Viral-Derived Serp-1 as an Adjunctive Therapy for Percutaneous Coronary Intervention
Another Not Ready for Prime Time Player?

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The story of Serp-1 began in 1859 when Thomas Austin imported 24 European rabbits to Australia and released them into the wild for sport. Within 30 years, the rabbits had multiplied exponentially until the population reached into the millions and they had decimated the landscape. Nearly a century later, when other methods of population control had failed, the Australians acquired the myxoma virus from South America and introduced it into the rabbit population. This species-specific virus, which is harmless to humans, infected the rabbits and decreased their numbers by \( \approx 99.9\% \). The key to the success of the myxoma virus in eradicating the rabbit population was its ability to downregulate the rabbit host’s immune and inflammatory responses to infection, in part, by synthesizing and secreting Serp-1.\(^2,3\) Years later, it was recognized that the same properties that made Serp-1 devastating for the rabbits could also have therapeutic benefits in human inflammatory disorders. Consequently, viral-derived Serp-1 was purified for experimental testing and, ultimately, clinical use.

Serine protease inhibitors, also known as serpins, comprise up to 10% of plasma proteins and act as regulators of coagulation cascades, fibrinolysis, complement activation, and inflammation.\(^4\) Serp-1 is a myxoma virus–derived serpin that regulates endogenous thrombolyis by binding to and inhibiting urokinase- and tissue-type plasminogen activators and plasmin.\(^2,3,5,6\) Serp-1 decreases inflammation indirectly by preventing activation of the urokinase-plasminogen activator receptor. This, in turn, inhibits inflammatory cell migration, adhesion to the endothelium, matrix metalloproteinase–mediated invasion of the vessel wall, and proliferation at sites of injury.\(^3,5,6\) Serp-1 also limits inflammation directly by decreasing monocyte and T-lymphocyte expression of \( \beta \)-integrins, which are necessary for cell-cell and cell–extracellular matrix contact, as well as increasing fibrin expression to prevent cell adhesion and migration.\(^7\) Serp-1 can also influence thrombosis by binding to and inactivating Factor Xa and thrombin (at 10-fold higher molar concentrations) and inhibits thrombin-induced platelet activation in ex vivo studies.\(^5,6,8\) Thus, Serp-1, through its anti-inflammatory and antiplatelet actions, is an attractive therapeutic agent for use as an adjunct to percutaneous coronary intervention (PCI).

Observations from preclinical studies provide compelling evidence that Serp-1 can modulate inflammation and neointimal formation in vivo in atherosclerotic vascular injury models. For example, after balloon angioplasty injury, either infusion or bolus injection of Serp-1 was shown to reduce early macrophage and T-lymphocyte infiltration into the vessel wall. This was associated with a significant reduction in neointima formation at 30 days, even though the half-life of the protein was reported to be \(<24\) hours and it was given at low concentrations (picogram to nanogram).\(^5,9,10\) These findings were reproduced in other experimental models of inflammatory vascular disease, including transplant vasculopathy.\(^9,11\) Interestingly, subsequent studies of “chronic vascular injury,” either through repeated balloon dilatation or bare metal stent implantation, revealed that several consecutive daily doses of Serp-1 were required to achieve a significant decrease in plaque or neointima formation at the site of injury.\(^5\) In these later studies, Serp-1 administration was reported to have no effect on established atherosclerosis at other sites in the vasculature.\(^5\) Taken together, these studies indicated that Serp-1 should have its greatest therapeutic benefit when given early after vascular injury and would act by reducing early inflammation to decrease neointima formation.

