Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent

A report by Virmani et al. described a localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent in a 58-year-old man who died 18 months after stent implantation.

The authors discussed a localized hypersensitivity vasculitis in response to the Cypher stents, resulting in an acute myocardial infarction, secondary to late in-stent thrombosis at 18 months. The hypersensitivity reaction was thought to be either due to the metallic stent, the polymer, or the sirolimus coating. The exact mechanism, however, remained unclear, and it was postulated that polymers, like those used for coating of the metallic stent, may have been responsible for the hypersensitivity vasculitis. In October 2003, the US Food and Drug administration notified physicians of a possible generalized hypersensitivity reaction in 50 patients from >290 reports of subacute stent thrombosis. Sixty patients of those 290 reports died as a result of subacute stent thrombosis.

Although the authors postulate a hypersensitivity reaction to the polymer, we have previously observed in a rat model enhanced thrombus formation in synthetic vascular grafts treated by systemic or local administration of rapamycin. Thrombus formation was largest in animals that received high-dose oral rapamycin (3.0 mg/kg), or the same dose of rapamycin intraperitoneally, when compared with the control group, or animals treated with mycophenolate mofetil (Cell Cept).

Thus, our data suggest that rapamycin is effective for prevention of intimal proliferation but enhances thrombus formation. This observation would support the hypothesis of Virmani et al. that rapamycin, rather than the polymer coating, induces the hypersensitivity reaction.

Despite the reports of subacute and late stent thrombosis in several clinical studies, there is no direct evidence to date supporting sirolimus-eluting stents as more thrombogenic than bare metal stents. Although the FDA alert reports 250 cases of acute and subacute thrombosis (50 were fatal), the rate of subacute thrombosis remains within the expected rate for any stent.

Late in-stent thrombosis attributed to a secondary drug effect in our patient is unlikely because pharmacokinetic studies of Cypher stents in normal arteries show the drug is undetectable in the arterial wall by 60 days. Although release kinetics may be prolonged in human atherosclerotic coronary plaques (perhaps 6 months to 1 year), our patient developed thrombosis 18 months after receiving overlapping stent implants. Notably, the thrombosis occurred in a highly inflamed arterial wall with intense eosinophilia, sparse smooth muscle cells, and lack of endothelial coverage. Other cases of subacute thrombosis with Cypher stents examined by our laboratory have been ascribed to the discontinuation of antiplatelet therapy (clopidogrel or ticlopidine) or the stent was deployed at an arterial branch using the crush technique. It is important to emphasize that stent polymers are not benign and in some cases may induce hypersensitivity reactions. Similar suspected polymer reactions were observed in isolated cases involving rabbits with iliac artery Cypher or Taxus 90-day implants (R. Virmani, unpublished data, 2004).

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Response

We thank Drs Walpoth and Hess for the suggestion that rapamycin may be directly responsible for thrombus formation in our report describing a hypersensitivity reaction in CYPHER stents 18 months after implant.

In an earlier study, these authors reported findings of subacute thrombosis in synthetic vascular grafts implanted end-to-end in the infrarenal aorta of rats; animals were treated with high-dose rapamycin (3.0 mg/kg) systemically or locally soaked on the graft. No evidence of hypersensitivity was noted. Although this study suggests the potential for high-dose rapamycin to induce thrombosis, it is questionable whether the experimental graft model is adequate to explain the pathogenesis of in-stent thrombosis associated with sirolimus-eluting stents.
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