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Comparative analysis of clinical and anatomic outcomes in the treatment of exudative age-related macular degeneration with intravitreal injections of vascular endothelial growth factor inhibitors

Analiza porównawcza klinicznych i anatomicznych wyników leczenia wysiękowej postaci zwyrodnienia plamki związanego z wiekiem przy pomocy doszklistkowych iniekcji inhibitorów śródbłonkowego czynnika wzrostu naczyń

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Keywords

age-related macular degeneration, vascular endothelial growth factor inhibitor, ranibizumab, bevacizumab

Słowa kluczowe

zwyrodnienie plamki związane z wiekiem, inhibitor śródbłonkowego czynnika wzrostu naczyń, ranibizumab, bewacizumab

Summary

Introduction. Age-related macular degeneration (AMD) is the leading cause of severe visual loss in people over 50 years of age.

Aim. The aim of the study was to compare the results of exudative AMD treatment with intravitreal injections of two anti-vascular endothelial growth factor (anti-VEGF) drugs: ranibizumab and bevacizumab.

Material and methods. We selected treatment results of 55 patients with neovascular AMD and best corrected visual acuity (BCVA) equal or better than 1.0 (logMAR) for the retrospective analysis. The patients were treated with ranibizumab – 31 persons (31 eyes) and with bevacizumab – 24 persons (27 eyes). Mean follow-up period was one year.

Results. The mean BCVA did not deteriorate in both groups after one year of treatment (0.56 vs. 0.55 logMAR in the ranibizumab group and 0.62 vs. 0.60 logMAR in the bevacizumab group). Visual acuity stabilization/improvement was seen in 74.2% of eyes in ranibizumab group and 74.1% of eyes in bevacizumab group (statistically insignificant, $p = 0.99$). Absence of retinal fluid in OCT (optical coherence tomography) examination was noted in 45.2% of eyes in ranibizumab group and in 59.8% of eyes in bevacizumab group (statistically insignificant, $p = 0.28$). Loss of less than 1 line in BCVA was noted in 93.5% of eyes treated with ranibizumab and in 100% of eyes treated with bevacizumab (statistically insignificant, $p = 0.17$).

Conclusions. Ranibizumab and bevacizumab show similar effectiveness in stabilizing visual acuity and elimination of retinal fluid in patients with exudative AMD after one year of treatment.

Streszczenie

Wstęp. Zwyrodnienie plamki związane z wiekiem (ang. *age-related macular degeneration* – AMD) stanowi wiodącą przyczynę głębokiego upośledzenia ostrości wzroku u osób powyżej 50 roku życia.

Cel pracy. Celem pracy była analiza porównawcza wyników leczenia wysiękowej postaci AMD przy pomocy iniekcji doszklistkowych dwóch leków o charakterze inhibitorów śródbłonkowego czynnika wzrostu naczyń (ang. *anti-vascular endothelial growth factor* – anti-VEGF): ranibizumabu i bewacizumabu.

Materiał i metody. Do badania retrospektywnego włączono 55 pacjentów z wysiękową postacią AMD i najlepszą skorygowaną ostrością wzroku (ang. *best corrected visual acuity* – BCVA) równą lub lepszą niż 1,0 (logMAR). Grupa leczona ranibizumabem liczyła 31 osób (31 oczu), grupa leczona bewacizumabem – 24 osoby (27 oczu). Średni okres obserwacji wynosił 1 rok.

Wyniki. Po roku leczenia średnia BCVA nie uległa pogorszeniu w obu grupach (0,56 vs. 0,55 logMAR w grupie leczonej ranibizumabem i 0,62 vs. 0,60 logMAR w grupie leczonej bewacizumabem). Poprawa lub stabilizacja BCVA wystąpiła w 74,2% oczu leczonych ranibizumabem i 74,1% oczu leczonych bewacizumabem (różnica statystycznie nieistotna, $p = 0,99$). Brak płynu w siatkówce w badaniu OCT (optyczna koherentna tomografia) zanotowano w 45,2% oczu leczonych ranibizumabem i 59,8% oczu leczonych bewacizumabem (różnica statystycznie nieistotna, $p = 0,28$). Utrata o mniej niż 1 linię BCVA wystą-

Conflict of interest
Konflikt interesów

None
Brak konfliktu interesów

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piła w 93,5% oczu leczonych ranibizumabem i 100% oczu leczonych bewacizumabem (różnica statystycznie nieistotna, p = 0,17).

