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Review

Intravitreal systems for targeted drug delivery to the posterior eye segment: a systematic review

Elizaveta R. Orlova [1], Aleksandr V. Gorobets [2,3,4], Dmitry A. Dorofeev [5], Elena V. Kirilik [5], Irina V. Kozlova [6]

[1] Chelyabinsk State University, Chelyabinsk, Russia
[2] Ural State University, Chelyabinsk, Russia
[3] Center for Extracurricular Education of Kasli Municipal District, Kasli, Russia
[4] Kasli College of Industry and Humanities, Kasli, Russia
[5] Chelyabinsk Public Clinical Hospital No. 2, Polyclinic No. 1, Chelyabinsk, Russia
[6] Research Institute of Eye Diseases, Moscow, Russia

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Abstract: *Background* — Intravitreal implants solve a number of serious problems arising in diseases of the posterior segment of the eyeball. Unlike intravitreal injections, the implant provides a prolonged release of a pharmaceutical drug over time. The review presents the characteristics of existing systems for intravitreal drug delivery: nanosystems, non-biodegradable and biodegradable implants. The review also highlights the main advantages and disadvantages of various implants. Based on the conducted literature review, the following conclusion is formulated: the most promising means of targeted drug delivery of drugs to the posterior segment of the eyeball are biodegradable implants. However, currently existing biodegradable implants do not provide entirely controlled release of the drug (uncontrollable extraction episodes occur at times), which constitutes a serious issue requiring improvement.
Objective — to summarize the published data on existing systems for the targeted drug delivery into the vitreous chamber, identifying their major advantages and disadvantages.
Material and Methods — Information was searched in such databases as PubMed, Google Scholar and ClinicalTrials.gov, using the keywords in both Russian and English languages: intravitreal implants, intraocular implants, biodegradable implants, non-biodegradable implants, nanosystems, nanoparticles, liposomes, targeted drug delivery, posterior segment of the eye, etc.

Keywords: intravitreal implants, intraocular implants, biodegradable implants, non-biodegradable implants, nanosystems, nanoparticles, liposomes, targeted drug delivery.

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Correspondence to Elizaveta R. Orlova. Address: 129 Bratyev Kashirinykh St., Chelyabinsk 454001, Russia. Phone: +79517846529. E-mail: mrs.eagle2001@gmail.com.

Introduction

Targeted drug delivery systems play an important role in improving clinical efficacy, safety, and tolerability of medicines. In diseases of the eyeball, a significant problem is to break down the blood-ocular barrier, which prevents the necessary concentrations of the drug from reaching the target point [1]. According to some authors, one of the most effective methods of targeted delivery of medications to the eyeball is their intravitreal administration [2, 3]. The method allows creating a high concentration of the drug in the vitreous chamber, while systemic side effects are noticeably reduced due to a lower dose of the drug entering the systemic circulation. A serious limitation in using the method of intravitreal drug administration is the necessity of periodic repeated injections, which increases the risk of local complications. When injected into the vitreous chamber, its maximum concentration is reached immediately after the administration of the drug; and in most cases, a relatively long-term depot of the preparation is not created. Hence, the therapeutic effect declines as the concentration of the active substance decreases as a result of the drug absorption from the vitreous body into the systemic circulation [4]. The solution to the above problems is intravitreal implants, the release of the medicinal substance from which is determined in time and is set during the design of the implant. Contemporary models are aimed at creating modified slow-release drug delivery systems that provide maximum drug bioavailability, prolonged therapeutic effect, and reduced risk of side effects [5].

All currently existing systems for intravitreal drug delivery can be divided into three groups: biodegradable implants, non-biodegradable implants, and nanosystems [1].

Nanosystems

The concept of nanosystems includes nanoparticles (nanospheres and nanocapsules), liposomes (structures consisting of lipid bilayers surrounding an aqueous core), dendrimers (branched macromolecules with a tree structure), micelles (surfactant aggregates in a colloidal system consisting of a large number of amphiphilic molecules), nanoemulsions (colloidal

systems of nanoparticles with a size of 0.1-100 nm in a liquid solvent), hydrogels (three-dimensional networks of hydrophilic polymers with high water content), niosomes (single- or multilayer bubbles consisting of a double-layered shell of a water-insoluble nonionic emulsifier (surfactant), soluble macromolecules, etc. [7, 8].

