Predictive Factors for Visual Acuity After Intravitreal Triamcinolone Treatment for Diabetic Macular Edema

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Objective: To evaluate which factors influence maximum gain in best-corrected visual acuity after intravitreal injection of triamcinolone acetonide as treatment for diffuse diabetic macular edema.

Methods: This prospective clinical interventional study included 53 eyes with diffuse diabetic macular edema receiving an intravitreal injection of about 20 mg of triamcinolone. The mean±SD follow-up was 10.2±7.6 months.

Results: In a multiple linear regression analysis, maximum gain in best-corrected visual acuity after the intravitreal injection of triamcinolone was significantly (P < .001) and negatively correlated with an increased degree of macular ischemia and a higher preoperative visual acuity. Improvement in best-corrected visual acuity was significantly and positively correlated with increased degree of macular edema (P = .001). Change in best-corrected visual acuity after the intravitreal triamcinolone injection was statistically independent (P > .15) of age, sex, pseudophakia, and macula grid laser treatment before inclusion into the study. The results were comparable for gain in visual acuity at 6 months after the injection.

Conclusion: Pronounced macular edema may have a positive impact, and marked macular ischemia and a high preoperative best-corrected visual acuity may have a negative impact, on an increase in best-corrected visual acuity after intravitreal triamcinolone injection in patients with diabetic macular edema.


INTRAVITREAL TRIAMCINOLONE acetonide has increasingly been used as a treatment for intracocular proliferative, edematous, and neovascular diseases, such as central retinal vein occlusion,1-3 neovascular glaucoma without or with cataract surgery,4,5 proliferative vitreoretinopathy,6 chronic prephthisical ocular hypotony,7 chronic uveitis,8-11 persistent pseudophakic cystoid macular edema,12-14 exudative age-related macular degeneration,15-27 proliferative diabetic retinopathy,28,29 and retinal telangiectasia,30 and in other clinical situations, such as sympathetic ophthalmia.31-33 Recently, intravitreal triamcinolone also has been applied in eyes with diffuse diabetic macular edema,34-41 leading to an increase in visual acuity in some eyes.

With regard to the reported adverse effects of intravitreal triamcinolone, such as corticosteroid-induced ocular hypertension, pseudoendophthalmitis, and sterile or infectious endophthalmitis,42-48 it is important to know which patients may benefit from a treatment and should receive the therapy and which patients may not benefit from the therapy and should likely not undergo the treatment. It was, therefore, the purpose of the present study to evaluate which predictive factors are associated with an increase in visual acuity after an intravitreal injection of triamcinolone in patients with diabetic macular edema.

Methods: This clinical, interventional, prospective case-series study included 43 patients (53 eyes) (25 women; 23 right eyes) with diffuse diabetic macular edema who received a single intravitreal injection of about 20 mg of triamcinolone acetonide as the only treatment for diffuse diabetic macular edema during the study period. Their mean±SD age was 66.5±10.0 years (range, 28.2-81.5 years), and their mean±SD refractive error was 0.70±1.37 diopters (range, −1.75 to 4.50 diopters). The best-corrected visual acuity (BCVA) at baseline ranged between 0.03 and 0.50 (mean±SD, 0.15±0.09; median, 0.10 [Snellen charts]). Converted to logMAR (logarithm of the minimum angle of resolution) units, the preoperative BCVA measured a mean±SD of 0.92±0.28 (range, 0.30-1.52; median, 1.00). The intraocular pressure ranged between 9 and 21 mm Hg (mean±SD, 15.4±3.0 mm Hg; me-
amcinolone were described in detail previously.47 The technique and the preparation of triamcinolone acetonide for diabetic macular edema.

dian, 15 mm Hg). During the follow-up, no additional ocular surgery, including a cataract operation, was performed. All patients were fully informed about the experimental character of the treatment. All patients signed an informed consent. The ethics committee of the university had approved the study, which followed the tenets of the Declaration of Helsinki.

