LUCENTIS IN THE TREATMENT OF DIABETIC MACULAR OEDEMA, TWO-YEAR RESULTS

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SUMMARY

Aim: To evaluate, on the basis of two-year observations, the effectiveness of intravitreal treatment with Ranibizumab in patients with diabetic macular edema (DME) unresponsive to the previous laser treatment.

Cohort and Methods: A retrospective study evaluates 29 eyes of 29 patients with diffuse DME unresponsive to their previous laser treatment. The group of the patients consisted of 16 males (55.1%) and 13 females (44.8%); their mean age was 71.3. The mean duration of diabetes mellitus was 13 years (3–20). 19 patients (65.5%) were treated with insulin, 10 patients (34.4%) were treated with peroral antidiabetics (PAD); the mean HbA1c value was 52 mmol/l. The treatment was started with 3 initial doses of intravitreal injections of Ranibizumab 0.5 mg. There was a one--month interval between the applications. Subsequent evaluations and administrations of the following injections were made in the pro re nata (PRN) mode; the check-ups were carried out every month during the first year and on average every 3 months in the second year. The monitored parameters: the best corrected visual acuity (BCVA) measured on ETRDS (Early Treatment Diabetic Retinopathy Study) optotypes, the central retinal thickness (CRT). These parameters were monitored prior to the treatment and then in the 3rd, 6th, 9th, 12th, 18th and 24th months.

Results: A statistically significant improvement in the mean value of BCVA was detected. From the initial 65.4 ±10.61 letters it improved by 11.2 letters ($p < 0.05$) at the end of the two-year observations, when the improvement of BCVA by min six letters (compared to the initial VA) was achieved in 19 eyes (65.5%), stabilization (±5 letters) was detected in 7 eyes (24.1%) and worsening (by more than five letters) occurred in 3 eyes (10.3%). The mean CRT value declined after 2 years from the initial 450.5 ±139.3 µm by 89.5 µm ($p = 0,006$). The decline in CRT was significant in comparison with the baseline values (the mean of 450.45 µm) in 4 out of the 6 monitored intervals. The mean number of Ranibizumab injections was 5.45 ±1.8 during the first year of treatment, and 3.18 ±1.27 injections in the second year.

Conclusions: Intravitreal Ranibizumab injections reduce CRT and improve BCVA in patients with DME who did not show any improvement after laser treatment. The best effect was documented after the three initial applications of Ranibizumab and then at the end of the monitoring period. In two-year time period we detected CRT decline in 79.3% of the patients and BCVA improvement (by 15.3 letters on average) in 65.5% of the patients.

Key words: macular edema, Lucentis, anti-VEGF, visual acuity, optical coherence tomography

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INTRODUCTION

DME is the most common cause of VA (visual acuity) decline in patients with diabetic retinopathy (DR), and it is a serious health and socio-economic problem. The pathogenesis of DME is multifactorial and its development and progression occur primarily due to hyperglycaemia, hyperlipidaemia and systemic hypertension. Chronic hyperglycaemia can consequently damage endothelial cells (the internal haematoretinal barrier – HRB) of the retinal vessels. DME development is affected in addition by increased levels of vasoactive factors in the eye and by the state of the vitreoretinal interface [1].

DME is typical of fluid accumulation in the anatomically predisposed central part of the retina – the macula. The liquid is accumulated either inside the cells or extracellularly in the outer plexiform and inner nuclear layer [2]. The cause of intracellular oedema is a change in the distribution of cellular ions, which results in an excessive accumulation of sodium ions inside the cells and consequent hyperosmolar oedema. Extracellular oedema is mainly associated with internal and external HRB disorders [3].

The occurrence of DME is associated with the duration of diabetes mellitus (DM) and the stage of DR. DME was reported in a 10-year diabetes anamnesis in 20.1% of patients with type 1 DM, in 13.9% of patients with type 2 DM treated with PAD and in 25.4% of patients with type 2 DM treated with insulin [4]. In advanced stages of non-proliferative DR, a 63% incidence of DME is reported; while in proliferative DR, the incidence of DME is up to 74% [3].

Diffuse DME is one of the least impactable complications of DR. Chronic macular oedema causes irreversible damage to photoreceptors, so early treatment is important. Treatment of DME currently includes laser retinal photocoagulation, intravitreal administration of corticosteroids or anti-VEGF agents, and pars plana vitrectomy [5–9]. The improvement of central VA after photocoagulation treatment is not a general rule and is rather rare in diffuse oedema [3].

During the 2-year observations, we were evaluating the effect of intravitreal treatment with Ranibizumab in the pro re nata (PRN) mode in patients with diffuse DME unresponsive to previous laser therapy.

