

The Association of Suspected Adverse Drug Reactions with Patients Receiving Atorvastatin or Rosuvastatin in A Tertiary Care Hospital.

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Abstract: *Background:* Statins, primarily atorvastatin and rosuvastatin, are widely prescribed lipid-lowering agents proven to reduce cardiovascular morbidity and mortality. However, concerns regarding adverse drug reactions (ADRs), especially musculoskeletal complaints, often affect patient compliance and long-term outcomes. Comparative real-world data on their safety profiles in Indian clinical settings remain limited. *Objective:* To study the association of suspected ADRs with patients receiving atorvastatin or rosuvastatin in a tertiary care hospital. *Methods:* A prospective cross-sectional study was conducted in the Department of Pharmacology at Teerthanker Mahaveer Medical College and Research Centre, Moradabad, India. A total of 290 adult patients who received either atorvastatin or rosuvastatin and subsequently reported suspected ADRs were enrolled. Data were collected using a validated ADR reporting form. Causality was assessed using the WHO-UMC scale, while seriousness and outcome were evaluated per PVP and ICH guidelines. Statistical analyses included Chi-square tests and binary logistic regression, with $p < 0.05$ considered significant. *Results:* Among 290 patients, 191 experienced suspected ADRs, while 99 did not. Musculoskeletal disorders, including myopathy, joint pain, and limb discomfort, were the most commonly reported ADRs. Male patients exhibited a significantly higher incidence of ADRs than females ($p < 0.001$). Logistic regression revealed that rosuvastatin was associated with significantly fewer ADRs than atorvastatin ($p = 0.005$), indicating superior tolerability. The dose of statins did not show a statistically significant correlation with ADR occurrence ($p = 0.097$). *Conclusion:* Rosuvastatin demonstrated a better safety profile compared to atorvastatin, with a significantly lower incidence of suspected ADRs, particularly musculoskeletal symptoms. The unexpected gender disparity and lack of dose-ADR association highlight the complexity of statin-related adverse effects. These findings support the preferential use of rosuvastatin in patients at higher risk for intolerance. Further large-scale, multi-centric studies are warranted to validate these observations and guide personalized statin therapy.

Keywords: Statins, Atorvastatin, Rosuvastatin, Adverse Drug Reactions, Pharmacovigilance, Musculoskeletal disorders, Gender difference, India.

INTRODUCTION

The discovery of statins as a novel target of antibacterial action is the most significant outcome of research conducted in the field of microbiology. Substances that were believed to be inhibitors of hydroxymethylglutaryl-CoA (HMG-CoA) reductase were described in a substantial amount of literature in the years leading up to 1976. These substances included oleic acid, cyclic AMP, and others.¹ Statins reduce the amount of cholesterol that is present in cells, it restricts the generation of new cholesterol, and it lowers the levels of cholesterol that are present in the liver. They do this by directly blocking the enzyme HMG-CoA reductase with their actions. All of these factors contribute to an increase in the expression of LDL-receptors (LDL-R) in the membranes of the liver cells, which in turn leads to an improvement in the removal of circulating LDL cholesterol particles from the blood.² Certain individuals, namely those who have combined hyperlipidaemia, have a reduction in the hepatic production rate of lipoproteins containing apo B100 as a consequence of statin treatment. This, in turn, leads to a decrease in the concentrations of both cholesterol and triglycerides over time.³ It is possible that

the metabolic transformation of statins is partially responsible for the variable effectiveness of statins in decreasing cholesterol levels. It was demonstrated, following an analysis of a large number of CYP gene variations, that this genetic variability explains lipid reductions to a limited extent, at least when it comes to lowering cholesterol levels. Additional effects of statins, which some people regard to as "pleiotropic," may be the result of the direct action of the drugs themselves or the inhibition of cholesterol production and subsequent fall in plasma cholesterol.⁴ There is a wide range of qualities, ranging from those that appear to have little influence on vascular illness to those that result in vasodilation. These characteristics include increased endothelial function, which is achieved through the preservation of eNOS in endothelial cells. The vascular activities of statins have the potential to improve cardiovascular outcomes, for instance, following PTCA chemotherapy.⁵ It is possible that this will also result in a decreased susceptibility to plaque by preventing myocyte infiltration into the arterial wall and lowering metalloproteinase secretion. This is similar to the decrease in tissue factor expression and arterial macrophage accumulation that was observed

in cholesterol-fed rabbits that were treated with fluvastatin.⁶

MATERIALS AND METHODS

Study Design and Setting

This was a prospective cross-sectional study conducted in the Department of Pharmacology, Teerthanker Mahaveer Medical College and Research Centre, a tertiary care teaching hospital in Moradabad, U.P, India

