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Review

Inflammation and restenosis after percutaneous coronary interventions

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The role of inflammation in the development of restenosis after percutaneous coronary interventions has been investigated in several studies. There is an interaction of inflammatory activation and vascular wall response to injury leading to intimal hyperplasia. Percutaneous interventions trigger inflammatory reactions leading to the development of intimal hyperplasia. This reaction is even more prominent in atheromatic plaques in which inflammatory cells have already been activated. In the clinical setting there are several methods for the recognition of the inflammatory activation. In this article we review the data for the role of inflammatory process in restenosis and the significance of identifying the inflamed lesions prior to the intervention. Moreover, the therapeutic implications for the inhibition of inflammatory activation are mentioned.

Introduction

During the last decades percutaneous coronary intervention (PCI) has become a major weapon against coronary artery disease. This approach was compromised by the fact that restenosis was the main limitation. Great efforts have been made in resolving this vexing problem. Although the angiographic restenosis rate has been substantially reduced by stenting, especially with the drug-eluting stents, there still remains a problem particularly in a subset of patients and lesions. The predominant mechanism in the development of in-stent restenosis is intimal hyperplasia and anti-proliferative agents have been used for the elimination of restenosis.

Subsequent studies have supported a critical role of inflammation in the restenotic process. Other studies recognised the role of pre-existing inflammatory involvement in the target lesions, in which interventions were being performed. In this article we review: (1) the role of the inflammatory response to PCI in restenosis, (2) the impact of inflammatory status before the intervention in restenosis, and (3) possible treatment strategies.

Inflammatory response to PCI

Pathophysiology of the inflammatory response

Animal studies

The impact of arterial injury on the development of intimal hyperplasia has been examined in several studies.[1,2] There is strong evidence however that inflammatory response has a significant correlation with the degree of arterial injury, as the inflammatory reaction triggers a cascade of thrombotic and hyperplastic sequelae.

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Balloon dilatation of the arterial wall provokes de-endothelialisation and a layer of platelets and fibrin is deposited at the injured site.[1] Local platelet/platelet, platelet/leukocyte and leukocyte/endothelial cell complex formations are then mediated by adhesion molecules.[3–5] P-selectin mediates the adhesion of activated platelets with monocytes and neutrophils, and the rolling of leukocytes on the endothelium. This is the main pathophysiological substrate linking inflammation with thrombosis after arterial wall injury.

The activation of cytokines enhances the migration of leukocytes across the platelet-fibrin layer into the tissue. Growth factors are released from platelets, leukocytes and smooth muscle cells (SMCs) and fibroblasts proliferate and undergo a transformation to myofibroblasts 3—14 days after the intervention.[6]

Lately the ubiquitin—proteasome system of intracellular protein degradation is implicated as a key player in restenosis. This system regulates mediators of proliferation, inflammation, and apoptosis that are fundamental mechanisms for the development of restenosis. Proteasome is required for the activation of NFκB, which regulates a number of inflammatory genes by degrading its inhibitory IκB protein. In animal studies, blocking the proteasome system reduced intimal hyperplasia,[7,8] showing that inflammation contributes significantly to intimal hyperplasia.

The final common pathway of these mechanisms is the initiation of the first phase (G1) of the cell cycle, which is regulated by the assembly and phosphorylation of cyclin/cyclin dependent kinase (CDK) complexes. Growth factors trigger signaling pathways that activate these CDK complexes. Recent studies have shown dramatic efficiency in inhibiting the proliferation of SMCs by agents (e.g., rapamycin) binding to specific receptor (FKBP12) and inhibiting the mitogen-stimulated protein kinase. As other agents, such as tacrolimus, did not fulfill the expectations, the potent action of the effective agents can be explained by blockage of inflammatory cell activation.[9–11]

Stent vs balloon angioplasty. There are differences between balloon angioplasty and stenting in the pathophysiologic mechanism for the development of intimal hyperplasia, as the inflammatory reaction after stenting is more prominent. In animal studies, balloon angioplasty was followed only by an early neutrophil infiltration. In contrast, early neutrophil recruitment was followed by prolonged macrophage accumulation in stented arteries.[6] In stented arteries there is abundant recruitment of macrophages within the neointima, while in balloon-injured arteries a model devoid of macrophage infiltration has been documented.[12] These data suggest that the type and degree of arterial injury has a different impact in the local inflammatory activation.

