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Research Article

Ocular Pharmacotherapeutic Challenges.

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INTRODUCTION

The cases of potentially blinding eye diseases, such as diabetic retinopathy (DR), retinal vein occlusion (RVO), age-related macular degeneration (AMD) and cataract are exponencially growing worldwide due to population aging and rising life expectancy [1]. At present really only cataract is a surgically completely treated cause of blindness. Majority of ocular disorders, especially retinal vascular diseases require a medical therapy with a long-life follow-up.

Two decades ago ocular therapeutic armamentarium was enriched by vascular endothelial growth factor VEGF. inhibitors, opening a new era in ophthalmopharmacotherapy [2,3]. Importantly, this medical option universally targets VEGF overexpression pathway involved in multiple eye diseases and directed to induce a retinal angiogenesis, macular edema, etc [4].

It is well-recognized that despite given intravitreally in small amounts, VEGF inhibitors spread into blood stream reaching physiologically VEGF-depending end-organs, such as the heart, the kidney, etc [5]. With this in mind, it should be considered that intraocular antiangiogenic therapy could be associated with undesirable systemic cardiovascular and renal adverse events (AEs).

Accumulating evidence has suggested the cases of myocardial infarction, ischemic attacks thrombosis, pulmonary embolism, cerebrovascular accidents, proteinuria related to local administration of anti-VEGF agents in AMD, RVO, DR [6]. Recently, cardiovascular and renal safety concerns have gained a special attention [7-15]. It should be emphasized that systemic safety is extremally important, taken into account that vast majority of patients with retinal vascular disorders have a systemic co-morbidity- systemic hypertension, atherosclerosis, diabetes, etc [16,17]. This finding highlights the urgent need for thoughtful therapy.

Currently, retinal diseases management includes two unresolved challenges-medical and healthcare.

Medical challenge is multidimentional

Despite anti-VEGF transforming therapy, half of patients are not responsive in short- or long-term perspective, signaling an unmet need even in developed countries. On the one hand, intravitreal injection itself is related with procedural risks, such as endophthalmitis, retinal tear/detachment, etc [18]. On the other hand, antiangiogenics could cause a chemical compound-related ocular adverse effects, such as retinal ischemia, pigment epithelium atrophy [18].Besides, it must be taken into consideration the probability of aforementioned systemic AEs.

With a growing experience of VEGF inhibitors use in ophthalmology, the many similar unanswered questions still remain:

1. What biomarker may serve as a valuable one for successful therapy ?
2. Which anti-VEGF drug will be chosen for personalized therapy ?
3. What validated algorithm of therapy is indicated for each person in different retinal diseases ?
4. When it is indicated to switch to another anti-VEGF drug in order to avoid a resistance ?
5. How long the monotherapy by anti-VEGF injections will be continued ?
6. How to alleviate loss of vision ?

Ocular antiangiogenic pharmacotherapy have had major impacts on healthcare. Healthcare system faces a challenge, taken into account the rise of diseases like age-related macular degeneration (AMD), diabetic retinopathy (DR) and RVO, and especially their invasive therapy. The need for regular endless intravitreal injections by expensive drugs in elderly population accompanied by caregivers represents an economic burden [19-25] .

Besides, a high volume of intraocular procedures causes a pressure on eye care providers leading to professional burnout.

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Pharmacological alternatives will help to overcome aforementioned challenges.

The most influential trials findings indicate that monotherapy with VEGF inhibitors may not be an ideal approach to retinal diseases treatment [26,27].

Combination therapy, such as intravitreal anti-VEGF and corticosteroids as a triamcinolone in intravitreal or subtenon delivery or dexamethasone implant in macular edema secondary to CRVO and BRVO was evaluated in meta-analysis conducted by Namvar et al.[28] Authors concluded that this combination results in better visual outcomes comparing to antiangiogenic monotherapy at 6 months.

