American Journal of Medicine and Medical Sciences 2022, 12(2): 108-114
DOI: 10.5923/j.ajmms.20221202.08

Statins and Pro-Inflammatory Cytokines in Ischemic Heart Disease after Coronary Vessel Stenting

Soleeva Sitora Shaxobovna, Agababyan Irina Rubenovna*

Samarkand State Medical Institute, Samarkand, Uzbekistan

Abstract Today, the problem of ischemic heart disease remains the main cause of cardiovascular complications and death. With the development and implementation of new technologies for percutaneous coronary intervention (PCI), the problem of choosing between radical and conservative management of patients is becoming more and more urgent. The role of PCI in the treatment of patients with coronary artery disease has two main objectives: improving the prognosis and reducing the severity of angina pectoris and improving the quality of life. The main cause of coronary artery disease is atherosclerosis, which is influenced by inflammatory mediators, various proteins, proteins, enzymes of the lipid transport system and markers of myocardial damage. The primary trigger of the atherosclerotic process is the increased content of cytokines in the peripheral blood against the background of fluctuations in the initial cholesterol level. Atherogenic cholesterol is the central initial factor of cytokine overproduction in atherogenesis. Endothelial dysfunction is an early, preclinical phase of the development of coronary atherosclerosis and can be considered as the "gold standard" in assessing the functional state of the endothelium. A positive effect on endothelial function has been demonstrated in HMG-CoA reductase inhibitors, in particular rosuvastatin, which thus reduces the risk of PCI-related adverse events. Statins, in addition to their main hypolipidemic effect, have pleiotropic properties - anti-inflammatory, antithrombotic, and immunomodulatory effects. In addition, initial retrospective clinical trials have shown that statins have the potential to improve clinical outcomes in COVID-19 patients. If these benefits are proven in randomized trials, statins could also be a useful therapy for COVID-19. Despite the conduct of dozens of multicenter studies that have proven the hypolipidemic properties of statins, in particular, rosuvastatin, their questions regarding the correction of EF, lipid FRO processes, and the inflammatory reaction at the site of atherogenesis remain insufficiently studied, and this, in turn, has an important prognostic value.

Keywords Percutaneous coronary intervention, Ischemic heart disease, Statins, Pro-inflammatory cytokines, Tumor necrosis factor, Atherosclerosis, Stenting of coronary arteries, Covid-19, SARSCoV-2

1. Introduction

According to the World Health Organization, cardiovascular disease (CVD) has been the leading cause of death in the world for the past 20 years. Mortality from coronary heart disease has quadrupled since 2000 from more than 2 million to almost 9 million in 2019, which is 16% of the total number of deaths [49]. In Uzbekistan, 53% of deaths among the population aged 30 to 70 are associated with CVD. Over the past 5 years, the number of CVD cases has increased by 20%, even among young people. In general, CVDs are diagnosed in about 4 million people, which is 12% of the total population [50].

Today, according to the European Congress of Cardiology in 2021, statins are included in the mandatory standard of primary prevention and treatment of coronary artery disease and myocardial infarction - evidence level 1A [49].

At present, about 500 thousand PCIs with stenting of coronary arteries for coronary heart disease (CHD) are performed annually in the world; in our city of Samarkand, over 3000 PCIs were performed in 2021. Primary PCI in patients with acute coronary syndrome (ACS), especially those with ST segment elevation, is a very effective life-saving procedure [8,9]. The role of PCI in the treatment of patients with coronary artery disease after the procedure is less defined, which pursues two main tasks: improving the prognosis and reducing the severity of angina pectoris, improving the quality of life. With the development and implementation of new PCI technologies, the problem of choosing between radical and conservative tactics of patient management becomes more and more urgent.