Wnioski. Ranibizumab i bewacizumab wykazują podobną efektywność w zakresie stabilizacji ostrości wzroku oraz eliminacji płynu siatkówkowego u pacjentów z wysiękową postacią AMD po rocznym okresie leczenia.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe visual loss in people over 50 years of age. Exudative form of this disease, which substance is the development of choroidal neovascularisation (CNV), leads to chorioretinal scar formation in the final stage. It occurs in 10-20% of patients affected but is responsible for 80-90% of cases of severe degeneration of visual acuity in the course of AMD (1).

Vascular endothelial growth factor (VEGF) is a protein mediator, stimulating angiogenesis primarily in hypoxic circumstances (1, 2). VEGF-A type is the primary signal for the development of CNV in the course of exudative AMD (3). The presence of VEGF-A has been observed in CNV membranes and its increased concentration has been discovered in the vitreous humour of patients with exudative AMD (1-3). It was found that the VEGF-A inhibitors administered intravitreally inhibit experimentally caused CNV in laboratory animals (4). Introduction of drugs blocking VEGF-A through intravitreal injections was a major advancement in the treatment of exudative AMD. Currently, among these drugs, two have the widest clinical use: ranibizumab (Lucentis, Novartis Pharma, Basel, Switzerland and Genentech, San Francisco, USA) and bevacizumab (Avastin, Genentech, San Francisco, USA). Ranibizumab is a Fab fragment (antibody binding fragment) of a recombinant, humanised, monoclonal antibody which blocks all isoforms of VEGF-A (1, 5, 6). This drug has been approved for use in treatment of exudative AMD (5, 6). Its high clinical efficacy, not only related to stabilising but also improving visual acuity in the treatment of all types of CNV membranes in the course of AMD, has been proved by multicentre, randomized clinical trials MARINA and ANCHOR (7, 8). Bevacizumab is a full, recombinant, humanised monoclonal antibody which also blocks all isoforms of VEGF-A (1, 5, 6). Because the Fab domain of both drugs differs only by 6 amino acids (1), there are presumptions that they can have a similar clinical efficacy in the treatment of AMD. Bevacizumab is not approved for treatment of exudative AMD, but it is often used as an off-label alternative treatment. The main reason for this is a high cost of ranibizumab in comparison with bevacizumab.

AIM

The aim of the study is to compare functional and structural outcomes of the treatment of exudative AMD with intravitreal injections of two anti-VEGF drugs: ranibizumab and bevacizumab, in 12 month follow-up period.

MATERIAL AND METHODS

The results of the treatment of exudative AMD with intravitreal injections of anti-VEGF drugs: ranibizumab and bevacizumab, in 55 patients of the Department of Ophthalmology, Medical Center of Postgraduate Education were analysed retrospectively. For the analysis, 31 eyes of 31 patients (20 women and 11 men) aged 64-94 (average age 76.77 ± 6.56) treated with ranibizumab, and 27 eyes of 24 patients (18 women and 6 men) aged 56-88 (average age 75.91 ± 5.84) treated with bevacizumab were selected, with best corrected visual acuity (BCVA) equal or better than 1.0 logMAR. The presence of exudative AMD was confirmed on the basis of fundus fluorescein angiography – FA (Heidelberg Engineering). All types of lesions which size did not exceed 12 areas of the optic disc, without dominant haemorrhage, without features of permanent, structural damage of fovea (scarring or geographic atrophy), not previously treated for AMD, were eligible for the therapy. Before the treatment an examination of the fundus periphery was performed to exclude lesions which could risk retinal detachment. Patients with uncontrolled glaucoma were not qualified for injections. General criteria for exclusion were: uncontrolled hypertension, uncontrolled diabetes, unstable coronary heart disease, history of thromboembolic diseases more than 6 months ago.

