In this issue of Circulation, 2 studies report a positive outcome in patients who received oral pharmacotherapy for the prevention of restenosis after stent placement. In the randomized, double-blind, placebo-controlled Cilostazol for Restenosis Trial (CREST) trial, patients were given cilostazol, a phosphodiesterase 3 inhibitor with antithrombotic and antiproliferative properties, for 6 months starting immediately after implantation of a bare-metal stent in a de novo target lesion. Minimal lumen diameter, the primary end point of this study, which comprised 705 patients, was larger among patients treated with cilostazol than among those who received placebo. Other angiographic but not clinical outcomes were also more favorable among patients assigned to the active treatment arm.

The second study investigated the effect of a 6-month treatment with the thiazolidinedione pioglitazone on neointima formation measured by intravascular ultrasound 6 months after bare-metal stent implantation for de novo coronary artery lesions. In this small study, which comprised a total of 50 nondiabetic patients, neointima formation was significantly reduced among patients treated with pioglitazone compared with those who received placebo. Similarly, angiographic and clinical measures of restenosis were better among patients assigned to pioglitazone treatment. Although potential beneficial effects of thiazolidinedione regarding the prevention of neointima formation include antiinflammatory and antiproliferative effects, the exact mechanism by which pioglitazone led to a reduction of neointima formation among patients included in this study remains elusive.

The findings of these studies add to the existing evidence on the use of systemic pharmacological approaches to prevent restenosis. For most of these approaches, initial positive results in animal models of vascular injury and/or small pilot studies have been followed by disappointing results in large clinical trials. Basically, efforts aiming at the pharmacological prevention of restenosis should be considered in the light of drug efficacy, appropriateness of drug regimen, and method of administration.

Selection of Drug

Systemic treatments have targeted different mechanisms that have been identified as potential players in the development of restenosis, and their list includes antiplatelet and anticoagulant drugs, statins, calcium channel blockers, ACE inhibitors, vitamins, and antiproliferative drugs. Because platelets and thrombi were attributed a primary role in the cascade of events leading to neointimal proliferation, initial efforts to reduce restenosis after PCI focused on the use of antiplatelet and anticoagulant agents. Although antiplatelet and anticoagulant therapies were associated with improved outcomes, their use did not reduce neointimal hyperplasia and restenosis rates. Later efforts, which involved the use of statins and calcium channel blockers reported to possess antiinflammatory and antiproliferative properties, yielded similarly negative results. With regard to oral ACE inhibition, there have been conflicting reports spanning the range from a beneficial effect (as determined by intravascular ultrasound–based neointima assessment) to no effect or even evidence of an aggravation of restenosis. Likewise, conflicting results have been reported regarding the efficacy of vitamin therapy to decrease neointimal growth after PCI. One example for an antiproliferative drug that has been tested extensively is tranilast. This agent proved effective for the limitation of restenosis in different animal models, and a beneficial effect was suggested even from a clinical trial. However, the large Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial revealed no effect of oral treatment with tranilast for the prevention of restenosis in humans. Although several explanations have been provided for the lack of efficacy with the above-mentioned systemic treatment approaches in reducing restenosis, targeting the right mechanism with the most effective drug is a precondition for positive results. In this regard, in the double-blind, randomized, placebo-controlled Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial, Hausleiter et al recently showed that short-term treatment with sirolimus, an antiproliferative drug with antiinflammatory properties, effectively reduces restenosis. Importantly, even when it is used locally with drug-eluting stents (DESs), sirolimus appears to be the most effective drug to prevent restenosis after PCI.

Selection of Drug Regimen

In the OSIRIS trial, only patients receiving a high loading dose of sirolimus before stenting had improved outcomes with regard to angiographic and clinical restenosis. Furthermore, blood level of sirolimus at the day of intervention was significantly correlated with late luminal loss at follow-up; this correlation was less pronounced in the following days. These findings highlight the importance of providing a...
sufficient amount of the effective drug in the early days after stent implantation, when most critical events leading to neointimal formation take place. This is further supported by the fact that after pretreatment with the high loading dose, only a 10-day course with sirolimus was necessary to improve angiographic and clinical outcomes in OSIRIS trial, thus obviating the need for long-term oral therapy. Thus, in addition to drug efficacy, there are other relevant parameters, including timing of initiation of therapy, dosage of the drug, and duration of treatment, that determine the therapeutic success.

Systemic or Local Therapy for Prevention of Restenosis?

The crucial question is, how do systemic approaches for the prevention of in-stent restenosis compare in several respects to DES? A reliable measure of the efficacy of antirestenotic therapy is the assessment of late in-stent lumen loss after 6 to 9 months, which corresponds to the degree of neointima formation. As depicted in the Figure, the antirestenotic effect of commercially available DESs is reproducibly more profound than with oral treatment regimens. Intriguingly, even short-term local treatment with rapamycin by a novel polymer-free DES platform results in better outcome than systemic oral treatment with the identical compound, keeping in mind that both studies were performed on different lesion entities. Another important aspect is the safety of local versus systemic therapy. Local therapy provides the opportunity to deliver the antirestenotic drug exactly where it is needed and to use the smallest effective dose required to achieve sufficient drug concentration at the vessel wall to prevent neointima formation. In the OSIRIS trial, a slight increase in the number of infections was recorded, which might be attributed to the immunosuppressive properties of rapamycin. On the other hand, stent thrombosis is regarded as the most important safety concern for DESs, especially when patients are no longer receiving antithrombotic therapy, even at late time points; however, no prospective randomized DES trial thus far has reported a reproducible increased incidence of stent thrombosis.

The issue of local versus systemic antirestenotic therapy is pertinent not only to medical but also to economical aspects. A recent analysis has shown that DESs are cost-effective compared with bare-metal stents, at least in the context of the US healthcare system. Furthermore, it is expected that the upcoming availability of new DESs will decrease their price. Whether a 6-month treatment with cilostazol or pioglitazone is cost-effective remains to be determined.

In the end, is there a potential role for systemic antirestenotic therapy today? Given the superior performance of current DES platforms, there is no evidence that systemic approaches alone have a bright future for the prevention of restenosis, provided that no concerns exist about the long-term safety and performance of DES. However, a synergistic inhibitory effect on restenosis may become apparent, especially in high-risk patients, when both therapeutic strategies (local and systemic) are combined, aiming at different mechanisms of neointima formation. This hypothesis must be confirmed by randomized trials. Furthermore, systemic therapy has proved to be effective in another important proliferative vascular disease, cardiac allograft vasculopathy. In contrast to restenosis, which is a focal disease and well-suited for stent-based therapies, cardiac allograft vasculopathy is a more diffuse disease and, therefore, well-suited for a systemic therapeutic approach. Although the search for identification and optimization of suitable compounds for systemic antiproliferative vascular pharmacotherapy may continue, the “gold standard” for prevention of restenosis has already been set by DESs. From the current perspective and based on the experience of more than 2 decades of intensive research on restenosis therapy, it appears unlikely that the performance of the DES will be challenged by systemic therapy within the foreseeable future.

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References


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