

EFFECTS OF ANTI-VEGF AGENTS ON THE OCULAR NEOVASCULAR STRUCTURES IN DIABETIC RETINOPATHIES

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Key words : diabetic rethinopathys, angiogenesis, anti VEGF substance.

Abstract: In diabetic rethinopathys there are lot of aneurisms, neovesels at the peripheric retina and optic nerv disc, and difuz vascular leakage sometimes with severe hemorages. After anti VEGF action the neocular structures are remised.

INTRODUCTION

Diabetic retinopathy (DR) is a common ocular complication of the diabetes mellitus (DM). DR appears much more frequent to the patients with type I (40%) of diabetes comparative to the type II (20%), and it represents the main cause for blindness in the developing countries. About 90% of the diabetic patients develop DR after 20 years of diabetes (2).

From the pathogenic point of view, DR represents a microangiopathy that primary affects the retinal capillary network (arterioles and venules) and is characterized by loss of the pericytes, thinning of the vascular basement membrane, followed by the proliferation of the endothelial cells (2). At the blood flow level, the modifications consist of deformation of the red cells and increasing of the platelets aggregation leading to the lowering of the sanguine oxygen transport. Consequently, the ischemia develops at the tissues level, while the dilations of the vascular walls (microaneurisms) appear around the affected region. As a consequence of the high levels of the glycemia, different metabolic products appear as a result of aldoreductase pathway (sorbitol, galactitol). These products accumulate at the level of endothelial capillary cells, increasing the cellular volume and the thinning of the basement membrane. Finally, the dilatation of the capillaries, the thinning of the vascular basement membrane and the production of the vasoactive factors due to hypoxia determine the microvascular occlusion, leading finally to the aggravation of the tissue hypoxia and creating of a vicious circle (3). The final consequence of these pathological processes represent the breakdown of the blood-retinal barrier leading to the “leakage” of the plasma components in the retinal tissue, formation of hemorrhages, hard and soft exudates and edema (4).

From the *clinical point of view*, the DR follows the next three stages:

- **nonproliferative** in which the pathological modifications do not pass over the internal limiting membrane,
- **preproliferative** that represents an intermediate stage,
- **proliferative** in which the fibrovascular proliferation pass over the internal limiting membrane.

Recent studies showed the role of the growth and inflammatory factors in the appearance of tissue modifications in DR, this hypothesis being suggested by the high levels of the proinflammatory cytokines in the vitreous according to the severity of the disease: TNF-alfa, ICAM (adhesion molecule), VEGF (vascular endothelial growth factor). Our study has the aim to evaluate the role of the VEGF in the angiogenetic process in DR.

MATERIALS AND METHODS

The examined material was taken from the Ophthalmologic Department of the Railway University Hospital in Iasi and represents a diabetic male, 43 years old patient, having proliferative diabetic retinopathy on both eyes.

The eyes were examined by means of the following techniques:

- **biomicroscopic** examination of the anterior segment of the eye;
- direct and indirect **ophthalmoscopic** examination and **biomicroscopic examination** of the vitreous and the retina;
- **fluorescein angiography** of the ocular fundus realized by using 5 ml fluorescein 10% intravenously injected prior to the digital examination of the fundus. The ocular fundus pictures were taken by using VISUCAM – LITE ZEISS fundus camera in different moments of the evaluation of the patient. The dye contrasts the retinal vasculature revealing also the leakage, the retinal edema, the neovascular network arising on the retina and also into the vitreous, different areas of retinal atrophies, etc.;
- **red-free examination** was also realized by using the same fundus camera and revealed the neovascular fibrous tissue, the hard and soft exudates, the retinal scars and atrophic areas. It can also be used as a way to evaluate in dynamic the patient.

The right eye of the patient was injected with *Bevacizumab (Avastin)*, an anti-VEGF agent used off-label. The dose of 2,5 mg of Avastin was injected monthly and the patient monitorised by using the above mentioned techniques in order to detect possible complications and effects.

RESULTS AND DISCUSSIONS

The first investigation of the patient revealed, during ophthalmoscopy and red free examination, the presence of numerous new vessels covering the whole ocular fundus, including over the optic disc, hard exudates, microaneurisms, superficial retinal hemorrhages and macular edema (fig.1, fig.2 and fig.3).

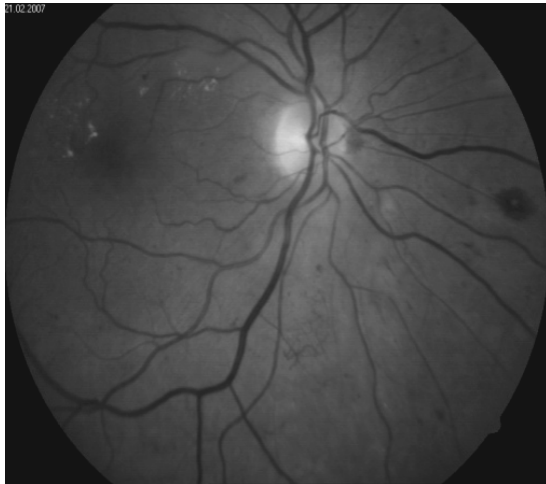


Fig.1 Right eye, ocular fundus.

