Review

Drug Eluting Resorbable Scaffolds Below the Knee – Leave the Right Thing Behind

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Abstract

The prevalence of peripheral artery disease (PAD) is increasing, and endovascular revascularization is arguably the preferred first line therapy. While percutaneous transluminal angioplasty (PTA) may be a cornerstone for interventional treatment of PAD compared to bare metal stents, they both have limitations regarding patency. Drug-eluting resorbable scaffolds (DRS) are an attractive alternative due to their improved patency.

Drug-eluting resorbable scaffolds have advantages over metal implants, particularly for management of PAD in critical limb ischemia. Currently, the evidence for their effectiveness is being securitized in randomized control trials. The results are highly anticipated with the potential to change the current treatment paradigm.

In this review, we examine the current state of bioresorbable technologies for peripheral arterial disease, particularly disease found below the knee.

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Introduction

The prevalence of peripheral artery disease (PAD) is increasing, driven by an aging population and increased incidence of diabetes and obesity.[2-4] Endovascular revascularization is arguably the preferred first line therapy for patients with PAD and critical limb ischemia (CLI), as it is minimally invasive, repeatable, and cost effective.[5-7] The cornerstone of interventional treatment for crural artery occlusive disease is percutaneous transluminal angioplasty (PTA). However, PTA has limitations due to its inability to manage elastic recoil, vessel wall calcification and dissection, factors which often lead to reduced rates of patency compared with other vascular territories. Even drug-coated balloons coated in anti-proliferative agents have failed to show a convincing patency benefit in crural arteries, suggesting that mechanical support is just as important as suppressing intimal hyperplasia.[1,8,9] In an effort to mechanically support, PTA stents have been investigated and results published in the literature.[10,11] While bare metal stents offer no patency advantage over PTA alone, coronary drug-eluting stents (DES) have improved patency in short, focal arterial lesions below-the-knee (BTK).[10,12-17] However, all permanent metallic stent implants have shortcomings. They eliminate options for future surgical anastomotic sites, may be prone to fracture, create artefact on cross-sectional imaging (CT and MRI), and may act as an impediment to future reintervention, both surgical and endovascular. Most recently, self-expanding, paclitaxel-coated stents have shown disappointing results, which reinforces the unmet need in this region and underscores the potential gap a bioresorbable scaffold might fill.[18]

Bioresorbable scaffolds. Drug-eluting, resorbable scaffolds (DRS) offer an attractive alternative concept for use in tibial arteries. They provide mechanical scaffolding, similar to metallic stents. They

are coated in an anti-proliferative drug which has been shown to improve patency when used on metallic stents.[12-16] They are then reabsorbed by the body in a gentle process which allows the blood vessel wall to remodel and, in some cases, restore its vasomotor function,[19] ultimately, leaving nothing behind to interfere with future cross-sectional imaging, surgery or reintervention.

The first report of the use of resorbable scaffolds in humans was published in 2000.[20] Drs Tamai and Igaki et al reported the use of 25 poly-L-lactic acid (PLLA) scaffolds in 15 patients. They observed both a 6-month binary restenosis rate and target lesion revascularization rate of 10.5% which was promising in the landscape of early coronary stenting at that time. That same stent was modified for use in the superficial femoral artery (SFA) where it was evaluated in the multicenter GAIA Study.[21] A single-arm cohort of 30 patients with a mean lesion length of 5.9 cm saw a binary restenosis rate of 67.9% and target lesion revascularization (TLR) rate of 57.1% at 12-months of follow-up. Neither the coronary nor femoral Igaki-Tamai scaffold had anti-proliferative drug on its surface. The ESPRIT trial was another to evaluate a poly-L-lactic acid polymer scaffold in the superficial femoral artery.

However, this scaffold was coated with the antiproliferative drug everolimus which has been effective at minimizing coronary artery in-stent restenosis.[22] This single-arm, multicenter study enrolled 35 patients with a mean lesion length of 3.6 cm. Their observed freedom from TLR rate at 36 months was an encouraging 88.1%, suggesting that the combination of PLLA scaffold and anti-proliferative drug had the potential to deliver stent-like results with several advantages inherent to their absorption properties.

