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Emerging drugs for the treatment of diabetic retinopathy

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Abstract

Introduction: Diabetic retinopathy (DR) is one of the main pathological features of the diabetes mellitus spectrum. It is estimated that in 2020 about 4 million people worldwide suffered from blindness or visual impairment caused by DR. Many patients cannot access treatment, mostly because of high costs, while others discontinue it prematurely due to the high number of intravitreal administrations required, or the occurrence of ocular complications, or discomfort in quality of life.

Areas covered: The aims of this paper are to summarize the current understanding on the pathogenesis and treatment of diabetic retinopathy, focus on the most promising new approaches to treatment that are being evaluated in clinical trials, and outline the potential financial impact of new drugs in future markets.

Expert opinion: Slow-release systems with steroids, anti-VEGF or sunitinib are promising. Oral imatinib would avoid the ocular complications of intravitreal drugs. Brolucizumab and abicipar pegol may be superior to aflibercept and ranibizumab with the advantage of less frequent administrations. Faricimab, active on Tie-2 receptors, is being evaluated in two phase 3 clinical trials. Further knowledge on the efficacy and safety of these drugs is necessary before their final approval for the treatment of diabetic retinopathy.

Keywords: Vascular Endothelial Growth Factor, Diabetes Mellitus, Diabetic Retinopathy, Intravitreal Treatment, Intravitreal Steroids

1. Background

DR represents the main cause of legal blindness (visual acuity 1/20 or less in the best eye) in working age in many industrialized countries and an independent predictor of cardiovascular mortality[1]. Therefore, timely diagnosis and correct treatment of DR is a priority to safeguard sight and quality of life of diabetic people. Prevention of blindness is based primarily on control of blood glucose and blood pressure and regular screening for the timely detection of asymptomatic, sight-threatening, treatable DR. Family doctors, diabetologists and internists should promote screening for DR which, regrettably, is left in most places to the individual initiative of willing doctors. Only few countries (Britain, Iceland and Sweden) have actively promoted national screening programs and these have allowed to progressively reduce diabetes-related blindness[2]. In most other countries only a minor share of patients are subjected to eye checks and only 30-60% of those found to have DR will make a second visit within a year[3]. Patient adherence to screening is also a problem and even the offer of economic incentives does not increase participation in eye checks[4].

2. Medical need

DR is the most important ocular complication of diabetes and, similarly to glomerulopathy, it is considered a form of microangiopathy[5]. However, DR today is considered as a neurovascular complication of DR, as impairment of the neuroretina may precede damage of the vessels. Therefore, we can talk about a “neurovascular unit” including capillaries, pericytes, neurons, astrocytes and Müller cells in a morpho-functional structure[6].

From a clinical and morphological point of view, DR can be differentiated in two main stages: non proliferative and proliferative (NPDR and PDR respectively). NPDR is in turn divided into mild, moderate and severe. Mild NPDR is characterized by microaneurysms and small retinal hemorrhages. When these became associated with other lesions, such as hard exudates and cotton wool spots, NPDR is defined moderate. Finally, venous beading (VB) and intraretinal microvascular abnormalities (IRMA) characterize the severe form of NPDR, also called “pre-proliferating NPDR”. PDR is hallmarked by the development of new vessel (with high risk of retinal

hemorrhages), fibroglial membranes, retinal detachment and, in increasingly rare cases*, rubeosis iridis* and neovascular glaucoma. Therefore, while NPDR is confined to the retina, PDR extends to the neighboring vitreous, iris and irido-corneal angle[7]. Both NPDR and PDR can be complicated by DME and all, if left untreated, can lead to visual impairment. In 2012, in a review of available surveys worldwide, Yau et al. estimated that DR can be found in 34.6% of all diabetic patients, PDR in 6.96% and DME in 6.81%[8]. In recent years, thanks to improved glycemic and blood pressure control, PDR has become less frequent than DME which, in turn, is now the main cause of visual loss[9]. Initially DME can regress, either spontaneously or with adequate treatment, whereas long-standing DME causes irreversible retinal damage with permanent deficit in visual acuity. Although severe DR is decreasing in incidence, the number of diabetic patients is increasing in the ageing population, with a consequent worldwide rise in the prevalence of DR, particularly DME. As a consequence, appropriate treatment of DR is paramount to safeguard the patients' eyesight and quality of life and to reduce the burden on healthcare and social systems.

The pathogenesis of DR and DME is multifactorial. Four mechanisms have been widely described: polyol accumulation, increased advanced glycation end-products (AGE), activation of protein-kinase C (PKC) and augmented flux through the hexosamine pathway. Brownlee hypothesized that increased production of reactive oxygen species (ROS) represents the unifying mechanism of these different biochemical pathways[10]. However, more factors are involved, among them HIF-1α, VEGF, PDGF, Tie-2, kallicrein, endothelin, angiopoietins, erythropoietin, and integrins. Hereafter their role as potential therapeutic targets will be further discussed.

3. Existing treatments

In order to stop the progression of severe NPDR, PDR and DME, both systemic and local treatments have been available for many years. Systemic options include metabolic and blood pressure control. Other approaches include anti-platelet agents, renin-angiotensin system blockers, fenofibrate and ruboxistaurin but they have not been validated by appropriate randomized controlled clinical trials. As all these options play at best marginal roles in the early stages of retinopathy, their description

goes beyond the purpose of this review. Laser photocoagulation (LP) has been for decades, and still remains of pivotal importance in the therapeutic approach to DR, however, DME has been revolutionized over the last two decades by the introduction of intravitreal drugs (anti-VEGF and corticosteroids) to treat DME. Vitrectomy is the fourth main pillar of treatment for DR.

