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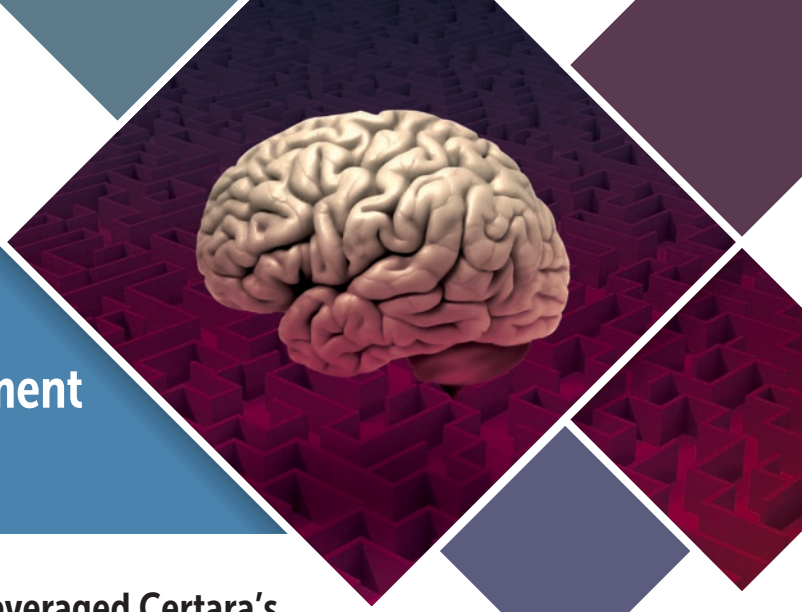

Modeling and Simulation Supports Dosing Guidelines for a Novel Treatment for Schizophrenia

A medium-sized biopharmaceutical company leveraged Certara's trial simulation software and PBPK modeling and simulation consulting services to facilitate regulatory approval for a long-acting injectable antipsychotic drug

Background

Despite the availability of effective treatments, schizophrenia patients frequently relapse due to poor medication adherence. To help patients achieve medication adherence, Alkermes developed aripiprazole lauroxil (AL), a novel long-acting injectable (LAI) atypical antipsychotic drug.[1]

Following injection, aripiprazole lauroxil is converted to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole, the active drug. Aripiprozole is primarily eliminated by the drug metabolizing enzymes CYP2D6 and CYP3A4.

Challenge

AL was designed to be injected either every four (at three possible dose levels) or six weeks at the highest dose level. The drug development team at Alkermes needed to understand the impact of different dosing scenarios, including missing doses, on aripiprazole concentrations since schizophrenia patients often have difficulty with medication adherence.

They also sought to evaluate the impact of concomitant administration of strong CYP3A4 inhibitors and inducers and strong CYP2D6 inhibitors on AL pharmacokinetics (PK). Since patients that are CYP2D6 poor metabolizers have a reduced ability to eliminate CYP2D6 substrates, they also wanted to know if these patients would require dose adjustments.

Solution

Using a previously developed population PK model, they leveraged Certara's Trial Simulator to perform Monte-Carlo simulations to evaluate different dosing scenarios including the impact of missing doses. For each simulation, 500 individual aripiprazole concentration-time profiles were generated.[2]

Challenge

The drug development team at Alkermes needed to understand the impact of variable dosing on its long-acting, injectable atypical antipsychotic, aripiprazole lauroxil (AL). They also sought to evaluate the drug-drug interaction potential for AL and the effect of CYP2D6 metabolizer status on aripiprazole pharmacokinetics.

Solution

They leveraged Certara's Trial Simulator to predict AL concentrations following a variety of dosing scenarios, including missed doses. Certara scientists used the Simcyp Simulator software to predict the impact of co-administration of CYP3A4 and CYP2D6 inhibitors/inducers in patients with varying CYP2D6 metabolizer status on aripiprazole exposure.

Benefit

The sponsor was able to develop guidelines for AL regarding missing doses and dose adjustments for CYP450 modulator use based solely on modeling and simulation. These recommendations were accepted by the US FDA for treatment of patients with schizophrenia.

