Open Access Journal of
Gerontology & Geriatric Medicine
ISSN: 2575-8543

Juniper Publishers
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Case Report
Volume 8 Issue 5 - May 2025
DOI: 10.19080/OAJGGM.2025.08.555750

OAJ Gerontol & Geriatric Med

Optimizing Dose Dependent Drug Interactions by AI Supported Interaction Checking: The Rosuvastatin – Leflunomide Case

Wolfgang Scholz*

Founder of SCHOLZ DataBank, SCHOLZ DataBank, Inc, NY, USA

Submission: May 19, 2025; **Published:** May 26, 2025

***Corresponding author**: Wolfgang Scholz, Founder of SCHOLZ DataBank, SCHOLZ DataBank, Inc, NY, USA
Email: wscholz@scholzdatabank.com

Abstract

The ADR CP is a drug interaction checker with features of an AI tool of drug information and drug decision support; it learns and remembers interaction relevant drug properties and applies the patterns of any simple or multiple drug interaction (MDDI) to similar medication scenarios; it reconciles also pharmacokinetic effects with impacts on vital signs and serious adverse effects; thereby drug interactions, their magnitude and clinical consequences may be predicted and avoided and costs of clinical in-vivo studies can be reduced. The way of working, particularly the management of dose dependency, is demonstrated with the drug interaction of rosuvastatin and leflunomide and the triple interaction of rosuvastatin, leflunomide, and ticagrelor. The ADR CP uses REST webservice APIs and all returns may be retrieved or exported in FHIR compatible formats such as Json or XML.

Case Report

The prevalence of polypharmacy among older adults in the U.S. increased between 1999 and 2012 from 24% to 39% [1]. The risk of drug interactions increases disproportionately with the number of drugs prescribed; the SCHOLZ DataBank U.S. Drug Interaction Clock computes the potential risk to prescribe contra-indicated drug interactions to 1.4% for 5-drug-medications and to 14.9% for 12-drug-medications [2]. Consequently, it is mandatory to identify and manage serious drug interactions effectively when treating elderly people with several drugs concomitantly. When serious drug interactions are identified there are different measures which can be taken to resolve the problem, in particular dose adjustment, dose time adjustment, or substitution of the disturbing drug.

Dose adjustment is the preferred measure to preserve a proven therapy regimen as far as possible. The drug interaction between rosuvastatin und leflunomide shall be elucidated in this respect supported by advanced AI software technology as provided by the Adverse Drug Risk Control Panel (ADR CP) of SCHOLZ Databank [3]. The ADR CP of SCHOLZ DataBank pursues the target to assess and compare drug and complex medication risks. The core of the system is the drug interaction checker with the "MDDI" module which is based on a multiple drug interaction model superior to the traditional pairwise interaction analysis [4-8]. Thereby assessments of how one drug is affected by all others of a polypharmacy medication can be answered for billions of polypharmacy scenarios. The ADR CP reconciles then in a "All-in-One" approach the pharmacokinetic and pharmacodynamic interactions in a way that the impacts on vital signs and serious adverse effects become transparent. As the system has been trained for many years, it is steadily learning and producing new insights into complex drug relationships. It can be classified as a powerful AI tool of drug information. A complete protocol of the MDDI and ADR status of a prescription can be retrieved at any time through FHIR compatible REST webservice APIs and formats such as Json or XML, too. The modules "Dose tune" and Quattro Optimizer may support the assessment and the comparison of ADRs dependent on dose and overdose of mono- and combo-medications [9].

The major potential adverse effect through this interaction is – apart from hepatic concerns - the renal toxicity due to elevated plasma levels of rosuvastatin by leflunomide's blocking of OATP1B1/B3 and BCRP transporters; it is recommended to lower the rosuvastatin doses to 10mg daily in this scenario, when leflunomide (standing for its active metabolite teriflunomide) is started and the rosuvastatin dose was then 20mg or more daily [10,11]. For a better understanding of this measure, it would be helpful to have some quantitative insights into the dose dependency of the drug interaction and the clinical consequences

respectively as the latter are finally what the prescribing physician is interested to know. Therefore, this contribution is an attemptto provide some insights with the focus on the potential adverse renal effect of rosuvastatin.

