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FORGIVENESS OF NON-ADHERENCE TO ONCE VS. TWICE DAILY LAMIVUDINE/ABACAVIR IN COMBINATION WITH EFAVIRENZ IN HIV-INFECTED CHILDREN

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SUMMARY

Optimisation of therapeutic management of infectious diseases is a priority in the European Union. Harmonisation of dosing regimens in order to encourage the development of fixed-dose combinations is therefore encouraged. Fixed-dose combinations are important as they can improve how well a patient is able to follow medical advice in terms of taking medicine at the right time and taking the correct number and combination of tablets. However, one of the main concerns of once daily dosing regimens based on fixed-dose combinations is the potentially lower robustness compared to twice daily dosing. This study was aimed at evaluating the forgiveness of non-adherence to once vs. twice daily lamivudine/abacavir.

Clinical trial simulations (CTS) were performed in R 2.14. Once and twice daily lamivudine/abacavir were administered with efavirenz to a hypothetical population of HIV-infected children between 3 and 12 years old (n=30). Different degrees of adherence to therapy were simulated for the two regimens. The primary efficacy endpoint was the measure of viral load at week 48.

Our results show comparable forgiveness of non-adherence to the two dosing regimens in case of treatment interruptions, doses randomly missed and delays in drug intake.

Based on these findings, it appears that once daily lamivudine/abacavir could be administered in combination with efavirenz to children between 3 and 12 years old without any risk of decreased efficacy, as compared to the currently recommended twice daily regimen.
10.1. INTRODUCTION

Several attempts have been made to improve patient adherence to antiretroviral therapy. Among other things, the development of fixed-dose combinations and the administration of once daily dosing options have determined a significant reduction in pill burden (1). Currently once daily dosing regimens seem to be the preferred treatment options to improve patient adherence (2). In this context, a once daily single tablet fixed-dose combination represents an important simplification of HIV treatment. Fixed-dose combinations include drugs with favourable pharmacokinetics that do not need dose adjustments, have no additional toxicities, and do not require dissimilar intake conditions (3). In fact, it has been shown that in newly diagnosed antiretroviral-naive patients, once daily dosing of antiretroviral drugs resulted in higher adherence than twice daily dosing (4).

Regardless of such advantages, one of the main regulatory concerns with modifications in a dosing regimen is that treatment response may change or be less robust as compared to the reference dosing regimen. In other words, despite the endorsement of current guidelines as to the importance of characterising the relationships between dose, drug concentrations and clinical response for the safe and effective use of drugs in individual patients, including the possibility to define dosage and administration instructions in the product label (5), confirmatory clinical trials are still deemed necessary to prove efficacy of new regimens for fixed-drug combinations, preferably by parallel group comparisons in which the new regimen is compared to the reference treatment (6). In most cases, these requirements appear to contradict each other, in that knowledge of pharmacokinetic-pharmacodynamic relationships should enable accurate inferences of efficacy and safety. One should therefore dispute the need for confirmatory trials. Scientifically, what should be evaluated is whether the underlying pharmacokinetic-pharmacodynamic relationships are not affected by changes in dosing regimen.

In reality, this concern pertains to the realm of quantitative clinical pharmacology and is closely related to the concept of compliance, treatment adherence and forgiveness. In conjunction with models of disease dynamics, pharmacokinetic-pharmacodynamic relationships can be used to explore whether simplified dosing regimens yield different response to therapy as compared to more frequent dosing regimens.

In chapter 9 we have shown that a model-based approach may be used to assess the effect of partial adherence to a fixed-drug combination of abacavir, lamivudine and efavirenz. Our results suggest that pharmacokinetic-pharmacodynamic relationships of antiretroviral drugs could be used as “proxy” of efficacy. Moreover, it shows that the evaluation of forgiveness of non-adherence for simplified dosing regimens is crucial to assess the feasibility of alternative treatment options.

In contrast to current guidelines, which impose pharmacokinetic, efficacy and safety trials to assess the suitability of a simplified dosing regimen, this study aims at showing how pharmacokinetic-pharmacodynamic relationships may be used as predictors of response to changes in dosing regimen, thereby avoiding the need to unnecessarily enroll children into an efficacy trial.

