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Improved Oral Bioavailability and Variability Control in Pharmacokinetic Data – Role of Formulations

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Introduction

In order to render the best possible outcome for effective *in vivo* human translatability of the preclinical efficacy measures for orally administered drugs certain clinical pharmacology attributes play a key role. In this regard, effective and predictable absorption is the most relevant one; followed by controlled and reasonable variability in the pharmacokinetic parameters. Hence oral bioavailability would be expected to play a vital role in delivering the drug to site(s) of action needed to attain the desired efficacy measures.

Two specifically chosen case studies are presented that provide the rationale for this editorial. The drugs that are being discussed are abiraterone and etravirine which were developed for the therapy of metastatic castration resistant prostate cancer (mCRPC) and treatment of human immunodeficiency virus-1 (HIV-1) infection, respectively.

Abiraterone

The marketed drug abiraterone acetate is a prodrug whose conversion to active metabolite abiraterone is the important first step for the inhibition of the enzyme 17α-hydroxylase/C17, 20-lyase (CYP17); CYP17 is essential for the biosynthesis of androgens in prostate, testicular and adrenal tumour tissues. The inhibition of CYP17 achieves lesser proliferation of androgen sensitive cell lines in tumour tissues enabling a relatively slower progression of prostate cancer progression in relevant patient population [1,2].

Abiraterone acetate (Zytiga) is an orally approved drug with the therapeutic dose of 1000 mg to be administered once a day using 4×250 mg tablets. The drug has poor oral bioavailability; although no formal absolute bioavailability study was conducted the oral bioavailability was projected to be approximately 10%. This assumption was supported by the positive food effect data which increased the oral exposure of abiraterone by 10-fold. Hence, there is a label recommendation to avoid concomitant food ingestion with Zytiga tablets since there is unpredictable and highly variable increase in drug exposure [3,4].

In order to address the issue of low solubility and large oral dose which impeded oral absorption of abiraterone acetate in clinical pharmacology studies, Solymosi et al. [5] created amorphous nanoparticles using continuous flow precipitation technology used frequently for such difficult drug substances [6,7]. This creative adaptation of published technologies enabled novel abiraterone acetate formulation that improved dissolution rate along with enhanced solubility [5].

A 3-way crossover clinical study was performed using the drug in bottle (DIB) containing the novel formulated abiraterone at doses of 100 and 200 mg relative to a single dose of 1000 mg of Zytiga tablets [5]. To keep the focus of the editorial, clinical pharmacokinetics comparison is only drawn between 200 mg DIB formulation versus 1000 mg Zytiga. In the two important parameters namely, peak concentration (C_{max}) and area under the concentration vs. time curve extrapolated to time infinity

(AUC_{inf}), the values obtained for 200 mg DIB were 206 ng/mL and 408 ng.h/mL, respectively; relative to the values of 93 ng/mL and 513 ng.h/mL, respectively, for the 1000 mg Zytiga tablets [5]. This clearly indicated that despite a 5-fold reduced oral dose of abiraterone acetate in DIB, the C_{max} was almost 2-fold higher and AUC_{inf} was 0.9-fold as compared to the respective values for the 1000 mg Zytiga reference product. Moreover, there was a remarkable reduction in pharmacokinetic variability of AUC_{inf} with the 200 mg DIB (29%) as compared to 1000 mg Zytiga tablets (59%). While the DIB formulated abiraterone acetate showed promising results including little impact of the food effect, there is still the need to develop a commercially viable product of the reduced dose which can show bioequivalence with respect to both rate and extent of absorption of abiraterone to enable the switch. In this regard, it was recommended that strength of 250 mg of the newly formulated product would yield bioavailability matching to that of 1000 mg Zytiga tablets [5]. In this regard, another novel formulation of abiraterone acetate fine particle (AAFP) at a 500 mg dose was deemed bioequivalent to the 1000 mg dose of Zytiga when co-administered with steroids (mean ratio of test: reference was 93, 96, and 112% for AUC_{inf}, AUC0–t, and C_{max}, respectively) with considerably lower pharmacokinetic variability [8]. Because there was the addition of methylprednisolone (4 mg twice daily) to AAFP or prednisone (5 mg twice daily) to the Zytiga tablets, there was the need of a single dose bioequivalence study to confirm the existence of bioequivalence of 500 mg AAFP versus 1000 mg Zytiga tablets [8]. The recently published work of Goldwater et al. confirmed that a single 500 mg dose of AAFP prepared using SoluMatrix Fine Particle Technology™ was bioequivalent with the 1000 mg Zytiga dose under fasted conditions [9]. The geometric mean of test: reference (90% confidence interval limits) were 91 (83.3 to 99.4) and 99.8 (86.3 to 115.5) for AUC_{inf} and C_{max}, respectively [9].

Etravirine

Etravirine is a 2nd generation non-nucleoside reverse transcriptase inhibitor (NNRTI) showing activity against both wild-type and NNRTI resistant HIV-1 [10,11]. Etravirine undergoes predominantly fecal excretion of approximately 81 to 85% of the administered dose with low oral bioavailability and renal excretion of the intact drug is very limited. Since etravirine is a Biopharmaceutics Classification System

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(BCS) IV drug with poor solubility and permeability, it poses a great challenge for the development of viable formulation with enhanced oral bioavailability [12].

During the phase 2 clinical development of etravirine, a parallel attempt was made to improve the oral absorption and bioavailability which in turn would support reduction in the dose burden to HIV-1 patients. The formulation work involved spray-drying technology to form solid dispersion of etravirine which has solved the problem for many water insoluble drugs [13]. The newly developed formulation was employed for the phase 3 development of etravirine after verifying the existence of favourable pharmacokinetics of the new phase 3-formulation versus the original formulation employed for phase 2 development.

