

Sirolimus in the Treatment of Retinal Diseases

mTOR inhibitors: A new class of therapeutics.

BY PRAVIN U. DUGEL, MD

While sirolimus, previously known as rapamycin, is new to the field of ophthalmology, it is not new to medicine. In fact, sirolimus and its derivatives are the active pharmaceutical ingredients in several US Food and Drug Administration-approved products that have been used safely in the prevention of organ rejection (Rapamune, Wyeth), prevention of coronary restenosis (Cypher stent, Johnson & Johnson), and most recently, in the treatment of advanced renal cell carcinoma (Torisel, Wyeth; and Afinitor, Novartis). Over the past few years, sirolimus has become the topic of intense research in the oncology community due to its ability to inhibit the mammalian target of rapamycin (mTOR). This kinase occupies a key point of convergence of multiple cellular pathways, regulating the body's response to both activating and inhibitory factors (growth factors, hormones, nutrient availability, oxygen tension, etc.).¹ Therefore, as an mTOR inhibitor, sirolimus possesses a broad spectrum of therapeutic action, including the ability to inhibit inflammation, proliferation, angiogenesis, fibrosis, and hyperpermeability. Perhaps most important for diseases involving a neovascular component (as in solid tumor oncology and neovascular macular degeneration), sirolimus inhibits the translation and activity of hypoxia-inducible factor-1 alpha (HIF-1 α), a stress-activated protein that activates numerous survival proteins involved in angiogenesis and hyperpermeability.² In fact, HIF-1 α is a potent stimulator of vascular

endothelial growth factor (VEGF), and its inhibition affects VEGF both upstream at the production level and downstream at the receptor level.³

Unfortunately, broad gaps currently exist in the management of retinal diseases such as neovascular age-related macular degeneration (wet AMD) and diabetic macular edema (DME). For instance, fibrosis represents an important component in many retinal diseases, causing irreversible photoreceptor death and severe loss of vision. Yet fibrosis is not addressed in the current treatment of these diseases. And, of course, the treatment burden required to provide optimum care with today's anti-VEGF therapy presents significant patient, clinical practice, and economic issues. Sirolimus, with its broad spectrum of activity, has the potential to address these and other gaps in current treatment paradigms. In addition, sirolimus has the potential to be an excellent combination agent, improving overall outcomes or prolonging the intervals between anti-VEGF injections.

SUSTAINED DRUG TISSUE LEVELS VIA TRANSCLERAL DIFFUSION

Recognizing the potential for mTOR inhibition in ophthalmology, a key challenge for MacuSight, Inc. (Union City, CA), was to develop a formulation that could minimize systemic exposure through local ocular administration while at the same time providing a stable, sterile product that is safe for ocular use. The approved mTOR inhibitor products mentioned above

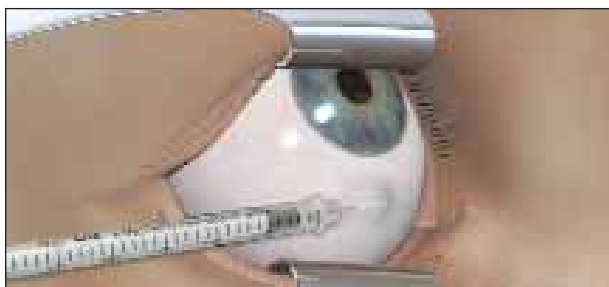


Figure 1. Subconjunctival injection of sirolimus product creates a drug depot.

are not suitable for ophthalmic application. Oral or intravenous administration presents the issue of systemic immunosuppression in elderly or diabetic populations already at risk of infection. Additionally, the products formulated for intravenous use contain significant amounts of alcohol, preservatives, and other inactive ingredients, that are unsafe for ocular use. In developing an ocular-safe and stable formulation, MacuSight recognized a unique opportunity to leverage the physicochemical properties of sirolimus in

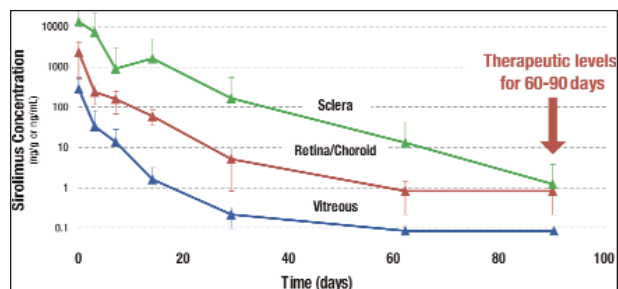


Figure 2. Ocular tissue concentrations of sirolimus following a single subconjunctival injection in New Zealand White rabbits.

order to achieve sustained retinal tissue concentrations through minimally invasive transscleral delivery. The result is a clear, liquid sirolimus product (Perceiva) that is administered through a subconjunctival or, alternatively, intravitreal injection using a standard 30-gauge needle. Following subconjunctival injection (Figure 1), this highly lipophilic drug preferentially migrates into the sclera, which subsequently acts as a reservoir, allowing the slow release of sirolimus into the intraocular tissues. As a result, retinal and

