Rational Dose Selection for a Nonnucleoside Reverse Transcriptase Inhibitor through Use of Population Pharmacokinetic Modeling and Monte Carlo Simulation

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GW 420867X is a new nonnucleoside reverse transcriptase inhibitor (NNRTI) of the human immunodeficiency virus type 1 (HIV-1) reverse transcriptase with potent activity, a prolonged half-life, and activity against some isolates already resistant to older members of this class. For any new drug class or for any new member of an already-extant drug class, the ability to rationally choose a dose will have a major impact on the ability to rapidly (and successfully) develop a drug.

For anti-infective drugs, there are a limited number of factors that impact upon the adequacy of drug therapy. Once one can account for each of these factors, the ability to rationally choose a dose of drug for a large Phase III study should be relatively straightforward.

In order to choose a dose, one first must have a goal of therapy, the attainment of which provides a high probability of a good clinical or microbiological outcome. Once a goal is clear, the factors that affect the goal attainment are the population pharmacokinetics of the drug (how drug concentrations differ across patients), the distribution of a measure of sensitivity (e.g., viral 50% effective concentration [EC50]) of the target pathogen to the drug in the population to be treated, and the degree of drug protein binding.

We therefore undertook the task of examining several proposed doses for the nonnucleoside analogue GW420867X and to predict which of three proposed doses would have maximal effect in a short (1-week) monotherapy trial, followed by a longer extension of the trial with combination chemotherapy.

For the analyses reported below, the underpinning assumptions were as follows: (i) Time > Threshold (EC90) is the pharmacodynamically linked variable for NNRTIs; (ii) protein binding needs to be taken into account; (iii) the free drug needs to exceed the EC90 not just the EC50, to develop full antiviral effect; and (iv) steady-state pharmacokinetics in volunteers is an accurate reflector of steady-state pharmacokinetics in HIV-infected patients.

For the first assumption, there are little published data. However, NNRTIs are reversible inhibitors of the HIV-1 reverse transcriptase. Further, there is no activation step as there is with nucleoside analogues. No active transport has been identified for these agents. Consequently, it is rational on first principles to assume that Time > Threshold will be linked to the antiviral effect for these agents. It should also be noted that Time > Threshold is the single most conservative choice, as Time > Threshold rises as the logarithm of the dose (i.e., the rate of rise of Time > Threshold with dose is slower than for other parameters such as area under the concentration-time curve/Threshold or Peak/Threshold, as these rise linearly with dose if the drug displays linear pharmacokinetics).

Again, while few published data exist regarding the impact of protein binding on the activity of nonnucleoside reverse transcriptase inhibitors (1), data from our laboratory have demonstrated that protein binding adversely affects the activity of HIV protease inhibitors (2, 3). We felt that it was highly likely that this was also true for NNRTIs, since in the presence of human α-1 acid glycoprotein the 50% inhibitory concentration for GW420867X increases approximately 7.6-fold.

We chose EC90 and not EC50 as the target threshold. Clearly, the ability of antiretroviral agents to decrease viral copy number and prevent emergence of resistance (4) is related to decreasing the number of rounds of viral replication. This is best accomplished by attaining free drug concentrations that are able to (near) maximally achieve complete suppression of viral turnover.
Finally, as the patients who were to enter the protocol for the evaluation of the drug were to be treatment naïve and were not suffering from an intercurrent illness, we felt that the assumption that the pharmacokinetics of GW420867X determined for volunteers was an accurate reflector of the pharmacokinetic profile for HIV-infected patients was a reasonable one. With these assumptions, we then employed Monte Carlo simulation to examine the adequacy of the proposed doses.

**EC50 determination.** The susceptibilities of the test HIV isolates were determined by the DOD/AIDS Clinical Trials Group consensus assay (6). In addition, this experiment was performed in parallel with determinations in which the growth medium was supplemented by 1.5 mg of human acid glycoprotein per ml, 4 mg of human serum albumin per dl, or both (J. P. Kleim, V. Burt, M. Maguire, P. Mutch, R. J. Hazen, and M. St. Clair, Abstr. 6th Conf. Retrovir. Opportunistic Infect., abstr. 599, p. 180, 1999). EC50s and EC90s were determined directly from the data.

**Population pharmacokinetic modeling of GW420867X.** Plasma concentration-time data were provided by the sponsor. The data were from a multiple-dose study of the oral administration of 50, 100, or 200 mg of GW420867X to normal volunteers once daily (eight drug-receiving subjects per treatment group) for 14 days (K. H. P. Moore, L. Cass, A. Kapoor, N. Dallow, A. Jones, W. Prince, and M. Boyce, Abstr. 6th Conf. Retrovir. Opportunistic Infect., abstr. 601, p. 180, 1999).

