Diabetic Macular Edema – New Possibilities for Treatment

The article summarizes data from the literature about new possibilities of the diabetic macular edema treatment. Comparing intravitreal application of triamcinolone and laser photocoagulation, the better effect of the laser treatment with its lower side effects was proven. In combined treatment of triamcinolone and laser photocoagulation comparing with the laser monotherapy, no better effect of the combined therapy was proven. The intravitreal implant releasing fluocinolone acetonide significantly improved the bestcorrected visual acuity (BCVA), but caused cataract progression and elevation of the intraocular pressure. Intravitreal application of ranibizumab significantly improved BCVA in the monotherapy, and in the combination with the retinal laser photocoagulation did as well. Intravitreal application of bevacizumab significantly improved BCVA, but its use is off-label only. Afflbercept is in the final stage of clinical trials.

Key Words: laser photocoagulation, triamcinolone, fluocinolone acetonide, ranibizumab, bevacizumab, aflibercept


INTRODUCTION

Diabetic retinopathy (DR) and diabetic macular edema (DME) are the most frequent complications of diabetes. Clinically significant DME affects 6 to 10% of patients with diabetes, and together with DR is the most frequent cause of blindness in persons aged 20-74 years in advanced industrial societies (5). Current treatment of DME covers laser treatment of the retina and surgical treatment via pars plana vitrectomy (PPV). The fundamental prerequisite for the treatment of DME and DR is correct compensation for diabetes, arterial hypertension and dyslipidemia. New possibilities for treatment of DME are intravitreally applied by corticosteroids and vascular endothelial growth factor (VEGF) blockers.

INTRAVITREAL APPLICATION OF CORTICOSTEROIDS

Corticosteroids inhibit the expression of VEGF and at the same time have an anti-inflammatory effect. Both lead to a reduction of vascular hyper-permeability and consequently to a reduction of macular edema. Corticosteroids are administered either directly into the vitreous area in the form of a solution (triamcinolone), or in the form of an implant, which is gradually broken down, with slow release of the active substance dexamethasone. Another possibility is the suture of a permanent intravitreal implant to the sclera, with slow release of the active substance fluocinolone acetonide into the vitreous area. A biodegradable implant slowly releasing dexamethasone has now been approved for the treatment of edemas in retinal vein occlusion (Ozurdex, Allergan, Inc.), and at present a three-year study is in progress, intended to evaluate its efficacy and safety in the case of DME. The results of three-year, multicentric, randomised, clinical trials with a permanent implant slowly releasing 0.59 mg of fluocinolone acetonide have demonstrated a high degree of efficacy. A statistically significant improvement of best corrected visual acuity (BCVA) by 3 or more rows has been determined in 31% of patients with DME. However, at the same time a worse safety profile of the preparation has been determined, because during the course of the observation cataract surgery was necessary for 91% of the treated patients, and occurrence of intraocular tension higher than 30 mm Hg was determined in more than 60% of patients. One third of these patients had to undergo a surgical procedure (filtration operation), in three patients it was necessary to explant the implant (10). The efficacy and safety of triamcinolone in the treatment of DME has been determined by a range of studies. Within the framework of the trial conducted by the Diabetic Retinopathy Clinic Research Network (DRCR.net), the efficacy of triamcinolone acetoni de (Trivaris, Allergan, Inc.) was determined in a dose of 1 mg and 4 mg as against standard treatment by laser photocoagulation of the retina. The trial included 840 eyes of 693 patients, who were randomised into three groups. The two-year results are presented in table 1. The trial demonstrated a superior effect of treatment of DME by laser than by intravitreal application of triamcinolone in terms of its smaller side effects (6). In a continuation of the trial by DRCR.net, the aim was to compare the efficacy of photocoagulation of the retina against combined treatment by laser with intravitreal application of triamcinolone. In the second two branches, the efficacy of intravitreal application of ranibizumab (Lucentis, Genentech Inc., Novartis Pharma AG) was compared in combination with early and deferred laser photocoagulation of the retina. The annual results of this trial are presented in table 2. In the case of the group of patients treated with triamcinolone in combination with photocoagulation of the retina, the resulting BCVA was the same as in the group treated only by laser. Upon an evaluation of the sub-group of patient with an artificial lens, the resulting BCVA was significantly better and was comparable with combined treatment with ranibizumab. The reason for the worse BCVA result was the cataractogenic effect of the corticoid. Another undesirable effect was elevation of intraocular pressure. Upon combined treatment with ranibizumab, both BCVA and central retinal thickness (CRT) were significantly improved in comparison with treatment of the retina by laser, with a good safety profile of the pharmaceutical (4).