METHODS AND COHORT

Our retrospective study included patients who were treated in the Department of Ophthalmology at the University Hospital of Hradec Králové from January 2015 to January 2019 and who met the condition of a 2-year observation period. The group consisted of 16 males (55.1%) and 13 females (44.8%); their mean age was 71.3. The mean duration of DM was 13 years (3–20). 3 patients (10.3%) were treated for DM of the first type and 26 patients (89.6%) were treated for the second type. 19 patients (65.5%) were treated with insulin, 10 patients (34.4%) were treated with peroral antidiabetics (PAD); at the beginning of the treatment with Ranibizumab, the mean HbA1c value was 52mmol/l.

Table 1 includes information about the patients and pre-operative data. A colour photograph of the ocular background, fluorescent angiography (FA) (Zeiss Visucam 500, Zeiss Cirrus, Germany) and optical coherence tomography with central retinal thickness (CRT) measurement (OCT; Zeiss Cirrus, Germany) were used to confirm the DME diagnosis. The mean time interval between the first retinal laser coagulation and the first dose of Ranibizumab was 3.5 months. Prior to the treatment with Ranibizumab, the patients had undergone 1.2 retinal laser treatments on average. Treatment with Ranibizumab was in the PRN mode, i.e. after the first 3 injections administered within a 1-month interval, regular monthly examinations followed and additional injections were administered in the case of persisting macular oedema (intra- and subretinal fluid according to OCT). The medicament was prepared and administered under aseptic conditions. Ranibizumab (0.5 mg in 0.05 ml) was administered under local anaesthesia, introducing a 30-gauge needle transclerally 3.5 from the limbus in the lower temporal quadrant in aphakic or artephakic patients, and 4.0 mm from the limbus in the lower temporal quadrant in phakic patients.

After the application of Ranibizumab, indirect ophthalmoscopy was used to check the condition of the retina and of the target of the optic nerve. Prior to the treatment and then in the 3rd, 6th, 9th, 12th, 18th and 24th months after the application, the development of BCVA measured on ETDRS optotypes, and CRT were monitored in all the patients. Furthermore, the intraocular pressure was measured with an applanation tonometer, and a slit lamp examination of the anterior segment of the eye was carried out. All patients signed an informed Consent Form prior to their treatment.

Statistical analysis was done using the IBM SPSS Statistics 23 software. Quantitative data are expressed in

Tabulka 1. Input demographic and clinical characteristics

Patients' demographic data	(n = 29)
Sex, female, n (%)	13 (44.8%)
Average age (years) ± SD	71.3 ±6.66
Average visual acuity, letter score ETDRS ± SD	65.4 ±10.61
Average central retinal thickness, µm ±SD	450.5 ±139.3
Duration of DM (years) ± SD (min–max)	13 ±3.4 (3–20)
Number of patients treated with insulin, n (%)	19 (65.5%)
Number of patients treated with oral antidiabet-ics, n (%)	10 (34.4%)
Average HbA1c (mmol/l) ± SD (min–max)	52 ± 6.8 (37–60)

n – number of eyes, DM – diabetes mellitus, ETDRS – Early Treatment Diabetic Retinopathy study, SD – standard deviation

terms of average and range. The BCVA and CRT values were analysed by the Kolmogorov-Smirnov normality test. Changes in BCVA and CRT were assessed using the paired Friedman test. The statistical significance was defined as $p < 0.05$.

RESULTS

The mean number of Ranibizumab injections was 5.45 ±1.8 (min 3, max 7) during the first year of treatment and 3.18 ±1.27 (min 0, max 5) during the second year.

Development of visual acuity

During the 2-year observations, we detected a significant improvement in the mean BCVA value. From the initial 65.4±10.61 letters of the ETDRS optotypes, it improved by 11.2 letters ($p < 0.05$) at the end of the 2-year observations, when the improvement of BCVA by min 6 letters (compared to the initial VA) was achieved in 19 eyes (65.5%), stabilisation (±5 letters) was detected in 7 eyes (24.1%) and worsening (by more than 5 letters) occurred in 3 eyes (10.3%). The mean baseline BCVA in our cohort was 65.4 ± 10.61 letters of ETDRS optotypes. Three months after the initialisation of treatment with Ranibizumab, we detected a statistically significant improvement in BCVA by 9.2 letters of ETDRS optotypes ($p = 0.014$). In the period started 3 months and finished 9 months after the beginning of the treatment, we found a slight statistically insignificant decline in BCVA by 1.4 letters of ETDRS optotypes ($p = 0.07$). During the observations carried out 9–24 months after the beginning of the treatment, we documented a further improvement in BCVA by 3.7 letters of ETDRS optotypes ($p = 0.14$). A detailed overview of the development of mean BCVA values and the time range of individual examinations are presented in Graph 1.