All statins are known for their risk of causing myopathy, rhabdomyolysis, CK elevations and consecutively acute renal failure through myoglobinurea with possibly fatal outcomes. The incidence of myopathy with CK> 10xULN for simvastatin 20, 40, and 80 mg daily is listed in Table 1 according to Prescriber Information based on a study with 24,747 simvastatin-treated patients; another 12,064-patient study mentioned indicates a rate of 0.9% for myopathy, and the incidence of rhabdomyolysis defined by myopathy and CK> 40xULN for 80-mg-simvastatin patients amounted to 0,4% (which explains why this high simvastatin dose is usually not any more recommended); in another 10,269 patient study the incidence of myopathy/rhabdomyolysis was < 0.1%; acute kidney injury (AKI) secondary to myoglubinurea and rare fatalities have been reported for simvastatin, too [12] . The prescriber information for rosuvastatin is not so precise, it indicates only a 2.6% incidence of elevated CK, and that myopathy is greater in patients on 40 mg daily compared to lower rosuvastatin doses; it mentions AKI secondary to myoglubinurea and rare fatalities, too [10].

Adverse drug effects are in most cases dose-dependent, meaning type A augmented dose-related effects [13]. The challenge is now to make a) an adverse drug risk (ADR) assessment for rhabdomyolysis and acute renal failure (ARF/AKI) as the most serious outcome of a statin therapy dependent on a dose increase or an elevation of the plasma level and the exposure (AUC) due to a drug interaction, and b) to identify a dose where the risk of a serious outcome such as acute renal failure is not multiplied and is preserved either < 0.1%, meaning rare or very rare, or in the range of what the maximum dose of 40 mg daily allowed causes.

Furthermore, the following assumptions are made: If the dose dependency is not clear, any %-incidence described for an adverse reaction is assigned to the medium dose whereby doubling (2-fold) the dose results in a disproportionate ADR increase, for example about the 3-fold. Looking at the pathophysiological event cascade of <dose-overdose-myopathy-CK>10xULN-rhabdomyolysis-acute renal failure> it is furthermore assumed that 10% of the patients experiencing myopathy accompanied by CK>10xULN are at risk of rhabdomyolysis with acute renal failure (ARF) or acute kidney injury (AKI); this is compared to literature data a conservative assumption [14-16]. Table 1 represents the ADR(ARF/AKI) dependent on statin dosings and interaction scenarios with leflunomide as assessed by the ADR CP.

The maximum tolerable ADR(ARF/AKI) for the maximum daily 40-mg-dose of rosuvastatin is 0.028%, highlighted yellow in Table 1. This ADR should not be exceeded. All green highlighted options have ADRs below this threshold whereby only the combo of rosuvastatin 10 mg and leflunomide 20 mg meets the therapeutic targets and the dose limit requirement for rosuvastatin. It should be noted that leflunomide itself may be the cause of renal failure [17].

Figures 1-5 illustrate how the ADR CP works and the different rosuvastatin/leflunomide scenarios are represented. The Quattro-Optimizer supports the direct drug risk comparison of different strengths as shown in Figure 6. It is also appropriate to compare similar active ingredients, their strengths and their impact on the ADR. Noteworthy: as mentioned above multiple kinetic and dynamic drug interactions can be processed through the MDDI module and the ADR CP enhancing the productivity of drug interaction checking compared to the traditional pairwise interaction check substantially. Figures 7 & 8 illustrate how the AUC of rosuvastatin and the ADR(ARF/AKI) is affected when other drugs inhibiting BCRP and/or OATP1B1/B3 such as ticagrelor are prescribed or added to the prescription of rosuvastatin and leflunomide.

Table 1: ADR(ARF/AKI) dependence on statin dosings and interaction scenarios with leflunomide as assessed by the ADR CP

Ingredient	Strength	Daily dose	f(AUCrel) &	CoMedication	ADR	Source
Rosuvastatin	10 mg	10 mg	1	-	0,0036%	(10) #
Rosuvastatin	10 mg	10 mg	4,22	Leflunomid 20 mg	0,017%	(10) #
Rosuvastatin	20 mg	20 mg	1	-	0,01%	(10) #
Rosuvastatin	20 mg	20 mg	4,22	Leflunomid 20 mg	0,044%	(10) #
Rosuvastatin	40 mg	40 mg	1	-	0,028%	(10) #
Rosuvastatin	40 mg	40 mg	4,22	Leflunomid 20 mg	0,12%	(10) #
-	-	-	-	Leflunomid 20 mg	0,002%	(17)
Simvastatin	20 mg	20 mg	1	-	0.003%	(12)
Simvastatin	40 mg	40 mg	1	-	0.008%	(12)
Simvastatin	80 mg	80 mg	1	-	0.061%	(12)

&: multiplication factor due to the relative AUC (AUCrel) increase by the leflunomide interaction with AUCrel = 2.5

#: ADR CP assessment of the about incidence for the ADR(ARF/AKI) based on Prescriber Information

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Figure 1: Rosuvastatin 20 mg and ADR(ARF/AKI).

Figure 2: Rosuvastatin 20 mg plus Leflunomid and ADR(ARF/AKI), elevated by the increase of the rosuvastin-AUC due to the pharmacokinetic interaction with leflunomide; MDDI button highlighted!

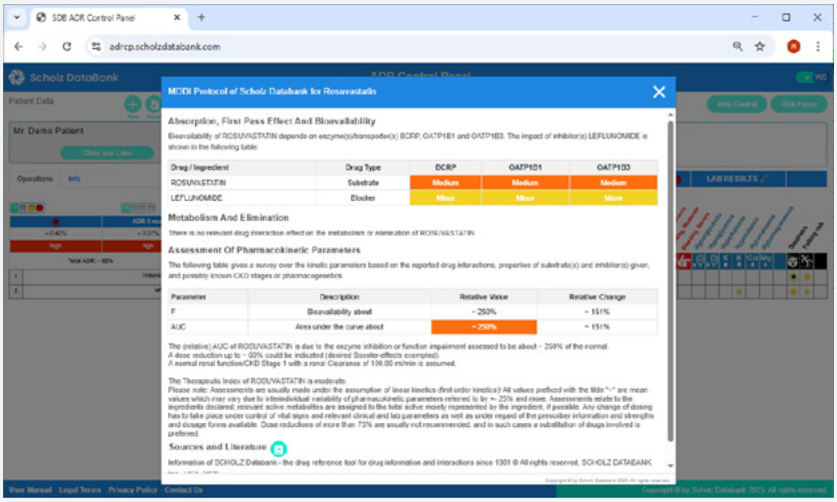

Figure 3: MDDI Protocol representing the inhibitions of BCRP and OATP1B1/B3 transporters through leflunomide resulting in an increase of the rosuvastatin-AUC to the 2.5-fold.

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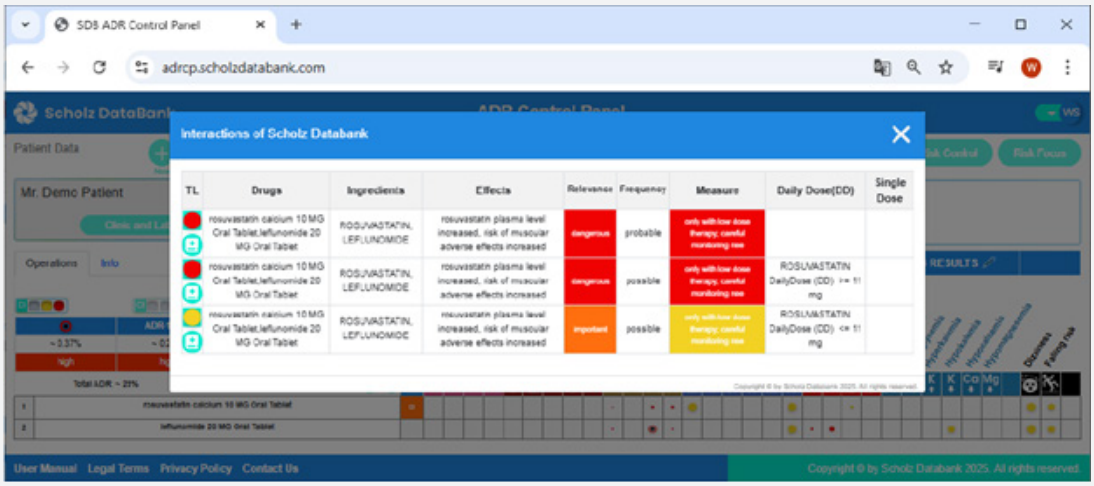

Figure 4: Rosuvastatin and leflunomide: traditional pairwise display of the drug interaction in- cluding the classification distinguishing the risk of administering 10 mg rosuvastatin or 20 mg and more rosuvastatin concomitantly with leflunomide.

Figure 5: Rosuvastatin 40 mg and ADR(ARF/AKI).

