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Short communication

Eosinophil cationic protein and clinical outcome after bare metal stent implantation

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ABSTRACT

Objective: we assessed the association between baseline eosinophil cationic protein (ECP) levels, a sensitive marker of eosinophil activation, and clinical outcome in patients undergoing bare metal stent (BMS) implantation.
Methods: basal ECP levels were measured in 110 patients (69 ± 11 years, 88 men) undergoing BMS implantation. Major adverse cardiac events (MACEs), defined as cardiac death, non-fatal myocardial infarction, or clinically-driven target lesion revascularization, were registered at 24-month follow-up.
Results: eighteen (16.4%) patients had MACEs and showed higher ECP levels compared with those without MACEs [20.1 (9.8–47.3) vs. 9.5 (5.0–27.2) g/L, $p = 0.02$]. At follow-up, ECP level >11 g/L was the only significant predictor of MACEs (HR 3.5, 95% CI 1.1–10.4, $p = 0.03$).
Conclusion: basal ECP levels are associated with MACEs after BMS implantation, suggesting that an allergic-mediated inflammation against the metal could explain some adverse reactions occurring after coronary stenting.

1. Introduction

Stent-related events along with native coronary atherosclerosis progression are the main determinants of long-term outcome in patients treated by percutaneous coronary intervention (PCI). With the introduction of drug eluting stents (DES) clinical restenosis has been abated but stent thrombosis has emerged as a new concern [1].

We recently demonstrated that allergic predisposition, assessed by measurement of eosinophil cationic protein (ECP), may help in risk prediction among DES patients treated [2]. However, due to the lack of a control group of bare metal stents (BMS) treated patients, we could not establish whether allergic predisposition would have been able to predict also the response to metallic struts, in the absence of a surrounding polymer, which was the most accountable at the time of the study protocol design [3].

Allergic reaction to BMS has been shown to contribute to restenosis [4,5] and eosinophils have been detected also in case of BMS thrombosis superimposed on the underlying restenotic tissue [6].

Thus, we aimed at evaluating the predictive value on clinical outcome of ECP, a sensitive marker of eosinophil activation, in patients undergoing PCI with BMS.

2. Methods

2.1. Patients

We included in the study 110 consecutive patients diagnosed with stable angina or acute coronary syndrome who underwent successful implantation of at least one cobalt-chromium BMS (Vision, Abbott, Santa Clara, CA, USA or Skylor, Invatec, Roncadelle, Italy). Overall, 306 patients were screened from September to December 2007. Exclusion criteria were: implantation of a stainless steel BMS or a DES either alone or in combination with a BMS in the same procedure or within the 12 previous months, in-stent restenosis, ST-elevation myocardial infarction (MI) within the previous 24 h, severe chronic heart failure, severe valvular disease, systemic inflammatory disease, evidence of immunologic disorder, use of antinflammatory or immunosuppressive drugs, liver disease, neoplasia, and recent (<3 months) surgical procedures or trauma.

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In all patients, cardiovascular risk factors were carefully examined. Acute coronary syndrome was defined by chest pain at rest in the last 48 h preceding admission associated with transient ST-segment depression on 12-lead electrocardiogram. Stable angina was defined as angina on effort with a stable pattern of symptoms for at least 6 months prior to admission.

2.2. Study protocol

Patients were enrolled in the catheterization laboratory immediately following the operator decision to implant a BMS. Patients were on dual anti-platelet therapy with aspirin and clopidogrel. Glycoprotein IIb/IIIa inhibitors were administred according to current recommendations [7]. After the procedure, patients received dual anti-platelet therapy with aspirin 75–160 mg indefinitely and clopidogrel 75 mg for at least 1 month.

Patients were clinically followed-up up to 24 months after the index procedure. The main focus of the study was the incidence of major adverse cardiac events (MACEs) defined as the composite of cardiac death, non-fatal MI and clinically-driven target lesion revascularization (TLR). Deaths of unknown cause were considered of cardiac origin, MI was identified by relapsing chest pain or electrocardiographic changes associated with creatinkinase levels elevation of at least 2 times the upper limit of the reference range, whereas TLR was defined as repeat symptom- or ischemia-driven revascularization by either PCI or by coronary-artery bypass graft (CABG) for significant (>50%) in-stent or in-segment (5 mm proximally or distally) restenosis. The study complied with the declaration of Helsinki and was approved by the institutional review board. All patients gave informed consent for participation in the study.

