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Long-term in vivo corrosion behavior, biocompatibility and bioresorption mechanism of a bioresorbable nitrided iron scaffold

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ABSTRACT

Pure iron as a potential bioresorbable material for bioresorbable coronary scaffold has major disadvantages of slow corrosion and bioresorption. However, so far, there are neither quantitative data of long-term in vivo corrosion nor direct experimental evidence for bioresorption of pure iron and its alloys, which are fundamental and vital for developing novel Fe-based alloys overcoming the intrinsic drawbacks of pure iron. This work systemically investigated scaffold performance, long-term in vivo corrosion behavior and biocompatibility of a nitrided iron coronary scaffold and explored its bioresorption mechanism. It was found that the 70 μm Fe-based scaffold was superior to a state of the art Co-Cr alloy stent (Xience Prime™) in terms of crossing profile, recoil and radial strength. Mass loss was 76.0 ± 8.5 wt% for the nitrided iron scaffold and 44.2 ± 11.4 wt% for the pure iron scaffold after 36 months implantation in rabbit abdominal aorta ($p < 0.05$). The Fe-based scaffold showed good long-term biocompatibility in both rabbit and porcine model. Its insoluble corrosion products were demonstrated biosafe and could be cleared away by macrophages from in situ to adventitia to be indiscernible by Micro Computed Tomography and probably finally enter the lymphatics and travel to lymph nodes after 53 months implantion in porcine coronary artery. The results indicate that the nitrided iron scaffold with further improvements shall be promising for coronary application.

Statement of Significance

Pure iron as a potential bioresorbable material has major disadvantages of slow corrosion and bioresorption. However, so far, there are neither quantitative data of long-term in vivo corrosion nor direct experimental evidence for bioresorption of pure iron and its alloys. Only this work systemically investigated long-term in vivo corrosion behavior and biocompatibility of a nitrided iron coronary scaffold up to 53 months after implantation and explored its bioresorption mechanism. These are fundamental and vital for developing novel Fe-based alloys overcoming the intrinsic drawbacks of pure iron. Novel testing and section-preparing methods were also provided in this work to facilitate future research and development of novel Fe-based alloy scaffolds.

1. Introduction

Bioresorbable scaffold (BRS) is undoubtedly the latest invention after percutaneous transluminal coronary angioplasty (PTCA), bare metallic stent (BMS) and drug-eluting stent (DES) in endovascular intervention. Several devices have been CE marked for sale, including the Absorb Bioresorbable Vascular Scaffold System (Abbott Vascular) in 2011, DESolve 100 (Elixir Medical) in 2014 and Magmaris (Biotronik) formerly known as DREAMS-2 in 2016. The

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former two are poly-L-lactide (PLLA) bioresorbable scaffold while the latter is the first clinically proven magnesium scaffold. Absorb GT1 also won US Food and Drug Administration (FDA) approval in 2016. At current, an ideal BRS should have comparable or superior device performance to the state of the art drug-eluting stent (DES), good handleability, reasonable corrosion and bioresorption period, safety and efficacy demonstrated to be non-inferior to the current DES in large-scale randomized clinical trials [1,2]. Despite some initial encouraging results on the performance of BRS especially the Absorb GT1, there are many limitations for these representatives of the first-generation BRS. Poor trackability and deliverability of BRS due to thick struts and high profile discount their handleability and efficacy in complex lesions [3–5]. Post dilation is needed for BRS, however, over-dilatation might lead to strut fracture for the current generation BRS [6,7], which are vulnerable to develop in-scaffold restenosis by reports from ABSORB B trial and the GHOST-EU registry [8,9]. Recent registries have challenged the initial claim that Absorb scaffold is immune from scaffold thrombosis (ST) [6], both early scaffold thrombosis [10,11] and very late scaffold thrombosis [12,13] have been reported. Degradation and bioresorption period of polymer-based BRS (approximately 4 years) [14,15] is not as short as expected. For Mg-based BRS, amorphous calcium phosphate is left in the strut footprint after complete resorption of magnesium in about 2 years, and whether it will be ultimately resorbed or not is still pending long-term results [2,16,17]. Based on the above, these novel devices are still immature to some extent, further refinements need to be performed and new devices need to be developed before BRS truly become a game-changer in the everyday practice in the catheter lab [4].

