Combination of alitretinoin and topical 5-fluorouracil in Darier disease

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INTRODUCTION

Darier disease (DD) is a rare autosomal dominant genodermatosis that is clinically characterized by papular keratotic lesions predominant in seborrheic areas (chest, back, armpits). Bacterial and viral superinfections are common complications. Histologically, DD lesions correspond to dyskeratosis and suprabasal acantholysis. Many heterozygous mutations in ATP2A2 are reported to be involved in this disease. Therapeutic options are numerous including retinoids (acitretin) and suited treatment against bacterial and viral superinfections. Other treatments reported are cyclosporine, vitamin A, systemic corticosteroids, topical 5-fluorouracil (5-FU), keratolytics with urea, topical retinoids, topical corticosteroids, or interventional treatment (laser, dermabrasion, excision). However, this disease is very often a therapeutic challenge, as the effectiveness of the available treatments is often partial, with a critical impact on patients' quality of life.

Alitretinoin is a retinoid recently approved for the treatment of chronic hand eczema. It has antiproliferative, anti-inflammatory and immunomodulatory properties. We report an original case of a man with DD efficiently treated with alitretinoin combined with topical 5-FU. To our knowledge, this is the first report of this treatment combination in DD.

Abbreviations used:

DD: Darier disease
5-FU: 5-fluorouracil

CASE REPORT

A 43-year man had a DD diagnosed at the age of 15. His mother, his uncle, and maternal grandfather were also affected. He had confluent keratotic papules and plaques on the armpits, inguinal folds, and head and neck area. The area affected was greater than 50% of body surface area (Fig 1).

Previously, he received several treatments: acitretin, 10 to 35 mg/d over 7.5 years, then systemic and topical corticosteroids without any control of the disease. The patient had frequent DD exacerbations associated with superinfections. Samples were positive for *Staphylococcus aureus* and herpes simplex virus 1 and 2, so the patient received several antibiotics and a long-term preventive dose of valacylovir.

Finally, because of the absence of other therapeutic options and the repercussion on daily quality of life, off-label alitretinoin treatment was proposed to the patient. After his approval, it was started at the dose of 30 mg/d combined with topical 5-FU. The tolerance was excellent; in particular, the patient had no cutaneous xerosis, no skin irritation or cheilitis, no hair loss, and no liver abnormalities. The patient achieved a clinically complete remission of DD in 4 months (Fig 2). The dose of alitretinoin was tapered to 20 mg/d but then rapidly reincreased to 30 mg/d because of an exacerbation of the disease. Alitretinoin treatment is still ongoing with a follow-up of 3.5 years at the same dose. Topical 5-FU was applied once daily on the most affected areas, such

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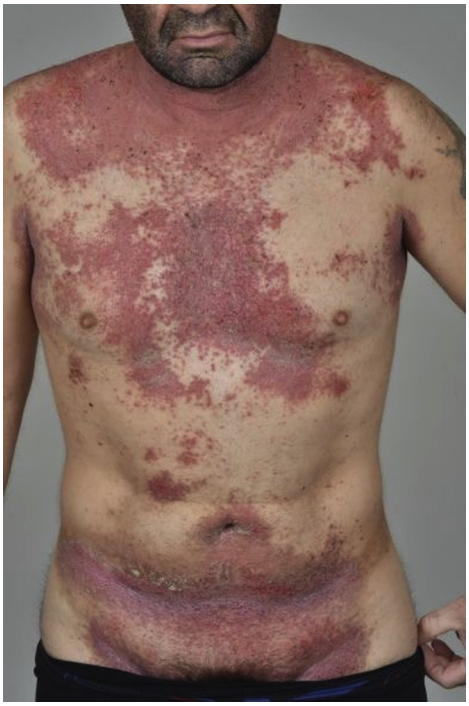

Fig 1. Typical aspect of Darier disease before treatment with large papular keratotic closets of the folds.

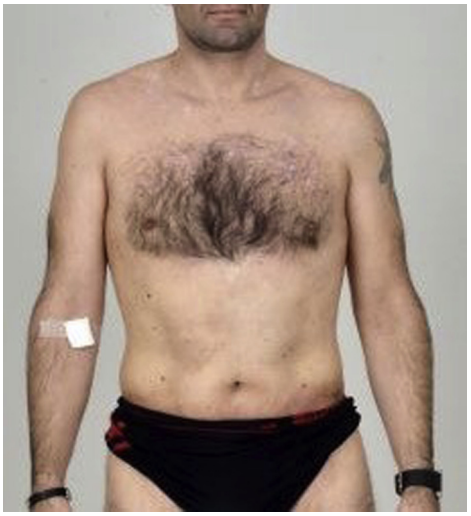

Fig 2. Clinically complete remission after 4 months of alitretinoin combined with topical 5-FU.

as large skin folds and neck (5%-10% body surface area) for 6 months. It has been used up to now occasionally (less than 20 g/mo).

DISCUSSION

We report an original case of DD successfully treated with of alitretinoin and topical 5-FU daily.

Retinoids are known for their action on the cellular processes of proliferation, differentiation, and keratinization of the epidermis. There are 3 generations of retinoids: alitretinoin belongs to the first one and acitretin to the second. Both are able to bind with several retinoid receptors (retinoic acid receptor and retinoic X receptor), whereas the third generation interacts with selected receptors. In addition, acitretin is an acid metabolite of etretinate and is the natural ligand of retinoic acid receptor. Alitretinoin (9-cis-retinoic acid) is an endogenous hormone related to vitamin A. It is indicated for the treatment of chronic hand eczema. In our case, acitretin was used previously but with a mild and short efficacy; therefore, we proposed an off-label treatment with alitretinoin.

