Treatment of recent onset central retinal vein occlusion with intravitreal tissue plasminogen activator: a pilot study

Agnès Glacet-Bernard, Dagmar Kuhn, Andrew K Vine, Hassiba Oubraham, Gabriel Coscas, Gisèle Soubrane

Abstract
Aims—To study the effects of intravitreal tissue plasminogen activator (tPA) in recent onset central retinal vein occlusion (CRVO).
Methods—15 patients with recent onset CRVO (from 1–21 days’ duration, mean 8 days) were given 75–100 µg of tPA intravitreally associate with low dose low molecular weight heparin. CRVO was perfused in nine patients and with mild ischaemia not exceeding 100 disc diameters in six patients. Follow up ranged from 5 to 21 months for 14 patients (mean 8 months).
Results—Visual acuity measurement, macular threshold (Humphrey perimeter), fluorescein angiography with the scanning laser ophthalmoscope with special emphasis on retinal circulation times, and retinal perfusion were performed at days 0, 1, and 8 and months 1, 3, and 6.
Conclusion—Intravitreal administration of fibrinolytic agents could be an appropriate treatment for retinal vein occlusion. However, thrombus formation as the primary event is always questioned, and the pathogenesis of retinal vein occlusion remains unclear.

Systemic administration of fibrinolytic agents had been performed in small series of CRVO patients.13–17 This treatment showed beneficial effects on retinal blood flow in some cases, but was associated with the risk of massive vitreous haemorrhage and severe systemic complications (cerebral haemorrhage) leading to the termination of some of these studies. Systemic administration of fibrinolytic agents is therefore not recommended in retinal vein occlusion.

Intravitreal administration of fibrinolytic agents, which avoids systemic complications of fibrinolytic therapy, has been evaluated in a pilot study (Lahey et al, presented at the AAO Annual Meeting, Chicago, 1996). This pilot study was designed to evaluate the effects of intravitreal injection of low doses of tissue plasminogen activator (tPA) combined with low molecular weight heparin on ocular status and particularly on retinal blood flow, and its influence on the course of CRVO.

Patients and methods
Fifteen patients were recruited between January 1997 and April 1998 for the study. The major inclusion criteria were the presence of CRVO of recent onset (less than 3 weeks) and a decrease in visual acuity (20/40 or less). CRVO was defined as the presence of retinal haemorrhages in all four quadrants. Diagnosis was always confirmed by fluorescein retinal angiography.

Excluded from the study were patients with late onset CRVO (duration of symptoms of more than 3 weeks); patients with only a slight decrease in visual acuity; patients with CRVO...
already complicated with anterior or posterior neovascularisation or already treated by laser photocoagulation; patients with other ocular disorders known to decrease visual acuity (such as uncontrolled glaucoma, cataract, age related macular degeneration, and diabetic retinopathy); pregnant women and children.

The nature of the study was explained to each patient, who were asked to give informed consent, according to the Helsinki-Tokyo declaration. The study protocol was approved by the ethics committee (Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale) of the Henri Mondor hospital.

A complete ophthalmological examination was performed just before the intravitreal injection (day 0), and at days 1, 3, and 6. Examination included oculocutaneous and medical history, visual acuity measurement with ETDRS chart, macular threshold testing with the Humphrey perimeter (Carl Zeiss, Le Pecq, France), biomicroscopy, application tonometry, fundus examination, and fluorescein angiography with the scanning laser ophthalmoscope (SLO, Rodenstock), with special emphasis on retinal circulation times and retinal capillary bed evaluation. The retinal transit time was defined as the difference between the laminar venous flow and the arterial flow in the major retinal vessels. Ischaemic areas were measured in disc diameters on central and peripheral fields. Improvement or deterioration in visual acuity was documented as two or more lines of difference on the logarithmic visual acuity chart. Improvement in macular threshold corresponded to an increase of two decibels in the measured area of 20 DD.

