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AMD Future Perspectives: New promising drugs

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Introduction

As researchers and clinicians begin to understand that wet age-related macular degeneration (wAMD) is a complex disease with angiogenic, vascular and inflammatory components, new pharmacological agents addressing multiple targets in its pathophysiology keep being introduced.

While some drugs are already available in human trials or even FDA and EMA-approved, most are still under laboratory investigation and little is known about them.

In this review, we will discuss promising emerging therapies for wAMD that aim to improve outcomes, safety and treatment burden through novel mechanisms of action. Due to its historical importance, we will also include the most significant drugs that did not achieve the desired clinical effects and never left the development pipeline.

For treatments for dry AMD, please refer to the chapter “Geographic Atrophy”.

VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS

Brolucizumab (RTH258, ESBA1008)

Mechanism of action: brolucizumab is a humanized single chain antibody fragment with high affinity to all VEGF-A isoforms. Its small molecular weight of 26 kDa (compared with 48 kDa for ranibizumab or 115 kDa for aflibercept) makes it possible to prepare higher molar concentrations and administer up to 6 mg

of the drug in a single 0.05mL intravitreal injection[(1)], resulting in longer duration of effect, rapid systemic clearance, and better ocular tissue penetration[(2)]

Developer: Novartis®

Posology: 3.0-6.0 mg intravitreal injection q4w-q12w

Highest development phase: Phase III (completed)

Status: The OSPREY (NCT01796964) was a phase II trial that compared the safety and efficacy of 6mg brolucizumab to 2mg aflibercept in subjects with untreated active choroidal neovascularization due to AMD[(3)]. Both groups received 3 monthly loading doses, were then treated every 8 weeks and assessed up to week 40. In the brolucizumab group, the final q8w cycle was extended to enable 2 cycles of treatment every 12 weeks until week 56. The mean BCVA change from baseline with brolucizumab was noninferior to aflibercept. During the q8w treatment cycles, the brolucizumab group had fewer unscheduled treatments than aflibercept (6 vs. 15) and more stable central subfield fluid thickness reductions. In addition, a greater proportion of brolucizumab treated eyes had resolved intraretinal and subretinal fluid compared with the aflibercept group. Approximately 50% of brolucizumab treated eyes had stable BCVA during the 12 week cycles and did not require unscheduled treatments[(4)].

Based on these results, more than 1800 patients were enrolled in two phase III studies: the HAWK (NCT02307682) and HARRIER (NCT02434328) trials. After three monthly loading doses, the brolucizumab groups were treated every 12 weeks, with the option of switching to 8-week dosing in case of disease activity. The aflibercept group was treated every 8 weeks. According to a press release from June 2017, brolucizumab was non-inferior to aflibercept through week 48, and 57% (HAWK) and 52% (HARRIER) of patients were maintained exclusively on a every 12 week interval immediately following the loading phase through week 48[(5)]. Further results should be presented in the upcoming months.

Abicipar Pegol (AGN-150998, MP0112)

Mechanism of action: Abicipar is an anti-VEGF-A designed ankyrin repeat protein (DARPin), genetically modified antibody mimetic proteins that exhibit highly specific and high-affinity target protein binding proprieties.

Developer: Molecular Partners®, licensed to Allergan®

Posology: 2mg intravitreal injection q8w-q12w

Highest development phase: Phase III (active)

Status: Phase II data suggests that abicipar might have better efficacy and longer duration of effect than ranibizumab: 3 monthly doses of 1 or 2 mg abicipar compared with 5 monthly doses of ranibizumab led to an improvement of BCVA at least as significant as ranibizumab and possibly with a longer duration of action after 20 weeks[(6)]. Two ongoing phase III trials (NCT02462928 and NCT02462486) are expected to be completed in 2019. These will compare 3 groups through 96 weeks: ranibizumab 0.5mg 4qw, abicipar 2mg q8w and abicipar 2mg q12w.