Here we use abacavir and lamivudine as a paradigm combination to explore the forgiveness of treatment to changes in dosing regimen. The use of dual nucleoside reverse transcriptase inhibitors (NRTI) is recommended as a part of combination antiretroviral therapy (7). Abacavir (ABC) and lamivudine (STC) constitute the NRTI backbone in HIV-therapy and are usually administered in adults and children in combination with one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one boosted protease inhibitor (PI). At present abacavir and lamivudine are administered as twice daily in children and once daily in adults. Among the various trials in which abacavir and lamivudine have been investigated in children, the PENTA 13 trial demonstrated similar pharmacokinetics between once and twice daily doses, after administration of either a liquid or tablet formulation (8). In the same study, acceptability data demonstrated that caregivers preferred once daily dosing only if all drugs in the regimen were once daily. The PENTA 15 trial also demonstrated similar pharmacokinetics between once and twice daily dosing with abacavir and lamivudine in children aged 3 months-3 years old (9). In addition, a sub-study of the ARROW trial (a randomised trial monitoring practice and induction maintenance of antiretroviral therapy regimens) (10) has shown that once daily regimens resulted in equivalent AUC0-24 to twice daily regimens in 3 to 12 year-old African children receiving World Health Organization (WHO) recommended doses of scored tablets. It should also be noted that two previous population pharmacokinetic analyses have been performed by our group, which showed comparable exposure of once and twice daily lamivudine and abacavir in a large simulation of a paediatric population including children between 3 months and 12 years old.

Based on the points discussed above, it is clear that the evaluation of once daily dosing of lamivudine and abacavir in children will be crucial for treatment optimisation and further alignment with its current use in the adult indication (11). Despite similar pharmacokinetic exposure for the two dosing regimens, the impact of non-adherence on treatment outcome should be investigated to ensure the robustness of once daily lamivudine/abacavir.

10.2. METHODS

Clinical trial simulation

The simulation scenarios described in the next paragraphs were performed in R (v 2.14.0) using a clinical trial simulations template, which was developed by our group (12). In figure 1 an overview is presented of the different simulation steps required to implement a clinical trial simulation aimed at the assessment of the impact of non-adherence for a combination of three drugs after once and twice daily dosing regimens.
Population demographics and treatment

A hypothetical population consisting of 200 HIV-infected between 3 and 12 years old was selected with individuals evenly spread across the body weight range relevant to this group. Body weight has been simulated from an empirical distribution represented by two clinical trials in which HIV-infected children were enrolled, namely PENTA 13 (8) and ARROW part 1 (10)). Simulations of body weight using a multivariate distribution were performed in R (v 2.14.0) according to the method described by Tannenbaum et al (13). The outcome of the treatment was split into two cases, namely perfect and imperfect adherence. Given the high number of scenarios evaluated and the computational time required, a smaller population was simulated (n=30) during the evaluation of the scenarios of poor adherence. However, more subjects (n=200) were evaluated when the sample size was deemed important for the interpretation of the results.

Three drugs (abacavir, lamivudine and efavirenz), currently used as first-line therapy in HIV-infected children (14), were administered according to body weight as established in the latest summary of product characteristics. The duration of the hypothetical trial was 48 weeks. The children received the drugs either as twice daily or once daily dosing regimens. The endpoint for efficacy was the probability of viral failure (HIV RNA higher than detection limit) at week 48. Viral failure was defined as a value of viral load higher than the detection limit. The thresholds used as detection limit were 50 and 400 copies/mL in case of perfect adherence. In the subsequent evaluation of the scenarios of poor adherence the strictest threshold of 50 copies/mL was used.

Models for drug pharmacokinetics, drug resistance and drug efficacy

Three mathematical models were subsequently used to predict the effect of sub-optimal adherence on treatment outcome after the use of once or twice daily doses of a fixed-dose combination. First a pharmacokinetic model was used to predict the time course of plasma concentrations for each drug. Subsequently a pharmacodynamic model was applied to predict the time varying inhibitory effect of the drugs and ultimately a disease model for viral replication and infection was employed to predict the time varying clinical endpoint (viral load).

