Editorial / *Editöryal Yorum*

Do pre-procedural laboratory parameters predict drug-eluting stent restenosis?

İşlem öncesi ölçülen biyokimyasal belirteçler ile ilaç kaplı stentlerde tekrarlayan darlığı öngörmek mümkün müdür?

Murat Gençbay, M.D.

Department of Cardiology, Kemerburgaz University Faculty of Medicine, Istanbul

Stent implantation provokes a local inflammatory response at the injured endothelial site. Drug-eluting stents (DES) blunt this reaction for a period of 6-8 months. Some authors claim a catch up phenomena of DES adverse outcomes in late follow-up,[1] while others do not.[2]

The histopathologic features of DES reactions are clearly different from those of bare metal stents (BMS). Allergic inflammation, largely mediated by eosinophils, has been involved in adverse reactions to DES.[3] Angioscopic and OCT data reveal that late restenosis in DES is different from that in BMS. DES yields a yellow neointima suggesting accelerated atherosclerosis and tends to have more fibrin and thrombosis.[3]

There are many systemic inflammatory markers; C-reactive protein (CRP), IL-6, IL-10, Lipoprotein(a), red blood cell distribution width (RDW), serum uric acid (UA), mean platelet volume (MPV), neutrophil to lymphocyte ratio (N/L ratio), matrix metalloproteinases (MMP), PAI-1, and complement components like C3a and C5a, Pentraxin-3, etc. Numerous studies have investigated all of these in the setting of coronary stenting to stratify the risk of both angiographic and clinical outcomes. CRP, which represents a sensitive marker of systemic inflammation, is the most widely studied biomarker in patients undergoing PCI.

CRP is an acute-phase protein produced mainly by hepatocytes in response to stimulation by inflammatory cytokines, primarily interleukin (IL)-6. It has been shown to predict future cardiac events in both primary and secondary prevention studies.[4-6] Levels of CRP increase and peak at 48 hours, and the magnitude of CRP increase after the procedure has been shown to predict stent restenosis in patients undergoing BMS implantation.[5]

However, the relationship between CRP and DES restenosis remains unclear. In contrast to findings of studies on BMS, pre-procedural serum CRP levels do not appear to predict in-stent restenosis (ISR) in DES.[5-9] Gaspardone et al.[5] prospectively enrolled 160 consecutive patients with stable single-vessel disease undergoing implantation of BMS, sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), or dexamethasone-eluting stent (DEX), and assessed serum CRP changes at 48 h compared with baseline. Pre-procedural CRP levels were similar in all groups, and CRP levels significantly increased after coronary stenting in a similar manner across the 4 groups. Interestingly, the incidence of angiographic binary restenosis at 12 months was significantly lower in the SES and PES groups when compared to the BMS and DEX groups, suggesting that the lower rate of ISR observed after DES deployment was unlikely to be

Correspondence: Dr. Murat Gençbay. Kemerburgaz Üniversitesi Tıp Fakültesi, Medicalpark Bahçelievler Hastanesi, İstanbul, Turkey.
Tel: +90 212 - 484 14 84 e-mail: gencbaym@hotmail.com

related to a reduced acute systemic inflammatory response, but rather to a local blunted inflammatory response.[5] Dibra et al.,[6] enrolling 301 stable or unstable patients treated with BMS or SES implantation, showed a higher CRP change after the procedure to be a predictor of ISR in the BMS group, but not in the SES group. Moreover, a study by Kang et al.[7] failed to demonstrate an association between changes in CRP or IL-6 levels and neointimal hyperplasia evaluated by IVUS following SES or PES deployment.

Unfortunately, only a small number of studies have evaluated serum levels of CRP after stent implantation over time by serial assessment.

Serum levels of MMP, PAI-1 and complement components C3a and C5a have also been evaluated for risk prediction after DES implantation. Katsaros et al.[8] demonstrated that baseline MMP-9 and 24 h post-procedural MMP-9 and MMP-2 levels were significantly higher in patients with ISR at the 6- to 8-month angiographic follow-up compared with those in patients without ISR. Moreover, plasma levels of PAI-1 before and 24 h after PCI were associated with the occurrence of angiographic ISR.[9] Speidl et al.[10] found that serum levels of C3a before and 24 h after PCI, as well as baseline C5a levels, were significantly higher in patients developing ISR at the 6- to 8-month angiographic follow- up.

Another study[11] compared the relationship between inflammatory markers and neointimal hyperplasia (NIH) after DES implantation. This prospective intravascular ultrasound study showed that inflammatory response after PCI, as measured by hs-CRP levels, and not baseline hs-CRP level, predicts NIH after DES implantation. Neither a change in the IL-6 nor MMP-9 levels at any stage after PCI reflected NIH.[11]

In an intriguing study, soluble receptor for advanced glycation end products (sRAGE) is associated with in-stent restenosis in type 2 diabetes patients with DES.[12] In a recent study,[12] plasma pentraxin 3, which represents local inflammation better than CRP, has been found to be a good predictor of bare metal stent outcomes but not in DES. The authors of this stimulating study investigated the predictive value of CRP, neutrophil to lymphocyte ratio, red cell distribution width, serum uric acid and mean platelet volume for stent restenosis, as assessed by coronary angiography.

