Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2023;32:191-195
doi: 10.15570/actaapa.2023.34

Efficacy of alitretinoin in the treatment of Darier disease: a case report

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Abstract

Darier disease is a rare autosomal dominant genodermatosis that initially first presents in adolescence with scaly reddish brown keratotic papules and plaques with a seborrheic and intertriginous distribution. The absence of specific targeted medications complicates the treatment process, and managing resistant cases can prove challenging due to recurrent exacerbations that may result in serious complications such as secondary bacterial and viral infections. Treatments of choice include antiseptics, topical corticosteroids, and systemic retinoids, mainly acitretin and isotretinoin. We report the case of a female patient with Darier disease that was unsuccessfully treated with acitretin and isotretinoin but showed significant improvement with alitretinoin. Previous reports on the efficacy of alitretinoin in Darier disease are reviewed.

Keywords: Darier disease, alitretinoin, retinoids, systemic treatment, genodermatosis

Received: 10 September 2023 | **Returned for modification:** 16 October 2023 | **Accepted:** 23 November 2023

Introduction

Darier disease (dyskeratosis follicularis) is a rare genodermatosis characterized by persistent confluent greasy papular keratotic skin lesions that predominantly occur in seborrheic areas of the chest, back, forehead, scalp, nasolabial folds, ears, and armpits (1, 2). It can also affect intertriginous areas, the nails, and the mucous membranes. Its prevalence is estimated to range between 1:30,000 and 1:100,000 (2).

This autosomal dominant disorder is associated with numerous heterozygous mutations in the *ATP2A2* gene. These mutations result in malfunctioning of the sarco/endoplasmic reticulum Ca^{2+}-ATPase isoform 2 (SERCA2). SERCA2 is a calcium pump of the endoplasmic reticulum (ER) that transports Ca^{2+} from the cytosol to the lumen of the ER (3). Calcium depletion leads to loss of epidermal cell adhesion and abnormal keratinization of the skin (4). Acantholysis and focal dyskeratosis are the main histopathologic features of Darier disease (4, 5).

The disease itself leads to a significant decrease in the quality of life (4). According to new observations, Darier disease should be considered a systemic condition because it is associated with numerous non-dermatological diseases, such as neuropsychiatric disorders, mild intellectual disability, epilepsy, and psychiatric disorders (bipolar disorder and schizophrenia), as well as diabetes and heart failure (4, 5).

Case report

A 59-year-old female with hypothyroidism, hyperlipidemia, and papular keratotic skin lesions on her trunk, sacral area, forearms, and anterior thighs was first diagnosed with Darier disease in adolescence. The diagnosis was confirmed by histopathological examination. In addition, one of her two sons is also affected with Darier disease.

During many years of follow-up at our department, her disease went through repeated cycles of exacerbation and improvement. She was mainly treated with topical corticosteroids, topical retinoids, and emollients. However, in the past 3 years, the disease was poorly controlled most of the time. Skin lesions were widespread on the trunk and extremities, with pruritic and painful crusted reddish brown keratotic papules, coalescing into plaques with malodorous maceration in the submammary and inguinal areas. She also exhibited typical nail lesions with longitudinal ridges and numerous papules on the hard palate. Due to associated hypothyroidism and hyperlipidemia, she was regularly treated with levothyroxine and rosuvastatin tablets.

She had been receiving acitretin for 3 years, with a daily dose up to 25 mg/kg, which was discontinued due to profound hair loss resulting in almost total alopecia and severe paronychia. Despite receiving all these treatments, she experienced frequent bacterial superinfections with mixed Gram-positive and Gram-negative bacteria, which often required treatment with systemic antibiotics.

In 2016, the patient received treatment with isotretinoin, initially at a daily dose of 30 mg, which was later reduced to 20 mg. During this treatment, paronychia was observed without other significant side effects. However, frequent exacerbations of the disease persisted, leading to discontinuation of the medication after 1 year. In 2018, she was admitted to our department due to a severe exacerbation (Fig. 1), which was further complicated by staphylococcal sepsis and generalized eczema herpeticum. Prolonged intravenous antibiotic and antiviral therapy was needed.

Because the patient did not respond well to conventional treatments, she was offered off-label treatment with alitretinoin. She agreed, and an initial dose of 30 mg was initiated. The first signs of improvement were visible after 1 month of treatment with reduction in pain and burning sensation. Further follow-ups in the following months found regression in skin lesions to mildly scaly erythema (Fig. 2). Maceration of the skin folds was greatly diminished. In addition, the patient did not report any significant side effects, and the laboratory values (complete blood count, urea, creatinine, lipid test, liver tests, and thyroid test function) were within normal ranges at all times. However, when we tried to taper off the dosage of alitretinoin, exacerbation of the lesions started to occur, leading to a return to the initial daily dose of 30 mg.

