

Received Date : 11-Jun-2015  
Revised Date : 04-Oct-2015  
Accepted Date : 18-Nov-2015  
Article type : Research Letter

## **Alitretinoin: treatment for refractory palmoplantar keratoderma**

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**Type of study:** Clinical trial (Therapeutic trial in one patient)

**Keywords:** Alitretinoin; Acitretin; Palmoplantar keratoderma; Mal de Meleda; Side effects; Contraception

**IRB approval:** Not required.

**Funding sources:** None.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.14327

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**Conflicts of interest:** None declared.

**Prior presentation:** None.

**Running head:** Alitretinoin: treatment for refractory palmoplantar keratoderma

*DEAR EDITOR*, Mal de Meleda (MDM) is an autosomal recessive form of palmoplantar keratoderma caused by mutations in the *ARS* gene, encoding SLURP-1.<sup>1</sup> It has been reported that etretinate and acitretin, which are aromatic retinoids, are effective treatment modalities for MDM.<sup>2</sup> However, early and long-term use of these retinoids are associated with several well-known adverse effects, such as dryness, teratogenicity and liver toxicity.<sup>1</sup>

A 20-year old woman, diagnosed with MDM by identification of gene mutation in SLURP-1 in our previous report,<sup>1</sup> presented with extensive palmoplantar hyperkeratosis which extended to the dorsal surfaces of the hands and feet since birth. She also complained of frequent recurrence of athlete's foot with malodor. Previous treatments included keratolytic ointments, topical steroid, and topical and systemic antifungal agents. Over the past 30 months, oral acitretin, 10 or 20 mg/day, was administered additionally because her increased cosmetic concerns. A modest improvement of palmoplantar hyperkeratosis was observed, but most of lesions did not show significant changes (Fig. 1a, 1b). Due to mucocutaneous discomfort and the need of a long period of contraception, acitretin was replaced by new alitretinoin. After 3 months of treatment with alitretinoin 30 mg/day, her symptoms and signs improved significantly. Especially, the extent and thickness of hyperkeratosis were markedly reduced (Fig. 2a, 2b). In addition, she reported less mucocutaneous side effects after drug replacement.

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Advanced lesions of MDM may show conical tapering of the fingertips, sometimes leading to spontaneous amputation of the digits, which justifies early interventions.<sup>1</sup> Since MDM is a rare genetic disorder, no standardized treatment protocol has yet been established. There have been some reports on the efficacy of acitretin in MDM.<sup>1,2</sup> Acitretin has been used for treating severe forms of the keratoderma. In a variety of disorders of keratinization, it normalizes epidermal cell proliferation, differentiation and cornification.<sup>3</sup> Importantly, however, early and prolonged use of retinoids is associated with several adverse effects such as cheilitis, hepatotoxicity and lipid derangement.<sup>2,3</sup> Especially, because of the teratogenicity of acitretin, women taking acitretin should use contraception for 2-3 years after discontinuation of treatment.<sup>3</sup>

Alitretinoin (*9-cis-retinoic acid*) is a novel pan-agonist retinoid, which binds to retinoic acid receptors (RAR) A and X, in contrast to acitretin which binds to only RAR A.<sup>4</sup> Alitretinoin is thought to have more potent anti-inflammatory and immunomodulatory properties compared to other retinoids, by directly affecting cytokine production in keratinocyte and suppression of leukocyte activation.<sup>5</sup> Alitretinoin is also known to occur less mucocutaneous adverse effects than other retinoids. In addition, alitretinoin requires only 1 month of contraception after therapy is completed, so it is considered a beneficial alternative treatment of acitretin for women of childbearing age.<sup>4,5</sup> Recently, Raone et al.<sup>4</sup> reported a case of 41-year old woman with hereditary punctate palmoplantar keratoderma, showing significant improvement with alitretinoin. By comparison, our patient is an unmarried 20-year-old woman with more severe forms of keratoderma, and her lesions showed a greater improvement. In conclusion, our case reinforces the concept that alitretinoin could be a new, effective and promising treatment option for refractory palmoplantar keratoderma, including MDM.

## Abbreviations used

MDM: Mal de Meleda

RAR: retinoic acid receptors

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## Figure Legends

Figure 1. Patient showed waxy ivory-yellow, palmoplantar hyperkeratotic plaques on both palms (a) and soles (b) before drug replacement.

Figure 2. After 3 months of treatment with alitretinoin, the extent and thickness of palmoplantar hyperkeratosis decreased markedly, respectively (c, d).