Perivascular response in arterial injury. Although previous reports described adventitial inflammation after balloon injury,[13] only recent studies support the concept that inflammatory and proliferative foci arise from the adventitia. Neutrophils accumulate in adventitia in the first 3 days, followed by macrophages after angioplasty. Interestingly, the main inflammatory and proliferative foci were not limited to the adventitia but rather extended from the injured vessel throughout the surrounding tissues.[14] Consequently, the impact of adventitial inflammatory cells on the development of intimal hyperplasia after arterial injury needs to be further studied.

Human studies

Pathology studies. The most convincing evidence for the role of inflammation in the process of restenosis arises from human arterial segments. In the initial phase, post-stent implantation, a mural thrombus is formed followed by invasion of SMCs, T-lymphocytes and macrophages. This early neointima, which completely covers the stent struts after 4 weeks, contains minimal amounts of extracellular matrix. Later, extracellular matrix increases and fewer SMCs are observed with lymphocytes adjacent to the struts, but also distributed uniformly throughout the complete segment.[15]

A correlation was found between stent strut penetration with inflammatory cell density and neointimal thickness. Neointimal inflammatory cell content was 2.4-fold greater in segments with restenosis, and inflammation was associated with neoangiogenesis. Coronary stenting that is accompanied by medial damage or penetration of the stent into the lipid core induces increased arterial inflammation, which is associated with increased neointimal growth.[16]

Atherectomy specimens. In atherectomy specimens after PCI an increase of monocyte chemoattractant protein-1 (MCP-1) was observed in restenotic lesions.[17] Atherectomy specimens from restenotic lesions revealed an increased number of macrophages in restenotic lesions.[18] These results indicate that local expression of macrophage activity may be associated with the mechanisms of intimal hyperplasia.

Inflammatory activation as a prognostic marker post-PCI

Recently several studies in humans have been performed to investigate the role of inflammation in prognosis after PCI (Table 1, Fig. 1).

Genetic

Polymorphism of genes regulating several inflammatory factors has been shown to be involved in the restenotic process. In particular, IL-1 regulates a number of procedures, such as mitogenesis of SMCs, thrombogenic response of endothelial cells, leukocyte adherence, and vascular permeability. In certain gene polymorphisms, the production of its natural antagonist (IL-1ra) is increased with a lower risk for restenosis especially in younger patients.[19]

Peripheral blood

Measurement of several factors in blood samples has provided significant information regarding the role of inflammation after PCI. In coronary sinus blood sam-

