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Original Research Paper

Cardiovascular

CLINICAL EXPERIENCE OF ROSUVASTATIN IN PATIENTS WITH CARDIOVASCULAR EVENTS: INSIGHTS FROM A REAL-WORLD STUDY

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ABSTRACT **Background:** Dyslipidemia is a common risk factor for cardiovascular diseases, and can be effectively managed with rosuvastatin. This study evaluated the efficacy and safety of different doses of rosuvastatin among patients with cardiovascular diseases. Methods: This retrospective, multi-centric, real-world study was conducted across Nepal, which included patients of either gender aged ≥18 years with cardiovascular events requiring statin therapy. Data were extracted from hospital medical records. The primary endpoint was a percent change in low-density lipoprotein cholesterol (LDL-C) from baseline after rosuvastatin treatment, and secondary endpoints involved changes in total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride. **Results:** A total of 297 patients were included in the study. High salt intake (90.59%) and dyslipidemia (83.50%) were the common risk factors. Rosuvastatin 10 mg (58.45%) was the most common drug received. The majority of patients received rosuvastatin for both primary (88.52%) and secondary prevention (91.67%). After rosuvastatin initiation, LDL-C decreased significantly by a mean of 63.4 mg/dL (95% CI: 43.0 to 83.8; P<0.001), while HDL-C increased by -5.0 mg/dL (95% CI: -6.7 to -3.3; P<0.001). Total cholesterol decreased by 67.4 mg/dL (95% CI: 59.9 to 74.9; P<0.001), and triglyceride levels decreased by 93.9% (95% CI: 77.5 to 110.2; P<0.001). Only 3.03% of patients reported adverse events related to rosuvastatin. Physician global evaluation showed good to excellent efficacy and tolerability to rosuvastatin by 97.1% and 97.2%, respectively. **Conclusion:** Physicians favor rosuvastatin 10 mg for both primary and secondary prevention of cardiovascular events demonstrating its clinical efficacy and safety in improving lipid profile.

KEYWORDS : Dyslipidemia, low-density lipoprotein cholesterol, lipid profile, salt intake

INTRODUCTION

Cardiovascular diseases (CVDs) continue to be the leading causes of death globally and substantially impact overall health and healthcare costs[1]. In Nepal, the prevalence of cardiovascular diseases across all age groups has increased from 2,783.24 to 3,993.27 per 100,000 people between 1990 and 2019. Likewise, the all-age mortality rate for CVD increased from 111.11 to 152.88 deaths per 100,000 people between 1990 and 2019 [2]. Dyslipidemia is one of the common risk factors for CVDs, among young adults [3]. Behavioral and metabolic risk factors also elevate the total risk of developing acute cardiovascular events [4].

Several studies have demonstrated the relationship between the raised level of total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) in the development of coronary heart disease. Most current guidelines prioritize LDL-C as a primary target for initiating and adjusting dose for dyslipidemia management [5-8]. According to the American Heart Association/American College of Cardiology (AHA/ACC) 2018 and the European Society of Cardiology (ESC), treatment guidelines for dyslipidemia recommended high-intensity statin therapy as a primary as well as secondary prevention of CVD to achieve≥50% reduction in LDL-C [9].

Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors and effectively reduce LDL-C and TC. Rosuvastatin is a selective and new-generation competitive inhibitor of HMG-CoA reductase, which exhibits four times higher affinity for HMG-CoA reductase than affinity of HMG-CoA for the enzyme. The notable benefits of rosuvastatin include low extrahepatic tissue penetration, low potential for cytochrome P450 3A4 (CYP3A4) interactions and a strong ability to lower LDL-C [10]. A noteworthy study has shown that rosuvastatin offers superior lipid-lowering efficacy over other statins. Compared with other potent statins, rosuvastatin has a longer half-life period (20 h) with optimal LDL-C reduction in a range of 38.8 mg/dL to 54.7 mg/dL along with a favorable safety profile at a dose ranging from 5 to 40 mg [11].

