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Review

Drug-eluting biostable and erodible stents

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ABSTRACT

This paper reviews the latest research and development of drug-eluting stents. The emphasis is on coronary stenting, and both biostable and bioerodible stents are covered in this review. The advantages and shortcomings of the bioactive molecules used in these stents are analyzed, along with the rationale for using bioerodible coatings. The overall emphasis is on the performance of these stents in the clinic. Based on the evaluation of the different stent types, we conclude that fully-erodible stents with a coating of antiproliferative drug will slowly gain market share in the near future, and that the search for a more selective anti-proliferative compound will continue. Dual-drug eluting stents (DDESs) will have their market share but possibly a much smaller one than that for single-drug eluting stents due to the complexities and costs of DDES unless significantly superior performance is demonstrated in the clinic.

Contents

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1. Introduction

In 2009, we published a review in Journal of Controlled Release [1] that surveyed the clinical success of drug-eluting stents, and some of the issues associated with controlled delivery of bioactive agents from such stents. At that point of time, the drug-eluting stents in the clinic or in the marketplace were all biostable and eluted a single drug, predominantly an anti-proliferative. This review updates their status in clinical practice, and also surveys the inroads made by fully degradable and dual-drug eluting stents.

2. Biostable drug eluting stents (BDESs)

The current family of drug-eluting stents can be classified into:

(a) Limus-type elution from biostable coating
(b) Non-limus drug elution from biostable coating
(c) Limus-type elution from biodegradable coating
(d) Anti-proliferative in combination with another drug (dual-drug eluting stent).

The first generation of DES includes the sirolimus-eluting stent (Cypher®) and the paclitaxel-eluting stent (Taxus®) and demonstrated impressive reductions in restenosis. But their long-term use has been marred by the incidence of late stent thrombosis due to incomplete healing, especially after discontinuation of dual antiplatelet therapy [1]. In addition, the use of paclitaxel for this indication has been more or less discontinued due to fears of cardiotoxicity. The second generation of DES using limus derivatives such as the zotarolimus-eluting stent (Endeavor®) and everolimus-eluting stent (Xience V®) has been introduced with promising anti-restonotic efficacy as well as long-term safety. They differ from the first generation stents with respect to the antiproliferative agent, the polymer layer and the stent frame. In view of the differences in clinical success of the different drug types, it is instructive to examine the mode of action of these drugs briefly.

2.1. Mechanism of action of drugs

Several immunosuppressive and antiproliferative molecules, such as dexamethasone, actinomycin D, cytochalasin D, 17-beta-estradiol, mycophenolic acid, and angiopeptin, have been tested during the last decade for their effect on inhibiting the pathway of neointimal hyperplasia, but the drugs that have been demonstrated to have superior performance in a consistent and reproducible fashion both in preclinical and clinical trials are the “Limus” family compounds and paclitaxel.

2.1.1. Limus family

Six limus family compounds are currently being used in DES: these compounds target either the mammalian target of rapamycin (mTOR) (sirolimus, everolimus, zotarolimus and biolimus A9) or calcineurin (tacrolimus and pimecrolimus).

The mTOR inhibitors (sirolimus, everolimus, zotarolimus and biolimus A9) share an almost identical lipophilic chemical structure and bind to their major cytosolic FK-506 binding protein-12 (FKBP12) forming a complex which subsequently inhibits the mTOR. The major cellular effects include a decrease of the positive (blockage of the p70S6 kinase pathway of the cyclin-dependent kinases) and an increase of the negative (through inhibitor p27 kip1) regulators of the cell cycle [2]; they stop the cell cycle at the G0/G1 phase inhibiting both cell (mainly smooth muscle cells) proliferation and migration, so the mechanism of action is cytostatic rather than cytotoxic.

Tacrolimus and pimecrolimus are not analogs of the archetypal rapamycin; after they bind intracellularly to FKBP12, the complex in turn binds to and blocks calcineurin, and in this way inhibits the T-cell transduction pathways and the synthesis of pro-inflammatory cytokines [3]. *In vitro* cell work indicates that tacrolimus allows earlier endothelial regeneration than sirolimus; however, inhibitory activity on human vascular smooth muscle cells with tacrolimus is much less than sirolimus [4].

2.1.2. Paclitaxel

Paclitaxel is a lipophilic molecule with potent antiproliferative and antimigratory activity. The drug is a microtubule-stabilizing agent which enhances formation of microtubular polymerized structures and thus, decreases the concentration of tubulin required for new microtubule formation. Paclitaxel impacts primarily the M phase of the cell cycle inhibiting growth factor-induced DNA synthesis and cell proliferation, and leads to apoptosis or cell death. Compared with the limus family, the mode of action of paclitaxel is primarily cytotoxic (Fig. 1).

2.2. Drug release kinetics

2.2.1. Zotarolimus-eluting stent (ZES)

Zotarolimus is the first ever drug synthesized exclusively for treatment of in-stent restenosis. Zotarolimus is produced by the tetrazole ring substitution of the hydroxyl group at the C_{40} position of sirolimus, as shown in Fig. 2.

The presence of a tetrazole ring instead of a hydroxyl group makes zotarolimus extremely lipophilic. This hydrophobicity restricts the solubilization of zotarolimus in the luminal blood flow, leading to an immense decline in the systemic exposure risk; negligible concentrations of the anti-proliferative agent in the systemic circulation may also be conducive to stent re-endothelialization. Similar to sirolimus, the biologic effects of zotarolimus are mediated by the intracellular receptor FK506-binding protein 12, blocking progression from G1 to S in the cell cycle.

To date, three ZESs were evaluated in human clinical trials: Endeavor ZES (Medtronic CardioVascular Inc., Santa Rosa, CA), ZoMaxx ZES (Abbott Vascular, Santa Clara, CA), and Resolute ZES (Medtronic CardioVascular Inc., Santa Rosa, CA). All three have the same zotarolimus loading of 10 μg/mm^2, but with different metallic platforms and polymeric coatings, exhibit different release profiles.

The Endeavor ZES [7,8] combines zotarolimus with a phosphorylcholine (PC) coating, and a cobalt–chromium alloy stent as base. Unlike other durable or biodegradable polymer, PC coating mimics the cell membrane of red blood cells in the plasma, thereby avoiding hypersensitivity and inflammatory reactions. However, because of the structure of the PC and with no other top layer to control drug release, approximately 95% of total zotarolimus is released within 15 days.

The Resolute ZES [9,10] is the second generation ZES developed by Medtronic. It uses a newly developed biodurable polymer — BioLinx™ (hydrophobic component C10: 60/40 (by weight) mixture of n-butyl methacrylate (BMA) and vinyl acetate (VA); hydrophilic