Table 1 Human studies implicating inflammation in the process of restenosis

Study	Model	Agent	Follow up	Results
Pietersma et al.[36]	Peripheral blood	IL-1, IL-6, fibrinogen, CRP, and lipoprotein(a)	Angiographic (6 months) Patients ($n = 32$) MACE ($n = 6$)	Luminal renarrowing could be predicted ($R^2 = 0.65$; $p < 0.0001$) by the expression of CD66 from granulocytes and the production of IL-1β from stimulated monocytes
Kastrati et al.[19]	Peripheral blood	Allele 2 of IL-1RN gene	Angiographic (6 months) Patients ($n = 1850$) MACE ($n = 506$)	Carriers of allele 2 of IL-1RN had a lower risk for angiographic restenosis (OR = 0.78) and TVR (OR = 0.73)
Gottsauner-Wolf et al.[23]	Peripheral blood	CRP	Angiographic (6 months) Patients ($n = 40$) MACE ($n = 11$)	CRP levels were higher in patients with restenosis vs no restenosis ($p = 0.038$)
Hokimoto et al.[27]	Peripheral blood	Plasma MCP-1 antigen levels	Angiographic (3 months) Patients ($n = 70$) MACE ($n = 27$)	MCP-1 antigen levels were increased in restenotic segments vs not restenotic (735 ± 35 vs 571 ± 32 pg/ml, $p < 0.05$)
Gaspardone et al.[25]	Peripheral blood	CRP	Clinical (12 months) Patients ($n = 76$) MACE ($n = 13$)	Incidence of MACE was higher in patients with high CRP levels vs patients with low CRP
Schillinger et al.[63]	Peripheral blood	CRP, SAA	Ultrasonography (6 months) Patients ($n = 108$) MACE ($n = 15$)	CRP level at 48 h, was significantly associated with 6-month restenosis
Fukuda et al.[26]	Peripheral blood	Monocytes	IVUS (6 months) Patients ($n = 107$)	Multiple regression analysis revealed that in-stent neointimal volume was independently correlated with maximum monocyte count ($r = 0.35$, $p < 0.001$)
Inoue et al.[22]	Blood samples from coronary sinus	CD11b, 8B2, Mac-1 activation	Angiographic (6 months) Patients ($n = 62$)	Multiple regression analysis showed that lumen loss was correlated with the CD11b increase ($R = 0.42$, $p < 0.01$) and the 8B2 increase ($R = 0.55$, $p < 0.001$) after the procedure
Hokimoto et al.[17]	Atherectomy specimens	MCP-1 and macrophages	Angiographic (6 months) Patients ($n = 27$)	MCP-1 immunoreactivity was found in all patients with restenosis. Macrophage expression was higher in the restenosis group than in de novo group
Moreno et al.[18]	Atherectomy specimens	Macrophages and smooth muscle cells	Angiographic (4 months) Patients ($n = 30$)	Macrophage-rich areas were larger in restenotic lesions (20.4 ± 2%) vs non-restenotic lesions (9.3 ± 2%) ($p = 0.0007$)
Farb et al.[16]	Post-mortem	Macrophages, T-cells, B-cells	10 months Specimens ($n = 116$)	Neointimal inflammatory cell content was 2.4-fold greater in restenotic versus non-restenotic lesions

CRP: C-reactive protein; ICAM-1: intracellular cell adhesion molecule; IL-1: interleukin-1; IL-1RN: interleukin-1 receptor antagonist gene; MCP-1: monocyte chemoattractant protein-1; SAA: serum amyloid A; TVR: target vessel revascularisation.

ples 15-min after angioplasty an increased expression of adhesion molecules on the surface of neutrophils and monocytes was observed.[20] Late lumen loss was correlated with the changes of IL-6 concentrations post-PCI and MAC-1 activation in coronary sinus blood.[21,22]

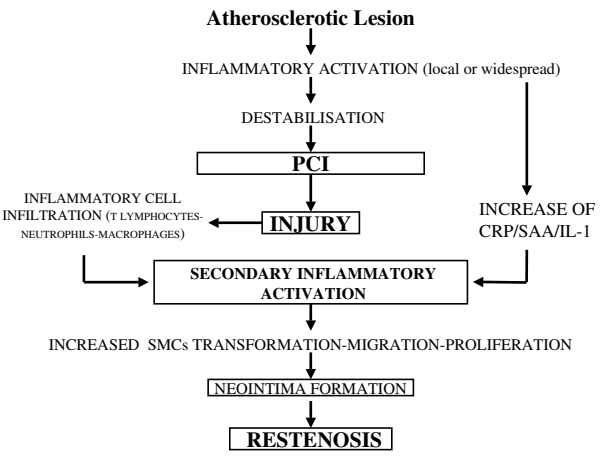

Fig. 1 The mechanisms by which inflammation is involved before and after percutaneous coronary intervention. (CRP: C-reactive protein; PCI: percutaneous coronary intervention; SAA: serum amyloid A; IL-1: interleukin-1; SMCs: smooth muscle cells.)