In this issue of Circulation: Cardiovascular Interventions, Tardif et al\(^12\) report the results of a double-blind phase II trial of Serp-1 as an adjunctive therapy to PCI in patients with acute coronary syndromes. This trial represents a first-in-man and first-in-class study of the purified viral-derived protein Serp-1. Although the study did not include the originally specified high-dose arm (50 \( \mu \)g/kg), owing to slow enrollment, the reported results are intriguing nonetheless. The highest dose of Serp-1 tested (15 \( \mu \)g/kg), when administered as an intravenous bolus at daily intervals for 3 days, decreased post-PCI biomarkers of myocardial necrosis without increasing adverse events. Despite this finding, there was no observed difference between the Serp-1 and placebo groups with respect to systemic inflammatory or coagulation markers, neointimal volume assessed by intravascular ultrasound, or clinical outcomes at 6 months. Thus, in this early limited experience, Serp-1 appears safe at the doses tested; however, questions regarding the efficacy of Serp-1 remain unresolved.
The finding that Serp-1 decreased post-PCI biomarkers of myocardial necrosis in a dose-dependent manner must be interpreted with some caution because all of the patients enrolled in the study had elevated biomarker levels before receiving the first dose of Serp-1. Although it has been well documented that limiting the rise in post-PCI biomarkers of myocardial necrosis is important, even in patients with preprocedure biomarker elevations, this study was underpowered to detect the effect of this finding on outcomes. It is also unknown if Serp-1 decreased the post-PCI rise in biomarkers by stabilizing the culprit lesion, decreasing myocardial inflammation and necrosis associated with activated plaque embolization, preventing inflammation related to the PCI procedure, or a combination thereof. Serp-1 has been shown to stabilize vulnerable plaques in animal models by preventing early macrophage infiltration, resulting in increased vascular smooth muscle cell and collagen content. Given that there was an 8-hour time interval between the initial dose of Serp-1 and the first observed difference in biomarker levels between groups, each of the proposed mechanisms remains plausible. This also raises the question as to whether or not Serp-1 would be beneficial in patients with acute coronary syndromes when used upstream of PCI or if Serp-1 would have limited use in patients with chronic stable angina, in whom the presence of an active or inflamed atherosclerotic plaque is less likely. Finally, it should be noted that patients randomly assigned to Serp-1 (15 μg/kg) had lower baseline troponin I levels than patients in the placebo or Serp-1 (5 μg/kg) treatment groups at study entry, suggesting that the magnitude of the observed benefit attributed to Serp-1 may not be as great as indicated.

The fact that Serp-1 had no effect on any of the systemic markers of inflammation measured in this study is not surprising. In this study, all patients enrolled were treated with statins and clopidogrel, both of which have purported anti-inflammatory effects. Furthermore, in preclinical studies, Serp-1 had no effect on systemic markers of inflammation yet decreased monocyte and macrophage infiltration at sites of acute mechanical vascular injury. Therefore, it may only be possible to detect local changes in inflammation, and measuring translesional or transcardiac gradients of inflammatory markers or superparamagnetic nanoparticle-enhanced, high-resolution MRI methods may be required to detect biologically meaningful differences in inflammation that could be attributed to Serp-1.

Interestingly, Serp-1 had no effect on neointimal volume assessed by intravascular ultrasound at 6 months. It is likely that patients were treated with drug-eluting stents, which are known to induce a delayed vascular inflammatory response. Pathological examination has shown that some drug-eluting stents induce granulomatous changes with peristrut infiltration of macrophages, lymphocytes, multinucleated giant cells, and eosinophils, whereas others elicit more of a fibrinous response with increased vascular smooth muscle cell death. Given this stent-induced inflammatory response, it also would be of interest to know if Serp-1 is able to modify the local inflammatory environment. Because we do not know for certain if Serp-1 had any post-PCI vascular anti-inflammatory effects, we can only speculate as to whether or not this negative result is due to an inadequate Serp-1 dosing, duration of treatment, or length of follow-up.

It should also be noted that Serp-1, as a viral-derived agent, stimulates an antibody response that may have importance for long-term or repeated use. These circulating antibodies could either neutralize function or influence pharmacokinetics. Here, the authors did not detect neutralizing antibodies to Serp-1; however, 4 of 36 (11%) patients did have antibodies to Serp-1 at titers of 1/8 to 1/256 that were detected only during late follow-up. The net effect of this antibody response on Serp-1 half-life or the ability to readminister Serp-1 to patients remains unknown.

As interventionists, we are often early adopters and quick to trial new therapies that will decrease periprocedural adverse events and improve clinical outcomes. Serp-1 clearly falls within this purview. It is easy to see the appeal of developing Serp-1 as a therapeutic, especially given its novel mechanism of action and its ability to target inflammation specifically. Although the present study provides us with some preliminary safety information, we can only speculate about the true efficacy of Serp-1 and if it will ever occupy a position in our lineup of adjunctive therapies used to treat patients undergoing PCI. This can only be determined in future clinical studies that are designed rationally to remove any ambiguity about the Serp-1 mechanism of action and efficacy in patients undergoing PCI. We look forward to the results from these more definitive studies to determine if Serp-1 will make the leap to prime time.

Sources of Funding
This work was supported by National Institutes of Health/National Heart, Lung, and Blood Institute grants HL105301 and HL700819.

Disclosures
None.

References


KEY WORDS: Editorials • acute coronary syndrome • stent • Serp-1 • serpins
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Circ Cardiovasc Interv. 2010;3:528-530
doi: 10.1161/CIRCINTERVENTIONS.110.959684
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/3/6/528

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