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Intravitreal Anti VEGF Application During Covid – 19 Pandemic in Kosova

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Abstract

Purpose: to present our experience in applying anti VEGF - Bevacizumab (Avastin), in Kosova Public Health Services, during the Covid-19 pandemic in patients with various retinal diseases.

Methods: The research is of descriptive methodology. After consulting the literature and experience of clinics around the world, we were able to prepare Avastin monodoses from a single 16ml/400mg ampoule. The prepared monodoses were proven to be microbiologically sterile and biologically active, if stored in dry/dark conditions as well as at 4 * C. Doses are stored for up to one month and used daily.

Results: for six months (September 2020 to March 2021), we applied 1466 doses. Of these, 743 are male and 723 females. Patients were of all ages from 6 months to 80 years, 45% of age 61-70 years. We have no reports of severe complications other than conjunctival hemorrhage. Conclusion: preparation of monodoses from a single ampoule is possible. These monodoses are biologically active/ microbiologically sterile for up to one month if stored in dark/dry conditions and at +4 * C temperature. This course

of action has been shown to be effective from a social point of view as well. It has reduced the cost of public services and proved to be effective during the Pandemic-Covid-19, when the gathering of patients was prohibited.

Keywords: Bevacizumab, Monodose, Pandemic, Consumption.

Introduction

More than 55 years ago, a man had a dream. Judah Folkman (1933-2008) hypothesized that cancer could be treated if its supply of nutrients and oxygen were cut off.¹ The term antiangiogenic therapy was coined, and Bevacizumab (Avastin-Genentech) became the first FDA-approved therapy (11.10.2006).²⁻⁴ Thus Bevacizumab was designed to inhibit angiogenesis in tumors (initially colorectal carcinoma). Anti-VEGF has been used in ophthalmology since 2006. Bevacizumab is a humanized monoclonal IgG-1 antibody with a molecular weight of 170 kD, directed against all biologically active forms of VEGF-A. It is produced from Chinese mouse ovaries.⁴ Anti-VEGF is used in neovascular AMD (Age-related Macular Degeneration) as well as in PDR (Proliferative Diabetic Retinopathies), but over time the indications for use have expanded (including using it for purposes explained in the OFF LABEL form). ^{5,6} This is a common medical practice in many parts of the world for several reasons: licensed marketing drugs for certain purposes, may not always be available (for children, pregnant women, or patients with rare diseases), a drug used off label may be more effective than a registered therapy, such as Rituximab for Multiplex Sclerosis, might have a similar effect while being also cheaper than the drug authorized by marketing.²⁻⁶

This is the case with bevacizumab (Avastin; Roche, Basel, Switzerland –amp.4ml / 100mg. & 16ml / 400mg.). Although bevacizumab has only been approved as systemic therapy for cancer, it is used worldwide intravitreally to treat retinal diseases such as age-related macular degeneration (AMD), retinal vein occlusion (CRVO & BRVO), and diabetic macular edema (DME). ³⁻¹⁰ At the same time, the off-label ophthalmic use of bevacizumab has caused great controversy due to ethical, legal, economic and political issues. 5 Bevacizumab is a humanized monoclonal antibody as anti-VEGF. It was originally developed for the treatment of gastrointestinal, breast, and lung malignancies. 4,7 However, many studies conducted on the use in ophthalmic diseases, especially AMD, have proven to be highly safe and effective. The first research was the British one for the inhibition of choroidal neovascularization (IVAN), 6 and the American one for AMD wet form (CATT). IVAN research has proven that ranibizumab (Eylea) and bevacizumab (Avastin) have similar efficacy in treating eye pathologies. A group of other studies such as BRAMD, MANTA, GE-FAL, and LUCAS have later confirmed that bevacizumab is not inferior to ranibizumab for the treatment of wet AMD, and other retinal pathologies.^{6,8,9-14} On the other hand, studies published in prestigious journals show that in many European countries bevacizumab is still used as an anti-VEGF.

The purpose of this paper is to show how we managed to use bevacizumab in Kosova in the conditions of the Covid 19 pandemic, its effects and benefits

Methodology

This is a cohort retrospective study including patients with retinal diseases that were treated with intravitreal Avastin from September 2020 to March 2021, at the Ophtalmology Clinic, the University Clinical Center of Kosovo (UCCK), in Prishtina and in Regional Hospitals of

Mitrovica, Prizren, Peja, Gjakova and Gjilan for January 2021 - June 2021. The data are extracted from the protocol register of the University Clinical Center of Kosovo (UCCK) and Regional Hospitals. In Kosova, bevacizumab has been used since 2012 as an anti-VEGF in retinal diseases. At the University Clinical Center of Kosovo (UCCK), we have practiced the method of using a single vial (Avastin 16ml / 400mg. Roche) daily. Within the span of a day, we applied 120 to 150 doses in terms of respect the sepsis and antisepsis. (2, 7, 15-18) The pandemic made it impossible for us to continue working likewise since the gathering of patients was not allowed. We had interruptions of almost six months. Elected cases were also discontinued. The Covid-19 pandemic made us think differently. Thus faced with the need to continue working, even though in such conditions, and after consulting the literature, and obtaining information on how the largest European and World centers behaved and worked, we were able to find and apply the method for creating bevacizumab monodoses (0.05ml / 1.25mg.Avastin). They can be stored and used for up to six months if kept in dark/dry conditions and at temperatures up to 4 * C. (2, 4, 5, 7, 15, 16, 18) Monodoses were prepared under sterile conditions. They were applied in the operating room. (4, 7, 15, 16, 17) It is worth mentioning that we sent the monodoses to the Laboratory of Clinical Microbiology at the National Institute of Public Health of Kosova (NIPHK) for evaluation, to determine whether they were contaminated or sterile. Samples were sent on 30.09.2020 and resulted sterile. Toxicological and biological analyzes have not been performed for lack of laboratories in Kosova. On September 16 th, 2020, we started their application on a daily basis for only ten patients per day (we had to respect- to the institutional recommendations for protection against the spread of Covid-19). We immediately started the preparations for the expansion of the service network in the regional hospitals: Prizren, Mitrovica, Peja, Gjakova, and Gjilan. This method proved effective in many aspects. The data extracted from the protocol register were entered into an exell database and processed in SPSS version 25. Differences by variables were tested with Chi square test, Exact Fisher test and t test. The total number of patients examined was 1466.

