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Chapter

Angiopoietins as Targets for Diabetic Retinopathy Treatment

Lauren M. Ciulla, Nimesh A. Patel, Nicolas A. Yannuzzi and Rehan M. Hussain

Abstract

Diabetic eye diseases, such as diabetic retinopathy (DR) and diabetic macular edema (DME) are among the leading causes of blindness in developed countries. Anti-VEGF therapies such as, ranibizumab, aflibercept and off-label bevacizumab have become first-line treatment for DME. While randomized controlled trials show significant improvement in vision, these anti-VEGF agents have limited durability leading to a significant treatment burden, as reflected in real-world studies, which generally demonstrate under-treatment and less favorable visual acuity outcomes than observed in prospective trials. Alternative pathways, such as the Tie-2 angiopoietin pathway may address unmet needs, with potential for greater efficacy or durability when compared to anti-VEGF monotherapy. While some Tie-2 angiopoietin therapeutic agents, such as nesvacumab, ARP-1536 or AKB-9778, did not meet primary endpoints in clinical trials, other agents have shown promise. One such agent is faricimab, a bispecific antibody inhibiting both VEGF-A and Ang-2. The phase 3 DME trials (YOSEMITE and RHINE) demonstrated favorable safety, visual, and durability outcomes; patients receiving faricimab injection every 4 months achieved similar visual gains as those receiving aflibercept injection every 2 months. Another agent, AXT107 is a peptide that inhibits VEGFR2 and modifies Ang-2 to behave more similarly to Ang-1, promoting vascular stability. This drug is currently undergoing phase 1/2a trials for safety and bioactivity to be completed in May 2022.

Keywords: diabetic retinopathy, diabetic macular edema, angiopoietins, Ang-2, Ang-1, Tie2 receptor, faricimab, AXT107, nesvacumab, AKB-9778, ARP-1536

1. Introduction

The global prevalence of diabetes and its comorbidities has rapidly increased, likely due to an aging population and a high prevalence of obesity [1]. As such, DR has become one of the leading causes of blindness within the Western World [2]. Several pooled analyses have disclosed the prevalence of DR within diabetic populations is greater than 30% [3]. Previously, diabetic macular edema (DME) resulted in approximately half of affected patients losing two or more lines of visual acuity within two years [4]. Historically, laser photocoagulation was validated in clinical trials to slow visual loss in patients with DME and proliferative diabetic retinopathy (PDR), an advanced form of DR involving neovascularization, potentially complicated by vitreous hemorrhage, tractional retinal detachment, and neovascular

glaucoma. However, recent and continuing medical advancements in intravitreal corticosteroids and anti-vascular endothelial growth factor (VEGF) agents have led to improvements in clinical outcomes. This chapter reviews the current treatment options and those under development for diabetic eye disease specifically in the Tie-2/Angiopoietin vascular stability pathway.

2. Diabetic retinopathy pathophysiology

Chronic hyperglycemia, hyperlipidemia, and hypertension are involved in the development of DR [5]. Specifically chronic hyperglycemia has been linked to changes within the retinal microvasculature. Chronic hyperglycemia can result in damage through multiple mechanisms including osmotic alterations due to sorbitol accumulation from the polyol pathway, increased nonenzymatic glycosylation of proteins and reactive oxygen species, and activated protein kinase C [6]. These mechanisms contribute to dysfunction of endothelial cells and pericytes, ultimately leading to DR and potentially DME. Endothelial cells support the blood-retinal barrier and pericytes regulate capillary blood flow [7]. Damage to endothelial cells results in fluid accumulation in the macula [4, 8]. Damage to pericytes causes poor regulation of blood flow and microaneurysms within these vessels [9]. Ultimately, microvascular damage of the retina culminates in vision loss due to poor retinal perfusion and ischemia, upregulation of growth factors and inflammatory cytokines, and angiogenesis [6, 10]. Among these growth factors and inflammatory cytokines, VEGF and angiopoietins play important roles and are targets of interest for therapeutic interventions [11].