The pharmacokinetic profiles over time for each drug were simulated based on validated models available in literature (15–17). The median inhibitory concentration (IC_{50}) was used to quantify agent-specific drug susceptibility. To model within-host changes over time in IC_{50} attributable to the emergence of new-drug resistant mutations the function described in equation (1) was used (18):

\[
IC_{50}(t) = \begin{cases} 
I_0 + \frac{I_r - I_0}{t_r} & \text{for } 0 < t < t_r \\
I_r & \text{for } t \geq t_r 
\end{cases} 
\]

where \(I_0\) and \(I_r\) are, respectively, the values of IC_{50}(t) at baseline and time point \(t_r\) at which the resistant mutations dominate. If \(I_r = I_0\) no new drug resistant mutation is developed during treatment. More complicated models for IC_{50} are available in literature (19, 20), however in clinical practice it is common to collect IC_{50} values only at baseline and failure time (21). The values of IC_{50} for the drugs included in our analysis were obtained from literature, such as the values of \(I_r\), which is based on phenotypic resistance tests for each drug (22–24).

Drug efficacy was considered to be constant over time in several viral dynamic studies (25–27). However, drug efficacy may vary because of the differences in drug concentration and other factors (i.e. development of resistance), which may vary during treatment. A pharmacodynamic additive sigmoid Imax model was used to describe the concentration-effect relationship of three drugs and subsequently predict time-varying efficacy during the course of therapy with the drug combination:

\[
y(t) = \frac{\text{ConcEFV}(t)/IC_{50,EF}(t) + \text{Conc3TC}(t)/IC_{50,3TC}(t) + \text{ConcABC}(t)/IC_{50,ABC}(t)}{\Phi + \text{ConcEFV}(t)/IC_{50,EF}(t) + \text{Conc3TC}(t)/IC_{50,3TC}(t) + \text{ConcABC}(t)/IC_{50,ABC}(t)} 
\]

where ConcEFV(t) is time-varying efavirenz concentration, Conc3TC(t) is time-varying lamivudine concentration, ConcABC(t) is time-varying abacavir concentration, IC_{50,EFV}(t) is efavirenz IC_{50}, IC_{50,3TC}(t) is lamivudine IC_{50} and IC_{50,ABC}(t) is abacavir IC_{50}; \(\Phi\) is a factor which defines the in vitro-in vivo correlation. In our simulations, \(\Phi\) was fixed to 1.
Time varying efficacy $\gamma(t)$ of the treatment ranges from 0 to 1 and is referred to as the treatment efficacy index (the inhibition rate of viral replication) in the viral dynamic model (Equation 3-5). If $\gamma(t) = 1$, the treatment is 100% effective, whereas if $\gamma(t) = 0$, the treatment has no effect.

**Mathematical models for HIV dynamics**

A widely used model for viral infection and replication was used to simulate the time course of the clinical endpoint (viral load) (21). The model consists of 3 compartments: uninfected target cells ($T$), free virions ($V$) and infected target cells ($T^*$). Although more complex models for viral replication were available in literature, this simple model showed characteristics of stability and robustness which were suitable for the purpose of our analysis.

The model for viral replication is defined by three differential equations (equation 3, 4 and 5). Several parameters are used to describe the viral and immunological processes: $\lambda$ (day$^{-1}\times$mm$^{-3}$) is the birth rate of new T cells created in the body, $dt$ (day$^{-1}$) is the death rate of the T-cells, $N$ is the amount of virions produced by each of the infected target cells, $c$ (day$^{-1}$) is the clearance of the free virions, $k$ (day$^{-1}\times$mm$^{-3}$) is the infection rate, $\delta$ (day$^{-1}$) is the death rate of infected target cells; $\gamma(t)$ is the time varying inhibitory effect of the combination, predicted using the pharmacodynamic model depicted in equation (2).

$$
\frac{dT}{dt} = \lambda - d_t - [1-\gamma(t)]kTV
$$

$$
\frac{dT^*}{dt} = [1-\gamma(t)]kTV - \delta T^*
$$

$$
\frac{dV}{dt} = N\delta T^* - cV
$$

**Correlation between adherence and resistance**

A correlation between adherence and resistance in antiretroviral drugs has been previously established by Bangsberg et al (28). Despite their initial findings, different correlations appear to exist for different classes of antiretroviral drugs (29). For example, most of the NNRTI and lamivudine mutations occurred in patients showing low adherence, suggesting that these two drugs have different adherence–resistance relationships compared to PIs and NRTIs. In our investigation a relationship between adherence and resistance was considered for efavirenz and lamivudine, given that these drugs are known to be more susceptible to resistance than abacavir (30, 31). Such a relationship was described in terms of a logistic regression, in which the probability of resistance is linked to the number of days during which the levels of efavirenz remain below the target therapeutic level or lamivudine remains below the quantification limit. The final model describing the correlation and the corresponding parameter estimates used in the simulations were derived from published data (32, 33).

