BRIEF REPORT

Impact of Disease and Treatment Response in Drug–Drug Interaction Studies: Osimertinib and Simvastatin in Advanced Non-Small Cell Lung Cancer

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A phase I, open-label study (NCT02197234) assessed the effects of osimertinib on simvastatin exposure in patients with advanced epidermal growth factor receptor (EGFR)-mutated non-small cell lung cancer and disease progression post-EGFR tyrosine kinase inhibitor treatment. Here, we report on a retrospective analysis of two patients (patients 1 and 2) who had liver metastases and high simvastatin exposure prior to osimertinib treatment, which changed following treatment. Patients received single oral doses of simvastatin 40 mg on day (D) 1 and D31, and osimertinib 80 mg once daily on D3–32. At baseline, both patients had abnormal liver function tests (LFTs; Child-Pugh scores of 6 and 8, respectively), significant liver metastasis, and, after a single simvastatin dose, had higher (~ 10-fold) exposure compared with all other patients. Following 31 days of continuous osimertinib treatment, simvastatin exposures (area under the plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration (C_{max})) and LFTs, such as alanine transaminase, aspartate aminotransferase, and bilirubin normalized to population mean values. Additionally, ~ 50% and ~ 80% reductions in liver metastases were observed on computed tomography scans in patients 1 and 2, respectively. High simvastatin exposure on D1 likely resulted from impairment of hepatic first pass metabolism due to liver metastases. Reduction in hepatic disease burden due to osimertinib treatment likely resulted in liver function returning to normal levels.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that potently and selectively inhibits both EGFRm and EGFR T790M and has demonstrated efficacy in non-small cell lung cancer central nervous system metastases.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ The study addressed the query of whether there are interactions between osimertinib and cytochrome (CYP)3A: the study found that osimertinib is unlikely to have any clinically relevant interaction with CYP3A substrates.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ Treatment with even one cycle of osimertinib significantly reduced hepatic disease burden of two patients with concurrent improved liver function by laboratory testing and CYP-mediated clearance.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ Highly efficacious treatments can potentially impact drug–drug interaction evaluations, and need to be considered appropriately in the context of clinical pharmacology studies.

Drug–drug interactions (DDIs) are a concern in oncology due to the presence of comorbidities, comedications, and treatment-related toxicities that may require multiple supportive therapies. In DDI studies, underlying disease is expected to be unchanged during pharmacokinetic (PK) evaluation so changes in exposure may be understood. However, infiltrative liver disease by primary/metastatic tumors may impair liver function, leading to reduced metabolic capacity, decreased drug-excretion, and drug-clearance[1]; hence, potential to modulate cytochrome (CYP) 450 enzyme-mediated DDIs.[2,3]

Osimertinib is a third-generation, irreversible, oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that potently and selectively inhibits both EGFR-tyrosine kinase inhibitor-sensitizing (EGFR mutant (EGFRm)) and

EGFR T790M mutations and has demonstrated efficacy in non-small cell lung cancer (NSCLC) central nervous system metastases.[4–8] Osimertinib 80 mg is approved for first-line treatment of patients with metastatic EGFRm NSCLC.[9–11]

Osimertinib exhibits linear PK across the 20–240 mg dose range and once-daily administration leads to a threefold accumulation within 15 days.[12] *In vitro*, osimertinib has potential to inhibit intestinal CYP3A4 and pregnane × receptor-mediated induction of CYP3A enzymes but not inhibit OATP1B1/OATP1B3 transporters.[9,13]

Hence, a DDI study (NCT02197234) was conducted assessing the impact of multiple doses of osimertinib on the PK of simvastatin (a sensitive CYP3A4 substrate) in patients with NSCLC. The study showed that osimertinib is unlikely to produce clinically relevant interactions with CYP3A4 substrates.[13]

This report focuses on two patients from this study who had high exposures of simvastatin and its metabolite, simvastatin acid, prior to osimertinib treatment.

METHODS
Trial design
A phase I, open-label, single-arm study in patients with EGFRm NSCLC investigated the impact of multiple doses of osimertinib on the PK of simvastatin and simvastatin acid to identify the potential for DDIs. Trial methods have been previously published.[13] Briefly, on day (D) 1 (period 1), patients received oral simvastatin 40 mg (single dose), underwent clinic-based PK and safety assessments over the course of 32–34 hours, then received osimertinib 80 mg orally once-daily for 28 days (period 2; D3–30) with weekly clinic-based PK assessments. On D31 (period 3), patients received another single oral dose of simvastatin 40 mg, in combination with osimertinib 80 mg, and underwent clinic-based PK and safety assessments over 32–34 hours. PK samples were collected at predose, then 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 28, and 32 hours postdose on both D1 and D31.