Study Population

Patients of either gender aged 18 years and above, who were prescribed either atorvastatin or rosuvastatin for any clinical indication and subsequently reported with adverse drug reactions (ADRs), were included in the study.

Inclusion Criteria

- Patients aged ≥ 18 years.
- Patients receiving atorvastatin or rosuvastatin.
- Patients who experienced any suspected ADR during the study period.
- Patients willing to provide informed consent.

Exclusion Criteria

- Patients who are not receiving statins therapy
- Patients who refused to give informed consent.

Sample Size

A total of 290 subjects were enrolled.

Data Collection Tools

Data were collected using a predesigned, validated Suspected Adverse Drug Reaction Reporting Form (developed as per PvPI/WHO-UMC guidelines).

Assessment of ADRs

- All ADRs were evaluated for:
- Causality using the WHO-UMC Causality Assessment Scale.
- Seriousness based on criteria defined by the Pharmacovigilance Programme of India (PvPI) and ICH guidelines.
- Outcome (recovered, recovering, not recovered, fatal, unknown).
- System Organ Class (SOC) classification based on MedDRA.

Ethical Considerations

The study was approved by the Institutional Ethics Committee (REF NO.- TMU/IEC/2024-25/PG/87). Patient confidentiality and data protection were maintained throughout the study.

Statistical Analysis

The data were entered and analysed using R version 4.4.1. Categorical variables were expressed as frequencies and percentages. Comparative analysis of ADRs between atorvastatin and rosuvastatin was performed using the Chi-square test. Binary logistic regression was used to assess the association between independent variables like (drug type, dose, age and gender) and dependent variable i.e occurrence of ADRs. A p-value < 0.05 was considered statistically significant.

RESULTS

LOGISTIC REGRESSION MODEL TO DETERMINE THE ASSOCIATION BETWEEN THE INDEPENDENT VARIABLES (AGE, GENDER, DRUG TYPE, DOSE) AND DEPENDENT VARIABLE (OCCURRENCE OF REACTION)

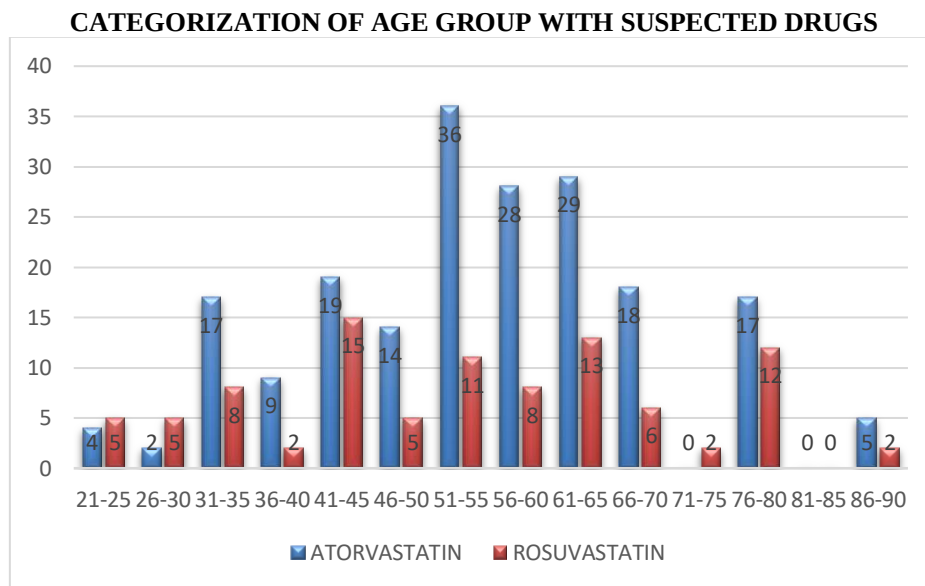
PARAMETERS	ESTIMATE	STD. ERROR	Z VALUE	P VALUE
CONSTANT	3.11	1.184	2.625	0.00867
AGE	0.0034	0.009	0.384	0.70103
GENDER	-1.16	0.272	-4.256	< 0.001
DOSE	-1.76	1.061	-1.658	0.0972
SUSPECTED DRUG	-2.95	1.067	-2.764	0.0057