Results

The collected results were statistically processed and presented in tabelar and graphical form: During the period September 2020 - March 2021, we applied a total of 1466 Avastin (0.05ml / 1.25mg) at the Ophthalmology Clinic.

Table 1. Avastin application in relation to gender.					
Gender	Males	Females	Totally		
Number (%)	743 (50.7%)	723 (49.3%)	1466 (100.0%)		

Graf. 1. Application of Avastin in relation to gender.



 Table 2. Avastin application in relation to age.

Age (years)	<1	1-10	11-20	21-30	31-40	41-50	51-60	61-70	>70	Total
Number %	9 (0.6%)	13 (0.9%)	4 (0.3%)	10 (0.7%)	25 (1.7%)	120 (8.2%)	259 (17.7%)	662 (45.2%)	364 (24.8%)	1466 (100.0%)

Graf. 2. Avastin application in relation to age.



Out of a total of 1466 patients, nine were less than 1 year old, 13 were 1-10 years old, 4 were 11-20 years old, 10 were 21-30 years old, 25 were 31-40 years old,

120 were 41-50 years old, 259 were 51-60 years old, 662 were 61-70 years old and were over 70 364 years old. (table 2, graf. 2)

Diagnosis:		OD (Right eye)	OS (Left eye)	Totally
		n (%)	n (%)	n (%)
DR(Diabetic Retinopathy)		498 (64.3%)	474 (68.5%)	972 (66.3%)
BRVO (Branch Retina IV ein Occlusion)		31 (4.0%)	34 (4.9%)	65 (4.4%)
CMO (Cystoid Macular Oedema)		56 (7.2%)	60 (8.7%)	116 (7.9%)
AMD (Agerelated Macular degeneration)		78 (10.1%)	55 (7.9%)	133 (9.1%)
Hematovitreus		47 (6.1%)	32 (4.6%)	79 (5.4%)
ROP (Retinopathy Of Prematurity)		14 (1.8%)	4 (0.6%)	18 (1.2%)
Others*		50 (6.5%)	33 (4.8%)	83 (5.7%
Totally	n (%)	774 (52.8%)	692 (100.0%)	1466 (100.0%)

Table 3. Application of Avastin in relation to the respective disease.

Graf. 3. Application of Avastin in relation to the respective disease.



Table 4. Avastin applied in Regional Hospitals.

Applicated Avastin in Regional Hospital, january - june 2021 (n/%)					
Prizren	310 (25.4%)				
Mitrovica	201 (16.5%)				
Gjilan	80 (6.5%)				
Peja	180 (14.7%)				
Gjakova	446 (36.6%)				

Table 5. Potential complications related to treatment

Potential complications related to treatment	n (%)
Corneal abrasions	11 (0,75%)
Lens damage	1 (0,06%)
Endophthalmitis	0 (0%)
Retinal ablation	0 (0%)
Slight discomfort	52 (3,5%)
Scratching Transient increase of TIO	75 (5,1%)
Transient increase of TIO	22 (1,5%)
Subconjunctival hemorrhage	43 (2,9%)









Social Aspects

Avastin application in private clinics, especially during the Pandemic, varied from 150 to 300 Euros per dose. Consequently, 1466 doses would have costed 219900 Euros (150 Euros per dose) or 439800 Euros (300 Euros per dose). Patients had to pay for each dose from their own pocket. The financial burden placed upon them is a very strong reason for using our method, especially when considering the Covid-19 pandemic.

Discussion

We still have to stand humble in the face of inaccuracies regarding the treatment of eye diseases. Statistical data on the number of applications, complications and costs for both, patients and the public health system, show that we have achieved positive results. During the period September 2020 - March 2021, at the Ophthalmology Clinic, a total of 1466 Avastin were applied. Out of the total number, it turns out that 0.61% of patients were less than 1 year old, 0.88% were from 1-10 years old, 0.27% were from 11-20 years old, 0.68% were between 21-30 years, 1.7% were between 31-40 years, 8.18% were aged 41-50 years, 17.66% were aged 51-60 years, 45.15% were aged 61-70 years and 24.8% have been over 70 years. With regard to diagnosis, it turns out that 1.22% were found with ROP, 4.47% were with BRVO, 5.38% were with Hematovitreus, 7.9% were with CMO, 9.07% were with AMD, 66.35% had RD and 5.66% other diseases (CRVO, ablatio retinae, panuveitis, myopathia alta degenerativa, glaucoma neovascularis, CNVM, st.post. PPV). Based on these results, cases with diabetic retinopathy dominate. It is universally known that diabetes mellitus represents a 8% incidence. A relatively large number of these patients have retinopathy. This means that treatment with anti-VEGF has been shown and imposed as a necessary treatment.

Conclusion

This research is limited in: data on pathologies, case follow-up process - i.e., treatment efficiency, number of series / dose applications. Qualitative research remains to be done in the future, such as the effectiveness of therapy, and the need to switch to other types of anti-VEGF.

Conflict of Interests

The authors of this research have adhered to the statement and the charter of patient rights, related to clinical research. They have no material interest from any company or funding institution.

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