Several clinical trials have analyzed the effects of rosuvastatin on LDL-C. In particular, the Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) study showed that rosuvastatin demonstrates superior LDL-C reduction compared to atorvastatin, simvastatin, and pravastatin. Likewise, rosuvastatin increased high-density lipoprotein cholesterol (HDL-C) and decreased triglyceride (TG) levels [12]. A meta-analysis of 44 studies involving 34,196 patients confirmed rosuvastatin as the most potent statin for reducing LDL-C levels over other statins [13]. Additionally, rosuvastatin offers several added advantages, such as anti-inflammatory, antioxidant, antithrombotic, and vascular protective effects [14].

However, the effectiveness and safety of rosuvastatin following CVD have not been widely studied in Nepal, especially in a real-world context. In view of the lack of real-world evidence study evaluating the efficacy of rosuvastatin in terms of CVD, this study was undertaken to explore the efficacy and safety of the different doses of rosuvastatin among patients with CVD.

MATERIALS AND METHODS

STUDY DESIGN AND ETHICS CONSIDERATIONS

This was a retrospective, non-comparative, non-randomized, multi-centric real-world cross-sectional study conducted at multiple tertiary care centers across Nepal. It involved the analysis of medical records of adult patients who had

received treatment with rosuvastatin or rosuvastatin-based combination as a lipid-lowering therapy for primary and secondary prevention of cardiovascular events.

INCLUSION AND EXCLUSION CRITERIA

Adult patients (≥18 years) with cardiac events requiring statin therapy primary or secondary prevention. Patients were excluded if they had documented statin use in the past 3 months, any contraindication to HMG-CoA reductase inhibitors, and patients who were taking a concomitant non-statin lipid-lowering agent. Patients with blood TG level of > 400 mg/dL, aspartate transaminase (AST) or alanine transaminase [ALT]) ≥3 upper limit normal, or serum creatine kinase (CK) >5 upper limit normal were also excluded from this study. ACS patients who had surgery (including percutaneous coronary intervention [PCI]) or hospitalization within the last 3 months were excluded.

DATA COLLECTION

Information on baseline characteristics [gender, age, weight, height, body mass index (BMI), and location], risk factors, medical history, treatment patterns, and adverse events were retrieved from patient's medical records available at hospitals/clinics and entered into case report forms.

STUDY ENDPOINTS

The primary endpoint was the percent change from baseline in LDL-C levels after treatment. The secondary endpoints included the percent change from baseline in TC, HDL-C, and TG, after treatment; and the percent change from baseline. The safety and tolerability of rosuvastatin were assessed by evaluating the incidence and severity of adverse events (AEs).

STATISTICAL ANALYSIS

Data were analyzed using Statistical Package for The Social Sciences (SPSS) software, version 23.0. Qualitative data was presented as numbers and percentages, while quantitative data was presented as mean (standard deviation [SD]) or median (range). A paired non-parametric Wilcoxon Signed Rank Test was used to compare variables pre- and post-treatment

RESULTS:

A total of 297 patients were included in this study. The demographic characteristics of these patients are represented in Table 1. The majority of them were men (62.86%). The mean (SD) age (n=284) of the patients was 55.65 (12.65) years. The median (range) BMI of the patients was 27.55 (12.05-51.14) kg/m2. Majority of physicians (90.59%) reported that high salt intake was the most common risk factor among the patients. Out of 297 patients, 52 had a family history of CAD (70.27%). Majority of the patients had dyslipidemia (83.50%), followed by hypertension (61.62%) and type 2 diabetes mellitus (44.78%) in their medical history.

TABLE 1: DEMOGRAPHICS DATA

Parameters	Number of patients (N = 297)*
Gender, (n=280)	
Men	176 (62.86)
Women	104 (37.14)
Age [years], mean (SD) (n=284)	55.65 (12.65)
Weight [kg], mean (SD) (n=267)	70.06 (11.87)
Height [cm], mean (SD) (n=257)	160.45 (13.15)
BMI [kg/m2], median (range) (n=257)	27.55 (12.05-51.14)
Location (n=275)	
Urban	139 (50.55)
Semi urban	89 (32.36)
Rural	40 (14.55)
Semi-rural	7 (2.55)
Risk factors	
Salt intake	231 (90.59)
Smoking	130 (52.42)
Stress	99 (54.10)
Family history (n=74)	
CAD	52 (70.27)
ASCVD	22 (29.73)
Medical history	
Dyslipidemia	248 (83.50)
Hypertension	183 (61.62)
Type 2 diabetes mellitus	133 (44.78)
ACS	47 (15.82)
Heart failure	12 (4.04)
Stroke/TIA	10 (3.37)
PAD	2 (0.67)
Any other	
BPH	1 (0.34)
Atrial fibrillation/COPD	1 (0.34)
Hypothyroidism	1 (0.34)

