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PERSPECTIVE

PBPK perspective on alternative CYP3A4 inducers for rifampin

INTRODUCTION

Rifampin is the most frequently used inducer in drug–drug interaction (DDI) studies to evaluate the impact of cytochrome P450 (CYP), particularly CYP3A4, induction on the pharmacokinetics (PKs) of investigational drugs. However, there is a need for an alternative CYP inducer due to 1-methyl-4-nitrosopiperazine (MNP) impurity exceeding the acceptable limit in rifampin products.[1] The US Food and Drug Administration (FDA) advised against using rifampin products with MNP impurity above 0.16 ppm in healthy volunteers.[1] Here, we compared phenytoin, phenobarbital, efavirenz, and carbamazepine as alternative CYP3A4 inducers using a physiologically-based pharmacokinetic (PBPK) approach.

PBPK SIMULATION TRIAL DESIGN

PBPK simulations were performed using the Simcyp human population-based simulator (version 20) to compare induction potentials between rifampin (600 mg q.d.) and the proposed inducers, including phenytoin (300 mg q.d.), phenobarbital (100 mg q.d.), efavirenz (600 mg q.d.), and carbamazepine (100 mg b.i.d. on days 1–2, 200 mg b.i.d. on days 3–4, and 300 mg b.i.d. on days 5–14). These library compounds were previously verified and used as default with no modification.[2,3] Model parameters are provided in Tables S1–S6. For each inducer, simulation of 10 trials of 10 healthy men aged 20–50 years was carried out. Simcyp healthy volunteer population was developed based on White individuals. An inducer was orally dosed for 2 weeks (days 1–14), followed by oral co-administration of the inducer and midazolam (5 mg) on day 15. The area under the concentration-time curve from 0 to 24 h (AUC_{0-24h}) and peak concentration (C_{max}) of midazolam were simulated in the presence and absence of inducers.

PBPK SIMULATION RESULTS

Based on the simulated midazolam DDI-to-control geometric mean ratios (GMRs) of AUC_{0-24h} and C_{max}, carbamazepine was determined to be the strongest CYP3A4 inducer second to rifampin (AUC GMR [90% confidence intervals] = 0.208 [0.194, 0.224] vs. 0.0709 [0.0628, 0.0800]; C_{max} GMR = 0.259 [0.244, 0.274] vs. 0.107 [0.0952, 0.121]), which is followed by phenytoin (AUC GMR = 0.224 [0.203, 0.248]; C_{max} GMR = 0.284 [0.260, 0.310]), phenobarbital (AUC GMR = 0.225 [0.209, 0.243]; C_{max} GMR = 0.295 [0.276, 0.314]), and efavirenz (AUC GMR = 0.302 [0.282, 0.324]; C_{max} GMR = 0.415 [0.392, 0.440]; Figure 1a). However, simulated CYP3A4 dynamic profiles reveal that the strong induction potential of carbamazepine is due mostly to increased gut CYP3A4 (>5-fold) whereas hepatic CYP3A4 was only marginally increased (<2-fold; Figure 2a). In contrast, efavirenz has the highest induction potential for hepatic CYP3A4 among the proposed alternatives, inducing CYP3A4 by >3-fold in the liver but <2-fold in the gut (Figure 2a).

Given the narrow therapeutic index of carbamazepine and phenytoin, induction with these inducers were further explored using different dosing scenarios to achieve higher induction potential.

Carbamazepine was titrated to achieve 300 mg twice daily (b.i.d.; regimen 1), 200 mg thrice daily (t.i.d.; regimen 2), 400 mg b.i.d. (regimen 3), 500 mg b.i.d. (regimen 4), or 600 mg b.i.d. (regimen 5), as illustrated in Figure 1b. Following dosing regimen 5, the midazolam AUC and C_{max} GMR were 0.119 [0.110, 0.129] and 0.157 [0.147, 0.168], respectively, which were close to those following rifampin (Figure 1b). Despite similar levels of induction in the gut on day 15 compared to rifampin, carbamazepine induced hepatic CYP3A4 by less than half of that achieved by rifampin (Figure 2b). Following carbamazepine regimen 1–5, carbamazepine C_{max} was above its therapeutic window (4–12 μg/ml)[4] in 0%, 0%, 6%, 16%, and 27% of the simulated subjects, respectively.

