Clinical and biochemical effects of zileuton in patients with the Sjögren-Larsson syndrome

Abstract The Sjögren-Larsson syndrome (SLS) is an inborn error of lipid metabolism, characterised clinically by congenital ichthyosis, mental retardation and spasticity. Patients also suffer from severe pruritus. The degradation of leukotriene (LT) B₄ is one of the defective metabolic routes in SLS. Zileuton inhibits the synthesis of LTB₄ and the cysteiny1 leukotrienes. Five SLS patients were treated with zileuton for 3 months. Favourable effects were found on pruritus score \( (P = 0.006) \), general well-being, and background activity of electroencephalographic studies. Neuropsychological test results did not change significantly. There was, however, a clinically important trend towards improvement in the speed of information processing. Results of cerebral MRI and proton magnetic resonance spectroscopy did not change during therapy. Urinary concentrations of LTB₄ and \( \omega \)-OH-LTB₄ decreased significantly \( (P = 0.02 \) and \( P = 0.003 \) respectively), while their concentrations in CSF were normal at baseline and remained so after therapy. Conclusion: patients with Sjögren-Larsson syndrome might benefit from treatment with zileuton, especially with respect to the agonising pruritus. The findings reported here, point to a crucial role for leukotriene B₄ in the pathogenesis of pruritus.

Keywords Fatty aldehyde dehydrogenase deficiency · Leukotriene B₄ · 5-lipoxygenase inhibition · Pruritus · Sjögren-Larsson syndrome

Abbreviations ANT Amsterdam neuropsychological task · FALDH fatty aldehyde dehydrogenase · GMFM gross motor function measure · LT leukotriene · \(^{1}H\)-MRS proton magnetic resonance spectroscopy · SLS Sjögren-Larsson syndrome

Introduction

The Sjögren-Larsson syndrome (SLS, McKusick 270200) is a rare genetic neurocutaneous disorder, originally described as the clinical triad of congenital generalised ichthyosis, mental retardation and spasticity [27]. Most patients exhibit additional signs and symptoms, including severe pruritus, preterm birth, and ocular abnormalities [9, 20, 21, 28, 31]. MRI of the brain reveals variable degrees
of disturbed myelination of the CNS and proton magnetic resonance spectroscopy (1H-MRS) shows the presence of a highly characteristic ‘lipid’ peak in the cerebral white matter [14, 18,28]. The ichthyosis and severe pruritus especially hamper the everyday life of SLS patients, although the neurological handicaps present the most salient problems. Treatment of SLS is predominantly symptomatic because effective causal therapy strategies (including dietary regimes) are not available [21]. The neurological disease often leads to severe spasticity and contractures, which necessitate surgical procedures. Topical keratolytic agents such as urea and lactic acid, and systemic retinoids such as etretinate, are useful in the treatment of the cutaneous symptoms [21].

SLS is caused by deficient activity of the microsomal enzyme fatty aldehyde dehydrogenase (FALDH), due to mutations in the FALDH gene [21]. FALDH catalyses the oxidation of different long- and medium-chain fatty aldehydes derived from fatty alcohol metabolism and ether glycerolipid catabolism, the α-oxidation of branched-chain phytanic acid, and the α-oxidation of leucotriene (LT) B4 (Fig.1) [20, 21, 22, 23, 32,34]. It is assumed that the accumulation of fatty alcohols and aldehyde-modified lipids is involved in the pathophysiology of SLS, as might be reflected by the ‘lipid’ peak on 1H-MRS of the brain, and by the presence of crystalline deposits in the ocular fundus. The crucial role of FALDH in the α-oxidation, i.e. the inactivation, of LTB4 leads to elevated concentrations of LTB4 and α-OH-LTB4 in SLS. These metabolites are biologically highly active and could as such contribute to the pathogenesis of SLS. LTB4 is a pro-inflammatory mediator synthesised from arachidonic acid via the 5-lipoxygenase pathway (Fig.1) [11, 16,25]. It is known to be involved in different disease processes, but its (patho)physiological significance in the CNS and skin in general is largely unknown [11, 15, 16,17]. Moreover, SLS has no clinical and histological features that could point to an underlying inflammatory process.

Zileuton is a commercial available drug, used in the treatment of asthma, which blocks the synthesis of LTB4 and the cysteinyl LTs by inhibiting 5-lipoxygenase (Fig.1) [13]. Following our first promising experience with zileuton in the treatment of one patient with SLS [33], we studied its effects in five additional SLS patients. This paper describes the effects of zileuton in these patients and discusses future treatment protocols.

**Fig. 1** Metabolic pathways of biosynthesis of LTs, prostaglandins (PGs), and thromboxanes (TXs), and microsomal degradation of LTB4 to α-COOH-LTB4. SS-hydroxyperoxy-6,8,11,14-eicosatetraenoic (5-HPETE). The enzymes denoted are: (1) 5-lipoxygenase, which is inhibited by zileuton, and (2) the ‘SLS-enzyme’ fatty aldehyde dehydrogenase (FALDH).

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**Subjects and methods**

Patients and treatment schedule

Five patients (Patients 1–5) with SLS, one boy and four girls, aged 14 to 21 years, were treated with zileuton after having obtained informed parental consent and with permission of the hospital’s Medical Ethics Committee. The patients had the characteristic clinical features of SLS including pruritus and juvenile macular dystrophy with crystalline deposits in the retina. They did not suffer from any other disorder besides SLS. Pruritus was a constant and impairing symptom in all patients. Diagnosis of SLS had been proven biochemically by demonstrating FALDH deficiency in cultured skin fibroblasts and by molecular studies of the FALDH gene. Zileuton was administered in 600 mg doses three times daily during the first 1.5 months and 600 mg four times daily during the second part of the study. Extensive clinical, neuroradiological, and laboratory parameters were evaluated at start (t=0) and after 3 months of treatment (t=3). Monitoring of serum transaminases and urinary α-OH-LTB4 was also performed at t=1.5 months.

Clinical observations

Since pruritus scoring systems are lacking for young, mentally handicapped patients, we developed a simple scoring system for the parents based on our experience in the previous case study [12,33]. The parents scored the severity of the child’s pruritus twice daily. The first score represented the parental impression of the child’s sleep disturbance during the preceding night. This score depended mainly on the aspect of the bedclothes and skin and was rated on a three-point scale: 0 = none; 1 = mild; 2 = moderate to severe. At the end of each day they scored the severity of pruritus during that day on a four-point scale: 0 = none; 1 = mild (pruritus without visible scratches); 2 = moderate (pruritus with visible scratches);