Recent studies demonstrated that stent deployment is associated with an increase in C-reactive protein (CRP).[23] Interestingly, CRP plasma levels were significantly higher and more prolonged in patients with restenosis compared to patients without restenosis. Similar findings were reported lately in a series of patients with stable angina that underwent PCI.[24] The percentile rise of CRP was significantly higher in stable plaques rather than unstable plaques, although the absolute values of CRP were higher in the latter group. The association between the extent of vascular inflammatory response with long-term outcome was even observed in patients with stable angina undergoing stent implantation.[25]

Lately, an interesting study showed that the inflammatory response after stent implantation can be assessed by measuring the circulating monocytes in the peripheral blood. The maximum monocyte count after stent implantation showed a significant positive correlation with in-stent neointimal volume at 6-month follow-up. On the contrary other fractions of white blood cells were not correlated with in-stent neointima volume.[26]

These findings demonstrate that there is an inflammatory response after PCI, which needs to be assessed for the risk stratification for restenosis. In the clinical setting the inflammatory activation can only be assessed by measuring indices in the peripheral blood. Although several indices have been correlated with clinical restenosis, the main limitation of these studies is the lack of angiographic follow-up. Three studies demonstrated that angiographic restenosis is correlated with the levels of CRP, leukocytes and MCP-1 (Table 1).[23,26,27] Although, the number of patients included in these studies is limited there was a statistically significant correlation of these inflammatory markers with the development of angiographic restenosis.

The role of inflammatory status prior to PCI

The aforementioned studies proved that vascular injury caused by PCI triggers inflammation locally in the atherosclerotic plaque. However, at the time of stent implantation the overall inflammatory status is not equivalent in all patients and subsequently in all atherosclerotic plaques. Therefore, PCI in an already inflamed plaque may have significant impact on clinical and angiographic outcome (Fig. 1).

Several studies support this statement as demonstrated in Table 2. A recent experimental study showed that nonspecific stimulation of the innate immune system by injection of bacterial lipopolysaccharide induced persistent macrophage infiltration after stent implantation. This effect was abolished by anti-CD14 Ab administration.[28]

Moreover, a correlation between pre-interventional inflammatory activation and post-interventional responsiveness was found. In patients with unstable angina and elevated baseline CRP, SAA and IL-6 values an increased responsiveness to angioplasty was observed compared to patients with normal baseline values.[29]

Pre-procedural CRP level is an independent predictor for one-year MACE (major adverse cardiac events) in patients not receiving statins. CRP levels were significantly higher in patients with recurrent angina compared with asymptomatic patients.[30,31] The lack of angiographic follow-up in these studies does not allow the elucidation of whether inflammatory process was related to restenosis at the target lesion, or to progression of disease.

Recurrent unstable angina after PCI is related to the extent of initial coronary plaque inflammation, which was assessed by histological analysis of atherectomy specimens. Macrophage areas were larger and the number of T-lymphocytes was also greater in patients with recurrent unstable angina than in patients with recurrent stable angina.[32] Moreover, the concentration of macrophages is an independent predictor for restenosis.[18] These results underline the role of ongoing smouldering plaque inflammation in the recurrence of unstable angina after PCI.

Walter et al.,[33] found that tertiles of CRP levels were independently associated with a higher risk of MACE and angiographic restenosis after stenting. Buffon et al.,[34] showed that baseline CRP and SAA levels were independent predictors of clinical restenosis. Additionally, Patti et al.,[35] found that pre-procedural IL-1 receptor antagonist (IL-1Ra) plasma levels was an independent predictor of MACE during the follow-up period. Furthermore the overall activation status of the immune system, estimated by the amount of IL-1β produced by monocytes, had positive correlation with late lumen loss, while the expression of CD66 by granulocytes has shown to prevent luminal re-narrowing.[36]

In a large study including 1152 patients with stable angina undergoing coronary stenting, elevated CRP levels were associated with an almost twofold increase in the rate of death or myocardial infarction after stenting. Most of the difference in the event rates developed within the first 30 days, possibly due to pro-thrombotic actions of CRP.[37] However, baseline CRP levels did not correlate with angiographic restenosis.[38]

