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Model-based assessment of pharmacokinetic changes of sunitinib, tacrolimus, and everolimus in a patient with metastatic renal cell carcinoma after renal transplantation

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Abstract

The safety of the coadministration of sunitinib with tacrolimus and everolimus with regard to therapeutic drug monitoring has not been demonstrated. Here, we report a patient who showed high sunitinib concentrations, in addition to pharmacokinetic changes in tacrolimus and everolimus after sunitinib therapy. A living-donor renal transplant patient treated with tacrolimus and everolimus was diagnosed with pulmonary and pleural metastases of renal cell carcinoma. The patient received sunitinib therapy (37.5 mg/day, 2 weeks on and 1 week off). This patient exhibited a high total sunitinib concentration (sunitinib, 105.8 ng/mL; *N*-desethyl sunitinib, 27.9 ng/mL) on day 10 postinitiation and experienced grade 3 diarrhea. The observed sunitinib concentrations were a little higher than those reported in the 421C>A polymorphism of the *ATP-binding cassette subfamily G member 2* gene carrier. The observed concentrations of both tacrolimus and everolimus gradually decreased compared with the Bayesian-predicted values after the onset of sunitinib therapy, and the doses of tacrolimus and everolimus were increased. Careful therapeutic drug monitoring of sunitinib, tacrolimus, and everolimus concentrations is necessary during combination therapy, especially after episodes of diarrhea.

Keywords

sunitinib: tacrolimus: everolimus: metastatic renal cell carcinoma: renal transplantation: Bayesian analysis

1. Introduction

Sunitinib, an oral multiple tyrosine kinase inhibitor, is a first-line therapy for patients with metastatic renal cell carcinoma [1]. Sunitinib frequently induces severe toxicities, such as thrombocytopenia, anorexia, fatigue, and diarrhea [2]. Sunitinib is primarily metabolized by cytochrome P450 (CYP) 3A4 to its major pharmacologically active metabolite, *N*-desethyl sunitinib, which is further metabolized to inactive compounds by the same enzyme [3]. A previous *in vivo* study revealed that a total sunitinib (sunitinib plus *N*-desethyl sunitinib) concentration ≥50 ng/mL is necessary to achieve an antitumor effect [4]. A recent clinical study performed in Japan showed that patients with total sunitinib concentration <100 ng/mL had a significantly longer progression-free survival time than did patients with concentrations ≥100 ng/mL [5]. Therefore, it is desirable to maintain the total sunitinib trough concentration in the range of 50–100 ng/mL.

Herein, we report a patient with metastatic renal cell carcinoma who started receiving sunitinib therapy together with combined immunosuppressive therapy including tacrolimus and everolimus after living-donor renal transplantation. One case of sunitinib therapy for the recurrence of renal cell cancer in the native kidney after renal transplantation was reported previously; however, it did not include drug-concentration data [6]. Although tacrolimus and everolimus are metabolized by CYP3A4 [7,8], no report has demonstrated the safety of the coadministration of sunitinib with tacrolimus and everolimus with regard to therapeutic drug

monitoring. A previous pharmacokinetic study reported that ethnic difference is a significant covariate associated with lower sunitinib clearance in Asian patients [9]. This ethnic difference in sunitinib clearance is due to the polymorphism of *ATP-binding cassette subfamily G member 2* (*ABCG2*), which encodes breast cancer resistance protein (BCRP), because the *ABCG2* 421C>A allele frequency is relatively high in Asians (~30%) [10]. Here, we evaluated the possibility of an *ABCG2* 421C>A allele carrier for high sunitinib concentrations, in addition the pharmacokinetic changes in tacrolimus and everolimus during sunitinib therapy using model-based pharmacokinetic analyses.

