Emerging Therapeutic Options in Age-Related Macular Degeneration

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Abstract

Intravitreal injection of anti-VEGF drugs currently represents the standard of treatment for exudative age-related macular degeneration. Several therapeutic options including steroids, inhibitors of complement factors, anti-platelet-derived growth factor agents, new anti-VEGF drugs, designed ankyrin repeat proteins, sustained drug delivery devices as an alternative to intravitreal injections and encapsulated cell technology are the objects of several studies and trials worldwide in association with anti-VEGF therapy or not. Expectations are that such efforts will help overcome limitations of current therapy with anti-VEGF, extending the duration of effects and hopefully contributing to the regression of neovascular lesions.

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Introduction

Age-related macular degeneration (AMD) is a multifactorial disease; the exudative or neovascular form is characterized by choroidal neovascularization (CNV), vascular permeability and inflammation.

Intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) drugs currently represents the standard of treatment for exudative AMD. Several therapeutic options including steroids, inhibitors of complement factors, anti-platelet-derived growth factor (anti-PDGF) agent, new anti-VEGFs, designed ankyrin repeat protein family, sustained drug-delivery devices as an alternative to intravitreal injections and encapsulated cell technology are the objects of several studies and trials worldwide in association with anti-VEGF therapy or not. In this review we analyse the role of new therapies for exudative AMD.

Steroids

Since the 1950s, steroids have been widely used for the treatment of retinal diseases thanks to their anti-angiogenic, anti-oedematous and anti-inflammatory proper-

ties [1]. Galenic preparations have been progressively substituted and today steroid implants guarantee more safety and a longer pharmacological effect, thus allowing decreasing the number of retreatments and the severity of the side effects.

According to numerous publications, steroids for retinal diseases are best administered intravitreally; the only products approved for this use are sustained-release implants.

The main effects of the steroids on the retina are stabilization of the haemoretinal barrier, decreasing exudation and down-regulation of the inflammation. However, the exact mechanism has not been demonstrated yet [2]. The anti-inflammatory action has an effect on VEGF and induces the expression of other anti-inflammatory factors such as PDGF.

Thanks to their powerful anti-inflammatory effects, dexamethasone and fluocinolone acetonide have been considered (in combination or in monotherapy) as promising therapeutic options for a wide spectrum of retinal diseases, including exudative AMD.

Many authors have described the so-called triple therapy, which includes a vaso-occlusive therapy (photodynamic therapy), an anti-VEGF agent and a steroid. Recent studies have demonstrated that the triple therapy (bevacizumab, dexamethasone implant and photodynamic therapy) is able to reduce the number of injections needed to stabilize vision in patients who do not respond anymore to monotherapy anti-VEGF [3].

A randomized clinical trial has evaluated the combined use of dexamethasone intravitreal implant (Ozurdex®, Allergan, Irvine, Calif., USA) and ranibizumab (Lucentis®, Genentech, Inc., South San Francisco, Calif., USA/Novartis AG, Basel, Switzerland) to treat patients with neovascular AMD. The authors demonstrated that the implant reduced the total number of ranibizumab injections [4].

Fluocinolone acetonide, a synthetic corticosteroid, has comparable activity to dexamethasone. Its solubility is different from that of dexamethasone and this permits a longer period of action of the molecule. The Iluvien® implant (Alimera Sciences, Alpharetta, Ga., USA) is currently being evaluated in phase II studies for the treatment of dry AMD (ClinicalTrials.gov identifier: NCT00695318). Another study has compared the 0.2- and 0.5-mg fluocinolone acetonide intravitreal implant to ranibizumab in neovascular AMD (ClinicalTrials.gov identifier: NCT00605423). The results showed an improvement in visual acuity for both groups at 6-month follow-up.

Inhibitors of Complement Factors

As in many other diseases with an inflammatory component, the alternative complement pathway has been implicated in the development of AMD [5]; this mechanism of action is now well known and described [6].

Each one of the three complement pathways (alternative, lectin and classical) starts an amplification of pro-inflammatory reactions and activates the C3 molecule (fig. 1). This is an auto-sustained mechanism in which proteolysis activates C3 to C3b and forms a new C3 convertase molecule which will activate more C3. The pathway continues with the C5 convertase, this enzyme then cleaves C5 to C5a, a potent anaphylatoxin, and C5b which is part of the membrane attack complex. The membrane attack complex initiates cell lysis and releases proangiogenic molecules such as PDGF and VEGF. Inhibition of the complement system is therefore considered a very promising therapeutic approach for the treatment of AMD.

Zimura® (Ophthotech Corp., Princeton, N.J., USA) is a chemically synthesized aptamer that inhibits complement factor C5, which seems to have a role in the pathogenesis of AMD. A phase II clinical trial (ClinicalTrials.gov identifier: NCT00709527) has evaluated the safety, tolerability and pharmacokinetics of multiple doses of Zimura® intravitreal injection when administered in combination with Lucentis® 0.5 mg/0.05 ml in subjects with subfoveal CNV secondary to AMD. Patients receiving Zimura® were reported to obtain significant improvements in best-corrected visual acuity at the end of the study.