Pure iron, as candidate material for BRS, has mechanical strength inferior to 316L stainless steel and Co-Cr alloy (traditional materials for fabricating permanent stents), long corrosion period and slow clearance of corrosion products [18–20]. However, iron has been demonstrated safe in vascular applications [21–24] up to 18 months. Theoretically, it is easy to strengthen pure iron, and corrosion period of pure iron scaffold can be shortened by increasing corrosion rate of material itself and/or decreasing scaffold mass or volume [25], but it is more important to obtain adequate biodegradation-strength-ductility balance [26]. Results of the past studies show that it is difficult to achieve high corrosion rate and good comprehensive mechanical performance without deteriorating biocompatibility. For example, corrosion rate and material strength of pure iron can be increased by alloying [27–29], but cytocompatibility deteriorates due to toxicity of introduced metallic elements, especially Mn [30–33]. Fe-Mn alloys with very low Mn concentrations exhibit good mechanical features and biocompatibility but show no significant corrosion after 9 months implantation [34]. Electroformed or cross-rolling iron exhibited good biocompatbility, increased corrosion rates and/or high strength but reduced plasticity [35–37]. There are numerous considerations from material to device [38]. However, new hope has been lightened by our recently published study [39], which demonstrated that a newly developed sirolimus-eluting nitrided iron scaffold with a protection layer of electrodeposited pure zinc had high strength and plasticity and completely corroded after 13 months implantation in a rabbit model. Unlike Fe alloying with Mn, this Fe-0.07 N alloy would not deteriorate the good biocompatibility of pure iron.

A lot of studies have investigated in vitro corrosion behaviors of newly designed or modified Fe-based materials [40–43], however, few studies have investigated in vivo corrosion behaviors and mechanical performance evolution with corrosion in a systematical and quantitative way. The reported longest follow-up was 18 months by Peuster M et al. [21] in a qualitative way. Materials developed for BRS should be tested in vivo because in vitro tests do not completely simulate the in vivo physiological environment. A recent report demonstrated differences between in vivo and in vitro corrosion behaviors of Fe-Mn alloys with low Mn concentrations (maximum Mn 6.9 wt%) [34]. Moreover, no in vitro and in vivo correlation (IVIVC) concerning corrosion is established to facilitate a quick corrosion assessment of newly designed or modified Fe-based alloys. IVIVC plays a very important role in screening newly developed materials and quality monitoring of devices in vitro for purposes of animal protection and saving time since in vivo investigation generally lasts for months or years. More importantly, although iron is not favored for extremely slow bioresorpion, actually so far, there are no any data concerning in vivo bioresorption of iron. Besides the clinically invasive and non-invasive methods [44], more methods for evaluating corrosion and bioresorption of Fe-based alloys remain to be established. All these are fundamental and vital for developing novel bioresorbable Fe-based alloy scaffolds.

In this study, device performance of a nitrided iron scaffold (Fe alloyed with 0.074 wt%N) [45] was evaluated and compared with a pure iron scaffold, a state of the art Co-Cr stent (Xience Prime™, Abbott), PLLA-based Absorb GT1 (Abbott) and Mg-based Magmaris (Biotronik) bioresorbable scaffolds. Corrosion test performed under simulated blood flow condition was designed to assess the in vitro corrosion profile of the nitrided iron scaffold. The in vivo corrosion profile of the nitrided iron scaffold in terms of mass loss and radial strength evolution was investigated up to 36 months implantation in a rabbit model with pure iron scaffold as control. The composition and distribution of corrosion products of the nitrided iron were characterized by scanning electron microscope (SEM) and Energy dispersive spectroscopy (EDS). In vivo thrombus risk of the nitrided iron scaffold was evaluated by observing endothelialization and acute thrombosis in rabbit model. Moreover, histopathological observation was conducted to investigate the local tissue response to the implanted nitrided iron scaffold with 316L SS stent having the same design as control. Finally, in a porcine coronary artery model, long-term biosafty and bioresorption of the insoluble corrosion products of the nitrided iron scaffold were evaluated after 33 and 53 months implantation by micro-computed tomography (Micro-CT), transimission electronic microscope (TEM) and histopathological analyses. This porcine model study was initiated in the beginning of year 2012 to investigate the long-term biosafety and bioresorption of nirided iron.

2. Materials and methods

2.1. Materials

The composition and microstructure of pure iron and nitrided iron (Fe alloyed with 0.074 wt%N) scaffolds were reported in our previous study [45]. Pure iron scaffolds, nitrided iron scaffolds (Φ3.0 × 18 mm, thickness ~70 μm, weight ~12 mg), 316L SS stents (Φ3.0 × 18 mm, the same design except for strut thickness of 90 μm) were all manufactured by Lifetech Scientific Co., Ltd. (Shenzhen, China). Vacuum plasma nitriding for 2 h at 500 °C with 50 Pa pressure (N_2:H_2 = 1:3) was applied to obtain the nitrided iron scaffolds and plates using an in-house designed vacuum nitriding furnace. All the scaffolds/stents used in tests and implantation experiment were electrochemically polished, then crimped onto balloon of rapid exchange catheter (Φ3.0 × 18 mm) by automatic crimping machine and finally ethylene oxide sterilized. All the plates were electrochemically polished and then ethylene oxide sterilized. A clinically widely-used polymer-coated drug-eluting Co-Cr alloy stent (Xience Prime™, Abbott Vascular, Santa Clara, CA, USA) was chosen as the control for device performance bench testing.