3.1. Photocoagulation

LP has been for years the only available treatment for DR and still represents a therapeutic option of pivotal importance for the treatment of peripheral retina complicated by ischemia and retinal proliferation. It aims to stabilize visual acuity. In DME, focal or grid laser treatment is applied directly to localized microaneurysms and intraretinal vascular abnormalities. In the last decade LP of the macula for the treatment of DME was overshadowed by the advent of intravitreal injections of anti-VEGF and corticosteroids in the management of DME. Relative indications for macular laser include the vasogenic subform of DME which is characterized by the clinical identification of focally grouped microaneurysms and leaking capillaries. Laser has been shown effective even in eyes with DME and persistent vitreomacular adhesion. In contrast, when DME is associated with vitreomacular traction, vitrectomy is needed[11].

LP is an effective therapeutic approach in PDR without DME. Pan-retinal photocoagulation (PRP) is performed in PDR, placing laser burns over the entire retina but sparing the macular area. Thanks to laser, PDR blindness was reduced by 95%[12]. The mechanisms by which laser counteracts both the growth of new vessels and edema is not completely understood, but it seems to reduce local release of VEGF and other inflammatory and pro-edemigenous factors with consequent improved vascularization of the deep retinal layers[13].

Several ophthalmic lasers are employed in the treatment of DR. They induce thermal damage after absorption of energy by tissue pigments. They vary according to wavelength and the source of optical radiation. Green light argon laser (514 nm) is the standard of care, while krypton (647 nm) or diode laser (810 nm) are preferred in particular conditions such as cataract or intravitreal bleeding, for their higher penetration properties. Since 2006, lasers have been introduced which, unlike

traditional ones, deliver multiple spots simultaneously, with consequent reduction in treatment time, pain and side effects while maintaining unchanged effectiveness[14]. Pulsed sub-threshold laser reduces thermic damage to the neuroretina and choroid and the risk of reduced contrast and blind spots, as well as permeability of the blood retinal barrier (BRB).

3.2. Anti-VEGF agents

Anti-VEGF agents, bevacizumab (Avastin©), ranibizumab (Lucentis©) and aflibercept (Eylea©), reduce the angiogenic and pro-edemigenous effects of VEGF in PDR and DME. Bevacizumab was developed for systemic use in oncology whereas, in ophthalmology, is administered off label in doses on average 150 times lower[15]. The other two are registered specifically for ophthalmic use. Bevacizumab is a humanized monoclonal murine antibody with a molecular weight of 149 kDa. Ranibizumab is a recombinant humanized IgG1k isotype antibody fragment with a molecular weight of 48 kDa. Aflibercept is a 115 kDa soluble decoy receptor, made up by the second domain of VEGFR1 and the third domain of VEGFR2 [16,17]. In the management of DME aflibercept, ranibizumab and bevacizumab are usually injected once monthly for 3 months and then switched over to maintenance therapy with less frequent administrations, according to clinical judgement. However, several regimens has been proposed. The most common treatment regimens in clinical practice are an individualized dosing regimen as the pro-re-nata (PRN), which are based on an as-needed treatments after the initial loading phase. As alternative, a treat-and-extend (TREX) protocol uses monthly injections until signs of disease activity are resolved. After this therapeutic outcome has been achieved, the interval between injections is lengthened, with a progressive increase of the interval between injections as long as there are no signs of disease activity[18].

These drugs improve BCVA in patients with center involved DME depending on baseline visual acuity. If the deficit at baseline is mild, there are no significant differences between aflibercept, bevacizumab or ranibizumab while whereas, if the initial damage is already more advanced, aflibercept is more effective at improving vision[19].

Although administered intravitreally, bevacizumab and aflibercept remain in the systemic circulation for at least 30 days while ranibizumab has a lower half-life because it does not have the Fc component[20]. Aflibercept and, less so, ranibizumab reduce blood levels of VEGF. The reduction in plasma free VEGF correlates inversely with the levels of circulating anti-VEGF[21]. As a consequence, intravitreal anti-VEGF agents could have systemic effects, such as increased arterial pressure, and thrombotic events[22]. Many systematic reviews and meta-analysis have tried to establish the extent of the risk but with conflicting results. Thulliez et al in an overview of 21 meta-analyses in DME, AMD and RVO stated that anti-VEGF do not increase the risk of systemic events although particular caution should be taken in patients with AMD[23]. Starr and Dalvin stated instead that they are safe[24,25]. Maloney et al reported an increased risk of systemic events in DME in routine clinical practice compared with controls treated with macular laser or intravitreal corticosteroid: anti-VEGF treatment was not associated with higher risk of cerebrovascular disease or myocardial infarction but with increased risk of post treatment all-cause hospital admission[26]. Reibaldi et al, in a recent meta-analysis, further confirmed no difference in terms of mortality rate between patients on intravitreal anti-VEGF and controls. Higher mortality in studies with longer follow-up were observed but definitive evidence has not been consistently shown[27]. Therefore, despite potential complications, the key role of anti-VEGF agents in the treatment of DME deserves to be fully emphasized. Furthermore, Wubben et al. highlighted the high risk of worsening of visual acuity, even with irreversible blindness, if they are suddenly and prematurely interrupted [28].

Conbercept (Lumitin®), is used in China for the treatment of several macular diseases including AMD and DME. It is a recombinant fusion protein of 141 kDa of the second domain of VEGFR1 and both the third and fourth Ig domains of VEGFR2 on the Fc fragment of a human IgG1. It is similar to Aflibercept (115kDa) from which it differs for higher molecular weight[29].The drug has shown good efficacy and safety[30].

