OBSERVATION

Topical Tacrolimus Is Not Effective in Chronic Plaque Psoriasis

A Pilot Study

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Background: Cyclosporine for the treatment of psoriasis constitutes a new approach. Alternative systemic cyclosporine derivatives have been studied to find an immunosuppressive drug with fewer adverse effects. Tacrolimus is one of these new immunosuppressive drugs. Systemically, it has been proven effective in treating psoriasis. A topical formulation of tacrolimus is attractive because it has fewer adverse effects and is useful for a large group of patients. We report for the first time on the efficacy of nonocclusive topical tacrolimus in the treatment of psoriasis.

Observations: After a washout phase of 2 weeks, patients were randomized to receive 0.005% calcipotriol ointment twice daily, placebo ointment once daily, or 0.3% tacrolimus ointment once daily. One psoriatic plaque was treated with a surface area of 40 to 200 cm^2. Efficacy was estimated using the local psoriasis severity index. The reduction in the local psoriasis severity index score after 6 weeks was 62.5% in the calcipotriol group, 33.3% in the tacrolimus group, and 42.9% in the placebo group.

Conclusions: There was no statistically significant difference between the efficacy of tacrolimus and placebo ointment ($P = .77$). Calcipotriol ointment, applied twice daily, had a better effect than tacrolimus ointment and placebo ointment once daily.

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THE INTRODUCTION of systemic immunosuppressive therapy with cyclosporine [1] for psoriasis forms a new approach in its treatment. Cyclosporine has also been found to be useful in other dermatological diseases, such as atopic dermatitis, lichen planus, and pyoderma gangrenosum. Alternative systemic cyclosporine derivatives have been studied to find an immunosuppressive drug with fewer adverse effects, ie, hypertension and nephrotoxicity. Oxeclosporine has been found to be effective in the treatment of psoriasis[2] but was later found to have potential hepatotoxic effects (unpublished data, European Study Group, 1992), and thus was not further developed. Another promising drug is systemic tacrolimus. After initial uncontrolled studies,[3] a placebo-controlled study was conducted by the European Study Group.[4] When given systemically, tacrolimus was found to be effective in treating patients with psoriasis.

For dermatology, a topical formulation of these macrolactam-type cyclic immunosuppressive drugs is an interesting pharmaceutical option. The first studies with topical tacrolimus were performed in 1987.[5] Topical tacrolimus was not effective, either in psoriasis or in allergic or atopic eczema.[6,7] The ascomycine derivative ASM 281-240[8] has also been used topically under occlusion in psoriasis, with promising results. However, a confirmatory study has not been published. Topical tacrolimus was studied in atopic eczema and contact allergy, where it has been successful.[9-12] Topical tacrolimus also has been studied under occlusion on descaled psoriatic skin in microplaques, and in this model topical tacrolimus showed efficacy.[13]

We have studied the possible efficacy of topical tacrolimus in psoriasis in a 3-armed study for 6 weeks.

RESULTS

Seventy patients were studied: 23 in the calcipotriol group, 24 in the tacrolimus group, and 23 in the placebo group. At baseline, patients in the tacrolimus and calcipotriol groups had a median LPSI score of 7.0, and the median LPSI score in the placebo group was 8.0. After 6 weeks, the LPSI score decreased by 33.3% in the tacrolimus group, 62.5% in the calcipotriol group, and 42.9% in the placebo group.

PATIENTS AND STUDY DESIGN

After a washout phase of 2 weeks, patients were randomized to receive 0.005% calcipotriol ointment twice daily, placebo ointment (ointment base free of tacrolimus) once daily, or 0.3% tacrolimus ointment once daily. The study was double-blinded except for the calcipotriol group for whom the investigator was not blinded because of the instruction to use the medication twice daily. Only 1 psoriatic plaque with a surface area of 40 to 200 cm^2 was treated. Efficacy was estimated using a modified psoriasis area and severity index adjusted for 1 lesion, the local psoriasis severity index (LPSI). The minimum LPSI score was 6.0 at entry.

There was no statistically significant difference ($P = .77$) between the efficacy of tacrolimus and placebo ointment. The difference between calcipotriol and tacrolimus ointment was statistically significant, as estimated by the 2-tailed Mann-Whitney test ($P<.005$).

COMMENT

This study shows that the tacrolimus ointment, when used once daily, was not better than a placebo ointment for the treatment of psoriatic plaques. The study also shows that calcipotriol ointment, used twice daily, had a better effect than tacrolimus ointment and placebo ointment used once daily. Because the effect of a placebo ointment used twice daily was not studied here, it is incorrect to conclude from this study that calcipotriol ointment is superior to placebo or tacrolimus ointment. It should be noted that this was a pilot study with relatively small numbers of patients and only indicates a direction.

Tacrolimus is a 822.05-d molecule that appears to be effective in atopic eczema but not in psoriasis when used as a topical drug. This result might be explained by assuming that the molecular weight prevents penetration into psoriatic skin. Systemic tacrolimus is effective in treating psoriasis. Because of a probable skin barrier defect, molecules with a molecular weight between 800 and 1200 d can penetrate the skin and thus are effective in treating atopic eczema. Furthermore, it is striking that all cyclic topical immunosuppressive drugs have a molecular weight greater than 800 d. Both corticosteroids (mean molecular weight around 450 d) and calcipotriol (molecular weight, 413 d), the 2 drugs that have been proven to be effective in psoriasis, have molecular weights less than 500 d. Until now the only exceptions to the 500-d barrier hypothesis are the studies with oxyclosporine (SDZ 281-240) by Rappersberger et al[8] and the study with topical tacrolimus by Remitz et al,[13] in which these macrolactams with a molecular weight slightly greater than 800 d were found to have an effect on psoriasis. The efficacy might be related to the occlusive effect of the Finn chambers used in these studies. If a topical formulation could be designed that will enhance penetration in psoriatic skin by first disrupting the skin barrier function, macrolactam-type cyclic immunosuppressive drugs probably would be effective in a topical formulation. Another option is the development of cyclic immunosuppressant drugs with a lower molecular weight.

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Correction

Wrong Words and Incorrect First Name Published. In the observation titled, "Topical Tacrolimus Is Not Effective in Chronic Plaque Psoriasis," published in the September issue of the ARCHIVES (1998;134:1101-1102), an incorrect first name was published. Theo Ruzicka, MD, should have read Thomas Ruzicka, MD. Also, the text of the second paragraph on page 1101 reads, "The first studies with *topical tacrolimus* were performed in 1987. *Topical tacrolimus* was not effective, either in psoriasis or in allergic or atopic eczema." The text should have read, "The first studies with *topical cyclosporine* were performed in 1987. *Topical cyclosporine* was not effective, either in psoriasis or in allergic or atopic eczema."