2. Case

A 74-year-old Japanese man (height, 161 cm; weight, 43.8 kg) received living-donor renal transplantation approximately 20 years before the current event. Computed tomography (CT) performed in July 2017 revealed the presence of a mass lesion in the right native kidney. The stage of the tumor was determined to be cT1aN0M0. The patient underwent laparoscopic radical right nephrectomy in October 2017 and was histopathologically diagnosed with clear cell renal cell carcinoma (pT3a). Based on CT, pulmonary and pleural metastases of renal cell carcinoma were suspected in January 2019. Sunitinib therapy was initiated, with the initial dose (37.5 mg/day, 2 weeks on and 1 week off). Immunosuppression after renal transplantation involved extended-release tacrolimus, everolimus, mizoribine, and

methylprednisolone. In addition, the patient was treated with aspirin, azelnidipine, candesartan, atorvastatin, benzbromarone, famotidine, estazolam, potassium citrate, and sodium citrate hydrate. The target trough blood concentrations of tacrolimus and everolimus were set at 3–4 ng/mL and 6–8 ng/mL, respectively. Figure 1 shows the daily doses (A) and blood concentrations (B) of these drugs, as well as the stool frequency (C), recorded during the patient's hospitalization. On day 7 after the onset of sunitinib therapy, the patient experienced grade 2 diarrhea; therefore, treatment with an antiflatulent agent was initiated. The trough plasma concentration of total sunitinib was 133.7 ng/mL (sunitinib, 105.8 ng/mL; *N*-desethyl sunitinib, 27.9 ng/mL) on day 10. On day 12, because pyrosis and grade 3 diarrhea were observed, famotidine was switched to esomeprazole. On day 14, sunitinib was discontinued and the patient started receiving loperamide therapy at a dose of 4 mg/day. On day 18, the loperamide dose was reduced to 2 mg/day. By day 21, as the stool frequency had decreased, sunitinib therapy (25 mg/day) was restarted. Severe diarrhea was not observed after the reduction of the sunitinib dose. We increased tacrolimus and everolimus doses according to the measured concentrations (Fig. 1). The trough plasma concentration of total sunitinib was 102.7 ng/mL (sunitinib, 74.9 ng/mL; *N*-desethyl sunitinib, 27.8 ng/mL) on day 35. The patient was discharged from the hospital on day 36. We did not observe liver abnormalities during this period.

3. Simulation and assessment of drug concentrations

As routine laboratory testing, we measured whole-blood trough tacrolimus and everolimus concentrations using an electrochemiluminescence immunoassay. In addition, we measured plasma trough sunitinib and *N*-desethyl sunitinib concentrations by liquid chromatography–tandem mass spectrometry (LC-MS/MS). A simulation of drug concentrations was performed using the MwPharm++ software (Mediware, Prague, Czech Republic). Population pharmacokinetic parameters were entered into the appropriate sections of MwPharm++. The population pharmacokinetic parameters for sunitinib were set based on the previous report [10], and mean values were as follows: apparent volume of distribution (Vd/F), 1680 L; apparent oral clearance (CL/F), 26.2 L/h for *ABCG2* 421C>A noncarriers and 14.3 L/h for *ABCG2* 421C>A carriers; absorption rate constant (Ka), 0.418 h^{-1}; and lag-time, 1.6 h. The population pharmacokinetic parameters for everolimus were set based on the previous report [11], and mean values were as follows: apparent central volume of distribution (Vc/F), 83.2 L; apparent peripheral volume of distribution (Vp/F), 308.8 L; CL/F, 10.0 L/h; apparent intercompartmental clearance (Q/F), 36.1 L/h; and Ka, 1.66 h^{-1}. The population pharmacokinetic parameters for tacrolimus were the default values in MwPharm++, and mean values were as follows: Vc/F, 0.78 L/kg; Vp/F, 5.81 L/kg; CL/F, 28.3 L/h/1.85 m^2; Q/F, 156.1 L/h/1.85 m^2; Ka, 0.58 h^{-1}; and lag-time, 0.956 h.

The Bayesian individual parameter estimates of each drug were obtained using the concentration of tacrolimus or everolimus observed before the onset of sunitinib therapy (day

−13). Figure 2 shows the Bayesian-predicted concentration curve and observed concentrations of tacrolimus (A) and everolimus (B). The observed concentrations of both tacrolimus and everolimus decreased compared with the predicted values on days 23 and 17, respectively, after the onset of sunitinib therapy. On day 23 after the start of sunitinib, the tacrolimus and everolimus concentrations were 21.7% and 24.3% lower than the Bayesian predictions, respectively. The individual CL/F values of tacrolimus predicted by the Bayesian method using the concentration on days −13 and 23 were 19.7 and 23.9 L/h/1.85 m^2, respectively. The individual CL/F values of everolimus predicted by the Bayesian method using the concentration on days −13 and 23 were 5.57 and 7.49 L/h, respectively. Figure 2C depicts the observed and typical predicted concentrations of sunitinib in *ABCG2* 421C>A carriers and noncarriers [10]. The observed concentrations of our case were a little higher than those reported in the patients who are *ABCG2* 421C>A carriers.