OPT-302 (soluble VEGFR-3; VGX 300)

Mechanism of action: OPT-302 is a soluble form of VEGFR-3 comprising the extracellular domains 1-3 of human vascular endothelial growth factor receptor (VEGFR)-3 and the Fc fragment of human IgG1. It binds and neutralizes the activity of VEGF-C and VEGF-D on endogenous VEGFR-2 and VEGFR-3, possibly resulting in a more complete blockade of the VEGF family when combined with anti-VEGF-A agents[(7)].

Developer: Ophtheaâ

Posology: intravitreal injection

Highest development phase: Phase IIA (completed)

Status: A phase I/IIA dose escalation study (NCT02543229) that included 20 patients met its primary objective, demonstrating OPT-302 safety and tolerability as monotherapy and in combination with ranibizumab. The combination group had better visual results and previous poor responders to anti-

VEGF-A therapy fared better with the addition of OPT-302[8]. The company is planning a phase IIB study for the 2nd semester of 2017.

PF-655 (PF-04523655, REDD14NP, RTP801i)

Mechanism of action: A siRNA is a protein that binds to and activates the RNA-induced silencing complex (RISC) that then degrades mRNA molecules. A single activated RISC can destroy hundreds of mRNAs, thus preventing translation and protein synthesis. Therefore, siRNA might be an efficient mechanism for preventing the expression and synthesis specific harmful proteins[9]. PF-655 is a siRNA that inhibits expression of the hypoxia-inducible gene RTP801, which in turn inhibits the mammalian target of rapamycin (mTOR) pathway and reduces VEGF-A production[10].

Developer: Quark Pharmaceuticalsâ, licensed to Pfizer®

Posology: intravitreal injection q4w

Highest development phase: Phase II (completed)

Status: PF-655 showed efficacy in halting angiogenesis in animal models and its effect appears to be complementary to the anti-VEGF mechanisms of ranibizumab and bevacizumab.[11] The Phase II MONET trial (NCT00713518) evaluated the efficacy of different dosing paradigms of PF-655 versus ranibizumab in 151 subjects with wAMD[12]. The BCVA change from baseline in the combination group was greater than in the ranibizumab group (9.5 vs 6.8 letters, respectively), but the difference was not statistically significant. The combination and ranibizumab groups had similar mean reductions in central subfield retinal thickness and total CNV area. A phase II clinical trial focused on Diabetic Macular Edema, the MATISSE Trial (NCT01445899), has been completed but no results have been published[13].

Rabinizumab Port Delivery System

Mechanism of action: The Ranibizumab Port Delivery System (RPDS) is a refillable reservoir system with a diffusion-control mechanism designed to gradually release ranibizumab. It is placed under the conjunctiva, fixed to the pars plana, and no sutures are needed. The port is then refilled as an in-office procedure that uses a proprietary refill needle system that simultaneously introduces drug into the reservoir and removes any remaining contents.

Developer: ForSight Vision4®, licensed to Genentech®

Posology: subconjunctival implant refilled with ranibizumab as needed (estimated every 4-6 months)

Highest development phase: Phase II (recruiting)

Status: A proof-of-concept phase I trial enrolled 20 patients. There were 3 patients with serious adverse effects, all associated with the placement of the RPDS – a case of endophthalmitis and two cases of persistent vitreous haemorrhage. Over 12 months, the average gain of BCVA was 15 letters if the 2 nonevaluable patients with persistent vitreous hemorrhage were excluded. The average number of refills for the full 20-patient cohort was 4.8[14]. A phase II LADDER trial (NCT02510794) is currently recruiting and planning to enrol 220 patients. It will evaluate the efficacy, safety and pharmacokinetics of three different formulations of ranibizumab delivered via the RPDS.

Aflibercept Hydrogel Depot

Mechanism of action: hydrogel-based drug delivery depot that gradually dissolves and releases aflibercept for up to 6 months[15].

Developer: Ocular Therapeutixâ, licensed to Regeneronâ

Posology: intravitreal injection

Highest development phase: Preclinical

Status: Phase I studies are in the planning stages[16].