In the current issue of the Archives of the Turkish Society of Cardiology, Tanındı et al.[14] performed a retrospective study, an analysis was made of the biochemical and angiographic data of 285 patients who were implanted a total of 315 DES between 2012 and 2014. A routine coronary angiography was performed on the study group. DES were 2nd generation and consisted of zotarolimus-eluting and biolimus-eluting stents. Zotarolimus-eluting stents are made of a persistent polymer which is resorbed after 6-8 months. The authors concluded that none of the pre-procedural blood parameters independently predict DES stenosis.

There are several limitations to this study. Its retrospective nature and the inclusion of a limited number of patients precludes robust conclusions. With studies for biochemical predictors of DES outcomes so scarce, large prospective studies with serial follow-up of high-sensitive CRP, or perhaps better indicators like pentraxin-3. should be planned.

Conflict-of-interest issues regarding the authorship or article: None declared.

REFERENCES

1. Wessely R, Kastrati A, Schömig A. Late restenosis in patients receiving a polymer-coated sirolimus-eluting stent. Ann Intern Med 2005;143:392–4. CrossRef
2. Caixeta A, Leon MB, Lansky AJ, Nikolsky E, Aoki J, Moses JW, et al. 5-year clinical outcomes after sirolimus-eluting stent implantation insights from a patient-level pooled analysis of 4 randomized trials comparing sirolimus-eluting stents with bare-metal stents. J Am Coll Cardiol 2009 Sep 1;54:894–902. CrossRef
3. Gonzalo N, Serruys PW, Okamura T, van Beusekom HM, Garcia-Garcia HM, van Soest G, et al. Optical coherence tomography patterns of stent restenosis. Am Heart J 2009;158:284–93. CrossRef
4. Haverkate F, Thompson SG, Pyke SD, Gallimore JR, Pepys MB. Production of C-reactive protein and risk of coronary events in stable and unstable angina. European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Lancet 1997;349:462–6. CrossRef
5. Gaspardone A, Crea F, Versaci F, Tomai F, Pellegrino A, Chiariello L, et al. Predictive value of C-reactive protein after successful coronary-artery stenting in patients with stable angina. Am J Cardiol 1998;82:515–8. CrossRef
6. Dibra A, Ndrepepa G, Mehilli J, Dirschinger J, Pache J, Schühlen H, et al. Comparison of C-reactive protein levels before and after coronary stenting and restenosis among patients treated with sirolimus-eluting versus bare metal stents.

Am J Cardiol 2005;95:1238–40. CrossRef

7. Kang WC, Ahn TH, Moon CI, Han SH, Shin EK, Kim JS, et al. Comparison of inflammatory markers and angiographic outcomes after implantation of sirolimus and paclitaxel-eluting stents. Heart 2009;95:970–5. CrossRef
8. Katsaros KM, Kastl SP, Zorn G, Maurer G, Wojta J, Huber K, et al. Increased restenosis rate after implantation of drug-eluting stents in patients with elevated serum activity of matrix metalloproteinase-2 and -9. JACC Cardiovasc Interv 2010;3:90–7. CrossRef
9. Katsaros KM, Speidl WS, Kastl SP, Zorn G, Huber K, Maurer G, et al. Plasminogen activator inhibitor-1 predicts coronary in-stent restenosis of drug-eluting stents. J Thromb Haemost 2008;6:508–13. CrossRef
10. Speidl WS, Katsaros KM, Kastl SP, Zorn G, Huber K, Maurer G, et al. Coronary late lumen loss of drug eluting stents is associated with increased serum levels of the complement components C3a and C5a. Atherosclerosis 2010;208:285–9.
11. Kang WC, Il Moon C, Lee K, Han SH, Suh SY, Moon J, et al. Comparison of inflammatory markers for the prediction of neointimal hyperplasia after drug-eluting stent implantation. Coron Artery Dis 2011;22:526–32. CrossRef
12. Park HJ, Seo SM, Shin WS, Kim HY, Choi YS, Koh YS, et al. Soluble receptor for advanced glycation end products is associated with in-stent restenosis in patients with type 2 diabetes with drug-eluting coronary stents. Coron Artery Dis 2011;22:12–7. CrossRef
13. Hudzik B, Szkodzinski J, Pietka-Rzycka A, Danikiewicz A, Wojnar R, Lekston A, et al. Plasma pentraxin 3 may be a more sensitive marker of inflammatory response than high-sensitivity C-reactive protein after bare-metal stent compared to drug-eluting stent implantation. J Interferon Cytokine Res 2013;33:280–4. CrossRef
14. Tanındı A, Ekici B, Töre HF. Do pre-procedural laboratory parameters predict drug-eluting stent restenosis? Turk Kardiyol Dern Ars 2015;43:457–64.