The clinical study was conducted in accordance with International Conference on Harmonization–Good Clinical Practice guidance; the protocol was reviewed and approved by an institutional ethics committee and institutional review board prior to implementation.

Participants and analysis methods
Of 52 patients treated, 2 were identified (retrospectively) as having liver metastases and significantly high exposures of simvastatin and simvastatin acid on D1, before receiving osimertinib. For these patients, hepatic function was classified according to the Child-Pugh system.[14,15] No other patient had levels of hepatic biochemistry parameters indicative of significant liver metastases at baseline. Patients with hepatic metastases and with aspartate aminotransferase or alanine aminotransferase > 5 times the upper limit of normal were excluded; therefore, this was not a protocol deviation. A detailed description of the bioanalysis and PK methods utilized has been previously reported.[13]

The PK parameters investigated included area under the plasma concentration-time curve from zero to infinity (AUC) and maximum plasma concentration (C_{max}) along with other relevant PK parameters.

RESULTS
Patients
A retrospective investigation of both patients using computed tomography (CT) scans before study entry, indicated significant liver tumor burden. The presence of liver metastases was not an exclusion criterion; therefore, the patients had been enrolled correctly. Baseline demographics and disease characteristics (**Table 1**) were consistent with the overall study population.[13] Nine other patients had minor liver metastases but normal hepatic biochemistry parameters. Neither patient had a significant medical or surgical history or concomitant medication at trial entry. Liver biopsies had been performed in both patients 1 week before study screening to establish EGFR T790M status. No changes were noted on the concomitant medications received by the patients throughout the investigation.

Treatment response
The left-hand panels of **Figure 1a** show CT scans of patients 1 and 2, respectively, with heavy tumor burden at the screening visit before D1 of the study. Patient 1 had hypoalbuminemia (29 g/L) and an alkaline phosphatase level of 635 U/L at baseline, with a Child-Pugh score of 6, denoting mild liver impairment; patient 2 had hypoalbuminemia (22 g/L) and an alkaline phosphatase level of 491 U/L at baseline, with an international normalized ratio of 2.44, and a Child-Pugh score of 8, denoting moderate liver impairment (**Table 1**).

Hepatic metastases improved with osimertinib treatment, as shown by the CT scan (right-hand panels, **Figure 1a**) and the stabilization of hepatic biochemistry parameters to within normal limits by the end of period 3 (D31; **Table 1**). Both patients received osimertinib after the PK phase. There was radiological evidence of clinically significant reduction in liver metastases from baseline by visit 3 during the follow-up period, 7–8 weeks after D1 (~ 50% and ~ 80% reduction for patients 1 and 2, respectively; **Figure 1a**).

Pharmacokinetics
Figure 1b shows simvastatin concentration over time on D1 and D31. Patients 1 and 2 had simvastatin AUC and C_{max} values of 700 ng h/mL and 240 ng/mL, and 893 ng h/mL and 176 ng/mL, respectively, on D1 vs. the arithmetic mean (SD) for AUC and C_{max} of 97.0 (66.6) ng h/mL and 30.7 (20.0) ng/mL, respectively, for all other patients receiving simvastatin in period 1.[13]

After dosing with simvastatin plus osimertinib in period 3 (D31), both patients had a reduction in simvastatin AUC at D31 to < 5% of the D1 values (30.7 and 41.9 ng h/mL, respectively) and reductions in simvastatin C_{max} of ~ 2.5% and 11% of that at D1 (5.8 and 19.7 ng/mL, respectively). The arithmetic mean (SD) for AUC and C_{max} were 96.1 (92.2) ng h/mL and 23.9 (22.6) ng/mL, respectively, for the other patients.