It is of great importance to carry out adequate drug therapy to reduce the risk of cardiovascular complications (CVC), including periprocedural myocardial infarction (MI) in patients with PCI. The possibilities of using statins before performing PCI are widely discussed throughout the world [26,28,33,43]. One of the most studied drugs in this class is

* Corresponding author:
salimdavlatov@sammi.uz (Agababyan Irina Rubenovna)
Received: Jan. 15, 2022; Accepted: Feb. 8, 2022; Published: Feb. 15, 2022
Published online at http://journal.sapub.org/ajmms

rosuvastatin, which has a good evidence base.

2. The Role of Cytokines in the Pathogenesis of Ischemic Heart Disease

Today, it is known that atherosclerosis is a systemic disease that affects various parts of the arterial system [1]. In recent years, the role of immune factors, in particular the cytokine cascade, in the development of the most formidable complication of atherosclerosis, MI, has attracted increasing interest of researchers [4,13]. The commonality of inflammation and atherosclerosis is quite natural, since both syndromes form the same cells of loose connective tissue: endothelial and SMC, fibroblasts, monocytes and macrophages, neutrophils, platelets and, to a lesser extent, T- and B-lymphocytes [3].

Numerous studies show that atherosclerosis is a multifactorial disease that mobilizes metabolic and inflammatory processes [16,17]. In addition to the well-known risk factors, there are other factors with a proven influence on the course of atherosclerosis, which are more difficult to identify and correct. These include inflammatory mediators, various proteins, proteins and enzymes of the lipid transport system, markers of myocardial damage [44].

Cytokines are constituents of a complex regulatory system that provides paracrine, and in most cases autocrine connections between cellular participants in atherogenesis [48]. The inflammatory process is a key link in all stages of atherosclerosis, and in addition, inflammation contributes to the progression and development of complications [20,40].

Ikeda U. et al. were among the first in the world to study the problem of the activation of proinflammatory cytokines in IHD [42]. Later, first Seino Y. et al. and Rus H.G. in the experiment, an increased expression of IL-6 in atherosclerotic plaques was described, and after Kaneko K. et al. the same data were confirmed by immunohistochemical study of atherosclerotic plaques in coronary arteries in patients with MI [14,16,21].

The pathophysiological theory of atherogenesis is that the accumulation and increased content of cytokines in the peripheral blood against the background of fluctuations in the initial cholesterol level may be the primary trigger of the atherosclerotic process [36]. It is known that atherogenic cholesterol is present in the form of LDL, and currently there is a hypothesis that modified (oxidized) LDL is the central initial factor of cytokine hyperproduction in atherogenesis [33]. Oxidized LDL causes the migration of smooth muscle cells s and their division, which is supported by their own mitogens [32,35].

Cytokines play an important role in the processes of regulation and neovascularization within atherosclerotic plaques. Many pro-inflammatory and proatherogenic mediators (IL-1, IL-6, IL-8, TNFa, IL-12) activate neoangiogenesis in ischemic segments of atheroscrerotic plaques. [50]. Tumor necrosis factor (TNFa) enhances the expression of adhesion molecules, procoagulant activity, induction of cytokine synthesis by endothelium (induces the synthesis of IL-1). TNFa is secreted mainly by activated macrophages, monocytes, T-lymphocytes, antigen-stimulated endothelial and SMC cells, and neutrophils [29]. IL-1 and TNFa have a pro-inflammatory effect, including stimulation of collagen production, and an increase in the expression of adhesion molecules required for extravasation of leukocytes [30]. The concentration of TNF-a is higher in atherosclerotic plaques with high inflammatory activity [25]. Also, IL-6 in IHD stimulates the expression in the vascular wall of pro-inflammatory and prothrombotic factors - tissue factor, LDL. IL-6 has a thrombogenic effect due to its effect on fibrinogen and platelets. Epidemiological evidence suggests that high levels of IL-6 are associated with the risk of coronary heart disease, as much as some major risk factors [28].

3. The Role of Endothelium in the Pathogenesis of Atherosclerosis and Its Complications

Currently, the endothelium is defined as a single layer of specialized cells lining the entire inner surface of blood vessels. The area of the lined surface is about 900 m, and the total weight of the endothelial tissue is more than 1500 grams [6].

