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Pre- and perioperative prophylaxis of anti-VEGF therapy in patients with exudative macular degeneration

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HIGHLIGHTS

Maintaining the proper condition of the ocular protective apparatus in the preoperative period in patients qualified for surgical procedures determines the lower risk of complications. Eyelid margin hygiene is one of effective methods of prevention.

ABSTRACT

Macular degeneration is one of the leading causes of blindness worldwide. Nowadays, the gold standard treatment for its exudative form is intravitreal injections with vascular growth factor inhibitor preparations performed on a once-daily basis. Great importance is now attached to the appropriate prophylaxis in the pre- and perioperative period in order to minimise the risk of complications, which often lead to irreversible damage to vision.

Key words: age-related macular degeneration, intraocular inflammation, intravitreal injections, eyelid margin hygiene

INTRODUCTION

The new approach in medicine associated with same-day hospital care is associated with better and more efficient organization of a given unit, lower treatment costs and often shorter waiting periods for surgery or medical treatment. Numerous ophthalmic procedures performed on a same-day basis, such as intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents and cataract surgery, have facilitated access for a wide range of patients without affecting the quality and achieved health outcomes, but at the same time have raised concerns in the medical community about how to properly protect patients from dangerous postoperative complications. More attention began to be paid to the proper patient preparation in the preoperative period, related primarily to the condition of the protective apparatus of the eyeball and the anterior surface of the eyeball. It is now an essential part of any ophthalmic procedure, improving safety and often affecting recovery.

MACULAR DEGENERATION – EPIDEMIOLOGY, CLASSIFICATION, CLINICAL FEATURES

Age-related macular degeneration (AMD) is a disease process affecting the macula, leading to loss of central vision. In highly developed countries, it is one of the leading causes of blindness in patients over the age of 65 [1]. According to the epidemiological studies, the percentage of patients diagnosed with AMD determined in the 45–85 age group (regardless of stage) is currently 8.7%. Due to the aging of the population, the percentage of people with AMD is projected to increase steadily over the next few years. It is estimated that by 2040, the number of patients with early-stage macular degeneration in Europe will range from 14.9 million to as many as 21.5 million, while late-stage AMD will affect 3.9 to 4.8 million people [2]. Patients with newly diagnosed AMD are also increasing in the Polish population. Currently, their number is about 1.2–1.9 million, of which 130–140,000 are patients with the more severe stage of AMD [2, 3]. According to epidemiological projections, the number of people with AMD could rise to as many as 3.6 million by 2060.

The initial stages of the disease are characterized by single drusen (deposits that include products of retinal metabolism) in the fundus, pigment regroupings and small atrophic lesions. Over time, the condition progresses in two directions: geographic atrophy (non-ischemic form) or neovascularization (exudative form), referred to as advanced stages of AMD. Development of advanced AMD can last from a few weeks to even several years and is associated with gradual loss of central vision [4]. Macular degeneration is divided into two forms:

- dry AMD, which includes initial degenerative changes occurring in the retina and advanced geographic atrophy (atrophy of the retinal pigment epithelium, choriocapillaris and photoreceptors in the macula)
- exudative (wet) AMD, related to the appearance of neovascular membrane.

Dry AMD is the most common, occurring in about 80–90% of patients. It is characterized by a mild course with slow progression leading to degenerative changes, resulting in deterioration of central vision. It has been shown that it is possible for the dry form to convert to a wet AMD [5, 6].

Only less than 10–20% of patients develop the wet form with much more severe course, which can lead to an irreversible decrease in visual acuity in a short period of time. The process of retinal cell damage in this form is associated with the formation of pathological blood vessels in the neovascular membrane. Newly formed choriocapillaris have an abnormal wall structure, causing them to have increased permeability of blood morphotic elements to the extravascular space. This results in thickening, detachment, swelling and formation of cystic spaces localized under the retinal pigment epithelium, intra- or subretinal. In addition, some patients may experience rupture of newly formed thin choriocapillaris, resulting in hemorrhage into the subretinal, supraretinal space or vitreous body [5, 6]. Complications observed in patients with untreated wet form of AMD include the formation of a disc-shaped fibrous scar or the coexistence of exudative retinal detachment. All of the above-mentioned processes consequently lead to irreversible damage to photoreceptors [7, 8].