The steady-state data were modeled employing a nonparametric expectation maximization (NPEM) approach (7), with a program produced by R. Jelliffe and A. Schumitzky (NPEM3). Models were discriminated by the Akaike Information Criterion (8). One- and two-compartment open models with first-order absorption and elimination were evaluated. Population values were used to produce maximum a posteriori probability Bayesian estimates for each individual patient employing the "population of one" utility within NPEM. Scatter plots were examined for individual patients and for the population as a whole. Since preliminary information indicated that the different doses to be evaluated (50, 100, and 200 mg) were not linear in their area under the concentration-time curve, individual population analyses were performed for each dose.

**Monte Carlo simulation.** The mean parameter vector and covariance matrix from the population pharmacokinetic models were embedded in Subroutine PRIOR of the ADAPT II package of programs of D’Argenio (ADAPT II User’s Guide, Pharmacokinetics/Pharmacodynamics System Analysis Software; Biomedical Simulations Resource, Los Angeles, Calif.). The population simulation without process noise option was employed. Both normal and log-normal distributions were evaluated. These were discriminated on their ability to recreate the original mean parameter values from the population analyses. Three 1,000-subject Monte Carlo simulations were performed. The parameter values were employed to simulate concentrations at trough of a steady-state dosing interval. (Interested readers may obtain the full covariance matrices by request from the author.)

**TABLE 1. Population pharmacokinetic parameter values for three doses of GW420867X**

<table>
<thead>
<tr>
<th>Dose of GW420867X (mg)</th>
<th>Mean (SD)</th>
<th>V/F (liters)</th>
<th>K_a (h⁻¹)</th>
<th>SCL/F (liters/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>282 (52)</td>
<td>4.85 (3.51)</td>
<td>4.04 (1.54)</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>282 (38)</td>
<td>4.97 (3.50)</td>
<td>4.65 (0.69)</td>
<td></td>
</tr>
<tr>
<td>200</td>
<td>227 (119)</td>
<td>2.10 (2.07)</td>
<td>5.09 (1.06)</td>
<td></td>
</tr>
</tbody>
</table>

*K_a, first-order absorption rate constant.

![FIG. 1. Percentage of subjects simulated with trough free drug of GW420867X > 10 times the EC50 of HIV. A Monte Carlo simulation of 1,000 subjects performed three times was employed to estimate the fraction of these subjects whose concentration-time curve would produce maximal viral suppression on the basis of the target values. The evaluation was performed for doses of 50, 100, and 200 mg of GW 420867X, administered once daily by mouth.](http://aac.asm.org/)

Regimen evaluation. The goal of optimal viral suppression was determined from the assumptions set forth above. Once the goal was set, the concentration-time data were imported into a statistical package (SYSTAT for Windows v8.0; SPSS, Inc., Chicago, Ill.). Plasma concentration-time data for each of the simulated subjects at the goal-defined time (steady-state trough) were transformed from nanograms per milliliter into nanomolar concentration values and corrected for protein binding, using data from the protein binding effect on EC50 determination experiments (assuming a 7.6-fold increase in in vitro 50% inhibitory concentration in the presence of human binding proteins) and the approximate 10-fold difference between EC50 and EC90 based on in vitro data. For theoretical viral isolate EC50s of 1 to 75 nM, the proportion of subjects attaining the therapeutic target among each of the three 1,000-subject simulations was determined. The means and standard deviations of the proportions were determined.

The results of the effect of protein binding on EC50 determination and the difference between EC50 and EC90 were determined from the data of Kleim et al. (see above). The EC50 determined in the presence of both human α-1 acid glycoprotein and albumin increased 7.6-fold compared to that determined in the presence of growth medium only (data not shown). Therefore, this value (7.6-fold) was used for all calculations to correct plasma concentrations for protein binding.

The EC90s were all 8 to 10 times the EC50s (again, from Kleim et al.). For this reason, a value of 10 was employed to correct theoretical EC50s to EC90s for the purposes of target attainment analysis.

Population pharmacokinetic analyses all demonstrated that a one-compartment open model with first order input and elimination was the choice for each of the doses. The mean values for steady-state trough after the maximum a posteriori probability-Bayesian step for each of the doses were concordant with actual mean values observed in healthy volunteers. The population pharmacokinetic parameter values for the three doses are displayed in Table 1.

