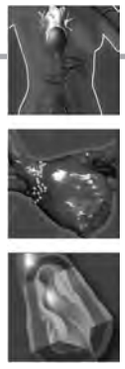

Outcomes following coronary stenting and a role for eosinophils: evidence from eosinophil cationic protein

"*Along with common inflammatory pathways involving neutrophils, monocytes and lymphocytes, a new role is emerging for allergic inflammation involving eosinophils in determining the clinical outcome after drug-eluting stent implantation.*"

KEYWORDS: coronary stent ■ eosinophil cationic protein ■ eosinophils ■ in-stent restenosis ■ stent thrombosis

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In-stent restenosis (ISR) and stent thrombosis are the main adverse reactions to coronary stent implantation, where an important role is played by individual susceptibility, along with procedural and stent-related factors [1]. In particular, the individual inflammatory reaction profoundly affects vessel response to the implanted stent. In the bare-metal stent (BMS) era, many studies suggested that C-reactive protein levels were able to predict the risk of ISR, while its role in predicting stent thrombosis was less established [1].

Drug-eluting stents (DES) have abated ISR rates occurring in the classical 1-year window, but new concern is emerging regarding late restenosis and thrombosis [2]. Interestingly, in this setting, baseline inflammation as assessed by C-reactive protein levels has been associated with stent thrombosis but not to ISR [3]. Along with common inflammatory pathways involving neutrophils, monocytes and lymphocytes, a new role is emerging for allergic inflammation involving eosinophils in determining the clinical outcome after DES implantation. Indeed, the pathogenesis of late events seems to be related to delayed healing and to allergic reactions to polymers, a process in which eosinophils play an important role [4]. Of note, a possible role for eosinophils in ISR and stent thrombosis has also been reported for BMS [5,6].

In addition to histological studies, the potential role of an allergic reaction to implanted stents also derives from studies utilizing patch test or, more recently, serum levels of eosinophil cationic protein (ECP), a marker of eosinophil activation.

Eosinophils & adverse reactions to coronary stents: evidence from pathological studies

Post-mortem studies and observations based on histological assessment of thrombectomy specimens have clearly documented local hypersensitivity associated to late-stent thrombosis after DES implantation [7–9]. These findings were confirmed by the results of the Research on Adverse Drug Events and Reports (RADAR) project, which documented intra-stent eosinophilic inflammation, thrombosis and lack of intimal healing in four autopsies, in addition to evidence of allergic reactions in 17 cases, which were likely or certainly caused by the stent, of which nine lasted longer than 4 weeks [10]. Of note, eosinophils have also been detected in some cases of BMS thrombosis [6] and have been documented around metallic stent struts after BMS, but not in restenotic tissue after balloon angioplasty [11,12]. Eosinophils appear to play a greater role, however, in restenosis after DES than after BMS. Accordingly, animal studies have shown persistent eosinophil infiltration in 25% of pigs receiving DES [13] with a threefold increase in eosinophil recruitment around paclitaxel-eluting stents when compared with BMS. In a case report of a sirolimus-eluting stent implanted to treat restenosis of a BMS implanted in a saphenous vein graft, eosinophil infiltration was present surrounding the sirolimus-eluting stent but not the BMS [14]. Current evidence suggests that hypersensitivity both to the polymer [15,16] and to the metal may cause eosinophil recruitment [17].

Eosinophils & adverse reactions to the coronary stent: evidence from clinical studies

Post-mortem studies are extremely important from a pathophysiological point of view, but they cannot guide the management of patients receiving coronary stents. By contrast, the demonstration of an increased susceptibility to allergic reaction using biomarkers may be useful

part of future medicine fsg

in risk stratification after stenting. Furthermore, monitoring of allergic reactions may help to assess the efficacy of potential anti-allergic treatments.

Koster *et al.* initially showed that a positive patch test to metal allergy was associated with ISR after BMS [17]. Although the patch test may be useful in some cases, multiple and specific allergens should be tested, including metals, drugs and polymers, which are not always easy to identify, especially considering the variety of polymers used in different DES. A more widespread evaluation of susceptibility to allergic reactions and of intensity of allergic reactions may be obtained by measuring serum biomarkers related to allergy.