3. Existing treatments: VEGF inhibitors, corticosteroids, and focal laser

VEGF proteins contribute to the regulation of vascular permeability and growth through tyrosine kinase receptors called VEGF receptors [12]. Binding of VEGF protein ligands to their VEGF receptors activates the mitogen-activating protein kinase (MAPK) signaling pathway and causes angiogenesis via increased endothelial cell growth and survival [13]. There are multiple VEGF proteins including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF) [14]. VEGF-A primarily targets VEGF receptor 2 (VEGFR2) and increases angiogenesis, vascular permeability, and leukocyte adhesion [15, 16]. See **Figure 1** for a schematic of the relationship between the various VEGF ligands and receptors. Due to its significant role in the pathogenesis of DR/DME, many drugs inhibit the VEGF-A (referred to as simply VEGF for the remainder of this chapter) pathway to halt and decrease angiogenesis and vascular permeability within the disease [17]. Currently, two anti-VEGF medications are approved by the US Food and Drug Administration (FDA) for the treatment of DME: aflibercept (Eylea, Regeneron, Tarrytown, NY, USA) and ranibizumab (Lucentis, Genentech, South San Francisco, CA, UA). In addition, one anti-VEGF agent is frequently used off-label, bevacizumab (Avastin, Genentech, South San Francisco, CA, USA).

Ranibizumab was originally approved for the treatment of neovascular age-related macular degeneration (nAMD) in the United States in 2006, and it was approved for DME in 2012 based on the phase 3 RISE and RIDE studies [18]. It is administered intravitreally on a monthly basis. Aflibercept was approved in 2011 for nAMD and in 2014 for DME after positive results from phase 3 VIVID and VISTA studies [19]. It can be dosed in longer eight-week intervals, after 5 monthly loading doses. Bevacizumab was approved in 2004 for use in metastatic colorectal
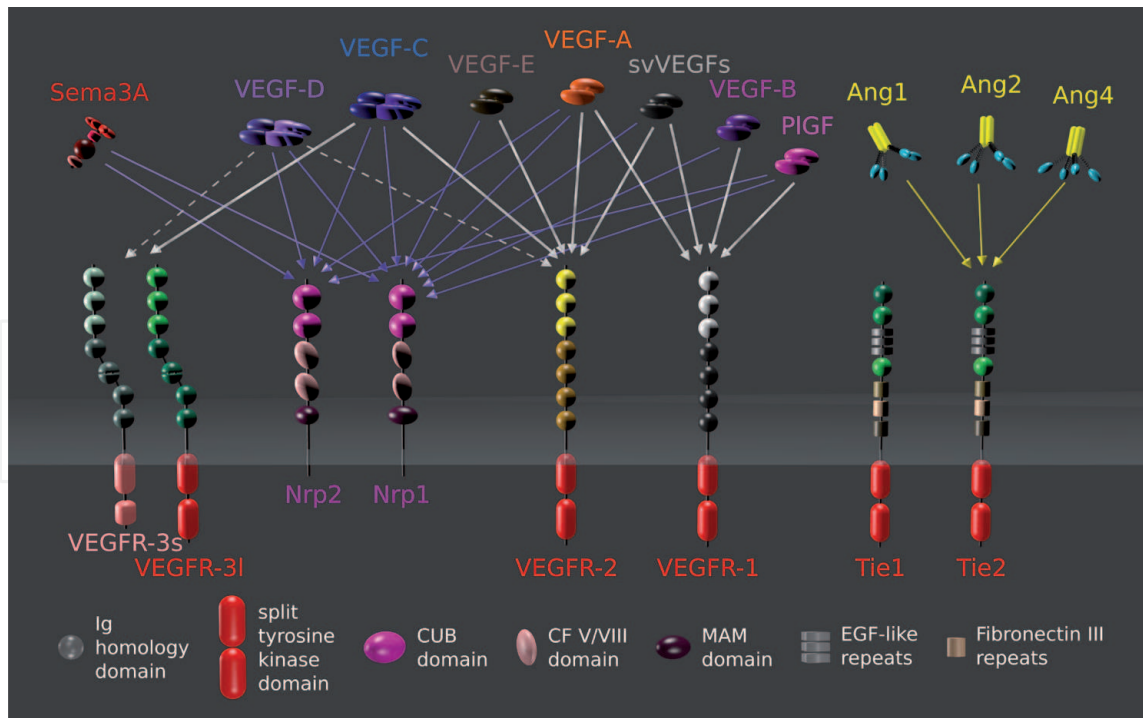
Figure 1.
Schematic depiction of the major interactions between endothelial-specific growth factors and their receptors. (Reproduced here from https://commons.m.wikimedia.org/wiki/File:Endothelial_receptors_and_growth_factors_01.png, licensed under the creative commons attribution-share alike 4.0 international license).

cancer; however, it is often used off-label for DME and is dosed intravitreally similarly to ranibizumab [20].

