

Alitretinoin and hair texture changes

Introduction

Alitretinoin (Toctino®) is a vitamin A derivative that belongs to the systemic retinoids. Alitretinoin is indicated for use *in adults who have severe chronic hand eczema that is unresponsive to treatment with potent topical corticosteroids*. The duration of treatment (30 mg once daily, or 10 mg when experiencing ADRs) usually is 12-24 weeks, depending on response. Alitretinoin was granted marketing authorization in the Netherlands in 2009 (1). Patients in whom the eczema has predominantly hyperkeratotic features are more likely to respond to treatment than in those in whom the eczema predominantly presents as vesicular hand eczema.

There is a difference between kinked hair and curled hair. However, kinking can lead to a curly appearance of the hair. Curling of the hair is the result of an oval hair shaft, which grows out the scalp under an angle. The amount of disulfide bonds between the hair proteins and hair shaft give rise to a certain degree of curling of the hair. With kinking of the hair, the hair looks curly due to torsion and irregularities in hair structure. Hair thinning can cause kinking of the hair. Why hair thinning may cause kinking of the hair is not known, since factors determining the different hair shapes are not completely understood. Factors that may be implicated include change in the shape of the hair follicle during miniaturization, irregularities of mitosis within the hair bulb, and changes in the arrangement of the keratin filaments within the hair shaft (2).

In the SmPC of alitretinoin, alopecia is mentioned as an adverse effect. Hair texture changes are not described (1). However, hair texture changes are mentioned in SmPCs of other systemic retinoids, such as isotretinoin and acitretin (3;4).

Reports

From 5 January 2016 to 10 September 2017 the Netherlands Pharmacovigilance Centre Lareb received two reports of hair texture changes associated with the use of alitretinoin. The reactions were coded with the MedDRA® terms 'hair texture abnormal' or 'straight hair curled'.

Report 211927

This report from a consumer concerns a female aged 51-60 years, with hair texture abnormal (diffuse curly hair) following administration of alitretinoin for drug use for unknown indication with a latency of 9 months after start. The dose for alitretinoin was reduced to 10 mg. The patient outcome is unknown. Concomitant medication was tramadol*. There is no known medical history and no known past drug therapy.



Pictures used with permission of the patient

* The Dutch SmPC of tramadol does not report hair texture abnormalities as adverse reactions (5).

Report 246683

This report from a consumer concerns a female aged 41-50 years, with straight hair which curled and alopecia (diffuse) following administration of alitretinoin 30 mg for hand eczema with a latency of 5 months after start. The dose for alitretinoin is not changed. At time of reporting, 9 months later, the patient's hair has not changed back to straight. Concomitant medication was not reported. The patient mentioned her hair started changing and falling out after approximately half a year and that the change was visible at the root of the hair. There is no known medical history and no known past drug therapy.



Pictures used with permission of patient

Other sources of information

SmPC

The Dutch SmPC of alitretinoin mentions alopecia as a commonly occurring adverse reaction. Hair texture changes are not mentioned as an adverse reaction (1).

In the Dutch SmPCs of the other systemic retinoids isotretinoin, acitretin, tretinoin and bexarotene, different hair disorders are mentioned, which are described in table 1 (3;4;6;7).

Table 1. Hair disorders mentioned in §4.8 of the Dutch SmPCs of systemic retinoids (3;4;6;7).

Drug	Adverse reaction	Occurrence
Alitretinoin	Alopecia	Common (1-10%)
Tretinoin	Alopecia	Very common (>10%)
Isotretinoin	Alopecia	Rare (0,01-0,1%)
	Hair disorders	Very rare (<0,01%)
	Hirsutism	Very rare (<0,01%)
Acitretin	Alopecia	Very common (>10%)
	Abnormal hair texture	Common (1-10%)
Bexarotene	Alopecia	Common (1-10%)
	Hair abnormality	Uncommon (0,1-1%)

Literature

The association between alitretinoin and the curling of hair was mentioned in a few case reports (8;9). A 41-50 year-old man taking alitretinoin for chronic hand eczema, developed curling of the hair after 4 months of treatment. The patient suffered from vitiligo since she was 31-40 years old. Other causes for the curling of the hair could not be elicited. The patient did not take any other drugs. Family anamnesis and several allergy skin tests were negative. Hormonal influences that could lead to hair structure changes were also not present. The figure shows the hair before (A) and after (B) alitretinoin treatment (8).