Monte Carlo simulation using a log-normal distribution accurately recaptured the starting mean parameters.

Steady-state total plasma trough concentrations were corrected for the difference between milligrams per liter and nanomolar concentrations. These values were then divided by 10 to correct for the difference between EC50 and EC90. The resultant values were divided by 7.6 to correct for the difference between total and free drug. The resultant values were tested to see if they were above EC50 (obtained in fetal calf serum-supplemented media, human protein free) from 1 to 10 nM in steps of 1 nM and from 10 to 75 nM in steps of 5 nM. This is presented in Fig. 1.

As can be seen, each of the doses provides >95% target attainment for EC50 values from 1 to 10 nM. The 100- and 200-mg doses show target attainment rates in excess of 95% up to 25 and 30 nM, respectively. At the time of this analysis, there were 16 isolates with determinations of EC50 to GW420867X available, all of which were less than 8 nM. The slopes are different between groups because each represents a separate population pharmacokinetic analysis. Had the analysis been performed with all doses in the same PK analysis, the slopes would have been parallel.

GW420867X is a new NNRTI. It differs from efavirenz in that its protein binding is lower. It also possesses potent activity against HIV-1, with viral EC50s against 16 isolates being 8 nM, or less. Further, when one examines the pharmacokinetic parameter values (Table 1), it is obvious that it has a profile that would allow once-daily administration as the calculated population half-lives \(\frac{\ln(2)\cdot(SCL/F)}{V/F}\), where SCL is serum clearance, F is bioavailability, and V is volume of distribution) are 30 to 40 h.

When a new drug is to be evaluated in the clinic, it is important that the dose be likely to be efficacious. This can be
evaluated in a number of ways. The dose can be efficacious for wild-type viruses by virtue of copy number fall. However, it may make selection and amplification of resistant mutants more difficult or it may provide efficacy against strains that have already acquired a first resistance mutation (e.g., K103N or Y181C for this agent).

For the first goal, it is apparent that all three doses evaluated would provide free-drug plasma concentrations above the EC50 for the entire (24-h) dosing interval for isolates with an EC50 of 8 nM, or less. Therefore, if the isolates encountered in a Phase I/II trial have susceptibilities like those examined preclinically, it will be impossible to differentiate these doses based on the viral-load decline observed in the trial.

Indeed, this was the case. GW420867X was examined in a Phase I/II trial, as monotherapy for 1 week, followed by the addition of zidovudine-lamivudine, with 15 patients per treatment group. The viral-load changes for the patients enrolled in this trial are displayed in Fig. 2, and the day 8 fall of viral copy number for the three dosing groups ranged from 1.48 to 1.52 log10 (K. Arasteh, M. Muller, R. Wood, L. Cass, K. H. P. Moore, N. Dallow, A. Jones, V. Burt, J. P. Kleim, and W. Prince, Intersci. Conf. Antimicrob. Agents Chemother., abstr. 504, 1999). As can be seen, all three dosing groups provided essentially the same viral-load decline in the monotherapy phase. Addition of zidovudine-lamivudine did not materially change the conclusion.

It is also possible to examine Fig. 1 and speculate about the other endpoints, such as delay or prevention of resistance or activity against isolates that have already attained the first mutation. In either of these scenarios, the 100-mg or, more likely, the 200-mg dose would be preferred, assuming safety and tolerability at these doses. A single point mutation like K103N or Y181C may provide a 20-fold change in viral EC50 for GW420867X. According to the results shown in Fig. 1, it is possible that a number of single point mutants may still be able to be inhibited at the larger doses. At 200 mg once daily, approximately 50% of a population of patients may still retain activity against isolates with in vitro EC50s of 50 to 60 nM. On the other hand, the lower doses might be preferable, on a tolerability basis, to the 200-mg dose.

Our method of target setting and then examining the distribution in pharmacokinetic properties and the distribution in EC50 for the target pathogen has, in this instance, provided an accurate estimate of the antiviral activity as seen in a Phase I/II clinical trial of a new member of the NNRTI class of antiretrovirals. It should also be recognized that a similar evaluation, but carried out for an antibacterial compound, likewise provided a correct prediction, this time of drug failure (5). Newer agents evaluated in this fashion will provide more data for the utility of this approach in correctly predicting clinically appropriate drug doses. The ability of the approach to predict doses that counterselect emergence of resistant mutants needs evaluation.

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REFERENCES