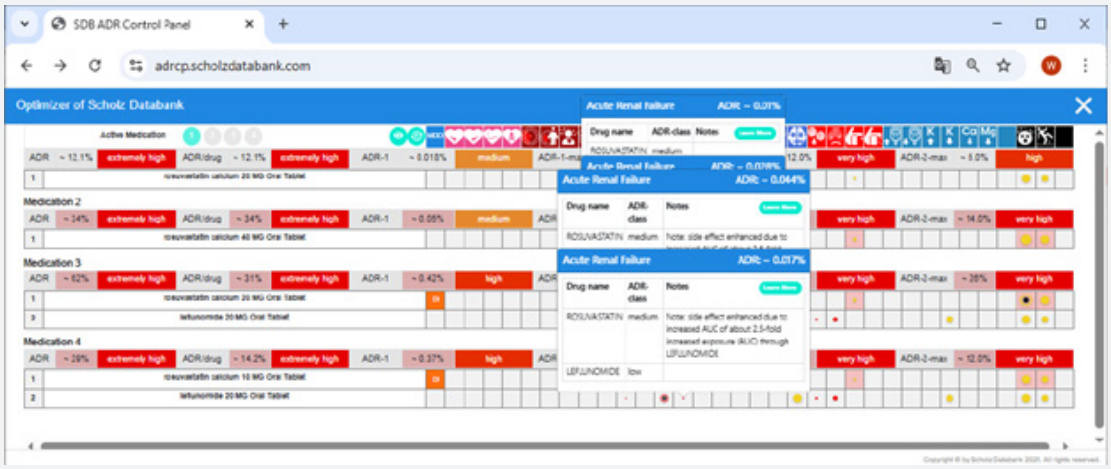

Figure 6: The Quattro-Optimizer representing the ADR(ARF/AKI) for rosuvastatin 20mg, for rosuvastatin 40 mg, for rosuvastatin 20 mg plus leflunomide and for rosuvastatin 10 mg plus leflunomide.

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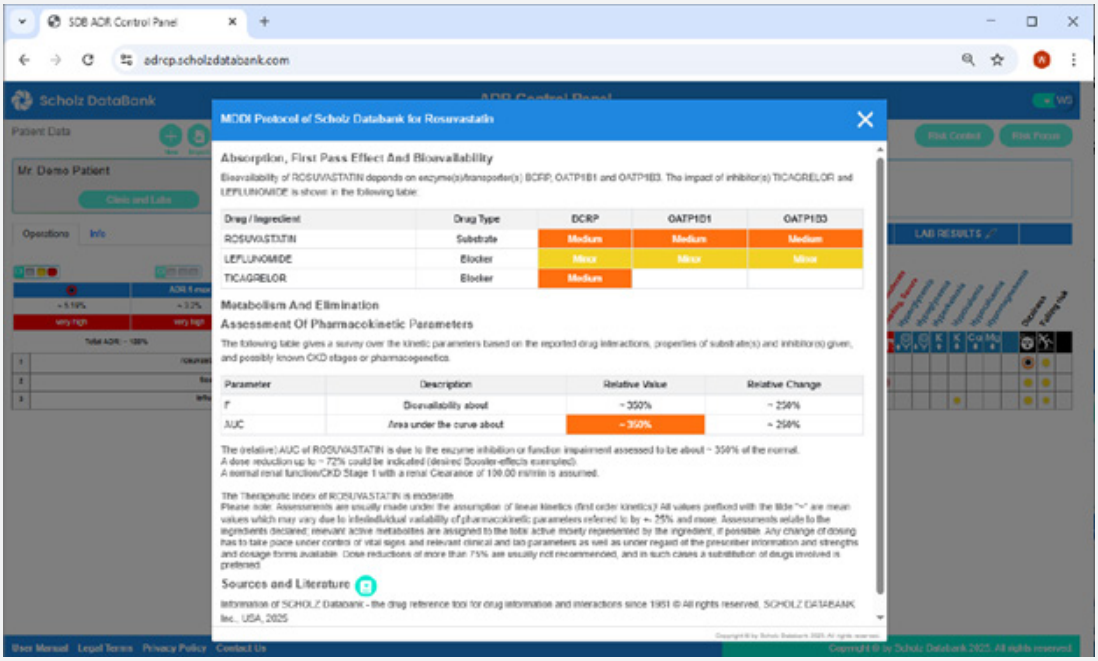

Figure 7: MDDI Protocol representing the inhibitions of BCRP and OATP1B1/B3 transporters through leflunomide and ticagrelor resulting in an assessed increase of the rosuvastatin-AUC to the 3.5-fold.

Figure 8: Rosuvastatin 20 mg plus Leflunomid plus ticagrelor and ADR(ARF/AKI), elevated by the increase of the rosuvastin-AUC due to the pharmacokinetic interaction with leflunomide and ticagrelor; MDDI button highlighted!

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