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Modeling the Influence of Ethnicity on Drug Disposition

Physiologically-based pharmacokinetic (PBPK) modeling and simulation in virtual populations can uncover changes in drug disposition due to ethnic differences, providing supporting information for regulatory review and helping identify and optimize essential bridging studies

Background

Ethnic diversity in drug response and its impact on dosing has been well described for some drugs.[1] A recent study of the most widely prescribed proprietary drugs in the US showed that, in around half of all cases, the recommended doses in Japan were considerably lower than both the US and European doses.[2] Investigating the potential impact of ethnicity on pharmacokinetics (PKs) often involves repeating clinical studies in different populations, which may be unnecessary in some cases.

Challenge

Reducing the total number of clinical studies undertaken to secure regulatory approval without compromising patient safety is a major goal for both pharmaceutical companies and the regulatory agencies worldwide. A major global pharmaceutical company—which had identified China as a strategically important market—approached Certara scientists to develop a virtual Chinese population so that potential differences in PKs between populations could be simulated to assist with decision-making regarding clinical trials. This builds on the prior capabilities of the Simcyp Simulator in capturing differences in clearance observed between Japanese and North European Caucasian subjects.[3]

Solution

Demographic, physiological and genetic data were gathered from literature sources and from a Pfizer database of Chinese healthy volunteers. The information was used to build a virtual Chinese population within the Simcyp Simulator. Significant differences between Chinese and Caucasian populations were noted for liver weight, the frequency of CYP2D6 poor and intermediate

Challenge

Understanding the influence that ethnic differences may have on drug disposition often requires dedicated *in vivo* PK studies which add considerable costs to drug development.

Solution

Certara scientists have developed Chinese, Japanese and North European Caucasian virtual populations to model the impact of demographic, physiological and genetic differences on PKs.

Benefit

PBPK modeling in virtual populations can help avoid unnecessary duplication of *in vivo* studies as well as provide critical information to optimize trial design and improve safety for participants.

metabolizers, the frequency of CYP2C19 poor metabolizers and the hepatic abundance of CYP2C19. Simulations showed good agreement with clinical data when the model was tested using drugs metabolized predominantly by specific CYP enzymes with minimal impact of transporters and low biliary or renal clearance.[4]

Scientists at Janssen Pharmaceuticals Inc have also used Simcyp simulations to investigate variability and ethnicity differences in pharmacokinetics as part of its New Drug Application for Olysio® (simeprevir). Simulations showed a 2.2-fold higher exposure in virtual healthy Chinese subjects compared with healthy Caucasians—a very close match to the 2-fold increase observed in clinical studies. Although no dosage recommendations for specific subpopulations are made in product labeling for Olysio, subsequent simulations in virtual Caucasian, Japanese and Chinese populations were requested by FDA reviewers to provide additional information on the impact of disease state and ethnicity on drug exposure.[5]

Benefit

In silico predictions may decrease the need to repeat pharmacokinetic studies in different ethnic groups[3] and expedite the regulatory approval process in regions remote to where original clinical development took place. Furthermore, accessing distinct virtual Japanese and Chinese populations within the Simcyp Simulator can overcome some of the difficulties that arise when clinical data collected in Japanese, Korean and Chinese individuals are combined and reported for a single "Asian" population.[4]

Impact

Speeding the regulatory review process in different global regions brings new medicines to patients faster and can have considerable financial benefit for pharmaceutical companies.

References

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About Certara

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