

CLINICAL IMPLICATIONS OF BASIC RESEARCH

Targeting Intraocular Neovascularization and Edema — One Drop at a Time

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Barring death, blindness is one of the most feared complications of human disease. In developed countries worldwide, the vast majority of visual loss results from pathologic neovascularization of the choroid and retina or retinal edema, conditions that are thought to be mediated primarily by the angiogenic and vasopermeability molecule called vascular endothelial growth factor (VEGF). These complications are treated with either laser photocoagulation, which destroys areas of otherwise functional retina, or antiangiogenic agents that are repeatedly injected into the center of the eye. Recent studies by Schepcke et al.¹ and Doukas et al.² indicate that a different approach may be feasible.

Pathologic neovascularization of the choroid and retina and uncontrolled retinal vascular leakage that leads to retinal edema are the principal events common to the leading causes of visual loss — age-related macular degeneration, diabetic retinopathy, retinal-vein occlusion, retinopathy of prematurity, and numerous inflammatory and neoplastic conditions. Until recently, laser photocoagulation was the only primary therapeutic option. In addition to destroying areas of retina to preserve central vision, the procedure is not universally effective and is associated with unavoidable side effects. These limitations have inspired investigation into mechanisms underlying the development of these conditions.

VEGF is a principal mediator of neovascularization and vascular permeability in these diseases, and therapeutic use of VEGF inhibitors that are injected into the eye has revolutionized the treatment of age-related macular degeneration, allowing recovery of lost vision that in the past would have been irretrievable.³ Intravitreal injection of VEGF inhibitors has quickly supplanted laser and other therapies as the primary treat-

ment for this condition. However, current VEGF inhibitors, such as ranibizumab and pegaptanib, that have been approved by the Food and Drug Administration for the treatment of age-related macular degeneration are large molecules that must be injected intravitreally each month. This treatment regimen is associated with discomfort in patients and is critically dependent on the availability of an ophthalmologist. In addition, both ranibizumab and pegaptanib are very expensive, and intravitreal injection incurs the rare but visually devastating risks of retinal detachment and endophthalmitis.

The efficacy of VEGF inhibitors in disorders that are characterized by neovascularization and retinal edema is an active area of clinical investigation, especially in patients with diabetic retinopathy and retinal-vein occlusion. Preliminary studies using aptamers, modified antibodies, and corticosteroid preparations have had positive short-term results, but establishing their long-term efficacy and adverse-events profile will require the completion of the large, randomized, well-controlled trials that are under way.

There is mounting evidence that the response to VEGF inhibitors in patients with retinal neovascularization differs from that in patients with retinal edema. Proliferative diabetic retinopathy and neovascular glaucoma are exquisitely sensitive to treatment with VEGF inhibitors. Resolution of abnormal vessels often begins 1 day after treatment, and complete regression is commonly observed. In contrast, early studies indicate that although some patients with retinal edema have a response to treatment, the response is often partial and higher doses may be required, implying that pathways other than that of VEGF are involved. Thus, the response of a patient with retinal edema to a VEGF-specific inhibitor may

