

## SHORT COMMUNICATION

### Oral Tacrolimus Treatment of Pruritus in Prurigo Nodularis

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The main indication for systemic administration of tacrolimus is immunosuppression in transplant recipients. Tacrolimus is widely used topically to treat skin diseases, particularly atopic dermatitis. A few studies have explored the use of oral tacrolimus in inflammatory skin diseases, such as atopic dermatitis and psoriasis (1–3).

The calcineurin inhibitor tacrolimus was discovered in 1984. Tacrolimus inhibits early T-cell activation and the transcription of interleukin 2 (IL-2), and other cytokines (4). In addition, tacrolimus may have a direct effect on epidermal nerve endings by desensitization of transient receptor potential vanilloid-1-receptors, which decrease the perception of itch (5).

Prurigo nodularis is a rare, chronic skin disease characterized by several to hundreds of extremely pruritic nodules and papules on the trunk and extremities. The aetiology of prurigo nodularis is poorly understood, but it is thought to be a combination of inflammation in the skin and changes in the dermal and epidermal nerve fibres (6). Treatment of prurigo nodularis is challenging; the most frequently used treatments are topical corticosteroids, intralesional corticosteroids, topical capsaicin, phototherapy, oral thalidomide and oral cyclosporine.

To our knowledge, oral tacrolimus has never been used in prurigo nodularis. We describe here a recent case from our department.

#### CASE REPORT

A 42-year-old woman had had prurigo nodularis for 18 years. She had previously had hepatitis B and did not report any atopy. She had been out of work as a nurse-assistant for several years because of her skin disease. She had been admitted 3 times to the in-patient ward and had attended more than 100 dermatological consultations. Her skin findings over the years were generalized excoriated nodules. The following treatments had been tried: local and systemic steroids, psoralen plus ultraviolet A (PUVA), dapsone, azathioprine, and methotrexate. During the period 2003–2007 she used cyclosporine with good effect and she returned to full-time work. However, cyclosporine was discontinued because of hypertrichosis. She started cyclosporine again in 2009 and has used it periodically ever since. From 2012 she used oral tacrolimus periodically, alternating with cyclosporine, and her hypertrichosis became less severe.

However, the cost of tacrolimus was not covered by the government healthcare and it was too expensive for the patient to purchase herself. She then used tacrolimus 10 mg daily in combination with 100 mg cyclosporine, but would have preferred to use only tacrolimus.

We decided to document the use and effect of tacrolimus in this patient. She stopped both cyclosporine and tacrolimus in March 2014 (day 1). At day 8 her blood pressure was 134/76 mmHg, creatinine 75 µmol/l (normal 45–90 µmol/l). At day 11 she was severely affected by itch, which she reported as 7 on a visual analogue scale (VAS) (where 0 = no itch, and 10 = worst itch imaginable). Her score on the Dermatology Life Quality Index (DLQI) was 18. Her skin findings were not developed into nodules, but were rather prurigo papules (Fig. S1A and C<sup>1</sup>). She could not tolerate being without treatment any longer and started tacrolimus 10 mg twice-daily (0.29 mg/kg body weight/day). Her weight was 70 kg. At day 25 her VAS was 4.5, DLQI 13, and she had side-effects with headache and nausea, her blood pressure was 141/80 mmHg, serum level of tacrolimus was 18.8 µg/l (trough-level) and creatinine was 86 µmol/l. She continued this dosage until day 65 and then reduced it to 15 mg daily (0.21 mg/kg body weight/day). At day 70 (Fig. S1B and D<sup>1</sup>) her VAS was 2, DLQI 3, blood pressure 136/85 mmHg, tacrolimus 18.1 µg/l and creatinine 123 µmol/l. Her itching was greatly reduced. In addition, tacrolimus made her hypertrichosis gradually disappear and she became less affected by sebaceous hyperplasia. She continued with oral tacrolimus until day 130 and then changed back to using cyclosporine 100 mg once daily in combination with tacrolimus 10 mg once daily over the following months. At day 145 the creatinine value was normal at 88 µmol/l, blood pressure 158/92 mmHg, and the unfortunate side-effects of hypertrichosis and sebaceous hyperplasia had returned.

#### DISCUSSION

Oral tacrolimus had a significant effect on this patient's skin disease, resulting in a dramatic reduction in itching and improvement in her dermatology-related quality

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of life. This is not surprising, since tacrolimus and cyclosporine share similar mechanisms of action; both are calcineurin inhibitors. The effect of cyclosporine in prurigo nodularis is documented in a study with 14 patients (7).

The main reason for choosing oral tacrolimus in our patient was that, although cyclosporine had a positive effect, it had the unfortunate side-effect of hypertrichosis, which was highly disturbing to this patient, who had dark red hair and light skin. Hypertrichosis is a frequent side-effect of cyclosporine therapy and has been reported in 30–95% of patients (8). The side-effect profile appears to be similar for tacrolimus and cyclosporine, with nephrotoxicity and hypertension as the most important side-effects (9, 10). Compared with oral cyclosporine hypertrichosis, hypertension and gingival hyperplasia are probably less pronounced in oral tacrolimus (10). Our patients had no hypertension on cyclosporine or on tacrolimus.

Two studies have earlier been reported (1, 2) of oral tacrolimus treatment in atopic dermatitis. A case series of 4 patients using 5 mg twice-daily for up to 14 months showed poor effect in 3 of the patients (2). An open-label study with 12 patients used, first, oral tacrolimus for 3 weeks, subsequently both oral and topical tacrolimus for 3 weeks, and finally topical tacrolimus alone for 8 weeks (1). This was found to be effective and well-tolerated in 10 of 12 adult patients with severe atopic dermatitis. As atopic dermatitis is highly itchy and is one of the co-morbidities of prurigo nodularis, these findings support the effect of tacrolimus in our case.

Our patient required high serum levels of tacrolimus in order to control her pruritus. She had previously needed high levels of cyclosporine to control her pruritus, and in 2011 she found that a dose of 10 mg/day oral tacrolimus was too low. Possible rare side-effects of cyclosporine and tacrolimus are serious infections and cancer (11). The patient was informed about possible side-effects, but because her skin disease was so debilitating, she was willing to take the medication under close monitoring. It is likely that the dose can be reduced in long-term use, but there are no studies on correct dosing in patients with prurigo nodularis. We would recommend starting with lower doses of oral tacrolimus in other patients with itchy skin diseases.

In conclusion, prurigo nodularis is a debilitating chronic itchy skin disease with limited treatment options. Our patient did not have typical nodular findings prior to treatment, but had prurigo papules, and her history was consistent with prurigo nodularis. Tacrolimus may act both on the immune system and directly on epidermal nerve endings. Despite the fact that tacrolimus is more expensive than cyclosporine, there may be cases in which treatment with tacrolimus is superior to treatment with cyclosporine, as in the present case.

*Conflicts of interest.* Tacrolimus (Prograf®) was provided by AstellasPharma Inc. for the 3 first months of the study.

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