A randomised, placebo controlled clinical trial of the aldose reductase inhibitor CT-112 as management of corneal epithelial disorders in diabetic patients

M Nakahara, K Miyata, S Otani, T Miyai, R Nejima, S Yamagami, S Amano

D iabetic patients are vulnerable to such corneal epithelial disorders as superficial punctate keratopathy (SPK) and epithelial erosion. Moreover, damage to the corneal epithelium during vitreous surgery and retinal photocoagulation sometimes induces vision threatening corneal epithelial complications such as persistent epithelial defects and recurrent erosion. Two mechanisms have been proposed for these diabetic keratopathies, an activated polyol pathway and accumulation of advanced glycation end products (AGE) in the basement membrane of the corneal epithelium.” Efficacies of inhibitors of aldose reductase, the first enzyme of polyol pathway, have been evaluated as anti-polyol pathway drugs. The oral aldose reductase inhibitor (ARI) ONO-2235 decreases corneal epithelial changes in diabetic patients through recovery of corneal sensation and tear production. In addition, topical ARL CT-112 (5-[3-ethoxy-4-pentyloxyphenyl]-2,4-thiazolidinedione) improves corneal sensation in clinical cases and corneal epithelial barrier function in galactose fed rats. These findings are suggestive but not conclusive. We therefore established a randomised, double masked clinical trial in which diabetic patients were treated topically with CT-112 or a placebo; we evaluated changes in corneal fluorescein staining based on our earlier reported scoring method and measured corneal epithelial permeability to fluorescence with an anterior fluorophotometer.

**PATIENTS AND METHODS**

This was a prospective, randomised, double masked, placebo controlled study. The research protocol adhered to the tenets of the Declaration of Helsinki. Participants comprised a consecutive series of diabetic patients who visited Miyata Eye Hospital. Exclusion criteria were contact lens wearer, tear deficiency (less than 5 mm in Schirmer test), active ocular infection, atopic keratoconjunctivitis, and severe superficial punctate keratopathy graded more than A1D1 in our earlier reported method. In addition, other exclusion criteria were the intake of oral ARI within 6 months and the use within 30 days of ocular ointments and eye drops such as sodium hyaluronate, sodium chondroitin sulfate, vitamin B2, and other drugs known to modify the ocular surface. After we obtained their informed consent, 36 diabetic patients were enrolled and randomly assigned to treatment with 0.25% eye drops of CT-112 (Senju Pharmaceutical, Osaka, Japan) or a placebo four times a day for 8 weeks. The placebo was the base solution of CT-112. Two patients in the CT-112 group were excluded because one was found to have used a prohibited eye drop before treatment and the other could not undergo the weekly follow up examination. In total, 34 patients (22 in the CT-112 treated group and 12 in the placebo group) were followed for the duration of the study.

SPK magnitude was scored according to our reported method that uses lesion area and density as parameters. Scores are defined in table 1. Area grade is defined as the total SPK lesion area. Grading is shown as combined of area and density grades—for example, A2D3. In this study, the sum of the area and density grades has been designated the score for each eye.

Corneal epithelial permeability to fluorescence was measured with a slit lamp fluorophotometer (FL-500, Kowa, Tokyo) as described previously. Briefly, autofluorescence intensity was measured at the central corneal stroma before the instillation of fluorescein, and the value obtained designated the background fluorescence. Sodium fluorescein (3 μl; Alcon, Fort Worth, TX, USA) distilled to 0.5% in balanced salt solution (BSS Plus, Alcon) was instilled to the lower conjunctival sac through a micropipette. Ten minutes after instillation, the ocular surface was washed thoroughly with 20 ml of BSS PLUS. Thirty minutes after instillation, fluorescence intensity was measured at the central corneal stroma. The background intensity was subtracted from the average of 10 measurements. Values obtained were converted to fluorescein concentrations based on calibration curves obtained with a 0.5 mm wide slide glass corneal model.

Corneal sensitivity was measured with a Cochet-Bonnet anaesthesiometer. Nylon length measured in millimetres was

**Abbreviations:** AGE, advanced glycation end products; ARI, aldose reductase inhibitor; BSS, balanced salt solution; SPK, superficial punctate keratopathy
Table 1  Definitions of the area and density grades of superficial punctate keratopathy

<table>
<thead>
<tr>
<th>Area (total sum of the affected area)</th>
<th>Density</th>
</tr>
</thead>
<tbody>
<tr>
<td>A0: no punctate staining</td>
<td>D0: no punctate staining</td>
</tr>
<tr>
<td>A1: the area occupies less than one third of the cornea</td>
<td>D1: sparse density</td>
</tr>
<tr>
<td>A2: the area occupies one third to two thirds of the cornea</td>
<td>D2: moderate density</td>
</tr>
<tr>
<td>A3: the area occupies more than two thirds of the cornea</td>
<td>D3: high density and lesions overlap</td>
</tr>
</tbody>
</table>