3.3. Corticosteroids

Corticosteroids have anti-inflammatory and anti-angiogenetic effects and stabilize the blood retinal barrier (BRB)[31]. Many metabolic pathways and cells releasing

inflammatory factors are involved in the pathogenesis of DR and, even more, DME. Corticosteroids used in the treatment of DME include on-label (dexamethasone and fluocinolone acetonide) and off-label formulations (triamcinolone acetonide). Dexamethasone in a slow-release biodegradable implant represents the first-line therapy in patients with history of cardiovascular or cerebrovascular events. The MEAD trial assessed it's utility in patients with DME previously treated with anti-VEGF [32]. Fluocinolone acetonide is a second-line therapy administered by a non-biodegradable polymeric delivery system which can release the drug in the vitreal cavity for up to 36 months[33]. Fluocinolone acetonide can be implanted in patients who do not respond to previous intravitreal anti-VEGF or macular laser treatment in pseudophakic eye without history of ocular hypertension. The FAME trials showed its efficacy and safety in DME and a post hoc analysis of the same trials revealed a decreased progression of DR compared to controls [34]. In addition, in patients affected by chronic DME the rate of patients who gained ≥ 15 letters was greater than in patients affected by acute pattern of DME. Triamcinolone acetonide was the first intravitreal steroid used off label for the treatment of refractory DME [35]. The DRCR network evaluated ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for DME and reporetd that triamcinolone acetonide plus laser has a similar efficacy to ranibizumab plus laser [36]. These drugs have demonstrated efficacy and safety but a significant rate of ocular hypertension and cataract was observed, especially in eyes treated with triamcinolone[37]. However, both dexamethasone and fluocinolone acetonide are valid therapeutic tools, especially for patients who may not be compliant with therapeutic protocols based on monthly visit and treatments. Half the patients on triamcinolone need therapies to lower eye pressure.

3.4. Vitrectomy

Pars plana vitrectomy continues to play a critical role in patients affected by DR associated to vitreous hemorrhages, tractional retinal detachment, vitreoretinal interface abnormalities and recalcitrant DME non-responding to intravitreal injection. In theory, removal of the vitreous body and the hyaloid membrane during surgical vitrectomy improve retinal oxygenation, increase turnover of intraocular cytokines and remove mechanical barriers to the egress of fluid and metabolites[38,39]. The

necessity of peeling of the Inner Limiting Membrane during vitrectomy for DME is still debated. Several studies have shown the benefit of anti-VEGF injections in minimizing intraoperative and postoperative hemorrhages [40,41]. Vitrectomy today is performed less than in the past, as other less invasive and more acceptable treatments have become available.

4. Market review

The business around DR is huge and is going to rise over the coming years. According to Global Market Insight, the market has reached in 2018 a volume of 8 Billion USD and is expected to reach a Compound Annual Growth Rate (CAGR) of 6.9%, and hit a global revenue of 12 Billion USD in 2025[42]. The fastest growing market is expected to be the Asian-Pacific one, due to the combined effects of increasing prevalence of diabetes and life expectancy in China and South-East Asia. A study from Indonesia estimated that the health care costs of DR are expected to rise four fold from 2017 to 2025[43].

The costs of DR, already high, will increase even more in the future. Expenditure is partly borne by Health Systems and partly as out of pocket money, by the patients themselves who are required to have considerable time available for repeated visits and therapies. Access to care is often insufficient, especially in developing countries where many patients remain untreated or insufficiently treated[44].

5. Current research goals

In clinical practice intravitreal treatments, mostly anti-VEGF, requires a great effort for both the medical team and the patients because of the necessity of frequent intravitreal injections and visits. The high cost of most agents is a relevant burden for patients and healthcare systems, especially in low-income countries. These downsides of current therapies push some patients to suddenly stop therapy with serious risk of irreversible blindness[28]. To overcome such problems, alternative treatments are being developed. Slow release formulation drugs may reduce the number of intravitreal injections. Another direction is to develop administration routes

alternative to the intravitreal one. Each emerging drug needs to conciliate spending review with the necessity of improving patient compliance.

6. Scientific rationale

VEGF acts on two types of receptors, VEGFR-1 and VEGFR-2 [45], and plays a key role in angiogenesis in physiological and pathological conditions. In normal conditions, VEGF is essential for survival of retinal and endothelial cells and its deficiency can lead to atrophy of choroid capillaries and degeneration of photoreceptors. Upregulation of VEGF production in the hypoxic environment of diabetic retinopathy, however, is a key pathogenic factor for both DME and PDR[46]. Although excessive release of VEGF is believed to be the main culprit for both PDR and DME, another pathway presumably involved is that of angiopoietin 1 and 2, acting through the Tie-2 way. Increased angiopoietin2 in the vitreous can be observed in PDR[47].

Tie-2 is a transmembrane tyrosine-kinase receptor expressed in endothelial cells and its activation plays a role in inhibiting capillary leakage and suppressing inflammation and apoptosis in endothelial cells[48]. Tie-2 modulators exist in two isoforms[49]. In mice, angiopoietin-1 (Ang-1) has a protective effect in DR, suppressing VEGF-A induced neovascularization via Tie-2 activation[50], whereas Ang-2 exerts an opposite effect, promoting vascular inflammation and permeability, inducing pericyte apoptosis and BRB breakdown[51]. Pre-clinical research led to clinical application, showing the superiority of dual inhibition of VEGF-A and Ang-2 compared to VEGF-A inhibition alone[52]. In addition leukostasis plays a role of pivotal importance in the dysfunction of BRB in DR by the upregulation of reactive oxygen species and inflammatory cytokines. This pathological cycle causes the enhance of vascular permeability[53].