Marcelo L. Occhiutto et al. [8] provide the following examples of nanosystem-based ophthalmic drug delivery systems (*Table* 1). The studies presented in the table suggested the possibility of using various nanosystems to resolve an issue of bioavailability of medications and prolong their therapeutic effect. At the same time, synthetic polymers (polymer micelles, dendrimers, hydrogels), lipids (liposomes), proteins (albumin nanoparticles), and even inorganic compounds (cerium oxide nanoparticles) are mainly used for intravitreal administration [7]. According to Miki Honda et al., microemulsions and dendrimers, as systems for delivering drugs to the posterior eye segment, are inferior to micro/nanospheres and liposomes, since microemulsions are not suitable for a prolonged therapeutic effect (which, in our opinion, is associated with their physicochemical properties: spread of the drug in the vitreous chamber is not restricted by any capsule or membrane, only the viscosity of the injected substance changes); besides, among dendrimers, only a few are safe in vivo [21].

Nanoparticles (nanospheres, nanocapsules) are objects, the dimensions of which, sensu International Union of Pure and Applied Chemistry (IUPAC) classification, do not exceed 100 nm in at least one dimension. It is important to note that not all nanoparticles used in medical applications meet this size requirement. A key factor in the use of nanoparticles is the ratio of their surface area to volume and mass, as well as their capability to adsorb and transport other compounds. Thus, it is acceptable to consider nanoparticles used for targeted drug delivery as spherical particles of various diameters up to 1,000 nm [22]. For targeted drug delivery, nanoparticles made from lactic, glycolic and hyaluronic acids, as well as polycaprolactone, are most habitually used [23].

Table 1. Examples of nanosystem-based ophthalmic drug delivery systems

Active substance	*Delivery system*
Ibuprofen Cyclosporine Diclofenac sodium	Solid lipid nanoparticles [9, 10]
Cyclosporine Dexamethasone Pilocarpine hydrochloride	Nanoemulsion [11, 12]
Dexamethasone	Micelles [13]
Flurbiprofen	Nanosuspension [14]
Timolol maleate	Dictyosomes [15]
Pilocarpine nitrate Dexamethasone	2-Hydroxypropyl-β-cyclodextrin [16, 17]
Acetazolamide Inulin Oligonucleotides Pilocarpine hydrochloride Diclofenac sodium	Liposomes [18]
Tropicamide Pilocarpine nitrate	Dendrimers [19]
Cyclopentolate	Niosomes [20]

The release of the drug occurs both due to the spread of nanoparticles from the injection site, and by diffusion of the active substance from the nanoparticles per se. Diffusion proceeds in several stages: first, the medicine is extracted evenly, followed by biodegradation of the nanoparticle surface, which, due to destruction of the structure and integrity, is accompanied by a rapid release of the active agent [24].

An important characteristic of nanoparticles, which allows using them for intravitreal administration, is the interaction of the surface of negatively charged particles with Müller cells, due to which the nanoparticles are able to pass through all layers of the retina and reach the layer of photoreceptors [25].

Gomez-Gaete et al. developed dexamethasone-loaded PLGA nanoparticles (230 nm) and optimized the solvent evaporation process to obtain particles with maximum drug uptake [26]. After that, a new carrier for the intravitreal delivery of dexamethasone was developed: Trojan particles formed by spray drying of 1,2-dipalmitoyl-SN glycero-3-phosphocholine, hyaluronic acid, and various concentrations of suspensions of PLGA nanoparticles loaded with dexamethasone [27]. Trojan particles provide slower medicine release due to the excipient matrix protecting encapsulated nanoparticles.

Merodio et al. investigated the toxicity of bovine serum albumin nanoparticles with ganciclovir during prolonged intravitreal exposure. Based on histological evaluation, they concluded that it was well tolerated in vivo, and that there was no inflammatory reaction [28]. Irache et al. demonstrated that albumin nanoparticles were effective and safe for delivering anticytomegalovirus drugs to the vitreous body in intravitreal administration [29]. Duvvuri et al. developed empirical equations to describe the release of ganciclovir from PLGA microspheres in vitro [30].

Another variant of nanoparticles are photosensitive particles. Huu et al. developed nanoparticles based on a polymer that was decomposing in far ultraviolet (UV) light. Exposure to low-power light can trigger drug release non-invasively. According to the results of histological examination, tomography of the cornea and retina, as well as electroretinograms, light-sensitive nanoparticles are biocompatible and do not adversely affect the organ of vision [31].