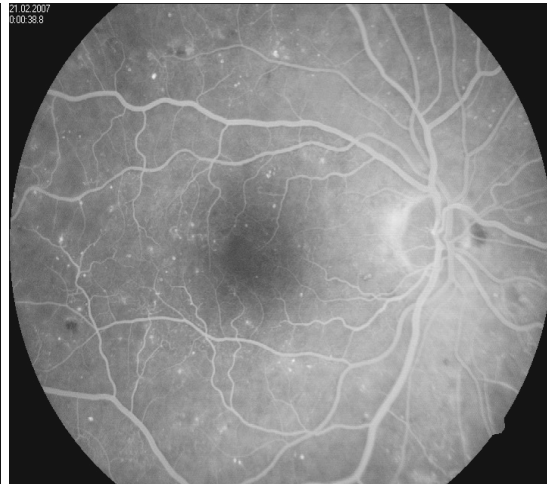


Fig. 2 Right eye, fluorescein angiography.

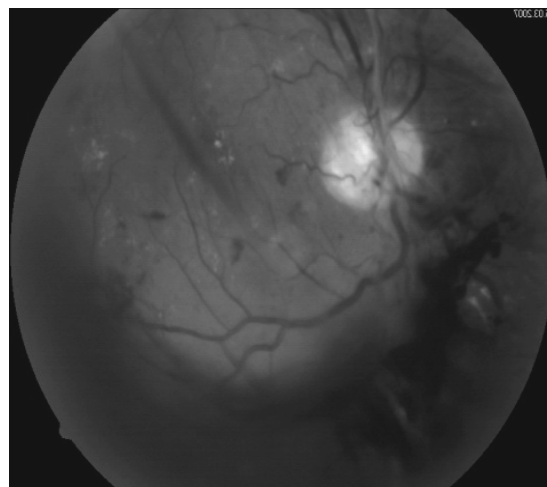


Fig. 3. Left eye, ocular fundus.

One month after Avastin injection, the fluorescein angiography and red free examination revealed in this patient the regression of the neovascular network and reducing in the volume of the fibrous component also. The retinal exudates and edema also decreased, leading to the improvement of the visual acuity of the patient (fig.4, fig. 5, fig.6 and fig. 7).

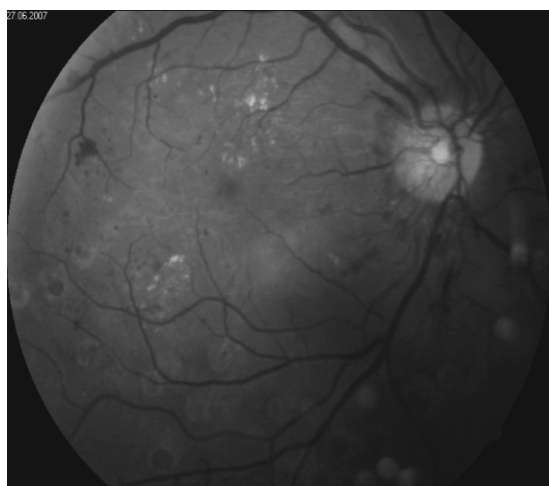


Fig.4 – Right eye, ocular fundus, bevacizumab, one month examination.

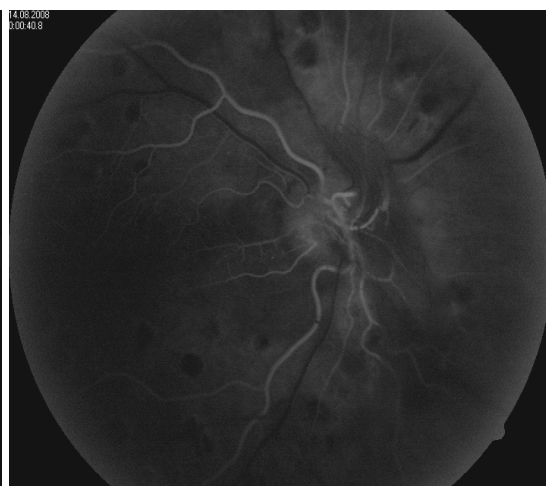


Fig. 5 – Right eye, fluorescein angiography, bevacizumab, one month examination.

