UD-014, a novel, selective, orally available, long-acting vascular adhesion protein-1 inhibitor improves albuminuria in a streptozotocin (STZ)-induced diabetic nephropathy model in rats

Masaru Shinohara, Koji Itoh, Tetuo Kawaguchi, Hiroyoshi Kawada, Akishi Ninomiya, Kenichi Komori, Noriaki Iwase and Shigeru Ushiyama, Pharmaceuticals Research Laboratory, Ube Industries, Ltd., Ube

1. Abstract

Vascular adhesion protein-1 (VAP-1)/semicarbazide-sensitive amine oxidase (SSAO) is recognized to increase in plasma of patients with inflammation-associated diseases, and is considered a potential therapeutic target for various inflammatory diseases, including diabetic complication.

UD-014 is a novel, potent and orally active SSAO/VAP inhibitor with an extended duration of action. The aim of this study is to investigate the efficacy of UD-014 on kidney function in a STZ-induced diabetic nephropathy model in rats. UD-014 inhibited the human SSAO/VAP-1 potently and highly selectively with an IC50 value of 3.2 nM. When orally administered at single doses (0.1-10 mg/kg) to normal SD rats, UD-014 inhibited plasma SSAO/VAP-1 activity dose dependently up to 24 hrs. SD rats were subjected to type-1 diabetes by an i.v. injection of streptozotocin (50 mg/kg) and orally administered with UD-014 (1 and 3 mg/kg) once daily for 4 weeks after STZ treatment. Urinary albumin and urinary L-FABP, a marker of proximal tubule disorder and oxidative stress, were reduced significantly by UD-014 treatment. SSAO/VAP-1 activity in the plasma was measured on the last day. SSAO/VAP-1 activity increased about 2-fold in the STZ rats compared to the control rats. UD-014 inhibited the elevated plasma SSAO/VAP-1 activity dose-dependently. We also observed that SSAO/VAP-1 was expressed in the glomeruli in the kidney using immunofluorescence staining, and co-localized with α-SMA, a marker of transformed mesangial cells. These results suggest that the SSAO/VAP-1 inhibitor, UD-014, has a potential for a therapeutic agent to ameliorate kidney functions in diabetic nephropathy.

2. In vitro Pharmacological profile

Potency and Selectivity

<table>
<thead>
<tr>
<th>IC50 [nM]</th>
<th>SSAO/VAP-1</th>
<th>MAO-A</th>
<th>MAO-B</th>
<th>DMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>UD-014</td>
<td>3.2</td>
<td>6,100</td>
<td>12,000</td>
<td>690</td>
</tr>
<tr>
<td>Molseline</td>
<td>5.2</td>
<td>550</td>
<td>0.51</td>
<td>ND</td>
</tr>
<tr>
<td>Clopentine</td>
<td>ca.10,000</td>
<td>2.6</td>
<td>4.10</td>
<td>ND</td>
</tr>
<tr>
<td>Parglyline</td>
<td>ca.10,000</td>
<td>2,000</td>
<td>73</td>
<td>ND</td>
</tr>
</tbody>
</table>

UD-014 is a potent and selective inhibitor of SSAO/VAP-1.

SSAO/VAP-1 activity was determined by a radio-enzymatic procedure using 14C-labelled benzylcaine as a substrate, MAO-A/B activity was measured by a fluorescence-based method, using non-labelled benzylcaine.

3. PK and PD profile

(A) Plasma SSAO/VAP-1 activity from day 1 to day 28 after STZ injection

(B) Expression of SSAO/VAP-1 in the kidney

(C) Serum glucose

(D) Urine L-FABP (4 weeks)

4. Effect of UD-014 on kidney function in STZ-induced diabetic nephropathy model in rats

(A) Protocol

(B) Body weight

(C) Albuminuria (3 weeks)

(D) Albuminuria (4 weeks)

(E) Plasma SSAO/VAP-1 activity

5. SSAO/VAP-1 expression in STZ-induced diabetic nephropathy model in rats

(A) Plasma SSAO/VAP-1 activity increases in plasma and SSAO is upregulated in glomeruli in the kidney in STZ rats.

(B) Expression of SSAO/VAP-1 in the kidney

(C) Identification of SSAO/VAP-1 upregulated cells

Conclusion

1. UD-014 is a newly identified, orally available, potent, selective, and long-acting SSAO/VAP-1 inhibitor.

2. UD-014 improves kidney functional marker (albuminuria and L-FABP, a marker of proximal tubule disorder) at 1 and 3 mg/kg, q.d. without affecting the body weights and albuminuria in the STZ-induced diabetic nephropathy model in rats.

3. In the STZ model, SSAO activity increases in plasma and SSAO is upregulated in the glomeruli in the kidney.

These results suggest that UD-014 has a potential for a therapeutic agent to ameliorate kidney functions in diabetic nephropathy.

Please refer to 499-P for the MOA studies.

COI Disclosures, All authors: UBE Employers

Contact information: Name: Shigeru Ushiyama E mail: 34752u@ube-ind.co.jp