In the fall of 2021, the patient contracted COVID-19 with respiratory failure, requiring mechanical ventilation. During her stay

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in the intensive care unit, alitretinoin was discontinued. After discharge, she experienced a severe and widespread relapse of Darier disease, and she resumed alitretinoin treatment at a daily dose of 30 mg, which led to improvement. Throughout subsequent follow-ups, we observed significant long-term improvement without recurring secondary skin infections. At the time of writing this case report, the patient is receiving alitretinoin at a daily dose of 20 mg.

Discussion

Darier disease is notoriously difficult to treat due to the absence of targeted treatments. Treatment outcomes are often unsatisfactory, and inflammation frequently arises from secondary skin infections. Patients have an increased risk for secondary infections caused by *Staphylococcus aureus*, *Candida* spp., and herpes simplex virus, the latter often progressing to widespread eczema herpeticum (2). Infections may lead to exacerbation of symptoms with severe maceration and erosions, as well as systemic complications, as was observed in our patient.

Currently, no gold-standard treatment exists for Darier disease. Numerous reported modalities for addressing Darier disease can be categorized as either topical or systemic interventions (1, 2, 4, 6–13). Fundamental measures include the adoption of cool clothing and avoidance of warm environments, along with the regular application of moisturizing agents containing urea or lactic acid, and the utilization of antiseptic washes (14). Topical interventions involve the use of corticosteroids and retinoids such as adapalene, tazarotene, and tretinoin, which have proved effective in diminishing hyperkeratosis (4). Given the common occurrence of irritation as a side effect, topical retinoids can be employed concomitantly with emollients and topical corticosteroids to mitigate inflammation. Case reports also suggest successful outcomes with 5-fluorouracil, pimecrolimus, 3% diclofenac sodium, and vitamin D3 analogue (calcipotriol and tacalcitol) when combined with sunscreen (2, 15, 16). Other possible therapeutic modalities include surgery, laser, photodynamic therapy, and botulinum toxin injections (2, 17).

Within systemic treatment modalities for treating Darier disease, retinoids (acitretin, isotretinoin, etretinate, and alitretinoin) are the most efficacious. These agents demonstrate effectiveness in diminishing hyperkeratosis, smoothing papules, and mitigating lesion odor (3, 4, 18, 19). However, their use is constrained by the frequent occurrence of side effects and the inherent risk of

