Topical sirolimus for oral pemphigus vulgaris: 3 unresponsive cases

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Mucosal lesions greatly influence the quality of life in a substantial proportion of pemphigus vulgaris (PV) patients. Lesions are recurrent and frequently therapy resistant. Systemic corticosteroids may provide relief, but are often accompanied by debilitating systemic side effects. Therefore not only the use of systemic steroid-sparing drugs is important, but also the search for effective non-systemic topical therapies. Here, we report the use of topical sirolimus in 3 PV patients with predominant oral mucosal involvement.

In all three cases, the diagnosis PV was based on the detection of suprabasal acantholysis, intraepidermal depositions of IgG on keratinocyte cell surfaces, and the demonstration of circulating anti-desmoglein 3 antibodies by ELISA. All patients were female, age ranging from 31 to 51 years. All three patients had persistent painful erosions of the oral mucosa, lasting 4 to 6 months, with inadequate response to high dose steroids. One patient had also received azathioprine, dapsone and rituximab treatment, without sufficient effects. This patient furthermore suffered from steroid related side-effects including weight gain, facial swelling and fatigue. In addition, another patient had a history of hypertension and diabetes mellitus, whereby further treatment with steroids was not preferred. It was therefore decided to treat the patients with topical sirolimus, using 5 ml of a 1mg/ml sirolimus solution (Rapamune) twice daily as mouthwash. In one patient, sirolimus was used alongside a reduced prednisone dose of 20mg/d, while in the other two, no other medications were used. Blood sirolimus levels, measured in one patient after 8 days of treatment, were undetectable. The mouthwashes were well tolerated in all patients, without local irritation, and treatment was continued for 2 to 3 weeks for all patients. However, none of the patients showed improvements of their mucosal symptoms during this time. In fact, symptoms gradually worsened. It was therefore decided to stop further treatment, and switch to high dose steroids in combination with azathioprine. This gave improvement of mucosal symptoms in all three patients.

Sirolimus is used systemically as an immunosuppressive drug for kidney transplantation patients. Topical use of sirolimus has been reported to be beneficial for chronic erosive lichen planus patients, mediated probably through local anti-inflammatory effects. For pemphigus, studies suggest that pretreatment with a single intradermal injection of sirolimus locally protects keratinocytes against acantholysis by inhibiting pemphigus IgG mediated mammalian target of rapamycin (mTOR) signaling in neonatal mice. In line with this, a recent case report suggested systemic sirolimus, used alongside intravenous immunoglobulins, to be beneficial in a PV patient. Due to the rapid clinical improvements observed in this patient, it was concluded that besides a systemic immunosuppressive effect, sirolimus might indeed directly influence keratinocytes. One would expect this direct effect to also be achieved with topical therapy. This was not seen in the three patients we describe here. Instead, worsening of mucosal symptoms was observed. Possibly, the dose or duration of therapy used here was insufficient. However, a more concentrated sirolimus solution was not commercially available, and the severity of mucosal symptoms did not allow further continuation of local sirolimus therapy. Alternatively, the findings of mTOR signaling in a neonatal pemphigus mouse model may not apply to the human situation. In conclusion, these three cases underline that systemic immunosuppressive therapy is at present still the preferred treatment of pemphigus vulgaris. In addition, we propose that further studies are needed to more precisely evaluate the role of mTOR signaling in pemphigus patients.
References