ANTI-VEGF PREPARATIONS USED IN THE TREATMENT OF WET AMD

Currently available therapies to inhibit the progress of AMD primarily address its wet form. Anti-VEGF agents, injected into the vitreous body, have proved to be a revolution in treatment, significantly reducing the risk of severe vision loss or functional blindness. Current formulations with proven therapeutic effects registered for intravitreal injections include [9]:

1. Ranibizumab – a fragment of a recombinant humanized monoclonal antibody produced in *Escherichia coli* cells. It acts selectively on a protein termed human endothelial vascular growth factor-A (VEGF-A), inhibiting the proliferation of endothelial cells, thereby preventing the tumorigenesis of pathological vessels and excessive vascular permeability.
2. Aflibercept – a recombinant fusion protein that includes fragments of the extracellular domains of human VEGF1 and 2 receptors fused to the Fc fragment of human IgG1. It is produced in K1 cells of the Chinese

hamster ovary. It acts selectively on human endothelial growth factor types A and B (VEGF-A, VEGF-B) and placental growth factor (PlGF) and shows higher affinity than their natural receptors (VEGFR1 and VEGFR2), inhibiting pathological vascular tumorigenesis and excessive vascular permeability.

3. Brolucizumab – a single-chain fragment of recombinant humanized Fv monoclonal antibody (scFv), produced in *Escherichia coli* cells. It exhibits a strong affinity for VEGF-A isoforms (e.g., VEGF110, VEGF121 and VEGF165), thereby preventing VEGF-A from binding to its VEGFR-1 and VEGFR-2 receptors, which in turn makes it inhibit pathological vascular tumorigenesis and excessive vascular permeability.

Many ophthalmology centers around the world also use a formulation called bevacizumab. It is widely used in oncological diseases (colon, bronchial and kidney cancer), but due to its low treatment cost and observed efficacy, it has also found use in the treatment of ophthalmic conditions, including many retinal edematous conditions and macular choroidal neovascularization, mainly in wet AMD. The product has been administered by intravitreal injection outside of its registration indication, or off label, since May 2005. Bevacizumab is a recombinant humanized monoclonal antibody produced in Chinese hamster ovary cells. Its action involves binding to VEGF, which in turn inhibits its binding to Flt-1 (VEGFR1) and KDR (VEGFR2) receptors on the surface of endothelial cells, reducing pathological vascular tumorigenesis and excessive vascular permeability [10].

Currently, there is a steady increase in the number of patients undergoing intravitreal therapy with anti-VEGF preparations. On the one hand, it is related to the increase in the number of patients with newly diagnosed disease eligible for treatment, and, on the other hand, to the persistent number of patients continuing previously implemented treatment (undergoing multiple injections over the years). The list of indications for ranibizumab and aflibercept therapy is also expanding, and now includes:

- exudative form of AMD
- diabetic macular edema (DME)
- macular edema in the course of retinal vein occlusion (RVO)
- subretinal neovascularization in myopia.

INTRAOCULAR INFLAMMATION AS ONE OF THE MOST DANGEROUS COMPLICATIONS OF INTRAVITREAL INJECTIONS

Current anti-VEGF therapies still involve frequent medical checkups to assess the disease progress, which is considered one of the most significant, intractable problems for the patient. Also, the very process of administering the drug, its intensive dosing, which often translates into a monthly or bi-monthly regimen, is a significant limitation of this method, as well as increasing the risk of complications. The most commonly observed complications associated with anti-VEGF administration include:

- sterile or bacterial inflammation of the inside of the eyeball
- retinal tears/dehydration
- hemorrhages into the vitreous chamber
- cataract development
- sudden increase in intraocular pressure.