INTRAVITREAL APPLICATION OF VEGF BLOCKERS

The VEGF blockers used in the treatment of DME include bevacizumab (Avastin, Genentech, Inc., Roche Ltd.) and ranibizumab. In the final phase of the clinical
Triamcinolone 1 mg +3 -9% +9 -139 3 -17 14 -77
Triamcinolone 4 mg -102 -3 40 11% 14% -131
Ranibizumab + early laser -13 4 (+8 in case of pseudophakia)
Laser 51 20 14% -127 14%

The pharmaceutical approved for the treatment of DME is ranibizumab. The
first group and 68 µm in the second group. These results were attained most
frequently by the application of 9 injections of bevacizumab and three laser
treatments of the retina (8). Arevalo et al. compared two doses of bevacizumab in
a group of 139 eyes with DME: 1.25 mg and 2.5 mg. Over 2 years of treatment they
observed the comparable improvement of BCVA. In the group with a 1.25 mg dose
of bevacizumab BCVA was improved from an average initial value of 20/150 to an
average value of 20/75 in the final evaluation, and in the group with a 2.5 mg
dose of bevacizumab there was an improvement from an initial value of 20/168 to
20/114 after 2 years. An average of 5.8 injections were applied in both groups in
the observed period (1).

The pharmaceutical approved for the treatment of DME is ranibizumab. The
fundamental clinical trials which demonstrated its efficacy in the case of DME
were the RESOLVE and RESTORE trials. The main aim of the RESOLVE trial was to
determine whether ranibizumab is effective on patients with DME. The patients
were randomised into three branches. In the first branch a placebo was applied, in
the other two branches ranibizumab was administered in two different doses of
0.3 and 0.5 mg. Ranibizumab was applied once per month for the first three
months and thereafter every month upon fulfilment of the relevant criteria. On average
it was necessary to administer 10 injections of ranibizumab per year. In both
groups with ranibizumab a significant improvement of BCVA was determined in
comparison with the placebo, with an average gain of +7.8 letters. The reduction of
CRT was by 129 µm was also statistically significant. The number and characteristics of severe undesirable effects were no different between the group treated with ranibizumab and the group treated with the placebo (7).

The RESTORE trial aimed to determine whether ranibizumab was effective in
monotherapy or in combination with laser treatment. The design of the trial was similar to
that of the RESOLVE trial, in the first three months an injection of ranibizumab was
applied once per month and further injections were administered upon fulfilment
of the relevant criteria. Indication for laser treatment was dependent upon the
decision of the individual investigators. The result of the study was a statistically
significant improvement of BCVA in patients in both branches treated with ranibi-
zymab in comparison with standard laser treatment of the retina. The difference in
BCVA between monotherapy by ranibizumab and a combination of ranibizumab
was minimal. Upon treatment with ranibizumab, either in monotherapy
or in combination with laser treatment, there was an improvement of BCVA by 3
or more rows of ETDRS optotypes in 23% of cases. The reduction of CRT was similar in
both groups with ranibizumab and was significantly higher than in patients treated
with laser monotherapy. The average number of applications of ranibizumab,
whether in monotherapy or in combination with laser, was 7 injections per year.
No endophthalmitis was reported in the entire trial (9).