Intravitreal corticosteroids such as triamcinolone acetonide (Triescence, Alcon, Fort Worth, TX, USA), dexamethasone intravitreal implant (Ozurdex, Abbvie/Allergan, Irvine, CA, USA), and fluocinolone acetonide intravitreal implant (Iluvien, Alimera Sciences, Alpharetta, GA, USA) are also commonly used as a second line treatments for DME, and help reduce exudation by their broad inhibition of inflammatory cytokines. They are often used in combination with anti-VEGF therapy but have potential side effects of cataract progression and ocular hypertension [21]. Focal laser photocoagulation to leaking microaneurysms in the macula has been shown to reduce vision loss compared to no treatment, but does not provide the visual acuity gains achieved with anti-VEGF therapy [19, 22].

Although the use of anti-VEGF agents has greatly improved treatment outcomes in DR/DME patients, these agents have limited durability and require dosing as frequently as monthly, which may be required indefinitely in some cases. Additional treatment barriers include limited treatment efficacy and financial burden, particularly for the branded agents [23]. Anti-VEGF therapy has shown lower efficacy in 'real-world' studies when compared to clinical trial outcomes in DME and in nAMD patients [24–26]. This is partially due to under-treatment in clinical practice, resulting in approximately one line less of visual acuity gains compared to large randomized clinical trials. One real world database study showed that over one year U.S. DME patients received a mean of 7.5, 7.9 and 7.7 injections of aflibercept, bevacizumab and ranibizumab, respectively, which is lower than the 9.2, 9.7, and 9.4 injections received for these same drugs in the DRCR Protocol T Study [25, 27]. For the RISE and RIDE studies, DME patients received monthly ranibizumab injections (12 total), and for the VIVID and VISTA studies patients received bimonthly treatment of aflibercept after 5 monthly doses (8 total). Additionally, it has been shown that blockade of VEGF-A can lead to upregulation of other members of the VEGF family which also have pro-angiogenic effects [28]. For these reasons, there

has been a heightened focus on the development of medications that target alternate pathways, such as the Tie-2/angiopoietin pathway.

4. Tie-2/angiopoietin pathway

Recently, there has been great interest in drug development within the Tie-2 transmembrane tyrosine kinase receptor pathway in exudative diseases such as DME and nAMD. This receptor is found on endothelial cells and is responsive to the opposing angiopoietins, Ang-1 and Ang-2 (see **Figure 2**) [29]. These growth factors are integral players in vessel homeostasis, permeability, and angiogenesis. Ang-1 activates the Tie-2 receptor and leads to vascular stability [30]. Ang-2 acts as a competitive antagonist to Ang-1, turning off the Tie-2 receptor, leading to abnormal vascular growth, leakage, and increased inflammatory signals within endothelial cells [31, 32]. Tumor necrosis factor α (TNFα), a central inflammation mediator, induces Ang-2 release from endothelial cells to enhance its stimulation of inflammation and vascular leakage [33]. Additionally, the enzyme vascular endothelial protein tyrosine phosphatase (VE-PTP) inactivates the Tie-2 receptor and therefore interferes with the vascular stabilizing effects of Ang-1 [34].

A number of preclinical studies have supported the importance of the Tie-2/ Ang-2 pathways in DR and DME pathophysiology. Studies in the developing retina and in ischemic retinal mouse models have shown increased expression of both Ang-2 and VEGF which correlated to increased neovascularization [35, 36]. A study in double transgenic mice expressing both Ang-1 and VEGF showed that increased expression of Ang-1 led to decreased neovascularization and suppression of VEGF [37]. Additionally, high levels of Ang-2 and VEGF have been found in samples from diabetic patients following vitrectomy [38, 39]. During times of stress such as, hyperglycemia, ischemia, and oxidative stress, Ang-2 levels increase and result in aberrant vascular leakage and growth. Therapeutic interventions for exudative diseases may focus on inhibiting Ang-2 or VE-PTP therefore preventing their counterregulatory effects on the Tie-2 receptor.

