Topical Application of a Platelet-activating Factor (PAF) Antagonist in Atopic Dermatitis

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Platelet-activating factor (PAF) acether is a lipid mediator with a potent proinflammatory activity. Results derived both from in vitro and in vivo studies suggest a possible role of this substance in the pathophysiology of atopic dermatitis. A double-blind, randomized, multi-center, within-patient study was performed to evaluate the efficacy of a topically applied PAF antagonist (RO-24-0238) in 36 patients with atopic dermatitis. Over a period of 28 days, 0.25 ml of the PAF antagonist and the vehicle (placebo) were applied twice daily on opposite sites of symmetrical lesions (measuring 10 to 20 cm² each). The overall assessment of the therapeutic efficacy did not demonstrate a superior effect of the PAF antagonist in comparison to placebo, and this was the same with the individual study parameters erythema, scaling, induration and exudation. For reducing pruritus, as assessed by the patient using a visual analogue scale, a statistically significant action was documented during the first 2 weeks of the study (p < 0.04; Wilcoxon rank sum test), with a continued, yet not statistically significant efficacy after weeks 3 and 4. The exact role of the pathological events of atopic dermatitis that might be influenced by a PAF antagonist remains to be determined, but the anti-pruritic component of this substance especially deserves further scientific interest.

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Although atopic dermatisis (AD) is clinically a well-characterised disease, the pathogenesis of AD still remains unclear. A disturbance in cellular interactions within the immune system seems to be one of the important underlying factors (1, 2). The multiplicity of immunobiochemical abnormalities in AD concerns also the vascular reactivity which is the basis for the relevant inflammatory process. This leads to irregular release of certain proinflammatory mediators, e.g. histamine, PAF, leukotrienes, cysteinyl leukotrienes, etc. (3-7), inducing itch, contact urticaria or late-phase reactions, which in conjunction with the scratch reflex finally result in typical eczematous skin changes. PAF acether is a soluble naturally occurring phospholipid, which is generated by phospholipase A2 activity on membrane phospholipids. In response to allergen stimulation, PAF acether is released by several inflammatory cells, such as basophils, mast cells, neutrophils and eosinophils (8). In vivo, PAF acether increases vascular permeability (1, 9). Intradermal administration of PAF acether provokes a dose-related biphasic skin response in both normal and atopic persons. An early seal and flare reaction caused by vasodilation and increased vascular permeability is followed by late-onset erythema. This cutaneous reaction produced by PAF acether is probably due to the release of mast cell-bound histamine in the dermis, since local administration of H1-antihistamine inhibits this skin response (10).

Compared to this normal skin response, an early eosinophilic accumulation with maximum recruitment of eosinophils after 24 h could be seen in atopic skin specimens after i.d. injection of PAF (11). Due to these potent proinflammatory and vasoactive characteristics PAF acether is credited to play a crucial role as a mediator of atopic inflammation.

Several PAF antagonists have been developed so far (12-15).

The one chosen for this study (RO-24-0238) is a specific synthetic compound (16), which in addition inhibits the inflammatory pathway linked to arachidonic acid. In vivo studies of dinitrochlorobenzene-(DNCB-) sensitized mice resulted in decreased ear thickness following topical application of RO-24-0238. Toxicity trials in animals revealed satisfactory toleration of RO-24-0238 (16).

MATERIAL AND METHODS

The study was designed as a multicenter (Aarhus, Denmark; Hamburg, Germany; Linköping, Sweden; Strasbourg, France; Warsaw, Poland), double-blind, randomized within-patient study. According to the study design patients were required to have moderate to severe AD, according to the clinical criteria of Hanifin & Rajka (17) and grossly symmetrical lesions measuring 10 to 20 cm² each, located either on the limbs or the trunk, with hands, feet or head to be excluded. Forty-four patients were enrolled in the study, out of which 36 patients were evaluated (19 females and 17 males; mean age 27.8 years; range 18-64 years).

Systemic therapies such as corticosteroid or UV radiation therapy were discontinued at least 4 weeks before the start of the study; antihistamines or other medication potentially influencing the disease were stopped at least 1 week before the start of the study. No topical therapy of any kind with the exception of bland emollients was permitted 2 weeks prior to the investigation.

Concomitant therapy for other medical conditions was unchanged during the study period in all subjects, and patients on medication known to affect AD adversely were excluded. The composition of the topical PAF antagonist solution was the following: PAF antagonist RO-24-0238 10.0 (v/v), 1'-z-tocopherol 0.1 (v/v), diethyleneglycol mono ethylether (transcutol®) 100.0.

All 36 evaluable subjects applied 0.25 ml of the PAF antagonist and the vehicle (z-tocopherol and transcutol® only) twice daily on opposite sites for a duration of 28 days. The solution was collected with a 1 ml disposable syringe without a needle and then spread over the designated area. After the application of the test substance an interval of 5 min was chosen to allow soaking into the skin.

Before the start of the therapy and on each weekly visit the eczematous lesions were rated by the investigator. Erythema, scaling,
induration and exudation were clinically graded each time, using a 5-point grading scale covering a range from 0 (=absence of the criterion assessed) to 4 (=criterion assessed in its maximum expression). In addition, the criterion pruritus was graded equally according to the patient’s information and also by using a 10-cm visual analogue scale comparing the right and left side. At the end of active treatment an overall assessment of the therapeutic activity using a 6-point scale (0=total clearing, 1=marked improvement, 2=mild improvement, 3=no change, 4=mild worsening, 5=marked worsening) and an estimation of site preference were performed. Local tolerability, adverse events and laboratory parameters (hematology and clinical chemistry, endocrinology and urine analysis data) were also monitored throughout the study.

