THE ANTI-VEGF THERAPY IN THE OPHTHALMOLOGICAL

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Cuvinte cheie: *Degenerescență macular legată de vârstă, Avastin, Lucentis, anti-VEGF*

Rezumat: *Lucrarea prezintă aspecte teoretice privind tratamentul antiangiogenic al anumitor afec□iunilor oftalmologice, în particular degenerescen□a macular legată de vârstă. Sunt prezentate principalele substan□e ce blochează factorul de cre□tere a endoteliului vascular implicat în procesul de angiogeneză precum □i indica□iile, tehnica de efectuare □i posibilele complica□ii ale acestui tratament.*

Keywords: *age related macular degenerescence, Avastin, Lucentis, anti-VEGF*

Abstract: *This paper presents theoretical aspects regarding the anti-angiogenic treatment of several ophthalmologic disease, particularly age related macular degenerescence.There are presented the main substances that are blocking the growth factors of the vascular endothelium implicated in the angiogenesis process asthe indications, the technique used and possible complications of this treatment.*

SCIENTIFICAL ARTTICLE OF THEORETICAL PREDOMINANCE

VEGF (vascular endothelial growth factor) represents a protein with role of chimical signal, produced by the cells that stimulates the growing of new blood vessels, in the process named angiogenesis. There are several types of VEGF, the most important being VEGF-A. The agents anti-VEGF are substances that stop the formation and the growing of the blood vessels.

In the ocular globe there are several affections that evolve with hypoxia: age related macular degenerescence, diabetic retinopathy, vascular obstructions. The normal reaction of the organism against this hypoxia consists in the formation of new blood vessels that may furnish the oxygen and necessary nutritive substances. But those blood vessels aren't normal, are instable, fragile, and are easy to harm producing hemorrhage. So, the anti-angiogenic agents act through the linking of the VEGF prevents from the formation of those blood vessels.

The tehrapy anti-VEGF is used in ophthalmology in several affections, among which: age related macular degenerescence (DMLV), proliferative diabetic retinopathy with diabetic maculopathy and clinical significative macular edema, glaucoma secondary neovascular, prematurity retinopathy, macular edema from the obstruction of the central retinian veins.

The anti-VEGF treatment in DMLV

The most frequent affection that benefits of the anti-VEGF therapy is the macular degenerescence, also being the main cause of sight loss at the persons over 50 years. DMLV is presented under two forms: dry and humid. The differential diagnosis is realized through angiofluorography, and the pursuing of the disorders evolution at the patients in treatment with the anti-VEGF agents is realised through tomography in optical coherence (OCT). The dry form of the DMLV has no response at this treatment, but only the humed form. Also, we have to mention that not all the patients with DMLV humid forme is lended to the treatment with anti-VEGF. This is efficient only when the affection is active, the neo-vessels at the choroidian level are bleeding, so there is hemorrhage. If the affection is older, there appears cicatricial tissue that doesn′t answer the the treatment, and the sight reduction is permanent.

The anti-VEGF agents

At present there are three drugs used in the treatment of the DMLV humid form.

1. Macugen (Pegaptanib) represents an aptamer anti-VEGF pegylat that is linked specifically to the VEGF 165. It was approved in SUA by the Food and Drug Administration (FDA) in December 2004, and in Europa by the European Medicines Evaluation Agency (EMEA) in february 2006. It has been proved that it maintains the visual acuity in approximativelly 70% of the cases and is improving it in approximativelly 20% of the cases. The treatment consists in intravitreal injection 0,3mg every three weeks for at least two years .

2. Lucentis (Ranibizumab) represents a fragment of monoclonal antibody (Fab) that is linked by the VEGF-A. It was approved by FDA in June 2006, by the EMEA in January 2007. The studies showed that maintaines the visual acuity in approximativelly 90% of the cases and an improvment in approximativelly 40% of the cases. The treatment consists in a series of three intravitreal injection 0,5mg in 0,05ml at four weeks and then, in accordance with the evaluation results, if it is necessary it is continued with the intravitreal injection at an intervall of four weeks.

3. Avastin (Bevacizumab) represents a monoclonal antibody with molecular weight greater than Lucentis that is linked by the VEGF-A. It didn′t received the FDA approval or EMEA for intraocular use. It was approved for the treatment of the colorectal cancer with or without metastasis and of the pulmonary cancer. Despite all those, Avastin is used "off-label", forth the approved indications, by numerous ophtalmologues in the whole world for the treatment of the DMLV humid forme. The treatment scheme is similar with the one for Lucentis, the dose being of 1,25-2,5mg in 0,05-0,1ml.