The endothelium is not just a barrier or filter. It is a large gland with endocrine, autocrine and paracrine properties. The strategic location of the endothelium on the border of the internal media of the body allows it to maintain vascular homeostasis. The endothelium plays a key role in the regulation of vascular tone and blood flow, coagulation processes, thrombosis and fibrinolysis, immune and inflammatory reactions, and neovasculogenesis.

The general mechanism of action of all damaging factors is an increase in the adhesiveness of the endothelium in relation to platelets and leukocytes, the isolation of their activation factors. The procoagulant properties of endothelial cells are also enhanced, vasoactive molecules, cytokines and growth factors are formed. If such an inflammatory response is not neutralized or the effect of the damaging factor does not stop, the migration and proliferation of smooth muscle cells of the vascular wall will ensure the formation of the initial stage of atherosclerotic damage. The accumulation of monocytes in the subendothelial space is morphologically defined as the first stage of the fat spot. Further progression consists in an increase in the number of macrophages and lymphocytes in the lesion, and an increase in the plaque volume to the extent that obstructs blood flow [38,43]. A further increase in the number of macrophages and lymphocytes in the plaque, their active state leads to the production and release of hydrolytic enzymes, cytokines, chemokines and growth factors, which contribute to the

expansion of the affected area and the formation of local zones of necrosis [45,47]. Expansion and restructuring of the damaged area of the vascular wall leads to the formation of a massive atherosclerotic plaque with a fibrous cap and a lipid-necrotic nucleus. At this stage, the artery is no longer able to compensate for the growth of plaque by dilatation, which, combined with the lack of adequate synthesis of endothelial factors regulating vascular tone, an excess of hypercoagulable factors, leads to a significant violation or cessation of blood flow - the clinical manifestation of atherosclerosis [4,28]. In numerous studies devoted to the identification of the earliest stages of coronary atherosclerosis, the prevailing position is that the presence of endothelial dysfunction is considered a marker of initial, preclinical coronary atherosclerosis. R.Ross, A.Lerman, AM.Zeiher, D.Hasdai believe that endothelial dysfunction is an early phase in the development of atherosclerosis and can be considered as a "gold standard" in assessing the functional state of the endothelium [14]. Based on the assumption that endothelial dysfunction is reversible, Bonetti et al. believe that early detection of dysfunction has therapeutic and prognostic value [3]. Violation of endothelium-dependent vasodilatation is observed already in the early stages of atherosclerosis and may precede them.

Restoration of endothelial function contributes to the regression of structural atherosclerotic changes. Studies have demonstrated a positive dynamic of endothelial function and positive changes in the vascular wall when smoking cessation, following a rational diet, taking vitamins C, E [14,30,34]. The endothelium is the target organ for therapeutic treatments. Currently, almost all groups of drugs are being tested for their interaction with the endothelium. A positive effect on endothelial function has been demonstrated in ACE inhibitors, some beta-blockers, and HMG-CoA reductase inhibitors [26].

4. The Effect of Statins on the Prognosis of Patients with Ischemic Heart Disease

Correction of lipid metabolism disorders by controlling low-density lipoprotein (LDL) cholesterol is critical in reducing the risks of developing cardiovascular events [16,44]. A breakthrough in this direction at one time was the appearance of statins - drugs that lower cholesterol levels by competitive inhibition of the activity of HMG-CoA reductase. For the first time, the efficacy and safety of statins in patients with coronary artery disease was proved in 1994 in a randomized clinical trial 4S (The Scandinavian Simvastatin Survival Study) involving 4444 patients. Simvastatin at a dose of 20-40 mg statistically significantly reduced the level of LDL cholesterol by 35%, as well as the risk of CVS, including a 37% reduction in the risk of coronary revascularization. There have been a lot of studies on Rosuvastatin. The results of the CORONA test have been published. It evaluated the efficacy and safety of the active statin - rosuvastatin at a dose of 10 mg / day in elderly (aged 60 years and older) patients with ischemic heart disease with signs of heart failure. Long-term use of rosuvastatin was accompanied by pronounced stable changes in the levels of LDL cholesterol and CRP. Despite this, there were no significant differences between the intervention group and the placebo group, either in the frequency of the primary outcome adopted in the trial, or in the incidence of such an important component as cardiovascular death [23,44].

