The Therapeutic Efficacy of OAT-889 (Dual AMCase/CHIT1 Inhibitor) in Comparison to Montelukast in HDM-induced Model of Chronic Airway Inflammation in Mice

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BACKGROUND
Acidic mammalian chitinase (AMCase) and chitotriosidase (CHIT1) are the enzymatically active chitinases, which have been implicated in the pathology of diverse lung diseases. While the mechanisms through which chitinases promote lung inflammation and airway remodeling have not been fully elucidated, several studies have demonstrated that chitinases mediate both the pro-inflammatory and the pro-fibrotic responses in the lung. AMCase expression is upregulated in tissue macrophages and epithelial cells in lungs of asthma patients and CHIT1 activity is elevated in the bronchoalveolar lavage fluid (BALF) from patients with the interstitial lung diseases. To assess effects of inhibition of chitinases on inflammation and lung remodeling and to compare it directly with montelukast – first-line oral therapy in asthma, we evaluated activity of a dual AMCase/CHIT1 inhibitor OAT-889 in a 7-week-long HDM-induced airway inflammation mouse model.

RESULTS

In Vitro Activity

OAT-889 is a highly potent dual AMCase and CHIT1 small molecule inhibitor with a nanomolar activity.

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>IC50 [nM]</th>
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<tbody>
<tr>
<td>AMCase</td>
<td>9</td>
</tr>
<tr>
<td>CHIT1</td>
<td>26</td>
</tr>
<tr>
<td>mAMCase</td>
<td>8</td>
</tr>
<tr>
<td>mCHIT1</td>
<td>29</td>
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In the 7-week-long HDM-induced airway inflammation model OAT-889 administered qd in a therapeutic regimen significantly reduced the total number of leukocytes in BALF. OAT-889 and montelukast moderately reduced the number of eosinophils in BALF.

The anti-inflammatory effects of OAT-889 and montelukast correlated with a significant reduction of chitinolytic activity in BALF and plasma.

CONCLUSIONS

OAT-889 demonstrated a profound anti-inflammatory activity in the chronic asthma model in mice as demonstrated by a reduction of the total cell number in BALF and IgE concentration in plasma. These effects were further confirmed by a histopathological assessment of peribronchial inflammation in the lung tissue. These results provide a rationale for developing a dual AMCase/CHIT1 inhibitor for the treatment of asthma.

MATERIALS AND METHODS

ETHICAL ACTS

For determination of inhibitory activity of the compound, the recombinant enzymes (AMCase and CHIT1), 4-methylumbelliferyl-β-D-N-acetylglucosaminide hydrate or 4-methylumbelliferyl-β-D-N-acetylglucosaminide substrates, enzyme and varying concentrations of the inhibitor in citrate assay buffer pH 5.2 were incubated at 37°C for 60 minutes. Substrate hydrolysis product 4-methylumbelliferyl was measured fluorimetrically.

EXPERIMENTAL: 7-weeks-old HDM-induced Asthma Inflammation Model in Mice

Four groups (n=10) of age-matched 8-week-old female C57BL/6 mice were exposed to intranasal HDM (10 µg in PBS) 5 times per week for 7 weeks. Control mice were intranasally challenged with PBS at times of HDM challenges (n=10). OAT-889 and montelukast (889 IC18) were administered orally once a day at dose of 30 mg/kg (2003) to select NaCl (dissolved in water) starting from week 5 onwards. The scheme is presented in the figure below.

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