Focal segmental glomerulosclerosis (FSGS) is commonly associated with nephrotic syndrome (NS) and is the most common primary glomerular disease leading to end-stage renal disease in the United States.

Histochemically, FSGS is characterized by focal lesions of the glomerulus due to podocyte damage, loss of foot processes, and podocyte apoptosis.

Proteinuria correlates with loss of glomerular permeability and proteinuria.

The goal of podocytology is to understand the basic mechanisms of those podocyte abnormalities that lead to proteinuria.

Statin treatment is effective in reducing albuminuria in patients with proteinuria, which highlights the need for future research to identify the potential role of statins in inhibiting podocyte apoptosis.

Reperfusion cortical injection (RCI)

RCI (H. P. Acthar® Gel, Mallinckrodt ARD Inc., Hazelwood, MO, USA) is a naturally derived product that contains a highly purified proteolytic analogue of adrenocorticotropic hormone (ACTH).

ACTH activates all of the 5 known mammalian receptor (MCR1-5) and has anti-inflammatory, anti-fibrotic, and anti-proliferative effects through activation of MCR on podocytes and glomerular cells.

RCI could potentially improve glomerular permeability and reduce proteinuria by targeting podocyte apoptosis and inflammation.

The studies presented here examined the renal protective effect of RCI in a non-inflamed, prednisolone-resistant proteinuria model that induced FSGS-like lesions.

Study Objective

This study assessed the efficacy of RCI on the reduction of proteinuria and protection of renal damage in a prednisolone-resistant model.

Methods

Preclinical porcine aminonucleoside (PAN) FSGS model

The pan-nucleoside model of FSGS generates progressive glomerulosclerosis and renal interstitial fibrosis, with levels of renal inflammation.

Pannucleoside is an immunosuppressant that inhibits podocyte protein synthesis and causes direct damage to the visceral epithelial cells in the glomerulus (podocytes).

The model was used to study the effects of RCI on the development and progression of PAN-induced FSGS.

Female Sprague-Dawley rats were treated with PAN to induce renal damage.

The treatment models of FSGS include 4 doses of PAN (0, 14, 21, and 28 days) and RCI (3, 10, and 30 IU/kg) were administered starting from day 7 after every week (Figure 1 and Table 1).

In the 12-week model, FSGS was induced within 5 doses of PAN (days 0, 14, 21, 28, and 35), and RCI was administrated at 10, 20, and 30 IU/kg every other day starting on day 1 (Figure 1 and Table 1).

Results

6-week study

At day 28, 30 IU/kg RCI significantly reduced proteinuria compared with PAN-saline treatment, p<0.05 (Figure 2A).

Significantly more podocyte survival (marker of podocyte injury) was expressed in the glomeruli of PAN-rats treated with 30 IU/kg RCI than saline-treated controls, p<0.05 (Figure 2B).

Podocyte expression inversely correlated with total urine protein concentration; r=-0.57, p<0.001 (Figure 2C).

Figure 2. RCI decreased proteinuria and increased podoplanin expression in podocytes.

Table 1. Study designs for rat FSGS model

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Glomerular Changes</th>
<th>Tubular Injury</th>
<th>Interstitial Fibrosis</th>
<th>Total Kidney Injury Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN 30 IU/kg</td>
<td>RCI 30 IU/kg</td>
<td>1.4 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>2.3 ± 1.0</td>
<td>8.0 ± 1.3</td>
</tr>
<tr>
<td>PAN 30 IU/kg</td>
<td>RCI 10 IU/kg</td>
<td>1.6 ± 0.5</td>
<td>1.0 ± 0.0</td>
<td>1.5 ± 0.5</td>
<td>5.9 ± 1.4</td>
</tr>
<tr>
<td>PAN 30 IU/kg</td>
<td>RCI 1 IU/kg</td>
<td>1.8 ± 0.5</td>
<td>2.0 ± 0.8</td>
<td>2.3 ± 1.0</td>
<td>9.0 ± 1.3</td>
</tr>
</tbody>
</table>

Table 2. RCI reduced histopathological scores at 8 weeks

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Fibrosis</th>
<th>Glomerular Changes</th>
<th>Tubular Injury</th>
<th>Interstitial Fibrosis</th>
<th>Total Kidney Injury Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline</td>
<td>1.6 ± 0.5</td>
<td>1.8 ± 0.5</td>
<td>2.3 ± 1.0</td>
<td>8.0 ± 1.3</td>
<td></td>
</tr>
<tr>
<td>RCI 1 IU/kg</td>
<td>1.6 ± 0.5</td>
<td>1.0 ± 0.0</td>
<td>1.5 ± 0.5</td>
<td>5.9 ± 1.4</td>
<td></td>
</tr>
<tr>
<td>RCI 10 IU/kg</td>
<td>1.8 ± 0.5</td>
<td>2.0 ± 0.8</td>
<td>2.3 ± 1.0</td>
<td>9.0 ± 1.3</td>
<td></td>
</tr>
</tbody>
</table>

Figure 3. PAN-induced mcrf mRNA expression in glomeruli.

Conclusions

In a preclinical FSGS model of renal injury, RCI was effective at reducing proteinuria, renal injury, and inflammation.

RCI reduced glomerular injury and increased podoplanin expression.

These data provide preclinical evidence to support RCI as a treatment for FSGS.

References

Acknowledgments and Disclosures

Presented at the National Kidney Foundation Spring Clinical Meeting in Austin, Texas April 13-15, 2019.