All patients received an intravitreal injection of about 20 mg of crystalline triamcinolone in 0.2 mL of isotonic sodium chloride solution (0.9% sodium chloride). The injection was performed through the temporal inferior pars plana, at 3.0 to 3.5 mm from the limbus. The technique and the preparation of triamcinolone were described in detail previously.47

At study baseline, the BCVA and intraocular pressure were determined, and fluorescein angiography was performed. The intraocular pressure was determined by Goldmann applanation tonometry. The degree of macular ischemia was graded as follows: 0 indicates no ischemia; 1, nonperfused area(s) outside of the temporal vessel arcade; 2, one nonperfused area within the temporal vessel arcade but without contact to the foveal avascular zone; 3, more than 1 nonperfused area within the temporal vessel arcade but without contact to the foveal avascular zone; 4, nonperfused area with contact to the foveal avascular zone, with parts of the fovea perfused; 5, whole fovea nonperfused, with the diameter of the nonperfused area smaller than or equal to 1 disc diameter; and 6, whole fovea nonperfused, with the diameter of the nonperfused area larger than 1 disc diameter. For the definition of an optic disc area, we used the description of the Macular Photocoagulation Study.68 The amount of macular edema was also graded on a scale ranging from 0 (no edema) to 6 (maximal edema), defined by the intensity of stain on standard nonstereoscopic photographs. For the statistical analyses of macular edema, the categories 0 to 2, 3 to 4, and 5 to 6 were combined; for the statistical analysis of macular ischemia, the categories 0 to 1, 2 to 4, and 5 to 6 were combined. In 27 (51%) of the eyes, macular grid laser coagulation was performed at least 3 months before inclusion into the study. The number of laser lesions was counted on the fluorescein angiograms. The assessment of macular edema, macular ischemia, and number of grid laser lesions was performed by a single examiner (J.B.J.) in a masked fashion without knowledge of the clinical outcome of the patient.

After the intravitreal injection, the patients were usually reexamined the first day after injection, followed by reexaminations at about 1-month intervals. The mean ± SD follow-up was 10.2 ± 7.6 months (median, 7.7 months; range, 1.0-32.6 months). The visual acuity was measured using Snellen charts. The BCVA was recorded on all occasions.

The change in intraocular pressure was analyzed using the t test for paired samples. Two different outcome measures were analyzed: maximum gain in BCVA and change in BCVA after approximately 6 months. For the latter outcome, the visual acuity measurement at the follow-up next to 6 months was selected. For both outcomes, the change in visual acuity was tested nonparametrically (Wilcoxon signed rank test). To obtain normal distributed values, in the regression analyses identifying predictive factors for change of visual acuity, the logMAR scale was used. Predictive factors were tested using simple and multiple linear regression analysis. In these analyses, binary variables were coded using dummy variables. For quantitative and ordinal predictors, linearity was examined by testing quadratic terms. None of these terms were statistically significant; thus, all of these variables were included using only 1 linear term. Multivariate analysis used backward and forward variable selection; results were identical for both approaches. Statistical analyses were performed by using a commercially available statistical software package (SPSS for Windows, version 11.5; SPSS Inc, Chicago, Ill). The level of statistical significance was .05 (2-sided) in all statistical testing.

During follow-up, the BCVA increased significantly (P < .001) by a mean ± SD of 2.8 ± 2.4 Snellen lines (mean ± SD, −0.28 ± 0.23 logMAR units) from the preoperative mean ± SD of 0.15 ± 0.09 (Snellen charts; median, 0.10) to a maximal mean ± SD of 0.28 ± 0.17 (Snellen charts; median, 0.25) (Figure 1). Of the 53 eyes, 34 (64%) had an improvement of 2 lines or more in BCVA and 10 (19%) had an improvement of 1 line. One (2%)
of the eyes lost visual acuity on follow-up by 1 line. After 6 months, 30 (57%) of the eyes had an improvement in BCVA and 13 (25%) of the eyes had a loss of visual acuity ($P = .006$). The intraocular pressure increased significantly ($P < .001$) from a mean±SD of 15.4±3.0 mm Hg (median, 15 mm Hg) at baseline to a mean±SD maximum of 20.7±5.6 mm Hg (median, 20 mm Hg; range, 11-38 mm Hg), with 20 (38%) of the eyes developing a maximum intraocular pressure higher than 21 mm Hg. Of the 53 eyes, 21 (40%) and 8 (15%) experienced an increase in intraocular pressure by more than 5 and more than 10 mm Hg, respectively.

Univariate regression analysis revealed that the postinjection change in BCVA, expressed in logMAR units, was statistically independent of age ($P = .79$), sex ($P = .18$), right or left eye ($P = .35$), pseudophakia ($P = .22$), and status after macular grid laser therapy ($P = .78$). The degree of macular ischemia at baseline showed a significant ($P = .003$) and negative association with the postinjection change in BCVA (Figure 2). Furthermore, a high baseline visual acuity, a low increase in intraocular pressure, and a small degree of macular edema were negatively correlated with the postinjection change in BCVA (Table). Results were not substantially different for visual acuity after approximately 6 months (Table).

