

A Review of the Major Drug-Eluting Stents in Treating Coronary Artery Disease

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Abstract

Coronary artery disease is a leading cause of morbidity and mortality in western countries; the cost of open-heart surgery is prohibitive. Thus, there is a call for the development of less expensive and less invasive revascularization procedures. Percutaneous coronary revascularization relies on angiography and balloon angioplasty to compress occlusive plaques and restore coronary artery circulation. However, neointimal hyperplasia can result in bare-metal stent thrombosis and in-stent restenosis. Drug-eluting stents have been developed to provide optimal local tissue therapeutics to decrease the adverse events of bare-metal stent thrombosis and in-stent restenosis. Such stents can also be used as a treatment modality in other (non-coronary) vessels. Various drugs are employed in the utilization of specific stents. This paper summarizes these drug-eluting stents and the mechanisms of the associated drugs action in inhibiting stent-related adverse events.

Keywords: Coronary Artery Disease; Drug-Eluting; Neointimal Hyperplasia; Stent; Vitamin C

Abbreviation

CAD: Coronary Artery Disease; DES: Drug-Eluting Stent; ISR: In-Stent Restenosis; MAPK: Microtubule-Associated Protein Kinase; VEGF: Vascular Endothelial Growth Factor

Introduction

Coronary artery disease (CAD) due to atherosclerosis is one of the leading causes of morbidity and mortality in western countries. The associated costs and resources required for open-heart surgery have resulted in a push for the development of less expensive and less invasive revascularization procedures [1,2]. Percutaneous coronary revascularization is an endovascular procedure that uses angiography and balloon angioplasty to compress occlusive plaques against the vessel wall and restore blood flow in the coronary artery [3,4]. Further developments in the procedure have been accomplished, and bare-metal stents are being introduced at the lesion to provide expandable scaffolding within the vessel to maintain adequate blood flow and prevent restenosis of the vessel [3]. However, the incidence of bare metal stent thrombosis is at 2.0% and that in-stent restenosis (ISR) Ivanoff A, Kerna NA. occurred in 35–40% of cases, due to neointimal hyperplasia [5-7].

To decrease the incidence of ISR, thrombosis, and other stent-related adverse events and outcomes, drug-eluting stents (DESs) were developed to provide optimal local tissue therapeutics [7]. In particular, a DES should inhibit restenosis (antiproliferative/antineoplastic),

inhibit cellular migration (antimigration), and promote healing (enhanced endothelial healing factors) [7,8]. Although coronary artery stenosis caused by atherosclerosis is one indication for revascularization using stents, they have been used for a variety of indications and in many different vessels [9-11]. The following discussion describes the drugs used in DESs and their mechanisms of action.

Discussion

Antiproliferative drugs: Sirolimus, Everolimus, Zotarolimus, and Paclitaxel

Sirolimus (Rapamycin) was isolated from *Streptomyces hydropiscus*. It is a macrocyclic lactone and lipophilic; thus, during implantation, drug release into the bloodstream is limited [12]. At the site of implantation, sirolimus has a diffusion gradient that favors elution into tissues, not the blood [12]. Sirolimus is an immunosuppressive drug. When cultured with rat and human vascular smooth muscle cells, sirolimus was found to be a potent inhibitor of cellular proliferation, being a potential drug to prevent restenosis by blocking neointimal hyperplasia [13,14]. Sirolimus binds with the cytosolic FKBP-12 receptor inhibiting (mTOR phosphorylation ability) cell cycle regulators of proliferation, including cell-cycle kinases, cyclins, and pRb phosphorylation, leading to a lengthening of the cell cycle by introducing delays in the G1/S and G2/M transition points [14,15]. These delays are transient; sirolimus does not permanently block cell proliferation or halt protein synthesis [8,14].

Everolimus is a macrocyclic lactone that binds the FKBP-12 receptor and inhibits mTOR protein kinase and the expression of p70 S6 kinase, limiting the amount of ribosomal proteins required for smooth muscle proliferation through the G1/S cycle [8,16]. Everolimus is more lipophilic and polar than sirolimus; thus, slower release reduces the concentration at the DES implantation site and restricts release into the bloodstream, limiting systemic exposure risks and preventing restenosis [16].

Zotarolimus is similar to sirolimus and everolimus in its mechanism of action. It is highly lipophilic, which slows dissolution and prevents detectable amounts of the drug in the bloodstream, limiting systemic exposure risks [8,17]. However, it potentiates a higher risk of death and target lesion revascularization when compared to sirolimus-eluting stents [17].