Fewer than a dozen DD patients treated with alitretinoin are reported in the literature. Seven women and a man 18 to 41 years old received 30 mg/d of alitretinoin. This treatment led to an improvement in 7 cases and failed in 1. The delay of efficacy ranges from 4 weeks to 6 months. In reported cases, treatment was suspensive with a follow-up of 4 to 18 months (Table I).[1-6]

The use of topical 5-FU alone or combined with corticosteroids (n = 1) or acitretin (n = 2) was previously published in 10 observations of DD with significant improvement reported in 8 of 10 patients but never combined with alitretinoin (Table II).[7-11] 5-FU's mode of action is unclear, but an impact on the intracytoplasmic calcium has been hypothesized to improve dyskeratosis.

To our knowledge, our case is the first one describing the combination of alitretinoin and topical 5-FU in DD. The exacerbation of the disease when reducing the doses of alitretinoin and the absence of relapse when decreasing 5-FU until very few applications argue for the predominant role of alitretinoin in the control of the illness.

Another originality of our case is the long-term use of alitretinoin (3.5 years without any relapse including the absence of superinfection by bacteria or virus), whereas the longest use of retinoids in DD described is 1.5 years. In our case, we cannot conclude to the specific efficacy of 5-FU, as this treatment was started with alitretinoin, and the patient is still on complete remission with occasional use of it. The cost for 3.5 years of treatment with alitretinoin is almost 20328 € ($23,894) and almost 1600 € ($1880) for topical 5-FU (for our patient).

According to our case, alitretinoin combined with topical 5-FU seems to be an interesting option in patients with DD, as it can allow a durable clinically

Table I. Darier disease cases treated with alitretinoin

Study	Sex (M/F)	Age (y)	Significant improvement*	Delay before significant improvement (wks)	Duration of remission under treatment (mos)	Duration of remission after stopping treatment (mo)
Current case	M	43	Yes (CR)	16	42	Treatment ongoing
Shreberk-hassidim et al[1]	F	23	Yes*	NA	15	Treatment ongoing
Anuset et al[2]	F	38	Yes*	2	1	4
Letulé et al[3]	F	37	Yes*	NA	8	7
	F	33	Yes*	16	NA	Treatment ongoing
Zamiri and Munro[4]	F	41	Yes*	4	18	Treatment ongoing
	F	39	Yes*	6	4	Treatment ongoing
Barnstedt[5]	M	18	Yes*	4	13	NA
Balestri et al[6]	F	30	No	NA	NA	NA

NA, Data not available.
*Significant improvement was not scored in any publication. Various terms were used: *major cutaneous improvement*, *significant improvement*, *marked improvement*.

Table II. Darier disease cases treated with topical 5-FU

Study	Sex (M/F)	Age (y)	Treatment	Delay before significant improvement (wks)	Duration of remission under treatment (mo)
Current case	M	43	5 FU + alitretinoin	16	42
Le Bidre et al[7]	F	16	5-FU	3	11
	F	59	5-FU	16	13
	F	29	5-FU	1.5	3
Schmidt et al[8]	M	39	5-FU	Two of 4 patients exhibited improvement in 4 weeks	NA
	F	73	5-FU		
	F	57	5-FU		
	F	47	5-FU		
Yoon et al[9]	F	20	5-FU	4	NA
Knulst et al[10]	F	37	5 FU + acitretin	3	6
	M	58	5-FU + acitretin	2	2
Velasco and Guillet[11]	M	55	5 FU + topical corticosteroid	4	5

NA, Data not available.

complete remission with a good tolerance. A larger study is needed to confirm the efficacy of this combination in this chronic disease with limited therapeutic options.

REFERENCES

1. Shreberk-hassidim R, Sheffer S, Horev L, Zlotogorski A, Ramot Y. Successful treatment of refractory Darier disease with alitretinoin with a follow up of over a year: a case report. *Dermatol Ther*. 2016;29(4):222-223.
2. Anuset D, Goutorbe C, Bernard P, Reguiai Z. Efficacy of oral alitretinoin for the treatment of Darier disease: a case report. *J Am Acad Dermatol*. 2014;71(2):46-48.
3. Letulé V, Herzinger T, Ruzicka T, Molin S. Treatment of Darier disease with oral alitretinoin. *Clin Exp Dermatol*. 2013;38(5):523-525.
4. Zamiri M, Munro CS. Successful treatment with oral alitretinoin in women of childbearing potential with Darier's disease. *Br J Dermatol*. 2013;169(3):709-710.
5. Barnstedt SE. Successful treatment of Darier disease with oral alitretoin. *Hautarzt*. 2012;63(2):139-142.
6. Balestri R, Patrizi A, Bardazzi F. Alitretinoin and Darier disease: "all that glisters is not gold" *J Am Acad Dermatol*. 2015;72(2):363-364.
7. Le Bidre E, Delage M, Celerier P, De Muret A, Lorette G. Efficacy and risks of topical 5-fluorouracil in Darier's disease. *Ann Dermatol Venereol*. 2010;137(6—7):455-459.
8. Schmidt H, Ochsendorf FR, Wolter M, Geisslinger G, Ludwig RJ. Topical 5-fluorouracil in Darier disease. *Br J Dermatol*. 2008;158(6):1393-1396.
9. Yoon TY, Kim JW, Kim MK. Successful treatment of Darier disease with topical 5-fluorouracil. *Br J Dermatol*. 2006;154(6):1210-1212.
10. Knulst AC, De La Faille HB, Van Vloten WA. Topical 5-fluorouracil in the treatment of Darier's disease. *Br J Dermatol*. 1995;133(3):463-466.
11. Velasco S, Guillet G. Improvement of Darier's disease on treatment with topical 5-fluorouracil. *Ann Dermatol Venereol*. 2006;133(4):366-368.