One of the most serious complications observed after ophthalmic surgery is postoperative intraocular infection. According to numerous reports, the incidence rate of infection in the postoperative period is low, but its effects often lead to significant visual impairment. Current protocols for treating wet AMD recommend frequent anti-VEGF injections into the vitreous body. The risk of intraocular inflammation after this type of procedure, although low at only 0.022–0.16% [11, 12] in the average population, can increase significantly in patients with comorbidities such as insulin-dependent diabetes mellitus (the risk increases fourfold), upper respiratory tract infection, chronic inflammation of the eyelid margins and conjunctiva, as well as those receiving immunosuppression and as a result of contact lens use [13].

The results of numerous studies have helped identify the most common etiological factors affecting the risk of the aforementioned infection, namely microorganisms of the physiological flora found on the eyelid margins, on the surface of the conjunctiva or tear film. It has been observed that eyelid margin inflammation of varying severity occurs in about 94% of studied AMD patients [14]. The most common bacteria isolated from eyelids, conjunctivae and tears belonged to the Gram-positive bacteria family, mainly coagulase-negative staphylococci. This corresponds to the strains of microorganisms most commonly isolated in the course of post-inoculation intraocular inflammation, which include coagulase-negative strains of staphylococci and streptococci, less commonly *Bacillus cereus*, *Enterococcus faecalis*, *Staphylococcus epidermidis* or *Staphylococcus aureus*. It has been reported that streptococcal intraocular inflammation occurs three times more often as a complication of post-inoculation procedures than post-surgery [15]. Intraocular inflammation in patients receiving anti-VEGF preparations was usually diagnosed within 5–7 days after injection. However, the timing of the onset of intraocular inflammation, its severity and the clinical course depend on a number of factors, including: infection portal of entry, virulence, pathogen load, and the state of the patient's immune system. The most common symptoms observed in patients

with the aforementioned condition are severe eyeball pain, abnormal accommodation, diffuse congestion and swelling of the ocular conjunctiva, significant and sudden decrease in visual acuity, photophobia, inflammatory reaction in the anterior chamber with inflammatory exudate and pus level, inflammatory reaction in the vitreous body, often with absence of fundus reflex [16]. Any inflammation of the inside of the eyeball leads to irreversible loss of visual function in a short period of time, so it is extremely important to recognize it early and implement proper treatment as soon as possible.

In this regard, pre-injection prophylaxis carried out at various stages of the medical process, not only at the time of injection, but also in the pre-injection period, seems extremely important. It is also crucial to conduct pre-operative evaluation of the anterior segment of the eye and the protective apparatus by the attending physician, as well as a conversation with the patient about the role of the present abnormalities and the associated risks. One should remember that any inflammation of the eye surface or the protective apparatus is a contraindication to the administration of an intravitreal injection, which delays the drug dose and reduces the chances of success of the ongoing treatment regimen, and may eventually lead to an irreversible reduction in the quality of vision. Symptoms such as redness of the eyelid margins, recurrent chalazion or stye, the presence of dried discharge on the eyelashes, dry eye symptoms that do not resolve despite the use of moisturizing eye drops, infections of the eyes and tear ducts, and inflammation of the skin of the face, head and neck may require early treatment to reduce the risk of postoperative complications.