TABLE 1. LIST OF CLINICAL TRIALS CURRENTLY BEING CONDUCTED WITH PERCEIVA

Indication	Sirolimus Administration	Key Endpoint (months)	Number of Patients
MacuSight-Sponsored Studies			
Diabetic macular edema	q3mo X 2	6	131
Wet AMD (combination)	q2mo X 2 with Lucentis	4	62
Wet AMD (monotherapy)	q2mo X 3	6	20
Dry eye syndrome	once	1	143
NEI-Sponsored Studies			
Diabetic macular edema	q2mo X 3	6	5
Dry AMD (geographic atrophy)	q3mo X 8	24	15*
Anterior uveitis	Once	1	7*
Investigator-Sponsored Studies			
Posterior uveitis	q2mo X 3	6	30*

* Trial is currently enrolling. Number represents targeted enrollment.

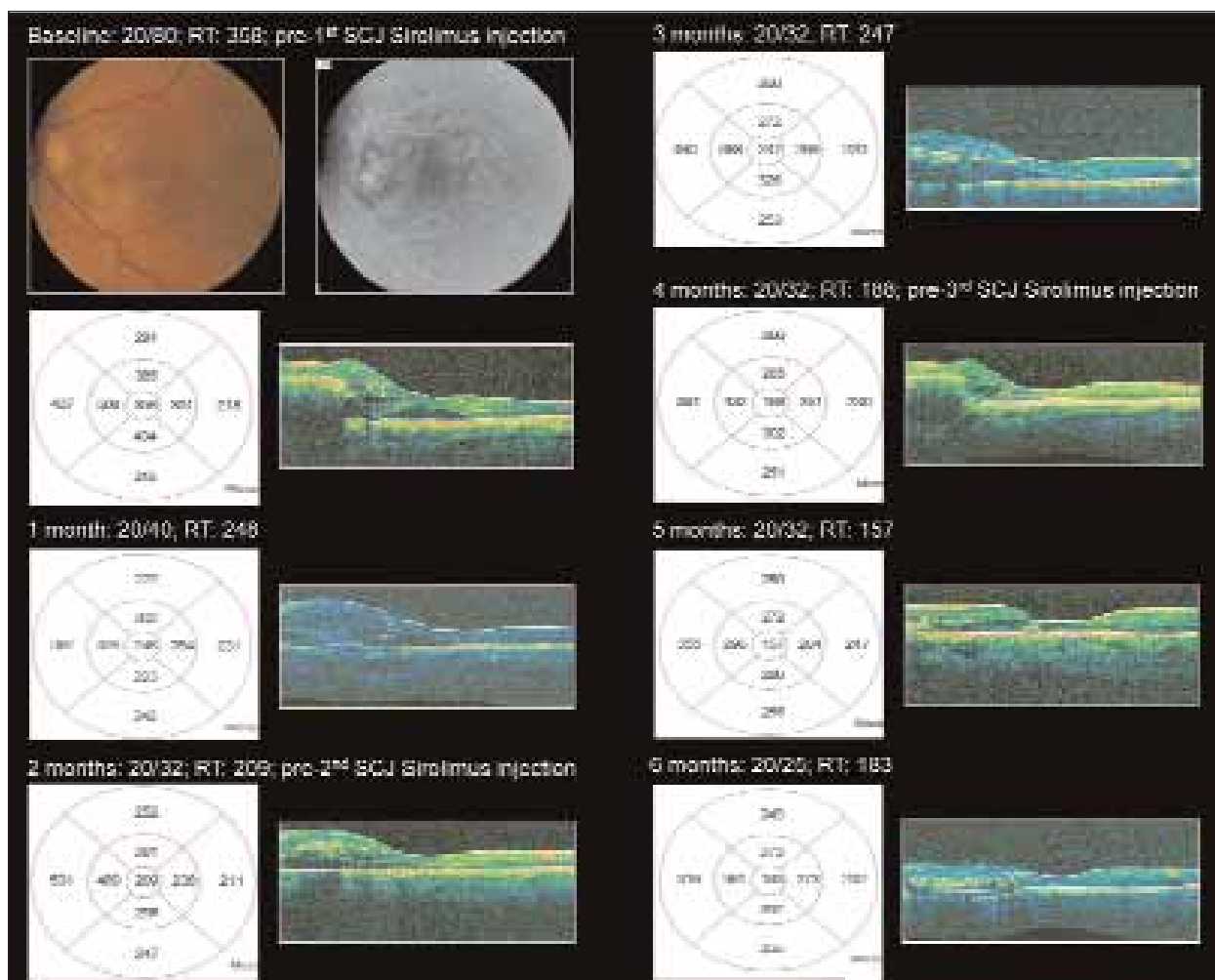


Figure 3. A 58-year-old woman with neovascular AMD treated by subconjunctival injection of sirolimus at baseline, 2 and 4 months. Improvements in visual acuity and retinal thickness were observed following the first dose. At 6 months, 2 months following the last injection, best corrected visual acuity had improved by more than five lines, and retinal thickness had been reduced by approximately 175 μm . No other treatment or intervention was received through the 6-month time point.

choroidal sirolimus levels were sustained for 60 to 90 days in rabbits following a single dose (Figure 2).⁴ The product acts, in effect, as its own drug delivery device.

