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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 di- or tetraplegia and intellectual disability. Mostly, the ichthyosis develops early in life. The neonatal skin has an erythrodermic appearance gradually evolving into a generalized ichthyosiform hyperkeratosis during infancy. Skin lesions follow a generalized distribution pattern being more prominent in the flexural areas, neck and lower abdomen sparing the central face. The hyperkeratosis thickens the skin, resembling lichenification, and produces a yellowish dark-brown color. 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) causing a disturbed lipid metabolism (2, 3). The lipid metabolism plays an important part in the normal formation of the water barrier in the stratum corneum. In SLS patients, lamellar bodies, synthesized in the stratum granulosum and normally containing essential precursor membranes, are misshapen and empty. This results in defective membrane formation and a leaky water barrier. To restore function, the skin reacts by hyperkeratosis resulting in ichthyosis (4 – 6).

However, the pruritus may 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 (7). This association was later confirmed in experimental mice studies (8).

In SLS, elevation of dermal LTB4, by either increased production or defective breakdown or a combination of both, probably plays an important role in the pruritus. Zileuton is an oral drug which 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 upon pruritis (9, 10). To further investigate the potential effects of zileuton, we performed this randomized controlled trial.

METHODS

For a complete description of the methods used and the results, we refer to the online supplement. We used a crossover design in this single-center RCT, resulting in each participant being its own control. Approval of the Regional Committee on Research involving Human Subjects was obtained. Patients with genetically and biochemically confirmed Sjögren-Larsson syndrome, aged 5-60 years were included in the study. Patients were required to continue current dermatological treatment during the study period.

All patients received treatment with either zileuton or placebo in two periods of 8 weeks, separated by a wash-out period of 4 weeks. Visits were scheduled (at t=0, t=8, t=12, t=20 and t=24 weeks respectively) during which a structured dermatological assessment was performed using the Sjögren-Larsson Severity Index (SLaSI), specifically designed for this study using items from the Psoriasis Area and Severity Index (PASI) (11). The SLaSI outcomes *erythema*, *desquamation*, *lichenification* and *excoriations* were scored separately on a 5-points severity scale assessing four different areas of the body (head, trunk, upper and lower extremities) each visit. To measure global changes, the Physician Global Assessment (PGA) tool (5-points severity scale) was performed during all visits (12). Primary caregivers weekly scored pruritus and excoriations in all patients during the entire study period using a Visual Analog Scale (VAS) instrument.

Primary outcome measures (POM) were the differences in group SLaSI and PGA scores before and after treatment with zileuton and compared with placebo treatment. To improve detection of responders, changes in SLaSI and PGA scores were also analyzed in each individual patient. Secondary outcome measures (SOM) were individual changes in VAS scores during zileuton and placebo treatment.

To measure *in vivo* activity of zileuton, urinary LTB4 and 20-OH-LTB4 concentrations were analyzed in each patient during each visit.

RESULTS

Included patients (n=10) were randomized in one of two treatment arms. All patients completed the current study and blinding was unaffected during the complete study.

Except for small effects on SLaSI scores for desquamation and PGA scores in the second treatment period, changes in mean scores were not significantly different between the zileuton and placebo groups. However, when analyzing individual results, one patient responded on zileuton treatment with substantial changes in almost every scoring item.

Regarding SOM, large intra-individual variability in VAS scores was seen in subsequent study weeks in some patients in both treatment and placebo period. There was also significant inter-individual variability in scores

illustrating differences in SLS phenotype. Substantial decreases in mean VAS scores were only detected in one patient (same patient who also responded with decreases in SLaSI and PGA scores). 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.

Urinary samples were collected for all patients during nearly all visits. Measurement of baseline concentrations of LTB4 and 20-OH-LTB4 however failed to detect the expected differences in LTB4 and 20-OH-LTB4 excretion between SLS patients and healthy controls due to as yet unknown reasons. Biochemical responses to treatment could not be confirmed (including the one 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, two other patients still use zileuton with lasting beneficial effects.

It remains unclear why only few patients respond to treatment.

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 three responders from these two 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, the intellectual disability in SLS patients may result in scratching becoming habitual behavior. Therefore, scratching may continue although the pruritus is diminished by zileuton treatment, disguising potential beneficial effects.

In regard to study findings, some other limitations have to be made.