2.3. Coronary angiographic evaluation

Angiographic images were evaluated both qualitatively and quantitatively as previously reported [2]. Digital angiograms were analyzed offline with the use of an automated edge-detection system (CMS; Medis Medical Imaging Systems, Leiden, The Netherlands). The following angiographic parameters were obtained: reference vessel diameter, minimal lumen diameter, and diameter stenosis percentage (at baseline and at the end of PCI), lesion length, total stent length and acute gain.

2.4. Laboratory assay

High-sensitivity C-reactive protein (CRP) was measured by an ultrasensitive nephelometric method (Dade-Behring BN-2, Siemens, Milan, Italy), with a lower detection limit of 0.2 mg/L, whereas ECP and total IgE were measured by enzyme-linked immunosorbent assay (UniCap, Phadia, Milan, Italy) and expressed as μg/L and kU/L, respectively. The ranges of detection for ECP and IgE were 0.5–200 mg/L and 2–5000 kU/L, respectively [2].

2.5. Statistical analysis

Continuous variables were compared by Student's *t* test or Mann–Whitney *U* test according to distribution. Categorical variables were compared by Pearson's chi-square test or Fisher's exact test as appropriate. Correlations analyses were performed by Spearman's rank correlation test. Survival curves were generated according to the Kaplan–Meier method and compared with the log-rank test. To evaluate predictors of event, a proportional hazards regression analysis was performed. Most important variables were considered as potential risk predictors. Cut-off points for dichotomisation of were determined by a described method [8]. To avoid over fitting, no multivariable model was build. The time span of the study was chosen to allow enrolling a specified number of patients with MACEs [2]. A p value <0.05 was required for statistical significance.

3. Results

3.1. Patients characteristics and outcome

Population characteristics and procedural data are summarized in Tables 1 and 2. Follow-up data were available for all patients enrolled in the study. At 24-month, 18 (16,4%) patients experienced a MACE: 4 (3.6%) patients died because of sudden cardiac death (n = 2, 1.8%) or severe heart failure (n = 2, 1.8%), 4 (3.6%) patients had non-fatal MI, 10 (9.1%) patients experienced a stent restenosis treated by PCI in 9 (8.2%) and by CABG in 1 (0.9%). One (0.9%) patient experienced stent thrombosis causing non-fatal MI, 4 days after stent implantation. In 63% of patients, MACEs occurred within 12 months after stent implantation, whereas in the remaining 37%, MACEs occurred between 12 and 24 months.

3.2. Predictors of major adverse cardiac events

Factors associated with the risk of MACEs are summarized in Tables 1 and 2. Patients with MACEs had higher ECP levels [20.1 (9.8–47.3) vs. 9.5 (5.0–27.2) μg/L, p = 0.02], when compared with those without MACEs. In contrast, CRP levels were similar in patients with MACEs when compared with those not having MACEs [4.6 (2.4–10.1) vs. 4.6 (3.0–12.3) mg/L, p = 0.49].

Significant predictors of MACEs were ECP levels >11 μg/L (HR 3.5, 95% CI 1.1–10.4, p = 0.032, and lesion length >18 mm (HR 2.8, 95% CI 1.1–7, p = 0.03), with previous ischemic heart disease, acute gain, and total stent length being of borderline statistical significance (p = 0.07 for all). Patients with ECP levels <11 μg/L had a lower MACE-free survival when compared with those having ECP levels >11 μg/L (p = 0.045, Fig. 1).

Lesion length was the only variable significantly associated with ECP levels (rho = 0.2, p = 0.04).

4. Discussion

In this study we demonstrate that ECP, a sensitive marker of eosinophil activation [9], predicts clinical outcome in patients receiving BMS.

Metallic implants may trigger an allergic reaction in predisposed individuals [10]. Indeed, activated eosinophil may promote chronic inflammation around metallic struts, which may contribute to neointima formation [11]. In our study, ECP was associated with overall MACEs rate including hard endpoints such as cardiac death and MI, which may be due to the pro-thrombotic actions of eosinophil granular proteins [12]. Due to the low number of events, however, it is not possible to dissect the relative contribution of eosinophil activation to restenosis or thrombotic complication against the implanted stent.

Along with our previous demonstration of the role of ECP in risk prediction following DES implantation [2], these data suggest that an allergic reaction may play an important role in patients undergoing stent implantation. Our data suggest that the stent type does not affect the predictive value of ECP and that allergic reactions are directed mostly against the metallic components of stent struts. However, the observation of a more pronounced eosinophil infiltration around DES as compared to BMS [13] suggests a more important role of either the drug or the polymer rather than metal struts on eosinophil recruitment.

Another intriguing possibility is that eosinophils might predict the outcome due to their direct involvement in coronary