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SHORT COMMUNICATION

Zileuton for Pruritus in Sjögren-Larsson Syndrome: A Randomized Double-blind Placebo-controlled Crossover Trial

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Sjögren-Larsson syndrome (SLS) is an autosomal recessive disorder characterized by ichthyosis, spastic diplegia or tetraplegia and intellectual disability. Ichthyosis largely develops early in life. The neonatal skin has an erythrodermic appearance that gradually evolves into a generalized ichthyosiform hyperkeratosis during infancy, which is most prominent in the flexural areas. Ichthyosis in SLS has a striking pruritic character, resulting in excoriations and scaling (1).

SLS is caused by a deficiency of microsomal fatty aldehyde dehydrogenase (FALDH), resulting in disturbed lipid metabolism (2). Lipid metabolism plays an important part in the normal formation of the water barrier in the stratum corneum. In patients with SLS, lamellar bodies, synthesized in the stratum granulosum and normally containing essential precursor membranes, are misshapen and empty. To restore barrier function, the skin reacts by hyperkeratosis, resulting in ichthyosis (3).

The pruritus may also have another pathophysiological origin. Previously, we showed an association between pruritus and elevation of pro-inflammatory leukotriene B4 (LTB4), which is also FALDH-dependent for its breakdown (4). This association was later confirmed in experimental studies in mice (5). In SLS, elevation of dermal LTB4, by increased production, defective breakdown, or a combination of both, probably plays an important role in the pruritus. Zileuton is an oral drug that blocks the formation of leukotrienes (including LTB4) from arachidonic acid.

Previously, we studied zileuton treatment in a non-placebo controlled study and found some beneficial effects on pruritus (6, 7). To further investigate the potential effects of zileuton, we performed this randomized controlled trial.

METHODS (See Appendix S1[1])

RESULTS

Included patients ($n = 10$; age range 7–40 years, equal sex distribution) were randomized to 1 of 2 treatment arms with either zileuton (dosage as for asthma) or placebo in 2 periods of 8 weeks, separated by a wash-out period of 4 weeks.

Except for small effects on severity scores Sjögren-Larsson Severity Index (SLaSI) for desquamation and Physician Global Assessment (PGA) scores in the second treatment period, changes in mean scores were not significantly different between the zileuton and placebo groups. However, when analysing individual results, patient No. 4 (an 8-year-old girl), responded on zileuton treatment (400 mg 4 times a day) with substantial changes in almost every scoring item (Table I).

Regarding secondary outcome measures, large intra-individual variability in pruritus VAS scores was seen in subsequent study weeks in some patients in both the treatment and the placebo period. There was also significant inter-individual variability in scores, illustrating differences in SLS phenotype. Substantial decreases in mean VAS scores were detected in only patient No. 4. Retrospective analysis of the medical records from all patients showed that, for this patient, only the parents reported a tremendous clinical improvement, especially regarding pruritus only, in the period when zileuton was administered. A complete setback was reported within days after discontinuation of zileuton at the wash-out visit.

For unknown reasons, measurement of baseline urinary concentrations of LTB4 and 20-OH-LTB4, failed to detect the expected

Table I. *Individual responders' analysis*

	SLaSI					VAS			
Patient	Erythema	Desquamation	Lichenification	Excoriations	PGA	Pruritus	Excoriations	Total score	Responder
1	–	–	0.75	1.25	–	–	–	2	–
2	0.5	–	0.5	1.0	1.0	–	–	4	–
3	–	1.0	–	1.25	2.0	–	–	3	–
4	–	1.0	0.75	0.75	2.0	+	+	6	+
5	–	0.75	0.5	–	1.0	–	–	3	–
6	–	2.0	1.0	–	1.0	–	–	3	–
7	–	–	–	–	–	–	–	0	–
8	–	–	–	–	–	–	–	0	–
9	0.75	–	–	–	–	–	–	1	–
10	–	–	–	0.75	–	–	–	1	–

Sjögren-Larsson Severity Index (SLaSI) and Physician Global Assessment (PGA) outcomes in individuals: sum of SLaSI mean score before zileuton treatment minus SLaSI mean score after zileuton treatment. Results are only given if sum was ≥0.5; otherwise the patient is considered a non-responder (–). Visual analogue scale (VAS) outcomes: positive score if difference in mean VAS scores during the treatment and placebo periods was ≥20 mm. Patient is considered to be a responder to zileuton treatment if the total score was ≥5.

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differences in LTB4 and 20-OH-LTB4 excretion between SLS patients and healthy controls. Biochemical responses to treatment could thus not be confirmed (including the only responding patient). No adverse events related to the study drug were observed.

DISCUSSION

This study could only detect convincing clinical effects of zileuton treatment in one patient. Upon parental request, the patient continued zileuton and was monitored closely. Follow-up (~1 year) after the study showed a consistent beneficial therapeutic effect. From the patients studied previously, 2 other patients still use zileuton with lasting beneficial effects. The reason why only a few patients respond to treatment is unknown.

Although genotypes in SLS differ, the corresponding clinical phenotype and degree of enzyme deficiency are usually quite homogeneous, making it impossible to predict responders. The 3 responders from these 2 studies have different genotypes and lack residual FALDH activity. Also, amongst the non-responders in this trial there were patients with the same genotype as the responding patient.

Furthermore, intellectual disability in SLS patients may result in scratching becoming habitual behaviour. Therefore, scratching may continue even when the pruritus is reduced by zileuton treatment, disguising potential beneficial effects. Due to unsuccessful urinary leukotriene analysis, we could not confirm biochemically that exposure to zileuton in this study was sufficient to decrease leukotriene production.

Epidermal LTB4 is produced by keratinocytes upon stimulation of specific receptors (5). Research in mice proved that orally administered zileuton has the ability to inhibit epidermal LTB4 production and decrease pruritus (11). However, correlations between zileuton dosages used in animal research and the dosages used in this study are unclear.

Use of zileuton in SLS is off-label, and no formal dose-finding studies have been performed. Dosages used were based on the treatment of asthma, in which leukotrienes are formed by mast cells that may have different biochemical responses to zileuton than keratinocytes (12). In addition, it is possible that dosages of zileuton in SLS should be higher than used here to sufficiently penetrate epidermal layers or have stronger inhibitory effects on leukotriene formation. Also, it is possible that pharmacogenetics play a part in the heterogeneous inter-individual response to treatment with leukotriene-modifiers (13).

Based on findings from our study it appears that only a few patients with SLS will benefit from zileuton treatment. However, responders can easily be detected clinically and will experience an improvement in quality of life. Therefore, when medical treatment for severe pruritus is warranted in SLS patients ≥ 5 years, a therapeutic trial with zileuton for a period of 4–6 weeks still may be considered. If no clear beneficial response to zileuton is noted, treatment should be discontinued.

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