Possibility of the treatment with ranibizumab depended on availability of the drug, while the treatment of bevacizumab depended on patient's agreement. The treatment with bevacizumab was possible as an experimental study, after receiving a permission from the Bioethical Commission of the Center. All patients have signed informed consent. After the complete approval for ranibizumab to treat exudative AMD by National Health Committee, patients from the bevacizumab group were switched to ranibizumab group. This, together with BCVA selection criterion, resulted in the small number of patients, enrolled in this study.

The following treatment schedule was applied: three consecutive injections of ranibizumab in a 0.5 mg dose every 4 weeks or bevacizumab in a 1.25 mg dose every 6 weeks, both in a 0.05 ml of solution (so-called initial phase: 2 months for treatment with ranibizumab and 3 months for treatment with bevacizumab). Because the half-life of bevacizumab is assumed 150% of the half-life of ranibizumab in the vitreous humour (in rabbits: the half-life is 2.88 days for 0.5 mg of ranibizumab and 4.32 days for 1.25 mg of bevacizumab) (9, 10), and the recommended protocol for ranibizumab is every 4 weeks injection, some authors apply bevacizumab every 6 weeks. After the initial phase, subsequent injections in 4 or 6 week intervals respectively for each given drug were performed, depending on the need dictated by current outcomes of treatment. This schedule was applied on the basis on PrONTO and SUSTAIN trials which suggests elastic approach to the treatment i.e. continuation of the anti-VEGF drug

injections (in the case of these studies – ranibizumab) after the initial phase, depending on the outcomes of the treatment, it allows maintaining proper therapeutic effects while minimising the number of injections (11). Monitoring the outcomes of treatments and qualification for next injection were carried out by means of visual acuity evaluation and optical coherence tomography OCT 3D (Topcon), performed every 4 or 6 weeks, in a week period before the prospective date of next injection. In selected cases, FA was performed to confirm the presence of active CNV. Qualification for the next injection was carried out on the basis of criteria applied in the PrONTO and SUSTAIN trials, and on the concept of "active change" (11). Those were: decrease of BCVA more than 1 line depending on active CNV, persistent accumulation of fluid in the lesion detected by OCT, dye leakage in FA, enlargement of the lesion detected by FA, new or persistent haemorrhage.

Injections of the drugs were administered in operating room conditions, with aseptic procedures adopted. Topical anaesthesia of conjunctival sac was used. Prior to injection, a 5% povidone solution was administered to the conjunctival sac for 1.5 minutes. Both drugs were administered via tuberculin syringe in 0.05 ml volume, in 3.5 mm distance from the corneal limbus. In the presurgery period (3 days) and in the post-surgery period (4 days) a patient was given antibiotic drops (ofloxacin) administered locally 4 times a day. On the day of injection, in the morning, patients received 2 tablets of acetazolamide (500 mg) per os to prevent a potential increase of intraocular pressure related to the treatment. The intraocular pressure was measured 30 minutes after the treatment with a pneumotonometer. Follow-up visits took place 1-2 days and 7 days after the treatment.

Comparison of the treatment outcomes between the two groups was performed after the initial phase (2 and 3 months of treatment respectively for the ranibizumab group and the bevacizumab group) and after 1 year of treatment on average (10-14 months). Chi-square test was used for statistical analysis and p values of less than 0.05 was considered statistically significant.