Recently Ma et al.[29] developed a multifunctional nanodrug containing small interfering RNA (siRNA) targeting VEGF and dexamethasone. Researchers evidenced antioxidative, anti-inflammatory and anti-angiogenic effects of this nanodrug and stated that "simultaneous delivery of all components to the target site, enhanced their combined therapeutic potential while reducing systemic exposure and adverse effects" with "potential as a versatile and effective treatment for multiple ocular conditions". The obtained results are promising and they deserve further scientific investigations.

The development of innovative approaches continues [30-33]. In addition to development of new topical preparations with increased drug retinal bioavailability through improved solubility and nanoparticles as nanocarriers, great interest lies in "rediscovering" existing, approved drugs, such as antiretroviral medication [34], lipid-lowering drugs and antidiabetic drugs, and repurposing them for the treatment of multiple diseases [35].

For the first time the randomized, double-blind, placebo-controlled trial was conducted by Pereira et al. [34] to assess the functional efficacy and safety of antiretroviral medication lamivudine comparing to placebo in cases of center-involved DME (CI-DME). Eligible patients (24 adults) were randomized to lamivudine group (10 patients; 16 eyes) or control group (14 patients; 21 eyes). Patients from study group received 150 mg lamivudine orally twice daily for 8 weeks. At week 4 additional intravitreal injection of bevacizumab (1.25 mg) was done on all patients. Researchers have documented the significant improvement of best-corrected visual acuity (BCVA) by 9.8 letters in patients treated by lamivudine in contrast to decrease of BCVA by 1.8 letters with placebo. Lamivudine have shown additive visual benefit to bevacizumab in CI-DME. It should be emphasized that positive functional outcomes of this study highlight a therapeutic potential of affordable oral lamivudine in DME, opening a new avenue in thoughtful management of DR.

Summarising, millennial-minded research in ophthalmopharmacotherapy should be aimed at development of topical multimodal drugs with noninvasive delivery route and oral multifunctional agents for eye diseases with bilateral involvement, such as DR and AMD, with simultaneous targets beyond the eye. The development of noninvasive patient- and provider- friendly more durable treatments may lead to earlier treatment initiation, greater patient convenience and reduced health care use and costs. The continued refinement of management algorithms have the potential to enhance visual functional outcomes and quality of life in patients with retinal vascular diseases.

In conclusion, the emerging multitarget agents will offer the paradigm-shifting possibility of millennial-minded ophthalmopharmacotherapy. New pharmacotherapeutic options will reduce the burden of treatment for the patients and health care workers simultaneously.

REFERENCES

1. Janakiraman N, Badrinarayanan L, Ratra D, et al. One Health Approach for Eye Care: Is It a Boon or Hype?. One Health: Human, Animal, and Environment Triad. 2023:221-41.

2. Santorsola M, Capuozzo M, Nasti G, et al. Exploring the Spectrum of VEGF Inhibitors' Toxicities from Systemic to Intra-Vitreal Usage in Medical Practice. Cancers (Basel). 2024;16(2):350. doi: 10.3390/cancers16020350.

3. Henriques C, da Ana R, Krambeck K, et al. Monoclonal Antibodies for the Treatment of Ocular Diseases. J Clin Medicine. 2024;13(19):5815.

4. Wang L, Liu WQ, Broussy S, et al. Recent advances of anti-angiogenic inhibitors targeting VEGF/VEGFR axis. *Front Pharmacol*. 2024;14:1307860. doi:10.3389/fphar.2023.1307860.

5. Avery RL, Castellarin AA, Steinle NC, et al. Systemic pharmacokinetics and pharmacodynamics of intravitreal aflibercept, bevacizumab, and ranibizumab. Retina. 2017;37(10):1847-58. doi: 10.1097/IAE.0000000000001493.

6. Khan RS, Frishman WH. Beyond the Local Effect: An Examination of Cardiovascular and Other Systemic Complications of Ophthalmologic Drugs. Cardiol Rev. 2024. doi: 10.1097/CRD.0000000000000801.