Figure from Herink et al. (8)

A 61-70 year old woman with longstanding hand eczema was prescribed alitretinoin. The patient also suffered from hypothyroidism and hypertension, for which she had been prescribed levothyroxine and bendroflumethiazide for over 10 years. Three months after start of the alitretinoin treatment, the patient reported changes in the hair texture, gaining a curly appearance. On examination, the hair was curly, but there were no changes in pigmentation or distribution. The drug was withdrawn. One year after withdrawal of alitretinoin, the hair remained curly, although much less so (9).



Figure from Trehan and Wilson (9)

Several case reports were published about kinking of the hair in association with the other systemic retinoids, acitretin (10-13), isotretinoin (14-17), and etretinate (15;18-22). These case-reports describe the persistence of kinked hair, after withdrawal of the drug. Etretinate is no longer on the market in Europe and the US. It has been replaced by acitretin, the active metabolite of etretinate.

Mechanism

With regard to retinoids, an influence on the keratinization of the inner root sheath (IRS) of the hair follicle has been put forward as a possible mechanism (8). The IRS is an important structure of the lower part of the hair follicle that surrounds and protects the growing hair. The IRS is essential for the proper moulding, adherence, and keratinization of the growing hair (23). This possible mechanism was first described for etretinate. It is speculative whether the affected hairs have regrown in follicles from which hairs have previously been lost. The keratinization of the inner root sheath could be the result from a dystrophic change of the hair root. A similar process is seen in acquired pili-torti, when distortion of the hair follicle results in twisting of the hairs (19). It is speculated whether there is an association between hair loss and acquired kinking of the hair, which resembles acquired progressive kinking of the hair (APKH). APKH is a relatively rare condition, where hair kinking affects the frontotemporal regions of the head. It is controversial whether APKH is a separate entity or a variety of

androgenetic alopecia (2). Given the chemical relationship of alitretinoin with the other retinoids and their effect on the retinoid acid receptors (RAR α , β , γ), a similar mechanism can be expected. However, since retinoids also activate the thyroid- and vitamin D-receptor modulating retinoid-X receptors (RXR α , β , γ), alternative mechanisms are also possible. These RXR-receptors are speculated to play a role in new hair growth (8).

Databases

Due to the limited reports on hair texture changes associated with alitretinoin, the level of disproportionality was not calculated in the Lareb and WHO databases (24;25). The WHO database contained three reports on 'hair texture abnormal', including the two reports from Lareb. The other report was coded as 'dry hair'. The Eudravigilance database contained eight reports of 'hair texture abnormal' in addition to the two from Lareb. The event in one of the reports was described as 'dull and frizzy hair'. The other events included alopecia/hair loss, hair thinning, and dry hair (26).

Table 2. Reports of the PT "hair texture abnormal" associated with alitretinoin, in the WHO, Lareb (24;25) and Eudravigilance database (26). Lareb received no reports of hair texture changes associated with isotretinoin, tretinoin, acitretine or bexarotene.

Database	MedDRA PT	Number of reports
Lareb	Hair texture abnormal	2
WHO	Hair texture abnormal	3
Eudravigilance	Hair texture abnormal	10

Prescription data

The number of patients using alitretinoin in the Netherlands is shown in table 3 (27).

Table 3. Number of patients using alitretinoin in the Netherlands between 2013 and 2016 (27).

Drug	2013	2014	2015	2016
Alitretinoin	241	1592	2000	2095

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received two reports of hair texture changes, from straight to curly hair, associated with the use of alitretinoin. These reports concerned two women, aged 41-50 years and 51-60 years. The patients did not use other drugs. The latency in the reports received by Lareb resembles the case reports described in the literature. With the current information, reversibility of the kinking of the hair cannot be established. Hair texture changes in case-reports about the other retinoids have described the persistence of kinked hair, after withdrawal of the drug. Hair texture changes are currently not described in the SmPC of alitretinoin, but several hair disorders are known ADRs for other systemic retinoids. Possible mechanisms for this association are keratinization of the inner root sheath of the hair, hair loss and possible influence of the RAR- and RXR-receptors. In conclusion, it is plausible that alitretinoin causes kinking of the hair.

