Literature Review

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Vascular endothelial growth factor inhibitors in exudative retinal diseases: overview of recent advances and prospects for further progress

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The incidence of blindness due to exudative retinal diseases reduced significantly over the twenty years of the use of anti-vascular endothelial growth factor (VEGF) therapy in ophthalmology. However, despite advances in recent years, current outcomes of anti-VEGF therapy for exudative retinal diseases are not always optimal. This review aims to highlight the advances in the development of VEGF inhibitors and identify potential ways of improving the outcomes of anti-VEGF therapy for, and solving current problems in the management of, exudative retinal diseases.

Introduction

Retinal disease is a major cause of blindness worldwide [1]. Neovascularization due to increased vascular endothelial growth factor (VEGF)-A production in response to retinal blood flow abnormalities, hypoxia, oxidative stress and activation of the complement system are a major mechanism of retinal diseases associated with macular edema such as neovascular age-related macular degeneration (nAMD), diabetic macular edema (DME), central or branch retinal vein occlusion (RVO) and myopic choroidal neovascularization (mCNV). This is why anti-VEGF agents are current standard of care and first-line therapy for these disorders [2-5]. The reducing incidence of blindness due to exudative retinal diseases has been driven in part by widespread introduction of anti-VEGF therapy [6]. There are, however, problems in the management of these disorders which can be solved in future. These include a significant therapeutic load on patients, high cost of treatment, inadequate patient compliance, limited monitoring of the disease course, and worsening of the achieved improvement in visual acuity with time [7]. This review aims to highlight the advances in the development of original biopharmaceutical drugs and biosimilars and identify potential ways of improving the outcomes of anti-VEGF therapy for, and solving current problems in the management of, exudative retinal diseases.

Expanding indications for anti-VEGF therapy

As of April, 2024, four anti-VEGF medications (aflibercept, brolucizumab, ranibizumab and faricimab) have been approved for ophthalmological use in Ukraine [8-11]. The list of indications approved for ophthalmic use of anti-VEGF drugs in Ukraine is presented in Table 1.

The next possible step in solving the problems in the management of exudative retinal diseases could be the Ukrainian national executive authority approval of the expansion of indications for use for anti-VEGF agents. Aflibercept has been already Food and Drug Administration (FDA) approved for diabetic retinopathy and FDA and European Medicines Agency (EMA) approved for retinopathy of prematurity (ROP). In addition, it has been approved in Japan for the treatment of neovascular glaucoma, whereas faricimab has been approved in the US for retinal vein occlusion (RVO) [12-15]. Moreover, bevacizumab has demonstrated clinical efficacy in the management of exudative retinal diseases in clinical trials, and is used off-label for exudative retinal diseases [16-17]. Outlook Therapeutics, Inc., a biopharmaceutical company focused on the commercialization and development of ONS-5010/LYTENAVATM (bevacizumab-gamma) for the treatment of retinal diseases, announced in May, 2024, that the European Commission has granted Marketing Authorization for LYTENAVATM, an ophthalmic formulation for the treatment of nAMD in the European Union [18]. If registered by the State Service of Ukraine on Medicines and Drug Control, this formulation may extend the list of anti-VEGF medications available for ophthalmological use in the country.

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Table 1. List of indications approved for ophthalmic use of anti-VEGF medications in Ukraine [8-11]

	aflibercept	brolucizumab	ranibizumab	faricimab
Neovasculae age-related macular degeneration	+	+	+	+
Diabetic macular edema	+	+	+	+
Central or branch retinal vein occlusion	+	–	+	–
Myopic choroidal neovascularization	+	–	+	–
Moderate od severe non-proliferative and proliferative diabetic retinopathy	–	–	+	–
Active choroidal beovascularization	–	–	+	–
Retinopathy of prematurity	–	–	+	–

Current clinical practice may be improved by expanding the indications for use for anti-VEGF agents to include the exudative retinal diseases for which there is still no effective approved treatment capable of not only reducing the rate of vision loss, but restoring vision in patients. There have been many reports on the efficacy of anti-VEGF agents in such exudative retinal diseases as choroidal neovascularisation secondary to chronic central serous chorioretinopathy [19, 20], Best vittelliform macular dystrophy [21, 22], choroidal neovascularizations secondary to angioid streaks in pseudoxanthoma elasticum [23, 24], choroidal neovascularization associated with chorioretinitis [25], Irvine-Gass syndrome [26, 27], neovascularization secondary to proliferative type 2 macular telangiectasia [28, 29], and macular edema associated with Coats disease [30, 31]. In addition, it has been reported on the successful experience of using anti-VEGF agents before vitrectomy for reducing intraoperative hemorrhagic complications and surgery duration [32].