Despite the obvious benefits of nanoparticles, there are legitimate concerns about their toxicity. This is especially true for nanoparticles created from synthetic substances [32]. According to Sibo Jiang et al., toxic and allergic reactions associated with the use of nanoparticles have not yet been studied well enough [7].

Liposomes

Liposomes are vesicles consisting of one or more bilayer membranes of a phospholipid nature. It is possible to use liposomes for targeted delivery of both hydrophilic and hydrophobic drugs (hydrophilic substances are located in the liquid core of liposomes, while hydrophobic substances are located in their lipid bilayer). Single layer liposomes can be small vesicles, 10-100 nm in size (small unilamellar vesicles, SUV), or large vesicles, 100-3000 nm in size (large unilamellar vesicles, LUV). There are also liposomes consisting of more than one bilayer (multilamellar vesicles, MLV) [33]. The release of the medicine from liposomes is associated with breaking the chemical bonds holding the nanocarrier-drug conjugate, in which the active substance is covalently bound to the carrier (it is also possible for the entire

conjugate to function without breaking the chemical bonds). Release can occur in several ways. The first is diffusion along the concentration gradient of the substance; over time, the rate of release of the active substance decreases (due to a decline in its concentration inside the liposome). The second is layer-by-layer degradation of the liposome. The release rate of the medicine depends on the rate of liposome degradation. This option is most preferable for controlling the release rate of the substance [34, 35].

Also, liposomes are able to interact with the cell membrane [22]:

- By fusion (in this case, the liposome becomes part of the membrane, as a result of which the properties of cell membranes may change towards an increase in their permeability due to formation of additional membrane channels);
- By way of endocytosis, i.e., an uptake of the liposome by the cell;
- Via adsorption of the liposome on the membrane;
- Through lipid exchange between liposomes and cell membrane.

Currently, two medicines in the form of liposomes are used in clinical practice: *Tears Again* (Optima Pharmazeutische GmbH, Germany) and *Visudyne* (QLT Ophthalmic, Inc., Menlo Park, CA, United States). *Visudyne* is used intravenously for age-related macular degeneration in patients with predominantly conventional subfoveal choroidal neovascularization, and for recurrent subfoveal choroidal neovascularization in myopia. *Tears Again* are eye drops used in instillations for moisturizing the surface of the eyes.

With regard to the intravitreal use of liposomes, liposome-encapsulated amikacin has been studied for treating bacterial endophthalmitis. The duration of stay for the drug in the vitreous body was increased, compared with conventional intravitreal administration of amikacin. The results of pharmacokinetic analysis showed that the liposomal form of amikacin was preferable to the conventional drug [36]. Carmen Claro et al. studied the pharmacokinetic parameters of foscarnet in vitreous body and retinal tissue of rabbits. The extraction of the drug was slower, liposomal foscarnet exhibited a stable therapeutic level in the retina and vitreous body (over 72 hours). The authors also studied lyophilized liposomes, but lyophilization of liposomes did not lead to an improvement in pharmacokinetics; however, the stability and dispersion of liposomes in an aqueous medium became higher [37].

Tacrolimus for the treatment of autoimmune retinal vasculitis was also tested in the form of liposomes: high treatment efficacy, long-term retention of the drug in eye fluids (14 days) in transretinal distribution of liposomal particles, and no toxic effect were observed [35]. Therapeutic effect extension of the liposomal form of the drug, compared with its traditional form, was also observed for bevacizumab [38]. It should be noted that in contrast to previously mentioned studies [35-37], where liposomes were obtained via reverse-phase evaporation, Abrishami Majid et al. performed the encapsulation for bevacizumab via the dehydration-rehydration method, which could affect the experimental outcomes [38].

charged liposomes and protamine. The study of using such platform yielded good results: high bioavailability, prolonged therapeutic effect, and a decrease in the toxic response to high concentrations of drugs. Apparently, such systems have great potential for minimizing the negative impact on the visual system in the course of intravitreal therapy [39].

The prevention of experimental choroidal neovascularization development in rats was investigated using an angiogenesis inhibitor (SU5416) encapsulated in liposomes modified with Ala-Pro-Arg-Pro-Gly (APRPG). Liposomes were obtained by thin-film hydration method. The authors suggested that their development represented a potential dosage form for the treatment of choroidal neovascularization, which would require a single intravitreal injection [40].