The results of these studies formed the basis for the following recommendations. Ranibizumab is administered once per month until the time when the patient’s
visual acuity is stable over the course of three consecutive months of evaluation.
If there is no improvement of visual acuity after the administration of the first three
injections, continued treatment is not recommended. After stabilisation of BCVA,
monitoring thereof once per month is recommended. Treatment is recommenced if a deterioration of visual acuity due to the influence of DME is determined upon observation of the patient.

The DA VINCI clinical trial assessed the effect of aflibercept on DME. Over
the course of a six-month observation period its effect was evaluated in four various
dosing scheme in comparison with laser treatment of the retina. The patients were
randomised into groups with intravitreal application of 0.5 and 2 mg of aflibercept

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Laser photoocoagulation</th>
<th>Triamcinolone 1 mg</th>
<th>Triamcinolone 4 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change of BCVA from commencement of treatment (number of letters)</td>
<td>+1</td>
<td>-2</td>
<td>-3</td>
</tr>
<tr>
<td>Improvement of BCVA by 3 or more rows of optotypes (%)</td>
<td>18</td>
<td>14</td>
<td>17</td>
</tr>
<tr>
<td>Change of CRT from commencement of treatment (mmmm)</td>
<td>-139</td>
<td>-86</td>
<td>-77</td>
</tr>
<tr>
<td>Arrest of increase of IOP by more than 10 mmHg (%)</td>
<td>10</td>
<td>20</td>
<td>40</td>
</tr>
<tr>
<td>Cataract surgery (%)</td>
<td>13</td>
<td>23</td>
<td>51</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of treatment</th>
<th>Laser</th>
<th>Ranibizumab + early laser (3-10 days after injection)</th>
<th>Ranibizumab + deferred laser (≥ 6 M after injection)</th>
<th>Triamcinolone + early laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA (number of letters)</td>
<td>+3</td>
<td>+9</td>
<td>+4 (+8 in case of pseudophakia)</td>
<td></td>
</tr>
<tr>
<td>OCT (µ)</td>
<td>-102</td>
<td>-131</td>
<td>-137</td>
<td>-127</td>
</tr>
<tr>
<td>Increase of IOP ≥ 10 mmHg</td>
<td>11%</td>
<td>9%</td>
<td>9%</td>
<td>50%</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>14%</td>
<td>14%</td>
<td>14%</td>
<td>59%</td>
</tr>
<tr>
<td>Number of applications over 1 year (median)</td>
<td>8</td>
<td>9</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>
every 4 weeks, 2 mg of aflibercept every month for a period of the first three months and subsequently every 8 weeks, and 2 mg of aflibercept every month for the period of the first three months and subsequently according to the clinical finding. In the groups with aflibercept there was an average improvement of BCVA by 8.5-11.4 letters in comparison with a gain of 2.5 letters in the group of patients treated by laser (2).

CONCLUSION

The present treatment of DR and DME is laser photocoagulation of the retina and surgical treatment. Laser treatment above all enables stabilisation of the clinical finding. According to the Early Treatment Diabetic Retinopathy Study (ETDRS) an improvement by more than three rows is possible approximately in 3% of patients (3). In the case of diffuse DME, above all if it is in connection with vitreomacular traction, PPV is used successfully, since removal of traction leads to a reduction of macular edema and an improvement of visual acuity. Of the new therapeutic options, corticosteroids and VEGF A blockers are used. The efficacy of trimacinolone is not greater than the efficacy of laser treatment of the retina, as demonstrated by the DRCR.net trial (4, 6). Fluocinolone acetonide is used in the form of a permanent implant applied to the vitreous area. The preparation is effective, nevertheless it has a worse safety profile, and within three years more than 90% of patients required cataract surgery, more than 60% of patients had intraocular pressure greater than 30 mmHg at least once over the course of three-year observation, which required surgery in more than 30% of these patients, mostly in the form of a filtering operation (10). Avastin improves BCVA in patients with DME, but its use is possible only off-label. Lucentis brings a statistically significant improvement of BCVA and the pharmaceutical has a good safety profile, does not lead to the formation of a cataract or elevation of intraocular tension (7, 9). In the final phase of the clinical tests aflibercept is applied (2).

LITERATURE