4. Discussion

This was the first report in which the concentrations of sunitinib and *N*-desethyl sunitinib, together with those of tacrolimus and everolimus, were monitored. The plasma concentrations of sunitinib and *N*-desethyl sunitinib observed in this case after the administration of 37.5 mg of sunitinib were higher than the reported concentrations detected in patients who received 50 mg of sunitinib daily [12]. A previous study provided a population pharmacokinetic model of sunitinib using the *ABCG2* 421C>A genotype as a

predictive covariate for CL/F [10]. A pharmacokinetic analysis showed that the sunitinib concentrations observed in this patient were a little higher than the simulated mean concentration in the patient who was an *ABCG2* 421C>A carrier (Fig. 2C). Although we did not determine the *ABCG2* genotype in the present case, we considered that this patient might be an *ABCG2* 421C>A carrier.

Concomitant medications, such as everolimus, tacrolimus, and azelnidipine, might have inhibited CYP3A4-mediated sunitinib metabolism and also might have partly contributed to high sunitinib concentrations in our patient [3,13–15]. Although we did not directly clarify these drug interactions in *in vivo* or *in vitro* studies, previous studies have reported that everolimus, tacrolimus, and azelnidipine inhibit CYP3A4 substrate metabolism besides sunitinib. Co-administration of 10 mg/day oral everolimus increases the area under the plasma concentration–time curve (AUC) of oral midazolam (a sensitive CYP3A4/5 substrate) by 30% compared to treatment without everolimus [13]. Applying human liver microsome data, *in vitro–in vivo* extrapolations estimated the AUC of midazolam to increase by 27% with tacrolimus [14]. When 10 mg of simvastatin (a CYP3A4 substrate) together with 8 mg of azelnidipine was administered to healthy subjects, the AUC of simvastatin increased by 1.9 times compared to treatment without azelnidipine [15]. Although the trough concentration ratio (*N*-desethyl sunitinib/sunitinib) was 0.43 [12], the ratio in our patient was 0.26 and 0.37 on days 10 and 35, respectively, indicating decreased sunitinib metabolism. Therefore, drug

interactions on CYP3A4 might explain the high sunitinib concentrations in our patient compared to the simulated typical value of the *ABCG2* 421C>A carrier.

In a phase 3 trial, grade 3 diarrhea was reported in only 5% of patients who received sunitinib [2]. We considered that a high total sunitinib concentration caused grade 3 diarrhea. In this case, the reduction of the dose of sunitinib (25 mg/day) and the onset of loperamide therapy reduced the grade of diarrhea, although the concentration of sunitinib on day 35 remained a little higher than the simulated mean concentration in the *ABCG2* 421C>A noncarrier administered 37.5 mg of sunitinib (Fig. 2 C).

In this patient, because the concentrations of tacrolimus and everolimus decreased gradually during the sunitinib therapy, the doses of tacrolimus and everolimus were increased (Fig. 1). The pharmacokinetic profiles of tacrolimus and everolimus during sunitinib therapy can be divided into three phases. During phase 1 (days 1–6), Bayesian-predicted concentrations, using the concentration before onset of sunitinib therapy (day −13), were in good agreement with observed tacrolimus and everolimus concentrations. Sunitinib is metabolized by CYP3A4 and is also an inhibitor of both BCRP and, to a lesser extent, P-glycoprotein (P-gp) [3]. A previous *in vitro* study showed direct interaction of sunitinib with substrate-binding pockets of these transporters, because it inhibits binding of the photoaffinity substrate [^{125}I]iodoarylazidoprazosin to P-gp (IC_{50} = 14.2 μM) and BCRP (IC_{50} = 1.33 μM) [16]. Another previous *in vitro* study showed ~50% direct and ~60%