For simvastatin acid: D1 AUC was 245 and 152 ng h/mL, which changed to 19.5 and 7.4 ng h/mL for patients 1 and 2, respectively, on D31. Similarly, D1 C_{max} was 34.1 and 18.7 ng/mL, which became 3.2 and 1.2 ng/mL on D31. The C_{max} and AUC ratios of simvastatin acid to simvastation $MRC_{max} = 0.14$, 0.11 on D1, and 0.55, 0.06 on D31;

Table 1 Hepatic biochemistry listings for two patients with significant liver metastases

Treatment period, day	Pre-trt −1	2 D10	2 D17	2 D24	3 D31	3 D32	Follow-up D40	Follow-up D47	Follow-up D54	Follow-up D61	Follow-up D89
Study median[a] (range)											
Albumin, g/L	40 (22–46)	39 (24–45)	40 (29–47)	40 (30–47)	39 (31–45)	37 (33–45)	40 (29–48)	40 (28–49)	41 (29–47)	40 (29–50)	41 (32–47)
ALT, U/L[b]	18 (6–58)	17 (8–65)	18 (7–81)	15 (5–92)	15 (5–47)	15 (8–50)	14 (6–42)	16 (6–57)	16 (6–53)	15 (6–44)	16 (5–42)
AST, U/L[c]	22 (16–84)	21 (13–135)	20 (12–44)	20 (10–95)	21 (12–59)	20 (13–45)	22 (12–102)	20 (12–140)	20 (11–145)	20 (11–233)	22 (12–47)
ALP, U/L	87 (44–635)	80 (51–576)	74 (53–429)	70 (44–248)	65 (45–259)	68 (46–180)	61 (35–298)	61 (40–334)	59 (37–555)	59 (35–545)	63 (32–145)
Bilirubin, μmol/L[d]	7 (2–22)	7 (3–19)	7 (3–25)	7 (3–36)	6 (2–17)	7 (3–12)	7 (2–19)	6 (3–14)	7 (3–21)	7 (2–19)	7 (3–15)
Patient 1											
Albumin, g/L	29	28	29	32	31	34	34	34	35	35	38
ALT, U/L[b]	49	34	18	14	21	27	25	21	12	9	9
AST, U/L[c]	40	46	27	26	24	27	25	20	19	17	23
ALP, U/L	635	576	429	248	103	107	94	77	73	71	50
Bilirubin, μmol/L[d]	22	15	14	15	5	10	7	9	12	10	10
Patient 2											
Albumin, g/L	22	24	30	31	32	33	35	34	35	35	38
ALT, U/L[b]	24	55	34	18	15	15	14	12	12	13	13
AST, U/L[c]	84	135	40	26	23	21	21	18	18	21	22
ALP, U/L	491	505	351	226	188	180	147	127	118	109	102
Bilirubin, μmol/L[d]	15	14	10	9	7	10	10	10	9	10	10

ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; D, day; trt, treatment.
[a]Patients 1 and 2 were included in the safety analysis set and were excluded only from pharmacokinetic analysis.
[b]ALT upper limit of normal = 50 U/L.
[c]AST upper limit of normal = 45 U/L.
[d]Bilirubin upper limit of normal = 21 μmol/L.

MRAUC = 0.35, 0.17 on D1, and 0.64, 0.18 on D31 for patients 1 and 2, respectively, similar and within variability to those observed for other patients (MRC$_{max}$ geomean (range) = 0.17 (0.03–4.96) on D1 and 0.22 (0.07–2.95) on D31; MRAUC geomean (range) = 0.41 (0.15–6.11) on D1, and 0.45 (0.17–5.54) on D31).

The steady-state AUC and C$_{max}$ of osimertinib and its metabolites on D31 were similar in these 2 patients (AUC at steady-state (AUC$_{ss}$): 11,300 and 7,750 nM hour and maximum steady-state concentration (C$_{ssmax}$): 599 and 383 nM) vs. the other patients (Geomean (range) AUC$_{ss}$: 11,530 (5,780–28,000) nM hour and C$_{ssmax}$: 620 (324–1,380) nM), indicating that there was no difference in osimertinib exposure following continuous daily dosing.

Safety

Both patients reported adverse events (AEs), which were mild or moderate in severity. Both had elevated transaminase levels, which the investigator considered possibly related to both osimertinib and simvastatin. Patient 1 experienced nausea and peripheral edema that were possibly related to osimertinib, and unrelated to simvastatin. Patient 1 had one AE of nausea caused by osimertinib that led to a dose interruption. Patient 2 did not have any AEs leading to dose interruption/discontinuation. Neither reported any

grade 3 or 4 AEs. No new safety concerns were identified and AEs were consistent with those observed in the AURA studies.[6,16]