Reference List

- (1) Dutch SmPC Toctino® 10 mg capsules. <https://db.cbg-meb.nl/IB-teksten/h100957.pdf> 2017 July 18 [cited 2018 Jan 2];
- (2) Tosti A, Piraccini BM, Pazzaglia M, et al. Acquired Progressive Kinking of the Hair - Clinical Features, Pathological Study, and Follow-up of 7 patients. *Arch Dermatol* 1999;135(10):1223-6.
- (3) Dutch SmPC Isotretinoïne 10 mg capsules. <https://db.cbg-meb.nl/IB-teksten/h26547.pdf> 2016 November 25 [cited 2018 Jan 9];
- (4) Dutch SmPC Acitretine (Neotigason®) 10 mg capsules. <https://db.cbg-meb.nl/IB-teksten/h13103.pdf> 2016 October 11 [cited 2018 Jan 9];
- (5) Dutch SmPC Tramadolhydrochloride 50 mg capsules. <https://db.cbg-meb.nl/IB-teksten/h18941.pdf> 2017 May 10 [cited 2018 Jan 9];
- (6) Dutch SmPC Tretinoïne (Vesanoid®) 10 mg capsules. <https://db.cbg-meb.nl/IB-teksten/h20455.pdf> 2017 May 16 [cited 2018 Jan 9];
- (7) Dutch SmPC Bexarotene (Targretin®) 75 mg capsules. http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000326/WC500034208.pdf 2015 May 27 [cited 2018 Jan 9];
- (8) Herink C, Schön MP, Mößner R. Development of curly hair under systemic therapy with alitretinoin. *Hautarzt* 2015;66(8):617-9.

- (9) Trehan P., Wilson NJ. Alitretinoin-induced curling of the hair. *Australas J Dermatol* 2016;57(2):155.
- (10) Clarke JT., Price H., Clarke S., George R., Miller JJ. Acquired kinking of the hair caused by acitretin. *J Drugs Dermatol* 2007;6(9):937-8.
- (11) Seckin D., Yildiz A. Repigmentation and curling of hair after acitretin therapy. *Australas J Dermatol* 2009;50(3):214-6.
- (12) Tosti A., Pazzaglia M. Drug reactions affecting hair: diagnosis. *Dermatol Clin* 2007;252(2):223-31.
- (13) Ward PD., Miller HL., Shipman AR. A case of repigmentation and curling of hair on acitretin therapy. *Clin Exp Dermatol* 2014;39(1):91-2.
- (14) Bunker CB., Maurice PD., Dowd PM. Isotretinoin and curly hair. *Clin Exp Dermatol* 1990;15(2):143-5.
- (15) Hays SB., Camisa C. Acquired pili torti in two patients treated with synthetic retinoids. *Cutis* 1985;35(5):466-8.
- (16) Shalita AR., Cunningham WJ., Leyden JJ., Pochi PE., Strauss JS. Isotretinoin treatment of acne and related disorders: an update. *J Am Acad Dermatol* 1983;9(4):629-38.
- (17) van der Pijl JW., Bavinck JN., de Fijter Jw. Isotretinoin and azathioprine: a synergy that makes hair curl? *Lancet* 1996;348(9027):622-3.
- (18) Archer CB., Cerio R., Griffiths WAD. Etretinate and acquired kinking of the hair. *Clin Exp Dermatol* 1987;12:239.
- (19) Graham RM, James MP, Ferguson DJ, Guerrier CW. Acquired kinking of the hair associated with etretinate therapy. *Clin Exp Dermatol* 1985;10(5):426-31.
- (20) Matthews RS. Congenital ichthyosiform erythroderma. *Br J Dermatol* 1984;111(26):75-6.
- (21) Mortimer PS. Unruly hair. *Br J Dermatol* 1985;113(4):467-73.
- (22) Schauder S, Tsambaos D, Nikiforidis G. Curling and kinking of hair caused by etretinate. *Hautarzt* 1992;42(8):509-13.
- (23) Joshi RS. The Inner Root Sheath and the Men Associated with it Eponymically. *Int J Trichology* 2011;3(1):57-62.
- (24) Lareb databank. www.lareb.nl 2018 [cited 2018 Jan 5];
- (25) Uppsala Monitoring Centre. WHO database Vigilyze. <http://www.vigiaccess.org/> 2015 [cited 2018 Jan 5];
- (26) European Medicine Agency (EMA). Eudravigilance database. <http://bi.eudra.org> (access restricted) 2016 [cited 2018 Jan 8];
- (27) GIPdatabase - Drug Information System of Dutch Health Care Insurance Board. <http://www.gipdatabank.nl> 2017 November 21 [cited 2018 Jan 5];

This signal has been raised on March 5, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl