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Detection and Management of Signals Associated with Adverse Drug Reactions from Atorvastatin and Rosuvastatin: An Observational Study

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ABSTRACT

Background: Statins are the mainstay of dyslipidaemia treatment, but individual agents display variable adverse drug reaction (ADR) profiles. Pharmacovigilance signal detection facilitates early identification of safety concerns and guides risk minimization.

Objective: To identify and compare ADR signals associated with atorvastatin and rosuvastatin and to evaluate management strategies in real-world settings.

Methods: Patients receiving atorvastatin or rosuvastatin at Teerthanker Mahaveer University were monitored for suspected ADRs. Causality was determined using WHO–UMC criteria, and seriousness per ICH E2A definitions. Signal detection employed disproportionality methods Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR).

Results: Signal detection analysis for system organ class was done by using frequentist disproportionality analysis (cluster-based disproportionality) method for the following organ classes like musculoskeletal disorder, gastrointestinal disorders and general disorders.

Conclusion: Comparative signal detection highlights distinct safety profiles for atorvastatin and rosuvastatin, underscoring the role of structured pharmacovigilance and individualized clinical management.

KEYWORDS: Pharmacovigilance, Signal Detection, Atorvastatin, Rosuvastatin, Adverse Drug Reactions, Disproportionality Analysis.

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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] Methods such as disproportionality analysis (e.g. Reporting Odds Ratio [ROR], Proportional Reporting Ratio [PRR]) and Bayesian Confidence Propagation Neural Network (BCPNN) are widely employed to quantify and validate potential safety signals.[7,8] Comparative real-world data regarding ADR signals of atorvastatin and rosuvastatin remain limited. Existing literature focuses largely on statins as a class rather than on drug-specific differences.[9-11] Evaluating these differences is clinically relevant, as selection of a particular statin may be guided not only by lipid-lowering efficacy but also by safety considerations in specific patient populations. The present study aims to detect and compare pharmacovigilance signals for atorvastatin and rosuvastatin and to describe how these ADR signals were clinically managed. By integrating structured

causality, severity, and seriousness assessment with quantitative signal detection, this study seeks to provide a robust safety comparison of two widely prescribed statins.

MATERIALS AND METHODS

Study Design and Setting

This was a cross-sectional, observational study conducted in the Department of Pharmacology, Teerthanker Mahaveer Medical College and Research Centre, Teerthanker Mahaveer University, a tertiary-care teaching hospital located in Moradabad, Uttar Pradesh, India. The study was carried out over a period form July 2024 till October 2025 as part of the institutional pharmacovigilance activities. The department functions as an Adverse Drug Reaction Monitoring Centre (AMC) under the Pharmacovigilance Programme of India (PvPI), enabling systematic collection and reporting of suspected ADRs.

Study Population

The study population comprised patients of either gender, aged 18 years and above, who had been prescribed atorvastatin or rosuvastatin for any approved clinical indication and subsequently presented with suspected adverse drug reactions (ADRs) during the study period. Patients were identified through outpatient departments, inpatient wards, and spontaneous reports received at the AMC.

Inclusion Criteria

- Adult patients aged ≥18 years.
- Patients receiving atorvastatin or rosuvastatin at any dose or duration
- Patients who experienced any suspected ADR during the study period with statin therapy.
- Patients willing to provide informed consent for participation in the study.

Exclusion Criteria

- Patients who are not receiving statins therapy
- Patients who refused to give informed consent.
- Their ADR was clearly attributable to other concomitant medications or pre-existing conditions without reasonable association to statin

Sample Size

A total of 290 subjects meeting the eligibility criteria were enrolled for analysis. The sample size was based on the number of consecutive ADR reports received for atorvastatin or rosuvastatin during the study duration.

The sample size was calculated using the formula

$N= 4pq/d^2$

Where p- proportion

q= (1-q)

d- margin of error (5%)

p- 0.2 (20% of patients have ADRs with statins)

so calculation- $4*(0.2)*(0.8)/(0.05)^{\wedge 2}$

we get n= 256

Therefore, with 290 subjects, the study achieves acceptable statistical precision, offering a 95% confidence margin of error of approximately ±5.8% for conservative estimates and ±4.1% for expected ADR proportions.

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using descriptive and inferential statistical methods. Categorical variables such as gender, type of ADR, causality categories, and SOC distribution were summarized using frequencies and percentages. Signal detection was performed using frequentist disproportionality analysis, specifically the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR), with ROR > 1 indicating a possible signal and PRR ≥ 2 used as the threshold for signal confirmation. All calculations followed standard pharmacovigilance formulas as recommended by WHO-UMC and international signal-detection guidelines. Because disproportionality analyses are exploratory and not hypothesis-testing tools, no p-values were generated.

Data Collection Tools

Data were collected using a predesigned and validated Suspected Adverse Drug Reaction Reporting Form, developed in accordance with PvPI and WHO-UMC guidelines. The form captured detailed information including:

- Patient demographics (age, gender, comorbidities)
- Drug details (statin type, dose, frequency, duration, concomitant medications)
- Description of the ADR (onset, course, severity, management)
- Relevant laboratory findings, if available
- Reporter details
- Data were obtained through patient interviews, clinical records, discharge summaries, and laboratory reports. All forms were checked for completeness and accuracy before entry into the database.

Assessment and Classification of ADRs

1. Causality Assessment: Each reported ADR was evaluated for its causal association with the suspected statin using the WHO–UMC Causality Assessment Scale, categorizing ADRs as certain, probable/likely, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable.
2. Seriousness Assessment: ADRs were assessed for seriousness based on definitions provided by the Pharmacovigilance Programme of India (PvPI) and ICH E2A guidelines. Serious ADRs included those resulting in:
    - Death
    - Life-threatening events
    - Hospitalization or prolongation of hospitalization
    - Significant disability/incapacity
    - Congenital anomaly/birth defect
    - Any medically important condition requiring intervention to prevent the above outcomes
3. Outcome Assessment: Outcomes of ADRs were categorized as:
    - Recovered
    - Recovering
    - Not recovered
    - Fatal
    - Unknown / follow-up not available
4. System Organ Class (SOC) Classification: Each ADR was coded according to MedDRA (Medical Dictionary for Regulatory Activities) terminology and classified under the appropriate System Organ Class (SOC) for standardized reporting.

Ethical Considerations

The study was approved by the Institutional Ethics Committee (REF NO.- TMU/IEC/2024-25/PG/87) of Teerthanker Mahaveer University. All participants provided written informed consent prior to enrolment. Confidentiality of patient information was strictly maintained in accordance with institutional and national ethical guidelines.

RESULTS

Signal detection analysis for selected System Organ Classes (SOCs)—musculoskeletal disorders, gastrointestinal disorders, and general disorders—was performed using frequentist disproportionality methods, specifically the Reporting Odds Ratio (ROR) and Proportional Reporting Ratio (PRR). A signal was considered suggestive when ROR > 1, and confirmatory only when accompanied by PRR ≥ 2. The details of ROR and PRR are shown in Table 1

Table 1- ROR And PRR With SOCs.

SOC	Atorvastatin ROR	Atorvastatin PRR	Rosuvastatin ROR	Rosuvastatin PRR
Musculoskeletal Disorder	1.42	1.25	0.70	0.80
GI Disorders	0.80	0.86	1.23	1.15
General Disorder	0.47	0.56	2.12	1.76

1. MUSCULOSKELETAL DISORDERS

For musculoskeletal disorders, atorvastatin demonstrated an ROR of 1.42, indicating a possible disproportionality (ror >1); however, the PRR was 1.25, which falls below the threshold of 2. Thus, no confirmatory signal was detected.
In contrast, rosuvastatin showed both ROR (0.70) and PRR (0.80) values below the signal threshold, indicating no disproportionality for this soc.
Interpretation:
Only atorvastatin showed a weak, non-confirmatory disproportionality for musculoskeletal events. Thus no confirmatory signal could be established.

2. Gastrointestinal Disorders

In the gastrointestinal SOC, rosuvastatin exhibited an ROR of 1.23, suggesting a possible disproportionality. However, the PRR value of 1.15 remained below the required cutoff, preventing signal confirmation.
Atorvastatin demonstrated ROR (0.80) and PRR (0.86) values below the signal thresholds, indicating no disproportionality for gastrointestinal adrs.
Interpretation:
Only rosuvastatin displayed a mild, non-confirmatory disproportionality for gastrointestinal disorders. Thus no confirmatory signal could be established.

3. General Disorders

For general disorders, rosuvastatin showed the highest disproportionality values among all SOCs analyzed, with an ROR of 2.12, indicating a potential signal; however, the corresponding PRR (1.76) remained below 2, preventing confirmatory signal detection.
Atorvastatin demonstrated low ROR (0.47) and PRR (0.56) values, indicating no disproportionality for this SOC.
Interpretation:
Rosuvastatin showed a meaningful disproportionality trend for general disorders (ROR >1), but this was not supported by the PRR threshold. Thus no confirmatory signal could be established.
Analysis for these interpretations has been provided in Figure 1.

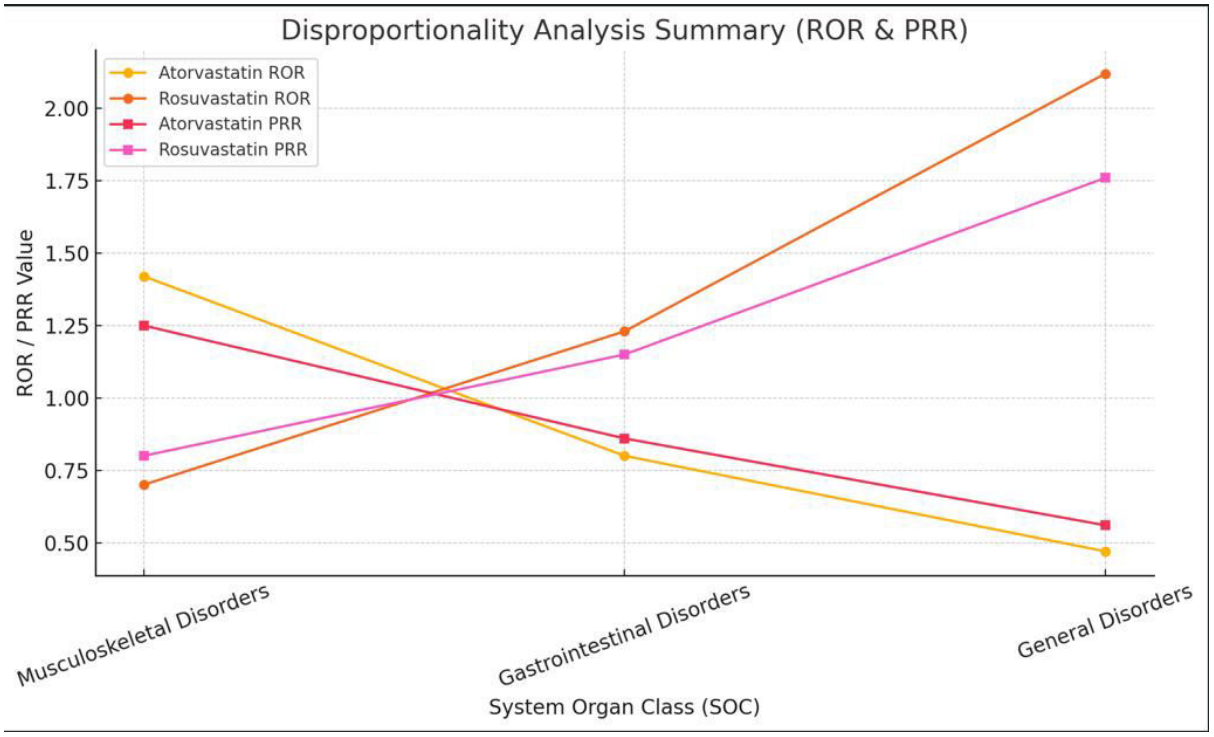

Figure 1- Disproportionality Analysis Summary of statins

DISCUSSION

The World Health Organization (WHO) defines ADR's as "a response to a medication that is noxious and unintended and occurs at doses normally used in man."[12] ADRs not only diminish patients' quality of life but also place a substantial burden on the health-care system, contributing significantly to increased morbidity and mortality.[13]
In this prospective observational study, 290 subjects receiving statin therapy—specifically atorvastatin and rosuvastatin—were evaluated at a tertiary care hospital. Among them, 114 were female and 176 were male. Patients aged 51–55 years most frequently received atorvastatin (36 subjects), while those aged 41–45 years were more often prescribed rosuvastatin (15 subjects). Overall, 191 subjects experienced at least one suspected adverse drug reaction (ADR), whereas 99 reported none. These findings are comparable to a prior study conducted among the United Arab Emirates (UAE) population, where 556 statin users (418 men; 138 women) were assessed and 237 patients were reported to have suspected ADRs.[14]
This study offers a practical, real-world comparison of atorvastatin and rosuvastatin through structured pharmacovigilance signal-detection methods. Statins are widely recognized for their potential to cause myopathy and hepatotoxicity, yet meaningful differences between individual statins often remain unclear outside controlled clinical trials.[9] Atorvastatin, for instance, is extensively metabolized via CYP3A4, which makes it more vulnerable to interactions with commonly used drugs such as macrolide antibiotics, azole antifungals, and other enzyme inhibitors, factors that may increase the likelihood of adverse

reactions.[14] Rosuvastatin, on the other hand, depends far less on hepatic metabolism and is therefore considered less interaction-prone, although post-marketing data have linked it to proteinuria, haematuria, and certain dose-related renal effects.[15]

Previous pharmacovigilance studies reinforce these distinctions. Muscle-related ADRs, such as myalgia and myopathy, tend to be reported more frequently with lipophilic statins like simvastatin and atorvastatin because they diffuse more readily into peripheral tissues. Hydrophilic statins such as pravastatin and rosuvastatin show comparatively lower muscle-related incidence due to their more hepatoselective distribution.[16],[17] Severe rhabdomyolysis, although relatively rare, has been documented for both atorvastatin and rosuvastatin, particularly when patients were taking interacting medications or receiving higher doses—highlighting that no statin is entirely exempt from serious muscle toxicity.[18],[19] Hepatotoxicity patterns have also varied across studies, with some evidence suggesting that atorvastatin may lead to higher elevations in liver transaminases than rosuvastatin, though findings remain inconsistent across different populations and dosing patterns.[20],[21]

Against this background, the findings from our study offer an important real-world perspective. When evaluating three major system organ classes—musculoskeletal disorders, gastrointestinal disorders, and general disorders—atorvastatin did not demonstrate any confirmatory pharmacovigilance signal using frequentist (cluster-based) disproportionality analysis. Although slight disproportionality trends were observed for some SOCs, particularly in musculoskeletal events, none fulfilled the combined criteria of ROR >1 and PRR ≥2 required to establish a true signal. Similarly, rosuvastatin showed mild trends in gastrointestinal and general disorder categories but again failed to meet the threshold for confirmatory signal detection. These results suggest that, within the context of this study population, both atorvastatin and rosuvastatin demonstrated acceptable safety profiles, with no SOC showing disproportionate reporting strong enough to raise concern. This contrasts somewhat with larger international pharmacovigilance databases, where muscle-related and hepatic ADRs often emerge as signal-rich categories. The absence of strong signals in our cohort may be attributed to factors such as population-specific prescribing habits, lower prevalence of drug–drug interactions, closer monitoring in tertiary-care settings, or underreporting of mild ADRs. Nevertheless, the findings underscore the value of continuous and methodologically rigorous ADR monitoring, as real-world data can reveal nuances that may not be apparent in controlled trials. While no confirmatory safety signals were detected, clinicians should continue to exercise vigilance, especially in patients receiving multiple medications or higher statin doses, where known risks of muscle, hepatic, and renal complications remain clinically relevant.

LIMITATIONS

This study has a few important limitations. Since the data came from just one hospital, the results may not reflect what happens in other settings or regions. We also relied on patients and clinicians reporting ADRs on their own, which means some reactions, especially mild ones may have been missed. Because this was a cross-sectional study, we cannot be sure that every ADR was directly caused by the statin. We were also unable to fully account for factors like other medicines patients were taking or their underlying health conditions. Finally, tools like ROR and PRR show statistical patterns, not definite cause-and-effect relationships.

FUTURE DIRECTION

Future research should involve multiple hospitals or larger national databases so findings are more representative. Studies that follow patients over time would help clarify when and how ADRs develop. Using electronic health records could improve the detection of statin-related problems by linking lab tests, prescriptions, and clinical outcomes. Exploring genetic factors may also help identify which patients are more likely to experience ADRs. Newer analytical approaches, including advanced statistics and machine-learning techniques, could make future safety signal detection more accurate and sensitive.

CONCLUSION

This study compared the safety profiles of atorvastatin and rosuvastatin using structured pharmacovigilance and disproportionality methods. Although mild disproportionality trends were observed in certain system organ classes, neither statin demonstrated a confirmatory safety signal. Overall, both drugs showed acceptable safety within this population. Continued monitoring remains essential to detect rare or emerging adverse effects in real-world settings.

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