time-dependent CYP3A inhibition of sunitinib at 55 μM (~22 μg/mL) [17]. Although, these inhibiting concentrations were much higher than the simulated plasma sunitinib concentrations in our patient, intestinal sunitinib concentrations at 37.5 mg oral dosing might have been higher than the plasma concentrations, temporarily. However, in this patient, extended-release tacrolimus and everolimus were given between meals (at 10:00, and 10:00 and 20:00, respectively), while sunitinib was administered after breakfast (08:00). Therefore, intestinal sunitinib concentrations were considered to be not high enough to show direct inhibition of the CYP3A4, P-gp, and/or BCRP during absorption process of tacrolimus and everolimus, and we believe that the pharmacokinetic parameters of tacrolimus and everolimus did not change from before sunitinib initiation in phase 1.

During phase 2 (days 7–15), the Bayesian-predicted tacrolimus and everolimus concentrations were also in good agreement with observed concentrations. Our patient showed the onset of diarrhea caused by higher sunitinib concentrations. The diarrhea episodes could decrease the absorption of tacrolimus and everolimus, as observed for other drugs [18], although a controversial study reported that the persistent afebrile diarrhea observed in mycophenolate-mofetil-treated renal transplant recipients was associated with increased trough concentrations of tacrolimus [19]. Consequently, decreased absorption due to diarrhea and time-dependent inhibition of intestinal metabolism and/or excretion by sunitinib might have led to in unchanged tacrolimus and everolimus concentrations.

During phase 3 (days 16–35), the observed concentrations of both tacrolimus and everolimus were lower compared with the corresponding Bayesian-predicted values (Figs. 2A, B), and the predicted individual CL/F values of tacrolimus and everolimus increased by 21% and 34%, respectively, compared to before therapy. Although the stool frequency was highest on day 12 after sunitinib therapy, grade 1 diarrhea continued in phase 3. Therefore, tacrolimus and everolimus concentrations began to decrease after days 23 and 17, respectively (Fig. 2A, B), because of decreased absorption due to diarrhea and recovered intestinal metabolism and/or excretion due to sunitinib withdrawal and dose reduction. These were our considerations with regard to the mechanisms underlying changed tacrolimus and everolimus pharmacokinetics. More therapeutic drug monitoring data (and *in vitro* data) are needed in order to determine the interaction mechanisms of tacrolimus and/or everolimus with sunitinib.

This study had several limitations. First, we did not determine the *ABCG2* genotype, so we could not determine the contribution of *ABCG2* 421C>A polymorphism to high sunitinib concentrations. Although the *ABCG2* 421C>A homozygous patient showed the highest dose-adjusted AUC of sunitinib, which was ~1.8 times higher than the median observed in heterozygous patients [20], the reported population pharmacokinetic parameters did not distinguish homozygous and heterozygous groups, because there was only one homozygous patient in the study [10]. The development of a population pharmacokinetic model for

distinguishing *ABCG2* 421C>A homozygous and heterozygous patients should be examined. Second, we did not perform model-based predictions of the *N*-desethyl sunitinib concentration because a population pharmacokinetic model including this active metabolite has not been reported previously. In our patient, *N*-desethyl sunitinib concentrations did not change after sunitinib dose reduction, although sunitinib concentrations showed a 30% decrease compared to the initial dose. Since the sunitinib dose was adjusted on the basis of the total sunitinib concentrations, a population pharmacokinetic model including both sunitinib and *N*-desethyl sunitinib in the Japanese should be created in a future study. Third, we used the default population pharmacokinetic parameters in MwPharm++ and previously reported parameters [11] for tacrolimus and everolimus, respectively, for Bayesian prediction. Some population pharmacokinetic analyses reported covariates for tacrolimus pharmacokinetics, such as ethnic differences, gender, age, clinical laboratory tests, and *CYP3A4* and *CYP3A5* genotypes [21,22]. Although Bayesian-predicted concentrations until days 20 and 15 for tacrolimus and everolimus, respectively, were in good agreement with observed concentrations in our patient, the population pharmacokinetic parameters used might affect predicted concentrations.

