LETTER TO EDITOR

Optimizing PCSK9 Inhibitor Integration for Cardiovascular Disease Management in Pakistan

Clinical Medicine Insights: Cardiology
Volume 18: 1–2

DOI: 10.1177/11795468241262648

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ABSTRACT: Cardiovascular illnesses (CVDs), particularly Coronary Artery Disease (CAD) and Ischemic Heart Disease (IHD), are major global health burdens, with a growing incidence in Pakistan. The development of PCSK9 inhibitors offers encouraging advantages in lowering LDL cholesterol and lowering cardiovascular risk, even though conservative treatments are still essential. However, access to them is severely hampered by their high cost, especially in environments with little resources. The financial limitations and scarcity of healthcare resources while examining the difficulties in obtaining PCSK9 inhibitors in Pakistan is essential. In order to develop solutions for affordability and fair access, it emphasizes the urgent need for multi-stakeholder collaboration, including governmental action, healthcare sector involvement, and pharmaceutical company engagement. It also emphasizes the need for data-specific research and the use of PCSK9 inhibitors in conventional treatment protocols.

KEYWORDS: PCSK9i, CVD in Pakistan, therapeutic monoclonal antibodies, hypercholesterolemia

Cardiovascular Diseases are one of the most prevalent life-threatening conditions throughout the world, with an estimated 19.1 million deaths globally attributed to Cardiovascular disease in 2020 alone.[1] Ischemic Heart Disease also called Coronary Artery Disease (CAD) is the most common of these Cardiovascular diseases, with a global estimation revealing that in 2020, around 244.1 million people were living with ischemic heart disease.[1] It is the third leading cause of mortality worldwide, associated with 17.8 million deaths annually.[2] In Pakistan, it is the second leading cause of mortality and has risen by an alarming 21.54% in a matter of 20 years from 1999 to 2019.[3]

Conservative treatment of CAD aims to stop the progression of atheromas present in the arteries. It comprises lifestyle alterations and diet changes, as well as medical therapy which serves as the cornerstone for conservative coronary artery disease management to lower the risks arising from invasive surgical treatment such as graft failure, re-stenosis of stents, and the possible need for future interventions with PCI.[4,5] It comprises anti-ischemic drugs including Beta blockers, calcium channel inhibitors and another set of drugs that prevent atherosclerotic events which comprise anti-platelet therapy such as clopidogrel, other therapies such as statin therapy, and the use of lipid-lowering agents.[5] Statins are the most common drugs that lower cholesterol, but they are not indicated for all patients, and may lead to serious side effects such as muscle pain, liver damage, type 2 diabetes, and neurological side effects or may not work in some patients owing to their cholesterol being resistant to statin. This begs the need for using supplementary or complementary potent lipid-lowering therapies.[6]

Proprotein convertase subtilisin/kexin Type 9 (PCSK9) is a serine protease primarily released by the liver and promotes the lysosomal degradation of hepatic low-density lipoprotein (LDL)-receptor after binding to it, leading to decreased blood LDL clearance.[7] It is identified as an important and major agent in hypercholesterolemia and the pathophysiology of atherosclerosis, and a case-control study in Chinese CAD patients revealed that PCSK9 levels had a positive and significant association with the incidence and severity of CAD.[8] PCSK9 inhibitors (PCSK9i) are a new class of drugs that lower LDL by blocking the activity of PCSK9 with monoclonal antibodies. They reduce the degradation of LDL receptors and increase the clearance of LDL-cholesterol, reducing cholesterol levels by an average of 50% to 60%. The medications are given as shots every 2 to 4 weeks.[6] A meta-analysis of 23 Randomized Controlled Trials with 41 932 patients revealed a statistically significant reduction in Myocardial Infarction (MI) on treatment with PCSK9i and a statistically significant reduction in coronary revascularization in 22 trials and 40 542 patients.[9] In 2015, the FDA approved 2 PCSK9i; Alirocumab and Evolocumab as an addition to diet and with maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease who require additional lowering of LDL.[10]

Lack of financial resources and low budget allocation in the healthcare sector can be a major barrier to preventing doctors from prescribing PCSK9i to patients with maximally tolerated statin therapy, which costs around US $14 000 for a year's supply[11] or around $1700 a month. In contrast, the monthly median treatment price of some essential statins in Pakistan ranges from $5.00 to $7.50 per month,[12] which is a monumental difference in cost. According to the data from the Household Integrated Economic Survey 2018 to 2019, 22% of the population of Pakistan already lives below the poverty line,[13] and these issues have led to only 1% of physicians in Pakistan prescribing PCSK9i to lower cholesterol for adults with familial hypercholesterolemia compared to 92.2% of physicians who used Statins alone or in combination with other drugs.[12]

Pakistan spent 1.2% of the total GDP in 2020 to 2021 on healthcare compared to the 5% recommended by the World Health Organization (WHO). As a result of this disparity, 64% of health expenditure relies on out-of-pocket payments, which further aggravates the socioeconomic position and pushes families to the brink of poverty.[12] In 2019, Pakistan ranked at the bottom 10th of countries in terms of effective Universal Health Coverage, where patients are left to bear the entire burden of their treatment.[3]

Due to the extensive costs of PCSK9 inhibitor therapy, only a slight percentage of the population would be able to afford the out-of-pocket payments.

The sharp rise in risk factors directly associated with the prevalence of CAD such as diabetes, hypertension, and smoking[14] in the Pakistani youth is also a matter of great concern for the healthcare sector of Pakistan. The consequent rise in adverse outcomes will be detrimental to the country's future with the patient population slowly creeping higher.[3] The need of the hour is that the major stakeholders in Pakistani healthcare along with the government devise an emergency plan to incorporate PCSK9i into standard therapy for ischemic heart disease for enhanced lowering of LDL. Data specific to the Pakistani population identifying the risk factors and patient outcomes for FDA-approved PCSK9i; Alirocumab and Evolocumab are unfortunately non-existent, and multicenter studies specific to the Pakistani population are urgently required. The partnership of multinational pharmaceutical companies and the endorsement of future table meetings with concerned panels to discuss medical coverage are necessary, along with an extended public healthcare expenditure by the government. An update of standard therapy to refit current guidelines by raising physician awareness and quality of practice in mass influx public sector as well as private sector hospitals with regards to cardiac care would also lead to positive outcomes. Due to its high costs, strategic formulation and implementation of patient eligibility criteria and a program for widespread screening within the country are also required.

The use of therapeutic monoclonal antibodies to target PCSK9 represents a novel approach to the prevention of atherosclerotic cardiovascular disease and the management of hypercholesterolemia. A better understanding of its cost-effectiveness will determine the future role of this therapeutic class in the country.[15]

Author Contributions

Muddassir Syed Saleem: Bringing up the concept of the study, drafting of the work, final approval and agreeing to the accuracy of the work, also reviewed and revised the manuscript. Shahzaib Samad: Final approval, also reviewed and revised the work. Added relevant changes to the concept of the study. Syed Shahmeer Ahmed: Drafting of the work, final approval and agreeing to the accuracy of the work. Nadia Mehmood: Drafting of the work, final approval and agreeing to the accuracy of the work.

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RECEIVED: May 12, 2024. ACCEPTED: May 29, 2024.

TYPE: Letter to the Editor

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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