The results showed that men were more likely than women to experience a reaction, which was also highly significant ($p < 0.001$). The use of Logistic Regression model, in this prospective cross-sectional study, has provided the evidence that subjects who were prescribed with Rosuvastatin showed a statistically significant interpretation for the less likelihood in the occurrence of ADR as compared to those who were prescribed with Atorvastatin ($p = 0.005$).

CHI SQ TEST. FOR ASSOCIATION BETWEEN GENDER AND OCCURRENCE OF SUSPECTED REACTION

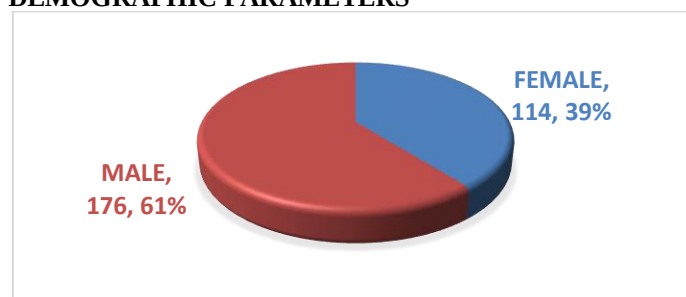
PARAMETERS	REACTION OCCURRED	REACTION NOT OCCURRED	χ^2 VALUE	p value
MALE (OBSERVED)	134	42	21.02	<0.0001
MALE (EXPECTED)	116	60		
FEMALE (OBSERVED)	57	57		
FEMALE (EXPECTED)	75	39		

The Chi-Square test showed a relationship between gender and side effects with a score of 21.29, which is pretty significant ($p = 4.517 \times 10^{-6}$).



The subjects of age group of 51-55 years, was mostly administered with atorvastatin (36 subjects), while the subjects aged between 41-45 were mostly administered with rosuvastatin (15 subjects)

CATEGORIZATION OF DEMOGRAPHIC PARAMETERS



290 subjects were administered with statins particularly atorvastatin and rosuvastatin at a tertiary care hospital, out of the 290 subjects, 114 subjects were found to be female and 176 subjects were found to be male

DISCUSSION

In this prospective observational study, 290 subjects were administered with statins particularly atorvastatin and rosuvastatin at a tertiary care hospital, out of the 290 subjects, 114 subjects were found to be female and 176 subjects were found to be male. The subjects of age group of 51-55 years, was mostly administered with

atorvastatin (36 subjects), while the subjects aged between 41-45 were mostly administered with rosuvastatin (15 subjects). 191 subjects showed the occurrence of suspected adverse drug reaction while 99 subjects were not suspected to any adverse drug reaction. As per a prior study, conducted among the United Arab Emirates (UAE) population, 556 patients (418 men; 138 women) taking statins were investigated and it was found

that the occurrence of suspected adverse drug reactions (ADRs) was observed in 237 patients (186 men; 51 women).⁷ It has been noted that older individuals and women experience greater adverse events when using statins. Although there was no correlation between age and AEs in this investigation, the rate of AEs was substantially greater in females.⁸ The interpretation of our study showed that the major suspected ADRs were associated with the musculoskeletal disorders that included suspected adverse effects like (Arthralgia, Back Pain, Joint Pain, Jaw Pain, Leg Pain, Limb Discomfort, Myopathy, Shoulder Pain and Weight Bearing Difficulty), while other previously conducted studies made it evident that the statins caused fatal cases of rhabdomyolysis or other musculoskeletal disorders, owing to which it raised the question on the safety, effectivity and tolerability of statins. However, there were other evidences that stated that the reduction of dose and consideration of an alternative class, may be considered in the worse conditions particularly when the adverse effects are intolerable. There were few other studies that stated that statins were associated with an increased risk of type 2 diabetes mellitus or other hepatic conditions, with no statistically significant effect on musculoskeletal conditions like rhabdomyolysis, myalgia or myopathy which makes it contrary to our interpretation.^{9,10}

