Systemic Pharmacokinetics of Everolimus Eluted From the Absorb Bioresorbable Vascular Scaffold

An ABSORB III Substudy

The Absorb bioresorbable vascular scaffold (BVS) (Abbott Vascular, Santa Clara, California) is designed to reduce chronic adverse cardiovascular events that may occur from the permanent presence of a metallic stent and/or durable polymer. The systemic pharmacokinetic (PK) profile of BVS has not been described. ABSORB III PK is a prospective, open-label, non-randomized substudy of the ABSORB III randomized trial (1), in which either 1 (n = 8) or 2 (n = 4) BVS were implanted in de novo coronary artery stenoses. Inclusion/exclusion criteria were the same as for ABSORB III (1), namely noncomplex lesions in patients with stable ischemic heart disease or stabilized acute coronary syndromes. All patients provided written informed consent for this substudy and were enrolled following successful BVS deployment at 2 U.S. sites between June 2, 2014, and September 17, 2014.

Detailed methods for the PK analysis are described elsewhere (1). Briefly, subjects had blood drawn at 16 time points between pre-procedure and 30 days (prior to implantation of the first BVS and at 10 min, 30 min, and 1, 2, 4, 6, 12, 24, 48, 72, 96, 120 [day 5], 168 [day 7], 336 [day 14], and 720 [day 30] h after last BVS deployment). Everolimus blood concentrations were measured, and noncompartmental analysis was performed to determine PK parameters (Cmax, tmax, t1/2, AUC24h, AUClast, and AUC0–∞). To explore dose proportionality of everolimus, a regression analysis on dose-normalized (to 1 μg) PK parameters for everolimus was performed. Blood concentration-time profiles and PK parameters of everolimus were compared with prior PK results obtained from the Xience V cobalt chromium everolimus-eluting stent (CoCr-EES) (Abbott Vascular) in the SPIRIT II and III (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Subjects with de Novo Native Coronary Artery Lesions) trial substudies (2,3).

Twelve patients were enrolled, all of whom remained in the PK substudy through 30 days. The mean age was 60.1 years, and 91.7% of subjects were male. Risk factors included current tobacco use (25.0%), diabetes (33.3%), hypertension (100%), dyslipidemia (100%), and prior MI (18.2%). Stable or unstable angina was present in 75% and 25% of subjects, respectively. The target lesion was the left circumflex artery in 50% of patients, the left anterior descending artery in 42%, and the right coronary artery in 8%. One-third of lesions were moderately or severely calcified. Mean lesion length was 12.2 ± 4.4 mm, and mean pre-procedure reference vessel diameter was 2.73 ± 0.41 mm. Scaffold diameters ranged from 2.5 to 3.5 mm, and scaffold lengths ranged from 8 to 28 mm. The average total length of scaffold implanted at the lesion site was 24.5 ± 8.6 mm. The total dose of loaded everolimus ranged from 181 to 443 μg.

Individual tmax ranged from 0.17 to 2.37 h across all dose levels. Everolimus blood concentrations could be quantified for up to 168 h after implantation of the last BVS (Figure 1A). Individual Cmax values increased proportionally with dose, ranging from 1.085 to 4.460 ng/ml. Similarly, individual AUC24h (ranging from 12.09 to 44.22 ng h/ml), AUClast (ranging from 25.37 to 104.60 ng h/ml) and AUC0–∞ (ranging from 33.15 to 120.80 μg h/ml) increased proportionally with dose. Terminal half-life ranged from 45.9 to 115.0 h, with no obvious trend with dose. Interindividual variability (% coefficient of variation) in everolimus exposure after BVS deployment ranged between 23.3% and 35.6% for dose-normalized Cmax, AUC24h, AUClast, and AUC0–∞.

Although short-lived, individual Cmax values (1.085 to 4.460 ng/ml) were slightly higher than the minimum systemic, chronically maintained therapeutic level of ≥3.0 ng/ml required for effective prevention of organ rejection (4). However, everolimus blood concentrations declined rapidly after reaching Cmax and were <3.0 ng/ml in all subjects by 4 h after the last scaffold deployment. In addition, Cmax levels obtained after Absorb BVS were well below mean steady-state Cmax (61 ng/ml) observed in
patients with solid tumors treated with 10 mg/day of everolimus (9).

These results are consistent with 2 prior PK studies of everolimus elution from the metallic XIENCE V stent (2,3), which has the same drug dose density as BVS (100 μg/cm²) (Figure 1B). Examining the concentration-time PK results from the BVS scaffold and the CoCr-EES stent with a common load of 181 μg of everolimus, both devices demonstrated a rapid increase in systemic everolimus levels after stent/scaffold deployment, reaching maximal concentrations within 2.5 h, followed by a biexponential decline, with an initial rapid phase followed by a slower terminal phase; levels remained above the limit of detection (0.1 ng/ml) for up to 168 h after stent/scaffold deployment. Similar to CoCr-EES, an increase in total everolimus dose by BVS resulted in a proportional increase in Cmax and AUC (Figure 1A). Although the early peak everolimus concentrations with BVS appear slightly higher than with CoCr-EES, inferences should not be drawn from small differences as the studies with the 2 devices were done at different times in different patients.