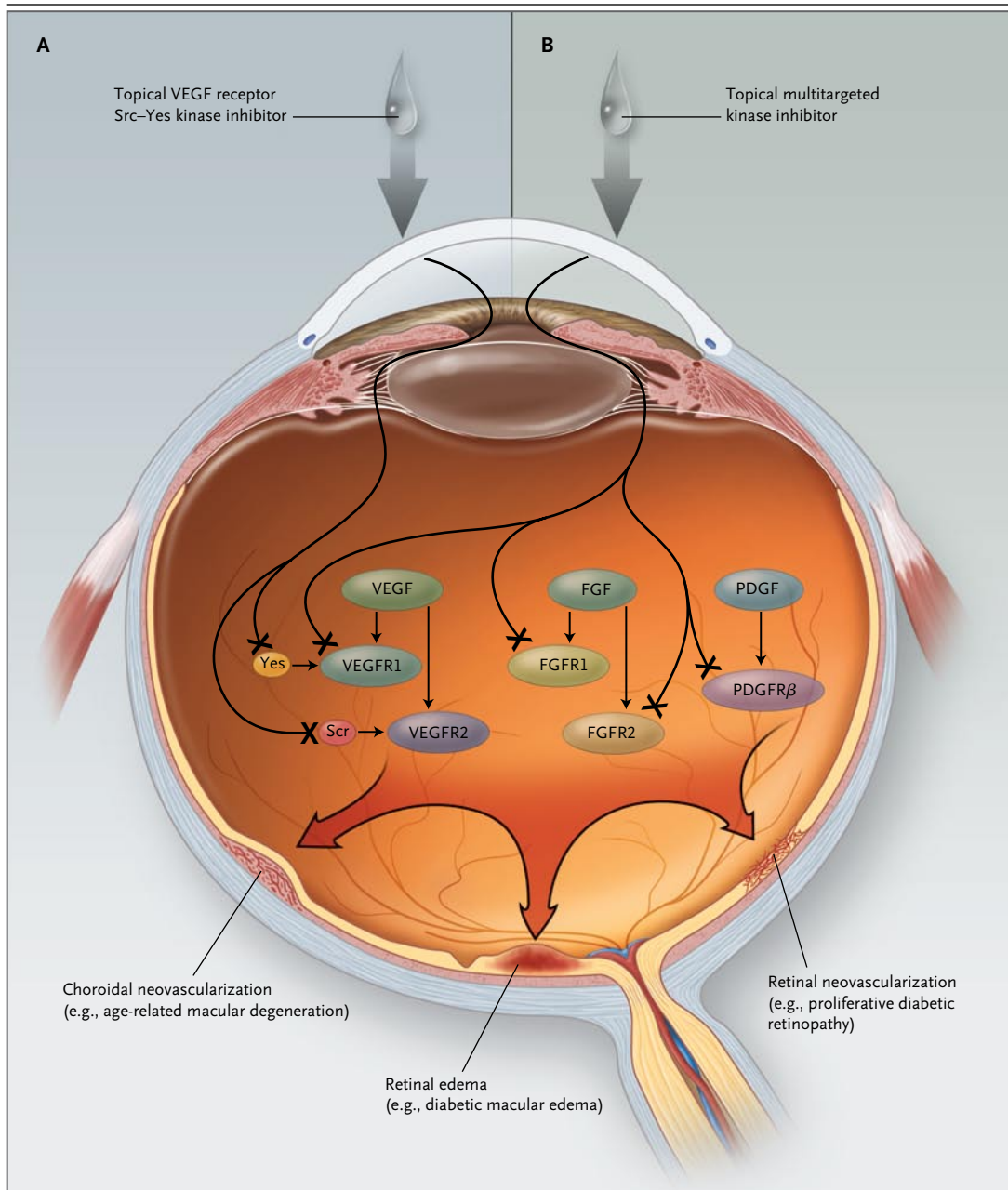


Figure 1. Topical Use of Kinase Inhibitors.

Retinal edema and neovascularization of the choroid and retina are the primary causes of vision loss in most developed countries. Multiple mechanisms mediate these changes, including pathways involving vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) receptor kinases. These growth factors bind a variety of receptors, including VEGFR1, VEGFR2, FGFR1, FGFR2, and PDGFR β . A recent study by Schepke et al.¹ showed that topical application of a VEGF receptor Src-Yes kinase inhibitor can essentially eliminate retinal edema in animals (Panel A). A similar study by Doukas et al.² showed that a topical multitargeted kinase inhibitor of VEGF, PDGF, and FGF pathways can reduce choroidal neovascularization and retinal edema in animals (Panel B).

reflect the extent to which the VEGF pathway is involved — a contribution that may vary over time or among patients.

Recent work has implicated VEGF-independent mechanisms in retinal disease. For example, erythropoietin has been implicated in diabetic neovascular disease⁴ and the carbonic anhydrase–kallikrein system in diabetic retinal edema.⁵ The inhibition of multiple targets simultaneously tends to result in a robust therapeutic effect, suggesting that targeting of more than one pathway supporting angiogenesis may increase the clinical benefit in the eye. Since the relative contributions of different pathways may vary in different patients (and possibly over time in the same patient), the optimal treatment strategy may involve multidrug therapies that are initiated serially, similar to the approach used to treat glaucoma.

The study by Schepcke et al. underscores the importance of understanding the mechanisms of VEGF action. The authors have established a role for Src and Yes kinases in VEGF-mediated retinal vascular permeability, since Src and Yes knockout mice were markedly resistant to VEGF-induced retinal vascular permeability and much less susceptible to retinal edema after laser-induced vein occlusion than were control mice (Fig. 1). The authors also observed that systemic or topical application of a VEGF receptor 2–Src kinase inhibitor abrogated vascular leakage induced by the intraocular injection of VEGF. Doukas et al. applied a topical, multitargeted kinase inhibitor of VEGF, platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF) pathways. As in the study by Schepcke et al., Doukas et al. observed reduced vascular leakage associated with topical use of the agent. They also observed partial protection against laser-induced retinal edema and choroidal neovascularization, perhaps because multiple pathways were targeted.

The ability to provide effective topical therapies for intraocular neovascularization and retinal edema could revolutionize the current care of many diseases that lead to these conditions. The benefits would include ease of therapy, a reduced risk of complication, and ease of combining multiple therapies. The targeting of multiple pertinent pathways with a single molecule has a potential for efficacy that is greater than that of a compound directed at a single molecule.

However, this approach also has a potential risk of increased side effects. Indeed, Doukas et al. found substantial toxic effects when their compound was administered systemically but not when it was administered topically (although the animals received the drug for only 28 days). Topical delivery in these instances has the added benefit of providing less systemic exposure and thus potentially fewer side effects. The studies by Schepcke and Doukas provide evidence that multitargeted and topical therapy could become a reality for many of the most severe sight-threatening conditions of our time.

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