Due to unsuccessful urinary leukotriene analysis, we could not confirm biochemically that exposure to zileuton in this study was sufficient to decrease leukotriene production. Furthermore, epidermal LTB4 is produced by keratinocytes upon stimulation of specific receptors (8). Research in mice proved that orally administered zileuton has the ability to inhibit epidermal LTB4 production and decrease pruritus (13). 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 (14). 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 leukotrienes-modifiers (15).

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

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Zileuton for pruritus in Sjögren-Larsson syndrome

Online-supplement

Trial Registration:

European Clinical Trials Database (EudraCT). Reference 2009-015895-87

MATERIALS AND METHODS

Study design and participants

We used a crossover design in this single-center RCT. Patients with genetically and biochemically confirmed Sjögren-Larsson syndrome, aged 5-60 years were included in the study. All patients continued current dermatological treatment during the study period.

Treatment

Zileuton is FDA approved for treatment of asthma in patients ≥12 years. Inhibition of LTB4 biosynthesis in blood is directly related to zileuton plasma concentration (1-4). Since we expected the same mechanism of action to be responsible for reduction of pruritus in SLS, our aim was to achieve similar exposure to zileuton as in asthmatic patients.

For patients ≥ 12 years of age, dosages as currently approved for the treatment of asthma were used. To determine dosages for younger patients (≥5 and <12 years of age) , the guidance for pediatric dosing was used (5).

Randomization and Allocation to Treatment

Based upon findings from pharmacokinetics and pharmacodynamics, all patients received treatment with either zileuton or placebo in two periods of 8 weeks, separated by a wash-out period of 4 weeks (6,7). Treatment order was randomly assigned and randomization was

performed by the hospital pharmacy. Assessors and patients were blinded to assignment of treatment.

Data collection

Visits were scheduled for all patients at t=0 (start first treatment period), t=8 weeks (stop first treatment period), t=12 weeks (stop wash-out period and start second treatment period), t=20 weeks (stop second treatment period) and t=24 weeks (stop second wash-out period). Baseline measurements (t=0) were performed by two assessors (M.S. & J.F.) producing one mutual assessment for all patients. All subsequent measurements were performed by one assessor (J.F.).

During all visits, structured dermatological assessment was performed using the Sjögren-Larsson Severity Index (SLaSI). For each SLaSI outcome, the mean of all body areas scored was calculated for each patient at each visit leading to 'SLaSI mean scores'. To measure global changes, the Physician Global Assessment (PGA) tool (range 0-5; 5 being most severe) was performed during all visits (8).

Urine samples were collected at each visit and stored at -80 °C within maximally 6 hours after collection. Unused capsules were returned to the study staff at each visit to measure treatment compliance.

Primary caregivers weekly scored pruritus and excoriations in all patients during the entire study period using a Visual Analog Scale (VAS) instrument consisting of 100-mm horizontal lines.

Primary Outcome Measures (POM)

POM were the differences in SLaSI mean scores and PGA scores before and after treatment with zileuton or placebo.

Secondary Outcome Measures (SOM)

SOM were individual changes in VAS scores.

Statistical Analysis

Primary analysis involved studying changes in SLaSI mean scores and PGA scores during treatment. Data were analyzed for the two treatment periods combined and separately using paired samples t-tests, comparing: 1) scores at the start of the treatment period with those at the end of the treatment period (treatment); 2) scores at the end of the treatment period with those at the end of the wash-out period (wash-out); and 3) scores at the start of the treatment period with those at the end of the wash-out period (treatment + wash-out).

SOM were studied by calculating all individual mean VAS scores during treatment periods with zileuton and periods with placebo treatment for the outcomes pruritus and excoriations separately.

Previous experience led to the assumption that only a minority of patients would respond to zileuton. Therefore, POM were also analyzed in each individual patient to detect responders. Regarding SLaSI and PGA scores, we defined a positive response to zileuton as a decrease of ≥0.5 after treatment. Based upon use in psoriasis, a positive VAS response was defined as a decrease of ≥20 during treatment (9). All separate outcomes scoring positive were given one point (maximum score 7 points). Patients scoring ≥5 points were considered responders.