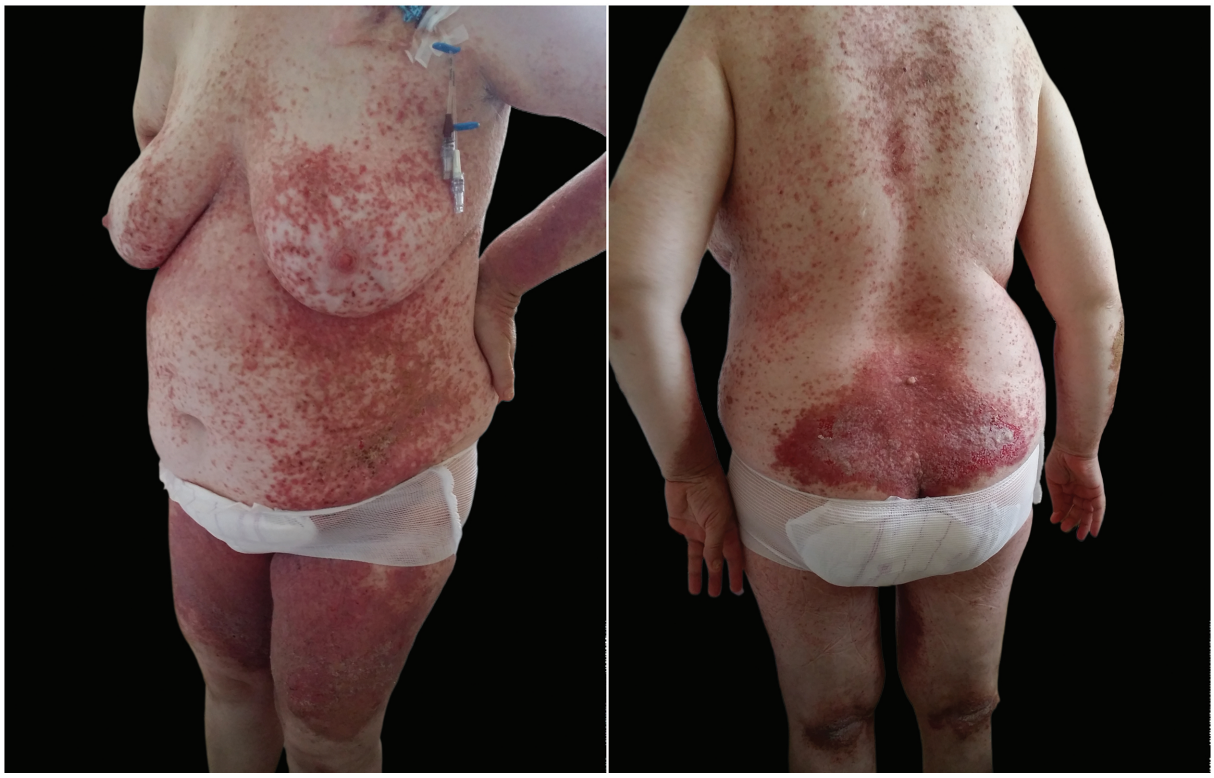

Figure 1 | Severe exacerbation of Darier disease, complicated by secondary staphylococcal infection and eczema herpeticum.

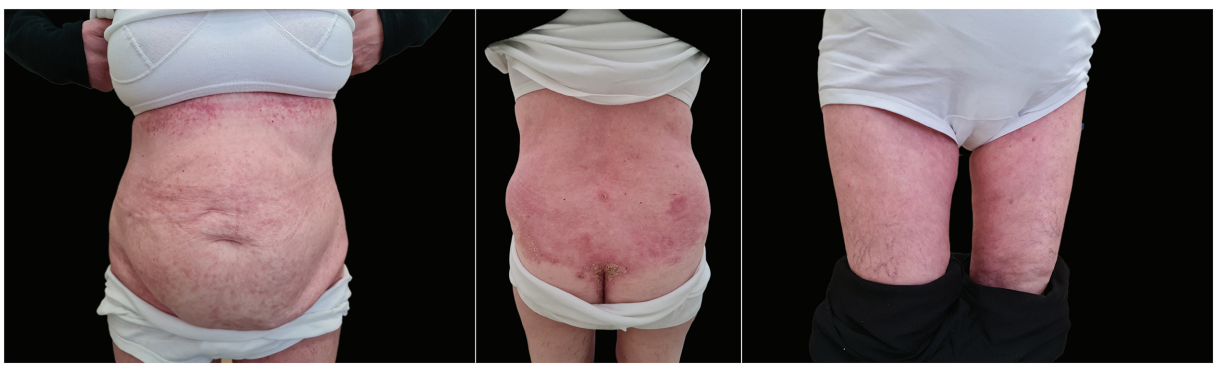

Figure 2 | Improvement of skin lesions after 2 years of treatment with alitretinoin.

teratogenicity (2, 20). Doxycycline and cyclosporin have also been used with variable clinical response (21, 22). Systemic corticosteroids can only be recommended for severe exacerbations and for limited periods of several weeks (2).

Retinoids have structural or functional similarities with vitamin A, binding to several classes of proteins, including retinoid-binding proteins and retinoid nuclear receptors (23). This ultimately leads to the activation of specific regulatory regions of DNA (retinoic acid response elements) involved in cell growth regulation, differentiation, and apoptosis (23). Based on their molecular structure and receptor selectivity, they are classified into four generations (23). First-generation retinoids are formed by changing the polyene side chain and polar end group of vitamin A. The second generation is characterized by replacing vitamin A's cyclic end group with various substituted and non-substituted ring systems, and the third generation involves cyclization of the polyene side chain (23). In the fourth generation there is the recently approved selective retinoic acid receptor-γ agonist trifarotene (24). Isotretinoin and alitretinoin belong to the first class, and acitretin to the second.

Retinoids help normalize cell turnover and cell cohesion, inhibit cell proliferation, and have anti-inflammatory effects (4). They may reduce hyperkeratosis in Darier disease but do not target the primary pathogenesis. In clinical practice, acitretin and isotretinoin are most often used in severe Darier disease (4).

The recommended initial daily dose of acitretin is 0.2 to 0.3 mg/kg, which should slowly be increased up to the dose needed for optimal clinical improvement (2). However, this dose can be individually different. In our patient, the discontinuation of acitretin was necessitated due to severe side effects. In clinical practice, isotretinoin was used in 0.5 mg/kg daily dose (2). The most probable reason for lack of efficacy of acitretin and isotretinoin in our patient was the low daily dose, which did not exceed 0.3 mg/kg with acitretin and was lower than 0.5 mg/kg with isotretinoin. Although a higher dose of isotretinoin might have been a potential option, the presence of minor side effects led us to opt for discontinuation and transition to alitretinoin instead.