DISCUSSION

Here, both patients had higher than expected simvastatin exposure prior to receiving osimertinib; likely due to significant hepatic metastases. Following 31 days of osimertinib treatment, there was a significant reduction in the patients' liver metastases and their simvastatin exposures were reduced to a level concordant with that of other patients in the study.[13] In a DDI study, typically conducted in healthy volunteers or patients, it is anticipated that PK changes are due to co-administered drugs. However, when conducted in patients, pharmacological activity of a co-dosed drug may alter the underlying disease, which can result in normalization of the disease-impaired metabolic pathways. Here, it seemed that simvastatin metabolism was impaired due to underlying disease and the efficacy of osimertinib altered their disease and metabolic characteristics, thereby affecting simvastatin PK.
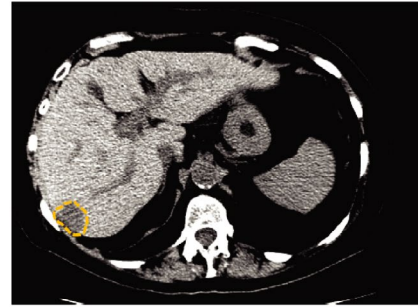
Simvastatin is a sensitive CYP3A4 substrate, thus any change in liver function could potentially have a substantial impact on its first pass/metabolic clearance. The contribution
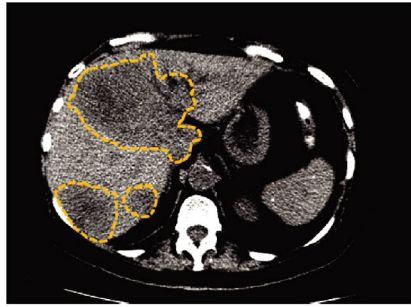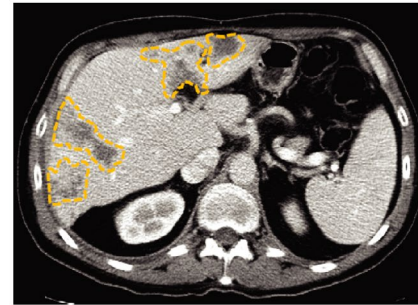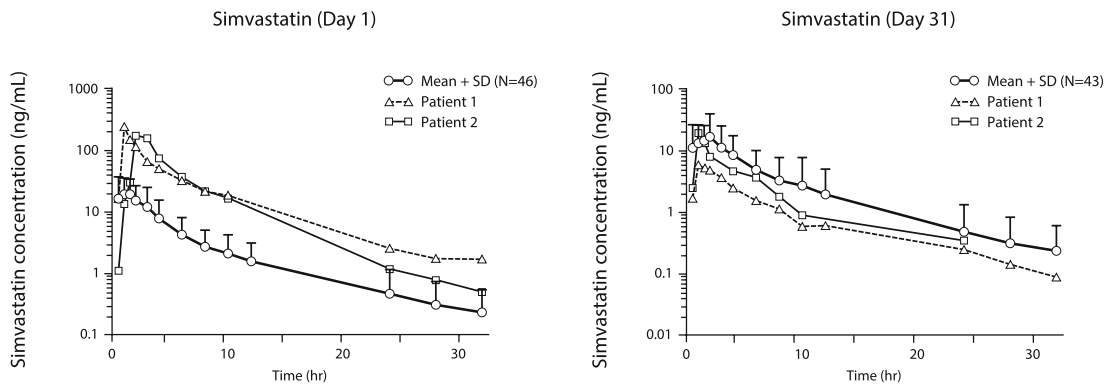
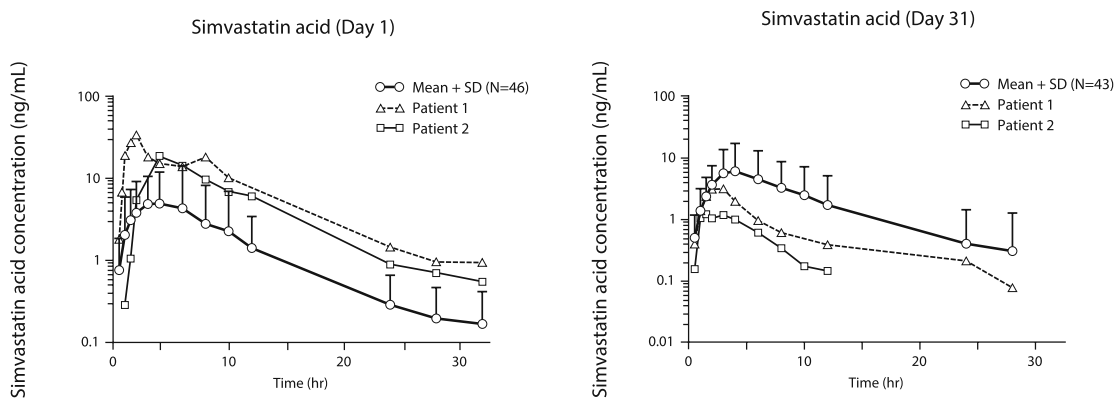**Figure 1** Patients 1 and 2: (**a**) Computed tomography scans from both patients' livers. (**b**) Simvastatin concentration on day 1 (simvastatin alone) and on day 31 (simvastatin + osimertinib). (**c**) Simvastatin acid concentration on day 1 (simvastatin alone) and on day 31 (simvastatin + osimertinib). TPD1, treatment period day 1.

