Prednisone: the last gasp of immunosuppressive therapy for restenosis prevention

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Online publish-ahead-of-print 9 April 2013

This editorial refers to ‘Long-term clinical follow-up of the multicentre, randomized study to test immunosuppressive therapy with oral prednisone for the prevention of restenosis after percutaneous coronary interventions. Cortisone plus BMS or DES versus BMS alone to Eliminate Restenosis (CEREA-DES)’, by F. Ribichini et al., on page 1740

Once restenosis was recognized as a major limitation of percutaneous coronary intervention (PCI), investigations probed the mechanisms and developed therapeutic antirestenosis strategies to combat this phenomenon. Early on in the efforts to understand the mechanisms responsible for restenosis, two primary processes were identified following mechanical injury by the balloon angioplasty to the vessel wall: recoil of the vessel and neointima formation. The balloon injury triggered a healing response characterized by intravascular inflammation and smooth muscle cell (SMC) proliferation. Thus, within hours following vascular wall injury, inflammatory cells appeared at the site of injury.†‡ These cells secrete an array of factors, including cytokines, growth factors, and reactive oxygen species,†‡ that in turn contribute to the stimulation of SMC migration and proliferation.†‡ Restenosis occurs in those in whom this healing response is excessive or is not appropriately turned off, results probably mediated in part by genetic and/or epigenetic determinants.†§

Therapeutic strategies derived from this mechanistic paradigm led to the testing of a large array of approaches for restenosis inhibition (Figure 1). The approach that gained the most traction and near-uniform utilization was the deployment of metallic stents. This approach completely eliminated early recoil and late vascular remodelling, but exacerbated the inflammatory responses to the injury and to the foreign body (the implant). These inflammatory responses were reported to be associated with an allergic reaction leading to neointima formation (sometimes exuberant) within the stent struts, known as in-stent restenosis.10

The concept of stent-based local delivery of antiproliferative drugs, known as drug-eluting stents (DES), was proposed as an ideal solution. Such stents are embedded with—and gradually elute—antiproliferative agents, which dramatically reduce restenosis rates post-stenting. DES then became one of the major breakthroughs in percutaneous coronary intervention (PCI). DES were universally adopted in one formulation or another, and recognized as the panacea to combat restenosis. Soon after their launch in clinical practice, DES were found to be associated with (at least) three important complications: stent thrombosis,11 in-stent restenosis,12 and (recently reported) late neoatherosclerosis;13 all of which significantly impact on patients’ long-term outcomes.

Stent thrombosis was the most serious complication that led to a particularly malignant outcome (i.e. patients with this complication do not usually present with new-onset or worsening angina, but rather with myocardial infarction or death). As a result, patients undergoing DES implantation were subject to the adoption of an aggressive and prolonged duration of dual antiplatelet therapy that successfully attenuated the incidence of stent thrombosis, but was associated with continued bleeding hazard.14 For the treatment of in-stent restenosis, the most effective modalities proved to be vascular brachytherapy15 and drug-coated balloons.16 Currently, there is no available therapy to prevent the development of neoatherosclerosis; lower rates are reported with bare metal stents (BMS). Finally, DES are relatively expensive and are considered a cost burden to the healthcare systems of many countries.

Such concerns, inherent in current stenting systems, and in particular with DES, motivated investigators to develop an alternative approach to combat the neointimal proliferation/restenosis problem. Scientists re-evaluated what could be considered ‘outmoded’ strategies to inhibit the development of restenosis (i.e. delivery of the therapeutic agent systemically as an adjunct to BMS or balloon angioplasty alone). However, systemic pharmacotherapy carried the potential of serious side effects theoretically averted by local drug delivery to the PCI site. Among the systemic strategies using immunosuppressive drugs are oral rapamycin,17,18 i.v. systemic paclitaxel via nanoparticles,20 and oral prednisone.21 Studies testing systemic immunosuppressive therapy described a...
relatively short course of high-dose drugs from days to weeks and reported modest efficacy when compared with BMS, but inferiority with respect to the robust efficacy of DES. These studies were small in size, most of them were uncontrolled, and they were not free from side effects related to the drug. Most patients, however, were able to complete the short course of the systemic immunosuppressive therapy.17–21

Systemic immunosuppressive therapy was rarely used in clinical practice. With respect to the oral prednisone strategy, steroids were identified as an attractive treatment for restenosis and were tested both locally on a stent and systemically. The molecular activities of steroids that could potentially influence restenosis processes are diverse, and a detailed account of these activities is beyond the scope of this Editorial. However, given that steroids exert potent effects on immune and inflammatory pathways, inhibit secretion of cytokines influencing SMC proliferation, inhibit extracellular matrix deposition and remodelling, and are antiallergens, there was good reason to hypothesize that steroids might inhibit restenosis.22,23 Further support came from preclinical studies that demonstrated that administration of steroids was shown to inhibit injury-induced neointimal proliferation when administered systemically at high doses for several weeks.24

In 2011, Ribichini et al. expanded on this and initiated an investigator-sponsored trial,25 and should be commended for their efforts to investigate the potential of oral prednisone for restenosis prevention. They administered high doses of prednisone, starting within 48 h of PCI and continued for 40 days in a non-diabetic, non-hypertensive patient cohort. The original trial25 measured outcome at 1 year and demonstrated that patients in whom a BMS (alone) was deployed had significantly worse outcomes than did those with a BMS plus prednisone. Importantly, the latter arm had an identical outcome to those in whom a first-generation DES was deployed.

Ribichini et al. have now reported the long-term (4-year) results of the original study.26 They found that the 1-year results persisted; patients in whom a BMS alone was deployed had significantly lower event-free survival (75.3%) compared with 84.1% in the prednisone/BMS group [hazard ratio (HR) 0.45; \( P = 0.007 \)] and with 80.6% in patients in whom a DES was deployed (HR 0.52; \( P = 0.03 \)). The need for target vessel revascularization remained lower in the prednisone/BMS and DES groups (13.6% and 15.2%, respectively), compared with the BMS group (23.2%); however, many patients were lost to follow-up at 4 years. Of note, the investigators found no evidence of serious adverse effects in the prolonged administration of high-dose steroids.

This can be explained by the broad exclusion criteria necessitated by the side effect profile of prednisone, and the potential for serious complications. Further, the study is underpowered to rule out this possibility definitively. The study is also underpowered to detect differences with regard to major clinical events seen among the treatment strategies. The angiographic late loss published in patients treated with oral prednisone published by the authors is inferior to the late loss reported with DES. This suggests that if the study is sufficiently powered, a potentially lower event rate could be seen in the DES arm vs. the oral prednisone arm, especially when applied to more complex patient and lesion subsets. Finally, the comparator group in this study was first-generation DES, which are reported to be inferior to second-generation DES currently used in clinical practice.

These limitations question the applicability of the oral prednisone strategy in today’s clinical practice and question the overall role of systemic immunosuppressive therapy for restenosis.
Conflict of interest: none declared.

References


