AFLIBERCEPT IN THE TREATMENT OF DIABETIC MACULAR EDEMA

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SUMMARY

Diabetic retinopathy is together with the diabetic macular edema the most common cause of vision loss in the working population. It is also the most common diabetic microvascular abnormality. Aflibercept is approved for the diabetic macular edema treatment, it is a recombinant fusion protein, binding VEGF A, B, and P1GF. The efficacy and safety of the treatment comparing with the laser treatment were set by VIVID-DME and VISTA–DME studies. The T DRCR.net study protocol confirmed the efficacy of aflibercept, ranibizumab, and bevacizumab in the treatment of diabetic macular edema. The best results in the whole group were obtained if using aflibercept, especially in the group of patients with worse initial visual acuity. In all three studies, the safety of intraviteraly applied aflibercept was proven.

Key words: diabetic macular edema, aflibercept, ranibizumab, bevacizumab

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INTRODUCTION

Diabetic retinopathy (DR) is the most common microvascular complication of diabetes, and is the main cause of loss of sight in the working population in the Western world (4). Blindness in diabetes is most frequently caused by diabetic macular edema (DME), especially in type 2 diabetics (1). The prevalence of DME is stated at 15% among type 1 diabetics and 23% among type 2 diabetics, and increases with the length of duration of diabetes and the incidence of nephropathy and neuropathy (10). According to the results of the extensive "Wisconsin Epidemiologic Study", DME is practically non-existent in type 1 diabetics up to 5 years from diagnosis of diabetes, whilst after 20 years DME affects almost 30% of patients. In type 2 diabetics, DME occurs more frequently in patients treated with insulin than in patients receiving peroral therapy with antidiabetic drugs. The prevalence of edema increases also with a higher level of glycated haemoglobin and with proteinuria (3).

Macular edema originates as a consequence of a breach of the haemato-ocular barrier, which results in an accumulation of extracellular fluid in the retina, the formation of retinal edema and a depositing of proteins and lipids in the form of hard exudates. The fundamental element in the origin of DR and DME is hyperglycaemia. Long-term hyperglycaemia results in a malfunction of microcirculation. The subsequent extravasation of fluid leads to the formation of retinal edema and to functional damage to the retina. In the pathophysiology of DME a role is played also by chronic systemic inflammatory processes of the capillaries. During the course thereof, inflammatory mediators are released which activate changes of the nerve and ganglion cells of the retina. The consequence of the above-described processes is deepening hypoxia of the macular region. Hypoxia leads to a production of vascular endothelial growth factor (VEGF), increasing the permeability of capillaries, which is followed by an accumulation of extracellular fluid (9).

Aflibercept in the treatment of DME

Aflibercept (Eylea ™, Regeneron and Bayer Healthcare) is a recombinant fusion protein composed of parts of VEGF 1 and 2 receptors and Fc portion IgG1 (fig. 1) is a newly approved pharmaceutical in the treatment of DME. Following intravitreal application, it acts via its receptors as a trap for VEGF A, B and placental growth factor (PlGF), and thus inhibits its effect on the receptors of the endothelial cells of the retinal and choroidal blood vessels. The effectiveness and safety of intravitreally applied aflibercept in the treatment of DME has been demonstrated by the two clinical trials VISTA-DME and VIVID -DME. The clinical trial VISTA-DME, which was conducted in the USA, evaluated 466 respondents. The VIVID-DME trial, which was conducted in Europe, Japan and Australia, included a total of 406 patients with DM types 1 or 2 with clinically significant DME, whose baseline best corrected visual acuity (BCVA) was 20/40 to 20/320. In both trials the patients were randomised into three different groups in a ratio of 1:1:1. In the first group of patients, aflibercept was applied in a dose of 2 mg every four weeks, in the second group aflibercept was applied in a dose of 2 mg every eighth week following five initial monthly applications, and in the third group laser treatment of DME was performed at the beginning of the evaluation and further after the third month of observation according to the clinical finding.