POT-4 is a potent inhibitor of complement factor C3 activation. A phase I clinical trial has been designed to evaluate the safety and the tolerability of POT-4 administered by intravitreal injections (ClinicalTrials.gov identifier: NCT00473928). Preliminary results showed good tolerability and safety (no intraocular side effects were reported). Even though no significant improvement of visual acuity was observed, there was no significant visual loss either [7].

Anti-PDGF Agents

Anti-PDGF agents, which block PDGF, are promising new tools for exudative AMD. Even though anti-VEGF brought great results in the treatment of the disease, recent studies have shown that the pharmacological effect in the long term seems to diminish. The SEVEN-UP study [8] analysed the long-term results (7–8 years) of ANCHOR, MARINA and HORIZON, three clinical trials in which ranibizumab was administered every month.

Fig. 1. Schematic diagram of the pathway of the complement (alternative, lectin and classic). Each one of the three complement pathways starts an amplification of pro-inflammatory reactions and activates the C3 molecule. This is an auto-sustained mechanism in which proteolysis activates C3 to C3b and forms a new C3 convertase molecule which will activate more C3. POT-4 is a com-

plement inhibitor, which shuts down the complement activation cascade that could otherwise lead to local inflammation, tissue damage and up-regulation of the angiogenic factors. A phase I clinical trial has been designed to evaluate the safety and the tolerability of POT-4 administered by intravitreal injections. Reprinted from Mollnes et al. [16] with permission from Elsevier.

The study highlighted that, after a progressive improvement in the first months of treatment, there was a 'plateau effect' and also that in the long term visual acuity regressed to low levels in a significant percentage of patients.

The SECURE study [9] analysed the long-term results of 200 patients who were treated with ranibizumab according to a PRN protocol. Also in this study the visual improvement was more prominent in the first months of treatment and had a tendency to diminish in the long term.

These along with other findings raised questions about atrophy linked to the use of anti-VEGF [10] and the resistance to anti-VEGF [11].

Researches are now focused on the role of pericytes, cells that are implied in the production of VEGF in order to sustain the neovascularization. These cells seem to have an important role in the resistance to anti-VEGF therapy. Since PDGF is implied in the recruitment of the pericytes, PDGF inhibitor may play an important role in reducing the neovascularization, especially when associated with anti-VEGF agents (fig. 2).

Fig. 2. Schematic diagram of VEGF and PDGF in CNV. As neovessels grow, PDGF is overexpressed in CNV. PDGF helps in the recruitment and maturation of pericytes, which send a survival signal to the neovascular cells (a) and therefore will not be affected by anti-VEGF; CNV does not regress (b). When anti-PDGF is administered, it strongly binds to PDGF-b. At this point the pericytes disappear and the CNV becomes extremely sensitive to treatment with an anti-VEGF agent (c). Simultaneous targeting by these two agents brings a significant reduction in the volume of the neovessels of the CNV (d). Courtesy of Samir Patel, MD.

Fovista[®] is an anti-PDGF agent. A multicentre, randomized, double-masked, controlled phase IIb clinical trial has evaluated the efficacy and safety of Fovista[®] (Ophthotech Corp., ClinicalTrials.gov identifier: NCT02214628). Ranibizumab was administered alone or in combination with Fovista[®] which was well tolerated with no significant side effects. Patients receiving the combination therapy obtained a significantly higher final visual acuity; a mean gain of 10.6 letters from baseline was achieved compared to a mean gain of 6.5 for patients in monotherapy.

A phase III randomized, double-masked, controlled trial (ClinicalTrials.gov identifier: NCT01940900 and NCT01944839) is currently underway to establish the safety and efficacy of intravitreal administration of Fovista[®] in combination with ranibizumab compared to ranibizumab monotherapy in subjects with subfoveal neovascular AMD. The study is recruiting patients in the USA, South America and Europe. The first results are expected in 2016.

Additional trials are planned to test the efficacy of Zimura[®] combined with Fovista[®] in neovascular AMD and the efficacy of Zimura[®] in geographic atrophy.

New Anti-VEGF Agents

Conbercept (KH902; Chengdu Kanghong Biotech Co., Ltd., Sichuan, China) consists of the VEGF binding domains of the human VEGFR-1 and VEGFR-2 com-

bined with the Fc portion of the human immunoglobulin G1. It binds the VEGF-A along with VEGF-B and placental growth factor [12]. The AURORA study is a randomized, double-masked, multicentre, controlled-dose and interval ranging phase 2 clinical trial (ClinicalTrials.gov identifier: NCT01157715). Recently the results from the first 12 months have been published [13]. Conbercept seems to improve best-corrected visual acuity both with a PRN regimen and with monthly injections. Intravitreal conbercept was well tolerated; no cardiovascular events were reported in the study.

