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Discovery Approaches for Novel Dyslipidemia Drugs

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Abstract: *Introduction*: Dyslipidemia is increased fasting level of total cholesterol (TC), LDL cholesterol (LDL-C), and triglycerides (TG), along with decreased levels of HDL cholesterol (HDL-C). Owing to effect on the cardiovascular system and increased chances of metabolic diseases, it is needed to review novel under development drugs and new approaches in drug discovery for dyslipidemia. *Areas Covered*: This article reviews all phases I to IV clinical trials and preclinical trials with results associated with novel treatment of dyslipidemia. Drug discovery for dyslipidemia, toward newer targets has been addressed. *Findings*: Statins are, currently available, best choice of drugs for treating dyslipidemia and coronary diseases. In addition to this, lipid lowering drugs support treatment to a great extent, either as monotherapy or in combinations with other groups. Pravastatin used in combination with cholesteryl ester, transfers protein inhibitors (CETP) to produce efficient results. Peroxisome proliferator-activated receptor agonists (PPAR) like muraglitazar, aleglitazar and tesaglitazar are PPAR α/γ receptor agonist, dual in action performs better in phase 3 clinical study and reduces renal and cardiovascular events. By targeting both receptors, a better treatment for cardiovascular and diabetic problems can be achieved. Proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors like humanized monoclonal antibodies, are newly discovered inhibitors that reduce the risk of cardiovascular diseases. During the past few years, nucleic acid–based therapies targeting lipid and lipoprotein metabolism, such as microsomal TG transfer protein (MTP) may be a promising therapeutic approach to treat vascular diseases. Gene regulating transcription factors involved in bile acids and cholesterol metabolism can be controlled by FXR agonists in dyslipidemia. To overcome these drawbacks, many thyroid hormone analogues have been developed to lower down cholesterol level by targeting specifically thyroid hormone β receptors abundantly present in the liver without severe side effects. Virtual screening, an important tool in screening databases of the lead compounds, provides a good platform to access new compounds. In this review, examples of novel FXR modulators, thyromimetic agents, cholesterol absorption inhibitors and other new anti hyperlipidemia scaffolds have been addressed.

Keywords: Cardiovascular disease, diabetes mellitus, dyslipidemia, FXR modulators, PCSK9 inhibitors, statins, synthetic drugs, virtual screening.

1. INTRODUCTION

Since the very beginning of the nineteen century, there has been a great concern about infectious diseases responsible for the high mortality rate [1]. The development of vaccines and antibiotics helped in the management of such diseases and decreased mortality rate. However, in the recent years, mortality rate from metabolic and cardiovascular diseases has reached to alarming level [2, 3]. Dyslipidemia has been reported as the main cause for metabolic and cardiovascular diseases causing increase in death rate. Dyslipidemia is described usually by raised fasting levels of TC, low density lipoproteins-cholesterol (LDL-C), and TG, along

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