RESULTS

Mean BCVA (logMAR) before the treatment was 0.56 (± 0.34 SD) in the group treated with ranibizumab and 0.62 (± 0.32 SD) in the group treated with bevacizumab. After the initial phase, BCVA was 0.53 (± 0.34 SD) in the ranibizumab group and 0.59 (± 0.33 SD). After 1 year of therapy, BCVA remained on the before-treatment level in both groups, and amounted to 0.55 (± 0.36 SD) for the ranibizumab treated group and to 0.60 (± 34 SD) in the bevacizumab treated group.

Considering the natural course and prognosis of untreated exudative AMD, which is an average loss of approximately 3 lines in VA after 1 year of the duration of the disease (12) we have determined the percentage of eyes with loss of less than 3 lines after 1 year of treatment. In both groups it was very high and amounted to 93.5% in the ranibizumab treated group and 100% in the bevacizumab treated group (statistically insignificant difference, $p = 0.17$, chi-square test). In both groups we also calculated the percentage of eyes which did not lose even a single line (stabilization and improvement of the VA) after 3 injections and 1 year of treatment, what means, in the case of qualification for treatment criteria adopted, that they maintained BCVA ≤ 1.0 (logMAR). This was also a very high and comparable percentage of eyes: after 3 injections it amounted to 80.6% in the ranibizumab treated group and 81.5% in the bevacizumab treated group (statistically insignificant difference, $p = 0.93$, chi-square test), and after 1 year of treatment: 74.2 and 74.1% respectively (statistically insignificant difference, $p = 0.99$, chi-square test). Absence of fluid in the area of lesion in OCT after 3 injections was very well correlated with the stabilization/improvement of VA in the ranibizumab treated group (no indication of fluid in 80.6% of eyes), whereas to a lesser degree in the bevacizumab treated group (no indication of fluid in 63% of eyes) (statistically insignificant difference, $p = 0.13$, chi-square test). After 1 year of treatment, absence of fluid was observed in a lesser percentage of eyes: 45.2% in the ranibizumab treated group and in 59.8% in the bevacizumab treated group (statistically insignificant difference, $p = 0.28$, chi-square test).

During the course of treatment, no serious local side effects have been noted (intraocular inflammation, vitreous or retinal haemorrhage, lens injury, retinal detachment) in any of the two groups. An increase of intraocular pressure after injection has been sporadically noted in predisposed persons i.e. with glaucoma or ocular hypertension, and it has been temporary, pressure normalised on the second day after injection. In both groups no systemic complications, related to the possible effects of anti-VEGF group drugs i.e. thromboembolic diseases, have occurred.

DISCUSSION

Common "off-label" use of bevacizumab in therapy of AMD (bevacizumab has been registered as treatment for certain neoplasms) as an alternative therapy for expensive treatment with ranibizumab, prompted us to perform a clinical evaluation of the effects of ranibizumab and bevacizumab in the course of exudative AMD in own material. Recently, the results of multicentre randomised clinical trials, comparing the outcomes of the treatment of exudative AMD with intravitreal injections of these drugs have been reported (CATT in USA, IVAN in UK) (13-15).

The two VEGF inhibitors are significantly different from each other. Ranibizumab is Fab fragment, its molecular mass is 48 kDa, while the molecular mass of bevacizumab, as a full antibody, is almost three times larger – 149 kDa (1). Smaller size of the molecule may cause the drug to penetrate the retinal layers better and, as a consequence, leads to a higher probability of a successful therapeutic effect (1). It was suggested that only the penetration of the Fab fragment through retina is rapid and complete (1). However, previous studies indicating that penetration of intravitreally administered full antibody in primates is inhibited on the level of retina internal limiting membrane (1) are not confirmed by more recent research, which have proven that after intravitreal administration, bevacizumab

diffused to the pigment epithelium and deeper, to the choroid (16). This remains in correlation with the therapeutic effectiveness of both drugs in clinical evaluation. The results of our study are consistent with previous results of other authors and indicate a comparable effectiveness of therapy with ranibizumab and with bevacizumab in exudative AMD (13-15, 17-21).