### Table 1 Clinical course of CRVO after intravitreal TPA injection, classified from the shorter to the longer duration of symptoms before treatment

<table>
<thead>
<tr>
<th>Case no</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Associated medical conditions</th>
<th>CRVO duration before TPA injection (days)</th>
<th>Dose of TPA</th>
<th>Initial visual acuity</th>
<th>Initial form of CRVO</th>
<th>Visual outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>64</td>
<td>M</td>
<td>Hypertension, smoking, activated protein C resistance, CRVO in the second eye</td>
<td>1</td>
<td>75 µg</td>
<td>20/70</td>
<td>non-ischaemic CRVO</td>
<td>20/20, non-ischaemic CRVO</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>F</td>
<td>Hypercholesterolaemia, glaucoma, HRT</td>
<td>2</td>
<td>100 µg</td>
<td>20/40</td>
<td>non-ischaemic CRVO</td>
<td>CF, ischaemic CRVO, PRP</td>
</tr>
<tr>
<td>3</td>
<td>70</td>
<td>M</td>
<td>Hyperlipidaemia</td>
<td>4</td>
<td>75 µg</td>
<td>20/30</td>
<td>peripheral ischaemic area of 30 DD</td>
<td>CF, ischaemic CRVO, PRP, preretinal neovascularisation</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>None</td>
<td>5</td>
<td>100 µg</td>
<td>20/400</td>
<td>non-ischaemic CRVO</td>
<td>20/400, CME, unchanged ischaemic area</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>M</td>
<td>Glaucoma</td>
<td>5</td>
<td>100 µg</td>
<td>20/200</td>
<td>non-ischaemic CRVO with cilioretinal AO</td>
<td>20/125, non-ischaemic CRVO, CME</td>
</tr>
<tr>
<td>6</td>
<td>57</td>
<td>M</td>
<td>Diabetes, stopped smoking</td>
<td>5</td>
<td>75 µg</td>
<td>20/40</td>
<td>non-ischaemic CRVO</td>
<td>20/400, ischaemic CRVO, CME</td>
</tr>
<tr>
<td>7</td>
<td>53</td>
<td>M</td>
<td>Myocardial infarction, hyperlipidaemia, stopped smoking</td>
<td>5</td>
<td>75 µg</td>
<td>20/30</td>
<td>non-ischaemic CRVO</td>
<td>non-ischaemic CRVO, CME</td>
</tr>
<tr>
<td>8</td>
<td>74</td>
<td>M</td>
<td>Stopped smoking</td>
<td>5</td>
<td>100 µg</td>
<td>20/70</td>
<td>non-ischaemic CRVO</td>
<td>non-ischaemic CRVO, CME</td>
</tr>
<tr>
<td>9</td>
<td>37</td>
<td>F</td>
<td>Smoking</td>
<td>6</td>
<td>75 µg</td>
<td>20/40</td>
<td>non-ischaemic CRVO</td>
<td>20/15, non-ischaemic CRVO</td>
</tr>
<tr>
<td>10</td>
<td>72</td>
<td>F</td>
<td>Hypertension, overweight, hypercholesterolaemia</td>
<td>8</td>
<td>75 µg</td>
<td>20/40</td>
<td>non-ischaemic CRVO</td>
<td>non-ischaemic CRVO, CME</td>
</tr>
<tr>
<td>11</td>
<td>72</td>
<td>F</td>
<td>Hypertension</td>
<td>8</td>
<td>100 µg</td>
<td>CF</td>
<td>ischaemic CRVO</td>
<td>CF, ischaemic CRVO, PRP, non-ischaemic CRVO, CME</td>
</tr>
<tr>
<td>12</td>
<td>49</td>
<td>M</td>
<td>Hyperlipidaemia, overweight, stopped smoking</td>
<td>14</td>
<td>75 µg</td>
<td>20/50</td>
<td>peripheral ischaemic area of 30 DD</td>
<td>20/40, unchanged ischaemic area, CME</td>
</tr>
<tr>
<td>13</td>
<td>61</td>
<td>M</td>
<td>Hypertension, myocardial infarction, stopped smoking</td>
<td>15</td>
<td>75 µg</td>
<td>20/160</td>
<td>non-ischaemic CRVO</td>
<td>20/25, non-ischaemic CRVO</td>
</tr>
<tr>
<td>14</td>
<td>67</td>
<td>M</td>
<td>Hypertension, glaucoma, myocardioc infarction, hypertension, hyperlipidaemia, angina pectoris, stopped smoking</td>
<td>21</td>
<td>75 µg</td>
<td>20/400</td>
<td>peripheral ischaemic area of 20 DD</td>
<td>CF, ischaemic CRVO, ruberosis iridis, PRP, non-ischaemic CRVO</td>
</tr>
<tr>
<td>15</td>
<td>60</td>
<td>M</td>
<td>Hyperlipidaemia, angina pectoris, stopped smoking</td>
<td>21</td>
<td>75 µg</td>
<td>20/50</td>
<td>non-ischaemic CRVO</td>
<td>20/20, non-ischaemic CRVO</td>
</tr>
</tbody>
</table>

PRP = panretinal photocoagulation; HRT = hormone replacement therapy for postmenopausal woman; DD = disc diameters; CMO = cystoid macular oedema; AO = artery occlusion; CF = counting fingers.
Treatment of recent onset CRVO with intravitreal tissue plasminogen activator

showed a moderate but significant slow down

perimeter) were grossly similar to those of

visual acuity ranging from 20/200 to 20/30,

visual acuity of 20/30 or better, five (36%) had

At the end of follow up, five (36%) eyes had

worsened in four eyes (28%).

