

Sirolimus and mTOR Inhibition in Ocular Disease: An Update

Due to the broad immunomodulatory and antihypoxic-response activities of sirolimus, the drug has the potential to fill a critical unmet need: The prevention of CNV in AMD.

BY MARK S. BLUMENKRANZ, MD

S irolimus, also known as rapamycin, is a macrolide that has been widely used systemically as an immunosuppressive agent and for the prevention of restenosis in coronary stents after angioplasty. It is currently being investigated in phase 1 clinical trials as a potential therapeutic agent for the treatment of choroidal neovascularization (CNV) and diabetic macular edema.

Originally dubbed rapamycin because it was isolated from a *Streptomyces* species found on Easter Island (Rapa Nui),¹ sirolimus is structurally similar to other immunosuppressive agents such as cyclosporine and FK-506.² Its physical properties make it a promising candidate for sustained ocular delivery; it is a small molecule and highly lipophilic.

The mammalian target of rapamycin, or mTOR, is a protein kinase that regulates cell growth and metabolism in response to changes in the environment, such as the availability of nutrients or the presence of growth factors.³⁻⁵ A number of cellular processes are regulated by mTOR, including protein synthesis, nutrient transport, and autophagy.

IMMUNOSUPPRESSIVE AND ANTINEOPLASTIC PROPERTIES

Sirolimus was originally identified because of its antifungal properties,¹ but it was soon found to have immunosuppressive and antineoplastic properties through its binding with and inhibition of mTOR. Similar to steroids, sirolimus has been found to have a broad range of activities in *in vitro* and *in vivo* testing. It is anti-inflammatory, reducing the expression of several genes related to inflammation.⁶ It inhibits migration induced by platelet-derived growth factor (PDGF).⁷ It is antifibrotic,

decreasing proliferation of fibroblasts induced by PDGF and basic fibroblast growth factor in human Tenon's capsule cultures.⁸ It is antiproliferative, blocking hypoxia-responsive growth factors such as fibroblast growth factor-1. Finally, it is antiangiogenic; it decreases vascular endothelial growth factor (VEGF) and transforming growth factor-beta1,¹⁰ and it down-regulates hypoxia-inducible factor 1-alpha (HIF 1-alpha), which regulates VEGF and other angiogenic growth factors.¹¹

Sirolimus was approved by the US Food and Drug Administration (FDA) in 1999 for prevention of transplant rejection and in 2003 for use in drug-eluting coronary stents. The combination of activities of sirolimus—immunosuppressive, antiangiogenic, antiproliferative—makes it a promising candidate for use as a therapeutic agent for the treatment of retinal and choroidal vascular disease associated with neovascularization (Figure 1).

Inhibition of VEGF is the method of action of two FDA-approved treatments for CNV in age-related macular degeneration (AMD), pegaptanib (Macugen; OSI/Eyetech and Pfizer, both in New York, NY) and ranibizumab (Lucentis; Genentech, San Francisco). Sirolimus also inhibits VEGF, and it acts through two separate pathways; the inhibition of mTOR by sirolimus causes a decrease in production of VEGF-A, and further downstream it also decreases the response of endothelial cells to VEGF activation through down-regulation of intracellular signaling.

INHIBITS CELL PROLIFERATION

mTOR inhibition also inhibits the activity of HIF 1-alpha, which acts to decrease VEGF production and inhibit VEGF-induced endothelial cell proliferation, as well.¹² This hypoxic response effect is the rationale