Expanding the knowledge on pharmacological properties of anti-VEGF agents

Pharmacodynamics and pharmacokinetics are the two branches of pharmacology, with pharmacodynamics studying the action of the drug on the organism and pharmacokinetics studying the effect the organism has on the drug. A healthcare practitioner dealing with prescribing agents, selecting their doses and administering pharmacological therapy should have good knowledge of pharmacological characteristics of all prescribed medications [33]. Correspondingly, further expanding the knowledge on pharmacodynamics and pharmacokinetics of anti-VEGF agents will improve clinical decision making of retinologists [34].

Pharmacokinetic properties of anti-VEGF molecules are now rather well known due to studies by anti-VEGF drug developers [35]; however, there is a paucity of data on some aspects of anti-VEGF pharmacokinetics (such as elimination half-life of the drug, the route of drug elimination from the eye, binding affinity of drug molecule to ligands, and relationship between the drug dose, the frequency of drug administration and drug pharmacokinetics), and these data were obtained from animal studies and modeling approaches. In order to expand our knowledge on the pharmacology of anti-VEGF agents, further research is required with cohorts of healthy volunteers and patients enrolled, e.g., in comparative clinical trials, particularly with regard to the novel drugs that have only recently appeared on the market [36-38].

The introduction of treat-and-extend anti-VEGF injection regimen due to meticulous investigation of the duration of effective VEGF-A suppression with, and properties of anti-VEGF molecules is an example of a beneficial effect of the expansion of knowledge on the pharmacology of anti-VEGF agents. The long-term benefits of implementing a treat-and-extend pathway may include a reduced number of intravitreal injections compared to the fixed protocol, which was reflected particularly in the national guidelines [39].

It seems promising to conduct further research on the potential for increased concentration of anti-VEGF agents for improved outcomes of treatment for, and lower treatment burden on patients with, exudative retinal diseases. Research in this field resulted in the development of and studies on aflibercept injection of an increased dose, EYLEA HD (aflibercept) injection 8 mg. The FDA approval of EYLEA HD (aflibercept) injection 8 mg is based on the results of PULSAR and PHOTON, two double-mask, active controlled pivotal trials evaluating EYLEA HD compared to EYLEA (aflibercept) injection 2 mg. Aflibercept injection 8 mg has been FDA approved for the treatment of patients with nAMD, DME and DR, and EMA approved for wAMD and DME [40, 41].

A substantial number of non-VEGF proteins and non-VEGF growth factors are involved in the pathogenesis of exudative retinal diseases, and most anti-VEGF agents suppress only VEGF-A, which may potentially limit treatment efficacy [42, 43]. However, recent in vivo data suggest that anti-VEGF agents currently used for the treatment of retinal diseases could provide beneficial effects beyond direct binding of VEGF [44, 45]. Therefore, further research on the impact of anti-VEGF agents on other major pathways involved in the pathogenesis of exudative retinal diseases may improve treatment approaches, with an improvement achieved through a more balanced selection of the agent, with the consideration of additional beneficial effects in a particular patient's clinical picture.

The importance of expanding knowledge on the safety profiles of anti-VEGF agents deserves separate consideration. At present, limited data is available on the impact of properties of anti-VEGF drugs on the development of intraocular and systemic side effects [46]. In addition, it is of clinical interest to assess anti-VEGF drug concentration in systemic circulation after simultaneous bilateral intravitreal injection. Although several studies have confirmed a low risk of intraocular and systemic side effects in simultaneous bilateral intravitreal anti-VEGF injection, the impact of the pharmacokinetics and pharmacodynamics of anti-VEGF agents on the risk of the development of intraocular and systemic side effects requires further research [47, 48].

