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INVITED EDITORIAL

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# From cardiovascular prevention to treatment of critically ill COVID-19 patients

Numerous studies showed that more intensive compared with less intensive LDL-cholesterol (LDL-C) lowering is associated with a greater reduction in risk of total and cardiovascular mortality. Statins are firstline agents used in patients with dyslipidemia, with established benefits in reducing lowdensity lipoprotein cholesterol (LDLC) levels and decreasing the rate of cardiovascular events [1, 2]. The aggressive statin treatment is associated with a 25–50% reduction in LDL cholesterol, and 20–37% in CRP [3, 4]. However, a considerable number of patients on statins do not achieve target LDLC levels, even at maximally tolerated statin doses, or are intolerant to intensive statin therapy. The ROSEZE study showed that treatment with rosuvastatin and ezetimibe in patients with coronary artery disease previously ineffectively treated with statin only, further reduced LDL-C levels by an average of almost 40% and by as much as 60% in those whose baseline LDL-C level was in the highest quartile [5, 6]. This effect was accompanied by a significant reduction of triglycerides (TG) by 15% and of hs-CRP by 23% after switching from monotherapy with a statin to double hypolipemic treatment (DHT) with rosuvastatin and ezetimibe. Despite this impressive LDL-C reduction 27% of patients still did not achieve desired therapeutic target [6]. Hypolipemic and antiinflammatory effects of a diet based on a high intake of omega3 fatty acids and balanced omega6/omega3 ratio in patients at high cardiovascular risk should also be taken into account as a possible supplementary option [7].

Treatment with proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors can lower LDLC by additional 45% to 65% [8]. Recently, Chlebus et al. Published the results of the experience of three Polish centers with the use of PCSK9 inhibitors in 55 patients with familial hypercholesterolaemia (FH) [9]. The treatment with PCSK9 inhibitors has been shown to be safe and effective, resulting in LDL-C and TG reduction by 65% and 28% respectively in patients with dyslipidemia [10, 11]. In the paper published by Chlebus et al., neither CRP levels nor other inflammatory markers were reported [8]. However, several experimental studies showed anti-inflammatory effect of PCSK9 inhibition [12–14]. These observations have not yet been directly confirmed in clinical trials [15]. Nevertheless, Walley et al. [16] demonstrated that human PCSK9 loss-of-function genetic variants were associated with a decrease in systemic inflammatory cytokine response in patients with septic shock and in healthy volunteers after lipopolysaccharides (pathogenic lipid moieties from Gram-negative bacteria cell walls) administration. Moreover, Ruscica et al. [17] reported a positive correlation between plasma levels of PCSK9 and TNF-$\alpha$, in healthy subjects. These observations further support the hypothesis of the probable impact of PCSK9 inhibition on systemic inflammatory response [16, 17]. Thus, PCSK9 inhibitors act as a potent lipid-lowering therapy with potential additional anti-inflammatory and anti-platelet effects [18]. The question of a possible anti-inflammatory effect of inclisiran remains open [19].

Combination of different therapies for the management of dyslipidemia should be considered to obtain optimal clinical effects. More profound lipid reduction and anti-inflammatory action associated with platelet inhibition are considered to have the potential to fur-

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Medical Research Journal 2022; Volume 7, Number 3, 187–189; 10.5603/MRJ.a2022.0031; Copyright © 2022 Via Medica; ISSN 2451-2591; e-ISSN 2451-4101

ther reduce the rates of adverse cardiovascular and thrombotic events, particularly in ACS patients. Therefore, "Hit fast, hit hard" approach regarding novel lipid-lowering therapy should be considered as the first-line of treatment in both stable and unstable high-risk patients. [20–25]. With extremely effective drugs at disposal, the adherence of patients to the prescribed therapy remains the most serious challenge [26–34].

The promising reduction of CRP concentrations associated with lipid-lowering therapy requires further understanding of the pathophysiological links between lipoproteins and inflammation [35]. Moving upstream in the inflammatory cascade from CRP to interleukin 6 (IL-6) and IL-1 provides novel therapeutic opportunities that focus on the central IL-6 signaling system [36]. Future investigations of dyslipidemia therapies considering an anti-inflammatory and antithrombotic effect in high-risk populations are needed to identify optimal therapeutic strategy.

Cytokine storm with excessive release of inflammatory mediators induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a major cause of COVID-19 severity and death. In patients with SARS-CoV-2 infection, IL-6 level was shown to be the best predictor of death. Due to its pivotal role in the cytokine storm during COVID-19, IL-6 signaling has been targeted as one of the most promising treatment options. [37]. Recently, we have postulated that PCSK9 inhibition may represent a novel therapeutic pathway in COVID-19. We have designed a pilot study: Impact of PCSK9 inhibition on clinical outcome in patients during the inflammatory stage of COVID-19 (IMPACT-SIRIO 5); ClinicalTrials.gov Identifier: NCT04941105 [38]. The study has been successfully finished and presentation of the final results should appear soon.

The expected demonstration of the clinical efficacy of a PCSK9 inhibitor in the treatment of patients with critically severe inflammation in the course of COVID-19, regardless of LDL-C level, may open new therapeutic options in the treatment of patients with various inflammatory diseases.

Conflict of interest: *None.*

Funding: *None.*

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