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Using PBPK to Support the Approval of Imbruvica®, a Breakthrough Cancer Drug

Background

Pharmacyclics' (now AbbVie) Imbruvica (ibrutinib) is an anticancer drug targeting B-cell malignancies. It blocks a specific protein called Bruton's tyrosine kinase (BTK). Imbruvica was originally developed and approved in late 2013 by the US Food and Drug Administration (FDA) to treat patients with mantle cell lymphoma, a rare blood cancer, impacting fewer than 3,000 people a year. Under an accelerated approval process, it was approved in February 2014 for the treatment of chronic lymphocytic leukemia (CLL), a form of non-Hodgkin's lymphoma. The initial and conditional CLL approval was revised in mid-2014 after additional data demonstrated its safety and efficacy for patients who had tried one or more prior treatments unsuccessfully. In January 2015, Imbruvica was approved by the FDA for treatment of Waldenström's macroglobulinemia, and in March, 2016 it was approved for first-line treatment of CLL.

Challenge

Understanding a drug's pharmacokinetic profile is essential to developing safe and efficacious dosing recommendations. Imbruvica is a CYP3A substrate. Because of its very high clearance rate, it is particularly susceptible to drug-drug interactions (DDIs). To evaluate the DDI liability, a physiologically-based pharmacokinetic (PBPK) approach using the Simcyp Simulator was utilized (US FDA 2013). The model was developed using *in vitro* and clinical PK data. Then, the model was verified with two clinical DDI studies with ketoconazole (a strong CYP3A inhibitor) and rifampin (a strong CYP3A inducer). Since the model robustly predicted the observed change in C_{max} ratios and AUC (area under the curve) ratios for ketoconazole and rifampin, it was then applied to untested clinical DDI scenarios—moderate and weak CYP3A inhibitors and inducers. The knowledge gained from PBPK simulations informed the labels for Imbruvica as such:

- Moderate CYP3A inhibitors may increase the AUC of Imbruvica by 6- to 9-fold

- Moderate CYP3A inducers may decrease the AUC of Imbruvica by up to 3-fold

While the modeling affected Imbruvica's label, the full impact of PBPK was in providing a dose optimization strategy. The ideal dose of a drug successfully balances efficacy with safety. Co-administration of a CYP3A substrate and CYP3A inhibitors can cause safety issues as the plasma concentration of the drug rises to potentially toxic levels.

The recommended dose for Imbruvica is 560 mg per day. The highest recommended doses are 840-1400 mg; doses higher than this present safety issues. Likewise, the lowest recommended

Challenge

Pharmacyclics sought to bring its new tyrosine kinase inhibitor therapy targeting rare B-cell malignancies to market.

Solution

Leveraging the US FDA's accelerated approval programs, the company generated PBPK models using the Simcyp Simulator to inform dose, dosing regimens, and DDIs.

Benefit

Approved initially for mantle cell lymphoma as a breakthrough therapy, Imbruvica is now approved for multiple uses, including first-line CLL.

dose of Imbruvica is 140 mg; doses below this are unlikely to be effective. Thus, in the case that a moderate CYP3A inhibitor must be used, it is recommended that the dose be reduced to 140mg to stay within established safety limits.

The opposite situation is seen in the case of co-administration of CYP3A inducers. Now, the concern is that the CYP induction will result in an increase in drug clearance. Thus, patients need to be given a higher dose than usual to maintain drug efficacy. PBPK models suggested that doubling the Imbruvica dose could still maintain an efficacious level of drug exposure in the case of a moderate CYP3A inducer. However, in the case of a strong CYP3A inducer (rifampin), even doubling the dosage of Imbruvica would not maintain an efficacious level of drug exposure. Thus, the 2013 FDA clinical pharmacology review of Imbruvica states that clinicians should "avoid concomitant use of strong CYP3A inducers." Clearly, PBPK is going beyond just providing mere knowledge about drug mechanisms. This powerful tool guides and supports clinicians in providing the most effective and safest treatment for patients.

Benefit

The use of PBPK helped inform key safety and dosing issues necessary to support the accelerated timelines of this breakthrough therapy. Specifically, PBPK informed 24 individual DDIs, including:

- Predicted 5-8 fold increases with the use of moderate CYP3A4 inhibitors. Dose reduction to 140 mg is appropriate.

- Predicted 2-fold increase for a weak inhibitor. Dose reductions not necessary.

- Predicted 2-fold decreases for a moderate inducer. Dose reductions are not necessary.

- Effect of dose-staggering and/or dose reduction on ibrutinib exposure with concurrent use of strong or moderate CYP3A4 inhibitors used to inform dosing options.

PBPK was also used to inform the appropriate dose-response:

- Used to support dose reductions for safety that would not impact efficacy.

- Used to support dose modifications for DDIs of weak-moderate CYP3A4 inhibitors and moderate CYP3A4 inducers.

Impact

This breakthrough drug was specifically highlighted during the workshop entitled "Application of Physiologically-based Pharmacokinetic (PBPK) Modeling to Support Dose Selection" hosted on March 10, 2014 by the US FDA. Dr. Zhao discussed the New Drug Application review of ibrutinib (Imbruvica) to illustrate a successful application of PBPK in which the FDA used PBPK predictions to fill in clinical gaps during the evaluation of a breakthrough therapy drug. PBPK is now used in many fast-track, breakthrough, accelerated and/or priority reviews.

References

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