Phenytoin simulations were repeated with 100 mg t.i.d., 150 mg b.i.d., 150 mg t.i.d., 225 mg b.i.d., 300 mg q.d., and

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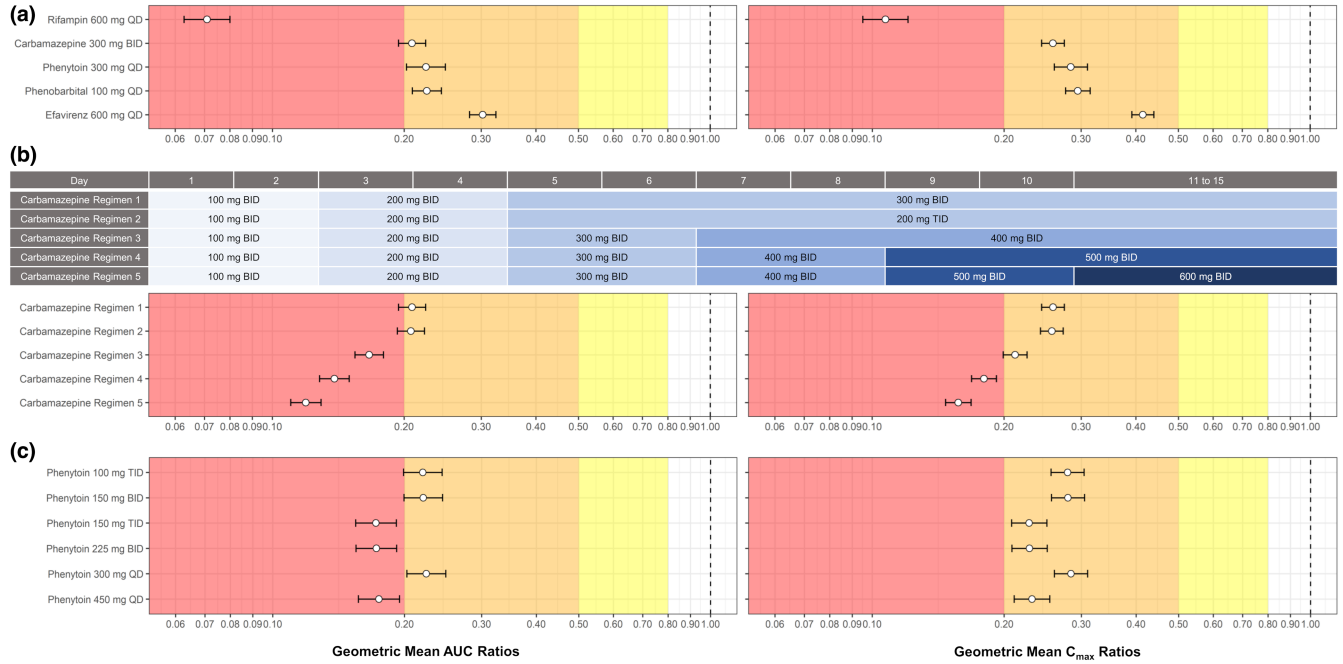

FIGURE 1 Summary of simulated geometric mean ratios for midazolam AUC (left) and C_{max} (right) on day 15 following co-administration of rifampin and its proposed alternatives (a), carbamazepine regimens (b), and phenytoin regimens (c). The bars represent the corresponding 90% confidence intervals. Carbamazepine titration regimens 1–5 are illustrated above panel b. The yellow, orange, and red areas represent weak, moderate, and strong induction, respectively. AUC, area under the concentration-time curve; C_{max}, peak concentration

450 mg q.d. At the highest daily dose (e.g., 450 mg q.d.), the changes in midazolam exposures (AUC GMR = 0.175 [0.157, 0.195]; C_{max} GMR = 0.231 [0.211, 0.254]) were comparable to those following carbamazepine 400 mg b.i.d. (AUC GMR = 0.166 [0.154, 0.179]; C_{max} GMR = 0.212 [0.199, 0.226]; Figure 1c). Compared to carbamazepine 600 mg b.i.d. on day 15, phenytoin 450 mg daily resulted in a slightly higher level of hepatic CYP3A4 but a lower level (~50%) of intestinal CYP3A4 (Figure 2c). Following these phenytoin regimens, phenytoin C_{max} exceeded its therapeutic window (10–20 μg/ml)[4] in 4%, 4%, 25%, 26%, 10%, and 32% of the simulated subjects, respectively.

DISCUSSION AND RECOMMENDATIONS

According to the simulated AUC and C_{max} GMR of oral midazolam, the CYP3A4 induction potential of rifampin and proposed alternatives ranks as follows: rifampin 600 mg q.d. > carbamazepine 300 mg b.i.d. > phenytoin 300 mg q.d. > phenobarbital 100 mg q.d. > efavirenz 600 mg q.d. (Figure 1a). This suggests that carbamazepine and phenytoin are the primary and secondary alternatives for rifampin, in agreement with a recent systemic review by Bolleddula et al.[5] based on DDI clinical studies. Lumacaftor, considered a potential alternative in the review, is not included in the analysis here due to insufficient published data for DDI verification. However, a preliminary simulation of lumacaftor 200 mg q.d. performed using a published model[6] suggests moderate induction (AUC GMR = 0.314 [0.297, 0.331]; C_{max} GMR = 0.324 [0.308, 0.342]), which would rank comparably with efavirenz.