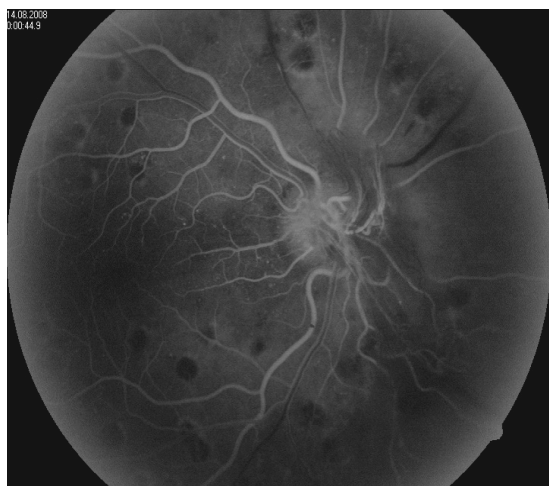


Fig. 6 Right eye, fluorescein angiography, bevacizumab, 10 secondes, one month examination.

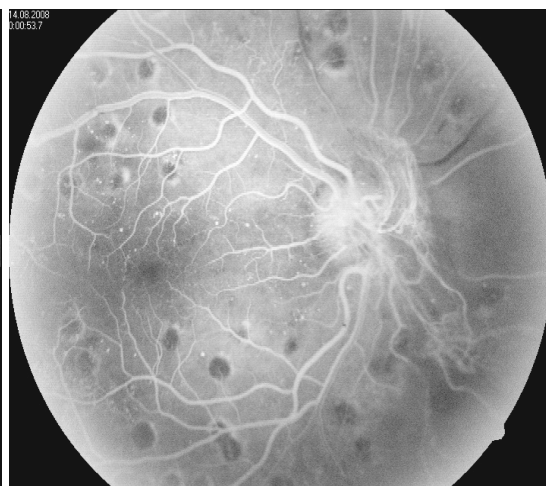


Fig.7 Right eye, fluorescein angiography, bevacizumab, 60 secondes, one month examination.

VEGF that inhibits “in vitro” the retinal endothelial cells’ growth is implicated in the appearance of the modifications in DR. The studies realized on animal models demonstrated a direct relationship between the VEGF concentration and the evolution or regression of the neovascular network. The vitreous concentration of this factor is higher in patients with proliferative DR comparative to the group with nonproliferative DR.

The perturbation of the glucidic metabolism induces troubles at different levels – vascular, neuronal and glial and is accompanied by the high concentrations of VEGF. However, it was also demonstrated that VEGF has an important neuronal benefic role maintaining for a time the survival in hostile conditions (phenomena called “preconditioning”), but it is toxic for the endothelium, aggravating the microangiopathy by increasing the capillary permeability leading to the appearance of edema, exudates and hemorrhages. VEGF-A a member of the VEGF family, has a central role: it is a protein having several isoforms, is present in the majority of the

tissues, free or bound to the extracellular matrix, is synthesized as a response to the hypoxia, estrogens, in hyper- or hypoglycemia, in inflammation, etc. Excessive producing of VEGF appears early in diabetes and represents a factor that starts the retinal proliferation. It is not known the exact mechanism through which the concentration of VEGF increases, but it was demonstrated that, mainly the high concentrations of VEGF determine the alterations of this factor concentrations equilibrium. It was also observed that except glycemia, the advanced glycation products influence the VEGF synthesis.

After the onset of the neovascular proliferation, the progression of angiogenesis is continuing in the less resistant areas. As an example, the absence of the internal limiting membrane at the optic disc level explains the prevalence of the neovascular growth into the optic nerve head. It was also observed that the neovascularization progresses easily when the conjunctive tissue is already developed, and the posterior vitreous detachment represents a convenient region for these new vessels growth (1).

The angiogenesis progresses to the next stage, in which is associated with the formation of the conjunctive tissue. By advancing the proliferative DR, the fibrous component continues to increase with or without developing of the new vessels. The fibrovascular component is oriented to the vitreal cavity or into the retinal surface and covers the optic disc, while the avascular form of the fibrous tissue results usually from the modifications develop at the posterior hyaloid level. The diffuse neovascularization extends until the posterior vitreous detachment appears and is characterized, diabetic patients, much more by the slow decrease of the whole vitreous volume than the formation of certain cavities inside of the vitreous. Thus, an idea was introduced, that the angiogenesis is not producing towards the vitreous cavity, but these vessels are tracked by the vitreous contractions to which they adhere (1). Because of the sudden contractions of the modified vitreous other retinal lesions appear: ruptures of the new vessels and onset of the vitreous hemorrhages, retinal ruptures or retinal detachment.

Another important idea is represented by the effect of anti-VEGF agents on the proliferative DR. Anti-VEGF agents may be used as monotherapy or associated with other therapeutic methods. The studies confirm their major effect in the regression of the retinal lesions that appear during DR and functional recovering of the patients.

CONCLUSIONS

Diabetic proliferative retinopathy is an ocular complication of the diabetes mellitus in which the VEGF seems to play an important role, as the anti-VEGF agents like off-label Bevacizumab has a strong regressive effect on the pathological vitreo-retinal lesions.

The retinas structure modifications in diabetic rethinopathys take a long time, while the administration of anti VEGF produce a more rapid reaction due to a high rate of cells autolysis and heterolysis.

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