Original biopharmaceutical drugs and biosimilars

A biosimilar is a biologic medication that is highly similar, but not identical, to another already approved biologic medication—the original biologic—also called the reference product. The aim of biosimilar development is to demonstrate biosimilarity—high similarity in terms of structure, biological activity and efficacy, safety and immunogenicity profile [49]. As of April, 2024, the EMA has approved several biosimilars for ranibizumab (Lucentis) [50, 51]. No biosimilar for any anti-VEGF drug has been approved for ophthalmological use in Ukraine, but these biosimilars could become available in this country in the future.

A biosimilar will only be approved once it is proven that it is highly similar to the reference product in physicochemical and biological terms and once it is demonstrated by comparative clinical studies that clinically meaningful differences between the biosimilar and the reference product can be ruled out. Studies on biosimilars commonly enroll smaller numbers of patients than studies on reference products and are not required to demonstrate bioequivalence for all indications. When biosimilarity is demonstrated in one indication, this can be used to approve the biosimilar for other indications, provided that the mechanism of action is the same for different indications; this scientific principle is called extrapolation [49]. Therefore, the accumulation and analysis of long-term data on safety and immunogenicity profiles of biosimilars is important for the effective and safe use of biosimilars in routine clinical practice [52]. That strict pharmacovigilance for biosimilars is important can be illustrated with an example. Previously, sterile inflammation (endophthalmitis) has been reported in patients receiving razumab, the first biosimilar of ranibizumab approved for ophthalmic use in India. These reports led to a recall of the drug by the manufacturer and subsequent changes in the formulation [53].

Updating clinical guidelines and treatment protocols

Recommendations issued by reputed ophthalmological societies with regard to management of exudative retinal diseases may provide some important guidance for practitioners. Currently no guidelines have been issued by the national ophthalmological societies and associations regarding the management of patients with exudative retinal diseases; therefore, Ukrainian retinologists have to be guided by recommendations issued by relevant European societies. Consequently, it is important to develop and adopt local guidelines on the management of patients with exudative retinal diseases, while taking into account the features of the diagnosis and management of these diseases in Ukraine.

With regard to the European guidelines, there is no significant need in revising them annually, but they have to be timely updated (particularly, with the advent of novel medications and treatment methods) to reflect current approaches to treatment. The European Society of Retina Specialists (EURETINA) guidelines for the management of nAMD have been last revised in 2014 [54], while those for the management of DME and RVO, in 2017 [55] and 2019 [56], respectively, and the EURETINA expert consensus recommendations on intravitreal injections have been last updated in 2018 [57]. There are, however, no recognized European guidelines for the management of e.g., mCNV. In addition, guidelines are lacking for the management of patients refractory to anti-VEGF treatment and for switching from one anti-VEGF therapy agent to another.

In recent years, reports have appeared on (1) an increase in the incidence of intraocular complications and (2) new side effects in the use of novel anti-VEGF agents [58]. One of these side effects is retinal vasculitis, which have not been reported until the publications on the results of abicipar pegol's phase 3 trial CEDAR and SEQUOIA and brolucizumab arrival into routine clinical practice [59]. Faricimab-related retinal vasculitis with or without RVO has been also reported [60]. Retinal vaculitis is a serious side effect that can lead to significant loss of vision [61]; therefore, the development and wide implementation of recommendations for its minimization would be beneficial for improved treatment outcomes of anti-VEGF therapy for exudative retinal diseases.

Promising candidate anti-VEGF drugs under investigation

There is still room for improvement in anti-VEGF drugs, and many candidate anti-VEGF drugs are under investigation which may potentially improve outcomes for patients with exudative retinal diseases. Below are presented major molecules which are currently being tested in Phase 1 to Phase 3 clinical trials for these diseases and are expected to come to market in the next 5-10 years.

KSI-301 (tarcocimab tedromer; Kodiak Sciences, Palo Alto, CA) is an antibody biopolymer conjugate with a molecular weight of 950 kDa designed for increased durability of VEGF-A inhibition. Despite varied results in the phase 2b/3 study for nAMD, there is a potential for KSI-301 to serve as a durable therapy for VEGF-mediated retinal disorders. Ongoing phase 3 trials for nAMD, DME and RVO will provide additional evidence on its efficacy, duration and safety profiles [62].

KSI-501, a novel bispecific antibody polymer conjugate targeting IL-6 and VEGF, has being designed also by Kodiak Sciences. First-in-human Phase 1 multiple ascending dose study is currently ongoing in the US, initially in DME patients [63].