Data shown as n (%), unless otherwise specified.
*N = 297, unless otherwise specified.
ACS, Acute coronary syndrome; ASCVD, atrioventricular cardiovascular disease; BMI, body mass index; BPH, benign prostatic hyperplasia; COPD, chronic obstructive pulmonary disease; PAD, peripheral artery disease; TIA, transient ischemic attack.

Table 2 represents the treatment pattern of this study. The most common treatment pattern observed in the patients was rosuvastatin 10 mg (58.45%). Majority of patients had rosuvastatin for both primary prevention (88.52%) and secondary prevention (91.67%). Dose titration was performed in 50 patients out of which 32 patients had up titration of dose while the remaining 18 patients had down titration. Among 28 patients, the most common reason for titration was uncontrolled lipid levels (53.84%). The combination therapy with rosuvastatin observed in patients (n=106) was multivitamins (58.49%) followed by fibrates (32.08%), and cholesterol absorption inhibitors (5.66). Non-steroidal anti-inflammatory drug (52.10%) was a commonly used treatment for concomitant medication in the patients (n=167).

TABLE 2: TREATMENT PATTERNS

Parameters	Number of patients (N =297)*
Treatment pattern	[n=296]
Rosuvastatin 5 mg	48 (16.22)
Rosuvastatin 10 mg	173 (58.45)
Rosuvastatin 20 mg	75 (25.34)
Primary prevention	162 (88.52)
Secondary prevention	77 (91.67)
Dose titration of rosuvastatin therapy	[n=50]
Dosage up titration	32 (64.00)
Dosage down titration	18 (36.00)
Reason for titration	[n=26]
Uncontrolled lipid levels	14 (53.84)
CV events	7 (26.92)
Improvement in condition	2 (7.69)
Uncontrolled DM	1 (3.84)
Uncontrolled HTN	1 (3.84)
Stress	1 (3.84)
Combination therapy with rosuvastatin	[n=106]

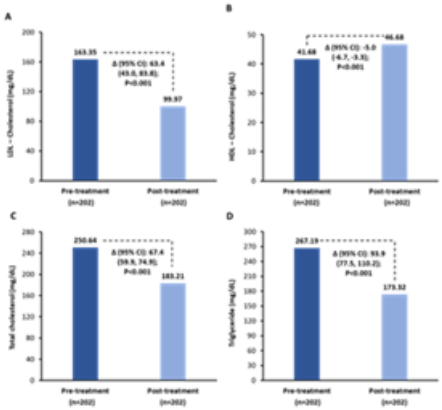
Multivitamin	62 (58.49)
Fibrates	34 (32.08)
Cholesterol absorption inhibitors	6 (5.66)
CCB	2 (1.89)
ARB	1 (0.94)
Any other	2 (1.89)
Treatment for concomitant medications (other than lipid lowering therapy), (n=158)	
NSAID	87 (52.10)
ARB	22 (13.17)
Antiplatelet medication	18 (10.78)
Antidiabetic drugs	16 (9.58)
CCB	12 (7.19)
Beta-blockers	5 (2.99)
Diuretic	4 (2.40)
ACE inhibitor	2 (1.20)

Data shown as n (%), unless otherwise specified.
*N = 297, unless otherwise specified.
ACS, Acute coronary syndrome; ACE, angiotensin converting enzyme; ARB, angiotensin 2 receptor blockers; ASVD, atrioventricular cardiovascular disease; CAD, coronary artery disease; CCB, calcium channel blocker; CV, cardiovascular; DM, diabetes mellitus; HTN, hypertension; NSAID, nonsteroidal anti-inflammatory drug.