7. Yang JM, Jung SY, Kim MS, et al. Cardiovascular and Cerebrovascular Adverse Events Associated with Intravitreal Anti-VEGF Monoclonal Antibodies: A World Health Organization Pharmacovigilance Study. Ophthalmology. 2025;132(1):62-78. doi: 10.1016/j.ophtha.2024.07.008.

8. Şahinbaş M, Çerik İB, Yalınbaş Yeter D. Investigation of the effect of intravitreal bevacizumab treatment on left heart function using speckle tracking echocardiography. Rev Port Cardiol. 2025;44(1):27-35. English, Portuguese. doi: 10.1016/j.repc.2024.07.006.

9. Toste JC. When cardiotoxicity demonstrated in Cardio-oncology is investigated in other contexts: Research into the cardiovascular effects of antiangiogenic drugs used in ophthalmology. Rev Port Cardiol. 2025;44(1):37-39. English, Portuguese. doi: 10.1016/j.repc.2024.

10. Chou YI, Chang HY, Lin MY, et al. Risk analysis for patients with arterial thromboembolic events after intravitreal ranibizumab or aflibercept injections. Sci Rep. 2023;13(1):7597. doi: 10.1038/s41598-023-34128-5.

11. Sui Y, Zhao Y, Zhou N, et al. Case report: heart failure related to intravitreal injection of anti-VEGF. BMC Cardiovascular Disorders. 2024;24(1):418.

12. Lye LF, Chou RH, Wu TK, et al. Administration of Bevacizumab and the Risk of Chronic Kidney Disease Development in Taiwan Residents: A Population-Based Retrospective Cohort Study. Int J Mol Sci. 2023;25(1):340. doi: 10.3390/ijms25010340.

13. Rangaswamy D, Nagaraju SP, Bhojaraja MV, et al. Ocular and systemic vascular endothelial growth factor ligand inhibitor use and nephrotoxicity: an update. Int Urol Nephrol. 2024;56(8):2635-2644. doi: 10.1007/s11255-024-03990-1.

14. Barkmeier AJ. Intravitreal Anti-VEGF Pharmacotherapy and Kidney Failure: Protecting Vision with an Eye on Renal Safety. Ophthalmology Retina. 2024;8(8):731-2.

15. Huang RS, Balas M, Jhaveri A, et al. Comparison of Renal Adverse Events Between Intravitreal Anti-Vascular Endothelial Growth Factor Agents: A Meta-Analysis. Am J Ophthalmol. 2025;271:466-477. doi: 10.1016/j.ajo.2024.12.023.

16. Feng J, Xie F, Wu Z, et al. Age-related macular degeneration and cardiovascular disease in US population: an observational study. Acta Cardiol. 2024;79(6):665-671. doi: 10.1080/00015385.2023.2295103.

17. Kha R, Kapucu Y, Indrakumar M, et al. Diabetic retinopathy further increases risk of cardiovascular disease mortality in a high-risk cohort. Sci Rep. 2025;15(1):4811. doi: 10.1038/s41598-025-86559-x.

18. Zehden JA, Mortensen XM, Reddy A, Zhang et al. AY. Systemic and Ocular Adverse Events with Intravitreal Anti-VEGF Therapy Used in the Treatment of Diabetic Retinopathy: a Review. Curr Diab Rep. 2022;22(10):525-536. doi: 10.1007/s11892-022-01491-y.

19. Hutton DW, Stein JD. Holistic Evaluation of the Burden of Eye Disease. JAMA ophthalmology. 2024;142(12):1130-1.

20. Paudel N, Brady L, Stratieva P, et al. Economic burden of late-stage age-related macular degeneration in Bulgaria, Germany, and the US. JAMA ophthalmology. 2024 ;142(12):1123-30.

