent (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone) (Ro 20-1724) vs vehicle have demonstrated that this compound can improve psoriatic lesions. Although Ro 20-1724 was not as effective as intensive occlusive treatment of psoriatic lesions with 0.025% triamcinolone acetonide, Ro 20-1724 had no adverse systemic or cutaneous effects. Ro 20-1724 and other cyclic nucleotide-altering agents may have therapeutic potential in the future treatment of psoriasis.

Psoriasis is the prototype of several common steroid sensitive proliferative skin diseases and afflicts approximately 1 to 2% of the population [1]. Although the precise role of cyclic nucleotides in psoriasis remains unclear [2–6], most investigators do agree that the epidermal cyclic nucleotide metabolism in psoriatic plaques may be misregulated.

Recent investigations [7] with the cyclic nucleotide phosphodiesterase (PDE) inhibitors papaverine and Ro 20-1724 (4-[3-butoxy-4-methoxybenzyl]-2-imidazolidinone) have shown that papaverine inhibits both cAMP-PDE and cGMP-PDE, whereas Ro 20-1724 selectively inhibits only cAMP-PDE. Furthermore, when psoriatic epidermis was incubated with papaverine or Ro 20-1724, Ro 20-1724 increased the levels of cAMP significantly greater than papaverine incubations. These studies clearly demonstrated the superiority of Ro 20-1724 to selectively elevate cAMP levels in incubated psoriatic epidermis.

Since the topical application of 1% papaverine cream produces a modest but significant improvement of psoriatic lesions [8], we anticipated that the marked *in vitro* superiority of Ro 20-1724 to elevate cyclic AMP levels and its lipophilic character would also result in the improvement of psoriatic lesions. Therefore, we investigated the clinical effectiveness of Ro 20-1724 in 3 double-blind clinical studies with psoriatic patients. In these studies, we compared the clinical effectiveness of Ro 20-1724 to vehicle and to 0.025% triamcinolone acetonide.

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Abbreviations:
cAMP: 3′,5′-cyclic adenosine monophosphate
cGMP: 3′,5′-cyclic guanosine monophosphate
PDE: phosphodiesterase
Ro 20-1724: 4(3-butoxy-4-methoxybenzyl-2-imidazolidinone)

MATERIALS AND METHODS

Comparison of 1% Ro 20-1724 Cream and its Vehicle

Seventeen outpatients with typical plaques of psoriasis, who had not treated the disease for one week, participated in a double-blind clinical study. Two lesions approximately 5 cm in diameter were selected on each patient and designated as site 1 and site 2.

Patients were 18 yr of age or older, with no history of significant cardiovascular disease. Women chosen were postmenopausal, had had a hysterectomy or were on oral-contraceptives. Patients being treated with insulin or oral hypoglycemics were not accepted to the study. For this clinical evaluation the creams were supplied by Hoffman-LaRoche, Inc., Nutley, New Jersey. The vehicle cream contained: glyceryl monostereate, cetyl alcohol, white petrolatum, methylparaben, prophyparaben, propylene glycol, and purified water. The Ro 20-1724 formulation consisted of the same cream with Ro 20-1724 added to a 1% final concentration. Each patient received vehicle cream and Ro 20 cream in tube containers. One of each pair of tubes had been randomly designated for use on site 1 and the other for use on site 2. Both creams had the same color. The code was not broken until completion of the study.

Patients applied the creams 4 times a day for 4 weeks under occlusion. The total occlusion was approximately 20 hr per day. Topical steroids and systemic medication for psoriasis were not permitted to be used concurrently. Clinical laboratory studies were conducted on all patients before using the creams and at the first 2 subsequent visits. The laboratory parameters obtained included electrolytes, urea nitrogen, total bilirubin, glucose, total protein, albumin, cholesterol, calcium, phosphorus, uric acid, creatinine, glutamic oxaloacetic transaminase, lactic dehydrogenase, alkaline phosphatase, white blood count, hematocrit, hemoglobin, red blood count and urine analysis for sugar, ketones and proteins.

Each test lesion was evaluated independently by 2 physicians, 2, 4 and 6 weeks after the initiation of the study. The final evaluation at 6 weeks was made following a 2-week period with no application. Improvement was judged by a decrease in lesion thickness, not by a loss of scale or change in color. Each lesion was assigned a score of 0 on the first day and improvement from the initial status was scored as follows: 0 = no improvement or worsening, 1 = minimal improvement, 2 = moderate improvement (decreased thickness and/or incomplete clearing), 3 = complete clearing with or without residual redness or change in pigmentation. When 2 physicians disagreed in their evaluation, the lower score was used for statistical analysis. Scores of 2 and 3 were called improved, and scores of 0 and 1 were called unimproved in the analysis of the results at either 2, 4 or six weeks of application.

