Standards by Example: Preclinical Safety of Bioresorbable Vascular Scaffolds (BVS) Based on the Abbott Vascular Experience

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Statement of Purpose: Drug eluting stents (DES) are the current standard for the interventional treatment of clinically evident occlusive coronary artery disease (CAD). However, the efficacy of DES is counterbalanced by drawbacks such as delayed vascular healing and device permanence when a transient remedy would suffice. Bioresorbable Vascular Scaffolds (BVS) are the next advancement in interventional technologies for CAD, providing appropriately targeted, transient treatment for the temporary problems of acute arterial recoil and restenosis. The inherent transience of BVS imparts unique aspects in regards to their performance yet special considerations relative to their safety assessment in preclinical models. Using Abbott Vascular's BVS (AV BVS) as a case example, the preclinical safety evaluation of bioresorbable scaffolds is discussed and contrasted with that of DES.

Methods: AV BVS is a scaffold composed of a PLLA backbone coated with PDLLA that elutes everolimus (100 $\mu g/cm^2$; D:P 1:1) at a rate comparable to XIENCE V™. A comprehensive preclinical safety program was conducted for this device, which included evaluation in non-atherosclerotic porcine coronary arteries (PCAs) from 1 to 48 months. Domestic farm swine (1month) and Yucatan mini-swine (≥ 3 months) were implanted with one or two BVS and a metallic DES in the main coronary arteries using 10% to 20% overstretch. Animals were evaluated at 1, 3, 6, 9, 12, 18, 24, 36, and 48 months angiographically and histologically (n = 8 to 16 BVS per time point). Supplemental to this, *in vivo* degradation in PCAs (n = 3 to 6 scaffolds per time point) was evaluated by gel permeation chromatography (GPC) to coordinate degradation with device performance (Onuma, 2010).

Results: At 1 and 3 months, the AV BVS performs comparable to a metallic stent by providing (1) luminal scaffolding to prevent acute recoil and (2) pharmacological suppression of neointimal proliferation that occurs in response to arterial injury incurred during implantation. Comparable to a DES, the latter effect is evidenced histologically by the presence of fibrin, which is largely resolved by 3 months. This is effectively the 'revascularization' phase of BVS, during which time there is negligible resorption of the polymer. Following revascularization (6 to 12 months), the AV BVS gradually assumes passivity as there is decline in strength, which is dually based on molecular weight loss and the acquisition of structural discontinuities observed histologically. This effectively is the phase of 'restoration.' While the composition of the arterial wall is qualitatively comparable to a DES during the restoration phase, coordinated loss of BVS's functional resistance to arterial forces evidenced histologically and with GPC) indicate that there are qualitative differences in function, as BVS accommodates to allow for the return of arterial vasomotion. The final phase is that of 'resorption' where by the AV BVS has the most rapid mass loss until PLA is below limits of quantification (24 months) to no longer detectable (36 months) by GPC. Most important during this phase was the biocompatibility, which for the AV BVS was demonstrated in PCAs by the minimal presence of leukocytes. Orchestrated with the resorption of the AV BVS, there is gradual connective tissue integration into the pre-existing strut foci and subsequent tissue remodeling, where by 48 months, minimal to no histological evidence remains of the pre-existing scaffold.

Conclusions: Using the AV BVS as a case example, there are several aspects to consider in preclinical safety evaluation applicable to all polymeric BVS. First, coronary arteries have a limited repertoire of responses (e.g. thrombosis, proliferation, fibrin, necrosis, inflammation); therefore, the standard histological indicators of safety for DES similarly apply for BVS (Schwartz, 2008). Second, BVS are triphasic in their functional lifespan, these phases being revascularization, restoration, and resorption. While these are shared by all BVS and are unique from the static nature of DES, the duration of these phases are degradation dependent and are thus specific to individual BVS. A comprehensive safety assessment should focus at minimum on each these three phases to ensure compatible responses throughout the device's lifespan. With this, biocompatibility is a critical assessment during all three functional phases but especially during polymer degradation. The impact the device has on the artery during its lifespan will accordingly weigh on how the artery ultimately responds and remodels. Finally, in contrast to DES, the acquired passivity of BVS necessitates a revisit to the modalities and means by which these disparate devices are assessed preclinically. Two aspects weigh into this: the visibility of polymeric devices angiographically and the post mortem dimensional artifacts induced by handling, formalin fixation, and histological sectioning. Metallic stents are readily visible angiographically and do not succumb as readily to post mortem dimensional artifacts, thus conventional preclinical programs for DES have relied heavily on angiographic and histomorphometrical assessments. Conversely, polymeric BVS are not easily visible angiographically and are readily yet variably susceptible to post mortem dimensional artifacts, the degree being dependent on the functional phase in the life of the device. Thus, alternate *in vivo* imaging (e.g. Optical Coherence Tomography, OCT) and histomorphological evaluation should be the dominating features in preclinical programs for a BVS.

References:

Onuma Y, et al. Circulation. 2010;122:1912-1924.
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