Avastin versus Lucentis

Some of the researchers assert that the two drugs have

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similar effects in the treatment of the DMLV. So, regarding the rapport cost/efficacity between Avastin and Lucentis, because the price/dose for Avastin is of approximativelly 40-50 dollars, and for Lucentis of 1600-2000 dollars, there is a significative difference. As both drugs are produced by the same firm, Genentech from the USA, this has no interest that Avastin to be approved and used in the intraocular treatment in the detriment of Lucentis, remaining "off-label". This utilisation "off-label" determined several controverses, culminating in octomber 2007 with the Genentech announce of not approving the pharmacies with Avastin. So, the doctors were in the situation of impossibility of treatment the patients with DMLV whose health insurance didn't cover the treatment with Lucentis, or other affections that were suited to be treated with Avastin. The ophthalmologic comunity, headed by the American Academy of Ophthalmology (AAO) and the American Society of Retinal Specialists (ASRS) riposted determining Genentech to change its decision and to continue to furnish Avastin to the pharmacies, those realizing the necessary dosage to use it intraoculary.

The National Eye Institute announced in octomber 2006 that it will finance a comparative study between Avastin and Lucentis regarding the safety and efficiency in the treatment of the DMLV. The study, named Comparison of Age-Related Macular Degeneration Treatment Trials (CATT Study), included 1200 patients, divided in four study groups:

1. Lucentis one injection each four weeks during one year, then in accordance with the evaluation results, if is necessary, the continuation of the injectable treatment at an intervall of four weeks.
2. Avastin in the same treatment scheme.
3. Lucentis in variable administration for two years, then monthly evaluation and the continuation of the treatment if is necessary.
4. Avastin in the same treatment scheme.

The results were published in 29 april 2011 and showed that the benefits of the Avastin and Lucentis treatment are practically identical at one year.

The technique of the Avastin administration

The treatment is realised in conditions of asepsis in the surgery room. There may be administered antibiotics drops few days before the injection to prevent the infections, although is not compulsory. Mydriatics are instilled with approximativelly 30 minutes before. The anesthesia is topical, drops being instillated with approximativelly 10-15 minutes before. The eye is covered with a sterile field. It is disinfected the ocular surface, and the eyelids and periocular skin with betadine and the blepharostat is applied. It is used an insulin syringe which has attached a needle of 30 Gauge. The intravitrean injection of Avastin is realised in the supero-temporal or supero-nasal dial in accordance with the treated eye, at 4mm of the limb in the faky eyes, respectivelly at 3,5mm in the afaky eyes or pseudifaky eyes. 0,05-0,1ml is injected. The perfusion in the central artery of the retina is verified through direct and indirect ophtalmoscopy. The eye is sterile bandaged till the second day and drops with antibiotics are recommended for 5-10 days.

The intravitrean administration of Avastin is not devoid of complications. One of the most frequent is the raising of the intraocular pression. Usually is temporary and needs no treatment. If is maintained raise, are administrated oculary hypotensors, and if the intraoculary pression passes of 50-55mmHg and the light perception is lost is necessary the paracentesis of the anterior chamber. Other dreaded complication is the intraocular infection, respectivelly the endophthalmitis that needs a promptly and aggressive antibiotic treatment, and sometimes vitrectomy. Other possible complications are the subconjunctival or intravitreal hemorhhages, the retinal decolation, cataract through the cristalin lesions, pain at the injection spot.

CONCLUSIONS

The anti-VEGF therapy of the different ophthalmologic affections and especially of the DMLV the humid form offers hope to the patients,so they may lose irreversibly their sight . Although there are necessary more studies to prove clearly the advantage of the benefits against the risks in using Avastin, the results show that untill this moment are pleasing . The clinical experience shows the following : a third of the patients answers favourably at the treatment, namely the visual acuity is improved (with one, two or even three lines at the optotype) and the affection regresses, one third answers the treatment meaning that the visual acuity and the affection are maintained at a constant level (there are no improvings, and no aggravations), and another third doesn't answer the treatment, the visual acuity continues to decline and the affection progresses.

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