A slight increase in retinal haemorrhages was

observed in six cases. New haemorrhages

occurred in previous ischaemic areas in four

eyes, and in two well perfused eyes. They were

often perivascular, transient, and without compi-
lcations.

The CRVO remained perfused in six eyes

(43%) and converted into an ischaemic form in
two eyes (14%). Four eyes (28%) with initially
mild or moderate ischaemia had an extension of
ischaemic areas. Therefore retinal ischaemia

was present at the end of follow up in eight eyes

(57%), including six cases (43%) in which it
appeared or extended, and two cases with no
change. Rubeosis iridis occurred in one eye,
pre-retinal neovascularisation in one other eye.
Panretinal photocoagulation was performed in
five eyes and limited peripheral photocoagula-
tion in one eye.

Posterior vitreous detachment probably oc-
curred in four eyes between days 1 and 7. Posterior vitreous detachment was difficult to ascertain by ocular examination in many cases and data about vitreous status were often questionable.

No complications were observed (no retinal detachment, vitreous haemorrhage, or endoph-
thalmitis) as a result of either the tPA injection

in retinal circulation times (of 2–3 seconds) in
six eyes (50%) immediately after injection, and
no change in six other eyes; no improvement in
retinal circulation times was observed at day 1.

At the end of follow up, an improvement in
retinal circulation times was observed in five
eyes (38%), a slow down in one eye, and no
change in seven eyes (54%).

Figure 1 Distribution of initial and final visual acuity in patients treated by intravitreal tPA injection.

Figure 2 Changes in visual acuity immediately, at 1 week, and at the end of follow up, after tPA injection.

Figure 3 Changes in macular threshold after tPA injection.

Before treatment, three (20%) eyes had visual acuity of 20/30 or better, nine (60%) had visual acuity ranging from 20/200 and 20/30, and three (20%) eyes had less than 20/200 (Fig 1). On fluorescein angiography, CRVO was well perfused in nine (60%) eyes; two other eyes had a good perfusion of peripheral retinal but displayed small ischaemic areas (2 and 5 disc diameters) at the posterior pole corresponding to a combined occlusion of a cilioretinal artery. Peripheral ischaemic area was present in four (27%) eyes at the first visit (20–30 disc diameters in three eyes, and 100 disc diameters in one eye).

tPA injection was accomplished according to the protocol without complication. Ophthalmological examination was performed according to the protocol schedule except for one patient who failed to return for follow up after the day 1 visit. Mean follow up was 8 months (5–21 months) for the others.

At day 1 after tPA injection, visual acuity dramatically improved in one patient (the one treated on the first day of a perfused CRVO), while it was unchanged in eight eyes (53%) and worsened in six eyes (40%, Fig 2). One week after injection, visual acuity had improved in three eyes (22%), was unchanged in nine eyes (64%), and had worsened in two eyes (14%).

At the end of follow up, visual acuity was improved in five eyes (36%), unchanged in five eyes (36%), and worsened in four eyes (28%).

At the end of follow up, five (36%) eyes had visual acuity of 20/30 or better, five (36%) had visual acuity ranging from 20/200 to 20/30, and four (28%) eyes had less than 20/200 (Fig 1). Variations of macular threshold (Humphrey perimeters) were grossly similar to those of visual acuity, as shown in Figure 3.

Fluorescein angiography with the SLO showed a moderate but significant slow down
or the subcutaneous low molecular weight heparin administration.

No correlation was found between visual acuity improvement and tPA doses (75 or 100 μg), or the time of the injection.