The role of pre-existing inflammation in the clinical outcome after stenting was also studied by measuring

Table 2 Studies implicating pre-existing inflammation in the development of restenosis

Study	Model	Index	Follow up	Results
Danenberg et al.[28]	Rabitt iliac arteries	IL-1β, CD14	Angiographic (4 weeks)	Systemic inflammation before stent implantation was associated with increased luminal stenosis (38 ± 4.2 vs 232.6%) and increased neointimal area (0.57 ± 0.07 vs 0.77 ± 0.1 mm)
Buffon et al.[34]	Human peripheral blood	CRP	Clinical (12 months) Patients ($n = 121$) MACE ($n = 51$)	Clinical restenosis was 63% in patients with high CRP levels vs 27% with normal CRP levels ($p < 0.001$)
Chan et al.[30]	Human peripheral blood	CRP	Clinical (12 months) Patients ($n = 937$) MACE ($n = 326$)	The incidence of MACE in patients not receiving statins was higher in patients with high CRP vs low CRP levels (hazard ratio = 1.32, $p = 0.001$)
Patti et al.[35]	Human peripheral blood	IL-1 receptor antagonist plasma levels	Clinical (18 months) Patients ($n = 73$) MACE ($n = 12$)	IL-1Ra level in the upper quartile was the only independent predictive factor of MACE (19% vs 0%; $p = 0.032$)
Rahel et al.[31]	Human peripheral blood	CRP, IL-6, Lp(a), and fibrinogen	Clinical (8 months) Patients ($n = 600$) MACE ($n = 54$)	CRP levels were higher in patients with recurrent angina ($p = 0.0322$). Lp(a) and fibrinogen concentrations were both related to MACE ($p = 0.0337$ and $p = 0.0253$, respectively)
Pietersma et al.[36]	Human peripheral blood	CD66 and IL-1β	Angiographic (6 months) Patients ($n = 32$) MACE ($n = 6$)	The expression of CD66 and production of IL-1β predict late lumen loss after PTCA ($R^2 = 0.65$, $p < 0.0001$)
Walter et al.[33]	Human peripheral blood	CRP	Angiographic (6 months) Patients ($n = 276$) MACE ($n = 112$)	Restenosis was higher in the two upper tertiles compared with CRP levels in the lowest tertile (45.5 vs 38.3 vs 18.5%, $p = 0.002$)
Dibra et al.[38]	Human peripheral blood	CRP	Angiographic (6 months) Patients ($n = 1152$) MACE ($n = 86$)	Elevated CRP levels were associated with an increase in the rate of death or myocardial infarction (OR = 1.8); the difference in the event rates developed within the first 30 days. Baseline CRP levels did not correlate with restenosis
Stefanadis et al.[39]	Human coronary arteries	Temperature of the culprit lesion	Clinical (18 months) Patients ($n = 86$) MACE ($n = 21$)	Incidence of MACE was higher in patients with high temperature (41% vs 7%, $p < 0.001$)
Meuwissen et al.[32]	Human coronary atherectomy specimens	Macrophage areas and T lymphocytes	Clinical (12 months) Patients ($n = 110$) MACE ($n = 37$)	Patients with recurrent unstable angina, had more inflammatory cells within the target lesion at intervention compared to patients with recurrent stable angina or asymptomatic

CRP: C-reactive protein; Lp(a): lipoprotein(a); LPS: bacterial lipopolysaccharide; MACE: major adverse cardiac events; IL-1: interleukin-1; SAA: serum amyloid A.

the temperature of the culprit lesion.[39] Patients with MACE had increased plaque temperature before the intervention. During a clinical follow-up of 18 months the incidence of MACE in patients with increased temperature was higher compared to patients without increased thermal heterogeneity. The adverse cardiac events were mainly due to restenosis at the culprit lesions.[39]

It is obvious that the overall and local inflammatory status at the time of PCI plays a significant role in the development of restenosis. Therefore in the clinical

setting the assessment of inflammatory activation should be performed in order to improve the risk stratification post-PCI. Widespread inflammatory status cannot be assessed by a single method for the characterisation of 'high-risk' patients for restenosis. The current evidence arises from studies combining data from the clinical syndrome and peripheral markers of inflammation. For patients with unstable clinical syndromes and increased levels of monocytes and CRP there is strong evidence for increased risk of restenosis. The measurement of other inflammatory indices such as SAA, IL-6, IL-1 β, (IL-1Ra) plasma levels, Lp(a), fibrinogen, seems to provide additional information.