PHASE 1 PROGRAM

Two phase 1 studies have been completed: one for DME (manuscript submitted), and one for wet AMD (manuscript in preparation). As with most phase 1 trials, the primary goals were to demonstrate safety and observe for biological signals. The safety profile across the two phase 1 studies, representing a total of 80 patients, was excellent. There were no dose-limiting toxicities, ocular inflammation, or increase in intraocular pressure. The majority of ocular adverse events were related to the injection procedure and these were mostly mild and transient in nature. Importantly, sys-

temic exposure was negligible and insufficient for systemic immunosuppression.

With regard to activity, both phase 1 studies showed clear and temporally-related biological signals. As phase 1 studies, only patients with advanced disease and guarded prognosis were recruited. A total of 50 patients, the majority (82%) of whom had failed previous laser photocoagulation, were enrolled into the DME trial. Likewise, in the wet AMD study, 30 patients, many with considerable fibrosis, were enrolled. In both dose-escalation studies, a single subconjunctival or intravitreal injection resulted in visual acuity improvement and reduction of OCT that lasted at least 90 days. When the data was subdivided, the subconjunctival route was as effective as the intravitreal route, confirming the observed transscleral pharmacokinetic properties of the product.

PHASE 2 PROGRAM ACROSS MULTIPLE INDICATIONS

Based on the promising phase 1 results, a broad phase 2 clinical program was initiated across multiple major indications consistent with the opportunity for mTOR inhibition in ophthalmology (Table 1). The first, a phase 2 DME study, known as the DIAMOND trial, rapidly completed enrollment of 131 patients. In this dose-ranging, placebo-controlled trial, patients receive a subconjunctival injection at baseline and again at 3 months. Prior therapy was allowed in order to duplicate real-world experience. Primary endpoints include changes in visual acuity and OCT at 6 months.

In wet AMD, a phase 2 study, known as the EMERALD trial, is evaluating the therapeutic potential of Perceiva in combination with current anti-VEGF-specific therapy (ranibizumab [Lucentis], Genentech, Inc.). Down-regulation of VEGF production and signaling through inhibition of the hypoxic response together with other broad, potentially beneficial inhibitory effects of sirolimus, such as antifibrosis, may provide additional improvements in visual function or decrease the need for frequent treatment. Enrollment has also been completed for this multicenter, dose-ranging trial. The study design, which again allowed for prior therapy in order to mimic real-world conditions, calls for patients to receive an intravitreal injection of ranibizumab followed immediately by a subconjunctival injection of Perceiva at baseline and again at 2 months. Patients in the control group will receive ranibizumab at baseline, 1 and 2 months, with a placebo subconjunctival injection at baseline and 2 months.

Although sirolimus may be ideally suited as a combination therapy agent in wet AMD, no study has investigated sequential dosing as a monotherapy agent. Therefore, a small 20-patient trial was initiated to evaluate the benefit of repeat dosing at 2-month intervals. This monotherapy trial is being conducted at a single center (Retinal Consultants of Arizona, Phoenix, AZ) and has completed enrollment. Figure 3 presents preliminary results for one patient being treated in this study. Best corrected visual acuity improved from 20/80 at baseline to 20/25 at 6 months, 2 months following the third subconjunctival injection of sirolimus. This functional improvement was accompanied by a reduction in retinal thickness from 358 μ m at baseline to 183 μ m at baseline and 6 months. It is expected that the results from this study, together with the combination study (EMERALD), will provide strong insight into the potential application and benefit of sirolimus in current treatment paradigms for wet AMD.

The broad antiinflammatory and immunomodulatory

activities of sirolimus, coupled with the ability to administer sustained drug levels via a minimally invasive periocular injection, suggest this product may also be applicable to the treatment of geographic atrophy and prevention of neovascularization. A 2-year study is currently being conducted by the National Eye Institute (NEI) evaluating quarterly treatment with Perceiva. In addition, a number of other NEI and investigator-sponsored trials are currently under way (Table 1).

The broad potential application of mTOR inhibition to ophthalmology is represented by the diversity in the phase 2 clinical program for sirolimus, not only in the posterior segment but also in the anterior segment. Its broad mechanism of action, combined with its safety, ease of administration, and potential as a combination agent, makes this a very promising drug for ophthalmology. In all, more than 500 patients will have participated in the phase 1 and 2 programs for this product. The three phase 2 DME and wet AMD trials described above are fully enrolled and will complete key efficacy time points this year. The presentation of results from these studies is planned for scientific meetings in 2010. The depth and variety of data from these diverse trials should provide us with a better understanding of the role that sirolimus and mTOR inhibition may play in the management of retinal diseases. ■

Pravin U. Dugel, MD, is Managing Partner of Retinal Consultants of Arizona and Founding Member of the Spectra Eye Institute in Sun City, AZ. He is a Retina Today Editorial Board member. Dr. Dugel reports that he is a consultant to Macusight. He can be reached at pdugel@gmail.com.



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