Patients showing differential improvement, i.e., who had a lesion respond to Ro 20 while the matched lesion did not respond to a vehicle, or who had a lesion respond to vehicle while the matched lesion did not respond to Ro 20, were used for statistical evaluations employing a sign test [9].

Comparison of 3 Ro 20-1724 Concentrations at the University of Miami

A second study comparing Ro 20 at concentrations of 0.25%, 0.5%, and 1% vs vehicle cream was conducted at the University of Miami by one of us (G.W.) in part to look for a dose response effect. Nine patients

were treated simultaneously with three Ro 20 concentrations and vehicle cream in a double-blind psoriasis therapeutic study. Patients did not receive any systemic or topical antipsoriatic medications during the study. On multiple similar psoriatic plaques, 10 sites were delineated approximately 1-½" square which were randomly assigned to be treated with the different Ro 20 concentrations and vehicle cream. Approximately 0.5 ml of each concentration of Ro 20 and vehicle were applied in duplicate to the appropriate sites. The remaining 2 sites were untreated controls. Creams were applied daily under occlusion for 6 days, treatment was stopped on the 7th day, then applications were resumed for an additional 6 days. All test applications in the study were made by a technician to insure the greatest accuracy in the drug being applied each time to the same site. Each site was scored as 0 if there was no change from initial status, 1+ if there was minimal improvement, and 2+ if there was substantial improvement or clearing. Daily evaluations were recorded after the treated sites had been washed with water and acetone. The final evaluation was made on the 15th day, 2 days after the final treatment.

Comparison of 1% Ro 20-1724 Cream and 0.025% Triamcinolone Acetonide Cream

Thirty-three outpatients participated in a third study which compared the effect of 1% Ro 20-1724 vs 0.025% triamcinolone (TMC). The patients and psoriatic lesions were selected in the identical manner to the first study. The TMC was in a vehicle which contained: sorbic acid, potassium sorbate, mono- and diglycerides, squalane, polysorbate 80 USP, stearyl alcohol USP, polysorbate 60, spermaceti USP, and sorbitol solution USP in a water base. This vehicle and that for Ro 20 were identical in color and odor. The Ro 20 formulation was identical to that used in the first clinical study. The methods of application and evaluation from the first study were employed (see "Comparison of 1% Ro 20-1724 Cream and its Vehicle").

RESULTS AND DISCUSSION

Twelve of 17 patients completed the first clinical study. Two patients were disqualified because they did not occlude the lesions regularly, and 3 requested to be removed because their untreated psoriasis was flaring. The clinical laboratory studies did not reveal any abnormalities which could be attributed to 1% Ro 20-1724.

Table I summarizes the data obtained from the 4th week evaluation of those 12 patients. Nine of 12, 75%, of the patients improved only with the Ro 20 preparation and 8% (1 of 12) improved only with the vehicle. The Ro 20 treated site was improved in 9 of 10 patients showing differential improvement ($p = .011$).

The results of this study can be compared with the results of the previously reported papaverine vs vehicle psoriasis bioassay [8]. Utilizing the percent relative difference ± SE [10], the proportion of patients expected to improve with 1% Ro 20 or 1% PAP cream who did not improve with the respective vehicle creams can be determined. This comparison shows that Ro 20 is a much superior agent in treating psoriasis since 73 ± 15% of patients would be expected to improve with 1% Ro 20 cream in contrast to only 39 ± 12% receiving 1% PAP cream ($p = .05$).

Nine psoriasis patients completed the second (University of Miami) clinical study. All 54 sites treated with the 3 concentrations of Ro 20-1724 showed either minimal or substantial improvement (Table II). The placebo preparation had only 4 minimial responses out of 18 test sites suggesting a definite therapeutic effect from the Ro 20-1724 preparations ($p < .01$). A dose related effect is suggested at the 0.25% concentration, however, this concentration may also be too high to demonstrate this point.

Thirty of thirty-three patients completed the third clinical study. Two patients were dropped from the study because they did not apply the creams regularly and the other patient was disqualified because he did not occlude the lesions. None of the clinical laboratory studies revealed any abnormalities attributable to 1% Ro 20-1724.