Limited information is available for the local status of inflammation at the site of the plaque. Coronary thermography is a functional method for the assessment of local inflammation and indeed, in a single study, local temperature was correlated with clinical restenosis.[39] Although, several methods are emerging lately for the functional and morphological characterisation of an inflamed plaque, such as elastography and optical coherence tomography, there are no studies correlating the local inflammatory status assessed by these methods with the development of restenosis. Future studies need to be performed in order to investigate their potential additive prognostic value.

Role of infection

The role of infection in restenosis has been investigated in several studies. The interest was mainly focused in cytomegalovirus (CMV) and *Chlamydia pneumoniae*. CMV infection prior to PCI could lead to increased restenosis rates by inhibition of the eukaryotic tumour suppressor protein p53.[40,41] The initial enthusiasm was compromised by more recent studies that failed to demonstrate correlation between prior infection and restenosis rates.[42–44] Similarly, the administration of roxythromycin prior to PCI had no effect on angiographic restenosis, except for treated patients with high *Chlamydia pneumoniae* antibody titres.[45] These controversial results emphasise the need for an extensive investigation of the role of infection in restenosis.

Treatment of inflammation after percutaneous coronary interventions

Systemic

Several agents with potentially anti-inflammatory action have been used including statins, which have been studied more extensively.

Statin therapy significantly attenuates the increased risk for MACE in patients with elevated CRP levels undergoing coronary stenting. In patients with elevated CRP levels without statin therapy, an increased risk for MACE during the follow-up was observed compared to treated patients. Angiographic follow-up showed that statin therapy reduced the risk for restenosis in patients with elevated CRP levels.[46] In the Regression Growth Evaluation Statin Study (REGRESS), treatment with pravastatin reduced 2-year clinical and angiographic restenosis.[47] In a retrospective study late lumen loss and net gain were favorable in treated patients. Angiographic restenosis rates were significantly lower in the statin group and statin treatment was an independent predictor for restenosis.[48] Walter et al., showed that statins reduce the angiographic restenosis rate and improve clinical outcome after coronary stenting in carriers of the Pl(A2) allele of the platelet glycoprotein IIIa gene. Thus, statins interfere with the functional consequence of a genetically determined platelet-mediated risk factor.[49]

In the LIPS (Lescol Intervention Prevention Study) study, 1677 patients following their first PCI with average cholesterol levels were randomly assigned to fluvastatin or placebo. During the follow-up period of almost 4 years, MACE were increased in the control group compared to the treated patients. The effect was independent of the baseline total cholesterol levels. This was the first randomised trial demonstrating the favorable effects of statins in patients with average cholesterol levels undergoing PCI.[50] The major benefit of fluvastatin was observed mainly in the first 6 months, suggesting that statins had a favourable effect on restenosis.

However, treatment with fluvastatin did not affect the angiographic restenosis rate in the FLARE (FLuvastatin Angiographic REstenosis) trial. The angiographic restenosis rate was not influenced by fluvastatin, although a significantly lower incidence of total MACE was observed in the fluvastatin group.[51] In addition, in the PREDICT (Prevention of Restenosis by Elisor after Transluminal Coronary Angioplasty) study, late loss and net gain did not differ significantly between treated and non-treated patients.[52]

Thus, there are still concerns regarding the effects of statins in the process of angiographic restenosis, despite the beneficial clinical outcome after PCI. It seems that their pleiotropic effects act favorably overall in the progression of the disease, rather than locally in the treated arterial segment.