After the elapse of the observation period of 52 weeks, the clinical trial VISTA-DME determined an improvement of average BCVA in the first group by 12.5 letters and in the second group by 10.7 letters. This result was statistically significantly better in comparison with laser therapy, in which the average achieved gain was 0.2 letters ($p<0.0001$). An improvement of BCVA, which was defined as a gain of three or more rows of ETDRS optotypes, was demonstrated in 41.6% of patients treated with monthly application of aflibercept 2 mg, in 31.1% of patients in the second group with bi-monthly application after initial five-month saturation treatment, and in 7.8% of patients who underwent laser therapy ($p<0.0001$).

In the clinical trial VIVID-DME an average gain of 10.5 letters was demonstrated in the first group, 10.7 letters in the second group and 1.2 letters in the third group ($p<0.0001$). An improvement in BCVA by three or more rows was demonstrated in 32.4% of patients in the first group, 33.3% of patients

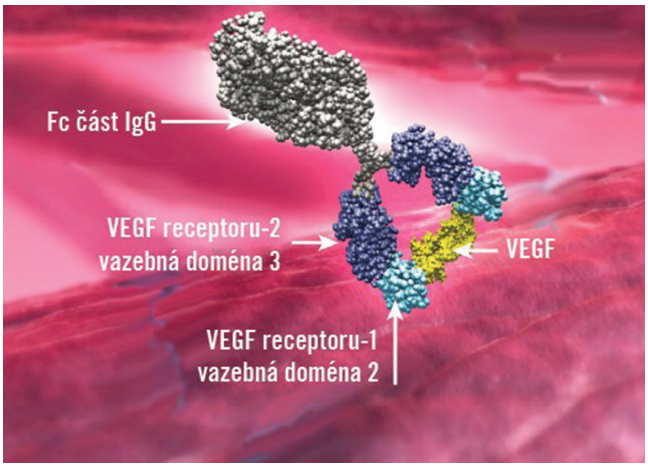

Fig. 1 Aflibercept is a recombinant fusion protein consisting of portions of human VEGFR-1 and VEGFR-2 extracellular domains fused to the Fc portion of human IgG1 (Ophthalmologic Drugs Advisory Committee: VEGF Trap-Eye briefing document. Tarrytown, NY: Regeneron Pharmaceuticals Inc.; June 17, 2011)

in the second group and in 9.1% of patients in the third group (p<0.0001). In both clinical trials a statistically significant effect on reducing central retinal thickness (CRT) was demonstrated upon administration of aflibercept in comparison with laser therapy. In the clinical trial VISTA-DME a reduction of CRT was determined in the first two groups treated with aflibercept, by 185.9 µm and 183.1 µm respectively, in comparison with patients treated by laser, in which a reduction of CRT by 73.3 µm was documented (p<0.0001). The attained results in the VIVID-DME trial were similar, with a reduction of CRT by 195 µm and 192.4 µm respectively in the first two groups, in comparison with the group of patients treated by laser, in which a reduction by 66.2 µm was determined (p<0.0001). Intravitreally applied aflibercept was very well tolerated. The incidence of ocular and serious overall side effects, including arterial thromboembolic events, was comparable in all groups of the clinical trials (5).

A comparison of the effectiveness and safety in eyes with DME treated with aflibercept 2 mg, bevacizumab 1.25 mg (Avastin®, F. Hoffmann-La Roche Ltd.) or ranibizumab 0.3 mg (Lucentis®, Novartis Pharma AG) was determined within the framework of the protocol T of the study DRCR.net (Diabetic Retinopathy Clinical Research Network). A total of 660 patients with DM type 1 or 2, who were being treated at 89 centres in the USA, took part in the multicentric study. The study included patients with baseline BCVA within the range of 20/32 – 20/320, CRT ≥ 250 µm measured on OCT Stratus (Carl Zeiss AG), in the case of measurement on a Spectralis instrument (Heidelberg Engineering) the requirement was CRT ≥ 320 µm in men and ≥ 305 µm in women, and in the case of measurement on OCT Cirrus (Carl Zeiss AG) the requirement was CRT ≥ 305 µm in men and ≥ 290 µm in women. Patients treated with VEGF blockers in the last 12 months before the commencement of the study were excluded, as were patients who had undergone any other treatment for DME in the four months before the start of the study. All the patients were randomised into three groups, in all the groups treatment by intravitreal injections of the active substance was repeated after four weeks if an improvement or deterioration of the finding was determined. No injection was applied if BCVA was 20/20 or better and the finding on OCT was within the norm, or if after the 24th week BCVA and the finding on OCT were stable after two consecutive applications. If BCVA or the finding on OCT deteriorated, the injection was again administered. Change of the finding was defined as an improvement or deterioration of BCVA by ≥ 5 letters or ≥ 10 % CRT on OCT since the last injection.