5. The Effect of Statin on Clinical Outcomes in Patients after Percutaneous Coronary Intervention

The ROMA study evaluated the effect of a loading dose of rosuvastatin before PCI [33]. This was a single-center, prospective, randomized study that included 160 patients with stable coronary artery disease without prior statin therapy who underwent PCI. Patients were randomized to a loading dose of rosuvastatin (40 mg single dose 24 hours before PCI) and a control group. The incidence of periprocedural myocardial infarction (defined as an increase in CPK-MV over 3 UHN after PCI) and major adverse cardiac and cerebral MACCE events (death, myocardial infarction, repeated myocardial revascularization and stroke) after 30 days and 12 months of observation was assessed. Thus, the frequency of an increase in CPK-MV 12 and 24 hours after PCI more than 3 upper limit of the norm was noted in 22.7% of patients in the control group and only in 7.1% in the rosuvastatin load group, $p = 0.003$. After 30 days and 12 months of observation, the incidence of MACCE was 30.0% in the control group and 8.7% in the rosuvastatin load group, $p = 0.001$ and 35.0% versus 12.5%, $p = 0.001$, respectively.

The obtained advantages of rosuvastatin loading over PCI are mainly due to a decrease in the incidence of periprocedural myocardial infarction: it was found in the control group in 26.4% of cases, in the rosuvastatin loading group - in 8.7%, $p = 0.003$. Thus, ROMA has shown that for patients with stable coronary artery disease who have not previously received statins, even a single dose of rosuvastatin administered within 24 hours before PCI can have a cardioprotective effect during PCI and significantly reduce the incidence of periprocedural myocardial infarction, as well as reduce the number of large cardiac and cerebral adverse events within 12 months after PCI.

The purpose of the ROMA II study was to compare the efficacy of a loading dose of rosuvastatin and atorvastatin in patients with stable coronary artery disease with indications for PCI who are already on prior statin therapy. This prospective randomized clinical trial included 350 people: 175 people were randomized to the rosuvastatin group and 175 to the atorvastatin group. The loading dose was a single, was prescribed 24 hours before PCI and amounted to 40 mg of rosuvastatin and 80 mg of atorvastatin, respectively. The

control group consisted of 100 patients without statin loading before PCI [33,37].

The primary endpoint was the incidence of periprocedural myocardial infarction (defined as an increase in the CPK-MB level more than 3 VGN) and the incidence of major adverse cardiac and cerebral events MACCE (death, myocardial infarction, repeated revascularization and hospitalization, stroke) after 30 days of observation, after 6 and 12 months of observation. According to the results of the study, clear advantages of loading doses of statins have been demonstrated both in the prevention of perioperative myocardial infarction and in the prevention of MASSE. Thus, the incidence of an increase in CPK-MB over 3 VGN was significantly lower in the groups with statin loading before PCI and amounted to 7.1% in the rosuvastatin group versus 25% in the control group, p = 0.003 and 6.1% - in the atorvastatin group versus 25% in the control group, p = 0.001 12 hours after PCI, 8.9% - in the rosuvastatin group versus 29.2% in the control group, p = 0.001 and 8.3% - in the atorvastatin group versus 29.2% in the control group, p = 0.0001 24 hours after PCI. There were no significant differences between the atorvastatin and rosuvastatin groups in terms of the increase in CPK-MB after 12 and 24 hours. The incidence of MASSE was significantly lower in the groups of loading doses of statins in comparison with the control group both after 30 days and after 6 and 12 months of observation (it was 8.9% in the rosuvastatin group versus 33% in the control group, p = 0.0001 and 8.3% in the atorvastatin group versus 33% in the control group, p = 0.0001 30 days after PCI, 10.2% in the rosuvastatin group versus 36% in the control group, p = 0.0001 and 8.9% in the atorvastatin group versus 36% in the control group, p = 0.0001 after 6 months and 11.4% and 12% versus 41%, respectively, p = 0.001). There were no significant differences between the atorvastatin and rosuvastatin groups in the incidence of MASSE over the entire observation period.