**Simulation scenarios of variable adherence to treatment**

Scenarios representing perfect adherence and different patterns of non-adherence to treatment (treatment interruption, delay in drug intake or single doses randomly missed throughout the clinical trial) were simulated. In each scenario of non-adherence all the patients participating in the trial were assumed to be non-adherent to treatment. For each scenario the period of non-adherence was randomly assigned to each subject across the duration of the trial. 100 replicates were simulated for each scenario. Simulations were performed with NONMEM v7 and R v 2.14.0 was used to produce the datasets for each simulation scenario and to numerically and graphically summarise the results. The impact of changes in dosing regimen was assessed by comparing the results obtained in each scenario of non-adherence with that of perfect adherence. A measure of viral load above the threshold of 50 copies/mL was selected to indicate viral failure at week 48.

The results were compared for twice daily and once daily dosing regimens. In order to obtain a quantitative relationship between the probability of viral failure and the percentages of doses randomly missed or the duration of treatment interruptions for each dosing regimen, the data were fitted using the -nls (nonlinear least squares) function in R.

**10.3. RESULTS**

During our analysis the forgiveness of non-adherence of once daily lamivudine/abacavir has been evaluated and compared to the forgiveness of the currently licensed twice daily dosing in children, both administered in combination with efavirenz as a fixed-dose combination. Initially, the two combination treatments were compared in terms of efficacy assuming perfect adherence to therapy. As shown in figure 2, the probability to experience viral failure at week 48 is not significantly different after once or twice daily doses. In addition, our results show that time-varying viral load remains indistinguishable during the whole trial period, i.e., 48 week. Moreover, the therapeutic equivalence of the treatment is observed at week 48 considering both the detection limits of 50 and 400 copies/mL.

Under the assumption of imperfect adherence, similar findings were observed. As shown in figures 3, 4 and 5, the probability of viral failure at week 48 for the two treatment combinations in a group of 30 HIV infected children does not reveal any significant differences between dosing regimens. The similarities were observed irrespective of whether non-compliance was due to delays in drug intake (figure 3), treatment interruptions (figure 4) or randomly missed doses (figure 5). As expected, delays in drug intake up to 4 hours were shown not to affect the outcome of the treatment (figure 3), whilst changes in the probability of viral failure could be observed for the scenarios depicting treatment interruptions or doses randomly missed. These differenc-
es were independent of the dosing regimen.

To ensure accuracy of the estimated effects, additional simulations were performed for a larger population (n=200), including the most significant scenarios of non-adherence, namely, 4 hours delay in drug intake, two weeks interruptions and 10% of the doses randomly missed. No differences were observed in the results compared to the same scenarios evaluated with 30 patients.

In figure 4 and 5 the quantitative relationships between the probability of viral failure and the duration of treatment interruptions and the percentages of doses randomly missed are shown, respectively. The fitting of the data, illustrated in figure 6, allowed us to derive the mathematical function that links the number of days of treatment interruption with the probability to experience viral failure. Practically, the same parameter estimates were obtained for both once daily and twice daily dosing regimens. As shown in figure 6, a function linking the percentage of doses randomly missed with the probability of viral failure was also obtained for the two regimens.

Figure 2. Probability of viral failure in case of perfect adherence for once and twice daily dosing regimen at the end of the treatment (left panel) and across the whole duration of the treatment (right panel).

Figure 3. Probability of viral failure associated with variable delay in drug intake for twice daily (left) and once daily (right) dosing regimen. On the x-axis the hours of delay in drug intake are displayed. In parenthesis the percentage of days in which the delay takes place is represented.

Figure 4. Probability of viral failure associated with variable duration of treatment interruption for twice daily (left) and once daily (right) dosing regimen. On the x-axis the duration of the treatment interruption is displayed.
10.4. DISCUSSIONS AND CONCLUSIONS

Efficacy of once vs. twice daily lamivudine/abacavir in children

This investigation shows the robustness of a simplified treatment combination (efavirenz + lamivudine/abacavir once daily) in terms of its impact on treatment outcome as compared to the currently licensed regimen (efavirenz + lamivudine/abacavir twice daily), taking different patterns of non-adherence into account.

