

Oral Alitretinoin in Congenital Ichthyosis: A Pilot Study Shows Variable Effects and a Risk of Central Hypothyroidism

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Congenital ichthyosis is a large group of hereditary skin disorders with different aetiologies, all of which are present at birth (1). The patients have dry, widespread scaling and thickened skin (2). At present there is no cure for ichthyosis and therapy is mostly symptomatic. Life-long treatment with emollients is essential, and some patients also use systemic therapy with retinoids, especially acitretin (3). The most serious adverse effect of retinoids is teratogenicity, which is a special concern for acitretin as it is excreted from the body slowly (3).

Alitretinoin (9-*cis* retinoic acid) is a fairly new oral retinoid with more rapid clearance than acitretin. In contrast to acitretin and isotretinoin, alitretinoin binds to both types of nuclear retinoid receptors, retinoic acid receptors (RARs) and retinoid X receptors (RXRs). It is indicated for chronic hand eczema in most European countries and has been found to be well-tolerated (4). We report here our preliminary experiences from an uncontrolled study of alitretinoin in 4 patients with congenital ichthyosis.

PATIENTS AND METHODS

Four adult patients (two women and two men, age range 32–74 years), one with ichthyosis variegata (OMIM 609165) due to a *KRT10* mutation (Danish patient no. 1) and 3 with lamellar ichthyosis (OMIM 242300) due to *TGM1* mutations (Swedish patients nos. 2–4), were invited to participate in this study after informed consent. The patients were all healthy except for the oldest man (patient no. 4) who was on warfarin for atrial fibrillation, having experienced a mild stroke several years before. The female patients used oral contraceptives. The patients' previous treatments for ichthyosis included systemic acitretin ($n=2$; 25–50 mg/day) or isotretinoin ($n=1$; 50 mg/day), and/or topical moisturizers and keratolytic agents 1–2 times a day ($n=4$). Systemic retinoids were stopped at least 3 weeks before baseline. All patients continued to use their ordinary topical treatment during the study.

The trial began in December 2009. The Danish patient was started on alitretinoin (Toctino, Basilea Pharmaceuticals A/S, Denmark) at a dose of 30 mg/day, whereas the Swedish patients started with a lower dosage of 10 mg/day, which was then gradually increased to 30 mg/day during the first month. If the clinical effect was insufficient at first re-visit and no side-effects had occurred, the dose was increased to 40–60 mg/day over a

planned treatment period of 3 months. Clinical and laboratory evaluations were performed before the start of therapy and at monthly intervals, and consisted of physical examination, photography, interviewing the patients about effects and side-effects of therapy, and blood sampling for analysis of haematological parameters, liver enzymes, creatinine, cholesterol, triglycerides, thyroxin (T4) and thyroid-stimulating hormone (TSH) levels.

RESULTS

All 4 patients completed the 3-month long trial, and two of them (nos 1 and 3) wished to continue alitretinoin therapy after the end of the trial. In the first month of therapy only the patient with ichthyosis variegata (no. 1), showed significant improvement. The patients with lamellar ichthyosis using lower initial dosages effects showed minimal effects; only at the higher dose (30–50 mg) did the skin become smoother and less scaly (Fig. S1; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1302>). After 3 months, two patients (nos 1 and 3) considered alitretinoin equally effective or better than acitretin at 25–50 mg/day.

Dry lips were recorded by all patients at the highest dose. One patient (no. 4) experienced mild myalgia. All these side-effects were reversible on dose reductions. Blood lipid and liver parameters were within the normal range during therapy, but two patients (nos 3 and 4) showed treatment-related changes in the thyroid hormone levels (Table I). Within 1 month after stopping treatment the thyroid-stimulating hormone (TSH) levels in patient no. 4 reverted to baseline values. However, in patient no. 3, who wished to continue alitretinoin therapy despite both laboratory and clinical signs of hypothyroidism (tiredness), the T4 level remained low even after dose reduction to 20 mg/day. Her T4 value was normalized only after combined cessation of alitretinoin and adding substitution therapy with T4, which also cured her tiredness. Interestingly, her TSH value was border-line high at follow-up, and a subsequent investigation revealed laboratory signs of autoimmune hypothyroidism.

The 3 Swedish patients (nos. 2–4) resumed acitretin therapy after completing the alitretinoin trial, but the Danish patient (no. 1) is still (as of September 2011) on alitretinoin 60 mg daily with maintained clinical benefit and no hair-loss similar to what she experienced during previous acitretin therapy.

