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Published in:
Acta Dermato-Venereologica

DOI:
10.2340/00015555-1302

2012

Citation for published version (APA):

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

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Accepted October 20, 2011.

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 variagata (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 variagata (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.
Discussion

In this pilot study, 3 patients with lamellar ichthyosis who have indicated that other types of retinoid therapy (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.