Physiologically-based pharmacokinetic (PBPK) models describe the behavior of drugs in the different body tissues. Depending on the route of administration, the course of the drug can be tracked through the blood and tissues. Each tissue is considered to be a physiological compartment. The concentration of the drug in each compartment is determined by combining systems data, drug data, and trial design information. The systems data includes demographic, physiological, and biochemical data for the individuals in the study population. The drug data consists of its physicochemical properties, its binding characteristics, and information on its metabolism and solubility. The trial design information comprises the dose, administration route, dosing schedule, and co-administered drugs.

Certara scientists used the Simcyp Simulator PBPK platform to predict the impact of co-administration of CYP3A4 and CYP2D6 inhibitors/inducers on aripiprazole exposure in patients with varying CYP2D6 metabolizer status.[2]

Benefit

Simulations of aripiprazole time-concentration profiles showed that both monthly dosing of the high, medium, and low dose levels as well as dosing every six weeks at the high dose level resulted in concentrations within the established therapeutic window. These simulations also showed that aripiprazole concentrations are sustained following a missed dose and decline minimally when the time since the last injection is six to eight weeks or less. Recommendations for concomitant oral aripiprazole supplementation following missed doses were devised based on information from trial simulations.

Results from the PBPK model suggested that reduction of the high and medium dose to the next lower dose in the presence of strong CYP3A4 and CYP2D6 inhibitors is needed to keep aripiprazole exposure in the target range. Likewise, in the presence of a strong CYP3A4 inducer, the low dose needs to be increased to the next dose level to keep aripiprazole exposure within the therapeutic window. The PBPK model also supported recommendations for dosage adjustments for patients known to be poor metabolizers of CYP2D6 substrates who were also taking strong CYP3A4 inhibitors.

Impact

Aristada (injectable, extended-release aripiprazole lauroxil) received FDA approval in late 2015.[4] Dose adjustments were recommended on the drug label based on simulations that examined the effects of missing doses and co-medications on aripiprazole pharmacokinetics. The prolonged exposure profile of aripiprazole following AL administration provides sustained therapeutic coverage and eliminates the need for oral aripiprazole supplementation in the event of late or missed doses for up to four weeks.

The effect of patients' CYP2D6 genotype was also incorporated into PBPK models and informed label claims. The insights from modeling and simulation approaches as well as the product characteristics of AL provide clinicians with flexibility in devising safe and effective treatment plans for schizophrenia patients who have difficulty with medication adherence.

Dose Adjustments With Concomitant CYP450 Modulator Use for > 2 Weeks[3]

Concomitant Medicine	Dose Change for AL*
Strong CYP3A4 Inhibitor	Reduce the dose of AL to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated. For patients known to be poor metabolizers of CYP2D6: Reduce dose to 441 mg from 662 mg or 882 mg. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated.
Strong CYP2D6 Inhibitor	Reduce the dose of AL to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated. For patients known to be poor metabolizers of CYP2D6: No dose adjustment required.
Both Strong CYP3A4 Inhibitor and Strong CYP2D6 Inhibitor	Avoid use for patients at 662 mg or 882 mg dose. No dosage adjustment is necessary in patients taking 441 mg AL, if tolerated.
CYP3A4 Inducers	No dose adjustment for 662 mg and 882 mg dose, increase the 441 mg dose to 662 mg.

* For 882 mg q6wk, the next lower strength is 441 mg q4wk.

References

1. Meltzer HY, Risinger R, Nasrallah HA, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. J Clin Psychiatry. 2015;76(8):1085-1090.

2. Hard ML, Sadler B, Mills R, Rowland Yeo K, Turncliff R, and Citrome L. Aripiprazole Lauroxil Pharmacokinetics: Application of Modeling and Simulation for Dosing Considerations of a Long-Acting Injectable Antipsychotic in Persons With Schizophrenia. Presented at the American Society of Clinical Psychopharmacology 2016 Annual Meeting. May 30-June 3, 2016, Scottsdale, AZ.

3. ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing information. Waltham, MA: Alkermes, Inc. October 2015. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/207533s000lbl.pdf

4. U.S. Food and Drug Administration. FDA News Release: FDA approves new injectable drug to treat schizophrenia. 6 October 2015. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm465801.htm

About Certara

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CS Jul 2016 v2 041017