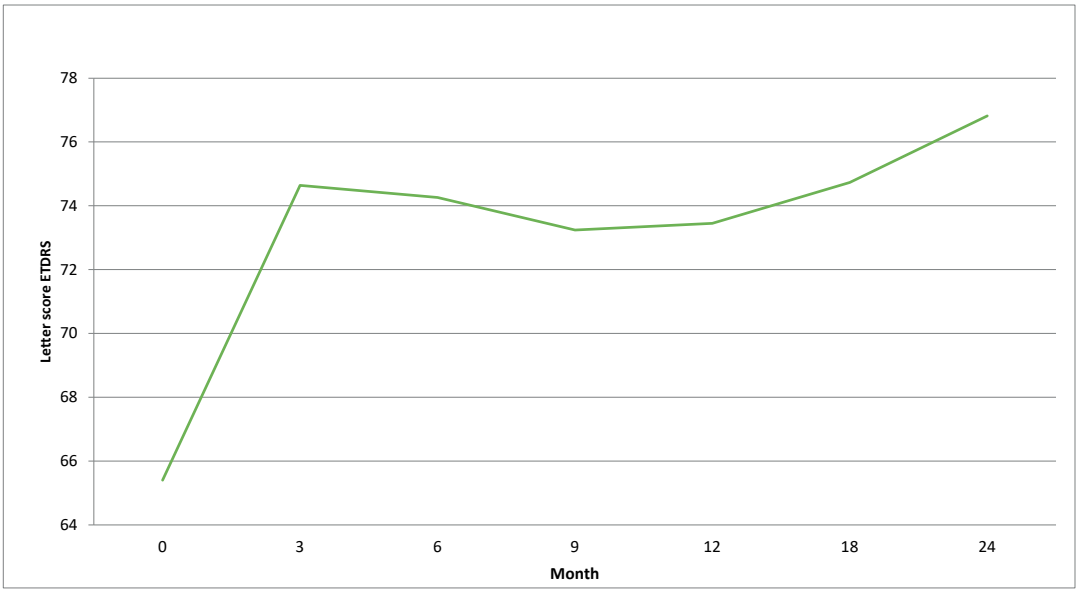
Anatomic results

The initial mean value of CRT in our cohort decreased after 2 years, from the initial 450.5 ± 139.3 µm by 89.5 µm ($p = 0.006$) (Graph 2). From the 3rd to the 9th month of our observations, there was a statistically insignificant increase in CRT by 50.61 µm ($p = 0.08$); during the observations carried out 9–24 months after the beginning of the treatment, we documented a further decline in CRT by 52.11 µm ($p = 0.06$). At the end of the observation period, CRT decreased in 23 eyes (79.3%), and an increase was detected in 6 eyes (20.7%). Due to the persistent DME, treatment with Ranibizumab was continued in all the patients. The decline in CRT was significant in 4 out of 6 observed intervals ($p < 0.05$).

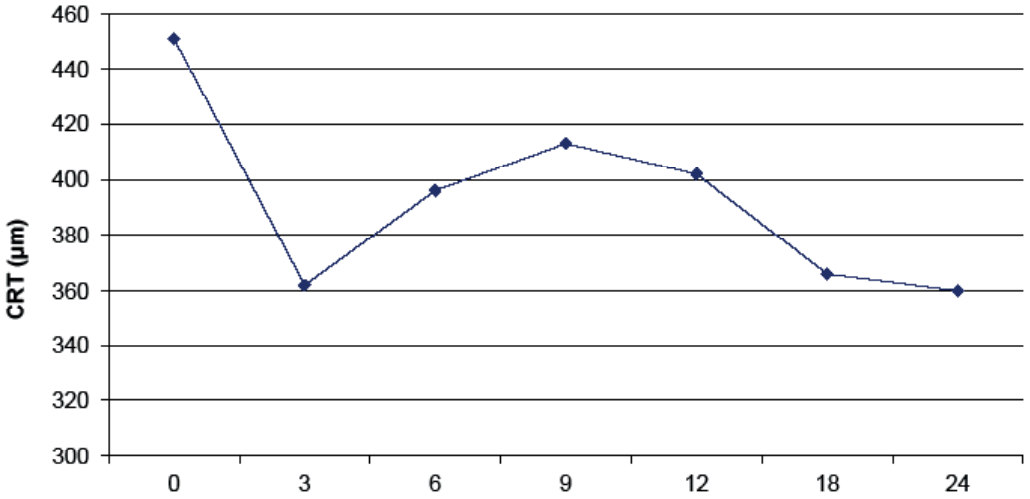
No serious ocular complications such as endophthalmitis, retinal rupture or detachment, vitreous haemorrhage, glaucoma, active uveitis or systemic side effects were detected. In three patients, transient elevation in intraocular pressure was detected after the administration of Ranibizumab. The elevation responded well to local hypotensive treatment with Cosopt gtt.