Leukotrienes Analysis

For LTB4 and 20-OH-LTB4 analysis samples were purified using anion exchange solid phase extraction with subsequent HPLC fractionation on a Acquity HSS T3 column (100 x 1 mm/ dp = 1.8 µm; Waters Chromatography, The Netherlands). Relevant fractions were measured

using an enzyme immunoassay (Leukotriene B4 Express EIA Kit, Cayman Chemical Company nr 10009292, USA and standard for 20-OH-LTB4 from the same company nr 20190). Reference values for age-matched healthy controls were determined in house. Total procedure was validated by performing recovery experiments for LTB4 and 20-OH-LTB4 which gave satisfactory results.

RESULTS

All included patients (n=10) completed the current study. Characteristics are given in Table I. The accounting for unused capsules showed no inconsistencies pointing to sufficient treatment compliance.

Primary Outcome Measures (POM)

Results of analyses on POM are presented in Table II by mean changes in scores for the two treatment periods combined and separate. In the combined analysis, a treatment effect was only seen for the PGA score. When analyzing treatment periods separately, treatment effects were seen for the SLaSI outcome desquamation and the PGA, respectively, both in the second period and both largely maintained during wash-out period. Thus, a reversal of beneficial effects from zileuton after discontinuation of treatment could not be detected. Simultaneously, the placebo group showed no effects for desquamation and PGA, thereby excluding seasonal influences upon these scores.

Scores did not change substantially from t=0 to t=8 and t=12 weeks in the placebo group in the first treatment period, indicating limited intra-observer and seasonal variability.

Secondary Outcome Measures (SOM)

In total, 181/210 (86%) scoring forms were returned. Substantial decreases in mean VAS scores were only detected in one patient.

Individual responders

One patient met our criteria for 'responder' with a score of 6 out of 7 (Table III).

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Table I
Patient characteristics

Patient	Age (years)	Gender (M/F)	Weight and body surface area (BSA) [a]	Daily dermatological treatment	Remarks	Zileuton treatment previously	Zileuton treatment period (weeks)	Zileuton dosage (qid)
1	26	F		Calmurid bid		No	t=0-8	600mg
2	27	F		Calmurid bid		No	t=0-8	600mg
3	9	M	22.8 kg 0.85 m^2	Daily bath and scrubbing Udder cream qid		No	t=12-20	400mg
4	8	F	19.7 kg 0.79 m^2	Cetomacrogol bid		No	t=12-20	400mg
5	12	F		Calmurid and Vaseline bid		No	t=12-20	600mg
6	40	M		Oral Acitretine and Calmurid bid	UTI at t=8	No	t=12-20	600mg
7	29	M		Vaseline		Yes	t=0-8	600mg
8	22	M		Vaseline		Yes	t=0-8	600mg
9	7	F	21.7 kg 0.84 m^2	Vaseline	Chickenpox at t=24	No	t=12-20	400mg
10	22	M		Calmurid bid		Yes	t=0-8	600mg

M = male; F = female. Bid = bis in die (twice a day). Qid = quater in die (four times a day).
UTI = urinary tract infection
[a] Weight and BSA used for dosage calculations (only in patients <12 years).
Dosage calculation: 15-<20 kg or < 0.60 m^2 : 200 mg qid
20-<32 kg or 0.60-1.0 m^2 : 400 mg qid
≥32 kg or >1,0 m^2 : 600 mg qid

