Journal of Controlled Release 159 (2012) 1

Contents lists available at SciVerse ScienceDirect

Journal of Controlled Release

journal homepage: www.elsevier.com/locate/jconrel

Cover Story

Dual drug-eluting stent

A drug-eluting stent (DES) is a coronary stent that releases a drug for about a month to control proliferation of vascular smooth muscle cells (VSMC). Like a bare metal stent (BMS), DES of course provides mechanical support to a vessel after angioplasty. Because a DES provides controlled release of compounds that interfere with restenosis, it was regarded, since its introduction in 2003, as the solution to the problems associated with using a BMS. We only wish that was the case. Restenosis is an adverse re-narrowing of a stented artery characterized by neointimal hyperplasia that is driven by proliferation of VSMC. Stent-based delivery of anti-mitogenic drugs inhibiting VSMC proliferation has been effective, but they were shown to act non-selectively. Proliferation of endothelial cells is also inhibited, and this can lead to delayed vascular healing after stenting angioplasty, which contributes to an increased risk of late in-stent thrombosis [1]. In fact, a recent review suggests that delayed re-endothelialization around stent struts is the "single best predictor" of late stent-thrombosis [2]. Currently, there is a need for stent-based therapies that can both attenuate neointimal hyperplasia and promote endothelial healing.

Resveratrol (R) and quercetin (Q) are two polyphenols found abundantly in grapes and implicated in the vascular benefits associated with red wine consumption. (Cheers!) These two compounds have been shown to elicit many physiological effects in the vasculature, including attenuation of VSMC proliferation, oxidation, platelet activation, and inflammation [3,4]. Importantly, oral administration of R has been previously shown to promote re-endothelialization in a rat model of arterial angioplasty [5]. Additionally, Sanchez and colleagues have demonstrated that oral administration of Q protects against angiotensin II-induced endothelial dysfunction, suggesting that Q may attenuate dysfunction after arterial injury [6]. Due to poor oral bioavailability of these polyphenols, however, a more efficient way of delivery is necessary. A DES platform is favorable for treating restenosis because of the ability of localized drug delivery directly to the site of injury. Due to the reported anti-restenotic effect of R and Q, as well as literature reports demonstrating their positive influence on endothelial function, Professor Dugas and her colleagues hypothesized that the local delivery of these compounds from a stent platform could inhibit neointimal hyperplasia while promoting re-endothelialization, at least in a rat model of stenting angioplasty [7]. A stent that releases multiple cardioprotective polyphenols is attractive due to the potential for affecting different mechanisms associated with restenosis. The ability to affect multiple pathways may increase efficacy while decreasing the dose required, reducing side effects and providing a more selective therapy. Additionally, a combination approach takes advantage of their ability to synergistically inhibit VSMC proliferation and inflammatory cell activation [8].

These polyphenols were incorporated into an arborescent poly(styrene-b-isobutylene-b-styrene) tri-block polymer, which is similar to the polymer used in the Taxus™ DES. The polyphenols were loaded at a low-dose (RQ1) or high-dose (RQ2) combination, and the coatings were applied to miniature stainless steel stents using an electronanospray process. The stents were deployed into rat common carotid arteries and the arterial response to stenting was evaluated at 10 and 28 days. Professor Dugas and her team found that a polymeric coating providing controlled release of R and Q can attenuate in-stent stenosis in a dose-dependent manner (lower-left and lower-right panels of the cover figure), with the high-dose combination (RQ2) increasing re-endothelialization by 50% compared with BMS. Furthermore, this dual drug-eluting stent attenuated persistent inflammation in the stented arterial wall, which is known to be driver of restenosis and may be integral to the observed protective effects. While further studies are needed to evaluate the efficacy of a stent releasing R and Q in a large-animal model (e.g., porcine coronary arteries), these results suggests that an R- and Q-eluting stent may serve as an attractive approach to promote vessel healing, potentially reducing the risk of late thrombosis associated with drug-eluting stents.

There is little doubt that delivery of multiple drugs from a DES is a key for successful treatment of restenosis and late thrombosis. But more advances need to be made for dual DES to be clinically useful. The current dual DES delivers two drugs simultaneously, but the most benefit of dual DES may come from controlling the drug release kinetics. Ideally, a drug for preventing VSMC proliferation is released first for the first few weeks, and then the second drug promoting re-endothelialization is released after a month or so. This sequential release from a thin layer in the range of 5–30 μm on a stent is very difficult to achieve. As the controlled drug delivery technology keeps evolving, however, we are cautiously optimistic to achieve such sequential release in the near future.

References

[1] C. Stettler, S. Wandel, S. Allemann, A. Kastrati, M.C. Morice, A. Schomig, M.E. Pfisterer, G.W. Stone, M.B. Leon, J.S. de Lezo, J.J. Goy, S.J. Park, M. Sabate, M.J. Suttorp, H. Kelbaek, C. Spaulding, M. Menichelli, P. Vermeersch, M.T. Dirksen, P. Cervinka, A.S. Petronio, A.J. Nordmann, P. Diem, B. Meier, M. Zwahlen, S. Reichenbach, S. Trelle, S. Windecker, P. Juni, Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis, Lancet 370 (2007) 937–948.
[2] M. Vorpahl, S.K. Yazdani, M. Nakano, E. Ladich, F.D. Kolodgie, A.V. Finn, R. Virmani, Pathobiology of stent thrombosis after drug-eluting stent implantation, Curr. Pharm. Des. 16 (2010) 4064–4071.
[3] R. Vidavalur, H. Otani, P.K. Singal, N. Maulik, Significance of wine and resveratrol in cardiovascular disease: French paradox revisited, Exp. Clin. Cardiol. 11 (2006) 217–225.
[4] L. Fremont, Biological effects of resveratrol, Life Sci. 66 (2000) 663–673.
[5] G. J, W. Cq, F. Hh, D. Hy, X. Xl, X. Ym, W. By, H. Dj, Effects of resveratrol on endothelial progenitor cells and their contributions to reendothelialization in intima-injured rats, J. Cardiovasc. Pharmacol. 47 (2006) 711–721.
[6] M. Sanchez, F. Lodi, R. Vera, I.C. Villar, A. Cogolludo, R. Jimenez, L. Moreno, M. Romero, J. Tamargo, F. Perez-Vizcaino, J. Duarte, Quercetin and isorhamnetin prevent endothelial dysfunction, superoxide production, and overexpression of p47phox induced by angiotensin II in rat aorta, J. Nutr. 137 (2007) 910–915.
[7] J.J. Kleinedler, J.D. Foley, E.A. Orchard, T.R. Dugas, Novel nanocomposite stent coating releasing resveratrol and quercetin reduces neointimal hyperplasia and promotes re-endothelialization, J. Control. Release 159 (2012) 27–33.
[8] J.J. Kleinedler, J.D. Foley, J.S. Alexander, S.C. Roerig, V.Y. Hebert, T.R. Dugas, Synergistic effect of resveratrol and quercetin released from drug-eluting polymer coatings for endovascular devices, J. Biomed. Mater. Res. B Appl. Biomater. 99 (2011) 266–275.

Kinam Park
Purdue University
Departments of Biomedical Engineering and Pharmaceutics
West Lafayette, IN, USA
E-mail address: kpark@purdue.edu

0168-3659/$ – see front matter
doi:10.1016/j.jconrel.2012.03.019