4.1 Faricimab

Faricimab, previously RG7716 (Roche, Basel, Switzerland and Genentech, South San Francisco, CA, USA) is a bispecific antibody that binds to and inhibits both VEGF and Ang-2. Phase 1 and 2 trials showed promising results, supporting advancement to phase 3 trials [40, 41]. Results from four phase 3 trials from both patients with DR/DME and nAMD were released in February, 2021 from Roche [42]. All four studies demonstrated non-inferior results when administered in long-lasting dosing intervals compared to aflibercept.
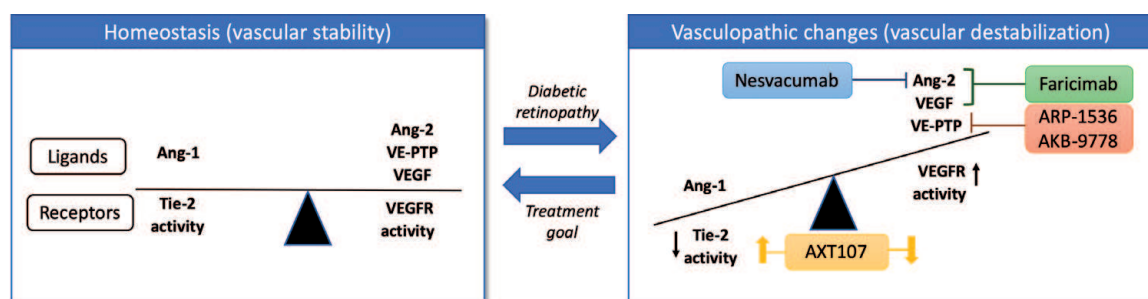
Figure 2.
Molecular targets and approaches to re-establish homeostasis in Ang–Tie-2 and VEGF–VEGFR pathways (reproduced with permission from [9]).

The YOSEMITE and RHINE studies are two identical phase 3 clinical studies that compared faricimab to aflibercept in patients with DME. The YOSEMITE and RHINE trials enrolled 940 and 951 patients respectively. These studies compared faricimab 6.0 mg given at individualized intervals (one, two, three or four months based on DR activity), faricimab 6.0 mg given at two-month intervals, and aflibercept 2.0 mg given at two-month intervals. Sham injections were given when patients within a treatment group were not scheduled to receive treatment to maintain blinding. The primary outcomes were average change in best corrected visual acuity (BCVA) at one year. Secondary outcomes were percent of individualized interval arm receiving doses at one, two, three, and four months at 52 weeks, percent of participants with a two-step or more improvement in diabetic retinopathy severity score (DRSS) from baseline, percent of participants with gain and percent without loss of 15 letters or more in BCVA, and change in central subfield thickness [43, 44].

YOSEMITE showed an average improvement of +11.6 ETDRS letters in the individualized interval faricimab arm, +10.7 ETDRS letters in the two-month interval faricimab arm, and +10.9 ETDRS letters in the aflibercept arm. Similarly, RHINE showed an average improvement of +10.8 ETDRS letters in the individualized interval faricimab arm, +11.8 ETDRS letters in the two-month interval faricimab arm, and +10.3 ETDRS letters in the aflibercept arm. Within the individualized interval faricimab arm, there were 151/286 (52.8%) participants in YOSEMITE that were dosed with a four-month interval at one year and 60/286 (21%) that were dosed with a three-month interval. Similarly, in RHINE, 157/308 (51%) participants were dosed with a four-month interval at one year and 62/308 (20.1%) achieved a three-month dosing interval. When compared to the aflibercept two-month dosing interval arm, both studies showed that the participants that achieved up to four-month dosing intervals of faricimab had larger reductions in central subfield thickness (CST) [42]. Roche has announced plan to submit a new drug application to the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of DME and nAMD.

4.2 AXT107

AXT107 (Asclepix Therapeutics, Baltimore, MD, USA) is a peptide that modifies Ang-2 to function more similarly to Ang-1. This peptide is derived from the non-collagenous domain of collagen IV and ultimately activates the Tie-2 receptor and stabilizes vascular permeability [9]. In studies using confluent monolayers of endothelial cells, AXT107 attached to Ang-2 binds to the Tie-2 receptor and disrupts α5β1 integrin, causing Tie-2 and α5 to move to cell junctions. Ultimately, Ang-2 modified by AXT107 serves as an agonist of the now junctional Tie-2 receptor and acts similarly to Ang-1 even in the presence of low concentrations of Ang-1 [45]. AXT107 also suppresses TNF-α induced vascular inflammation in endothelial cells, which may provide additional benefit in treating the chronic inflammatory component of DME and other retinal vascular diseases [33]. Additionally, in animal models, AXT107 increased breakdown of VEGFR2 which ultimately decreases the effects of VEGF [46]. Studies conducted in rabbit eyes injected AXT107 into the vitreous as a clear gel depot. This gel formulation slowly releases the AXT107 and could potentially decrease the need for many repeat injections. The rabbit model studies showed that AXT107 decreased leakage by 86% and 70% at one and two months, respectively. This was compared to aflibercept which reduced leakage by 69% at one month and did not reduce leakage at two months [47].