The changes in TC, LDL-C, HDL-C, and TG are represented in Figure 1. For LDL-C, a significant mean [95% confidence interval (CI)] change was observed at 63.4 (43.0 to 83.8; P<0.001) [Figure 1A]. Similarly for HDL-C, the significant mean (95% CI) change was observed at -5.0 (-6.7 to -3.3; P<0.001) [Figure 1B]. A significant mean (95% CI) change observed in TC levels between pre-treatment and post-treatment was 67.4 (59.9 to 74.9; P<0.001) [Figure 1C]. The significant mean (95% CI) change in TG levels between pre-treatment and post-treatment was observed at 93.9% (77.5 to 110.2; P<0.001) [Figure 1D].

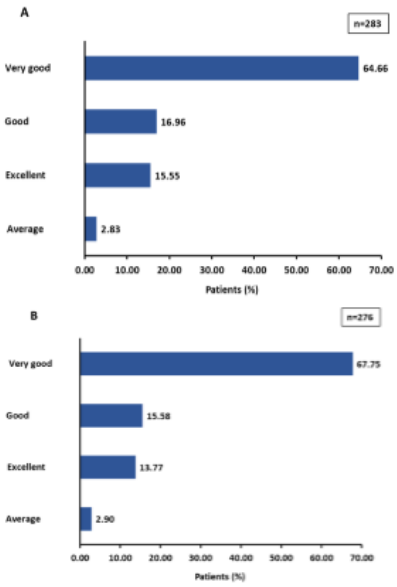
Only 3.03% of patients had adverse events in the last three years related to rosuvastatin/or combination. Physicians' opinions regarding the global evaluation of the efficacy and tolerability of rosuvastatin are represented in figure 2. Approximately 97.2% of physicians rated the efficacy of rosuvastatin as excellent to good. Similarly, about 97.1% of physicians rated the tolerability of rosuvastatin as excellent to good.

FIGURE 1: CHANGES IN A) LOW DENSITY LIPOPROTEIN CHOLESTEROL, B) HIGH DENSITY LIPOPROTEIN CHOLESTEROL, C) TOTAL CHOLESTEROL AND D) TRIGLYCERIDE



Data shown as mean change (95% CI): P value , mean change; CI. Confidence interval

FIGURE 2: A) PHYSICIANS' GLOBAL EVALUATION OF EFFICACY AND B) PHYSICIAN GLOBAL EVALUATION OF TOLERABILITY



DISCUSSION

This study assessed the efficacy and safety of rosuvastatin in a total of 297 patients with cardiovascular disease in routine clinical settings. The present study found that rosuvastatin was effective in improving the various parameters of lipid profile, including LDL-C, HDL-C, TC, and TG. Rosuvastatin was well tolerated in this study.

In Nepal, dyslipidemia appears to be a common condition among individuals suffering from coronary heart disease [15]. A previous descriptive cross-sectional study conducted on 105 patients admitted to a tertiary care center with a diagnosis of acute coronary syndrome found that the majority of patients had one or more conventional risk factors for CAD. These risk factors included dyslipidemia, diabetes, and hypertension, which align with findings from similar studies [16]. Additionally, recent research has highlighted the prevalence of dyslipidemia among young Nepalese university students, identifying it as a significant risk factor for cardiovascular disease [3]. In the present study, the majority of the patients with cardiovascular disease had dyslipidemia (83.50%). These findings underscore the significant role dyslipidemia plays as a major risk factor for cardiovascular disease in Nepal. It affects both younger and older populations in Nepal, making it essential to focus on the need for early detection and effective management strategies to mitigate the growing burden of heart disease.

The majority of patients in this study were treated with rosuvastatin 10 mg, with only 75 patients (25.34%) receiving the 20 mg dose. This is consistent with the data seen in other real-world studies in the Asian population, where 5 mg and 10 mg doses are used more frequently than higher doses [17,18].