> "*Current evidence suggests that hypersensitivity both to the polymer and to the metal may cause eosinophil recruitment.*"

In the past few years we have explored the role of ECP, a serum biomarker of eosinophil activation, in the prediction of cardiac events after DES or BMS implantation. This biomarker has extensively been used in the allergy setting both for diagnostic purposes and for the assessment of response to steroid therapy. ECP is a potent cytotoxic protein released by activated eosinophils and is effective towards bacteria and helminthic parasites through pore formation in target membranes. Moreover, ECP is involved in the development of subacute and chronic symptoms of allergy, promoting degranulation from mast cells and inducing direct damage to mammalian epithelial cells [18]. We have recently demonstrated for the first time that an enhanced eosinophil activation at baseline, assessed by preprocedural serum ECP levels, predicts the clinical outcome after implantation of first-generation DES [19]. Our study enrolled 200 consecutive patients undergoing sirolimus-eluting stent or paclitaxel-eluting stent implantation, with a clinical follow-up of 18 months. A major adverse cardiac event (MACE), a composite of cardiac death, myocardial infarction or clinically driven target lesion revascularization, was the end point of the study. Patients with MACE showed significantly higher serum levels of ECP compared with those without MACE, and at a Cox regression analysis, serum levels of ECP were a significant predictor of MACE. Of note, because target lesion revascularization rate was highly prevalent in the composite end point when compared with death or myocardial infarction, these findings should mainly be applied to this end point.

> "*Risk stratifications of susceptibility to allergy or the documentation of allergic reactions after stent implantation may have therapeutic implications.*"

More recently, we have explored the role of ECP for the prediction of cardiac events in a population of 110 patients undergoing implantation of BMS [20]. After 2 year follow-up, patients with MACE showed significantly higher serum levels of ECP compared with those without MACE. At Cox regression analysis, ECP was the only significant predictor of MACE. Thus, as ECP levels are associated with MACE not only after BMS but also after DES implantation, allergic inflammation against the metal could help to explain the adverse reactions occurring after coronary artery stenting, with a contributory role perhaps played by the polymer after DES implantation.

The role of biomarkers of allergy in predicting and in monitoring the response of the vessel wall against the stent should be the focus of future studies. In particular, data assessing inflammatory biomarkers at the time of late ISR or of stent thrombosis as well as data assessing the association of these biomarkers with measures of neointima formation are still lacking. Risk stratifications of susceptibility to allergy or the documentation of allergic reactions after stent implantation may have therapeutic implications.

Therapeutic implications of allergic reactions to coronary stents

Glucocorticoids exert their anti-inflammatory effects through complex mechanisms that affect the microvasculature, cell membranes and intracellular messengers, and include inhibition of phospholipase A2 and macrophages, a reduction in circulating cytokines levels and stabilization of lysosomial membranes. They also exert an immunosuppressive effect by inhibiting leukocyte trafficking and the access of leukocytes to the site of inflammation. Moreover glucocorticoids deplete circulating T cells, inhibit T-cell growth factor and antagonize the action of migration inhibitory factor. More importantly, with regard to allergy, steroids have been shown to reduce the production of cytokines released by eosinophils. Thus, steroid therapy might be considered in patients with elevated baseline ECP levels to reduce the risk of ISR [21].

Statins have several immunomodulatory effects. In particular, in a murine model of allergic asthma, simvastatin treatment reduced the total inflammatory cell infiltrate and eosinophilia in bronchoalveolar lavage fluid in response to inhaled allergen challenge. Simvastatin therapy was also associated with a reduction in IL-4 and IL-5 levels in bronchoalveolar lavage fluid and, at higher doses, with a histological reduction in inflammatory infiltrates in the lungs [22]. Thus, intensive statin treatment might be considered in patients with elevated baseline ECP levels to reduce the risk of ISR.

An allergen-specific desensitizing immunotherapy towards the stent polymer or metal or the introduction of bioabsorbable polymers or polymer-free stents may represent other promising therapeutic approaches [23], as well as the introduction of bioabsorbable stents [24].

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Bibliography

1 Niccoli G, Montone RA, Ferrante G, Crea F. The evolving role of inflammatory biomarkers in risk assessment after stent implantation. *J. Am. Coll. Cardiol.* 56(22), 1783–1793 (2010).

