Design Principles of Bioresorbable Polymeric Scaffolds

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KEYWORDS

• Bioresorbable vascular scaffold • Restoration • Vasomotion • Structural integrity

KEY POINTS

- Bioresorbable vascular scaffolds follow 3 performance phases: revascularization, restoration, and resorption.
- In the revascularization phase, the performance requirements are the same for bioresorbable vascular scaffolds and drug-eluting stents.
- A bioresorbable vascular scaffold is designed to disappear over time; the restoration phase is designated by the scaffold's loss of its structural integrity to allow for gradual return of vessel functions.
- In the resorption phase, the implant is resorbed in a benign fashion, leaving behind a patent and restored vessel.

INTRODUCTION

Frequently referred to in the literature as the fourth generation of percutaneous coronary intervention (PCI), bioresorbable vascular scaffolds (BRS) are promoted as having many potential advantages relative to traditional metallic drug-eluting stents (DES). By leaving nothing behind, these include the opportunity to restore the vessel to a healthy state, capable of natural vascular function; reduce complications associated with future reinterventions and surgeries; and improve patient quality of life.

The concept for a BRS combines the best features of the first 3 generations of PCI into a single device: safe and effective revascularization (balloon angioplasty, bare metal stents, DES), suppression of restenosis (DES), prevention of constrictive remodeling (bare metal stents, DES), and long-term restoration of the treated vessel to a more natural state (balloon angioplasty). The landscape of BRS has broadened considerably since the first device to be approved, Abbott Vascular's Absorb BVS, received CE Mark approval in 2011. Several companies have introduced BRS in clinical trials around the world, encompassing new materials and targeting alternative performance goals around duration of vascular support and resorption time.

In addition to the aliphatic polyester polylactide (PLA), first used in the Igaki-Tamai device and later by Abbott Vascular in its Absorb scaffold and in different forms by many others (Amaranth, Boston Scientific, Elixir, Meril, Terumo, Xinsorb, to name a few[1,2]), several other materials are being explored for use as BRS. These include bioresorbable metals such as magnesium (Biotronik) and iron (Lifetech) and other polymeric materials such as iodinated desaminotyrosine polycarbonate (Reva).[1,2] All materials considered for such devices must be hemocompatible and biocompatible. For simplicity, the illustrative examples contained herein focus on the BRS, Absorb BVS, for which the most data

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are available (see Table 2 in this article, Bioresorbable Scaffolds: Clinical Outcomes and Considerations by Capodanno D, in this issue).

The principles of operation of a BRS follow 3 phases of functionality, which reflect the different physiologic requirements over time, namely, revascularization, restoration, and resorption.[3,4] Most BRS designs make use of the continuum of hydrolytic degradation in aliphatic polyesters such as poly(L-lactide) (PLLA), in which molecular weight, strength, and mass decrease progressively in 3 distinct stages,[5] and the time scale of each process is adjusted to serve the *in vivo* need. These 3 phases, illustrated conceptually in Fig. 1, are discussed in more detail in later sections.

The challenge with BRS is to provide adequate vessel support for a minimum duration while also undergoing degradation and structural dismantling in a benign fashion and retaining vessel patency. It is this tradeoff that is of current debate as more companies explore options for BRS from both a design and material perspective.

Mechanisms for Polymeric Degradation

Given that most BRS currently available or under development are based on PLA, this material will be used as an illustration of the generalized degradation process for polymeric devices. In the initial stage, water infiltrates the polymer backbone until the material is fully saturated, which, in the case of semicrystalline PLLA, may only be about 0.5 wt%.[6] Chain scission via hydrolysis follows the hydration phase, with the amorphous regions of the polymer being more susceptible to undergoing hydrolysis. This finding results in a reduction of the overall molecular weight of the polymer backbone, with long polymer chains converted into shorter segments but still entangled (ie, molecular weight loss without mass loss). Because initially the crystalline domains are unaffected by hydrolysis, mechanical strength is maintained even during this early molecular weight loss.

For PLA, the rate of this molecular weight loss can be determined using the equation proposed by Weir and colleagues[7,8]:

$$M_n(t) = M_n(0)exp(-kt) \quad (1)$$

where $M_n(t)$ is the number-average molecular weight at degradation time t, $M_n(0)$ is the initial number-average molecular weight, and k is the degradation rate constant. Rearranging this equation leads to:

$$\ln\left(\frac{M_n(t)}{M_n(0)}\right) = -kt \quad (2)$$

which enables the degradation rate constant k to be estimated from a log-linear plot of normalized molecular weight versus degradation time. This model holds true as long as no mass loss has occurred.

Eventually, water penetrates into the crystalline domains, resulting in the simultaneous reduction of both the molecular weight and the mechanical strength. As the crystalline structure disappears, progressive chain scission further reduces the polymer chains into shorter fragments until, as oligomers and monomers, they are small enough to diffuse into adjacent tissue to be either metabolized or excreted from the body. This mass loss phase will always follow after strength loss, such that a polymer scaffold will always lose its mechanical function long before significant mass loss has occurred.

PRINCIPLES OF OPERATION

Revascularization

Mechanical properties and drug delivery play prominent roles in the revascularization phase,

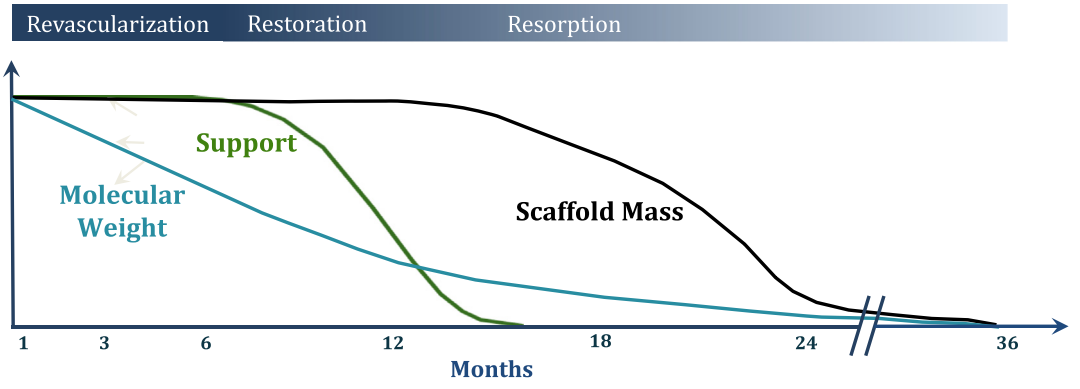

Fig. 1. Idealized relationship between the 3 performance phases of a BRS and the stages of hydrolytic degradation in an aliphatic polyester such as PLLA.