Intravitreal anti-PDGF agents administered together with anti-VEGFs represent a new field of interest. Other drugs modulate different potential pathogenic pathways, such as the Tie-2 receptor kinase, kallikrein, erythropoietin, SSAO/VAP-1 inhibitor, VE-PTP, PlGF and others. Finally, gene therapies with viral vectors will allow to stimulate continuous expression of anti-VEGF-A in the eye after a single administration[54]

7. Competitive environment

There are about twenty major manufacturers involved in DR. Novartis AG, Regeneron Pharmaceuticals Inc in collaboration with Sanofi, Allergan Plc, Hoffmann-La Roche through its subsidiary Genentech, Oxurion NV, Alimera Sciences, BCN Peptides, Glycadia Pharmaceuticals and Kowa Group are at the forefront of research. Most new drugs over the past years were developed by start-ups which later became subsidiaries to multinational pharmaceutical companies (e.g. Genentech and Hoffman-La Roche), or signed collaboration programs for commercialization with them (e.g. Regeneron and Sanofi). The most active start-ups are currently Kodiak Sciences LNC, Aerie Pharmaceuticals LNC, KalVista Pharmaceuticals LTD, Aerpio Pharmaceuticals LNC, Allegro Ophthalmics LLC, Momenta Pharmaceuticals LNC, all based in the United States, and YD Global Life Science Co, based in South Korea.

8. Potential development issues

DR has a multifactorial etiopathogenesis in which hyperglycemia represents the "*primum movens*". The hypoxic stimulus, related to microangiopathy and impairment of BRB, with consequent release of VEGF, is today the best known pathogenic mechanism. It is increasingly evident that other metabolic pathways, at least partially independent of VEGF, should be aimed at, such as PDGF and angiopoietins, as these contribute to retinal damage, especially DME. Anti-VEGF drugs remain the most used therapy but their administration exposes patients to potential systemic and local risks, the importance of which is not sufficiently defined[17,55]. Adverse effects imply huge financial resources and provoke loss of working days and impairment of patients' quality of life. Although safer and effective treatments and routes of administration are being sought, intravitreal administration currently guarantees the achievement of high drug concentrations in retinal tissues. Intraocular implant of devices is a newer strategy that aims to guarantee prolonged drug release with a single invasive procedure, reducing the risk of local complications and discomfort for patients.

Table 1 summarizes the most interesting recent clinical trials for DR. Only 2 studies in Table 1 are in Phase 1. All others are in Phases 2 or 3.

8.1. Drugs in Phase 1 study

8.1.1. AR-13503.

AR-13503 is as Rho Kinase and protein kinase C (PKC) inhibitor. In a preclinical model it reduces neovascularization, preserves blood retinal barrier and reduces retinal fibrosis both alone and in association with aflibercept[56]**. NCT 03835884** is an ongoing trial on the safety in humans of an AR-13503 sustained release intravitreal implant designed to be administered every 6 months in patients with AMD or DME.

8.1.2. KSI-301.

KSI-301 is a novel anti-VEGF antibody biopolymer conjugate (ABC) designed to maintain effective drug levels in ocular tissues longer than existing agents**. NCT 03790852**, a phase 1b trial, is evaluating efficacy, safety and tolerability of KSI-301 in subjects with AMD, DME and RVO. In DME, it shows improvement by 5.4 letters in BCVA and a 72 µm reduction in central retinal thickness. A pivotal phase 2 trial (DAZZLE) is underway in patients with nAMD (**NCT 04049266**).

8.2. Drugs in Phase 2 study

8.2.1. Imatinib mesylate (YD312)

Imatinib is an tyrosine-kinase inhibitor (including that of the PDGF receptor) initially developed for the treatment of chronic myeloid leukemia and later used also in acute lymphoblastic leukemia and stromal gastrointestinal tumors (GIST). Imatinib can be administered orally in DME, addressing VEGF-independent ocular angiogenesis. YD Global Life Science Co Ltd. sponsored a multi-center, randomized, double blind dose-finding phase 2 clinical trial to evaluate the efficacy and safety of YD312 tablets in center-involving DME compared to placebo and to determine the optimal dose of the drug (**NCT 03635814**). Primary outcome is change in BCVA from baseline at week 12. Patients are randomized into lower dose (YD 312 tablet 50 mg), middle dose (YD312 tablet 150 mg), and higher dose (YD312 tablet 350 mg) groups as well as a placebo group in a 1:1:1:1 ratio and the product is administered once a day for

12 weeks. This study enrolled 100 patients and estimated completion date is 20-03-2020.

8.2.2. Sunitinib malate (GB-102)

Sunitinib, initially developed for the treatment of pancreatic neuroendocrine tumors (pNET), inhibits tyrosine kinase receptors implicated in tumoral growth, neoangiogenesis and metastatic progression. It especially inhibits platelet derived growth factor (PDGF) receptors alfa and beta, VEGF receptors 1 and 2,-stem cell growth factor receptor (cKIT), FLT3 receptor, colony stimulating factor receptor 1(CSF-1R) and glial neurotrophic receptor (RET). Its anti-VEGF action suggests a possible use in ophthalmology. Tsujinaka et al incorporated sunitinib in a biodegradable polymer into a depot and showed that a single intravitreous injection suppresses choroidal neovascularization in mice for six months and maintains therapeutic levels in the choroid and retina for more than six months in rabbits[57]. **NCT 04085341** is a phase 2 multicenter, open label, parallel arm design study sponsored by Graysburg-Vision to evaluate safety, tolerability and pharmacodynamics of a single intravitreal injection of a sunitinib malate depot formulation (GB-102) comparing 2 dose levels (1 mg and 2 mg) in subjects with DME and retinal vein occlusion (RVO) who have received at least 3 prior treatments with anti-VEGF agents. This study enrolled 21 patients and it is expected completed in April 2020. Its primary outcome is evaluation of the occurrence of ocular and non-ocular adverse events.

