Zileuton, an Oral 5-Lipoxygenase Inhibitor, Directly Reduces Sebum Production

Ch.C. Zouboulis  A. Saborowski  A. Boschnakow
Department of Dermatology, Charité University Medicine Berlin, Campus Benjamin Franklin, Berlin, Germany

Introduction
There is evidence that leukotrienes are involved in the development of inflammatory acne lesions [1, 2]. The oral 5-lipoxygenase inhibitor zileuton (Zyflo™, Abbott, Abbott Park, Ill., USA) [3] was approved in 1997 for the prevention and chronic treatment of asthma in the USA and was withdrawn by Abbott in 2003 probably because it did not fulfill the company expectations. In an own previous study, zileuton was not only shown to significantly reduce the number of inflammatory lesions in moderate acne but also to inhibit synthesis of sebaceous lipids, especially of free fatty acids [4]. The latter finding was an intriguing aspect and we have suggested that it may occur due to an effect of zileuton on peroxisome proliferator-activated receptor-α (PPAR-α). PPAR-α regulates inflammatory response as well as differentiation, lipid metabolism, and apoptosis of various cell types, including sebocytes [5]. Interestingly, the 5-lipoxygenase product leukotriene B4 is a natural ligand for PPAR-α [6].

Patient and Methods
A 40-year-old female with mild disseminated sebaceous gland hyperplasia and seborrhea on face, scalp and neck since puberty presented with a greasy, orange-like skin pattern of the temples, mid-face and cheeks but no inflammatory lesions. She had a long-
Zileuton Directly Reduces Sebum Production

Dermatology 2005;210:36–38 37

term treatment with oral estradiol (35 µg)/chlormadinone acetate (2 mg) (Neueunomin®) as well as local treatment with elubiol (Elubiol-C/Elubiol-L®) and subsequently with an enzyme (lactoperoxidase, glucoseoxidase)/rhodanid/lactoferrin system (DermZwo®) for 3 months each without clinical improvement. Histology detected enlarged sebaceous glands with markedly augmented lobules at the upper dermis.

In order to detect whether zileuton directly reduces sebaceous lipid synthesis, as we have suggested before [4], we treated the patient with zileuton at a dosis of 4 × 600 mg/day over 3 weeks after receiving written consent. Casual skin surface lipids (CSSL) of the central forehead were always measured at 4 p.m. using a computerized photometric devise (CapilliCARE®, BME Electronics, Mar- seilles, France). The measurement procedure was as follows: a glass slide was applied to the defined skin area by an applicator, which guarantees a similar pressure for all measurements. The slide was placed in the lector and the software photometrically measured the amount of sebum from the sample on the slide given as percentage of a stored curve representing skin surface lipids in a large population sample. To determine new sebum synthesis (NSS), defined areas of the central forehead and the left temple were wiped twice with ethanol after measuring CSSL. NSS was detected 1 h later using the device as described above.

Table 1. Sebum synthesis before and after treatment with zileuton and low-dose isotretinoin

<table>
<thead>
<tr>
<th></th>
<th>CSSL, %</th>
<th>NSS (1 h), %</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>normal value ≤ 50%</td>
<td>average</td>
<td>change</td>
<td>forehead</td>
</tr>
<tr>
<td>Before treatment</td>
<td>65</td>
<td>47.5</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>Zileuton 4 × 600 mg/day over 3 weeks</td>
<td>50</td>
<td>34.5</td>
<td>-27</td>
<td>35</td>
</tr>
<tr>
<td>6 weeks after zileuton treatment</td>
<td>88</td>
<td>50</td>
<td>0</td>
<td>50</td>
</tr>
<tr>
<td>Isotretinoin 10 mg/2nd day over 2 weeks</td>
<td>52</td>
<td>34</td>
<td>-32</td>
<td>32</td>
</tr>
<tr>
<td>Isotretinoin 10 mg/2nd day over 5 weeks</td>
<td>58</td>
<td>29</td>
<td>-42</td>
<td>29</td>
</tr>
</tbody>
</table>

To determine casual skin surface lipids (CSSL) and new sebum synthesis (NSS), the patient was always invited at 4 p.m. and CSSL were measured at the central forehead, whereas NSS at defined areas of the central forehead and the left temple 1 h after wiping these skin areas twice with ethanol. Measurements were performed with a computerized photometric device.

Results

The patient presented an increased value of CSSL before treatment with zileuton (table 1). Before treatment average NSS was also increased. Under treatment with zileuton CSSL were normalized and NSS decreased. Six weeks after discontinuation of treatment CSSL were found increased again and average NSS had returned to baseline. Subsequently, low-dose oral Isotretinoin (Roaccutane®) 10 mg/2nd day was administered over 5 weeks leading to normalization of NSSL and decreased NSS after 2 and 5 weeks. No change of patients’ orange-like skin pattern could be observed under any of the therapeutic regimens.

Discussion

A few cases of sebaceous gland hyperplasia in young ages have been described with most of them being sporadic and others occurring as a familial disease (OMIM 601700). Boonchai and Leenutaphong [7] described a Thai family with premature sebaceous hyperplasia in 5 consecutive generations. Weisshaar et al. [8] described a family with familial nevoid sebaceous gland hyperplasia in 3 consecutive generations. The pedigree suggested autosomal-dominant inheritance with incomplete penetrance. The disorder presents as solitary or, in most cases, disseminated, elevated, soft, yellow papules with central umbilication on the face and excessive sebaceous secretion. It usually appears during puberty or just afterwards and represents an excellent model to study the effects on the sebaceous lipids in the absence of clinical inflammation. Very-low-dose isotretinoin, such as the dosis administered in our patient, is sufficient to reduce sebaceous gland volume and hyperseborrhea and to temporarily improve this disorder [8]. Zileuton inhibited sebum synthesis to a similar level with that of low-dose isotretinoin in our patient. Therefore, we suggest a direct inhibitory effect of systemic zileuton on sebum synthesis. This effect is transient, since sebum synthesis returned to baseline 6 weeks after discontinuation of treatment. Moreover, no
Effect on sebaceous gland hyperplasia could be clinically observed. On the other hand, zileuton was shown to inhibit sebaceous lipids, especially free fatty acids, and reduce the number of inflammatory lesions in the acne study [4]. Sebaceous free fatty acids exhibit a pro-inflammatory potential [1, 5]. Therefore, inhibition of lipid synthesis, especially of pro-inflammatory lipids, is likely to be the major effect of zileuton on sebaceous glands followed by reduction of inflammatory lesions in acne [4].

References