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Table I. Thyroid-stimulating hormone (TSH) and thyroxin (T4) levels before and after alitretinoin therapy in 2 patients with treatment-related hypothyreosis

Pat. no./age, years/sex: dose	Baseline	1 month	2 months	3 months	4 months	5 months	FU
3/40/F: Alitretinoin, mg/day	0	10–30	30–40	40	20	20	0
TSH (normal: 0.4–4.0 mIU/l)	2.71	1.44	NA	2.22	2.60	2.73	3.69
T4 (normal: 12–22 pmol/l)	13.3	11.5	NA	9.2	11.3	10.5	12.0
4/74/M: Alitretinoin	0	10–30	40–50	60	–	–	0
TSH, mIU/l	2.56	1.67	1.84	1.70	–	–	2.87
T4, pmol/l	15.5	11.2	11.0	9.4	–	–	14.0

FU: follow-up 1–2 months after stopping alitretinoin. Patient no. 3 started therapy with L-thyroxine (0.1 mg/day) 2 weeks prior to FU. NA: not available.

DISCUSSION

In this pilot study, 3 patients with lamellar ichthyosis when given alitretinoin in varying doses for at least 3 months did not perform better than previously observed while on acitretin. However, the patient with ichthyosis variegata due to a *KRT10* mutation (Sommerlund et al., unpublished observation) appeared to respond better, although rather high doses of alitretinoin had to be used, which in this case resulted in headache. Side-effects were otherwise similar to those usually seen in acitretin-treated ichthyosis patients, except for the decreased TSH levels observed in two (50%) of our patients. The latter observation is not unexpected because other RXR ligands, such as bexarotene, are known to frequently produce hypothyroidism via suppression of thyrotropin secretion (5). Although Aguayo-Leiva et al. (6) recently found a case of low TSH level during alitretinoin therapy of hand eczema, and Bissonnette et al. (7) noticed a < 10% incidence of low TSH or T4 levels, this side-effect has not been highlighted in larger trials of alitretinoin in patients with chronic hand eczema (8). However, it is possible that hypothyroidism predominantly occurs in predisposed individuals and may not be noticed when lower doses of alitretinoin are used, as is often the case in patients with eczema. It is reassuring though that one of our patients (no. 1) has now been on continuous alitretinoin therapy for 2.5 years without appearance of any serious adverse effect or hypothyreosis. This patient is fertile and prefers alitretinoin therapy because of its shorter elimination time, in case she wants to get pregnant.

In conclusion, alitretinoin might be an alternative to other oral acitretin in the treatment of congenital ichthyosis, especially in women of child-bearing age who want to become pregnant after stopping retinoid therapy and who do not respond to isotretinoin, or in the rare event of hypersensitivity to aromatic retinoids. However, the risk of hypothyroidism should be considered and checked carefully, especially if there is a previous history of thyroid disease. A larger controlled study is necessary to confirm or dispute our results, especially in the case of ichthyosis variegata. Our previous studies have indicated that other types of *KRT10* mutations are

particularly responsive to the down-regulatory effects of retinoid therapy (9).

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REFERENCES

- Krug M, Oji V, Traupe H, Berneburg M. Ichthyoses – part 2: congenital ichthyoses. *J Dtsch Dermatol Ges* 2009; 7: 577–588.
- Gånemo A, Pigg M, Virtanen M, Kukkk T, Raudsepp H, Rossman-Ringdahl I, et al. Autosomal recessive congenital ichthyosis in Sweden and Estonia: clinical, genetic and ultrastructural findings in eighty-three patients. *Acta Derm Venereol* 2003; 83: 24–30.
- Vahlquist A, Gånemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. *Acta Derm Venereol* 2008; 88: 4–14.
- Ruzicka T, Lynde CW, Jemec GB, Diepgen T, Berth-Jones J, Coenraads PJ, et al. Efficacy and safety of oral alitretinoin (9-cis retinoic acid) in patients with severe chronic hand eczema refractory to topical corticosteroids: results of a randomized, double-blind, placebo-controlled, multicentre trial. *Br J Dermatol* 2008; 158: 808–817.
- Sherman S, Gopa J, Haugen B, Chiu A, Whaley K, Nowlakha P, et al. Central hypothyroidism associated with retinoid X receptor-selective ligands. *N Engl J Med* 1999; 340: 1075–1079.
- Aguayo-Leiva IR, Urrutia S, Jaen-Olasolo P. [Response to treatment with oral alitretinoin in patients with chronic hand eczema that is refractory to treatment with potent topical corticosteroids: experience in 15 patients]. *Actas Dermosifiliogr* 2011; 102: 616–622 (in Spanish).
- Bissonnette B, Worm M, Gerlach B, Guenther L, Cambazard F, Ruzicka T, et al. Successful retreatment with alitretinoin in patients with relapsed chronic hand eczema. *Br J Dermatol* 2010; 162: 420–426.
- Diepgen T, Pfarr E, Zimmermann T. TOCCATA – effectiveness and tolerability of alitretinoin in chronic hand eczema under daily practice conditions. *Acta Derm Venereol* 2012; 92: 251–255.
- Virtanen M, Gedde-Dahl T Jr, Mörk NJ, Leigh I, Bowden PE, Vahlquist A. Phenotypic/genotypic correlations in patients with epidermolytic hyperkeratosis and the effects of retinoid therapy. *Acta Derm Venereol* 2001; 81: 163–170.