Paclitaxel is another antiproliferative drug used in eluting stents. It is derived from the bark of the Pacific Yew, and has been used in the treatment of ovarian, lung, and breast cancer [8]. Paclitaxel's antiproliferative mechanism of action is different from those of the limus family of drugs. Paclitaxel is highly lipophilic. It binds to microtubules and beta-tubulin causing tyrosine phosphorylation of microtubule-associated protein kinase (MAPK); thus, inhibiting microtubule depolymerization, stabilizing microtubules, and preventing the formation of spindle assembly: preventing metaphase, cell cycle transition into G1, and cellular proliferation [18-20].

These drugs have been studied in combination with each other and with other drugs in eluting stents. Each of these antiproliferative DESs has limitations. The rate of restenosis for each may vary; however, the development of drug-eluting stents has significantly reduced restenosis rates, efficacy, and long-term safety compared to bare metal stents [21]. Other antineoplastic and antiproliferative drugs that may have the potential for use in DESs include interferon, dexamethasone, cyclosporine, and tacrolimus [22]. The antineoplastic and antiproliferative effects of these drugs aid in preventing restenosis. However, cellular migration into the stents can result in restenosis; thus, specific drugs used in DESs have been designed to prevent such restenosis-inducing migration.

Antimigration drugs: Probucol, Carvedilol, Batimastat, and Atorvastatin

Probucol is a powerful antioxidant that, in rabbits, has been shown to inhibit the accumulation of macrophage foam cells in injured vessels post-operatively in rabbits [23]. It has been proposed that restenosis of vessels could be prevented by inhibiting macrophage foam cells and thus prevent the liberation of potent cytokines and growth factors at the lesion, which promotes hyperplasia [23]. Further studies have demonstrated that probucol mediates vascular remodeling after angioplasty by downregulating the ERK1/2 signaling pathway [24]. Probucol, when trialed in humans, was the first pharmaceutical shown to reduce coronary restenosis after balloon angioplasty, when

taken orally postoperatively [25]. Probucol (antimigration) in combination with antiproliferate drugs in eluting stents as dual therapy, demonstrates superior antirestenotic efficacy and noninferiority compared to first-generation DESs [26,27].

Carvedilol is a nonselective beta-adrenergic antagonist and antioxidant that inhibits smooth muscle proliferation and migration [28,29]. Small clinical studies have demonstrated that carvedilol inhibits neointimal hyperplasia without the occurrence of cardiac death, myocardial infarction, or stent thrombosis, at two post-procedure [29].

Batimastat is a metalloprotease inhibitor and a low-molecular weight peptide that inhibits the migration of smooth muscle cells in vessels by chelating the zinc atom in metalloprotease (which is needed for the smooth muscle cell migration) [30]. However, in a clinical trial using a batimastat-DES, it was determined to be ineffective in controlling coronary artery stenosis [31].

An atorvastatin-DES, when tested in animal models, showed no effect in inhibiting neointimal hyperplasia [32].

Enhanced healing factors: vascular endothelial growth factor (VEGF) and vitamin C

A VEGF-DES was theorized to provide the factors needed to accelerate re-endothelialization by providing local VEGF, thus preventing smooth muscle hyperplasia (restenosis) caused by endothelial damage [33]. However, the VEGF-DES, when studied in rabbit models, did not promote endothelialization or inhibit restenosis [33]. A recent study, using the porcine model, suggested that VEGF-coated stents become rapidly covered by tissue morphologically similar to native endothelium, through a mechanism of capturing endothelium progenitor cells at the site and accelerating tissue formation [34].

Vitamin C (L-ascorbic acid) promotes endothelial growth and inhibits smooth muscle growth in humans and cell cultures [35-38]. The mechanism of action in promoting endothelial growth involves collagen type IV synthesis of the basement membrane, essential for endothelial adhesion [37-39]. When applied in cell culture media with sirolimus and paclitaxel, L-ascorbic acid strongly encouraged endothelial cell growth and inhibited smooth muscle cell growth. However, its inhibitory effects are inferior to both sirolimus and paclitaxel [39]. L-ascorbic acid-DESs have been developed; elution studies have shown that L-ascorbic acid is released from the DES-matrix for up to 24 hours, indicating therapeutic application [40].

Conclusion

A common side effect of stent insertion is neointimal hyperplasia. Antiproliferative drugs inhibit neointimal hyperplasia and suppress restenosis. Some of these drugs have proved useful in a clinical setting; others have not. Specific antimigration drugs have demonstrated the ability to suppress smooth muscle migration into the stents. Other drugs promote rapid colonization of the stent matrix and endothelium-inhibiting restenosis by blocking migration and neointimal hyperplasia. The search for more efficacious drug-eluting stents is of utmost importance to the medical field and pharmaceutical industry.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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