DISCUSSION

The benefit of treatment with Ranibizumab in patients with DME has been demonstrated in several randomised clinical studies. The RESOLVE study, which evaluated the effectiveness of treatment with Ranibizumab in 102 eyes in a fixed mode (injections administered once a month), showed a significant improvement in BCVA by 10.3 letters of ETDRS optotypes at the end of the 1-year-long observations (the baseline BCVA was 60.2 letters) [8]. In our research study, we detected a gain of 8.1 letters, 12 months after the beginning of the treatment with the mean number of 5.5 injections during the 1-year tre-



Graf 1. Best corrected visual acuity progression



Graf 2. Central retinal thickness progression

atment (the baseline BCVA value was 65.4 letters). The mean decline in CRT in the RESOLVE study was 194.2 µm at the end of the 1-year-long observations, compared to the baseline values of 455.4 µm. In our cohort, the improvement in CRT improved by 48.4 µm from the initial values of 450.5. The lower gain in BCVA and the decline in CRT in our research can be explained by the fact that the mean number of injections administered in the first year of the treatment was lower by 7 injections, in comparison with the RESOLVE study (which is justified by the fixed mode of applications in the RESOLVE study).

The RETAIN study evaluated the effectiveness of treatment with Ranibizumab in 117 patients with DME in the PRN treatment mode [9]. The results of the BCVA evaluation show that, during the 2-year--long observations, there was an improvement by 8.1 letters of ETDRS optotypes, when the mean number of 10.7 injections of Ranibizumab was administered (the initial value of BCVA was 64.7 letters). In our cohort, we administered Ranibizumab injections in the same mode, and the results of our study can be evaluated as comparable to the RETAIN study.

The Diabetic Retinopathy Clinical Research Network (DRSR.net) Protocol T research study evaluated the benefit of Ranibizumab treatment in the PRN mode in one arm of the cohort, i.e. in 94 patients with DME [10]. During the 2-year-long observations, the BCVA improved by 16.1 letters of ETDRS optotypes from baseline values of 56.1 letters, when the mean number of 15 injections of Ranibizumab 0.3 mg was administered. In our cohort, 2 years after the beginning of the treatment, we documented an improvement in BCVA by 11.4 letters (the initial values of BCVA were 65.4 letters), when the mean number of 8.6 injections of Ranibizumab was administered. The smaller gain in BCVA in our cohort can be attributed to the small number of patients and to a significantly smaller number of injections (smaller by 6.6 on average), compared to the DRSR.net Protocol T study. The lower number of injections is justified by the financial budget constraints, caused by the reduction of the indication criteria for reimbursement from health insurance companies. At the end of the 2-year-long observations, the mean decline in CRT in the DRSR.net Protocol T study was -125 µm compared to the initial values of 430 µm. During our observations, we noticed a CRT decline by 89.5 µm from the initial value of 450.5 µm.

Our research has demonstrated that the application of Ranibizumab is a safe treatment method for patients with DME. The safety profile of intravitreally administered Ranibizumab in the PRN mode in DME patients was evaluated by the RESOLVE research study, with the following conclusions: central retinal artery occlusion occurred in 1.0% of the patients, development of endophthalmitis was documented in 2.0% of the patients and 22.5% of the patients developed post-injection subconjunctival haemorrhages [8]. During the observations, no patient in our cohort developed vision-threatening complications associated with the administration of Ranibizumab. Transient intraocular hypertension, which responded well to local hypotensive treatment with Cosopt gtt, was reported in 3 patients (10.3%) after Ranibizumab administration. 4 patients (13.7%) developed subconjunctival haemorrhages. The safety profile of treatment with Ranibizumab in our cohort is thus comparable with the RESOLVE study.

Limitations of this research are related to the relatively small group of patients and to a missing control group.

CONCLUSION

Intravitreal treatment with Ranibizumab in the PRN mode reduces CRT and improves VA in those patients with diffuse DME, in the case of whom there was no improvement after laser treatment. The best effect was observed in the first 3 months after application.

At the end of the 2-year observation period, we detected a decline in macular thickness in 79.3% of the patients and improvement in VA in 65.5% of the patients. Referring to our results, we can unreservedly recommend the administration of Ranibizumab in the treatment of laser-resistant DME.

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