Abstract

Introduction

Complications of atherosclerosis, such as myocardial infarction and stroke, are the leading cause of death worldwide. Among the risk factors for the disease, LDL cholesterol (LDL-C) is one of the most important modifiable therapeutic targets. Oral lipid-lowering drugs (especially statins) have confirmed their efficacy not only in reducing LDL-C concentrations but also in lowering cardiovascular (CV) risk and CV mortality. This is partially attributed to their impact on non-lipid atherosclerotic risk factors, including inflammation, thrombotic parameters, and platelet activity. The aim of this study was to determine the potential pleiotropic effects of a lipid-lowering drug (inclisiran) that interferes with the activity of proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients at high or very high cardiovascular risk, with or without diagnosed heterozygous familial hypercholesterolemia (HeFH).

Materials and Methods

The objective of this study was achieved based on three papers, including one review (Publication No. 1) regarding the extrahepatic occurrence of PCSK9 and the non-lipid effects of the protein, as well as two original publications evaluating the potential pleiotropic effects resulting from the modulation of PCSK9 activity by inclisiran (Publications No. 2 and 3). The study included 24 participants aged between 41 and 81 years (the same population studied in Publications No. 2 and 3). Group 1 consisted of 10 high-CV-risk participants with diagnosed HeFH and no history of cardiovascular events; Group 2 consisted of 14 very-high-risk participants with a history of cardiovascular events. The effects of the drug (including pleiotropic effects) were assessed by measuring blood lipid profiles and subclinical markers of atherosclerosis, including inflammatory parameters such as pentraxin 3 (PTX3), interleukin 18 (IL-18), and CD40L (Publication 2), as well as thrombotic parameters (i.e., coagulation factor VIII (FVIII), fibrinogen, plasminogen activator inhibitor-1 (PAI-1)) and platelet activity (i.e., platelet factor 4 (PF-4), P-selectin) (Publication 3) at baseline and after 3 months of inclisiran therapy.

Results

After 3 months, a statistically significant reduction in total cholesterol and LDL-C concentrations was observed in both study groups. Furthermore, a decrease in the concentration of subclinical inflammatory markers of atherosclerosis, including PTX3 and IL-18, was noted in both groups. Among the thrombotic markers, a decrease in concentration concerned FVIII (in both groups) and fibrinogen (in Group 2), while among platelet activation markers, only PF-

4 decreased (in Group 2). No statistically significant differences were observed between Groups 1 and 2 regarding the potency of the lipid-lowering or pleiotropic effects.

Conclusions

Inclisiran is an effective lipid-lowering drug regardless of the etiology and severity of atherosclerosis. Moreover, it may influence non-lipid markers associated with the pathophysiology of the disease, such as inflammation, thrombotic parameters, and platelet activity.

Keywords:

inclisiran, PCSK9, atherosclerosis, heterozygous familial hypercholesterolemia