Below-the-knee applications of DRS. The first resorbable scaffold to be used below the knee was the Absorbable Magnesium Scaffold (AMS, Biotronik).[23] Similar to the Igaki-Tamai scaffold, this metal scaffold had no anti-proliferative drug coating. Results of the 6-month analysis were published by Bosiers et al in 2009.[23] In a randomized controlled trial compared against PTA, 149 lesions were treated in 117 patients. A dismal primary patency of 31.8% was observed, which proved clear inferiority to PTA (59.0%; *P*=.013). This was an early indication that anti-proliferative drugs may be even more important in the arteries below-the-knee than in other vascular territories.

The Absorb (Abbott Vascular), coronary, drug-eluting resorbable scaffold (DRS) consists of a PLLA structure with a poly-D-lactic acid coating that contains everolimus which elutes with a similar profile to the Xience (Abbott Vascular) family of DES [24] **(Figure 1)**. Both PLLA and PDLLA are fully bioresorbable, and complete resorption of the scaffold occurs within approximately 3 years. The polymer degrades through bulk hydrolysis of ester bonds producing to lactic acid, which is ultimately metabolized into water and carbon dioxide through the Krebs cycle. PLLA degradation is a benign process that happens gradually with minimal inflammation.[25] The first-generation Absorb scaffold

FIGURE 1. The Absorb drug-eluting resorbable scaffold achieved excellent results in tibial artery occlusive disease. It was made of poly-L-lactic acid with an everolimus impregnated poly-D-lactic acid coating.

was first applied to crural arteries by Kum and Varcoe in 2012. Since then, there have been three centers to publish their observational data, individually, on polymer-based DRS[17,26-28] as well as a pooled analysis.[26-29] There is also a CE Mark device approved for use in arteries below the knee (Motiv Bioresorbable Scaffold, Reva Medical), which has begun an investigational device approval clinical trial in the US and Europe, as well as a large global multicenter RCT of the next generation Abbott Vascular scaffold that has completed enrollment (LIFE-BTK trial, NCT04227899).

The longest follow-up study was published in 2020 by our group at Sydney's Prince of Wales Hospital.[28] We enrolled 48 patients, treating 55 limbs (72.7% CLI) with 71 scaffolds, and followed them with duplex ultrasound for a mean of 35.2 months. Mean lesion length was 20.1 ± 10.8 mm with median percentage of stenosis at 80% and median target vessel diameter measuring 3.0 mm. Mild calcification grade for 43 patients, 9 and 3 for moderate and severe calcification respectively. Binary restenosis was detected in 11/71(15.5%) scaffolds. Primary patency and freedom from clinically driven TLR rates at 12, 24, 36, 48, and 60 months were 90.8%, 90.8%, 79.7%, 76.3%, 72.3% and 97.2%, 97.2%, 90.7%, 90.7%, and 90.7%, respectively. Demonstrating excellent efficacy in shorter lesions. An example of a case with long-term follow-up is given in **Figure 2**. Similarly, Kum et al demonstrated excellent results in a retrospective study of 41 CLI patients (53 lesions and 69 scaffolds) as part of the DISAPEAR registry. The mean

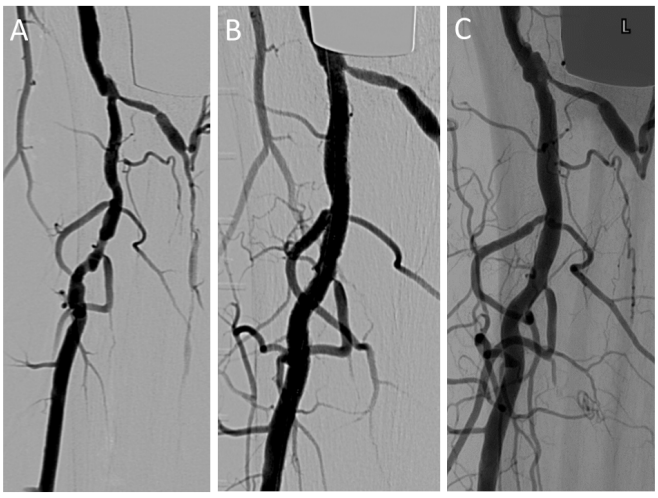

Figure 2. An angiographic image showing **(A)** a diffuse stenotic lesion of the tibio-peroneal trunk and peroneal arteries **(B)** treated with two abutting Absorb drug-eluting resorbable scaffolds. **(C)** A follow-up angiogram of the same patient 91 months after the procedure demonstrates smooth remodeling of the blood vessel wall with no evidence of restenosis.