STRATEGIES AND TREATMENTS IN THE PROCEDURE OF INTRAVITREAL INJECTIONS

Perioperative period preventive care

Researchers still endeavor to find optimal preventive strategies to safeguard against the occurrence of dangerous complications in the pre- and post-operative periods. Current assumptions and regimens mainly focus on the perioperative period, in which a clear course of action is developed before injection into the vitreous chamber. At present, performing this procedure can take place both in the operating room and in an appropriately prepared aseptic treatment room. Patient preparation begins with the administration of local anesthetic drops into the conjunctival sac (1% or 2% lidocaine gel can be used as additional anesthesia). The surgical field, i.e., the eyelids and skin, is then disinfected with a 5–10% iodopovidone solution, and in patients with a history of allergic reaction to iodine, a 0.05% chlorhexidine solution should be used. The procedure is performed using a sterile disposable surgical field drape, with the use of a sterile eyelid diverter, and after injecting a 5% iodopovidone solution into the conjunctival sac for at least 30 seconds (in the case of an allergic reaction, the use of a 0.05% chlorhexidine solution is recommended). To date, there has been no correlation between the use of disposable gloves and sterile draping and a reduction in the risk of intraocular inflammation, but according to current regimens, this is included as a preventive measure to reduce the risk of adverse postoperative events. Conversely, the advisability of using surgical masks has been proven, as well as limiting conversation, which has been reported to reduce the risk of oral microbial infection [17].

Topical antibiotic therapy is not currently recommended due to the risk of developing drug resistance to saprophytic strains found in the conjunctival sac. According to reports, perioperative antibiotic therapy does not reduce the risk of intraocular inflammation after intravitreal injection [18, 19]. Retrospective data from the Diabetic Retinopathy Clinical Research Network showed an even higher incidence of intraocular inflammation in patients who used topical antibiotics in the perioperative period (6/4694; 0.13%) than in those who did not (1/3333; 0.03%).

All of the abovementioned activities carried out during the perioperative period are aimed at minimizing the patient's risk of complications related to the procedure. After the injection, it is advisable to check the patient's approximate visual acuity (sense of light, movement of the hand in front of the eye, or counting fingers in front of the eye) and to inform them about symptoms that may suggest an adverse event, such as:

- inflammation of the inside of the eyeball – severe pain, redness of the eyeball, photophobia or blurred vision
- retinal detachment – the feeling of a veil in front of the eye, visual field disturbances
- stroke into the vitreous chamber – significant decrease in visual acuity.

Injections into both eyes are permitted during a single visit. To reduce the risk of pathogen transmission, the drug should be prepared from different packages, and the procedure itself should be carried out using two different kits [18].

Pre- and post-operative period prophylaxis in the treatment regimens of intravitreal injections

The high intensity of procedures that damage the eye's natural protective barriers in repetitive regimens necessitates the development of appropriate pre- and post-operative procedures to protect patients from complications, which include intraocular inflammation. Currently, there are no clearly defined guidelines on how to prepare a given patient for a safe ophthalmic procedure. Topical antibiotic therapy is not recommended in the preoperative and postoperative

periods due to the risk of developing drug resistance [18, 19]. It has been shown that it may even increase the risk of intraocular inflammation due to the destruction of the natural bacterial flora, which in turn promotes the presence of more virulent pathogens in the conjunctival sac.

One important recommendation is to maintain the proper condition of the protective apparatus of the eye and to hydrate the ocular surface in the preoperative period. Properly developed recommendations for preparing the anterior surface of the eye and the protective apparatus, supplemented by the use of appropriate eyelid margin preparations and artificial tear preparations, as well as the length and frequency of application in the pre- and post-operative periods, should be an integral part of any ophthalmic surgical procedure. Properly performed eyelid hygiene in the preoperative period has been shown to reduce the risk of complications by reducing bacterial flora in the eyelids and conjunctiva. This is because the purpose of the aforementioned procedure is to remove inflammatory debris lingering on the eyelid margins and to improve tear film stability achieved by balancing the lipid layer condition [20]. Reports have described various forms of eyelid margin care, of which the most common included:

- warm compresses performed twice a day (morning and evening) – they increase the temperature at the edges of the eyelids, thus acting on the Meibomian glands, causing liquefaction of secretions and promoting their release
- eyelid margins massage – helps remove excess secretions from the Meibomian glands
- eyelid margins care using preparations designed for this purpose (liquids or wipes), usually performed twice a day to remove dirt accumulated around the eyelashes
- intensive use of artificial tear preparations
- (in severe cases) topical and/or general antibiotic therapy, topical anti-inflammatory agents (e.g., corticosteroids, cyclosporine).