A previous study demonstrated that among patients who achieved the target LDL-C goal, significantly fewer patients from rosuvastatin patients (8.3%) had titration compared with atorvastatin (17.0%), simvastatin (20.0%), pravastatin (20.7%), and lovastatin (23.5%) (all, P < 0.05). Further analysis revealed that patients who achieved their target LDL-C levels on other statins were significantly more likely to require dose titration compared to those on rosuvastatin [odds ratios (OR) 2.0-3.3; P < 0.05] [19]. On a similar line, a previous real-world study assessing rosuvastatin in patients with CVD revealed that during the course of treatment, rosuvastatin dose titration

was done only in 35.8% (642/1794) patient population, while up-titration was done in 487 and down-titration in 155 patients. Among the patients who required dose titration, the primary reason for intensifying rosuvastatin was uncontrolled lipid levels. Additional contributing factors included a sedentary lifestyle, stress, and smoking [17]. The present study aligns with previous findings, showing only 17% (n = 50) of patients had dose-titration out of which the majority of patients had up-titration (n = 32) and the remaining had down-titration (n = 18) due to uncontrolled lipid levels. These findings suggest that rosuvastatin is associated with fewer cases of dose titration.

In the present study, post-treatment showed a significant median change in LDL-C of 63.4 which is comparatively higher than that reported in other observational studies [20-22]. Recently reported observational study revealed that following a 12-week course of rosuvastatin therapy there was a significant reduction in LDL-C levels across the entire population. The mean reduction in LDL cholesterol was 30 mg/dL from baseline, corresponding to a notable 19% decrease from baseline levels [23]. These results have also been observed in a previous comparative study from Nepal where patients on rosuvastatin experienced a greater reduction in mean LDL-C levels compared to those on atorvastatin (26% vs. 8.7%) [24]. A similar trend has been observed in a previous multicenter, post-marketing observational study evaluating the efficacy and safety of rosuvastatin 40 mg/day in very high-risk or high-risk Indian patients. Rosuvastatin therapy led to an optimal reduction in LDL-C levels, with a decrease of 46.9 mg/dL (95% CI: -57.3 to -36.5) by week 6 and 40.5 mg/dL (95% CI: −52.0 to −29.0) by week 12 compared to baseline. These findings indicate a significant improvement in LDL levels over the course of treatment [22].

In the present study, rosuvastatin led to improvement in HDL-C, TC, and TG levels. Results from the CHARON (Hypercholesterolemia in Children and Adolescents Taking Rosuvastatin Open Label) study showed that in the ITT population at 24 months, there was also a significant reduction in TC, non-HDL-C, and a significant increase in HDL-C level (all, $P<0.001$) compared with baseline across all age groups and overall population [20]. A systematic review of 108 trials on rosuvastatin reported a 7.3% increase in HDL-C levels with rosuvastatin and a 19.7-26.7% reduction in TG levels for 10–40 mg/day of rosuvastatin use [25]. A recently published noteworthy study also showed similar observations [22]. In particular, the STELLAR study showed that it is a most powerful statin. Post 6 weeks of treatment, rosuvastatin increased HDL-C by 8-10% and decreased TG levels by 20-26% [12]. Recent literature suggests that alternative rosuvastatin dosing regimens have also improved lipid control in patients previously deemed intolerant to statins [26-28].

Rosuvastatin was well tolerated with lesser-known adverse events (3.03%). None of the AEs were categorized as serious in intensity. There were no deaths during the rosuvastatin treatment. These findings are consistent with the previous clinical trials with rosuvastatin [22]. Additionally, an observational study conducted in Nepal alluded that rosuvastatin had a lower incidence of adverse effects compared to atorvastatin (30.66% vs. 54.66%), with reported rates of fatigue, headache, gastritis, allergy, and insomnia [24].

LIMITATIONS

This study was an observational retrospective study that has its limitations. First, the retrospective nature of the study and the reliance on electronic medical records for data collection introduces the risk of missing critical information related to participants' backgrounds, laboratory results, or outcomes that may not be appropriately documented in the medical records.

CONCLUSIONS

This study suggests that physicians favor rosuvastatin 10 mg for both primary and secondary prevention of cardiovascular events. The moderate dose of rosuvastatin (5 mg to 20 mg) has demonstrated clinical efficacy and safety, which may provide a clinician with evidence-based reassurance. With the existing evidence of rosuvastatin's advantages in improving lipid profile, larger randomized prospective trials with a longer follow-up period are warranted to confirm the findings of the current study.

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