Laser therapy of the centre of the retina was chosen as salvage treatment, which could be used after the 24th week of observation if no improvement of DME was recorded after at least two consecutive injections of the active substance. Table no. 1 presents certain selected baseline characteristics of patients.

The best results with the used dosing scheme were determined after one year of observation upon treatment with aflibercept with an average gain of + 13.3 letters of optotypes. In the group of patients treated with ranibizumab a gain of + 11.2 letters was determined, in the patients treated with bevacizumab a gain of + 9.7 letters. The results of treatment with aflibercept in comparison with treatment with bevacizumab were statistically highly significant (p < 0.001), less significant was the comparison between aflibercept and ranibizumab (p=0.03). The results were different in patients with better ba-

Tab. 1 DRCR.net study, protocol T: selected baseline participant characteristics

	Aflibercept 2 mg (n=224)	Bevacizumab 1,25 mg (n=218)	Ranibizumab 0,3 mg (n=218)
Baseline BCVA (letter score)	69	69	68
CRT (µm)	387	376	390
Previous macular laser therapy (%)	36	39	37
Previous anti VEGF treatment (%)	11	14	13
Duration of diabetes (years)	15	17	16
Baseline HbA1c (%)	7,6	7,7	7,8

Tab. 2 DRCR.net study, protocol T: total number of injections and grid/focal laser treatments after one year follow up.

	Aflibercept 2 mg (n = 208)	Bevacizumab 1,25 mg (n = 206)	Ranibizumab 0,3 mg (n = 206)
Number of injections (mean)	9.2	9.7	9.4
Number of injections (median)	9 (8, 11)	10 (8, 12)	10 (8, 11)
(25th, 75th percentile)	37 %	56 %	46 %

Tab. 3 DRCR.net study, protocol T: selected ocular adverse events

	Aflibercept 2 mg (n = 224)	Bevacizumab 1,25 mg (n = 218)	Ranibizumab 0,3 mg (n = 218)
Endophthalmitis	0	0	0
Retinal tear, retinal detachment	0	<1 %	<1 %
Vitreous haemorrhage	2 %	4 %	3 %
Cataract	<1 %	<1 %	0
Intraocular pressure ≥ 30 mmHg	14 %	9 %	11 %

Tab. 4 DRCR.net study, protocol T: selected systemic adverse events

	Aflibercept 2 mg (n = 224)	Bevacizumab 1,25 mg (n = 218)	Ranibizumab 0,3 mg (n = 218)
Non-fatal myocardial infarction	2 %	<1 %	1 %
Non-fatal stroke	0	2 %	2 %
Vascular death	<1%	2 %	1 %
Any APTC (Antiplatelet Trialists' Collaboration) event	3 %	4 %	5 %

seline BCVA and worse BCVA. In the sub-group with baseline BCVA of 20/32 – 20/40 only statistically insignificant differences in attained BCVA were determined between the individual preparations. In the sub-group of patients with baseline BCVA of 20/50 and worse, statistically significant differences were demonstrated. After one year of treatment with aflibercept a gain of + 18.9 letters was determined, after treatment with ranibizumab a gain of + 14.2 letters and after treatment with bevacizumab a gain of 11.8 letters. The results of treatment with aflibercept were statistically significant in comparison with treatment with ranibizumab and bevacizumab. These functional results were accompanied also by anatomical results. Upon treatment with aflibercept a reduction of CRT by 210 µm was recorded, upon treatment with ranibizumab by 176 µm and upon treatment with bevacizumab by 135 µm. The reduction of CRT following treatment with aflibercept was statistically significant in comparison with treatment with bevacizumab, and there was a similarly significant reduction of CRT following treatment with ranibizumab in comparison with treatment with bevacizumab. The number of applications of the compared pharmaceutical preparations and the indication of laser treatment of the macula are presented in table no. 2.