OPT-302 (Opthea limited, Melbourne, Australia) is a recombinant fusion protein 'trap' molecule inhibits VEGF-C and VEGF-D. Intravitreal injections of anti-VEGF-A drugs are a standard of care, but these do not inhibit VEGF-C and D. In a Phase 2b randomized sham-controlled trial in patients with nAMD, significantly superior vision gain was observed in the group that received intravitreal 2.0 mg OPT-302 plus intravitreal 0.5 mg ranibizumab compared to the group that received a sham intravitreal injection plus intravitreal 0.5 mg ranibizumab [64]. Phase 3 studies are ongoing to evaluate the efficacy and safety of intravitreal 2.0 mg OPT-302 in combination with ranibizumab, compared with ranibizumab alone, in participants with nAMD [65, 66].

RGX-314 (RegenxBio, Inc., Rockville, MD) is an adeno-associated virus serotype 8 vector that expresses an anti-VEGF-A antigen-binding fragment, which provides potential for continuous VEGF-A suppression after a single subretinal injection. A Phase 1/2a, dose escalation study, nAMD patients treated with subretinal RGX-314 injections showed no clinically determined immune responses or inflammation beyond that expected following routine vitrectomy. Results from this study informed the pivotal programme to evaluate RGX-314 in patients with nAMD [67].

Ixoberogene soroparvovec (ixo-vec, formerly ADVM-022; Adverum Biotechnologies, Inc., Redwood City, CA), utilises a novel vector capsid, AAV2.7m8, carrying an aflibercept coding sequence under the control of a ubiquitous expression cassette. In preclinical studies, ixo-vec administration resulted in long-term, stable expression of aflibercept at levels expected to be adequate to treat nAMD with no measurable effect on normal retinal structure or function observed following long-term VEGF suppression. In the phase 1 open-label clinical trial (OPTIC), ixo-vec was well tolerated, maintained vision, and improved anatomical outcomes in nAMD, with a substantial reduction in anti-VEGF injections [68].

Studies are underway on potential candidate molecules for the treatment of exudative retinal diseases through the impact on various pathogenetic components: ATX107 (Asclepix Therapeutics, Inc., Baltimore, MD) inhibits type 2 VEGF receptors (VEGFR2) and activates Tie2 receptors [69]. Efdamrofusp alfa (formerly IBI302; In-novent Biologics, Suzhou, China) targets both VEGF and C3b/C4b complement [70]; PAN-90806 (PanOptica, Mount Arlington, NJ) is a potent and selective inhibitor of VEGF signaling which is administered topically in the form of eyedrops [71]; GB-102 (GrayBug Vision, Inc., Redwood City, CA) is a proprietary microparticle depot formulation of sunitinib malate injected intravitreally [72].

Conclusion

The incidence of blindness due to exudative retinal diseases reduced significantly over the twenty years of the use of anti-VEGF therapy in ophthalmology. Despite advances in recent years, current outcomes of anti-VEGF therapy for exudative retinal diseases are not always optimal. The review of the current literature allowed us to identify the following potential ways to improve the outcomes of anti-VEGF therapy for eye disease:

Expanding the indications for use for anti-VEGF agents to include the exudative retinal diseases for which there is still no effective approved treatment

Further expanding the knowledge on pharmacodynamics and pharmacokinetics of anti-VEGF agents, especially in studies involving humans

Characterizing more accurately the safety profiles of anti-VEGF agents and assessing more accurately the impact of their properties on the development of intraocular and systemic side effects

Improving pharmacovigilance for anti-VEGF agents and especially biosimilars which have only recently appeared on the market, have limited evidence of their efficacy and safety and have only recently arrived into routine clinical practice

Developing and implementing updated national clinical recommendations and guidelines on the management of patients with exudative retinal diseases, improving intravitreal injection methodology and minimizing risks for side effects after the use of anti-VEGF agents, and regular updating clinical guidelines issued by the leading European societies, and

Beginning new and continuing current research initiatives to address candidate molecules for the treatment of exudative retinal diseases while taking into account previous experience, including negative experience.

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Abbreviations: *DME, diabetic macular edema; EMA, European Medicines Agency; FDA, US Food and Drug Administration; mCNV, myopic choroidal neovascularization; nAMD, neovascular age-related macular degeneration; RVO, central or branch retinal vein occlusion; VEGF, vascular endothelial growth factor*