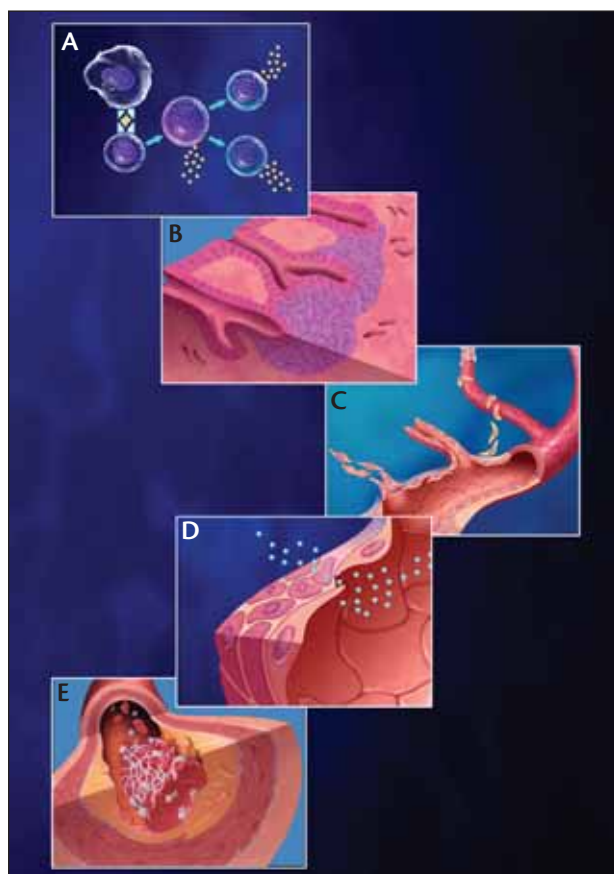


Figure 1. A number of the ocular disease mechanisms that the broad activity of rapamycin is able to impact: Recent data implicate immunological factors in the initiation of early events leading to AMD. Immunomodulatory agents, such as rapamycin, may prevent T-cell activation and cytokine production associated with these early immunological events. By having an impact on the factors that initially trigger wet AMD development, agents such as rapamycin may offer an opportunity for disease prevention (A). Endothelial cell proliferation is required for angiogenesis. Antiproliferative drugs, such as rapamycin, may inhibit cell proliferation required for angiogenesis (B). Angiogenesis is a complex process. VEGF is only one of several proangiogenic factors required in the process of vessel destabilization, cell proliferation and migration, tube closure, stabilization and maturation. Some compounds, such as bevacizumab, inhibit only VEGF. Others, such as rapamycin, have been shown to inhibit production of a number of key proangiogenic factors, including VEGF (C). Hyperpermeability of developing blood vessels during angiogenesis causes accumulation of fluid in the retina, which is responsible for much of the vision loss occurring in the early stages of wet AMD. Drugs that inhibit VEGF and other proangiogenic factors can reduce the edema and improve vision (D). The later stages of wet AMD are associated with fibrosis of the tissues and permanent loss of vision. Some drugs may be able to slow or halt this process. For example, rapamycin can inhibit fibrosis by decreasing PDGF and bFGF-induced human Tenon's capsule fibroblast proliferation (E).

behind the development of mTOR inhibitors as anti-cancer agents, but it also has implications for ophthalmic applications. Because HIF 1-alpha has been identified as having played several roles in retinal disease,¹³⁻¹⁶ it has been suggested that inhibition of HIF 1-alpha could have the effect of a combination treatment.¹⁷

Sirolimus has been widely used in cardiology to prevent restenosis, and there are similarities between the processes of coronary atherosclerosis and CNV. Both involve endothelial and fibrotic proliferation in response to cytokines. In preclinical studies, sirolimus markedly reduced neovascularization in a rat model of CNV.¹⁸ It also reduced choroidal and retinal neovascularization in mouse models of laser-induced CNV and hypoxia-induced retinopathy of prematurity, respectively.¹⁹ The drug has also been shown to be a potent inhibitor of VEGF-induced hyperpermeability in mice.²⁰

The ongoing phase 1 studies of sirolimus for ophthalmic applications aim to demonstrate the ability to achieve minimally invasive, safe, sustained delivery of the drug to retinal and choroidal tissues at targeted levels. In these trials, a versatile, proprietary sustained-release liquid formulation of sirolimus that allows both periocular and intravitreal drug delivery is being evaluated.

PERIOCCULAR ADMINISTRATION

Periocular subconjunctival administration of the sirolimus formulation appears to be well tolerated, delivering target drug concentrations to retinal and choroidal tissues for sustained periods of 3 months or more. This route requires a higher dose of sirolimus than intravitreal delivery, but systemic exposure is low. With intravitreal delivery, a depot formed in the vitreous provides sustained levels of drug delivery with lower doses and minimal systemic exposure.

One phase 1 trial will assess the safety of sirolimus in the treatment of CNV in AMD. A second will assess its safety in treatment of macular edema in diabetic retinopathy. Although the primary goal of the trials is to evaluate safety, they may offer a preliminary read on efficacy as well, through measurements of retinal thickness on optical coherence tomography at 45 days and 90 days after injection.

The trials will assess both routes of administration, subconjunctival and intravitreal, in a dose-escalation scheme. Three doses will be assessed for each route, with five patients per dose per route, a total of 30 patients in each trial.

Due to the broad immunomodulatory and antihypoxic-response activities of sirolimus, the drug has the potential to fill a critical unmet need: The prevention of CNV in AMD. It has been widely used systemically and found

MACULA

to be safe to date, and the ongoing phase 1 trials are confirming its safety for ocular use. Preliminary results of these trials are expected to be announced later this year.

Further studies will evaluate whether sirolimus, with minimally invasive administration and an infrequent dosing schedule, can ease the burden placed on physicians and patients by currently approved treatment options for CNV in AMD. ■

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