The significance of differences in improvement between the two treatment modalities for each individual parameter looked at was determined by the McNemar test at the end of weeks 1, 2, 3, and 4. The Wilcoxon rank test was used to analyse changes from baseline in the patients’ assessment of therapeutic activity on pruritus.

RESULTS

Out of the 44 patients initially enrolled, 36 could finally be evaluated. Out of the 8 patients not evaluable, 7 withdrew prematurely and one patient had to be considered a major protocol violator. This was due to the application of ointment containing preservatives. The local tolerability of the study medication was poor, with 15 patients out of the total study population complaining about problems like skin dryness and burning immediately after application of the solution. A gradual improvement in severity of the individual parameters studied could be stated for both the PAF antagonist and the placebo-treated areas. Responder rates were very similar for the two treatment sites, with the rates of 67% for the active solution and 69% for the placebo-treated areas, respectively (Fig. 1). However, in the assessment of therapeutic activity on pruritus a strong statistical difference between treated sites in favour of the PAF antagonist could be seen at day 7. A statistically significant difference between treatments could also be recorded at day 14 but was then lost, despite a continuing trend in favor of the active substance (Table I).

The results of the investigators’ overall assessment showed a similar distribution across the six categories for active- and placebo-treated lesions. According to the investigators almost 90% of the lesions in each treatment group were considered to have shown a marked or mild improvement at the end of treatment. One patient demonstrated a marked worsening on both treated sites in association with general deterioration of the non-tested skin areas.

In the overall estimation of site preference the PAF antagonist test site seemed to be preferred to the placebo site; however, this was not found to be statistically significant (Table II). This site preference could probably be ascribed to the PAF antagonist-treated sites being less pruritic than the placebo sites.

Safety results

Taking local tolerability into consideration a group of 15 patients out of the trial population (44 subjects) complained about problems like skin dryness and burning immediately after application of the treatment. These local events were experienced on both the PAF antagonist- and placebo-treated sites in the majority of cases, suggesting that these problems were due to the vehicle rather than the PAF antagonist itself. There was one case suspicious of contact dermatitis which was probably related to the trial medication, since typical skin changes developed on the PAF antagonist-treated site only. Another patient reported of bilateral severe erythema as a reverse effect, which the investigator judged as potentially being related to the trial medication. No systemic drug-related side effects could be detected.

DISCUSSION

This study, comparing the efficacy and safety of the PAF antagonist RO 24-0238 10% topical solution to its vehicle, shows no difference in morphological parameters, but significant improvement of subjective itch sensation.

The 10% solution of active substance used in the study had proved to obtain the best penetration rate in animals. The single dose was chosen to make sure that the vehicle would result in no irritation potential and thus, would not counteract the potential efficacy of the active ingredient. Although the local tolerability was poor for both the PAF antagonist and the PAF antagonist-free preparation, there was a general

<table>
<thead>
<tr>
<th>VAS score (mm)</th>
<th>Baseline</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>-0.3</td>
<td>+8.7</td>
<td>+7.0</td>
<td>+7.0</td>
<td>+7.2</td>
</tr>
<tr>
<td>Median</td>
<td>-15.0</td>
<td>+1.5</td>
<td>+2.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Range</td>
<td>-22.5+31.0</td>
<td>-25.0+49.0</td>
<td>-36.0+47.0</td>
<td>-50.0+47.0</td>
<td>-50.0+48.0</td>
</tr>
<tr>
<td><strong>p value</strong></td>
<td>0.02</td>
<td>0.003</td>
<td>0.02</td>
<td>0.07</td>
<td>0.14</td>
</tr>
</tbody>
</table>

*Wilcoxon signed rank test.

Acta Derm Venereol (Stockh) 77
**Table II. Overall assessment of therapeutic activity at day 28 (efficacy population (n=36))**

<table>
<thead>
<tr>
<th></th>
<th>RO 24-0238</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total clearing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Mild improvement</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>No change</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mild worsening</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Marked worsening</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

*Wilcoxon signed rank test.

The improvement of all treated sites during the study, possibly reflecting the known good local tolerance of the used diluant transcutol®, in the overall assessment of therapeutic activity, a superiority of the PAF antagonist in comparison to the vehicle control could not be demonstrated.

The individual parameters measured at the end of the study, such as erythema, scaling, induration and exudation, behaved in the same way. In contrast, the drug was found to have a statistically significant action in reducing the severity of pruritus during the first 2 weeks of the study. The reason for this effect is not clear at the moment. Besides a direct anti-pruritic effect of PAF antagonist another possible mode of action could be derived from the additional effect of the chosen compound, characterized by the inhibition of the inflammatory pathway linked to arachidonic acid through reduction of arachidonic acid metabolites like leukotriene B4 (LTB4) and thromboxane A2. Although the prostaglandins E1, E2 and the cyclic endoperoxide PGH2 have no or only weak pruritogenic effect when injected intradermally, they lower the itch threshold for histamine (18). In this way the inhibition of the arachidonic acid pathway with consecutive diminished generation of eicosanoids might be responsible for the documented reduction of pruritus. In this field further activities seem a worthwhile objective.

**REFERENCES**


16. IDB Ro 24-0238-F. Hoffman-La Roche Ltd. CH-4002 Basel.