An open label, 3-way randomized crossover study clinical study of etravirine was performed using two doses (100 mg BID and 200 mg BID) of newly developed phase 3-formulation versus one dose of phase 2-formulation (800 mg BID) in HIV-1 infected patients [12]. The study encompassed comparative evaluation of the two formulations after a single dose administration and after multiple doses at steady state. To keep the focus of the editorial, comparison of pharmacokinetic data is only made between 200 mg BID dose of the new phase 3-formulation versus 800 mg BID of the old phase 2-formulation [12].

Following single dose administration, the 200 mg dose (phase 3-formulation) showed a 1.8-fold and 1.7-fold greater C_{max} and AUC_{inf} values relative to 800 mg dose (phase 2-formulation); the respective C_{max} and AUC_{inf} values for the 200 mg dose were 125.9 ng/mL and 745 ng.h/mL and the corresponding values for the 800 mg dose were 70.6 ng/mL and 434 ng.h/mL. Regardless of the two formulations, there was no alteration in the occurrence of time to C_{max} (i.e., T_{max}) which ranged between 3-8 h for phase-3 formulation and 2-8 h for phase-2 formulation [12].

Following multiple dose administration (BID dosing for seven days) of the 200 mg dose (phase-3 formulation) showed approximately 1.4-fold higher C_{max} and AUC_{tau} (where tau = 12 h) relative to the 800 mg dose (phase-2 formulation); the respective C_{max} and AUC_{tau} values for the 200 mg dose were 451.3 ng/mL and 3713 ng.h/mL and the corresponding values for the 800 mg dose were 318.8 ng/mL and 2607 ng.h/mL. Furthermore, the trough concentration achieved was greater for the phase-3 formulation (235.9 ng/mL) as compared to the phase-2 formulation (148.8 ng/mL) [12]. Regardless of single or multiple dose pharmacokinetic data derived for etravirine, it was demonstrated that intra-subject variability was significantly reduced for the phase-3 formulation as compared to the phase-2 formulation. For instance, for AUC_{tau} at steady state, the inter-subject variability for the phase-3 formulation was 56% as compared to 82% observed for the phase-2 formulation. Due to improved and predictable pharmacokinetics of etravirine without compromising the safety profile in the patients, the switching of the formulation was made for the phase 3 development of etravirine.

Perspectives

In general, the ability to translate the *in vitro* pharmacology data and/or *in vivo* preclinical efficacy data in the clinic largely hinges on the exposure parameters such as C_{max}, AUC_{inf}, and AUC_{tau}. In addition, dosing frequency is frequently influenced by the elimination half-life of the drug in question and/or the desired pharmacodynamic end points. In case of oral route of drug administration unlike intravenous route, there are number of barriers for bioavailability: a) intestinal absorption which is dependent on solubility/permeability attributes; b) first pass metabolism governed by cytochrome (CYP) P450 enzymes and Phase 2 conjugative reactions via glucuronosyltransferase/sulfotransferase; c) efflux mechanisms driven by P-glycoprotein (Pgp) and breast cancer resistance protein (BCRP).

The discussed case studies attest to the importance of oral formulation to deliver improved and predictable exposure to enable clinical development of promising drugs. The need of an oral drug that could counter mCRPC was critical and perhaps, this may have influenced the use of a less optimized formulation of abiraterone acetate for clinical development and subsequent market approval. Therefore, the daily therapeutic dose was as high as 1000 mg delivered by 4 × 250 mg tablets of Zytiga. In addition, less optimized formulation of abiraterone acetate produced significant food effect causing an erratic and highly variable bioavailability of abiraterone. Therefore, there were restrictions on the oral dosing of abiraterone acetate in relation to food intake making it cumbersome and inconvenient for patients who were on chronic therapy. The work of Solymosi et al [5] suggested that due to novel formulation development there was an opportunity for a significant dose reduction of abiraterone acetate in clinical therapy. In addition, there would be an opportunity to dose abiraterone acetate without regard to food intake. In this context, there are data that support 50% dose reduction of abiraterone acetate using fine particle technology [8,9].

In case of etravirine, the strategy to switch to a better formulation was indeed innovative and commendable [12]. Because etravirine had issues of both poor solubility and low permeability (BCS class IV drug), the BID dosing requirement at high doses (i.e., 800 mg) would have been untenable to support large Phase 3 clinical development trials and subsequent market authorization. Here again, the emphasis on novel formulation technology with particle size mandate aided in reducing the dose of the drug by 4-fold. Despite the reduction in the dose of the newly formulated drug substance, the exposures (C_{max} and AUC) of etravirine were much higher than the parameter values reported for the full dose contained in the old formulation.

The key lesson learnt from the etravirine case study was that newer formulation options need to be probed during clinical development of the drug which is known to have characteristics of poor solubility and/or lower permeability. Even switching to a better formulation of the drug at Phase 2/3 clinical development should be factored in the overall strategic framework by bridging pharmacokinetics of the drug and as well as pharmacodynamics, if relevant. As always, it will be prudent to seek regulatory guidance and feedback before implementing such changes that may have a big impact on the entire program including the final approval of the product.

The key lesson learnt from abiraterone acetate case study was that despite marketing approval there may be still be a viable opportunity to optimize the drug product for significant dose reduction and removal of the impact of food intake; such changes in turn would improve patient compliance for a long-term therapy.

Conflict of Interest

The author is an employee of Cadila Health Care Ltd. (Ahmedabad, India). The manuscript was prepared with the intent of scientific exchange on an important topic pertaining to oral bioavailability in clinical pharmacology studies.

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