Orally Administered Rapamycin Can Inhibit Myointimal Hyperplasia: Should It Be Used?

Samuel E. Wilson, MD, Irvine, CA; Dmitri Gelfand, MD, Irvine, CA; Ian L. Gordon, MD, PhD, Irvine, CA

In a search of soil samples from Easter Island for microorganisms with antimicrobial properties, researchers discovered that Streptomyces hygroscopicus produced a potent antifungal agent, Rapamycin. This macrolide class antibiotic was effective against Candida albicans, but somewhat unexpectedly was found to have immunosuppressive activity on T-cell mediated autoimmune events.[1] In fact, Rapamycin proved to be up to 100 times more potent than cyclosporine, leading to its approval in 1999 for use in renal transplant recipients.[2] Cardiovascular physicians became interested in a particular activity of Rapamycin, which inhibits growth mediated proliferation of such cells as bovine aortic and human umbilical vein endothelial cells, fibroblasts, and smooth muscle cells.[1] Specifically, Rapamycin was shown to inhibit vascular smooth muscle proliferation and migration, key processes in neointimal hyperplasia. Initial experiments showed that oral administration of Rapamycin reduced the intimal thickening caused by balloon catheter induced carotid arterial injury in rats,[3] and oral Rapamycin was also found to reduce in-stent neointimal hyperplasia in a porcine coronary model.[4]

Thus, it seemed reasonable to add an antiproliferative drug such as Rapamycin to arterial wall stents in order to take advantage of a high local concentration through diffusion of the agent with the resultant systemic levels too low to cause adverse reactions. The elution of the agent could be slowed by applying a base coat of polymer and active drug to the in-stent and then a top coat which would serve as diffusion barrier.[5] Both rapid drug release, obtained with just the base coat, consisting of a polymer and drug, and slow drug release stents have been investigated clinically. Early studies conducted in São Paulo showed minimal neointimal hyperplasia in coronary stents4 months after placement for either slow release or fast release applications.[6] In a larger coronary artery in-stent study with 2-year follow-up, the end point was restenosis of greater than 50% of the luminal diameter.[7] This multicenter study conducted primarily in European hospitals showed that after 6 months, the degree of neointimal proliferation was significantly lower in the Rapamycin in-stent group compared with that in the standard in-stent. Just over a _quarter of the patients in the standard in-stent group developed restenosis of greater than 50% of the luminal diameter, but there was no significant restenosis in the Rapamycin in-stent group. Sousa and colleagues concluded that patients with angina who received Rapamycin eluting in-stents had no angiographic evidence of late luminal loss or in-stent restenosis at 6 months.[7] In another clinical study, target lesion revascularization was reduced in diabetic patients from 22.3% with bare metal in-stents to 6.9% with Rapamycin eluting in-stents at 270 days ($p < .001$).[8]

The major advantages of local delivery of an immunosuppressive agent is that the serum levels will be much lower than those experienced by patients undergoing higher doses for transplantation and therefore toxic effects would be expected to be decreased. Further tissue concentrations immediately adjacent to the in-stent may be higher than those obtained by systemic administration. On the other hand, the specific pharmacokinetic data on appropriate tissue concentration and the rate and duration of drug release over time is uncertain. Tissue concentration will be highest in those cells in close contact with the metal in-stent but concentration of the agent will drop off at a variable rate as diffusion weakens some distance from the in-stent. Pharmacokinetic data was collected by Klugherz and colleagues after Rapamycin eluting in-stents had been placed in rabbit iliac arteries to investigate the effect on local inflammation and vascular reendothelialization.[9] In addition, these investigators employed a porcine coronary in-stent model to study the pharmacokinetics of local and systemic Rapamycin levels. Neointimal area was decreased in a dose dependent relationship by Rapamycin eluting in-stents; however, there was no difference in local tissue inflammation and presence of thrombus between drug eluting and control in-stents. Three days after implantation 53% of Rapamycin was released from the in-stent with approximately 32% remaining on the in-stent at 28 days. Tissue levels of Rapamycin increased to the fourteenth day and thereafter declined. The peak serum level of Rapamycin obtained in this study of 0.9 ng/mL was considerably lower than the systemic levels obtained in renal transplant rejection which may range between 8 and 17 ng/mL. Since intimal hyperplasia manifests increased vascular smooth muscle cell and macrophage proliferation up to 14 days after the initial vascular injury, at least in the rabbit model, it would appear that there would be sufficient drug available for diffusion into the tissue during the critical formation period of neointimal hyperplasia.