21. Sivaprasad S, Bailey C, Downey L, et al. Real-world service costs for neovascular-AMD clinics in the United Kingdom: structured literature review and scenario analysis. Current Medical Research and Opinion, 2024;40(7), 1221-1233.

22. Chen CQ, Du LP, Liu Q, et al. Comprehensive evaluation of the use of intravitreal injection of anti-vascular endothelial growth factor drugs in patients with fundus lesions based on real-world data. medRxiv. 2024:2024-04.

23. Hodgson R, Walton M, Fulbright H, et al. A systematic review of the cost-effectiveness of anti-VEGF drugs for the treatment of diabetic retinopathy. Health Technology Assessment (Winchester, England). 2025:1.

24. Kümmel P, Arda H, Haritoglou C. EE646 Prescription Ratio and Costs of Intravitreal Injections for Diabetic Macular Oedema From 2015 to 2022. Value in Health. 2024; 27(12):S182-3.

25. Ruiz-Moreno JM, de Andrés-Nogales F, Oyagüez I. Cost-consequence analysis of extended loading dose of anti-VEGF treatment in diabetic macular edema patients. BMC ophthalmology. 2020;20:1-8.

26. Kumar A, Ferro Desideri L, Ting MYL, et al. Perspectives on the currently available pharmacotherapy for wet macular degeneration. Expert Opin Pharmacother. 2024;25(6):755-767. doi: 10.1080/14656566.2024.2354921.

27. Yan A, Jones C, Demirel S, et al. Diabetic macular edema: Upcoming therapies. Graefes Arch Clin Exp Ophthalmol. 2024. doi: 10.1007/s00417-024-06595-7. Epub ahead of print.

28. Namvar E, Yasemi M, Nowroozzadeh MH, et al.

Intravitreal Injection of Anti-Vascular Endothelial Growth Factors Combined with Corticosteroids for the Treatment of Macular Edema Secondary to Retinal Vein Occlusion: A Systematic Review and Meta-Analysis. Semin Ophthalmol. 2024;39(1):109-119. doi: 10.1080/08820538.2023.2249527.

29. Ma X, Cui Y, Zhang M, et al. A Multifunctional Nanodrug Co-Delivering VEGF-siRNA and Dexamethasone for Synergistic Therapy in Ocular Neovascular Diseases. Int J Nanomedicine. 2024;19:12369-12387. doi: 10.2147/IJN.S492363.

30. Yang R, Tang S, Xie X, et al. Enhanced Ocular Delivery of Beva via Ultra-Small Polymeric Micelles for Noninvasive Anti-VEGF Therapy. Adv Mater. 2024;36(32):e2314126. doi: 10.1002/adma.202314126.

31. Sil D, Kumar D, Kurmi BD, et al. Recent Progress in Polymeric Micelle-Enabled Targeted Nanotherapeutics for Diabetic Retinopathy. Journal of Drug Delivery Science and Technology. 2024:106448. doi:10.1016/j.jddst.2024.106448.

32. Sonowal L, Gautam S. Ocular drug delivery strategies using carbon nanotubes: A perspective. Materials Letters. 2025;379:137642.

33. Pal P, Sambhakar S, Paliwal S. Revolutionizing Ophthalmic Care: A Review of Ocular Hydrogels from Pathologies to Therapeutic Applications. Current Eye Research. 2025 ;50(1):1-7.

34. Pereira F, Magagnoli J, Ambati M, et al. Oral lamivudine in diabetic macular edema: A randomized, double-blind, placebo-controlled clinical trial. Med. 2025:100747. doi: 10.1016/j.medj.2025.100747.

35. Mauschitz MM, Verzijden T, Schuster AK, et al.; European Eye Epidemiology (E3) Consortium. Association of lipid-lowering drugs and antidiabetic drugs with age-related macular degeneration: a meta-analysis in Europeans. Br J Ophthalmol. 2023;107(12):1880-1886. doi: 10.1136/bjo-2022-321985.