Discussion
Recombinant human tissue type plasminogen activator (tPA) is a relatively clot selective fibrinolytic agent with a molecular weight 70 000 Da. Advantages of tPA over the non-selective fibrinolytic agents (such as streptokinase or urokinase) are its superior results in achieving reperfusion (demonstrated in myocardial infarction), higher efficacy in the lysis of older thrombi, its lack of antigenicity, and its enhanced fibrin selectivity, which leads to greater therapeutic activity. tPA was first successfully administered in ocular surgery to dissolve traumatic hyphaema or postcataract fibrinous membranes. Particularly striking was the rapidity of the fibrinolysis with disappearance of all products of fibrin dissolution within 4 hours. Results in treatment of postvitrectomy fibrin formation are controversial. tPA has been found effective in subretinal haemorrhages related to macular degeneration, either by the intravitreal or subretinal route. Intravitreal tPA was first tried in CRVO by Lahey et al to attempt to dissolve intravenous thrombi and to avoid systemic complications of intravenous administration of fibrinolytic agents.

In this study, 15 CRVO eyes treated with intravitreal injection of tPA were followed for a mean period of 8 months and underwent ophthalmological examination and fluorescein angiography with the SLO at each visit. Results on the first day and on the first week after the injection are disappointing because, based on previous studies on fibrin dissolution, we had expected a rapid effect on retinal outflow obstruction. A dramatic improvement in visual acuity was observed in only one case immediately after treatment. On the contrary, 40% of the eyes experienced an initial decrease in visual acuity and a slow down in retinal circulation times on fluorescein angiography, but the majority of them returned to their initial level in an 8 day period. One week after treatment, about the fifth of eyes showed an improvement in visual acuity and in retinal circulation times. tPA did not seem then to influence retinal circulation times and visual acuity within the first days of the injection. The transient decrease in visual acuity and retinal circulation times might be explained by a mild inflammatory reaction induced by the injection, but no inflammatory signs, media opacities, or increase in intraocular pressure were observed after treatment.

Our results seem similar to those previously reported by Lahey, using a similar protocol of treatment (intravitreal injection of 65–110 μg of tPA), who described an improvement in visual acuity to 20/40 or better in 33% of the patients followed for 6 months. Thus, tPA injection seems to favourably influence long term visual outcome, but does not improve early signs of CRVO, which was expected in our study.

No correlation was observed between visual outcome and the time of the treatment (Table 1), except for the patient treated on the day of the occurrence of the CRVO, a 64 year old hypertensive man with activated protein C resistance, who had experienced CRVO in the fellow eye 7 years earlier, with poor visual outcome (final visual acuity of 20/200). Improvement in visual acuity observed on the first day persisted with longer follow up, with total recovery at the final visit: final visual acuity was 20/20 in the treated eye. This suggests that tPA injection may be effective within the first hours of the CRVO, or that this treatment is effective only in patients with abnormalities of haemostasis leading to thrombus formation; in the majority of cases with normal haemostasis, the main contributory factor to CRVO is probably hyperviscosity which may not be influenced by fibrinolytic agents.

These findings may explain why intravitreal injection seems less effective than haemodilution therapy, which leads to a dramatic decrease in blood viscosity and rapidly improves retinal circulation times, with long term efficacy on visual acuity.

Good results have also been reported in a pilot study using intra-arterial fibrinolysis in CRVO. Urokinase (30 000 IU), delivered into the ophthalmic artery by transfemoral catheterisation, gave a dramatic improvement in visual acuity in 38% of cases, especially when CRVO was associated with delayed arterial retinal filling on fluorescein angiography. These cases of combined central retinal artery and central retinal vein occlusion represent probably a different entity which seems to respond more successfully to fibrinolytic therapy than standard CRVO. Intra-arterial injection would allow fibrinolytic agents to reach the site of the occlusion more efficiently than intravitreal injection. However, the diffusion of tPA though the vitreous gel and its passage through the venous wall remain to be elucidated. The occurrence of posterior vitreous detachment in some of our patients tends to demonstrate that tPA is effective in the vitreous cavity during some hours or days. Lewis recently showed that tPA does not diffuse through the neural retina to reach the subretinal space in the rabbit, but the passage through the venous wall and the presence of tPA at the lamina cribrosa have not yet been analysed.

In this study, no complications occurred after intravitreal injection of tPA, which appeared to be easy and safe. We did not observe retinal pigment changes after injection, as described by Ruiz LaPuente et al. This treatment is also free of contraindications, in contrast with haemodilution or intra-arterial fibrinolysis. However, a randomised trial is needed to establish if intravitreal injection of tPA actually improves visual outcome in CRVO.
Treatment of recent onset CRVO with intravitreal tissue plasminogen activator

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