Many reports have shown the effectiveness of eyelid margin hygiene carried out with dedicated preparations compared to the previously used antibiotic therapy. A study by Assumpta et al. analyzed the reduction of microbial flora during the use of eyelid margin wipes. The study was conducted on a group of 45 patients qualified for ophthalmic surgery; the patient performed eyelid margin hygiene on one eye, while the other eye served as the control group. The observation period was 5 days, and swabs were taken daily from the eyelid margin and conjunctival sac to identify microorganisms. The ocular surface microflora was estimated by measuring the area of the agar plate occupied by cultured colonies relative to the total area. Analyses showed a higher role of eyelid microflora compared to conjunctiva microflora (17.9% vs. 1.4%). There was also a percentage reduction in eyelid microflora of 58% on day three and 63% on day five, as well as on the conjunctiva microflora (72% and 69%, respectively). It has also been shown that properly performed care of the protective apparatus of the eye does not sterilize the tissue, does not affect the development of bacterial resistance, and does not reduce the saprophytic flora of the eyelid and conjunctiva, as is the case with antibiotic therapy [20]. The aforementioned observations were also confirmed by Hueso Abancens et al. In a study on a group of 30 patients, they reported a reduction in conjunctival microflora after using a solution containing capryloyl glycine [21]. The findings suggest that proper use of eyelid margin hygiene as a complementary prophylactic method before any ophthalmic surgery can reduce the risk of complications in the postoperative period. It is also related to the appropriate composition of eyelid preparations, which have not only antibacterial (thanks to the content of capryloyl glycine, zinc sulfate or *Centella Asiatica* extract), but often also anti-inflammatory effects, promoting the healing and regeneration process or regulating the function of Meibomian glands. An additional advantage is the availability of some preparations, such as disposable wipes in sterile sealed packaging, which is intended to maintain adequate microbiological purity and asepsis throughout the shelf life and provides protection of the finished preparation from contamination and microbial growth. In addition, it easily facilitates storage, transportation and application. An issue currently unexplored is the application frequency and length of such care, especially in the preoperative period. In addition, it also raises the question of whether long-term use of eyelid hygiene products will not adversely affect the saprophytic flora of the eyelids and conjunctiva.

Eyelid margin hygiene requires a lot of discipline from the patient and systematic, thorough care. This raises the question of whether patients will actually perform the recommended activities in the correct manner? The biggest problem perceived by doctors is the lack of regularity in the recommended regimen. It should be remembered that only regular hygiene of the eyelid margins carried out according to the recommended regimen can significantly calm the symptoms of chronic inflammation [21]. Compresses, massages and preparations designed to care for the eye's protective apparatus are generally sufficient. They should be used with caution in patients with advanced glaucoma (after filtration surgery) or with corneal neurotrophic ulceration. Therefore, it is up to the ophthalmologist to take into account the patient's individual capabilities and prepare the best possible treatment plan [22]. It is also important to remember that eyelid margin hygiene can be one of the tools to protect the patient from dangerous complications in the postoperative period. However, it cannot replace general preoperative procedures, applied on the day of surgery,

aimed at preventing contamination; these include the application of iodopovidone to the eyelids and conjunctival sac. However, it seems that eyelid hygiene should be a complementary prophylaxis to prevent possible intraocular inflammation.

CONCLUSIONS

The number of patients with macular degeneration is steadily increasing. There is also an increase in the number of patients taking anti-VEGF agents, which may lead to an increasing number of recorded post-injection complications. Intraocular inflammation, as one of the most dangerous complications, continues to pose a considerable challenge in both the prevention and treatment processes. It seems that the development of an appropriate preoperative prophylaxis regimen that includes proper hygiene of the eyelid margins could help increase safety and thus reduce the risk of complications, especially in an era of procedures performed as same-day surgery.

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