CERTARA

Getting a Novel Antibiotic to Patients

From pre-clinical toxicokinetics to final dose recommendations, Certara helped Cubist Pharmaceuticals obtain regulatory approval of a new treatment for complicated infections

Background

At least two million people become infected with treatment-resistant bacteria each year in the US alone. At least 23,000 die as a direct result; many more lose their lives to other conditions complicated by the infections.[1] With antibiotic resistance on the rise and a low rate of approvals for new antibiotics,[2] there is urgent need to make new treatment options available to patients quickly, efficiently, and safely.

Challenge

Certara experts in model-based drug development worked with Cubist Pharmaceuticals to bring the novel antibacterial agent Zerbaxa™ (ceftolozane/tazobactam) from pre-clinical studies through market approval to treat adults with complicated infections. Certara's model-based analyses incorporated subject data collected in up to 10 clinical studies to support confident go/no-go decisions, to improve understanding of drug exposure in diverse populations, and to anticipate and address regulatory needs for the drug's expedited review and approval.

Many particularly deadly, treatment-resistant pathogens create the enzyme ß-lactamase, which can break down commonly used antibiotics such as penicillins and cephalosporins, making them ineffective. The new drug Zerbaxa combines the cephalosporin antibiotic, ceftolozane, with an established ß-lactamase inhibitor, tazobactam (TAZ). TAZ potentiates the activity of ceftolozane against drug-resistant microbes, including the majority of extended spectrum ß-lactamase (ESBL)-producing gram-negative bacilli and some AmpC-overexpressed Enterobacteriaceae, as well as important anaerobic pathogens such as Bacteroides fragilis.

Solution

Early in Zerbaxa's development, Certara scientists helped to characterize the drug's toxicokinetic profile from pre-clinical data. Once the drug moved into clinical trials, the team assessed the

Challenge

Cubist Pharmaceuticals sought to bring the novel antibacterial agent Zerbaxa™ (ceftolozane/tazobactam) from pre-clinical studies through market approval to treat adults with complicated infections.

Solution

Certara scientists helped to characterize the drug's toxicokinetic profile from pre-clinical data and developed models describing the PK profile of ceftolozane and TAZ in healthy volunteers and patients.

Benefit

These models formed the basis for predicting the probability of attaining target drug exposures in diverse populations with varying demographics, renal function, and infection status.

pharmacokinetic (PK) profile of ceftolozane and TAZ in healthy volunteers given each drug alone and concomitantly in a 2:1 ratio of ceftolozane to TAZ.[3] Both single, ascending doses and multiple dosing were evaluated. Zerbaxa pharmacokinetic (PK) was dose-proportional and linear across a wide range of doses. Both drugs were primarily excreted renally.

The analysis showed that ceftolozane clearance was similar whether the drug was administered alone or in combination with TAZ, suggesting TAZ had no effect on ceftolozane clearance. The results established an initial understanding of Zerbaxa's PK profile in healthy adults, and supported continuing clinical development of the drug.

In preparation for larger-scale clinical trials, Cubist enlisted the help of Certara scientist, Dr. Samer Mouksassi, to explore the drug's likely PK and identify important sources of variability across patient groups.

Based on data from Phase I and II studies, Dr. Mouksassi and his colleagues created a population pharmacokinetic (PopPK) model for Zerbaxa in healthy adults, and for patients with renal impairment and complicated bacterial infections.[4] The team used Certara's industry-leading PopPK/pharmacodynamics (PD) software, Phoenix NLME, to perform PopPK analysis and identify the major sources of variability. Zerbaxa PK was described by a linear two-compartment model with first-order drug elimination. As expected, drug clearance was highly correlated with renal function.

Benefit

These models formed the basis for predicting the probability of attaining target drug exposures in diverse populations with varying demographics, renal function, and infection status. In addition, the results suggested that Zerbaxa could be an alternative to the currently recommended treatments for complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI) in patients with varying degrees of renal impairment, especially in cases of drug-resistant infections.

Zerbaxa was shown effective in treating cUTI in a clinical trial of 1,068 adults randomly assigned to receive Zerbaxa or levofloxacin, an antibacterial drug approved by the US Food and Drug Administration (FDA) to treat cUTI.[5] Zerbaxa in combination with metronidazole was shown effective in treating cIAI in a clinical trial with a total of 979 adults randomly assigned to receive Zerbaxa plus metronidazole or meropenem, an FDA-approved antibiotic.[5]

Impact

As an antibacterial human drug intended to treat a serious or life-threatening infection, Zerbaxa was designated a Qualified Infectious Disease Product (QIDP) and granted priority review by the FDA under the Generating Antibiotic Incentives Now (GAIN) title of the FDA Safety and Innovation Act.[5] The QIDP designation also qualifies Zerbaxa for an additional five years of marketing exclusivity without competition from generics.

In December 2014, the FDA approved Zerbaxa to treat adults with cUTI, including kidney infection (pyelonephritis), and to be used in combination with metronidazole to treat cIAI.[5]

The population PK model from Certara continues to prove useful. Monte Carlo simulations using the model recently supported dosing optimizations for patients requiring hemodialysis.[6] The modeling work remains a knowledge repository about the drug and disease, for potential future use in guiding dosing recommendations in additional populations, different pathogens of interest, and other indications such as nosocomial pneumonia infection.

References

1. U.S. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States, 2013. http://www.cdc.gov/drugresistance/threat-report-2013/index.html. Accessed 1 May 2015.

2. Boucher H, Talbot G, Benjamin D, et al. 10 x '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America. Clin Infect Dis. (2013) 56 (12): 1685-1694. Full text free on PubMed Central: PMC3707426.

3. Miller B, Hershberger E, Benziger D, Trinh M, and Friedland I. Pharmacokinetics and Safety of Intravenous Ceftolozane-Tazobactam in Healthy Adult Subjects following Single and Multiple Ascending Doses. Antimicrob Agents Chemother. 2012 Jun; 56(6): 3086–3091. Full text free on PubMed Central: PMC3370713.

4. Chandorkar G, Xiao A, Mouksassi MS, Hershberger E, Krishna G. Population pharmacokinetics of ceftolozane/tazobactam in healthy volunteers, subjects with varying degrees of renal function and patients with bacterial infections. J Clin Pharmacol. 2015 Feb;55(2):230-9. Epub 2014 Nov 14. Full text free on PubMed Central: PMC4303958.

5. U.S. Food and Drug Administration. FDA News Release: FDA approves new antibacterial drug Zerbaxa. 19 Dec 2014. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427534.htm.

6. Xiao A, Chandorkar G, Hershberger E, Krishna G. Ceftolozane/Tazobactam Dose Optimization in Patients With End-stage Renal Disease Requiring Hemodialysis Using Population Pharmacokinetics and Monte Carlo Simulations. Presented at IDWeek: A joint meeting of IDSA, SHEA, HIVMA, PIDS. October 8-12, 2014, Philadelphia, PA. https://idsa.confex.com/idsa/2014/webprogram/Paper45396.html. Accessed 1 May 2015.

About Certara

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