lesion length was 22.7 ± 17.2 mm with 10 lesions being severely calcified. They found a 12-month primary patency rate of 86%, corresponding to a 93% freedom from CD-TLR rate.[27] The third single center also found that the Absorb DRS is efficacious in these short crural lesions.[26] Dia et al followed 31 patients after implantation of the Absorb BVS for 2 years in advanced peripheral arterial disease. They treated 41 lesions with 49 scaffolds, with 93.5% of patients free from clinically driven target vessel failure at 24 months. Primary patency was 96.7% at 12 months, and 87.1% at 24 months. All patients were alive over that entire 24-month period.[26] For this study, the mean lesion length was 30.9 ± 9.2mm, mean stenosis 94%, and 79.4% of lesions were classified as TASC C complexity or above. While there were some differences in lesion and patient characteristics between these 3 studies, results were notably consistent.

Further to those individual studies, a pooled analysis published results which examined the use of 189 scaffolds in 126 limbs of 121 patients.[29] Most had CLI (75%), 63% were calcified, and 22% were chronic total occlusions. Median lesion length was 21 mm with median vessel diameter being 3.1 mm. Freedom from restenosis was 91.7% and 86.6% at 12 and 24 months respectively, and freedom from CD-TLR was 97.2% and 96.6%. Major amputation occurred in 1.6% of the limbs. Overall survival was 85% at 24 months.

Following on from those single center studies, the LIFE-BTK study is a prospective, randomized, multicenter, controlled trial which completed enrollment in August 2022. It enrolled 261 patients and randomized them 2:1 to the Esprit DRS (Abbott Vascular) or PTA. The 6-month primary safety endpoint is freedom from major adverse limb events and perioperative death, and the efficacy endpoint is a composite of duplex ultrasound adjudicated primary patency, freedom from target vessel occlusion and CD-TLR, as well as limb salvage at 12-months. 5-year follow-up is planned with first data release expected in late 2023.

Another polymer DRS (Magnitude, R3 Vascular Inc.) is being evaluated in BTK arteries in a 30-patient, single-arm, multicenter, first-in-human study over 3 countries (Austria, Canada, Italy) in the RESOLV I Clinical trial (NCT04912323). This trial was commenced in August 2021 and recently completed. No results have yet been released.

In Europe, the CE-marked Motiv (REVA Medical) Tyrosine amino acid, radio-opaque scaffold is the only DRS available for commercial use in BTK arteries. It is being evaluated in the physician-initiated Motiv BVS BTK study (NCT03987061). This is a single-arm, 58 patient, multicenter, European (Austria and Germany) trial which began recruitment in September 2019 and completed in mid 2022.

While intravascular ultrasound and optical coherence tomography were not used routinely in the application of drug-eluting resorbable scaffolds in infrapopliteal arteries by any of the studies in this review, it is generally thought that those technologies have a role to play in ensuring accurate sizing and avoiding scaffold malapposition to the blood vessel wall.[30] Many experts recommend their use, particularly when there is uncertainty around scaffold sizing due to the narrow post dilatation window properties of PLLA.

Conclusion

Drug-eluting resorbable scaffolds are a promising treatment choice for occlusive PAD with disease in the tibial arteries in patients with critical limb ischemia. They have several inherent advantages over metal implants related to their resorption properties which leave the blood vessel wall free of impediment to regain physiological function and maintain options for future intervention. Currently, evidence of their effectiveness has been derived from single arm studies. However, definitive randomized trials are currently underway with highly anticipated results imminent. This is an exciting space to observe as it has the potential to disrupt the treatment paradigm in this challenging vascular territory.

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