EDITORIAL
DOI 10.4070/kcj.2011.41.5.233

Print ISSN 1738-5520 / On-line ISSN 1738-5555

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Evolving Coronary Stents Coated With New Bioactive Agents

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α-lipoic acid (ALA) functions as a cofactor in the multi-enzyme complexes that catalyze the oxidative decarboxylation of a-keto acids such as pyruvate, c-ketoglutarate, and branched chain a-ketoacids. ALA, converted to dihydrolipoic acid (DHLA) in many tissues, was tentatively classified as a vitamin. ALA also has the components of the redox couple that effectively quenches a number of free radicals in both lipid and aqueous domains. It also acts synergistically with other antioxidants. So it has the specific advantages to aid in the recovery from an ischemia-reperfusion injury. After it is proven that ALA inhibition of platelet aggregation is mediated by PPARα/γ-dependent processes, which involve interaction with PKCα and COX-1, increase of cyclic AMP formation, and inhibition of intracellular Ca(2+), ALA has gained more attention.[1)]

The author suggested in a previous study that ALA feeding and ALA-coated stents inhibit neointimal hyperplasia in porcine ISR, possibly through inhibiting the activation of the NF-κb pathway and proliferation of PVSMC. So it is a promising agent for protecting neoatherosclerosis after drug-eluting stent (DES) stenting.[2)]

But several recently-published studies failed to demonstrate that ALA-coated stents actually reduced neointimal hyperplasia. It will be a problematic issue to deal with DES restenosis and obtain new optimal target macromolecules. Nevertheless, it was suggested that ALA increased p38 mitogen-activated protein kinase phosphorylation, and inhibition of p38 mitogen-activated protein kinase completely blocked ALA-induced vascular smooth muscle cell apoptosis, Nur77 induction, and cytoplasmic localization. In balloon-injured rat carotid arteries, ALA enhanced Nur77 expression and increased TUNEL-positive apoptotic cells in the neointima, leading to inhibition of neointimal hyperplasia.[3)]

Existing antioxidative agents have various drawbacks, including instability in water, lack of efficacy in clinical I/R conditions, and/or toxicity to healthy cells. DHL-HisZn is a new synthetic a-lipoic acid derivative that contains ALA, histidine, and zinc. It is soluble and stable in aqueous solutions. DHL-HisZn has anti-oxidative properties and exerts a strong protective effect against renal I/R injury. Thus, it is believed that DHL-HisZn has potential as an antioxidant for therapeutic applications.[4)]

Authors previously reported that an abciximab-coated stent was effective in the prevention of in-stent neointimal hyperplasia, and there was no acute or subacute stent thrombosis even in patients with acute myocardial infarctions and unstable angina. Possible explanation was that abciximab blocked platelet aggregation and reacts to CD11b/CD18 of vascular endothelial cells and macrophages, and inhibits inflammatory reactions and proliferation of vascular smooth muscle cells.[5)6)]

To obtain platforms able to surmount some issues associated with available devices and widen their fields of application, the current generation of DES has continuously evolved. By varying a polymer matrix, current stents have a tunable release rate in the first month of delivery. DES covered with anti-proliferative or anti-inflammatory drugs have actually made a significant difference in lowering restenosis rates from 30% to 5%. Nowadays, most agents loaded onto stents such as sirolimus, paclitaxel, or everolimus are relatively well established in terms of release kinetics with respect to the particular delivery system. However, in the development of new DESs, the main responsibility of delivery rates is a covered drug dissolution rate when eluted in a polymeric ma-

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• The author has no financial conflicts of interest.

trix. The delivery rate of therapeutics is thus a quite variable but very important field. So, studies about emerging approaches to improve potential therapeutic DES applications to the incorporation of bio-compatible anti-proliferative and anti-inflammatory agents other than widely-used low-molecular-weight lipophilic compounds were performed. Those agents are able to attain the desired anti-proliferative, biocompatible effect. Among all the candidates of molecules nowadays under consideration, anti-oxidatives and anti-inflammatories could play a crucial role. However, development of new combinations of therapeutic agents is required, implying that their use has been limited to few studies due to difficulties in having an efficacious duration and human trials. For the production of completely innovative DES, DES should be engineered to provide a fine tuning of delivery rate which is critical to drive full benefit and lesser traumatic on tissue compatibility. A full tuning of drug loading and release kinetics are much more challenging, not only characterized by unique pharmacological properties but also by specific delivery requirements in order to be successful. Therefore, the introduction of new delivery systems and favorable bioactive agents into the basic platform of the stent must be now taking place in clinical practices.

In all the current DES, the release of the drugs dispersed within the polymeric matrices is uniformly controlled by a diffusion mechanism. Especially for devices working in direct contact with biological fluids, such as blood in the case of the stent, the release kinetics of hydrophilic agents homogeneously dispersed in polymeric coating are expected to be too fast for achieving a prolonged therapeutic effect.[7]

In this study,[8] drug coatings in stents are done stepwise to get a strong binding between drug and stent polymer. However, all these activities to overcome the current DES limitation such as stent thrombosis and delayed endothelialization are still investigated more extensively in terms of the release of small lipophilic molecules. These works are at the initial stage of characterization, which can determine the further reduction of therapeutic windows from months to a few days or even hours. One of the big problems of DES-implanted patients was a complication of late stent thrombosis, which was completely associated with stent polymers. One of the postulated mechanisms of late stent thrombosis was hypersensitivity for polymers and inflammatory reactions. In this study, a dual-coating stent could prevent lymphohistiocyte infiltration despite failing to reduce the neointima area in a dual-coated stent compared with BMS. That means that it causes a lesser degree of inflammatory reactions in a dual-coating stent. As shown in Fig. 1,[8] dual-coated agents were almost completely released within two weeks. So the beneficial effects of early pharmacokinetics need to be elucidated further.

It is true that a lot of data and research to overcome the limitations of current DES stents has been introduced. Many investigators are scrambling to find the best solution. Therefore, we do ardently hope for the new therapeutic options and path-breaking technology about evolving the current state of DES.

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