Table 2  Participants’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>CT-112 group</th>
<th>Placebo group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of participants</td>
<td>22</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>69.5 (9.85)</td>
<td>69.4 (7.63)</td>
<td>0.15*</td>
</tr>
<tr>
<td>Duration of diabetes mellitus (years)</td>
<td>18.2 (8.88)</td>
<td>19.7 (8.93)</td>
<td>0.67*</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.97 (1.44)</td>
<td>7.52 (1.28)</td>
<td>0.37*</td>
</tr>
<tr>
<td>Schirmer test (mm/5 min)</td>
<td>9.8 (3.3)</td>
<td>12.0 (4.4)</td>
<td>0.21*</td>
</tr>
</tbody>
</table>

*Unpaired t test.

Table 3  Time course changes in superficial punctate keratopathy scores

<table>
<thead>
<tr>
<th></th>
<th>CT-112 group</th>
<th>Placebo group</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>0.46 (0.86)</td>
<td>0.67 (0.99)</td>
<td>0.52*</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0.82 (1.18)</td>
<td>0.50 (0.91)</td>
<td>0.42*</td>
</tr>
<tr>
<td>8 weeks</td>
<td>0.82 (1.18)</td>
<td>0.67 (0.99)</td>
<td>0.71*</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test.

DISCUSSION

The anterior fluorophotometer used detects subclinical changes in the corneal epithelium by quantitatively measuring its barrier function.15 21 In Göbbels’ and our previous studies,15 21 when the fluorophotometer was used, the average fluorescein concentrations in the diabetic patients were significantly higher than in the non-diabetic controls, indicative that the corneal epithelial barrier function is impaired in diabetic patients. This study showed that average fluorescein uptakes in the CT-112 group after 4 and 8 weeks of treatment were significantly less than in the placebo group, whereas there was no significant difference between the groups before treatment, evidence that there was recovery from impairment of corneal epithelial barrier function in the diabetic patients after topical application of CT-112.

In diabetic patients, increased epithelial permeability to fluorescein is correlated positively with the duration of diabetes mellitus and HbA1c.15 21 In our study, no significant differences were found in the background data for the CT-112 and control groups, confirmation of the validity of the comparison between the two groups. On the other hand, the study subjects were heterogeneous in terms of duration of diabetes mellitus, absence/presence of retinopathy, and preoperative ocular surface status. A future study with larger population is needed to clarify the effects of these background status.

ARI is posited to improve the corneal epithelial changes caused by diabetes through the recovery of corneal sensation and increased tear production.10 11 In our study, however, the application of CT-112 improved corneal epithelial barrier function but did not change corneal sensation or the fluorescein staining score. With the method we used, it may have been difficult to detect any subtle improvement in corneal sensation and change in the fluorescein score because our diabetic participants happened to have low fluorescein staining scores and almost normal corneal sensation, even before treatment. In contrast, change in corneal barrier.

Average corneal sensitivities in the CT-112 and placebo groups before treatment and 4 and 8 weeks after are shown in table 4. Average corneal sensitivity did not differ significantly between the two groups at any time point.

Time courses of the average fluorescein concentrations in the CT-112 and control groups before and after treatment are shown in figure 1. Although the average concentrations did not differ significantly before treatment, they did differ significantly 4 and 8 weeks after it (4 weeks, p = 0.0327; 8 weeks, p = 0.0143).

Figure 1  Time courses of the average fluorescein concentrations and standard deviations before and after treatment of the CT-112 (open circles) and control groups (solid squares). The average fluorescein concentrations do not differ significantly between the groups before treatment but do differ significantly 4 and 8 weeks after treatment (4 weeks, p = 0.0327; 8 weeks, p = 0.0143).
The corneal epithelial barrier function can be weakened in diabetic patients. This hypothesis needs to be tested by further experiments.

**Table 4** Time course changes in corneal sensitivity

<table>
<thead>
<tr>
<th></th>
<th>CT-112 group (g/mm²)</th>
<th>Placebo group (g/mm²)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>1.00 (0.19)</td>
<td>0.99 (0.08)</td>
<td>0.91*</td>
</tr>
<tr>
<td>4 weeks</td>
<td>0.96 (0)</td>
<td>0.96 (0)</td>
<td>0.99*</td>
</tr>
<tr>
<td>8 weeks</td>
<td>0.97 (0.04)</td>
<td>0.97 (0.04)</td>
<td>0.94*</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test.

**REFERENCES**


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