The potential of anti-VEGF (Vasotide) by eye drops to treat proliferative retinopathies

Jennifer L. Wilkinson-Berka, Devy Deliyanti

Department of Immunology and Pathology, Monash University, Melbourne, Australia

Correspondence to: Professor Jennifer L. Wilkinson-Berka. Department of Immunology and Pathology, Monash University, Level 6, 89 Commercial Road, Melbourne, Victoria 3004, Australia. Email: jennifer.wilkinson-berka@monash.edu.

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Ocular neovascularization and vascular leakage are major causes of vision loss and blindness and hallmark features of retinopathy of prematurity (ROP), proliferative diabetic retinopathy (PDR) and neovascular age-related macular degeneration (AMD) (1-3). These diseases comprise a significant global health burden. For instance, it is predicted that by 2035 over 592 million people will be diagnosed with diabetes and by 2040 around 288 million individuals will have AMD (4,5). The vision-threatening vasculopathy that develops is associated with the up-regulation of vascular endothelial growth factor (VEGF) in various cell types of the retina including Müller cells, ganglion cells and retinal pigment epithelium (6-8). The overwhelming evidence that VEGF is a potent and major driver of blood vessel growth and vascular permeability has led to intense research into the development of agents that effectively inhibit VEGF and can be safely used to treat proliferative ocular diseases (9).

VEGF is a homodimeric glycoprotein that has six members, VEGF-A to E, as well as placental growth factor (PlGF). VEGF-A is the most important for blood vessel growth and vascular permeability, and in humans is comprised of several isoforms of which $VEGF_{165}$ is the most common and critical for angiogenesis (9). VEGF-A binds to and selectively activates membrane-bound tyrosine kinase receptors named VEGFR 1–3. VEGFR-2 is perhaps the best studied and has a central role in cellular proliferation, angiogenesis and vascular permeability. However, of the three receptors, VEGF-A binds to VEGFR-1 with the highest affinity, and VEGFR-1 also binds to VEGF-B and PlGF. Apart from $VEGF_{121}$, all other isoforms of VEGF-A can interact with the neuropilin (NRP) receptors, NRP-1 and NRP-2 (10). NRP-1 is of particular interest as it can signal independently from the VEGFRs and also influence VEGFR-2 signalling (10). Furthermore, NRP-1 is a receptor for semaphorin 3A (SEMA3A), a secreted glycoprotein that has roles in angiogenesis, axon guidance and cell survival and migration (11). The interaction between NRP-1 and SEMA3A is of particular relevance to proliferative ocular diseases due to its promotion of vascular permeability and neovascular tuft formation (12).

For more than a decade there has been intense interest in blocking VEGF as a treatment for ocular neovascularization and vascular permeability (2,3). The VEGF-A/VEGFR-2 axis is the focus of VEGF-based therapies currently in clinical use for the treatment of diabetic macular oedema (DME) and exudative AMD, and includes ranibizumab (Lucentis, Genentech, San Francisco, USA), bevacizumab (Avastin, Genentech), and aflibercept (Eylea, Regeneron Pharmaceuticals, NY, USA). Ranibizumab is a monoclonal antibody fragment that inhibits VEGF-A, and thought to be similar in action to bevacizumab, although more expensive as a treatment per dose (13). Aflibercept, is a newer generation VEGF Trap that is a recombinant fusion protein consisting of VEGF binding portions from the extracellular domains of human VEGFR-1 and VEGFR-2 that are fused to the human IgG1 immunoglobulin (14). Aflibercept is of interest as it may have greater efficacy in patients with DME than ranibizumab and bevacizumab, with the Diabetic Retinopathy Clinical Research Network clinical trial reporting aflibercept was more effective in patients with initial poor visual acuity (15).

A key feature of current anti-VEGF treatments for severe ocular vasculopathy is their injection directly into the

vitreous cavity of the eye. This mode of delivery provides a major advance over previous standard of care, laser treatment; a surgical procedure that removes damaged tissue but does not halt disease progression and can injure healthy tissue (1-3). However, despite the benefits of current anti-VEGF treatments, it is clear that a substantial proportion of patients continue to have some degree of persisting DME and AMD (16,17). This situation has resulted in the search for more effective anti-VEGF treatments as well as the exploration of treatment delivery options that are inexpensive and less invasive than current practice. An obvious approach is the administration of anti-angiogenic agents by eye drops. However, the use of eye drops has not necessarily been considered a treatment option due to the assumption that drugs delivered by this manner do not reach the retina and choroid. Growing research into biomaterials and nanotechnology for novel methods of delivery to treat ocular neovascularization and vascular permeability is currently underway, albeit in early stages of development (18).