The results showed that men were more likely than women to experience a reaction, which was also highly significant ($p < 0.001$). However, the previous study showed that overall adverse events (AEs) were significantly more common in women (60%) than in men (44%), $p = 0.0194$.⁸ The use of Logistic Regression model, in this prospective cross-sectional study, has provided the evidence that subjects who were prescribed with Rosuvastatin showed a statistically significant interpretation for the less likelihood in the occurrence of ADR as compared to those who were prescribed with Atorvastatin ($p = 0.005$), this, nevertheless suggested that subjects who were administered with Rosuvastatin were well tolerated to the drug, than those who were administered with Atorvastatin. Rosuvastatin conferred lower risks for major adverse cardiovascular events and major adverse liver outcomes in a previous study that discovered variations in the risks of a few significant outcomes linked to atorvastatin and rosuvastatin. Many of the differences failed to meet conventional criteria for statistical significance, and the differences were quite little. To determine if these results may be confidently applied in clinical practice, further research needs to be conducted.¹¹ The regression model in our study has also interpreted that the dose of statins did not show any statistically significant relationship with the occurrence of the suspected adverse drug reaction ($p = 0.097$).¹²

CONCLUSION

This prospective cross-sectional study conducted at a tertiary care teaching hospital aimed to evaluate and compare the adverse drug reactions (ADRs) associated

with two commonly prescribed statins atorvastatin and rosuvastatin. The study involved 290 subjects, of whom a significant proportion reported suspected ADRs following statin administration. The findings offer important clinical insights into the safety and tolerability profiles of these two agents. One of the most notable outcomes of the study was the statistically significant difference in the occurrence of ADRs between the two statins. Rosuvastatin was associated with a significantly lower likelihood of ADRs compared to atorvastatin ($p = 0.005$), suggesting that rosuvastatin may be a safer and more tolerable option for patients requiring lipid-lowering therapy. This observation aligns with some existing literature that indicates rosuvastatin might have a comparatively favourable safety profile. Musculoskeletal disorders emerged as the most frequently reported category of ADRs, including symptoms such as arthralgia, myopathy, limb discomfort, and shoulder pain. This finding is clinically relevant as such side effects often lead to poor adherence and discontinuation of therapy in real-world settings. It also highlights the need for careful monitoring, especially in patients reporting unexplained muscle pain or discomfort during statin therapy. The study also revealed a gender disparity, with male patients showing a significantly higher incidence of ADRs ($p < 0.001$), which contrasts with some previous studies that reported higher ADR rates in females. This discrepancy underscores the complexity of statin-associated ADRs and suggests that other demographic, physiological, or pharmacogenomic factors may be contributing to these differences, warranting further investigation. Interestingly, the dose of statins did not show a statistically significant association with the likelihood of ADRs ($p = 0.097$), suggesting that even standard or lower doses can induce adverse effects, and dosage adjustments alone may not always mitigate risk. This finding emphasizes the importance of individualized therapy, where drug selection and patient characteristics should guide treatment decisions more than the dose alone. Although the study provides robust evidence in favour of rosuvastatin's tolerability, it is essential to acknowledge that statin intolerance and adverse effects are multifactorial. Genetic predisposition, drug-drug interactions, patient comorbidities, and pharmacokinetics all play roles. Therefore, the results should be interpreted within the context of the study's population and methodology. In conclusion, rosuvastatin demonstrated a more favourable safety profile than atorvastatin in this cohort, with fewer reported ADRs and better overall tolerability. These results advocate for the preferential consideration of rosuvastatin in patients at higher risk for ADRs or those who have previously experienced intolerance with atorvastatin. However, given the limitations of a single-centre observational design, larger multi-centric studies and randomized controlled trials are necessary to confirm these findings and inform clinical guidelines. Tailored therapy based on individual patient characteristics remains the cornerstone of effective and safe statin use.

Conflict of Interest- None

Funding- None

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