of intestinal CYP3A metabolism to simvastatin disposition is not well understood. One glass of low-strength grapefruit juice showed threefold increase, whereas double-strength grapefruit juice had 16-fold increase in simvastatin exposure, which was similar to the 19-fold increase observed with itraconazole.[17,18] However, simvastatin is well absorbed from the gastrointestinal tract and is highly extracted by the liver and only 7% of the dose reaches the general circulation intact.[19,20] Patients 1 and 2 had heavy hepatic tumor burden and impairment. Both had an ~ 10-fold higher exposure to simvastatin in period 1 (simvastatin alone) vs. all other patients dosed prior to daily osimertinib. C_{max} and AUC were both higher than those typically observed in the literature (C_{max} in the range of 10–34 ng/mL[21] and the pharmacokinetically equivalent AUCτ (95% confidence interval) of 30.5 ng h/mL (23.1, 40.2)) following a single 40 mg dose.[22] No specific studies on the impact of hepatic impairment on simvastatin PK have been conducted; however, use of simvastatin in patients with significant liver damage is contraindicated.[23,24]

The conversion of simvastatin to its metabolite occurs via hydrolysis of the lactone bond and esterases in the gut, liver, and plasma.[25] Further metabolism/elimination of simvastatin/simvastatin acid to hydroxy metabolites is via CYP3A enzymes, which might be affected by liver metastases. The high exposure (AUC and C_{max}) of simvastatin/simvastatin acid in patients 1 and 2 suggests that the process of hydrolysis and interconversion was not affected, whereas the subsequent metabolism and elimination via CYP3A during first pass was possibly via liver metastases and thereby hepatic function. We presume that liver metastases affected the CYP3A activity but not the esterase or hydrolytic activity; hence, the conversion to simvastatin acid was not affected.

Over the course of period 2's osimertinib treatment, hepatic function improved in patients 1 and 2, as shown by the normalization of hepatic biochemistry parameters. This improvement in hepatic function was likely due to clinically significant reduction in the bulk of the liver metastases (~ 50% and 80% in patients 1 and 2, respectively), seen between baseline and visit 3 during the follow-up period (7–8 weeks after D1), highlighted by CT scans in both patients. PK analyses during period 3 showed that simvastatin exposure following continuous osimertinib in patients 1 and 2 returned to levels similar to those seen in all other patients dosed in period 3 of the study. These data suggest that the high exposure to simvastatin seen in patients 1 and 2 during period 1 reflected the impairment of hepatic clearance as a consequence of metastatic disease.

Furthermore, 4β-hydroxy-cholesterol (endogenous marker for CYP3A4) activity increased 10–15% relative to baseline, following 28 days of osimertinib administration, in the overall patient group and was similar in patients 1 and 2.[13] Although this is not a validated marker, these changes in 4β-hydroxy-cholesterol concentrations do not seem to be reflective of the > 20-fold decrease in the simvastatin levels on D31 vs. D1.

Although factors, which are not explored here, may contribute to the high exposure during period 1, for example, OATP1B1/OATP1B3 uptake transporter inhibition or cholestasis, a reasonable explanation for these exposure changes is that it was due to impaired hepatic clearance of the drug as a consequence of their metastatic liver disease. Importantly, treatment with osimertinib significantly reduced the bulk of the liver metastases and returned liver function to normal levels in these patients. The impact of hepatic metastases should be considered when performing clinical pharmacology studies with drugs that have high hepatic metabolism in patients with cancer. To our knowledge, this is the first report of a drug-disease-metabolism interaction following treatment with an anticancer agent.

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