In this context the manuscript by Sidman and colleagues (19) is timely as the authors identified that inhibition of components of the VEGF pathway delivered by eye drops is effective in pre-clinical models of ocular vasculopathy. Rather than focussing on the interaction between VEGF-A and VEGFR-2, the authors explored other VEGF family members as potential treatment targets. VEGFR-1 and NRP-1, as well as their ligands VEGF-B and PlGF, have a prominent role in angiogenesis and are promising targets for therapy (11). In previous studies the team used a subtractive bacteriophage display library screening strategy to identify a small synthetic retro-inverted peptidomimetic $_{D}$(CPQPRPLC). They showed that a derivative molecule, $_{D}$(LPR), targeted to VEGFR-1 and NRP-1, penetrated the vitreous cavity when administered topically to the eye and had anti-angiogenic properties in experimental models of disease (20). The recent manuscript by Sidman and co-authors (19) evaluated a prototype peptidomimetic named Vasotide, which was administered by topical eye drops or intraperitoneal injection to three pre-clinical models of ocular vasculopathy. Comparisons were made to a control peptide.

The first model, oxygen-induced retinopathy (OIR) is a robust model of ROP, a disorder that occurs in some pre-term infants exposed to supplemental oxygen to assist breathing (1). OIR is a biphasic disease. In phase I exposure to hyperoxia results in vaso-obliteration in the central retina. In phase II, exposure to room air leads to relative retinal ischemia, which induces extensive neovascularization at the retinal surface with vessels that protrude into the vitreous cavity. Vaso-obliteration is present in phase II, although not as severe as in phase II. Vasotide administered topically three times per day for one week during phase II OIR appeared to reduce retinal neovascularization, albeit the quantitated data was not presented. The ability of Vasotide to inhibit SEMA3A, which misguides neovascularization from the retina and into the vitreous, may explain the benefits of Vasotide in this model. Vasotide did not reduce vaso-obliteration in phase II OIR, but it might be speculated that if delivered earlier during phase I OIR this pathology may have been attenuated. The second model to be evaluated was choroidal neovascularization (CNV), a hallmark feature of neovascular AMD in which aberrant new blood vessel growth occurs in the choroid, a vascular layer that lies between the retina and the sclera. Laser-induced CNV was induced in Old World monkeys to result in both neovascularization and vascular leakage. Vasotide eye drops administered twice per day from day 1 to day 5, post-laser treatment and then once per day from day 6 to day 21, resulted in reduced CNV, vascular leakage and inflammatory cell infiltration. The final model involved the very low density lipoprotein receptor (*vldlr*) knockout (KO) mouse, to evaluate the human AMD subtype, retinal angiogenesis proliferation (RAP). In the RAP form of AMD, neovascular vessels grow into the normally avascular photoreceptor zone of the retina. Sidman and colleagues (19) found neovascularization in the *vldlr* KO mouse to occur in most retinal layers and as early as postnatal (P) days 8 and 12. Mice were studied up to 214 days of age and treated once per day with Vasotide between P12-18, P48-54 and P208-214. Rather than topical treatment, Vasotide and control peptide were administered by intraperitoneal injection and reduced retinal neovascularization in *vldlr* KO mice. It would be of interest to determine if the delivery of Vasotide by eye drops would have similar results.

Collectively, the findings presented by Sidman and colleagues (19), indicate the potential of agents such as Vasotide, which inhibit VEGFR-1 and NRP-1 for the treatment of a variety of ocular diseases featuring neovascularization. Vasotide was not directly compared to current United States Food and Drug Administration (FDA)-approved agents such as aflibercept, ranibizumab and bevacizumab, which target VEGF-A and VEGFR-2. This assessment is important for not only understanding the relative efficacy of Vasotide, but also which components of the VEGF pathway are most critical for

attenuating ocular neovascularization, findings that may be particularly relevant to patients resistant to current anti-VEGF agents. Perhaps one of the most promising aspects for the future treatment of ocular neovascularization and vascular permeability is topical administration. If penetrance to the retina and choroid can be confirmed and then optimized, and robust pharmacokinetic and safety data obtained, eye drops would be preferable to currently monthly intravitreal injections and may result in significant economic savings.

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Footnote

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Comment on: Sidman RL, Li J, Lawrence M, *et al.* The peptidomimetic Vasotide targets two retinal VEGF receptors and reduces pathological angiogenesis in murine and nonhuman primate models of retinal disease. Sci Transl Med 2015;7:309ra165.

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