8.2.3. KVD001: Intravitreal plasma kallikrein inhibitor

Kallikrein is a proteolytic enzyme that splits kininogen into bradychinin. The kallikrein-kinin system is upregulated in DME, as demonstrated by overexpression of B1R and B2R (retinal bradykinin receptors) in retinal vessels in DME[58]. This upregulation increase Nitric Oxide production, which has a vasodilating and permeabilizing effect on the vessel wall, and activation of SRC Kinase, which increase permeability of BRB [59]. KVD001 is a plasma kallicrein inhibitor produced by Kalvista Pharmaceuticals. A phase 2 study (**NCT 03466099**) is now ongoing to evaluate efficacy, safety and tolerability of intravitreal administrations in subjects with center-involving DME with previous unsuccessful anti-VEGF treatment. In this study,

129 patients were randomized to three arms (high dose KVD001, low dose KVD001 and sham procedure) to receive four monthly intravitreal injections. The primary outcome is change in BCVA at four months. The secondary outcome is assessment of central subfield thickness. The primary outcome measures show that KVD001 is safe end well-tolerated and although not statistically significant, a trend towards protection is clear in terms of BCVA change and reduction of visual loss[60].

8.2.4. LKA651

LKA651 is an intravitreal anti-erythropoietin agent developed by Alcon for DME and AMD. The trial **NCT 03927690** sponsored by Novartis Pharmaceuticals evaluates safety and efficacy of multiple doses of intravitreal LKA651 in DME. This is a randomized active-controlled, patient and investigator-masked, multiple dose proof-of-concept study which enrolled 90 DME patients, the comparator being Ranibizumab. Primary outcomes are adverse events, safety, improvement of BCVA and central subfield retinal thickness. The estimated completion date is November 2020.

8.2.5. BI 1467335

BI 1467335, formerly known as PXS-4728A, is an SSAO/VAP-1 inhibitor*.* SSAO/VAP-1 is an endothelial-bound adhesion molecule with amine oxidase activity involved in neutrophil egress from microvessels during inflammation. This drug was initially developed for the treatment of non-alcoholic steatohepatitis (NASH) but the clinical trial to assess its efficacy on NASH (NCT03166735) was recently stopped by Boehringer Ingelheim for the potential risk of drug interactions in NASH patients. On the other hand, a phase 2, randomized, placebo-controlled clinical trial sponsored by Boerhinger Ingelheim is underway to evaluate its safety and tolerability in NPDR without center-involving DME (**NCT 03238963**). This study started in 2017, enrolled 79 patients who received once daily orally administered BI 1467335 for 12 weeks and will end in May 2020.

8.2.6. AKB-9778

AKB-9778 is a small molecule inhibitor of VE-PTP, the main negative regulator of Tie2. It binds to and inhibits the intracellular catalytic domain of VE-PTP that

inactivates Tie2. This drug, administered via a subcutaneous injection, is rapidly absorbed into the blood circulation and reaches the retinal vessels. The TIME-2a study, a phase 2a trial, showed its ability to improve visual acuity in DR. Hence, in 2017, the TIME-2b study was started to evaluate safety and efficacy of AKB-9778 15 mg once daily or 15 mg twice daily for 12 months in patients with moderate to severe NPDR (**NCT 03197870**). Actual reporting date: none.

8.2.7. REGN910-3 (Nesvacumab)

Nesvacumab is a monoclonal antibody targeting angiopoietin-2. Angiopoietins and VEGF regulate the maturation of blood and lymphatic vessels. An imbalance between these factors can promote both the development of pathological vessels (as in proliferative DR) and increase vessel permeability (as in DME). Regeneron and Bayer sponsored the RUBY Study, a phase 2 clinical trial (**NCT 02712008**), to assess safety and efficacy of intravitreal nesvacumab and aflibercept compared to aflibercept alone in patients with DME. 302 participants were randomized into three groups receiving nesvacumab 3 mg + aflibercept 2 mg (50 patients), nesvacumab 6 mg + aflibercept 2 mg (100 patients) and aflibercept alone 2 mg (152 patients). All cause mortality was 10%, 0% and 2.63%, and serious adverse events were 12%, 18% and 20.39% respectively. There was a single case of embolism and one of vitreal detachment in the first group. Nesvacumab, unlike faricimab (BOULEVARD Study), failed vs aflibercept. Further studies are needed to clarify the reasons for this different result.

8.2.8. ALG-1001 (Luminate)

ALG-1001 (Luminate®, Allegro Ophthalmics) is an integrin receptor antagonist. Integrins play a key role in the proliferation of new vessels. There are about 27 known integrin receptors. This drug targets four different integrin receptor sites and acts with two different mechanism: anti-angiogenesis and vitreolysis. ALG-1001 can be administered monthly intravitreally in monotherapy or with bevacizumab[61]. In 2014 Allegro Ophthalmics reported that ALG-1001 inhibits growth and leakage of new vessels and then started a phase 2 clinical trial **(NCT 02348918**) to compare safety and efficacy of Luminate vs bevacizumab in the treatment of DME. The trial showed that BCVA increased by 7.1 letters in the group treated with Luminate and

bevacizumab compared to + 6.1 letters in the control group with bevacizumab alone. Although a small improvement, the authors suggested that Luminate may be an interesting option to treat patients, particularly those who don't respond to anti-VEGF.