In our study, the average BCVA in both groups after 1 year of treatment with ranibizumab or bevacizumab has maintained at the output value level in both groups (0.56 vs. 0.55 in the ranibizumab group and 0.62 vs. 0.60 in the bevacizumab group respectively, before and after treatment). In the multicentre retrospective study, in which the effects of 1 year treatment with ranibizumab or bevacizumab in a large group of patients (452 participants, 324 treated with bevacizumab and 128 treated with ranibizumab) were evaluated, the authors also observed stability of vision in both groups and did not notice differences comparing changes in VA between the two drugs (19).

In two prospective randomised trials, comparing ranibizumab monthly with photodynamic therapy with verteporfin (PDT) in the treatment of predominantly classic CNV (ANCHOR study: 423 patients included, one third received ranibizumab in the 0.5 mg dosage), and ranibizumab monthly with sham injections in the treatment of minimally classic or occult CNV (MARINA study: 716 patients included, one third received ranibizumab in the 0.5 mg dosage), the improvement of mean BCVA after one year of ranibizumab treatment was 11.3 ETDRS letters in ANCHOR study (8) and 7.2 ETDRS letters in MARINA study (7). In two prospective randomised trials, comparing 1 year bevacizumab therapy with other therapeutic modalities: PDT with verteporfin for predominantly classic CNV, pegaptanib (Macugen, New York, USA) intravitreal injection or sham treatment for occult CNV (among 131 participants – 65 patients treated with bevacizumab in 1.25 mg dosage, 3 initial injections every 6 weeks followed by as needed treatment) (ABC trial) (22), and PDT plus triamcinolone intravitreal injection for all types of CNV (28 patients included, 14 treated with bevacizumab in 1 mg dosage, 3 initial injections every 4 weeks followed by as needed) (23), similar results of bevacizumab treatment efficacy were noted. In the first study, mean BCVA increased by 7.0 ETDRS letters (22) and in the second – by 7.5 ETDRS letters (23).

In a single-centre 6-month randomized prospective trial, completed by a small group of patients (20 persons), a comparable clinical efficacy of both drugs given as needed after first 3 injections was proven (20). In this study, in both groups an improvement of ultimate mean BCVA occurred: of 14.8 ETDRS letters in bevacizumab treated group and 7.0 ETDRS letters in ranibizumab treated group (difference statistically insignificant). One-year results of the same study revealed also comparable effects of bevacizumab and ranibizumab treatment: mean BCVA improvement of 7.6 and 6.3 ETDRS letters respectively (difference statistically insignificant) (21). Results of the multicentre randomized clinical trial CATT, performed on a very large group of patients (1208 persons), which compared the treatment effects of both drugs "head-to-head", given in standard doses 0.5 mg for ranibizumab and 1.25 mg for bevacizumab, proved a comparable efficacy of the drugs after one year of treatment and the improvement of mean BCVA by 8.5 vs. 8.0 ETDRS letters in groups receiving once ranibizumab or bevacizumab per month, and 6.8 vs. 5.9 ETDRS letters in groups receiving ranibizumab or bevacizumab as needed (differences statistically insignificant) (13). Using noninferiority limit of 5 letters, bevacizumab was equivalent to ranibizumab, both when the drugs were administered monthly and when the drugs were administered as needed (13). In the multicentre randomized IVAN trial (610 patients), after one year of treatment with ranibizumab (0.5 mg) or bevacizumab (1.25 mg) monthly or as needed (alternative as needed regimen was introduced in this study, requiring 3 injections of the drug if the disease is active), the VA comparison by drug was inconclusive (15). Bevacizumab was neither inferior nor equivalent to ranibizumab using the 3.5 letters noninferiority limit. Recently published results of the CATT study at 2 years confirmed similar clinical efficacy of both agents (14).