PAN-90806

Mechanism of action: topical VEGF-A inhibitor

Developer: PanOptica

Posology: daily topical administration

Highest development phase: Phase I/II (completed)

Status: A phase I/II trial (NCT02022540) included 50 treatment-naïve patients with wAMD that received topical PAN-90806 for 8 weeks. According to a press release from the study sponsor, there was positive biological response to topical PAN-90806 in 45-50% of treated patients, including outcomes such as vascular leakage, lesion morphology and vision. The most common adverse effect was punctate keratopathy[17]. Another phase I/II clinical trial, using a new drug formulation aiming to reduce the corneal toxicity, is planned for 2017.

LHA-510

Mechanism of action: topical VEGF inhibitor

Developer: Novartis®

Posology: daily topical administration

Highest development phase: Phase II (active)

Status: A phase II trial (NCT02355028) was designed to evaluate the efficacy and tolerability of LHA-510 as maintenance therapy for 84 days after ranibizumab injection. The study has reached its primary completion date in September 2016 but no results have yet been published.

ANTI-PLATELET DERIVED GROWTH FACTOR INHIBITORS

Anti-VEGF monotherapy in wAMD markedly reduces the hyperpermeability of the neovascular membranes but does not lead to long term regression of the neovascular complexes[18]. It has been proposed that pericytes may play an important role in this anti-VEGF resistance as they protect the endothelial cells when exposed to anti-VEGF. Pericytes share a common basement membrane with endothelial cells and provide them with VEGF-A and other growth factors via paracrine and juxtacrine signals([19]. Additionally, pericytes are a major source of myofibroblasts and appear to be involved in the development of subretinal fibrosis associated with CNVs[20].

Platelet derived growth factor (PDGF) is a protein that binds to a tyrosine kinase receptor on pericytes and is critical for their survival, recruitment, and maturation[21]. Therefore, inhibiting PDGF in order to strip pericytes from the neovacular complexes might be an adequate strategy to improve long-term visual outcomes in patients with wAMD, as it might leave the underlying endothelial cells more sensitive to the effects of VEGF blockade[22].

Pegpleranib (Fovista®, E-10030; E01AJ; OAP-030; X01E)

Mechanism of action: pegylated DNA aptamer that selectively binds to PDGF-BB and PDGF-AB, thereby disrupting the interaction with their tyrosine kinase receptors in the perycites and leading to perycite stripping from the underlying neovascular complex[23].

Developer: Ophthotech®, licensed to Novartis®

Posology: 1.5mg intravitreal injection

Highest development phase: Phase III (active)

Status: The OPH1002 (NCT01944839) and OPH1003 (NCT01940900) were two randomized, double blind, Phase III clinical trial studies designed to evaluate the safety and efficacy of pegpleranib in combination with ranibizumab versus ranibizumab monotherapy in patients with subfoveal wAMD. A total of 1,248 patients were enrolled across both studies. The studies did not meet the primary endpoint of superiority for the pegpleranib and ranibizumab combination therapy, measured as additional letter gains over ranibizumab monotherapy[(24)].
The results of these trials have decreased interest on pegpleranib. Still, a third phase III trial, the OPH1004 (NCT01940887), is underway. It is evaluating the safety and efficacy of 1.5mg pegpleranib administered in combination with 2.0mg aflibercept or 1.25mg bevacizumab anti-VEGF therapy compared to both in monotherapy for the treatment of wAMD. Results are expected in the second half of 2017.

Rinucumab (REGN2176-3)

Mechanism of action: monoclonal anti-PDGF receptor beta antibody, formulated with aflibercept in a single injection

Developer: Regeneron Pharmaceuticals®

Posology: 1.0-3.0mg monthly intravitreal injection with 3mg of aflibercept

Highest development phase: Phase II (completed)

Status: The Phase II CAPELLA study (NCT02418754), completed in August 2016, evaluated aflibercept co-formulated with rinucumab in 500 patients with wet AMD. Adding rinucumab to aflibercept showed no benefit on BCVA or on anatomic endpoints, including reduction in retinal thickness or in resolution of subretinal hyper-reflective material[(25)].