Table II. Primary Outcome Measures: SLaSI & PGA scores

SLaSI & PGA		Any treatment period	Treatment period T0 – T8			Treatment period T12 - T20		
		Zileuton group (n=10) mean change + 95%CI	*Zileuton Group (n=5)* mean change + 95%CI	*Placebo Group (n=5)* mean change + 95%CI	*P value*	*Zileuton Group (n=5)* mean change + 95%CI	*Placebo Group (n=5)* mean change + 95%CI	*P value*
Erythema	*treatment*	0.05 (-0.31 – 0.41)	0.05 (-0.41 – 0.51)	0.00 #	0.78	0.05 (-0.75 – 0.85)	**0.60 (0.04 – 1.16)***	0.16
	wash-out	-0.05 (-0.42 – 0.32)	-0.30 (-0.86 – 0.26)	0.30 (-0.26 – 0.86)	0.07	0.20 (-0.40 – 0.80)	-0.35 (-0.82 – 0.12)	0.08
	treatment + wash-out	0.00 (-0.36 – 0.36)	-0.25 (-0.91 – 0.41)	0.30 (-0.26 – 0.86)	0.11	0.25 (-0.19 – 0.69)	0.25 (-0.33 – 0.83)	1.00
Desquamation	*treatment*	0.40 (-0.19 – 0.99)	-0.15 (-0.76 – 0.46)	-0.35 (-0.87 – 0.17)	0.51	**0.95 (0.06 – 1.84)***	0.25 (-0.24 – 0.74)	0.09
	wash-out	-0.40 (-1.03 – 0.23)	-0.60 (-2.13 – 0.93)	**-0.60 (-1.08 – -0.13)***	1.00	-0.20 (-0.66 – 0.26)	-0.15 (-0.83 – 0.53)	0.87
	treatment + wash-out	0.00 (-0.83 – 0.83)	-0.75 (-2.22 – 0.72)	**-0.95 (-1.62 – -0.28)***	0.74	**0.75 (0.17 – 1.33)***	0.10 (-0.82 – 1.02)	0.14
Lichenification	*treatment*	0.23 (-0.22 – 0.67)	0.05 (-0.78 – 0.88)	-0.10 (-0.38 – 1.78)	0.65	0.40 (-0.31 – 1.11)	0.30 (-0.21 – 0.81)	0.76
	wash-out	-0.05 (-0.56 – 0.45)	-0.20 (-1.21 – 0.82)	-0.30 (-1.07 – 0.47)	0.83	0.10 (-0.68 – 0.88)	-0.50 (-0.76 – 0.66)	0.70
	treatment + wash-out	0.18 (-0.29 – 0.65)	-0.15 (-0.67 – 0.37)	-0.40 (-1.27 – 0.47)	0.51	0.50 (-0.41 – 1.41)	0.25 (-0.80 – 1.30)	0.63
Excoriation	*treatment*	0.43 (-0.89 – 0.94)	0.60 (-0.15 – 1.35)	0.15 (-0.66 – 0.96)	0.29	0.25 (-0.80 – 1.30)	**0.75 (0.17 – 1.33)***	0.28
	wash-out	-0.08 (-0.72 – 0.57)	**-0.75 (-1.33 – -1.7)***	-0.25 (-0.83 – 0.33)	0.13	0.60 (-0.24 – 1.44)	**-0.65 (-1.07 – -0.23)***	0.06
	treatment + wash-out	0.35 (-0.45 – 1.15)	-0.15 (-0.90 – 0.60)	-0.10 (-0.74 – 0.54)	0.89	0.85 (-0.83 – 2.53)	0.10 (-0.71 – 0.91)	0.30
PGA	*treatment*	**0.70 (0.11 – 1.29)***	0.20 (-0.36 – 0.76)	0.20 (-1.16 – 1.56)	1.00	**1.20 (0.16 – 2.24)***	0.20 (-0.36 – 0.76)	**0.05**
	wash-out	-0.20 (-0.50 – 0.10)	-0.20 (-0.76 – 0.36)	-0.20 (-0.75 – 0.36)	1.00	-0.20 (-0.76 – 0.36)	0.00 (-0.88 – 0.88)	0.61
	treatment + wash-out	0.50 (-0.50 – 1.00)	0.00 #	0.00 (-0.88 – 0.88)	1.00	**1.00 (0.12 – 1.88)***	0.20 (-0.36 – 0.76)	0.07

95%CI = 95% confidence interval around the mean change in SLaSI and PGA scores
treatment = score at the start of the treatment period minus score at the end of the treatment period
wash-out = score at the end of the treatment period minus score at the end of the wash-out period
treatment + wash-out = score at the start of the treatment period minus score at the end of the wash-out period
[#] 95%CI could not be computed as the standard error of the difference was zero

* relevant effects

Table III

Individual responders analysis

Patient	Individual responders analysis								
	SLaSI				PGA	VAS		Total score	Responder
	Erythema	*Desquamation*	*Lichenification*	*Excoriations*		*Pruritus*	*Excoriations*		
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	-

SLaSI and 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.
VAS outcomes: positive score if difference in mean VAS scores during the treatment and placebo periods was $\geq$ 20mm (Table 3).
Patient is considered to be a responder to zileuton treatment if the total score was ≥ 5