In antimicrobial therapy, systemic administration of an antibiotic, with few exceptions has been found to be more effective than local therapy. With systemic therapy the drug penetrates various tissues, yielding a known concentration, and the distribution is uniform. The penumbra effect created by the falling off of tissue levels as diffusion extends farther from the in-stent would be avoided. Assuming that Rapamycin is effective by local tissue delivery, we and others have reasoned that systemic administration would achieve at least the same effect. Arterial wall levels could be controlled according to the oral dose, tissue levels obtained prior to in-stent deployment (much as is done in perioperative antibiotics), and toxicity would be minimized by a relatively short, < 30-day, interval of treatment.

Laboratory data supported this approach. Farb and colleagues had found that oral everolimus, started 3 days before in-stenting and continued for 28 days, reduced in in-stent restenosis in rabbit iliac arteries by 46 and 42% depending on dosing.[10] We also studied the effect of oral Rapamycin on myointimal hyperplasia after rabbit aortic balloon injury.[11] Low-dose or high-dose Rapamycin was started 1 week before injury and continued for 3 weeks. The aortic intima/media area ratio was significantly reduced versus controls at 3 weeks and 6 weeks. However, the inhibition was similar whether the therapy was continued for 3 or 6 weeks indicating that exposure to the drug early, prior to the injury response is more important than prolonged treatment. Similarly, the antiproliferative effect of Rapamycin was demonstrated after oral dosing in the pig vascular injury model showing reduction of 59% in the maximal thickness in the intima when compared with control animals.4 In another study, short term systemic administration of Rapamycin was found to prevent neointimal hyperplasia in balloon injury of the aorta in rats after a 5-day course of Rapamycin was given intravenously.[12] These authors concluded that short term systemic Rapamycin was effective but that suppression of early cell migration and proliferation was pivotal. They postulated that a limited peri-interventional antiproliferative therapy may be of value as an adjunct to inhibiting stenosis after balloon angioplasty and in-stenting.

Two earlier clinical studies with oral Rapamycin were conducted in a nonrandomized fashion with somewhat disappointing results. Brara and colleagues found no clinical benefit in 22 patients at high risk for restenosis, and in 11 patients oral Rapamycin was discontinued early because of side effects or laboratory abnormalities.[13] Unfortunately Rapamycin was not begun until as long as 12 hours after the percutaneous intervention in Brara's study. In Rodriguez and colleagues' registry, the trend toward a lower restenosis was observed in de novo lesions particularly in patients with the higher Rapamycin blood levels.[14] Again treatment was not started until after the intervention.

The OSIRIS study provided a more optimistic outcome using a 10-day treatment course.[15] Three hundred symptomatic patients with in-stent restenosis were randomly assigned to a placebo or a usual or high-dose Rapamycin. A loading dose of Rapamycin was given 2 days before the repeat intervention and was followed by maintenance therapy for 7 days. Angiographic restenosis at 6 months was the primary end point of the study. Restenosis was significantly reduced from 42% in the placebo group to 22.1% in the higher-dose Rapamycin group. Revascularization of the target vessel was reduced from 25.5% in the placebo group to 15.2% in the high dose group. The Rapamycin blood concentration on the day of the intervention correlated indirectly and significantly with the late lumen loss at follow-up. In this clinical trial, short-term administration of Rapamycin over 10 days, 2 of which were for a loading dose before the intervention, resulted in significant reduction of angiographic restenosis after treatment of in-stent restenosis.

Restenosis after superficial femoral artery in-stenting may be the most appropriate lesion for study of short course of systemic Rapamycin given orally with a loading dose 2 days prior to intervention. In clinical study, restenosis of the SFA can be safely and accurately measured by noninvasive tests such as duplex or CTA over a much longer follow-up period. Should oral Rapamycin prove effective at this site, a major cost savings would be achieved in the management of patients with claudication.

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