The CONGO study is a phase 1/2a clinical trial that will evaluate the safety and bioactivity of AXT107. This is a non-randomized open label study with 18 participants with DME. Three treatment arms of low (0.1 mg), medium (0.25 mg), and

high (0.5 mg) doses are included. The primary outcome is safety measured by incidence of adverse effects. Secondary outcomes are efficacy assessed by change in CST, change in BCVA, and percentage of participants improving by greater than 5, 10, 15 letters on the eye chart. This study is expected to be concluded by May 2022 [48].

4.3 Nesvacumab

Nesvacumab (Regeneron, Tarrytown, NY, USA) is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds to and blocks Ang-2. Nesvacumab was coformulated with aflibercept and phase 1 trials showed promising results for nAMD and DME. The phase 2 ONYX (nAMD) and RUBY (DME) trials did not duplicate that success however; patients treated with nesvacumab-aflibercept combo did not show any significant benefit in BCVA or CST compared to aflibercept monotherapy. For the RUBY study, however, there was a significant difference in the proportion of patients with resolution of foveal edema and ≥2 step improvement in DRSS in the high dose co-formulation arm [49]. In 2017, Regeneron announced that Nesvacumab would not advance to phase 3 trials [50].

4.4 AKB-9778

AKB-9778 (Aerpio Pharmaceuticals, Cincinnati, OH, USA) is an antagonist of VE-PTP given via subcutaneous injection. The TIME-2a study was a phase 2 study that sought to determine the safety and efficacy of AKB-9778 in DME patients. There were three treatment arms within 144 participants: 15 mg AKB-9778 twice daily and monthly placebo intravitreal injections, 15 mg AKB-9778 twice daily and monthly 0.3 mg ranibizumab intravitreal injections, and placebo subcutaneous injection twice daily and monthly 0.3 mg ranibizumab injections. The primary outcome was mean change in CST at three months and secondary outcomes were BCVA, DRSS, and safety [51]. Mean change CST was significantly greater in participants receiving both AKB-9778 and ranibizumab (−164.4±24.2 μm) than in participants receiving ranibizumab alone (−110.4±17.2 μm). Regarding the secondary outcomes, the percentage of participants that gained ≥10 or ≥15 letters across the treatment arms were: 8.7% and 4.3% in the AKB-9778 alone group, 29.8% and 17.0% in the ranibizumab along group, and 35.4% and 20.8% in the combination group, respectively. The DRSS remained similar across the three groups and AKB-9778 was found to be safe [52].

The safety and efficacy of AKB-9778 in 167 patients with nonproliferative DR was studied in the Time-2b study. This study did not utilize anti-VEGF therapy in its treatment arms and instead used AKB-9778 alone. The treatment arms included: AKB-9778 15 mg once daily, AKB-9778 15 mg twice daily, and subcutaneous placebo injected twice daily [53]. The primary outcome of percentage of participants with improvement in their DRSS was not met at 48 weeks. There was a significant 20% improvement in urine albumin creatinine ratio in patients treated with AKB-9778 twice daily and there was also a significant reduction in intraocular pressure among the treatment groups versus placebo. Based on these results, Aerpio Pharmiceuticals is investigating the use of AKB-9778 in diabetic nephropathy and open angle glaucoma. AKB-9778 is also in a phase 2 study for use in hospitalized subjects with COVID-19 acute respiratory distress syndrome [54].

4.5 ARP-1536

ARP-1536 (Aerpio Pharmiceuticals, Cincinnati, OH, USA) has the same biologic activity as AKB-9778 however it is delivered by intravitreal injection rather than

subcutaneously. ARP-1536 is an antagonist to VE-PTP which activates the Tie-2 receptor and provides vascular stability. It is in pre-clinical studies in combination with anti-VEGF therapy for DME and wet AMD [54].

5. Conclusion

Diabetic eye diseases are among the leading causes of blindness within the Western world. Previously, laser photocoagulation was the mainstay of treatment for DME and PDR [55]. Over the past two decades, anti-VEGF agents have become first-line treatments for DME. Although these medications have significantly improved visual outcomes for DME, limitations have been noted in 'real-world' studies [24–26]. Most notably, anti-VEGF agents require frequent injection, which acts as a treatment barrier to patients and leads to under-dosing. The investigational drugs that target the Tie-2/angiopoietin pathway may produce greater drying effect on the macula, with prolonged durability and superior visual outcomes compared to anti-VEGF monotherapy. Future trials may focus on the ability of combination anti-VEGF and Ang-2 inhibitors to treat PDR.

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