8.2.9. THR-317.

THR-317 is a humanized antibody targeting PlGF. In 2019 Oxurion reported data from a phase 2 study that evaluated the efficacy, in terms of BCVA and safety, of 3-monthly intravitreal THR-317 combined with ranibizumab in center-involved DME compared with ranibizumab alone **(NCT 03499223**). No improvement was observed in BCVA at month 3 with the combination therapy compared to ranibizumab monotherapy in the overall population. However, the combination therapy showed a certain improvement at month 3 in patients with poor or no response to prior anti-VEGF agents and in patients with baseline BCVA ≤6 letters. THR-317 in combination with ranibizumab was safe and well tolerated and could play a role in the treatment of poor- and non-responders to previous anti-VEGF.

8.2.10. Abicipar pegol

Abicipar pegol (Abicipar®; Allergan plc/Molecular Partners) is a DARPin® (Designed Ankyrin Repeat Protein), a class of genetically-engineered proteins that mimic antibodies, typically exhibiting highly specific and high-affinity target protein binding. DARPins are built from tightly packed repeats of, usually, 33 amino acid residues. They comprise fixed aminoacidic positions that confers stability to the scaffolding and six variable positions per repeat module that can be potentially modified to engage in interactions with the intended target. Furthermore, a continuous convex paratope similar to the long CDR-H3 found in many antibodies, was introduced into the DARPin scaffolding to further increase affinity for the target [62]. DARPins® offer some therapeutical advantages compared to antibodies because they are smaller (approximately one-tenth in size and one-third the size of Fab fragments), have better tissue penetration, are active in very low concentrations and more stable so that their effect may last longer. Abicipar in particular, is a 14 kDa recombinant protein coupled to a 20 kDa polyethylene glycol (PEG)[63]. DARPin® proteins are used in oncology, for the human immunodeficiency virus infection and allergic

reactions, including allergic asthma[62,64]. The REACH trial assessed the efficacy and safety of abicipar in patients with naive neovascular AMD over a period of 20 weeks. Sixty-four patients were randomized to three branches. Reduction in CRT compared with baseline was 134, 113 and 131 µm at week 16 for abicipar 1 mg, abicipar 2 mg and ranibizumab, and 116, 103, and 138 µm at week 20, respectively. The study demonstrated the non-inferiority of abicipar compared to ranibizumab despite a lower number of administrations[65]. Two other phase II clinical trials, the BAMBOO and CYPRESS confirmed the effectiveness of abicipar every 12 weeks[66] and CEDAR and SEQUOIA, two phase III clinical trials, confirmed the non-inferiority of abicipar vs ranibizumab with less frequent injections and with less burden for patients[67]. However, the rate of adverse intraocular events, eg uveitis or vitreitis in REACH, CEDAR&SEQUOIA and BAMBOO&CYPRESS were significantly higher with abicipar than with ranibizumab. This observation stimulated research to produce a more purified abicipar. The MAPLE study with a new formulation of abicipar, showed a reduction in intraocular adverse events related to the abicipar itself[68]. A multicenter phase II clinical trial compared abicipar pegol vs ranibizumab and sham procedure in DME **(NCT 02186119**). The findings were presented at the American Academy of Ophthalmology annual meeting in 2016: abicipar was non inferior to ranibizumab in terms of BCVA and CRT[69].

8.2.11. Intravitreal steroids plus Anti-VEGF: Dexamethasone + ranibizumab

A phase 2 multicenter clinical trial in 116 adults with persistent DME after at least three anti-VEGF injections was carried out between 2014 and 2016 (**NCT 01945866**). This trial compared continued intravitreal ranibizumab alone with ranibizumab plus dexamethasone implant. Patients, divided into 2 arms, were randomly assigned to receive dexamethasone or sham treatment in addition to ranibizumab in both treatment arms. Primary outcome was BCVA. The study found that this strategy does not improve BCVA at 24 weeks more than ranibizumab alone in persistent DME[70].

8.3. Drugs in Phase 3 study

8.3.1. *Port Delivery System (PDS) ranibizumab*

The need for frequent intravitreal injections has spurred research to develop sustained-release anti-VEGF devices. PDS is a non-biodegradable port, surgically inserted through a small incision in the sclera and pars plana, with a 0.05 ml reservoir that can be refilled in the office. The port includes by four components: a extrascleral flange, a self-sealing septum that allows for implant refills, the body implant that contains the drug reservoir and a release control element that controls the diffusion of ranibizumab into the vitreous. The port system is being studied first in patients with AMD and then in DME. LADDER, a phase II study, enrolled 179 patients with AMD randomized to implant of PDS with 10 or 40 or 100 mg/ml. Best improvement of visual acuity was shown with 100mg/ml[71]. In 2019 PAGODA, a phase III study of efficacy, safety and pharmacokinetics of the PDS with ranibizumab in patients with DME **(NCT 04108156**), was started. The trial, sponsored by Hoffman-La Roche with estimated completion date 31 December 2022, enrolled 545 participants randomized to 2 arms. The PDS arm receives intravitreal ranibizumab injections every 4 weeks (loading phase) and then the PDS implant pre-filled with ranibizumab 100 mg/ml. PDS implant refill-exchange procedures are performed at fixed intervals every 24 weeks (Q24W). The second arm receives intravitreal ranibizumab 0.5 mg every 4 weeks.