Considering the longer half-lives of phenytoin and phenobarbital, simulations were also performed for a week longer. This resulted in minimal changes following phenytoin administration (AUC GMR = 0.221 [0.200, 0.245]; C_{max} GMR = 0.281 [0.258, 0.307]), whereas the induction level following phenobarbital (AUC GMR = 0.201 [0.186, 0.218]; C_{max} GMR = 0.268 [0.250, 0.286]) became comparable to that following carbamazepine. These simulations indicate the design of the clinical studies should be carefully considered. Increasing carbamazepine and phenytoin to the higher end of their recommended dose ranges raised the interaction level from moderate (orange areas in Figure 1) to strong induction (red areas in Figure 1). However, even at the highest dose levels simulated (i.e., 600 mg b.i.d. [regimen 5] for carbamazepine or 450 mg q.d. for phenytoin), the induction was still lower than that after rifampin 600 mg q.d. Caution has to be taken when using carbamazepine and phenytoin at these dose levels as the risk of adverse side effects increases. To keep the frequency of exceeding therapeutic windows under 10% of the population, we recommend the use of 300 mg b.i.d. for carbamazepine and 100 mg t.i.d. or 150 mg b.i.d. for phenytoin in DDI studies.

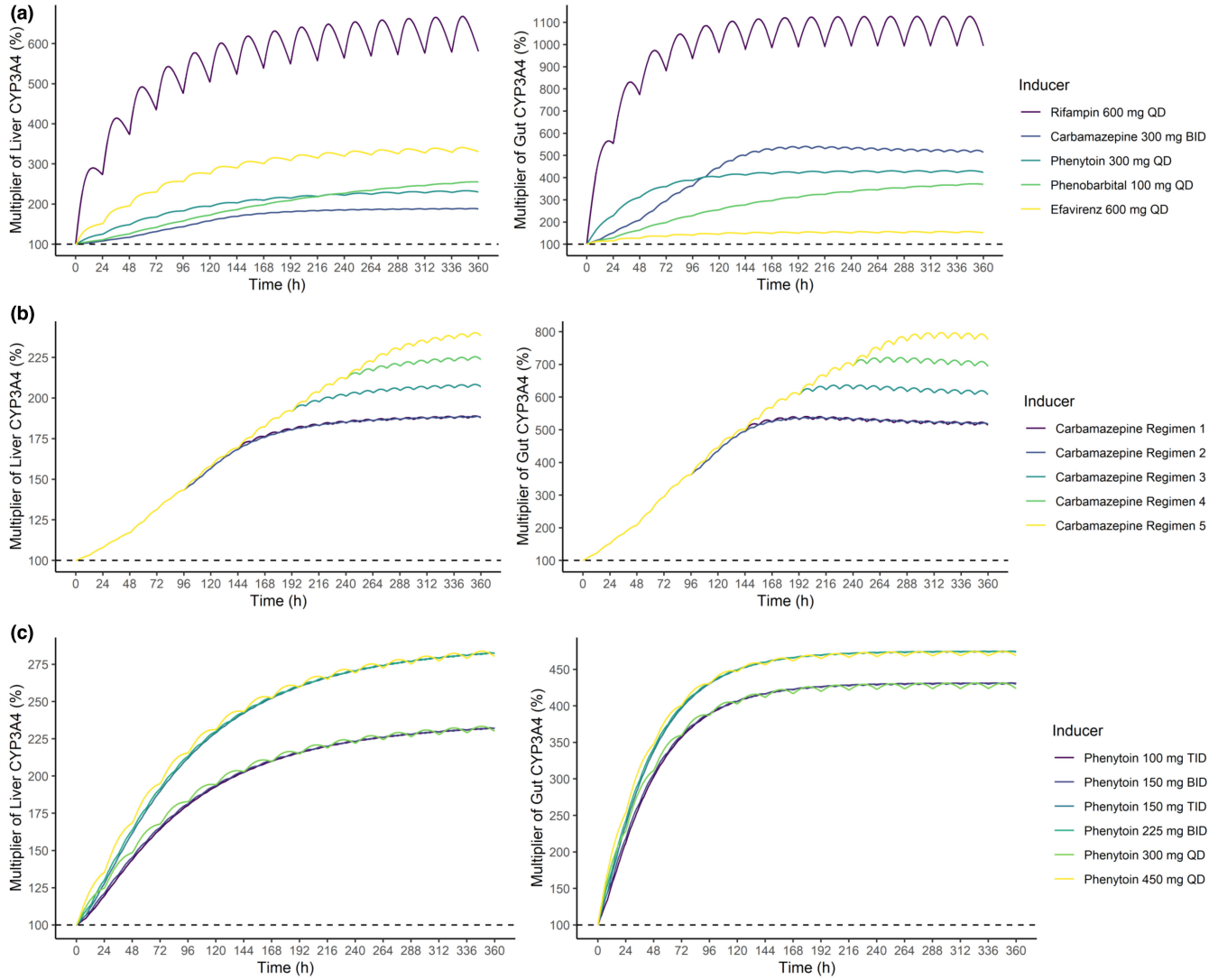

FIGURE 2 Simulated percentage of multipliers of hepatic (left) and intestinal (right) CYP3A4 levels over time following administration of rifampin and its proposed alternatives (a), carbamazepine regimens (b), and phenytoin regimens (c). The baseline (100%) is indicated by black dashed lines. Carbamazepine regimens are illustrated in Figure 1b

The simulated intestinal and hepatic CYP3A4 profiles show that induction by carbamazepine is much stronger in the gut compared to the liver (Figure 2b), indicating that orally administered CYP3A4 substrates undergoing extensive gut metabolism as a result of the first-pass effect would be markedly affected by carbamazepine. This is evidenced by the comparable AUC reduction between carbamazepine and rifampin in clinical DDI studies using simvastatin, where simvastatin AUC decreased by 75% and 87% following pretreatment with carbamazepine 600 mg q.d. and rifampin 600 mg q.d., respectively.[7,8] On the other hand, if the substrate is minimally metabolized in the gut, efavirenz would become the primary alternative based on the hepatic CYP3A4 profiles (Figure 2a). To illustrate this, oral midazolam was replaced with i.v. midazolam. Following carbamazepine 300 mg b.i.d. (regimen 1) and efavirenz 600 mg q.d., the simulated iv midazolam AUC GMRs [90% confidence intervals] were 0.763 [0.746, 0.780] and 0.672 [0.650, 0.694], respectively, suggesting that efavirenz leads to a marginally stronger induction effect compared to carbamazepine.