DE-120

Mechanism of action: double kinase receptor inhibitor that blocks both VEGF-A and PDGF.

Developer: Santen Pharmaceuticals®

Posology: intravitreal injection

Highest development phase: Phase II (completed)

Status: VAPOR1 (NCT02401945), a phase II study assessing the efficacy, safety and duration of effect of DE-120 as monotherapy and after induction with aflibercept as reached its primary completion date in June 2016. No results have yet been published.

Vorolanib (X-82, CM-082)

Mechanism of action: oral tyrosine kinase inhibitor (derived from anti-cancer agent sunitibib) that blocks the kinase activity of all receptor subtypes for VEGF and PDGF[(26)].

Developer: Tyrogenex®

Posology: 50-200mg daily oral administration

Highest development phase: Phase II (active)

Status: A phase I trial (NCT02452385) enrolled 35 patients, most (n=29) with heavily treated refractory wAMD, that were given 4 dose levels of vorolanib and were studied for up to 6 months. Anti-VEGF rescue treatment was administered if their macular thickness increased by 50 µm or if they experienced a 1-line decrease in BCVA. Twenty-five patients completed the follow-up period and 60% of these did not require anti-VEGF recue treatment - the mean increase in BCVA was 5.3 letters. Of the 10 patients that failed to complete the 24 weeks, 5 were due to adverse effects (transient transaminase elevations and gastrointestinal symptoms)[(26)]. Based on these results, a phase II APEX trial (NCT02348359) comparing daily voloranib with PRN aflibercept vs. PRN aflibercept monotherapy is underway and is estimated to be completed in January 2018.

ANGIOPOIETIN PATHWAY INHIBITORS

In the past years, the angiopoietin pathway has been evaluated as a target to improve outcomes of ocular vascular pathologies. Angiopoietin-2 (ANG2) is essential for retinal vascular development and causes disruption of the blood-retinal barrier, increasing vascular permeability. Similar to what occurs with VEGF, ANG2 is expressed in retinal and choroidal neovascularization, and ischemic/hypoxic retina increases its production[(27)]. ANG2 is significantly elevated in the vitreous of patients with retinal vascular pathologies, such as wAMD, diabetic retinopathy and retinal vein occlusion[(28)], and high-levels of VEGF at the inner surface of the retina do not cause retinal new vessels unless accompanied by increased expression of ANG2[(29)].

ANG2's effect is due to inhibition of the Tie2 tyrosine kinase, a receptor for the angiopoietin family of proteins[(30)]. Conversely, angiopoietin 1 (ANG1) binds to and activates Tie2, which stabilizes blood vessels[(31)]. ANG2 competes with ANG1 for Tie2 binding, consequently increasing the responsiveness of retinal vessels to VEGF and promoting vascular leakage and neovascularization. On the contrary, ANG1 reduces responsiveness to VEGF and reduces vascular leakage[(32)]. Therefore, inhibiting ANG2 and/or activating Tie2 are potential strategies to treat wAMD.

Nesvacumab (REGN-910-3)

Mechanism of action: human IgG1 monoclonal antibody directed against ANG2 that blocks its interaction with the Tie2 receptor[(33)].

Developer: Regeneron®, licensed to Bayer® outside the USA

Posology: intravitreal injection q4w

Highest development phase: Phase II (active)

Status: A phase I study (NCT01997164) including 20 patients with wAMD and diabetic macular oedema showed no significant adverse effects and good functional and anatomical outcomes[(34)]. Phase II trials for wAMD (ONYX, NCT02713204) and diabetic macular oedema (RUBY, NCT02712008) using nesvacumab combined with aflibercept are ongoing and should be completed in the 2nd semester of 2017.