Table 2. Non-biodegradable implants

Brand names	*Short description*	*Dimensions*
Vitrasert® [3, 43-45]	PVA / EVA (polyvinyl alcohol/ethylene vinyl acetate) implant. Provides controlled release of 4.5 mg ganciclovir. Extraction of the preparation lasts 5-8 months.	2.5 mm in diameter, 1 mm thick
Retisert® [44, 46-48]	PVA implant laminated with silicone. Contains 0.59 mg of fluocinolone acetonide. Provides prolonged release of the medicine up to 3 years.	5×2×1.5 mm
Iluvien® [49-51]	Corticosteroid implant made or a semipermeable membrane. Contains 190 μg of fluocinolone acetonide. Drug extraction lasts 36 months.	3.5 mm long, 0.37 mm wide
I-vation® [52, 53]	Titanium implant coated with a layer of triamcinolone acetonide (active ingredient) and semipermeable polymers (PVA and polybutylene methacrylate). Triamcinolone acetonide layer (0.925 μg). Extraction of the medicine lasts 24 months.	0.4 mm long, 0.37 mm wide
NT-501® [54, 55]	The device consists of a semipermeable polyethersulfone peripheral membrane and a polyethylene terephthalate core. Contains 2×10^5 CNTF (ciliary neurotrophic factor) secreting cells. Extraction of the drug lasts 24 months.	1 mm in diameter, 6 mm long
Port Delivery System® [56, 57]	The device is made of polysulfone, contains a silicone septum, and has a semipermeable titanium membrane at the distal end. Contains 20 microliters of ranibizumab. The device is filled with a special filling needle as needed.	Less than 3.5 mm

Table 3. Biodegradable implants

Brand names	*Short description*	*Dimensions*
Sorudex® [41, 61, 62]	Implant made of a copolymer of lactic and glycolic acids, and hydroxypropyl methylcellulose (HPMC). Contains 60 µg of dexamethasone. Resorbed in the anterior chamber of the eye within 7-10 days; extraction of the active substance from the implant matrix in the posterior eye segment lasts 2 weeks.	1.0×0.4 mm
Ozurdex® [63, 64]	Made of a copolymer of lactic and glycolic acids (PLGA). Contains dexamethasone at a dose of 0.7 mg. The implant stays in the vitreous chamber for 6 months.	6.5×0.45 mm
Durysta® [65, 66]	The implant is a polymer system of lactide, PLGA and polyethylene glycol polymers. Contains 10 µg of bimatoprost. Complete degradation occurs after 12-24 months or later.	200 µm in diameter, 1.1 mm long

Hence, liposomes and nanoparticles have great potential for use in intravitreal therapy due to the presence of various modifications that allow retaining the drug in the vitreous chamber and controlling its release. However, nanosystems require careful testing for toxicity and immune inertness.

Non-biodegradable implants

Non-biodegradable implants are made of polymers, such as vinyl acetate, ethylene vinyl acetate (EVA), polyvinyl alcohol (PVA), and polysulfone. PVA and EVA are used to produce implants for hydrophobic medications. Such implants are inert: they do not cause any immune response. Polysulfone implants are suitable for both hydrophobic and hydrophilic drugs. Due to the presence of macrovoids in the polysulfone structure, the surface area of the implant, available for the adsorption of the medicine onto it, increases [41, 42].

Common to all non-biodegradable implants is the necessity to remove them after the end of the drug release, which leads to additional surgical intervention and, as a result, to undesirable side effects. *Table* 2 presents a number of non-biodegradable implants that are currently used in clinical practice or have passed preclinical and clinical trials.

Vitrasert® (Bausch & Lomb Inc., USA) is one of the first implants of the kind. The device consists of two permeable PVA layers, between which there is a layer of impervious EVA. Such structure provides a ganciclovir release rate of 1 µg/h and is implanted for 5-8 months. According to clinical studies, the efficacy of implanted ganciclovir is significantly higher, compared with conventional therapy [43,44]. Complications include cataract, vitreous hemorrhage, retinal detachment, endophthalmitis, implant dislocation, temporary decrease in visual acuity, hypotension, formation of an epiretinal membrane, and others [3].

Retisert® (Bausch & Lomb Inc., USA) is an implant coated with PVA and silicone laminate containing 0.59 mg of fluocinolone acetonide. Retisert is used to treat chronic noninfectious uveitis but was also effective against diabetes-related edema and central retinal vein occlusion. Reductions in recurrence rates from 62% per year before implantation to 4%, 10% and 20% in the first, second, and third years after implantation, respectively, have been demonstrated [44, 46].