5. Conclusion

ABCG2 421C>A polymorphism might lead to high sunitinib concentrations, in turn, leading to the onset of severe diarrhea. Pharmacokinetic changes in tacrolimus and

everolimus occur during sunitinib therapy. Careful therapeutic drug monitoring of sunitinib, tacrolimus, and everolimus concentrations is necessary during combination therapy, especially after episodes of diarrhea.

Conflicts of interest

All authors have no conflicts of interest to disclose.

Authors' contributions

TI performed the simulation of drug concentrations and drafted the initial manuscript. KY, SO, JF, and TO revised the manuscript. KH and MF reviewed the manuscript. IY supervised the interpretation of data and critically revised the manuscript.

Figure legends

Fig. 1. Daily doses (A) and blood concentrations (B) of drugs and stool frequency (C) after the start of sunitinib therapy (day 1).

Fig. 2. Bayesian-predicted and observed concentrations of tacrolimus (A) and everolimus (B), and model-based-predicted and observed concentrations of sunitinib (C) in a patient. The Bayesian predictions of each drug were obtained using the tacrolimus or everolimus observed concentrations before the onset of sunitinib therapy (day −13). Model-based predictions of sunitinib were obtained for *ABCG2* 421C>A carriers and noncarriers in a previous report [10]. Sunitinib therapy was initiated with 37.5 mg/day, discontinued on day 14, and restarted with 25 mg/day on day 21.