The results of the second and the fourth week evaluation of those 30 patients are summarized in Table III. Every patient whose Ro 20-treated lesion improved by the 4th week also improved on TMC. The difference in the time course of improvement for TMC and Ro 20 can be seen in Table IV. Eighty-six percent of the patients had improved on TMC at the second week and the increase to 94% at the fourth week was not significant ($p = .25$). By contrast, the percentage for Ro increased from 43 to 77 which is significant ($p < .001$). Ro 20 and TMC appeared to be clinically similar.

Eight of the nine patients judged completely cleared at the 4th week on Ro 20 were seen 2 weeks after the applications were discontinued. Six of 8 (75%) had begun to relapse. Twenty of 23 patients who cleared completely on TMC were evaluated after two weeks without application. Eight of these (40%) partially relapsed.

These investigations indicate that Ro 20-1724 is capable of improving psoriasis. In 2 double-blind studies comparing Ro 20-1724 vs vehicle, Ro 20-1724 significantly improved psoriasis in geographically distinct (Michigan and Florida) patient populations. Although Ro 20-1724 is not as effective as 0.025% triamcinolone acetonide applied q.i.d. under occlusion, no atrophy, striae or other adverse steroid effects would be expected with Ro 20-1724 application.

The currently available therapeutic modalities to treat psoriasis have inherent limitations that restrict their effectiveness. Of those most commonly employed, topical steroids can induce atrophy and striae and UVB irradiation with topical coal tar usually requires hospitalization. Furthermore, the risk factors

TABLE I. *Percent of 12 psoriasis patients with matched lesions responding to 1% Ro 20-1724 vs vehicle at 4 weeks.*[a]

	Percent
Improved on *both* Ro 20-1724 and vehicle	0
Improved on Ro 20-1724 *only*	75*
Improved on vehicle *only*	8*
Unimproved on *both*	17
	100
Sign test (one-sided hypothesis)	* $p = .011$

[a] Categorized into 4 possible patterns of response (improved on *both*, improved on Ro 20 *only*, improved on vehicle *only*, unimproved on *both*)

TABLE II. *Clinical effects by drug concentration of Ro 20-1724 on psoriasis*[a]

Concentrations of Ro 20-1724	Number of test sites at each concentration				
	1%	.5%	.25%	Placebo	
	Response				
	2	11	11	8	0
	1	7	7	10	4
	0	0	0	0	14

[a] Each of the nine patients tested in duplicate sites with the preparations above (see text). A possible dose response effect may be present at the 0.25% concentration. Response was graded as follows: no improvement = 0, minimal improvement = 1, and moderate or better improvement = 2.

TABLE III. *Percent of 30 psoriasis patients with matched lesions responding to 1% Ro 20-1724 vs 0.025% triamcinolone categorized into the 4 possible patterns of response at 2 & 4 weeks*[a]

	Percent	
	2nd Week	4th Week
Improved on *both* Ro 20-1724 and Triamcinolone	43	77
Improved on Ro 20-1724 *only*	0*	0†
Improved on Triamcinolone *only*	43*	17†
Unimproved on *both*	14	6
	100	100
Sign test (one-sided hypothesis)	* $p < .001$	† $p = .03$

[a] Improved on *both*, improved on Ro 20 *only*, *improved on TMC only*, unimproved on *both*.

TABLE IV. *Percent of lesions improved in 30 psoriasis patients on .025% triamcinolone and 1% Ro 20-1724 at 2 & 4 weeks*

	Percent	
	2nd Week	4th Week*[a]
Triamcinolone-treated	86°	94°
Ro 20-1724-treated	43†	77†

Sign test (one-sided hypothesis) * $p = .25$, † $p < .001$.
[a] All lesions improved at 2nd week were also improved at 4th week.

of PUVA cannot be objectively assessed at this time. Ro 20-1724 and other cyclic nucleotide-altering agents are experimental agents that may have future potential in the treatment of psoriasis. Such agents may provide topical therapy with a minimum of adverse side effects which can be used as alternative forms of treatment for patients with psoriasis who are unable to use conventional forms of therapy.

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ANNOUNCEMENT

The Center for Disease Control of the Public Health Service is again offering a continuing series of short, intensive laboratory training courses during 1979-1980. Information and applications may be obtained from the registrar, Bureau of Laboratories, Center for Disease Control, Atlanta, Georgia 30333.