Pachyonychia congenita (PC) is an autosomal dominant skin disorder caused by heterozygous mutations of the keratin genes KRT6A, KRT6B, KRT6C, KRT16 or KRT17. Patients typically present with dystrophic nails, leucokeratosis, cysts and painful palmoplantar keratoderma that can be both debilitating and disfiguring. Painful keratoderma is a common clinical presentation in patients with PC, especially in those with KRT6A and KRT16 mutations. Affected individuals often have difficulty ambulating, and require systemic pain medications. To date, there is no Food and Drug Administration (FDA)-approved treatment for PC. A number of topical and systemic treatments have previously been evaluated for painful plantar keratoderma, but none has been found to be efficacious. Frequently used management for plantar keratoderma in patients with PC includes regular grooming such as paring/trimming, as well as topical application of products containing salicylic acid, lactic acid or urea. Off-label use of botulinum toxin and topical and systemic retinoids has been tried without success. Consequently, PC is a disease with unmet medical needs, and a targeted therapy is needed for the treatment of painful plantar keratoderma. We report two patients treated with topical sirolimus cream with rapid improvement of pain and ability to ambulate.

Two unrelated white middle-aged women both presented with painful plantar keratoderma and dystrophic nails. Both patients had mild hyperlipidaemia and hypertension, but were otherwise healthy. Both patients carried a mutation in the KRT6A protein; Patient 1 had the mutation p.Glu472Lys and Patient 2 had p.Phe174Ser. Despite taking prescribed analgesia regularly, the patients were able to manage only seated office jobs because of severe foot pain. Patient 1 had difficulty ambulating for >5 min without assistance and was nearly wheelchair-bound. Their condition had failed to respond to multiple topical treatments containing salicylic acid and lactic acid.

Based on recent studies, we decided to start topical sirolimus treatment. To avoid systemic toxicities, we compounded 1% sirolimus ointment for both of our patients to be used twice daily on both feet (Fig. 1). The patients used an average of 2.5–4.5 mg sirolimus daily for about 4 months, and kept a daily diary to document the severity of pain upon standing or walking, their level of physical activity and their use of pain medications.

Patient 2 had notable improvement of symptoms and thinning of the keratoderma on both feet within 2 weeks. The overall severity of pain reduced rapidly within 4 weeks of initiating treatment (Fig. 2). Patient 2 also noted similar results. Both patients were able to ambulate much better without support, although increased pain was reported with increased daily activities, especially on the preferred weight-bearing side. Because of the reduced keratoderma, they also required fewer podiatry sessions. Two months after treatment initiation, the thickness and size of the callosus was markedly reduced (Fig. 1b). Laboratory studies, including complete blood cell counts, metabolic panels, lipid profiles and serum sirolimus level were obtained at each clinic visit for three consecutive months, with no systemic exposure or toxicities detected. The clinical response was consistent during the 4 months of treatment. Patient 2 reported that her symptoms started to worsen approximately 2 weeks after the treatment was discontinued. Our preliminary results suggest that topical sirolimus could be a safe and effective treatment for painful keratoderma in PC.

Sirolimus, or rapamycin, is a mammalian target of rapamycin (mTOR) inhibitor. As an immunosuppressant,
it is approved by the FDA to prevent organ rejection post-transplantation and to prevent re-stenosis of drug-eluting stents in the USA. In addition to being immuno-suppressive, sirolimus also demonstrates antineoplastic activity, exerted through downregulation of angiogenesis and cell proliferation, and it also has anti-angiogenic activity.

A recent proof-of-concept study showed that sirolimus binds upstream from the 5' end of several keratin genes that contain a terminal 5' oligopyrimidine tract, such as KRT6 and KRT16, thereby inhibiting their expression and blocking the translation of inducible keratins. A previous study demonstrated reduced production of nonfunctional keratin and clinical improvement when systemic sirolimus was administered to patients with PC, supporting the effectiveness of this targeted approach. Patients with PC treated with oral sirolimus not only had reduced pain and thickness of plantar keratoderma, but also had improvement in their ambulation ability and quality of life. However, long-term use of systemic sirolimus results in potential adverse effects (AEs) such as opportunistic infections, elevated cholesterol and mucosal ulceration.

As with any genetic disorder, withdrawal of therapy resulted in rapid recurrence of the disease, and continued dosing is required to maintain clinical benefit.

Topical therapy therefore is ideal in minimizing systemic exposure and AEs. The clinical benefits we observed using topical sirolimus confirms that the medication could readily penetrate through the keratoderma, exerting a rapid effect within 3 weeks. The safety and tolerability noted in our patients were consistent with the literature. Unlike in animal models, systemic sirolimus exposure is less likely to reduce affected body surface area or lower body mass index in humans.

In summary, our results suggest that topical sirolimus could be a safe and effective treatment for painful keratoderma in patients with PC. To our knowledge, this is the first report of using topical sirolimus treatment for PC. While the effects observed are encouraging, large-scale placebo-controlled clinical trials are needed to validate the safety and effectiveness of this novel treatment. Owing to the central role of mTOR complex in angiogenesis and cell proliferation, topical sirolimus may have broader clinical applications.

Acknowledgement

We thank the Pachyonychia Congenita Project for their generous support and assisting patients with the cost of their medication.
Learning points

- PC is a hereditary autosomal dominant disease with debilitating painful keratoderma, especially in individuals with KRT6A and KRT16 mutations.
- Currently, there is no effective medical treatment for painful keratoderma in patients with PC.
- Sirolimus can reduce defective keratin production in the skin.
- Topical sirolimus may be administered safely without notable systemic toxicities.

Figure 2 (a,b) Patient 2. Significant pain reduction occurred within 2–3 weeks after initiation of topical treatment according to the patient’s daily diary: reduction of (a) standing pain and (b) overall pain in both feet (blue, left foot; red, right foot).

References


CPD questions

Learning objective

To gain up-to-date knowledge of the comorbidities of patients with pachyonychia congenital and the common side-effects of sirolimus.

Question 1

Which one of the following is the most debilitating manifestation among patients with pachyonychia congenita?

(a) Onychodystrophy.
(b) Multiple cysts.
(c) Leucokeratosis.
(d) Keratoderma.
(e) Disfigurement.

Question 2

What are the common side effects of sirolimus?

(a) Infection.
(b) Hyperglycaemia.
(c) Hyperlipidaemia.
(d) Mucosal ulcers.
(e) All of the above.

Instructions for answering questions

This learning activity is freely available online at http://www.wileyhealthlearning.com/ced

Users are encouraged to

• Read the article in print or online, paying particular attention to the learning points and any author conflict of interest disclosures
• Reflect on the article
• Register or login online at http://www.wileyhealthlearning.com/ced and answer the CPD questions
• Complete the required evaluation component of the activity

Once the test is passed, you will receive a certificate and the learning activity can be added to your RCP CPD diary as a self-certified entry.

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