RG-7716 (RO-6867461)

Mechanism of action: bispecific human IgG1 monoclonal antibody that binds to both ANG2 and VEGF-A[(35)].

Developer: Chugai Pharmaceutical®, licensed to Genentech®

Posology: 0.5-6.0mg intravitreal injection starting at q4w

Highest development phase: Phase II (active)

Status: A Phase I (NCT01941082) included 26 patients with persistent CNV activity despite =3 anti-VEGF injections. The drug was generally well tolerated and improvements in BCVA and OCT parameters were observed[(36)]. The AVENUE (NCT02484690) and STAIRWAY (NCT03038880) studies are ongoing phase II trials that will evaluate the efficacy and tolerability of different dosages and treatment intervals of RG-7716 in patients with treatment-naïve wAMD.

ARP-1536

Mechanism of action: monoclonal antibody that inhibits the catalytic activity of the VE-PTP enzyme (vascular endothelial protein tyrosine phosphatase), a negative regulator of the Tie2 receptor, therefore decreasing vascular permeability[(32)].

Developer: Akebia?, licensed to Aerpio Pharmaceuticals®

Posology: intravitreal injection

Highest development phase: Preclinical

Status: Phase I trials are projected to start in the 1st quarter of 2018.

AKB-9778

Mechanism of action: subcutaneously administered VE-PTP enzyme inhibitor[(32)].

Developer: Akebia®, licensed to Aerpio Pharmaceuticals®

Posology: daily subcutaneous administration

Highest development phase: Preclinical stages

Status: AKB-9778 for wAMD is currently in preclinical stages. Phase II trials to evaluate its efficacy were first started for DMO (NCT03197870, recruiting) and RVO (NCT02387788, completed).

ALTERNATIVE TARGETS

ICON-1 (hI-con1)

Mechanism of action: chimeric protein designed to bind to and inhibit Tissue Factor (TF) with higher affinity than monoclonal antibodies. This, in turn, triggers NK-cells to selectively destroy overexpressing TF tissues, such as pathologic neovascularization[(37)].

Developer: Iconic Therapeutics®

Posology: 0.3mg intravitreal injection

Highest development phase: Phase II

Status: The EMERGE study was a phase II trial (NCT02358889) that randomized patients to 3 groups: ICON-1 monotherapy, ranibizumab monotherapy or combination treatment. Patients received 3 initial monthly injections, then remained masked in their respective randomized group for additional 3 possible injections based on protocol retreatment criteria. The study results were presented in February 2017: mean BCVA increased from baseline to month 3 by 0.3 letters with ICON-1 monotherapy, 6.8 letters with ICON-1 in combination with ranibizumab, and 7.6 letters with ranibizumab monotherapy and was associated with central retinal thickness reduction in all treatment groups. BCVA gain was comparable in the ICON-1 combination and ranibizumab groups, although it was maintained with fewer treatments from month 3 to 6 with ICON-1 combination[(38)].

Carotuximab (DE-122, TRC105)

Mechanism of action: chimeric antibody to endoglin/CD105, a transmembrane glycoprotein that is expressed on proliferating endothelial cells and functions as a co-receptor of the transforming growth factor ß (TGF-ß) superfamily, which makes it essential for angiogenesis[(39)].

Developer: TRACON Pharmaceuticals®, licensed to Santen®

Posology: intravitreal injection

Highest development phase: Phase II (recruiting)

Status: A phase II trial has begun recruiting patients in July 2017 (NCT03211234).

Conclusion

Despite all the efforts that the scientific community has directed towards neovascular AMD research, the treatment options currently available remain suboptimal. Intravitreal injections, the current standard of care, are invasive and expensive procedures that require frequent patient monitoring. We have presented the most important drugs currently in development and, based on the data that we presented, Tie2 receptor modulation appears to be the most promising strategy to improve the visual outcomes of patients with AMD. Still, drug research & development is an ever-evolving field and several more therapies, such as complement pathway modulators, gene therapy and cell implants, are in the pipeline, promising future breakthroughs.

>> References

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