Advanced Drug Delivery Reviews xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

IN.PACT™ Admiral™ drug-coated balloon: Durable, consistent and safe treatment for femoropopliteal peripheral artery disease☆

Susan Peterson *, Melissa Hasenbank, Claudio Silvestro, Shashank Raina

Medtronic Vascular, 3850 Brickway Blvd., Santa Rosa, CA 95403, USA

ARTICLE INFO

Article history:
Received 1 March 2016
Received in revised form 9 October 2016
Accepted 17 October 2016
Available online xxxx

Keywords:
Peripheral vascular disease
Peripheral stenosis
Percutaneous transluminal balloon angioplasty
Drug coating
Paclitaxel
Arterial lesion revascularization
Anti-proliferative drug

ABSTRACT

Endovascular management of peripheral artery disease was until recently limited to percutaneous balloon angioplasty, atherectomy, stent grafts, and bare-metal stents. These therapies have been valuable, but plagued by high restenosis and revascularization rates. Important progress has been made with the introduction of combination devices, including drug-eluting stents and drug-coated balloons (DCB), designed to combat restenosis by locally delivering *anti*-proliferative drugs. In particular, promising clinical performance has been seen with the Medtronic IN.PACT™ Admiral™ DCB, with durable, consistent and safe results. Rigorous, randomized controlled trials have directly compared this and other drug-delivering devices to their non-drug-coated counterparts with data available through two years. Additionally, trials are ongoing to assess use of drug-coated technologies in combination with traditional therapies in hope of synergistic effects. This review gathers data from currently published clinical trials with the IN.PACT Admiral DCB for the treatment of femoropopliteal peripheral artery disease and explores the possible impact on continuing clinical practice.

Contents

1. Introduction

Peripheral artery disease (PAD) remains one of the often unrecognized manifestations of systemic arteriosclerosis, symptomatically affecting 3% to 10% of the population and 15% to 20% of persons over 70 years of age [1–3]. PAD has a major detrimental impact on quality of life and is a marker of multisystem vascular disease [4,5]. Chronic atherosclerotic disease of the pelvic and lower limb arteries, leading to lower extremity ischemia, is associated with morbidity and mortality [6,7], with a prevalence of intermittent claudication of approximately 4.5% and an incidence of approximately 15.5 per 1000 person-years [8]. Some patients even progress to chronic limb ischemia (CLI). It has been shown that 40% to 50% of people failing peripheral revascularization with CLI will undergo amputation and 20% will die within 6 months [9].

Options for PAD treatment include lifestyle modification, medical therapy, supervised exercise, surgical revascularization, and, more recently, endovascular therapies to restore arterial perfusion to the limb. Endovascular revascularization has evolved over the past two decades, from percutaneous transluminal angioplasty (PTA) to therapies such

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Drug Device Combinations".

* Corresponding author.
E-mail address: susan.peterson@medtronic.com (S. Peterson).

http://dx.doi.org/10.1016/j.addr.2016.10.003
0169-409X/

as self-expanding stents, atherectomy, laser angioplasty, stent grafts, cutting balloons and drug-eluting stents. Catheter-based techniques are now established as the preferred means of revascularization for ischemic lower limbs, with lower morbidity and mortality rates and shorter hospital stays compared with surgical bypass [10–12]. While PTA is often regarded as the standard of care, restenosis rates of 40–50% by 12 months are reported [13–15].

To address the problem of elastic recoil encountered with balloon angioplasty, stents have been employed to maintain vessel lumen patency [16]. However, the presence of a foreign body apposing the vessel wall can initiate an immunologic cascade, stimulating the proliferation and migration of vascular smooth muscle cells to create neointimal hyperplasia, exacerbating in-stent restenosis (ISR). As a result, restenosis in the femoropopliteal arteries after stenting reaches up to 40% within the first 12 months of intervention [14,17].

Drug-eluting stents (DES) were developed to address the restenosis problems associated with bare metal stents (BMS). In DES, the metal stent structure releases a drug to inhibit cell proliferation and hence inhibit restenosis. The first DES, for coronary application, was launched in 2003 and many others followed over the ensuing years [18], with differences in the anti-restenotic drug used and the associated release characteristics (the quantity of drug released and how rapidly this release occurs) [19]. DES, however, carry additional drawbacks. The anti-proliferative effect that prevents migration of vascular smooth muscle cells and development of neointimal hyperplasia also interferes with re-endothelialization of the vessel lumen. Hence, the stent struts remain exposed to blood flow and can serve as a focus for thrombus formation, necessitating anticoagulant therapy [20]. Studies have also shown that the absorption of the anti-proliferative agent coated onto the stent can be limited to the sites of physical contact between the stent struts and vessel wall, leaving inter-strut areas of the vessel wall untreated [21–23].