Recent studies have demonstrated that thienopyridines and glycoprotein IIb/IIIa receptor antagonists possess anti-inflammatory properties and might be more effective in patients with high CRP levels.[53] The role of these agents in reducing the inflammatory response post-PCI is however controversial.

Lately the application of non-specific anti-inflammatory agents such as prednizone in the prevention of restenosis was investigated in the IMPRESS study (Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation) with encouraging results. Patients with increased CRP levels after stenting were randomised to receive oral prednisone or placebo for 45 days. Six-month restenosis rate and lumen loss were lower in prednisone-treated than in placebo-treated patients. Twelve-month event-free survival rates were favorable in patients treated with prednisone.[54]

These conflicting results of anti-inflammatory treatment for the prevention of restenosis post-PCI may be

related to the variability of the inflammatory component within each patient. Therefore, inflammatory activation as assessed by CRP levels only predominates in some patients. In patients with inflammatory activation, a specific therapy for the prevention of inflammatory cell activation may be required. Recently, in an experimental study, liposomes with nitrogen-containing biphosphonates, which enter the monocytes or macrophages, were administered.[55] These liposomes undergo lipolysis and release anti-hyperplastic agents preventing cell activation. This approach will be evaluated clinically and may inhibit the cellular proliferation in patients in which the inflammatory component predominates.

Local

Several agents have been used for local delivery in the atherosclerotic lesion. The most prominent and extensively studied agent is rapamycin. Rapamycin was originally studied for its antimycotic properties but the door to clinical application was opened by the recognition of its potent immunosuppressive properties. The safety and efficacy of drug-eluting stents with sirolimus have been studied and the results were impressive regarding the restenosis rate.[56,57]

Paclitaxel also has anti-inflammatory and anti-proliferative properties. This agent is also delivered locally by drug-eluting stents and the first clinical trials were encouraging for the reduction of restenosis rate.[58,59] Moreover, new agents such as everolimus[60] are being investigated for the reduction of hyperplastic response after stent implantation.

In the era of drug-eluting stents with agents combining anti-inflammatory and anti-proliferative effects, the impact of inflammatory assessment prior to the procedure needs to be re-evaluated, as drug eluting stents may become the equaliser for the elimination of intimal hyperplasia independent of the local or systematic inflammatory activation.

The current treatment of inflammatory activation, either systemic or local, after PCI is dedicated to the prevention of restenosis. Although several methods have been applied for the treatment of restenosis, only brachytherapy is considered as an established method. There are limited data regarding the relation between brachytherapy and inflammatory activation. Kollum et al.,[61] have shown in animal models that CD-3-positive cells and macrophage densities are increased within the arterial wall after the application of brachytherapy, possibly due to the incomplete endothelialisation. The use of drug-eluting stents in the treatment of in-stent restenosis may address this limitation of brachytherapy.

Conclusions

Do we have enough evidence from clinical and angiographic follow-up that inflammation, assessed by the aforementioned methods, needs to be evaluated before the procedure? Furthermore, are we convinced from the available data that the restenotic process is indeed related to the degree of pre-existing and peri-procedural inflammatory processes?

There is evidence from experimental and clinical studies that restenosis is affected by the inflammatory process. However, there is no hard evidence from a dedicated prospective study to evaluate this statement. Such a study would provide valuable prognostic and therapeutic information. The main limitation of such a study is the lack of a safe, validated, and easily applied method for determination of the extent of inflammatory process. This already difficult task is even more complex, as inflammation is not only locally present at the target lesion but is rather widespread.[62] Another concern is the variability of inflammatory activation in patients undergoing PCI. A selection of patients in which an anti-inflammatory treatment may be required might be more reasonable according to the current information. We therefore need a method to identify the inflammatory activation in patients scheduled for PCI. A variety of non-invasive and invasive methods are emerging in order to evaluate the high-risk atherosclerotic plaque or patient. Randomised, prospective trials need to be performed to evaluate the accuracy and sensitivity of these methods. If these issues will be resolved, there will be major therapeutic implications, especially with the advancement of drug-eluting stents.

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