Thus, the results of the ROMA II study would be especially highlighted among others, since it was conducted on a less studied and most controversial group of patients - patients with stable coronary artery disease receiving prior statin therapy, and also due to the fact that this is the first randomized study. which compares the effectiveness of loading doses of the two main representatives of statins - rosuvastatin and atorvastatin.

In a meta-analysis, Pan at al. [26] included 14 randomized trials examining the loading dose of rosuvastatin before PCI. In total, the meta-analysis included 3273 patients, of which 1671 patients were in the high loading dose of rosuvastatin and 1602 were in the control group (low dose of statin or without it). Patients were also divided into subgroups depending on clinical characteristics (stable coronary artery disease and ACS), and also depending on the presence or absence of prior statin therapy.

The primary endpoints were the development of major adverse cardiac events MACCE (death, myocardial infarction, re-myocardial revascularization) and periprocedural myocardial infarction (defined as in the relevant studies). Of the 14 randomized trials under consideration, 10 were conducted exclusively in patients who had not previously taken statins, only one in patients on prior statin therapy, and three more included both. Thirteen studies used rosuvastatin loading for 24 hours before PCI, given once or divided into 2 doses; Thus, the minimum loading dose of rosuvastatin was 20 mg in one dose, and the maximum was 60 mg, divided into 2 doses before PCI. One study used long-term loading of rosuvastatin for 5-7 days before PCI, at 20 mg / day. The results of this meta-analysis indicate that rosuvastatin loading before PCI, as has been shown in previous studies for atorvastatin loading before PCI, reduces periprocedural myocardial damage during PCI and has a beneficial effect on long-term prognosis. Thus, large randomized studies to study the effect of loading doses of statins in patients with coronary artery disease undergoing endovascular treatment are still being carried out, which once again emphasizes the relevance of this topic and the great scientific and practical interest in it today.

A number of early studies investigated the effect of statins on the levels of markers of myocardial necrosis immediately after PCI, an increase in which is usually associated with an increase in the incidence of adverse outcomes [7,30]. One of these studies enrolled 451 patients with planned PCI who did not receive statins at baseline. Randomization was carried out to the group receiving statins before PCI (226 people) and the control group not receiving statins (225 people). Statin therapy was started on average 17 ± 8 days, at least 3 days before PCI. The majority of patients (84%) received statins for 2 or more weeks. After PCI, all patients were prescribed statins. Before the PCI procedure, as well as 6 and 12 hours after PCI, the levels of the CF fraction of creatine phosphokinase (CPK-MB) and troponin I (TnI) were determined. Prescription of statins before PCI in this study significantly reduced both the level of CPK-MB and TnI, and the frequency of increases in the levels of these indicators above 5 upper normal limits (ULN). Thus, the median values of CPK-MB after PCI was 1.70 (1.10-3.70) ng / ml in the statin group and 2.20 (1.30-5.60) ng / ml in the control group (p = 0.015). The median TnI values in the statin group were also lower compared to controls: 0.13 (0.05-0.45) ng / ml and 0.21 (0.06-0.85) ng / ml, respectively (p = 0.033). An increase in CPK-MB and TnI levels above 5 VLN in the statin group was noted significantly less frequently than in the control group: 8% and 15.6% (p = 0.01); 23.5% and 32% (p = 0.043), respectively. After PCI, MI was diagnosed in 5% of patients in the statin group and in 18% in the control group (p = 0.025). Based on the data obtained, the authors concluded that statins can reduce the risk of adverse events associated with PCI.