In the multiple linear regression analyses, the predictors that were univariately significant were included. Baseline visual acuity and degree of macular ischemia were associated negatively, and degree of macular edema was positively correlated, with the change in BCVA. Approximately half ($R^2 = 0.52$, $P < .001$) of the variation in change in visual acuity could be explained by the model (Table). Results were not substantially different for visual acuity after approximately 6 months (Table); however, prediction was less accurate for this outcome ($R^2 = 0.40$, $P < .001$). In the multiple regression analysis, the increase in intraocular pressure was no longer significantly ($P > .15$) associated with the postinjection change in visual acuity (Table).

One of the main reasons for reduced visual acuity in patients with diabetic retinopathy is macular edema. It can be divided into a focal type and a diffuse type. The Early Treatment Diabetic Retinopathy Study has shown that focal laser coagulation of leaking circumscribed retinal areas in eyes with focal diabetic macular edema is helpful for improving visual outcome compared with no treatment. In eyes with diffuse macular edema, however, laser treatment cannot be focused on localized spots of leakage because the entire macula is involved. Diffuse diabetic macular edema is, therefore, much less responsive to macular laser coagulation than focal diabetic macular edema. The recommendation for grid laser treatment covering the entiremacular region with a fine net of small laser coagulation spots has been controversial because only a few randomized prospective studies proving the efficacy of this treatment have been published. Recently, investigations have been reported on the use of intravitreal triamcinolone as a treatment for diabetic retinopathy and, especially, diffuse diabetic macular edema. These studies revealed that after intravitreal injection of triamcinolone, visual acuity can increase in some eyes. The response to intravitreal triamcinolone showed, however, a marked interindividual variability, with some eyes exhibiting a pronounced increase in visual acuity and other eyes showing no change in visual acuity.

The results of the present study suggest that there are some factors that are associated with the change in BCVA after the intravitreal triamcinolone injection. Eyes with a large ischemic area in the macula showed a less marked increase in BCVA after the intravitreal triamcinolone injection than eyes with less marked macular ischemia. This corresponds to the clinical experience that intravitreal triamcinolone might increase BCVA as much as macular ischemia will allow it.

Another predictive factor for the change in visual acuity after the intravitreal injection of triamcinolone may be the amount of macular edema. The more pronounced macular edema was, the higher the increase in visual acuity after the injection, in univariate and multivariate statistical analyses (Table). This reflects clinical observations that intravitreal triamcinolone can lead to an almost complete restitution ad integrum of the macula in an anatomical sense, with optical coherent tomographs showing a marked decrease in macula thickening with restoration of the foveal contour line after the intravitreal injection.

Figure 2. Scattergram showing the correlation between preinjection visual acuity and best-corrected postoperative visual acuity (in Snellen lines) during follow-up, depending on the degree of macular ischemia (0-1 indicates mild; 2-4, moderate; and 5-6, marked).
cal experiences that intravitreal triamcinolone can increase visual acuity as much as macular ischemia, and not macular edema, allows it.

An additional predictive factor for change in BCVA after the intravitreal triamcinolone injection was visual acuity at baseline. The lower the baseline visual acuity was, the more marked its increase was. Because eyes with a relatively high preoperative visual acuity also showed an increase in BCVA, the data of the present study do not allow the conclusion that the intravitreal injection of triamcinolone should only be performed in eyes with a low visual acuity. However, in the present study, only eyes with a baseline visual acuity of 0.50 or less were included. Partially, the effect might be explained by the regression to the mean phenomenon. This means that because of random variation, extreme results tend toward the mean of the sample in a repeated measurement if conditions do not change between both time points.57

Based on the results of the present investigation, and in agreement with previous reports and studies,34-41 one might infer that patients with persisting diffuse diabetic macular edema may undergo intravitreal injection of triamcinolone. There are, however, limitations of the present study that have to be considered if generalized statements are drawn from the investigation. The most important limitation may be the design as a case series study. Because it was the purpose of the study, however, to search for factors that may influence the change in BCVA after the intravitreal injection of triamcinolone, a comparative randomized study design with a study

<table>
<thead>
<tr>
<th>Independent Variable*</th>
<th>Univariate Regression Analysis</th>
<th>Multivariate Regression Analysis†</th>
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<tr>
<td></td>
<td>( \beta ) Value</td>
<td>( R^2 )</td>
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<tr>
<td>Baseline VA‡</td>
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<td>At 6 mo</td>
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<td>Macular edema</td>
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</tr>
<tr>
<td>Difference in intraocular pressure</td>
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<tr>
<td>At 6 mo</td>
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<tr>
<td>Maximum</td>
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<tr>
<td>At 6 mo</td>
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<tr>
<td>Pseudophakia</td>
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<td>At 6 mo</td>
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<tr>
<td>Hard exudates</td>
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<td>At 6 mo</td>
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<td>Macular ischemia</td>
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<tr>
<td>At 6 mo</td>
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<tr>
<td>Maximum</td>
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<td>At 6 mo</td>
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<td>Grid laser (yes or no)</td>
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<tr>
<td>At 6 mo</td>
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<td>0.01</td>
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</table>

Abbreviations: NA, data not applicable; VA, visual acuity.

