Characterization of VBY-129, a Cathepsin S Inhibitor Efficacious in a Mouse Model of Psoriasis

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Abstract

Cathepsin S is a cysteine protease that catalyzes the final proteolytic step in the processing of invariant chain in specific antigen presenting cells, essential in the maturation and loading of MHC Class II with antigenic peptides and subsequent activation of CD4+ T cells. Continuous presentation of antigenic self-peptides is thought to be involved in the maintenance of chronic diseases in autoimmune disorders including psoriasis. Inhibition of cathepsin S is likely to result in a reduction in humoral immune processes without an impact on innate immunity. ViroBay has developed a novel oral cathepsin S inhibitor, VBY-129, which may provide a new therapeutic option to treat psoriasis and other autoimmune diseases. VBY-129 is a neutral, competitive reversible inhibitor of cathepsin S with a mean inhibition constant (K_i) of 0.24 ± 0.046 nM. VBY-129 is greater than 1000-fold selective against other human cathepsins. VBY-129 inhibited cathepsin S activity and subsequent invariant chain processing in a human B cell line, as well as primary human peripheral blood mononuclear cells (PBMCs), resulting in the accumulation of the Iip10 intermediate in the processing of invariant chain with an IC_50 of 159 ± 29 nM respectively. VBY-129 was efficacious in reducing disease in therapeutic dosing of the mouse adoptive transfer SDI™ model of psoriasis. Two weeks of once-a-day dosing with VBY-129 at 50mg/kg reversed established disease as measured by changes in inflammation-induced ear thickness and ear histology. Sustained inhibition of cathepsin S was required for maximal efficacy. VBY-129 entered human clinical testing in a Phase 1 single-ascending-dose and multiple-dose trial in healthy subjects. These data indicate that VBY-129 may be an efficacious and novel oral therapeutic for the treatment of psoriasis with a unique mechanism of action.

Introduction

Cathepsin S Biology

- A competing new target for autoimmune disease
- Cysteine protease expressed in antigen presenting cells (APCs)
  - B cells, dendritic cells, and macrophages
- Cleaves the invariant chain (Ii) of MHC Class II dimer receptor
- Activates maturation of Class II, loading of antigenic peptides, and expression of the cell surface
- Activates presentation of endocytosed exogenous antigen
- Activates CD4+ helper T cells

Cathepsin S Inhibitors should have efficacy in diseases in which CD4+ T cells are activated via MHC Class II-antigen presentation

Results

Table 1. Enzyme inhibition activities and Fold Selectivity

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>K (app) [nM]</th>
<th>Fold Selectivity vs CatS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cathepsin S</td>
<td>0.00024</td>
<td>1</td>
</tr>
<tr>
<td>Cathepsin L</td>
<td>2.8</td>
<td>12,000</td>
</tr>
<tr>
<td>Cathepsin B</td>
<td>0.7</td>
<td>2,800</td>
</tr>
<tr>
<td>Cathepsin V</td>
<td>0.5</td>
<td>2,000</td>
</tr>
<tr>
<td>Cathepsin F</td>
<td>7.3</td>
<td>20,000</td>
</tr>
<tr>
<td>Cathepsin K (HPLC)</td>
<td>3.7</td>
<td>5,000</td>
</tr>
</tbody>
</table>

Figure 1: VBY-129 inhibits the cathepsin S enzyme and invariant chain processing in a human B cell line. In cells pre-treated with VBY-129, Iip10 is reduced compared to control. Cells were treated with VBY-129 for 4 hours. Percent inhibition of the cathepsin S enzyme was measured by fluorescent imaging of a cell-permeable activity-based probe. Complete inhibition of the cathepsin S enzyme in cells is required to inhibit invariant chain processing.

Figure 2: Psoriasis pharmacokinetics and pharmacodynamics of VBY-129. VBY-129 is orally bioavailable in mice and inhibits invariant chain processing in vivo in specific B cells.

Figure 3: Psoriasis: human skin with fluorescent detection of Iip10 with a fluorophore. Cathepsin S inhibitors should have efficacy in diseases in which CD4+ T cells are activated via MHC Class II-antigen presentation.

Conclusion

1. Selective oral cathepsin S inhibitors VBY-129 and VBY-891 are efficacious in animal models of psoriasis and atopic dermatitis
- To our knowledge, this is the first demonstration of efficacy of cathepsin S inhibitors in these models
- The efficacy of ViroBay inhibitors in models of inflammatory skin disease indicates that cathepsin S is critical for maintenance of activated T cells

2. VBY-129 has completed a Phase I single ascending dose and multiple dose study in healthy subjects. VBY-891 and VBY-036 are clinical candidates in advanced stage of development

3. Cathepsin S inhibitors may be efficacious and novel oral therapeutics for the treatment of psoriasis and atopic dermatitis, with a novel mechanism of action

4. Because cathepsin S inhibitors will effect only cell-mediated immunity and will not affect the action of a specific subset of T cells, they are expected to be immunomodulatory and not immunosuppressive.