6. The Value of Statin in the Treatment of COVID-19

Inflammation-mediated tissue damage is the main

mechanism involved in the pathogenesis of COVID-19 caused by coronavirus-2 (SARS-CoV-2) severe acute respiratory syndrome. Statins have well-established anti-inflammatory, antithrombotic, and immunomodulatory effects [10,24]. They can influence the penetration of the virus into human cells. They also have a different effect on the cholesterol content in cell membranes and interact with some coronavirus enzymes involved in the binding of ACE-2 receptors. Both of these actions can influence the penetration of SARSCoV-2 into cells through these receptors on the cell surface, which can facilitate the entry of viruses into cells, but at the same time can minimize tissue damage through the production of angiotensin [2,6]. Practical scientific research suggests a positive effect of statin use on the clinical outcomes of COVID-19.

Statins are one such drug class that may have potential benefits in patients with COVID-19 [22]. Because statins are inexpensive, readily available, and already widely used for the prevention of cardiovascular disease, the first positive results have generated considerable interest in further study of their role, efficacy, and the underlying mechanisms of their benefits in COVID-19 [14,24]. Statins also modulate the immune response by working at different levels such as immune cell adhesion, migration, and cytokine antigen production. These actions are mediated by statins [32,34].

Several observational studies have assessed the potentially beneficial role of statins in COVID-19 [35]. Zhang et al. conducted a large retrospective cohort study of 13,981 COVID-19 patients in Hubei Province, China, of whom 1219 received statins [29,41]. They observed significantly lower 28-day mortality in the statin group (mortality 5.5%) compared to the non-statin group (mortality rate 6.8%, P = 0.046). Cox's study, after comparison, found that the risk of 28-day all-cause mortality was 5.2% in the statin group and 9.4% in the non-statin group, with an adjusted hazard ratio of 0.58. Patients taking statins have also been found to have lower levels of C-reactive protein and IL-6 [39,44]. Daniels et al. recently published a retrospective, single center study that examined all patients admitted to their center between February 10, 2020 and June 17, 2020 [50]. A total of 170 patients were found to have SARS-CoV-2, of which 53% developed a serious illness. It was noted that pre-hospitalization statin use was associated with a significantly lower risk of severe COVID disease (adjusted odds ratio 0.29, 95 CI 0.11 to 0.71, p <0.01). Statins have also been associated with faster recovery times in those who do not have severe illness after controlling for comorbidity. The beneficial effect of statin uses on reducing the risk of developing severe illness was also observed in patients with negative COVID status in hospital (n = 5281), but this association was much weaker than in patients with coronavirus [32].

Kow CS et al. published a meta-analysis of relevant studies evaluating the effect of statins on clinical outcomes in COVID-19 [8,11]. Four studies that included 8,990 COVID-19 patients. Two of these studies have inadequately described the relationship between statin use and clinical outcomes. However, this pooled analysis found a 30% lower hazard (pooled hazard ratio 0.7 95% CI 0.53-0.94) for fatal or severe illness with statin use compared with statin withdrawal [2,50].

Thus, statins have well-studied anti-inflammatory, antithrombotic and immunomodulatory effects. Initial retrospective clinical trials have shown that statins can potentially improve clinical outcomes in COVID-19 patients. If these benefits are proven in randomized trials, statins can also become a useful therapeutic drug for COVID-19, due to their low cost, simplicity and availability, with proven safety, good tolerance, and having vast clinical experience of their use for other indications.

7. Conclusions

Thus, despite the conduct of dozens of multicenter studies that have proven the hypolipidemic properties of statins, in particular, rosuvastatin, their questions regarding the correction of EF, lipid FRO processes, the inflammatory reaction at the site of atherogenesis remain insufficiently studied, and this, in turn, has an important prognostic meaning.

Currently, the emphasis in research is on the use of medium and high doses of drugs, at the same time, taking into account the negative side effects of statins (inactivation of the cytochrome chain, including coenzyme Q10, metabolic processes, myopathy, rhabdomyolysis), which can occur when using high doses, it seems advisable to study low doses of statins in patients with mild dyslipidemia, or an increased level of atherogenic drugs that do not significantly exceed the target values.

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