8.3.2. Brolucizumab

Brolucizumab is a humanized single chain antibody fragment that inhibits all isoforms of VEGF-A. It has a small molecular weight of 26 kDa that facilitates higher molar concentrations in the vitreous than aflibercept. This drug was initially designed to treat wet AMD. The HAWK and HARRIER trials have demonstrated the efficacy and safety of Brolucizumab in wet AMD. The trials assessed the non-inferiority of brolucizumab vs aflibercept and its superiority in disease control[72]. In October 2019 Brolucizumab was approved by FDA for the treatment of wet AMD. The recommended dosage regimen is 6 mg (0.05 ml) via intravitreal injection monthly for the first 3 injection, then once every 8–12 weeks. In clinical practice, case reports of retinal vasculitis and intraocular inflammation after intravitreal injection of brolucizumab were reported. Novartis Pharmaceuticals sponsored a two-year phase III study assessing efficacy and safety of brolucizumab vs aflibercept in adult patients with visual impairment due to DME **(NCT 03481634**). The study recruited 534

participants and will end in 2021. Patients are divided into 3 arms: brolucizumab 3mg/0.05 ml 5 loading doses, brolucizumab 6 mg/0.05 ml 5 loading doses and aflibercept 2 mg/0.05 ml 5 loading doses. The primary outcome is change from baseline in BCVA at week 52.

8.3.3. MYL-1701P

A phase 3 study (**NCT 03610646)** is currently under way in 324 patients with center-involved DME randomized 1:1 to aflibercept or intravitreal MYL-1701P, a recombinant fusion protein that is an aflibercept biosimilar, developed by Momenta Pharmaceuticals in collaboration by Mylan N.V. Primary outcomes are BCVA, pharmacokinetics and immunogenicity of MYL-1701P. Estimated completion date is February 2020.

8.3.4. RG7716 (Faricimab)

Faricimab, developed by Hoffmann, is the first bi-specific monoclonal antibody. It consists of 2 heavy chains and 2 light chains and has two different targets: VEGF and angiopoietin-2. BOULEVARD, a Phase 2 trial sponsored by Roche and Genentech showed that the intravitreal administration of faricimab 6.0 mg improves VA at 24 weeks more than ranibizumab (13.9 vs 10.3 letters) and leads to longer duration of central subfield thickness reduction[73]. Two Phase 3 clinical trials, RHINE and YOSEMITE (**NCT 03622593 and NCT 03622580** respectively), are currently under way. They started in September 2018 and will end in 2021 and 2023. In both, faricimab is administered every 8 weeks and compared with aflibercept (which has a pure anti-VEGF action) every 8 weeks and with sham procedures. These two multicenter studies (199 study locations for RHINE and 188 for YOSEMITE) enrolling about 1,000 patients each will evaluate the effect on BCVA and safety of this promising new drug**.**

8.3.5. Ziv-aflibercept

Ziv-aflibercept (Zaltrap®), developed by Sanofi-Aventis and Regeneron Pharmaceuticals, is a drug that contains the same active molecules as aflibercept, originally approved for the treatment of metastatic colorectal cancer[74]. It differs from aflibercept for the buffer, giving it greater osmolarity than aflibercept, which

originally raised concerns about its safety in intravitreal injections[75]. Safety and efficacy were assessed by Meyer and Mansour, who considered Ziv-aflibercept, administered by intravitreal injections, effective and safe for treatment of DME[76,77]. However those papers had small samples (7 and 107 eyes respectively), so that further randomized studies with greater numbers of eyes are necessary[78].

9. Conclusion

Improvements in prognosis over the recent years, thanks to the drugs and devices available for the control of blood glucose, hypertension and dyslipidemia, will paradoxically result in longer survival of patients with more and more cases of DR worldwide, especially DME. Hence, it is increasingly necessary to have effective treatments available to avoid worsening of retinal damage and blindness. Here, we reviewed current options, emphasizing that there is no one-fit-for-all treatment in DR. The choice of the best strategy must take into account the severity of retinal damage and the general clinical situation of individual patients, in terms of cardiovascular risk, renal impairment and presence of critical peripheral artery disease. The right of patients to be fully informed about the risk and benefit of the different options proposed cannot be sufficiently emphasized, either. The large number of ongoing clinical studies is testament to the commitment of researchers, within and out of industry, to develop important new therapeutic tools, some of which will come to fruition in the near future. Within such context, it should be remembered that diabetes, a chronic, systemic disease, is an archetype for interdisciplinary collaboration between specialists: ophthalmologists, diabetologists, internists, nephrologists, cardiologists and many others, acting together for integrated patient management.

10. Expert opinion

The prevalence of diabetes is constantly increasing worldwide, its rise affecting both urban and rural areas. In addition to the absolute numbers of the disease, the prevalence of diabetes related complications is also predicted to rise in the next 20 years. In Western countries, diabetes is already the main cause of blindness in

working age groups. In the near future, Asia will be the major epicenter of diabetes epidemiological growth. The proportion of subjects affected by diabetic retinopathy will be on the rise as a consequence of the increasing expected lifespan of patients. This trend will be most evident in India and China. Diabetic macular edema is the main retinal complication of diabetes. Thus, future developments in research on DME detection and treatment will be of critical importance in the management of diabetes. Future treatments of DME will require close integration with the various national systems according to their available financing resources, health care organization and national priorities.

Various aspects should be taken into account in the evaluation of any new therapeutic option, including safety profile, cost effectiveness and patient adherence to treatment schedule.

Among anti-VEGF therapies currently under development, brolucizumab and abicipar pegol, have been shown to be effective in preliminary studies and, if these initial reports will be further confirmed, they may represent useful tools in managing the burden of DME treatments.

Future initiatives in the treatment of DR will focus on two main areas of intervention: developments in retinal imaging and the advent of new molecules to treat refractory patterns of DME. Newer developments in retinal diagnostic tools will allow earlier detection and more complete treatment of DME. In this respect, quantitative measurement of peripheral ischemia and ultra-widefield retinal imaging are major diagnostic innovations that can allow the detection of lesions in more peripheral areas of the retina in comparison to standard approaches. As far as treatment innovations are concerned, it is well known that many eyes affected by DME are poor responders to current therapies. New drugs with different mechanisms of action are needed to obtain a better response to therapy in eyes with refractory DME.