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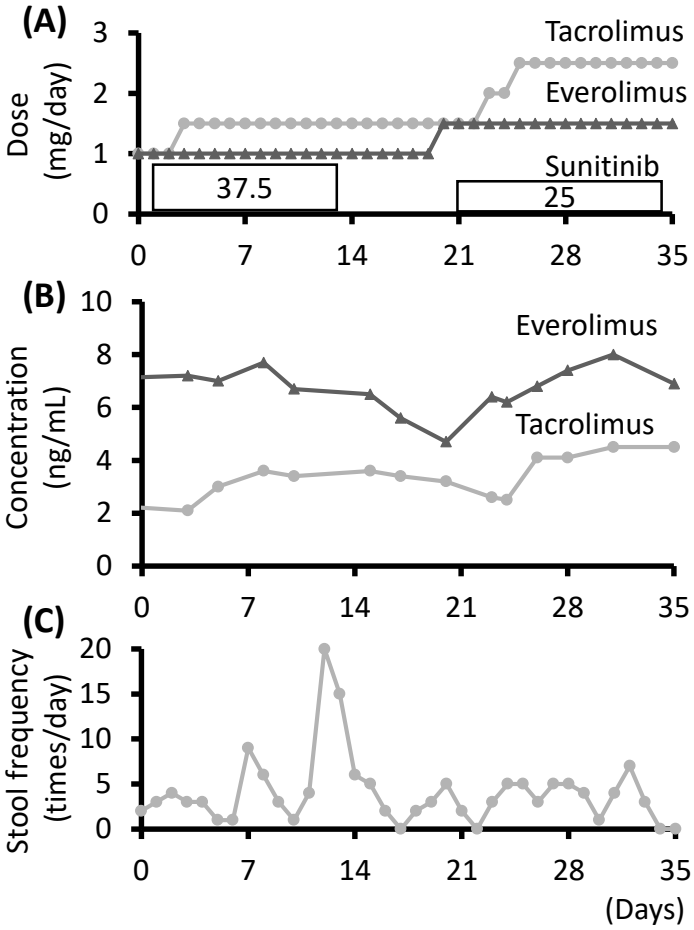
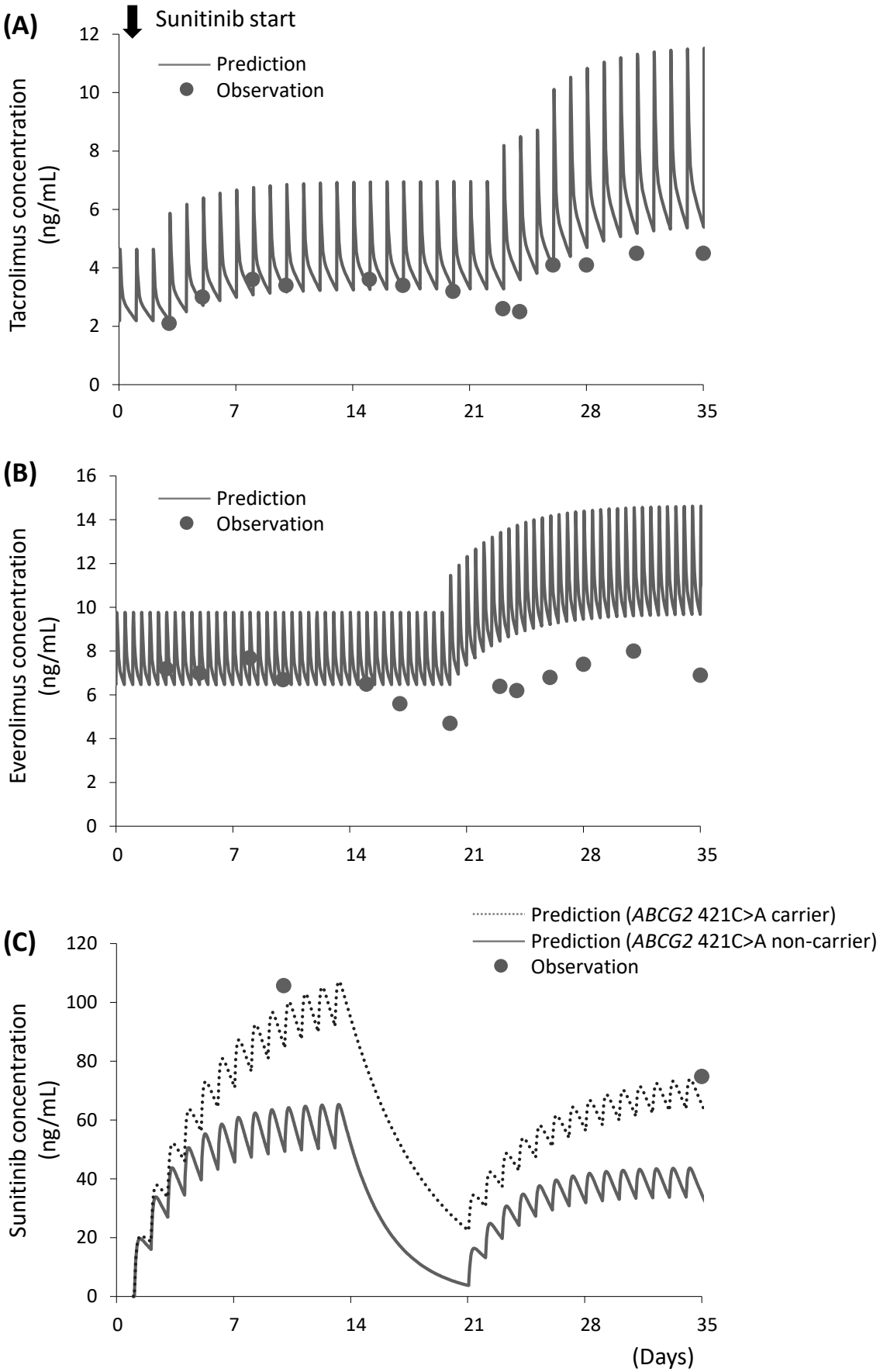

(A)
Dose (mg/day)
3
2
1
0
Tacrolimus
Everolimus
Sunitinib
37.5
25
0
7
14
21
28
35
(B)
Concentration (ng/mL)
10
8
6
4
2
0
Everolimus
Tacrolimus
0
7
14
21
28
35
(C)
Stool frequency (times/day)
20
15
10
5
0
0
7
14
21
28
35
(Days)


(A)
Sunitinib start
Prediction
Observation
Tacrolimus concentration (ng/mL)
0
2
4
6
8
10
12
0
7
14
21
28
35
(B)
Prediction
Observation
Everolimus concentration (ng/mL)
0
2
4
6
8
10
12
14
16
0
7
14
21
28
35
(C)
Prediction (ABCG2 421C>A carrier)
Prediction (ABCG2 421C>A non-carrier)
Observation
Sunitinib concentration (ng/mL)
0
20
40
60
80
100
120
0
7
14
21
28
35
(Days)