The incidence of selected adverse ocular effects is presented in table no. 3. The elevation of intraocular tension was transitory in all patients or manageable by means of medicamentous treatment, none of the patients had to undergo antiglaucomatous surgery. Table no. 4 presents an overview of selected systemic adverse effects. In a subsequently performed analysis the incidence of any cardiovascular event was determined in 19% of patients treated with aflibercept, in 16% treated with bevacizumab and in 26% upon treatment with ranibizumab. This difference was statistically significant only upon comparison of ranibizumab and bevacizumab (2).

DISCUSSION

The clinical trials VISTA-DME and VIVID-DME demonstrated a statistically significant effect of treatment with aflibercept for DME upon monthly dosing and upon extension of the interval for application of aflibercept to 8 weeks. In both trials its effectiveness was significantly higher in comparison with laser therapy. Both studies also demonstrated the safety of aflibercept, with a comparable incidence of side effects and overall adverse effects in comparison with patients treated by laser therapy (5). Within the framework of the protocol T of the DRCR.net study, the effectiveness of three anti-VEGF substances was demonstrated in the treatment of DME in a different dosing scheme. A fundamental improvement of

BCVA was attained after only 1 month from the beginning of treatment and persisted after a full year of observation. On average a greater improvement was attained upon treatment with aflibercept, although the effect differed according to baseline visual acuity. Patients with initial slight loss of sight (20/32-20/40), which was determined in 50% of the studied eyes, were not distinguished by a substantial difference in attained BCVA upon use of the individual anti-VEGF substances. Patients with worse baselind BCVA responded substantially better to treatment with aflibercept 2 mg than to treatment with bevacizumab 1.25 mg or ranibizumab 0.3 mg (2). Whilst the stated dose of bevacizumab is regularly used in the treatment of DME in Europe and the USA, ranibizumab 0.3 mg is approved for treatment of DME in the USA whilst in Europe a 0.5 mg dose of ranibizumab is approved. The use of a lower dose of ranibizumab in the USA ensues from the results of the RISE and RIDE trials, which demonstrated comparable effectiveness of 0.3 mg and 0.5 mg of ranibizumab on DME upon monthly application (8). In Europe the approved dose of 0.5 mg of ranibizumab is supported by the clinical trials RESOLVE and RESTORE, which demonstrated the effect of this dose (6, 7). We do not have any comparison of the effectiveness of 0.5 mg of ranibizumab with 2 mg of aflibercept and 1.25 mg of bevacizumab in the same dosing regime at our disposal at present. Bevacizumab had a smaller effect on the reduction of macular edema than the other two preparations, regardless of baseline visual acuity. The greatest effect on reducing CRT was demonstrated in the case of aflibercept, which was also the reason for the lowest percentage of use of salvage treatment by laser in this sub-group of patients. Serious side effects were demonstrated similarly in the individual groups. No significant differences were determined in the frequency of serious vascular events (IM, CMP). Upon a retrospective analysis of cardiovascular disorders, including arterial hypertension, a higher frequency was determined upon treatment with ranibizumab, which was statistically significantly higher in comparison with treatment with bevacizumab (2). This does not correspond with previous trials, and may represent a chance result (6, 7).

CONCLUSION

All three anti-VEGF preparations represent an effective treatment for deterioration of vision caused by DME. The effectiveness of aflibercept in the treatment of DME was demonstrated in a fixed dosing regime and in an individual PRN regime. The effect of aflibercept is demonstrably better in patients with worse baseline visual acuity. Good tolerance of intravitreally administered aflibercept was demonstrated, with a comparably low incidence of adverse effect in comparison with laser therapy and the other used VEGF blockers. The results of the clinical trials support the use of aflibercept in regular clinical practice.

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