These inducers affect a number of other CYP enzymes beyond CYP3A4 and act via different mechanisms. These factors should also be considered when choosing an appropriate alternative. Rifampicin, phenytoin, and carbamazepine are listed as strong CYP3A4 inducers by the FDA.[9] However, rifampicin is also a strong inducer of CYP2C19 and a moderate inducer of CYP1A2, CYP2B6, CYP2C8, and CYP2C9, whereas carbamazepine is also a strong inducer of CYP2B6 and a weak inducer of CYP2C9 and phenytoin is also a moderate inducer of CYP1A2 and CYP2C19. Phenobarbital and efavirenz are listed as moderate inducers of CYP3A4 and efavirenz is also a moderate inducer of CYP2B6 and CYP2C19. Rifampicin is an

agonist of PXR, whereas carbamazepine, phenytoin and efavirenz are CAR activators and phenobarbital has been shown to interact with CAR and PXR.[10,11]

In summary, based on this PBPK modeling analysis, carbamazepine and phenytoin are recommended as the best alternatives to rifampin to evaluate the effect of strong CYP3A4 induction on the PKs of investigational drugs. However, when intestinal metabolism is minimal, strong induction is not achievable with current alternatives, in this case, efavirenz has the strongest induction potential for hepatic CYP3A4 and could be considered.

Moreover, we would like to trigger future discussion by breaking the conventional study design that includes both itraconazole and rifampin in DDI liability assessment. In cases where strong inhibition has been observed, strong induction following rifampin co-administration is typically expected. Therefore, if a clinical induction study is required and strong inhibition has been observed, we propose to replace the strong inducer with a moderate inducer, such as efavirenz. We believe that this is more informative and adds predictive confidence in the region of moderate interaction.

Building on this, an International Consortium for Innovation and Quality (IQ) PBPK-modeling induction working group (PBPK-IWG) publication reported survey data indicating confidence in using PBPK modeling to predict induction by rifampin when strong induction is expected. Specifically, they highlight a case study where PBPK modeling was used in lieu of a rifampin clinical DDI study to inform ivosidenib labeling.[12] Therefore for cases like this, PBPK modeling may also be a viable alternative to a dedicated rifampin study.

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CONFLICT OF INTEREST

No author has an actual or perceived conflict of interest with the contents of this paper. All authors are employees of Certara and hold stock in the company.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.