Pazopanib (GlaxoSmithKline, Brentford, UK) is a multi-tyrosine kinase inhibitor having an effect on VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- α , PDGFR- β and other receptors. Recently 70 patients affected by CNV were treated with pazopanib eye drops at different concentrations for 28 days. A significant decrease from baseline in central retinal thickness and an increase in best-corrected visual acuity were observed only in a subset of patients [14].

Designed Ankyrin Repeat Protein Family

Designed ankyrin repeat proteins are small, single-domain proteins that can selectively bind to a target protein with high affinity and specificity. Abicipar pegol (Allergan), previously known as MP0112, is a recombinant protein of the designed ankyrin repeat protein family, which was recently evaluated in a phase I/II, open-label, multi-

centre, dose-escalation study. Currently a phase II randomized double-blind clinical trial (ClinicalTrials.gov identifier: NCT02181517) is evaluating abicipar pegol for AMD compared to ranibizumab. The first results from the phase II study were published [15]: patients received abicipar pegol every month for 3 months while the control group received ranibizumab monthly for the entire duration of the study. The study was not powered enough to show statistically significant differences between the two drugs, but it shows good results in terms of efficacy and durability of abicipar pegol.

Sustained Drug-Delivery Devices as an Alternative to Intravitreal Injections

ESBA1008 (Alcon, Fort Worth, Tex., USA) is a single-chain antibody fragment. Among the most interesting characteristics of single-chain antibody fragments are the small dimensions; this may permit using sustained drug-delivery devices as an alternative to intravitreal injections. A phase I study was conducted to assess the safety, tolerability and the effects of treatment on ocular outcomes following a single intravitreal administration of ESBA1008 compared with Lucentis® in patients with exudative AMD (ClinicalTrials.gov identifier: NCT01304693 and NCT01849692). A single injection of ESBA1008 or a single injection of ranibizumab 0.5 mg was administered to 194 patients in the prospective, randomized, multicentre study. Patients receiving ESBA1008 were divided into four cohorts, thus receiving four different doses. Further studies are currently recruiting patients to evaluate the effect of ESBA1008 applied by microvolume injection or infusion in subjects with exudative AMD.

Devices able to sustain a constant release of drug are an interesting option that would allow reducing the burden of the injections, reducing costs and lowering the incidence of risks of the injections.

Encapsulated Cell Technology

Encapsulated cell technology involves biotechnical implants that are able to produce continuously recombinant therapeutics. NT-503 (Neurotech Pharmaceuticals, R.I., USA), an intraocular implant delivering VEGF antagonist, is being tested in a prospective, multicentre two-stage study. Stage 1 (phase I) is open-label with all patients treated with the NT-503-3 encapsulated cell technology implant (ClinicalTrials.gov identifier:

NCT02228304). Stage 1 (phase I) patients will undergo explantation of the implant at year 2. Those patients who still need to receive anti-VEGF therapy will be re-implanted with a new NT-503-3 investigational product and followed for an additional 12 weeks before study exit. Stage 2 (phase II) is a separate, randomized, masked phase during which eligible patients will be randomized to the NT-503-3 group or the control group injected intravitreally with aflibercept (Eylea®; Regeneron, Tarrytown, N.Y., USA, and Bayer, Berlin, Germany) every 8 weeks.

sFLT-1 (soluble fms-like tyrosine kinase-1) is a tyrosine kinase protein, which encodes for the VEGF receptor 1. When administered in the eye and expressed by the host retinal cells, the sFLT-1 protein inhibits the formation of new blood vessels and reduces vascular permeability by binding and blocking VEGF activity.

Adeno-Associated Virus Vectors

AAV2-sFLT01 (Genzyme, Cambridge, Mass., USA) is an adeno-associated virus vector that expresses a modified soluble Flt1 receptor. A phase I clinical research study is currently underway to evaluate the safety and tolerability of this agent in patients with exudative AMD (ClinicalTrials.gov identifier: NCT01024998). This experimental study drug uses a virus to transfer a gene into cells within the eye, which should be able to diminish the growth of abnormal blood vessels under the retina. The duration of the gene effect is currently unknown, but might last for years.

Similarly AVA-101 (rAAV.sFLT-1 recombinant adeno-associated virus) contains a gene encoding sFLT-1, therefore reducing the effect of VEGF. In a phase I study, AVA-101 was shown to be well tolerated with no significant drug-related safety concerns and patients who received AVA-101 gained or maintained vision with minimal or no need for rescue treatment at 1 year (ClinicalTrials.gov identifier: NCT01494805).

Expectations are that such efforts will help overcome limitations of current therapy with anti-VEGF, extending the duration of effects and hopefully contributing to the regression of neovascular lesions.

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