In conclusion, the systemic PK characteristics of everolimus after BVS deployment are predictable with dose-proportional behavior. Local coronary arterial delivery results in limited systemic exposure, suggesting a low risk of systemic toxicity. The PK profile of systemic everolimus exposure from BVS is similar to that from the metallic CoCr-EES.

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REFERENCES

Epidemiological studies have consistently reported that high-density lipoprotein (HDL) cholesterol levels are inversely associated with the risk of cardiovascular disease (CVD) (1). In fact, plasma-derived and synthetic HDL, and/or its derivatives, have been shown to exert various cardiovascular protective effects ranging from reverse cholesterol transport, atherosclerotic plaque stabilization, improvement of endothelial dysfunction (2), and most lately, limiting sclerotic plaque stabilization, improvement of endothelial dysfunction, and/or its derivatives, have been shown to exert direct cardioprotective effects. We investigated whether the presence of high low-density lipoprotein cholesterol levels, a prominent risk factor for CVD, affects ability of HDL to exert direct cardioprotective effects. We conducted this study in a pre-clinical animal model of myocardial infarction (MI) as a biological readout of the differential effects of HDL when formed in a high-cholesterol pathological environment.

Young healthy pigs were distributed to receive during 10 days either a regular normocholesterolemic chow (NC) or a high-cholesterol diet (HyC) (non-HDL cholesterol 38.2 ± 3.5 mg/dl vs. 218.6 ± 27.6 mg/dl, respectively; p < 0.0001). On day 10, HDLs were isolated from NC- and HyC-fed animals by sequential ultracentrifugation (NC_HDL and HyC_HDL, respectively) and were quantified, sterilized, lyophilized, and kept at −80°C until use. Another set of young healthy pigs were randomized to receive 2 intravenous infusions 3 days apart of NC_HDL (15 mg/kg; n = 6), HyC_HDL (15 mg/kg; n = 6), or vehicle (phosphate-buffered saline; n = 6). One day after the second infusion, animals were subjected to 60-min closed-chest coronary balloon occlusion followed by reperfusion (experimental MI). Echocardiography revealed that 60 min of ischemia significantly and similarly worsened left ventricle ejection fraction in all animals showing the homogeneity of the employed methodological approach (vehicle: 19.6 ± 4.8%; NC_HDL: 20.6 ± 3.2%; HyC_HDL: 17.3 ± 2.1%; p < 0.05 vs. prior MI induction). Three days post-MI, all animals underwent cardiac magnetic resonance, and the following sequences were acquired: 1) “cine” (balanced steady-state free precession) imaging sequence to assess wall motion and cardiac function; 2) T2-short tau inversion recovery sequence to assess myocardial edema; 3) T2* to evaluate intramyocardial hemorrhage; 4) early gadolinium enhancement to evaluate the degree of no-reflow; and 5) late gadolinium enhancement to assess the extent of myocardial necrosis. Data were normally distributed (Shapiro-Wilk Test) and analysis of variance, Fisher least significant difference, and post-hoc Student-Newman-Keuls analyses were performed. A value of p < 0.05 was considered significant.

Infusion of NC_HDL before MI resulted in a significantly smaller infarct size, in terms of both absolute infarct mass and percentage of the left ventricle, compared with vehicle-infused animals (Table 1). This protective effect did not occur in animals infused with HyC_HDL. T2-weighted sequences revealed no differences in the extent of area-at-risk among the 3 groups. Consequently, the extent of salvage myocardium was significantly larger in the NC_HDL-administered group compared with the HyC_HDL and vehicle control groups. The extent of no-reflow was also significantly attenuated in the NC_HDL-infused group compared with HyC_HDL and vehicle animals and directly correlated with the extent of necrosis (p < 0.05; R = 0.63). No differences were observed between HyC_HDL-recipient animals and vehicle controls with regard to infarct size, myocardial salvage, and no-reflow. The extent of hemorrhage was comparable among the 3 groups. Although left ventricular ejection fraction assessed 3 days post-MI did not differ between the groups (Table 1), left ventricular volumes significantly improved in NC_HDL-recipient animals compared with HyC_HDL- and vehicle-infused animals.

We describe, for the first time, that hypercholesterolemia, a common risk factor for CVD, impairs the cardioprotective properties commonly associated with HDL. We provide evidence that HDL particles formed in a high low-density lipoprotein cholesterol niche lose their capability to attenuate myocardial damage in the setting of MI. As such, the degree of cardiac injury and cardiac impairment observed in HyC_HDL-infused animals is comparable to that observed in vehicle-infused animals. These observations suggest that the presence of comorbidities may alter HDL’s beneficial properties. Particularly noteworthy, in contrast to primary prevention, the association between HDL cholesterol and cardiovascular events is altered in patients with established CVD.