All patients required surgical removal of the cataract after the implantation, which was significantly higher in patients with uveitis using conventional therapy. Conjunctival hyperemia was observed in 31% of cases, conjunctival hemorrhage in 29%, hypotension in 11%, and eye pain in 52% of cases. An increase in intraocular pressure (IOP) within three years after implantation was observed in 78% of patients, 40% of whom required filtering antiglaucoma surgery [58, 59]. Furthermore, in 40.7% of cases, Retisert was prone to spontaneous separation (dissociation) into two main components: a medicating reservoir and a silicone base, which complicates explantation [48].

Iluvien® (Alimera Sciences Inc., USA) is an intravitreal fluocinolone acetonide implant for the treatment of diabetic macular edema. The introduction of this device is performed through the flat part of the ciliary body using the original 25-gauge injector, and the duration of the effect is 36 months. Iluvien is FDA approved. Among the side effects, an increase in IOP and cataracts should be mentioned [49-51].

I-vation® (SurModics, USA) is a titanium spiral (screw) implant coated with a layer of triamcinolone acetonide, while semipermeable polymers (PVA and polybutylene methacrylate) are applied on the outside. It is implanted through the flat part of the ciliary body through a sclerotomy incision. The screw shape allows increasing the surface area and anchoring the device in the sclera [52]. As result of its clinical trial, all patients developed cataracts. Phase 2b trials were discontinued, and no further clinical trials were completed [53].

NT-501® is an implant designed for targeted delivery of CNTF. It is attached to the sclera with a small titanium loop. It provides a controlled release of a therapeutic agent, CNTF, which plays an important role in axonal regeneration and has a neuroprotective effect, thereby promoting the survival of photoreceptors. The device solves the problem of targeted CNTF delivery and is significantly safer than intravitreal injections. It can be potentially used in some eye diseases, such as glaucoma, age-related macular degeneration, retinitis pigmentosa, uveitis, and neoangiogenesis [54, 55].

Port Delivery System (Genentech Inc., USA) is a reusable implant replenishable with a self-sealing septum, which allows the implant to be refilled with a medicinal substance without removing it from the eye. It is used to treat neovascular age-related macular degeneration with ranibizumab. The device is filled with a special filling needle, which flushes the device while simultaneously filling it with the medication. Ranibizumab is released from the reservoir into the vitreous chamber by passive diffusion across the semipermeable titanium membrane. The implantation procedure is considered quite safe; however, several cases of endophthalmitis and retinal detachment have been reported in clinical trials [56, 57].

Thus, non-biodegradable implants represent an effective solution for intravitreal treatment. Release control is possible via layering polymers of different permeability. To change the diffusion rate, it is also possible to change the thickness and surface area [53]. However, due to necessity of surgical removal of

worn-out implant, the risk of postoperative complications increases [60].

Biodegradable implants

Biodegradable implants are made of biocompatible materials metabolized in the body to non-toxic compounds. Therefore, there is no need to remove the carrier after medication extraction is completed, which significantly reduces the risk of injury to the eye. Biodegradable implants are made of polymers of lactic acid, glycolic acid, copolymers of lactic and glycolic acids, polycaprolactone, and poly (methylene malonate) [53].

The release of the medicine is provided by substance diffusion and implant degradation. In this case, the rate of medicine extraction depends on the molecular weight of the polymer and the packing of the active substance. The molecular weight of the medicine per se also affects its release rate: lower molecular weight substances are more rapidly extracted into the vitreous chamber [41].

The process of implant degradation and, accordingly, the active substance release can be conditionally divided into several stages [23]:

- Resorption of the implant surface layers accompanied by abundant release of the medicine;
- Gradual destruction of the implant matrix (uniform drug diffusion);
- Final degradation of the polymer structure (release of a large dose of the medication).

Table 3 presents a number of biodegradable implants that are currently used in clinical practice or have passed preclinical and clinical trials.

Sorudex® is a biodegradable implant made of a copolymer of lactic and glycolic acids and hydroxypropyl methylcellulose (HPMC) containing 60 μg of the active substance (dexamethasone). It is used to treat diseases of both the anterior and posterior segments of the eye. It is approved in a number of Asian countries, showing good efficacy and low complication rates [41, 61, 62].

