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Narrative Review

The Burning Necessity for Establishing National Guidelines - Side Effects of Lipid Lowering Drugs and Difficulty of using High Intensity Statins in Pakistani Population

Noor Dastgir[1]* and Wafa Qaisar[2]

[1]Department of Cardiology, Allama Iqbal Medical College, Jinnah Hospital, Lahore, Pakistan

[2]Department of Medicine, Akhter Saeed Medical College, Farooq Hospital Lahore, Pakistan

Lipid lowering strategy has been widely used in both the primary as well as the secondary prevention of atherosclerotic cardiovascular disease, particularly in managing patients who are either diagnosed with ischemic heart disease or stroke or face great susceptibility to developing these complications as a result of risk factors like diabetes, hypertension, sedentary lifestyle and so on [1,2].

The mechanism of action of Statins is by inhibition of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase which is the rate-limiting step in cholesterol synthesis [3]. Statins hence have a great impact on the lipid metabolism and play a vital role in prevention of atherosclerotic complications [4]. They reduce LDL-C, Total cholesterol, and Triglyceride levels; slightly increase HDL-C levels [5]; and are also thought to have anti-inflammatory and other plaque stabilization effects, referred to as their pleiotropic properties [6].

***Corresponding author:** Noor Dastgir, Department of Cardiology, Allama Iqbal Medical College, Jinnah Hospital, Lahore, Pakistan, Tel: +92 3215555189; E-mail: noordastgir@gmail.com

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The updated guideline on the use and dosing of statins was issued in 2013 by the American College of Cardiology (ACC) and the American Heart Association (AHA) where a classification was devised categorizing therapy into low, medium and high intensity therapy stating fixed doses, and clear indications as to which patients would be benefitted by which group [7,8].

High intensity statin therapy hopes to achieve LDL reductions of more than 50% of the baseline and mainly includes Atorvastatin (40-80mg) and Rosuvastatin (20-40mg) [9]. While all the benefits of lipid lowering therapy cannot be emphasized upon enough, it does bring out the question of challenges in compliance to treatment regimens comprised of such high doses owing to the side effects being experienced by the patients [10,11].

Statins may cause widespread systemic effects like hepatotoxicity, type 2 diabetes, cataract, polyneuropathy, memory loss, behavioral changes and, rarely, headache, gastrointestinal disturbance, rash etc [12].

Most common concerning consequences of statin therapy include musculoskeletal system involvement in the form of myopathy and tendinopathy that may present with muscle aches (myalgias) and sometimes even leading to muscle breakdown (rhabdomyolysis) causing elevated creatinine kinase levels with a pathophysiology not completely understood [13-16].

Studies done previously have reported that muscle and tendon related side effects were most commonly noticed in patients treated with rosuvastatin. The onset of myalgias may be variable ranging from a few weeks after treatment initiation to years. Older age, female gender, individual patient genetics and comorbid conditions like hypertension, diabetes and hypothyroidism are all factors that may increase the prevalence of such effects along with processes at molecular level like the CYP mediated statin metabolism and various drug-drug interactions [17,18].

In view of this, FDA recommends lowest effective dose of statins to reduce statin-associated myopathies and other untoward outcomes accompanying their use [19].

Inter-racial differences in response to statins have been previously reported [20]. Asian patients have been seen to have a mounted response compared to the Caucasian population due to differences in ethnicity and the genetic make-up affecting the metabolism [21]. In one such study, it was seen in the Japanese population that a lower dose of statins demonstrated similar relative risk reduction of cardiovascular events to a higher dose of statins in Western patients [22,23]. In fact, the maximum dose of atorvastatin in clinical practice was 40 mg per day in Japan, while the dose is 80 mg per day in the United States [24]. Most adverse effects of statins are dose related and in a directly proportional relationship [25].

It is important to understand that Pakistani patients may have a lower threshold for tolerance of statin therapy while at the same time, they may require perhaps a lower dose to achieve target levels of LDL. In a study conducted at Agha Khan University, it was concluded that even an alternate day regimen may have similar clinical benefits to standard daily dosing but with better tolerance and compliance [25].

Several studies have been done internationally studying the difficulties health care providers face while ensuring adherence to high dose statin therapy. We wish to explore the possibility of establishing these interracial differences in response to statin therapy, both in achieving the therapeutic goals as well the occurrence of intolerable side effects that may lead to discontinuation of medication despite clear clinical benefits. Hence it is important to emphasize the need of developing national guidelines keeping in mind our population regarding statin therapy.

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