*Maximum indicates regression analysis for maximum gain in VA; at 6 months, regression analysis for gain in VA at 6 months after the injection. For sex, 1 indicates female; and 2, male. For left/right eye, 1 indicates right; and 2, left. Length of follow-up (in months) was log transformed. For pseudophakia, 0 indicates aphakia; and 1, pseudophakia. For macular edema, the degree of macular ischemia was graded using the following scale: 0, no ischemia; 1, nonperfused area(s) outside of the temporal vessel arcade; 2, one nonperfused area within the temporal vessel arcade but without contact to the foveal avascular zone; 3, more than 1 nonperfused area within the temporal vessel arcade but without contact to the foveal avascular zone; 4, nonperfused area with contact to the foveal avascular zone, with parts of the fovea perfused; 5, whole fovea nonperfused, with the diameter of the nonperfused area smaller than or equal to 1 disc diameter; and 6, whole fovea nonperfused, with the diameter of the nonperfused area larger than 1 disc diameter. The amount of macular edema was graded on a scale ranging from 0 (no edema) to 6 (maximal edema), defined by the intensity of stain on standard nonstereoscopic photographs.

†\( R^2 = 0.52 \) for maximum gain and \( R^2 = 0.40 \) for gain after 6 months (\( P < .001 \) for both).

‡The VA was measured in logMAR (logarithm of the minimum angle of resolution) units.
group and a control group might not have been absolutely necessary. Furthermore, the primary outcome, best visual acuity during follow-up, is susceptible to statistical bias toward overoptimistic results. However, the preservation of the maximum level of visual acuity might be feasible if therapy is continued. Moreover, it was the aim of this study to establish predictive factors and not to prove efficacy of treatment with intravitreal triamcinolone. Considering these arguments, we decided to analyze the best visual acuity during the whole follow-up and the visual acuity at 6 months after the injection. By using the second approach, 13 (25%) instead of 1 (2%) of 53 eyes showed a loss in visual acuity compared with the baseline value. Interestingly, predictive factors did not differ substantially between both approaches. Finally, the present study using 53 eyes had only moderate power. The analysis was explorative, and no formal correction for multiple testing was applied in simple or multiple regression analyses. For simple regression analysis, P < .004 may be regarded as confirmatory.

Another limitation of the study might be that, although intravitreal triamcinolone will have increased the cataract, cataract surgery was not performed in combination with nor after the intravitreal injection of triamcinolone. The visual acuity–reducing effect of progressive cataract, however, might have hidden parts of a visual acuity–improving effect of triamcinolone so that this limitation of the study might serve to support the conclusion of the investigation that intravitreal triamcinolone might increase visual acuity in patients with diffuse diabetic macular edema. It may not be likely that the increase in cataract changed the influence of predictive factors on the change in BCVA after the intravitreal injection. Another limiting factor might be the relatively few patients included in the study. Despite the relatively few patients, however, the postinjection BCVA was significantly better than the baseline values, and the influence of some variables on the postinjection visual acuity was statistically significant, with an error probability of less than 5%. An additional limitation of the study might be the relatively high dose of triamcinolone injected into the eye. In all preceding studies of other study centers injecting intravitreal triamcinolone acetamide as treatment for diffuse diabetic macular edema or cystoid macular edema due to various reasons, a dose of 2 to 8 mg was used. The reason why we continued to inject about 20 mg of triamcinolone was that, from the beginning of our ongoing triamcinolone investigations that now include more than 550 patients with various diseases, we have used the same dosage and have not seen adverse effects so far; adverse effects have also not been described in the studies using the lower dose. Future studies concerning dosage are necessary to define the optimal dose in view of tolerability, frequency of adverse effects, and duration of action. 58, 59

In conclusion, the present study suggests that the increase in BCVA after the intravitreal injection of about 20 mg of triamcinolone in patients with diffuse diabetic macular edema might positively be influenced by a low degree of macular ischemia, a high degree of preoperative macular edema, and a relatively low preoperative visual acuity.

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