

Lack of Efficacy of Topical Calcineurin Inhibitor Pimecrolimus 1% on Pruritus of Severely Uremic Patients: A Randomized Double-Blind Study in 60 Patients

To the Editor:

Uremic pruritus (UP) is still one of the most vexing and disabling symptoms in chronic renal failure, afflicting up to 50% of patients on dialysis.¹ Considering the wide variety of probable causes of pruritus in hemodialysis patients,² several treatments have been suggested, but none of these treatments is known as the treatment of choice for this condition.³ The use of calcineurin inhibitor as a treatment for UP for the first time was described by Pauli-Magnus and colleagues.⁴ They showed that tacrolimus ointment is safe, and short-term treatment is a highly effective option for patients suffering from severe UP.⁴

As there were not many studies on this subject, we decided to do this randomized double-blind placebo-controlled study with a larger sample size and a longer duration of therapy with another calcineurin inhibitor, pimecrolimus 1%.

The study was conducted at our dialysis ward between January 2010 and April 2010. Eligible patients had to meet the following criteria: (1) known case of chronic renal failure, (2) 18 years of age to 60 years of age, (3) at least a 6-week history of pruritus, and (4) no systemic or topical treatment for the existing condition or for any other condition.

Exclusion criteria included the following: (1) pregnancy and breast-feeding; (2) known hypersensitivity to pimecrolimus; (3) presence of other known skin diseases, liver disorders, metabolic disorders, or any other condition

except for end-stage renal disorder causing pruritus; and (4) use of antihistamines or other antipruritus drugs in the previous 3 months.

Randomization was performed by using a simple random table, and the patients were randomly allocated to one of the two arms of the study: group A (pimecrolimus 1%) and group B (placebo). The patients were instructed to use the medication two times a day, starting immediately after dialysis for 1 week. Each patient was visited nine times in total: once at the beginning of treatment and weekly for 2 months. At each visit, patients were oriented on how to interpret their pruritus based on visual analog scale (VAS) numbers from 0 to 10 (0 representing no pruritus, and 10 representing the worst pruritus).

The reduction of the VAS scores of patients' pruritus in group A was compared with that of group B. We used repeated-measure analyses and the chi-square test between groups and reported results as mean value plus or minus the standard deviation.

After an 8-week course of treatment, all of the patients completed the study. Thirty patients in group A and 30 patients in group B were evaluated for efficacy. The average pruritus scores before administration of the drug in group A and group B were 8/5 2/1 and 8/2 3/2, respectively. In group A, the average score of pruritus gradually decreased to 2/6 1/3 at the end of week 8. Notably, the reductions of pruritus in these consecutive weeks were statistically significant ($p < .001$). In group B, the average pruritus score was 8/2 3/2 before placebo administration and 7/1 4/3 at 1 week after the start of administration. The pruritus score gradually decreased to 1/1 1/6 in this group at the end of week 8. The decline was also statistically significant ($p < .002$). Interestingly, the results of our study demonstrate that the pruritus followed the same decreasing pattern in both groups ($p < .001$), and there was no significant difference between the reductions of pruritus in both groups. In group A only, 23 patients reported a burning sensation that gradually subsided during the course of treatment and completely disappeared in all patients before the end of 8 weeks.

Since UP is considered to be partly an immune-mediated inflammatory process, immunosuppressive drugs such as tacrolimus may be beneficial.³ The use of calcineurin inhibitor as a treatment of UP for the first time was described by Pauli-Magnus and colleagues.⁴ They showed that tacrolimus ointment is a safe and effective

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treatment of UP.⁴ Another trial, conducted with 25 patients with UP by Kuypers and colleagues,³ reported a statistically significant reduction of pruritus after 6 weeks of treatment with tacrolimus. (Notably, this trial was neither blind nor randomized and placebo controlled.)

Interestingly, the results of our study demonstrate that the pruritus followed the same decreasing pattern in both groups ($p < .001$), and there was no significant difference between the reductions of pruritus in both groups. Recently, the results of a 4-week randomized double-blind trial with 22 patients showed that tacrolimus ointment 0.1% is not more effective than vehicle in relieving UP.⁵ Importantly, in comparison with the present study, that trial was performed with a smaller sample size and a shorter duration of treatment with another calcineurin inhibitor, tacrolimus 1%. This study, with a larger sample size and a longer duration treatment with pimecrolimus 1% and even though not exactly in line with the previous study by Duque and colleagues,⁵ confirms the results of the latter study. Thus, our trial (for the second time) demonstrated the lack of efficacy of immunomodulator ointment for the treatment of hemodialysis-related pruritus.

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