2 Maluenda G, Lemesle G, Waksman R. A critical appraisal of the safety and efficacy of drug-eluting stents. *Clin. Pharmacol. Ther.* 85(5), 474–480 (2009).

3 Park DW, Yun SC, Lee JY *et al.* C-reactive protein and the risk of stent thrombosis and cardiovascular events after drug-eluting stent implantation. *Circulation* 120, 1987–1995 (2009).

4 Niccoli G, Sgueglia GA, Crea F. The emerging role of allergic inflammation in adverse reactions after coronary stent implantation. *Atherosclerosis.* 217(1), 70–71 (2011).

5 Rittersma SZ, Meuwissen M, van der Loos CM *et al.* Eosinophilic infiltration in restenotic tissue following coronary stent implantation. *Atherosclerosis* 184, 157–162 (2006).

6 Zavalloni D, Bossi P, Rossi ML *et al.* Inflammatory substrate with eosinophils may be present in bare-metal stent thrombosis. *J. Cardiovasc. Med.* 10, 942–943 (2009).

7 Virmani R, Guagliumi G, Farb A *et al.* Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 109, 701–705 (2004).

8 Joner M, Finn AV, Farb A *et al.* Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. *J. Am. Coll. Cardiol.* 48, 193–202 (2006).

9 Cook S, Ladich E, Nakazawa G *et al.* Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* 120, 391–399 (2009).

10 Nebeker JR, Virmani R, Bennett CL *et al.* Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *J. Am. Coll. Cardiol.* 47, 175–181 (2006).

11 Nakatani M, Takeyama Y, Shibata M *et al.* Mechanisms of restenosis after coronary intervention: difference between plain old balloon angioplasty and stenting. *Cardiovasc. Pathol.* 12, 40–48 (2003).

12 Kawano H, Koide Y, Baba T *et al.* Granulation tissue with eosinophil infiltration in the restenotic lesion after coronary stent implantation. *Circ. J.* 68, 722–723 (2004).

13 Finn AV, Nakazawa G, Joner M *et al.* Vascular responses to drug eluting stents: importance of delayed healing. *Arterioscler. Thromb. Vasc. Biol.* 27, 1500–1510 (2007).

14 Rittersma SZ, van der Wal AC, de Winter RJ. Eosinophilic tissue response several weeks after sirolimus-eluting Cypher stent implantation within a bare metal stent in a coronary saphenous vein graft. *Catheter Cardiovasc. Interv.* 67(1), 38–40 (2006).

15 van der Giessen WJ, Lincoff AM, Schwartz RS *et al.* Marked inflammatory sequelae to implantation of biodegradable and nonbiodegradable polymers in porcine coronary arteries. *Circulation* 94, 1690–1697 (1996).

16 van Beusekom HM, Serruys PW, van der Giessen WJ. Coronary stent coatings. *Coron. Artery Dis.* 5, 590–596 (1994).

17 Koster R, Vieluf D, Kiehn M *et al.* Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 356, 1895–1897 (2000).

18 Venge P. Monitoring the allergic inflammation. *Allergy* 59, 26–32 (2004).

19 Niccoli G, Schiavino D, Belloni F *et al.* Pre-intervention eosinophil cationic protein serum levels predict clinical outcomes following implantation of drug-eluting stents. *Eur. Heart J.* 30, 1340–1347 (2009).

20 Niccoli G, Sgueglia GA, Conte M *et al.* Eosinophil cationic protein and clinical outcome after bare metal stent implantation. *Atherosclerosis* 215(1), 166–169 (2011).

21 Ferrero V, Ribichini F, Pesarini G, Brunelleschi S, Vassanelli C. Glucocorticoids in the prevention of restenosis after coronary angioplasty: therapeutic potential. *Drugs* 67(9), 1243–1255 (2007).

22 McKay A, Leung BP, McInnes IB, Thomson NC, Liew FY. A novel anti-inflammatory role of simvastatin in a murine model of allergic asthma. *J. Immunol.* 172, 2903–2908 (2004).

23 Gershlick A, De Scheerder I, Chevalier B *et al.* Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European Evaluation of Paclitaxel Eluting Stent (ELUTES) trial. *Circulation* 109, 487–493 (2004).

24 Erbel R, Di Mario C, Bartunek J *et al.* Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomisedmulticentre trial. *Lancet* 369, 1869 –1875 (2007).