Alitretinoin (9-cis retinoic acid) is a first-generation retinoid that acts as an agonist for both retinoic acid and retinoic X receptors (25). It was shown to affect keratinization and differentiation and to have immuno-modulatory, antiproliferative, and anti-inflammatory effects, and it is approved for treatment of hand eczema (3, 26).

Potential side effects of alitretinoin include headaches, abnormal serum lipid and liver enzyme levels, blood cell disorders, decreased levels of thyroid hormones, conjunctivitis, muscle and joint pain, skin dryness, higher risk of sunburn, psychiatric disturbances, alopecia, rash, and exfoliative dermatitis (26).

The decision for alitretinoin was based on several previous reports in the literature with favorable treatment results. It was also prescribed due to its perceived superior safety profile compared to other retinoids, especially considering that the patient experienced side effects while using an alternative retinoid. Consequently, she reported none of the aforementioned potential side effects associated with alitretinoin treatment. Regular rosuvastatin treatment likely prevented hyperlipidemia.

The short half-life of alitretinoin (similar to isotretinoin) allows its use in women of childbearing potential with the possibility of conception only 1 month after completing treatment. In contrast, pregnancy must be avoided for at least 2 years following the discontinuation of acitretin.

At the time of writing this article, a search for "Darier" and "alitretinoin" on PubMed yielded 10 reported cases (1, 3, 19, 27–31). Three males and seven females 18 to 48 years old were treated with 30 mg/day of alitretinoin. In eight cases out of 10, the treatment led to improvement, and one showed a partial response when isotretinoin was added. The reported delay in efficacy ranged from 2 weeks (29) to 32 weeks (31). The longest reported relapse-free period with ongoing therapy was 3.5 years.

In the referenced studies (1, 3, 19, 27–31), all patients received alitretinoin at a daily dose of 30 mg. For some patients, attempts were made to adjust the dose or discontinue it altogether, but in all cases except one a relapse occurred, leading to the reinstatement of the initial dose. The reported treatment duration ranged from 1 to 42 months (Table 1). Adverse effects were infrequent and included temporary headache, aseptic cellulitis of the breast, erosions, fever, hair dryness, hair loss, and pyogenic granulomas. The majority of patients did not experience any side effects. Compared to previous reports, follow-up in our patients has been the longest, more than 5 years.

Conclusions

Our case supports previous reports that alitretinoin is a viable therapeutic option for patients with Darier disease, offering improvement without considerable side effects. Because of its short half-life, it can be considered in young women of childbearing potential.

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Table 1 | **Review of case reports of Darier disease treated with alitretinoin.**

Reference	Sex	Alitretinoin dose (mg/day)	Delay before improvement	Was dose tempered?	Reported remission time on medication (months)	Remission duration after cessation (months)	Adverse effects	Skin areas involved
1	M	30	16 weeks to complete remission	Yes, relapse	42	Ongoing	No	› 50% body surface
30	F	30	A few weeks	Yes, 30 mg every 3 days	15	Ongoing	Mildly elevated total cholesterol and low-density lipoprotein levels	Chest, upper back, neck, face, hands
29	F	30	2 weeks	Discontinued, relapse	1	4	No	Generalized (in relapse)
19	F	30	Skin lesions and itching on the trunk disappeared within 6 months	Discontinued after 8 months, reinstated after 7 months	NA	7	Dryness of the eyes, moderate, reversible hair loss	Trunk, dorsa of both hands
	F	30	Skin lesions markedly improved after 4 months	NA	NA	NA	3 weeks of headache	Trunk, skin folds
3	F	30	4 weeks	Discontinued after 3 months and reduced frequency attempted, relapse	18	Ongoing	No	Trunk, chest, upper thighs
	F	30	6 weeks	NA	4	Ongoing	NA	Abdomen, chest, lower back and legs
28	M	30	1 week	NA	52 (relapse after 36 weeks due to local therapy cessation)	NA	No	Chest, back, face, neck
27	F	30	Moderate initial improvement (time not specified)	Discontinued after 12 months	NA	NA	Aseptic cellulitis of the breast, enlargement of pyogenic granulomas, several spring/summer recurrences of skin disease with extension to areas not previously involved, erosions, fever	Periodic recrudescence, pyogenic granulomas on the left breast
31	M	30	32 weeks	NA	NA	NA	NA	Trunk, both upper and lower extremities
Our case	F	30	4 weeks	Yes, relapse	60	Ongoing	No	Trunk, sacral area, forearms, anterior thighs

M = male, F= female, NA = not applicable.