Conceptually, our analysis also demonstrates the relevance of pharmacokinetic-pharmacodynamic relationships as a proxy for the assessment of efficacy when changes are made to dosing regimens. Initially, a comparison of the two treatments was made assuming perfect adherence in order to test whether the dosing regimens would show the same efficacy in ideal conditions. The results summarised in figure 2 clearly show comparable efficacy for both regimens and corroborate our previous evaluation of the pharmacokinetics of abacavir and lamivudine after oral administration performed in chapters 3 and 4. Besides being used as baseline to evaluate the forgiveness of non-adherence of once daily treatment, these findings reveal for the first time that the delivery of the same drug amount over 24 hours, as assessed in terms of systemic exposure (AUC), correlates with efficacy in children. In fact, such results are in agreement with Sosa et al., who have already shown non-inferiority of once daily fixed-dose combination abacavir/lamivudine compared to twice daily in adults (34).

Optimisation of antiretroviral therapy

In addition to the conceptual aspects of the methodology and the evidence of therapeutic equivalence of the two regimens, it is interesting to highlight that our approach allowed the identification of the level of adherence that is required or desirable to prevent the risk of viral rebound for each of the dosing regimens investigated here. The fitting of the data using a logistic model enabled us to obtain mathematical functions linking the number of days of treatment interruption and the percentage of doses randomly missed with the probability of viral failure for the two dosing regimens. Regarding treatment interruptions, our results show that an interruption of two weeks may have consequences for the clinical outcome and may increase the probability of viral failure from 0.1 to above 0.4, whilst a continuous interruption of 30 days yields a probability of viral failure of 0.9. On the other hand, randomly missing as little as 10% of the doses during a treatment of 48 weeks may increase the probability of viral failure from 0.1 up to 0.4. In practical terms, this means that continuous treatment interruptions with a NNRTI-based regimen are more likely to result in viral failure than when the same number of doses is randomly missed. These figures are in agreement with the investigation of Parienti et al. (35), who found that sustained treatment interruptions more closely predicted viral rebound than interspersed missed doses in 72 patients who were administered a NNRTI-based regimen. In their investigation a logistic regression model was used to estimate the relationship between treatment interruptions and probability of viral failure, with treatment interruptions of 15 days associated with a 50% probability of viral rebound. Our results also appear to be in agreement with Cohen et al. (36) and Dybul et al (37), who showed that virologic rebound is uncommon among NNRTI treated patients with repeated short cycles on and off treatment.

Figure 6 Fitting of the data of probability of viral failure associated with treatment interruption (figure 6a) and doses randomly missed (figure 6b). The fitting was obtained using the nls (Nonlinear least squares) function in R.
Use of clinical trial simulation
In addition to the findings which are specific to the fixed combination of abacavir, lamivudine and efavirenz, our results unravel an important aspect of model-based drug development. The use of models of disease dynamics in conjunction with models describing pharmacokinetic-pharmacodynamic relationships and differences in patterns of drug intake enables the assessment of the predictive value of pharmacokinetic-pharmacodynamic relationships. The ability to make inferences about treatment outcome using such data may avoid the need to expose children to the burden of clinical trial protocols. Based on our investigation, pharmacokinetic-pharmacodynamic studies, combined with pharmacokinetic and safety trials, may suffice for generating evidence of the suitability of a simplified dosing regimen. Furthermore, we show that clinical trial simulations may be applied to generate information which cannot be obtained in clinical practice. Despite improvement in clinical research, it is still impossible to control or explore all the scenarios of non-adherence investigated here. Clinical trial simulations provide a solid basis for study design optimisation before subjecting patients to a clinical protocol.

We are aware that our investigation relies on a hypothetical population of children, which cannot be replicated with real data, as the scenarios evaluated here cannot be easily generated in a clinical protocol. Nevertheless, we are confident in the results given the concordance with the findings observed by Parienti et al., which were based on real data. Formal validation would require a trial with a pre-defined set of scenarios, in which adherence varies as per protocol, rather than randomly.

Conclusions
In summary, we have shown that pharmacokinetic-pharmacodynamic relationships can be used as a proxy for efficacy and that a simplified once daily lamivudine/abacavir regimen administered in combination with efavirenz yields comparable efficacy as the currently licensed twice daily dosing in HIV-infected children between 3 and 12 years old. Moreover, our results show that both regimens show similar forgiveness of poor adherence, which implies exchangeability of the treatment options. These findings represent another step towards the availability of once daily regimens for fixed-dose combinations in children, which are crucial for increased patient adherence to HIV therapy, with direct implications for quality of life of the patients and of their caregivers.

References