In MARINA and ANCHOR trials, an inhibition of the natural progress of exudative AMD, which means loss of less than 15 ETDRS letters at 1 year of the disease duration, was noted in 94.6 and 96.4% of patients after one-year of treatment with ranibizumab in 0.5 mg dosage (7, 8). Also in ABC trial, 91% patients treated with bevacizumab lost fewer than 15 ETDRS letters after one year of therapy (22). In the CATT trial, the percentage of patients who did not lose more than 15 ETDRS letters after one year of therapy was 94.4 and 94.0% for groups receiving respectively ranibizumab or bevacizumab once per month and 95.4 and 91.5% for groups receiving ranibizumab or bevacizumab according to need (differences statistically insignificant) (13). Comparable to these is the result of our study: the percentage of eyes with loss of less than 3 lines has been 93.5% in ranibizumab treated group and in bevacizumab treated group all eyes (100%) maintained VA above the value expected, considering the natural progress of the disease (statistically insignificant difference between the two agents).

In our study, after 1 year of treatment the percentage of eyes with stabilised/improved VA was slightly smaller in both groups than after the initial phase (74.2 vs. 80.6% in the ranibizumab group and 74.1 vs. 81.5% in the bevacizumab group). This is consistent with the results of other studies in which the most significant improvement of VA was observed after three initial injections of ranibizumab (11). At 1 year we also observed the decrease of percentage of eyes with no fluid on OCT in comparison with the initial phase (from 80.6 to 45.2% in the ranibizumab group and from 63 to 59.8% in the bevacizumab group), the difference being not statistically significant between the drugs after the initial phase and after 1 year of treatment. In CATT trial, the percentage of patients with absence of fluid after 1 year of therapy was less than in our study – 23.9% for ranibizumab as needed and 19.2% for bevacizumab as needed (13). The better result noted

in our study could be connected with mandatory first injections of the drugs in the initial phase. Results of 1-year CATT study also revealed higher percentage of patients with no fluid, if the agent was given more frequently: 43.7% for ranibizumab monthly treated group and 26% for bevacizumab monthly treated group (13). In the CATT study, both, after one year and after two years of treatment, ranibizumab was more effective than bevacizumab in eliminating fluid from the macula (13, 14).

Because the method of therapy with VEGF inhibitors is still new, it will be vital to assess the effects of these drugs in future, not only in terms of their long-term efficacy but also safety of use, both general and local. In terms of systemic interactions, thromboembolic episodes in course of cardiovascular diseases are considered above all. In the retrospective study it was shown, that in patients treated with ranibizumab, when compared to ones treated with bevacizumab, hazard ratios of mortality, incident myocardial infarction, incident stroke were significantly lower (24). The results of 1-year CATT trial the percentage of patients with arteriothrombotic events was similar in patients treated with ranibizumab and bevacizumab, ranging from 2.0% for ranibizumab as needed group to 2.7% for bevacizumab as needed group (13). After two years of therapy, this percentage increased to 4.7% for ranibizumab treated patients and 5.0% for bevacizumab treated patients (difference not statistically significant) (14). In the IVAN study, at 1 year of treatment the incidence of arteriothrombotic events or heart failure was significantly higher in ranibizumab treated group than in bevacizumab treated group (2.9 vs. 0.7%, respectively) in spite of serum level of VEGF significantly lower in bevacizumab treated group than in ranibizumab treated group (15). In our study we did not noted any thromboembolic diseases in both treated groups. In terms of local interactions, the assessment of effects related to blocking of VEGF-A in the eyeball will surely be necessary because it is a determinant of the vascular endothelium cells' survivability and a neurotrophic factor for the retina cells (1).

CONCLUSIONS

The results of our study indicate a comparable clinical efficacy of both drugs, ranibizumab and bevacizumab, administered according to the need after the first three initial injections, in the therapy of exudative AMD during one-year of treatment, in terms of maintaining visual acuity and fluid elimination from the macula. The differences between the two agents were statistically insignificant. As it is non-randomised, one-center trial, based on not numerous group of patients, the conclusion from our study is limited, but it is consistent with the results of previously published studies, showing similar efficacy of both anti-VEGF drugs in the treatment of exudative AMD.

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