Ozurdex® is the best-known biodegradable implant. It is made of a copolymer of lactic and glycolic acids in the form of a rod, its introduction is performed through the flat part of the ciliary body using an original 22-gauge injector. It is used in clinical practice for treating the diabetic macular edema and retinal vein occlusion, along with noninfectious uveitis [63]. The implant remains in the vitreous chamber for six months: over the first two months, its maximum concentration is observed, then there is a gradual decrease [64].

Durysta® is a biodegradable implant containing 10 mg of bimatoprost. It is FDA approved and used to lower IOP in patients with open-angle glaucoma or ocular hypertension. The duration of treatment is 3-4 months. Data on the rate of complete decomposition of the implant vary. For instance, in some patients, the implant is completely decomposed 12 months after insertion, in others, it is detected during gonioscopy 24 months after insertion [65, 66].

The most common complications associated with the use of biodegradable implants are: increased IOP, cataract development, foreign body sensation, eye pain, photophobia, annd conjunctival hemorrhage [23, 41, 53].

It should be noted that there are many non-biodegradable and biodegradable implants (Glaukos' iDose™, OTX-TIC by Ocular Therapeutix, and some other) used to treat previously mentioned diseases [67]. However, these devices are implanted in the anterior chamber of the eye and are intended to replace drip therapy. The consideration of devices implanted in the anterior chamber of the eye is not included in this review.

To date, no neuroprotective drugs in the form of implants are on the market. However, there is a hypothesis that a number of medicines could potentially show higher efficacy when administered intravitreally via implants. This assumption is based on theoretical data and requires experimental confirmation. One of the promising medications for administration in the form of an implant is Retinalamin®, which belongs to the pharmacotherapeutic group of a tissue repair stimulator. The mechanism of action is determined by the metabolic activity of Retinalamin®: the medicine activates the metabolism of eye tissues, normalizes the functions of cell membranes, improves intracellular protein synthesis, regulates lipid peroxidation, optimizes energy processes via enhancing the activity of Müller cells and glutamate inactivation. Due to this, there is an improvement in the functional interaction of the pigment epithelium and the outer segments of photoreceptors, normalization of vascular permeability, prevention of oxidative stress and excitotoxicity, improvement of metabolism in the eye tissues, and improvement of blood flow in eye vessels.

Hence, the use of biodegradable implants reduces the risk of postoperative complications (due to no need to remove the implant matrix); however, it does not provide a prolonged uniform release of the medication, which leads to the risk of exceeding its safe concentration in the vitreous chamber during uncontrolled extraction episodes.

Conclusion

The development of methods for targeted delivery of medications to the posterior segment of the eyeball is an extremely relevant area of research, which is associated with the need to break down the blood-ocular barrier and, at the same time, achieve a prolonged action of drugs (via creation of a drug depot) in the vitreous chamber. The issue of reducing the risk of developing toxic effects and immune responses is relevant as well. The development of implants is carried out taking into account modern achievements in the field of biomedicine, physics, chemistry, and pharmacology. However, the best option meeting all requirements still does not exist. It is necessary to develop an implant, the use of which would be minimally invasive. Its material must be biocompatible, providing an ability to control the release rate, and not provoking the development of toxic effects.

Authors' contributions

Equal participation.

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Conflict of Interest

None declared.

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Authors:
Elizaveta R. Orlova – student, Chelyabinsk State University, Chelyabinsk, Russia. https://orcid.org/0000-0001-9568-1715.
Aleksandr V. Gorobets – Instructor, Department of Physics of Nanoscale Systems, Institute of Natural and Precision Sciences, Ural State University, Chelyabinsk, Russia; Center for Extracurricular Education of Kasli Municipal District, Kasli, Russia; Kasli College of Industry and Humanities, Kasli, Russia. https://orcid.org/0000-0001-9864-9833.
Dmitry A. Dorofeev – ophthalmologist, Chelyabinsk Public Clinical Hospital No. 2, Polyclinic No. 1, Chelyabinsk, Russia. https://orcid.org/0000-0003-3352-8170.
Elena V. Kirilik – ophthalmologist, Chelyabinsk Public Clinical Hospital No. 2, Polyclinic No. 1, Chelyabinsk, Russia. https://orcid.org/0000-0002-0189-9586.
Irina V. Kozlova – MD, PhD, Lead Researcher, Division of Glaucoma, Research Institute of Eye Diseases, Moscow, Russia. https://orcid.org/0000-0003-3885-9649.