New therapeutic targets addressing different steps in the angiogenesis cascade and innovative routes of drug administration will be explored to overcome the limitations of present therapeutic alternatives. There are great expectations in the development of the Port Delivery System, a refillable eye implant designed to continuously release a customized formulation of ranibizumab, which is suggested to reduce the

therapeutic burden for patients, allowing a treatment free interval up to 6 months. This approach may greatly improve patients quality of life and compliance.

On the other hand, specific antibodies targeting angiopoietin-2 have proven promising effects when coupled with intravitreal anti-VEGF in the treatment of DME. Lastly, suprachoroidal space delivery, which has the advantage of achieving the same therapeutic drug levels in the retina as compared to intravitreal injections while minimizing drug levels in the anterior segment appear to be one of the most promising treatments for the coming years. It should be highlighted that for all these new drugs and new routes of administration further studies are needed to establish their safety and efficacy in real life as well as in clinical trials.

The clinical history of DME is characterized by a relapsing and remitting course. Thus, regardless of the route of administration, the mechanism of action and the treatment schedule of any future treatment of DME will need to prove its efficacy in offsetting the reactivation of the disease.

Finally, it should be kept in mind that the effectiveness of any DME treatment is linked to the long- term glycemic control of diabetes. In a future perspective, each DME treatment will need to be associated with customized management of glycemic control in order to obtain stabilization of the disease in the long-term.

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Abbreviations

AMD - Age-related Macular Degeneration
BCVA - Best Corrected Visual Acuity
BRB – Blood Retinal Barrier
ciDME – central involved Diabetic Macular Edema
CRT - Central Retinal Thickness
cSRT – central Subfield Retinal Thickness
DME - Diabetic Macular Edema
DR - Diabetic Retinopathy
LP – Laser Photocoagulation
NPDR – Non Proliferative Diabetic Retinopathy
OCT – Optical Coherence Tomography
PDGF - Platelet-Derived Growth Factor
PDR – Proliferative Diabetic Retinopathy
PlGF – Placental Growth Factor
PRN - Pro-Re-Nata
PRP - Panretinal Photocoagulation
QoL – Quality of Life
RVO – Retinal Vein Occlusion
SSAO/VAP - Semicarbazide-Sensitive Amine Oxidase /Vascular Adhesion Protein-1
TREX - Treat-and-Extend
VEGF - Vascular Endothelial Growth Factor
VE-PTP - Vascular Endothelial - Protein Tyrosine Phosphatase

	NCT	Sponsor	Phase	Mechanism	Route	Participants	Pathology	Comparator
	03635814	YDGlobal Life Science.LTD	2 underway	Anti-VEGF	Oral	100	DME	placebo
	04085341	Graysburg Vision	2 underway	Anti-VEGF	IVT	21	DME-RVO	sunitinib
	03466099	Kalvista Pharmaceuticals	2	Kallicrein inhibitor	IVT	129	ciDME	Sham
b	04108156	Hoffman-La Roche	3 underway	Anti-VEGF	IVT	545	DME	ranibizumab
	03481634	Novartis Pharmaceuticals	3 underway	Anti-VEGF	IVT	534	DME	aflibercept
	03610646	Mylan Inc	3 underway	Anti-VEGF	IVT	324	ciDME	Eylea
	03927690	Novartis Pharmaceuticals	2 underway	Anti-erytropoietin	IVT	90	DME	Lucentis
	04116398	Hospices Civils de Lyon	2 underway	Anti-inflammatory	IVT	100	DME	none
	03622593	Hoffman-La Roche	3 underway	Anti-VEGF/anti angiopoietin2	IVT	1000	DME	aflibercept
	03622580	Hoffman-La Roche	3 underway	Anti-VEGF/anti angiopoietin2	IVT	1000	DME	aflibercept
	02186119	Allergan	2 completed	Anti-VEGF	IVT	151	DME	ranibizumab sham
	02911311	Sun Yat-sen Univerity	2 completed	Anti-VEGF	IVT	226	PDR	PRP
+	01945866	Jaeb Center for Health Research	2 completed	Anti-inflamm plus anti-VEGF	IVT	116 patients with 129 eyes	DME	ranibizumab alone
	03238963	Boeringher Ingelheim	2 underway	SSAO/VAP-1 inhibitor	Oral	79	NPDR	placebo
	03197870	Aerpio Therapeutics	2 completed	VE-PTP inhibitor	SC	167	NPDR	Placebo
	02712008	Regeneron/Bayer	2 completed	Anti-angiopoietin2 mAb	IVT	302	DME	aflibercept

	02348918	Allegro Ophthalmics	2 completed	Integrin receptor antagonist	IVT	218	DME	Bevacizumab
	03499223	Oxurion NV	2 Topline data	Anti PIGF	IVT	70	ciDME	Ranibizumab or sham
	03790852	Kodiak Sciences Inc	1 underway	Anti-VEGF	IVT	105	AMD, DME, RVO	2,5 mg vs 5 mg
	03835884	Aerie Pharmaceuticals	1 underway	Inhibitor Rho kinase and PKC	IVT	102	AMD DME	Alone or with aflibercept

Table 1. Summary of the emerging drugs to treat diabetic retinopathy

Legend. BCVA (best corrected visual acuity), ciDME (central involved diabetic macular edema), DME (diabetic macular edema), IVT (intravitreal), PDR (proliferative diabetic retinopathy), PRP (panretinal photocoagulation), RVO (retinal vein occlusion), SC (subcutaneous).