Drug-coated balloon (DCB) development began in the late 1990s as many studied new technologies to influence the process of restenosis, without involving stent-based local drug delivery. DCB devices also required different drug characteristics than for DES. While -limus drugs are effective in DES applications where their susceptibility to oxidation can be countered by combination with antioxidant compounds and protection within a polymer matrix, allowing their inhibition of cell growth to continue for a prolonged period, they did not prove effective for DCB treatment. Paclitaxel was also known to be an effective anti-restenotic drug from DES applications, and became the drug of choice for DCB application due to its high stability which allows it to function alone without a durable implant over an extended period of time, and its long-term biologic effect, fully blocking cell division and triggering apoptosis. However, studies have emphasized the importance of hydrophilic component(s) on DCB technology to increase the transfer efficiency of paclitaxel [24]. Without a hydrophilic excipient, the drug may not be released at a sufficient rate to prevent neointimal proliferation [25–27] as the drug may bind to both itself and the balloon surface, thereby reducing its ability to release from the balloon and transfer to the vessel wall during the time the balloon is inflated. Experiments by Speck and Scheller [25] initially focused on the addition of anti-proliferative drugs to a small amount of the hydrophilic X-ray contrast medium iopromide (Ultravist) as excipient. Supported by similar investigations [28,29], promising outcomes were seen during early animal trials in 2002 [25]. Consequently, the Paccocath® ISR I/II randomized study was initiated in patients with coronary ISR at the end of 2003. Feasibility of paclitaxel-coated balloon catheters to inhibit restenosis following balloon angioplasty was further shown in animal models [25] and clinical trials[30,31], with the first-in-human data on DCB angioplasty of the leg from the Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) trial [32]. Subsequent DCB improvements have focused on limiting drug loss before reaching the treatment site, and maximizing drug transfer to the arterial wall, with many clinical trials performed to study in-vivo DCB efficacy for the treatment of occlusive lesions in the coronary and peripheral vasculature [33].

The THUNDER and FEMPAC trials, in particular, opened the way to randomized, multicenter evaluations of primary endpoints by a blinded core lab. These trials compared DCB and PTA with regards to efficacy and tolerance in inhibiting restenosis in the peripheral arteries, both including a two-year follow-up. Based on the results obtained through these initial trials, development of paclitaxel-coated balloon catheters further expanded [33], including development work by Invatec S.p.a., an Italian medical device company later acquired by Medtronic. Early adopters also included Aachen Resonance and the Cotavance catheter system (controlled by Bayer), both based in Germany, along with USA-based Lutonix (later acquired by Bard) and Cook Medical.

Main improvements associated with DCB technology compared to DES are a more homogenous distribution of the anti-proliferative compound and no need for a permanent implant. DCB devices are combination products: a standard PTA balloon catheter coated with the anti-restenotic drug paclitaxel ($C_{47}H_{51}NO_{14}$). Paclitaxel, a mitotic inhibitor, was first approved by the FDA in 1992 for the treatment of multiple cancers including breast and ovarian cancer. It is also the same drug substance used in the TAXUS™ family of DES for the treatment of stenotic coronary artery offered by Boston Scientific, and the Zilver® DES for the treatment of stenotic superficial femoral artery offered by Cook Medical. This drug is effective for local delivery due to its lipophilic properties, short absorption and prolonged duration of effect, stabilizing microtubules to reduce cell proliferation. The primary mode of action for drug-coated balloons is physical dilatation of the vessel lumen by PTA, while the drug coating is intended to secondarily reduce the proliferative response that is associated with restenosis. As the balloon is inflated and unwraps, the coating is fully exposed and presented to the vessel wall, where the combination of paclitaxel's hydrophobicity, lipophilic nature and the increased solubility conferred by the excipient allows for rapid diffusion into the vessel tissue (Fig. 1; detail shown for the IN.PACT™ Admiral™ DCB, which uses urea as an excipient). Once in contact with the vessel wall, the paclitaxel adheres to the vessel; due to its solid-state form, only a fraction of the drug is immediately bioavailable, with the remainder serving as a depot to control neointimal proliferation over time. Randomized controlled clinical trials of balloons coated with different formulations of paclitaxel have demonstrated more durable efficacy and safety than PTA [34–36].

Currently, more than ten DCB devices have received CE Mark approval for peripheral vascular treatment (Table 1). Among these, the IN.PACT Admiral (Medtronic Vascular; Galway, Ireland) and Lutonix™ (Bard; Tempe, USA) DCB devices are also approved and available in the United States for treatment of femoropopliteal artery lesions. This article focuses mainly on the IN.PACT Admiral DCB which has demonstrated strong results in clinical testing. Specifically, statistically superior safety and effectiveness compared to PTA was seen through two years, with positive 12-month outcomes also reported in real-world patients with long lesions, chronic total occlusions, and in-stent restenosis lesions [36–44]. Favorable comparison of results from IN.PACT Admiral have been seen across other available therapies as well (Fig. 2; model derived using pooled target lesion revascularization (TLR) rates from cited references, following the meta-analysis methodologies described by Pietzsch et al., 2014 [45]).

2. Device overview

The development of the IN.PACT Admiral DCB focused on incorporating a drug coating onto an established and commercially available transluminal angioplasty balloon catheter technology to improve the clinical outcome from peripheral interventions by reducing the restenosis rate in the superficial femoral artery (SFA) patient population. The IN.PACT Admiral catheter body is based on the uncoated Admiral Xtreme PTA balloon catheter, with the addition of a proprietary FreePac™ coating. This coating consists of paclitaxel as the active pharmaceutical

Please cite this article as: S. Peterson, et al., IN.PACT™ Admiral™ drug-coated balloon: Durable, consistent and safe treatment for femoropopliteal peripheral artery diseas, Adv. Drug Deliv. Rev. (2016), http://dx.doi.org/10.1016/j.addr.2016.10.003