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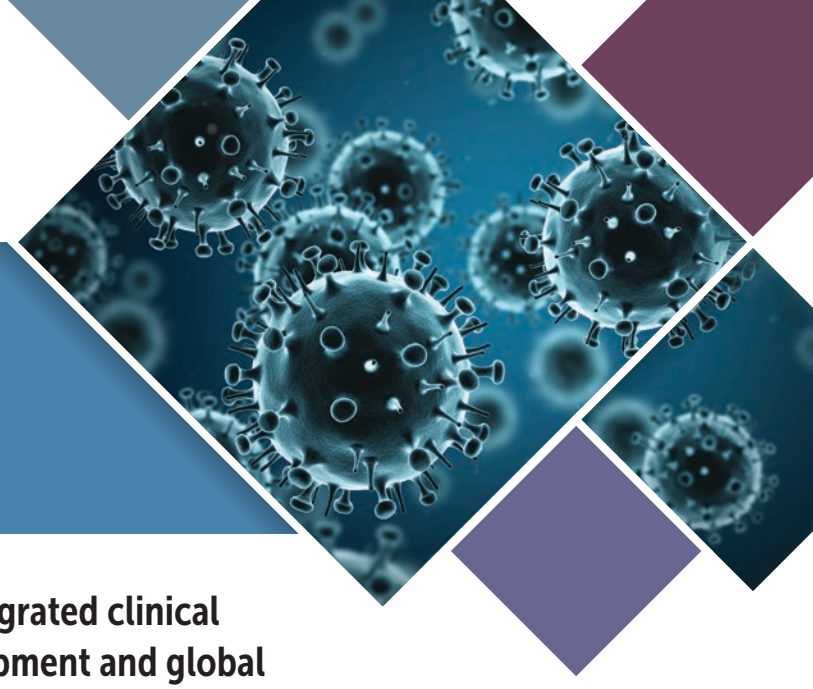

Extending the Use of Antivirals to Treat Influenza in Infants

Certara's scientists helped Roche apply an integrated clinical pharmacology program to support the development and global approval of Tamiflu for infants.

Background

A historical context for using Tamiflu in infants

Tamiflu (oseltamivir phosphate, OP) is an oral neuraminidase inhibitor that is now indicated to treat acute, uncomplicated influenza in patients 2 weeks of age and older. Oseltamivir phosphate is a prodrug that is converted to its active metabolite, oseltamvir carboxylate (OC), by the liver enzyme, human carboxyl esterase 1 (CES1).

OC exerts its therapeutic effect by modulating the influenza virus life cycle.[1] The virus infects epithelial cells in the respiratory tract. Infected cells produce new viruses, which infect more epithelial cells. Infected epithelial cells die, and the immune system clears virus. OC reduces viral production to reduce viral shedding, resolve symptoms of influenza infection and potentially decrease secondary complications.

The treatment indication for Tamiflu was initially restricted to children greater than one year of age, due to a toxicology signal in juvenile rats attributed to its prodrug.

Outbreaks of avian influenza and pandemic influenza highlighted the lack of treatments for babies. In addition, emerging off-label use for babies started to demonstrate the safety of oseltamivir in this patient group.

An overview of Tamiflu pharmacology

OC is trapped within hepatocytes and slowly leaches out, resulting in flip-flop pharmacokinetics (PK) and a half-life that enables twice daily dosing. Both the prodrug and metabolite are distributed in total body water, circulate in plasma, and are eliminated by glomerular filtration or tubular secretion.

Carboxyl esterase may be developmentally regulated. Its activity surges during the first month of life. The competence of CES1 raised questions as to the anticipated safety margins in oseltamivir and whether adequate metabolite concentrations could be produced. It also raised efficacy and resistance concerns for the very young.

Challenge

Roche/Genentech's pediatric oseltamivir program had to overcome limited data from clinical studies and differing health authority perspectives on dose, data-package and formulation requirements.

Solution

Roche/Genentech was able to navigate these roadblocks through the application of a creative, integrated clinical pharmacology strategy.

Benefit

The integrated clinical pharmacology strategy, including timing and sequence, data-packages and the scientific approach, helped optimize clinical trial design, identify safe and effective dosing, and facilitate regulatory approval.

OP's absorption, distribution, metabolism, and excretion (ADME) characteristics implied that it could be sensitive to developmental changes in PK. Significant changes in total body water occur over the first year as well as rapid changes in liver mass, body mass ratios, and renal function.

Challenge

Roche/Genentech sought to develop Tamiflu for infants. Available Phase 3 studies with oseltamivir in adults and children greater than one year of age suggested that children have similar disease progression and response to intervention as adults. Even so, the juvenile toxicology findings created heightened diligence when moving into infants.

The oseltamivir program also faced particular challenges with the decision to file, including differing health authority perspectives on dose, data-package and formulation requirements. Other key challenges related to the limited data across two studies.

Solution

Certara scientists, working as part of the Roche/Genentech team, developed a creative, integrated clinical pharmacology program that was core to their overarching pediatric filing strategy. In collaboration with commercial, regulatory, clinical, pharmacovigilance and drug product groups, this integrated clinical pharmacology strategy guided clinical trial design and dose justification.

Evaluating PK/safety/virology in infants

The development program began with study CASG 114 (study 114), led by the NIH with input from Roche/Genentech, using Roche's proprietary pediatric formulation.[2] Subsequently, Roche performed study WP22849 (study 849) that added to the available patient data base. Due to concerns over dosing accuracy of the proprietary formulation, they explored using an extemporaneous formulation. Ultimately, Roche/Genentech filed and registered the new proprietary formulation of oseltamivir in infants in the US and then in the EU, incorporating data from both studies.

Because of concern relating to the juvenile toxicology findings, study 114 was designed with significant controls and monitoring. The Phase 1/2 study used an adaptive design to evaluate pharmacokinetics (PK)/safety/virology.[2] Study 114 also incorporated key clinical pharmacology features including adaptive age de-escalation.[2] Within age-cohort dose adaptation was based on both safety and PK. In cases where minimum numbers of subjects failed to meet pre-specified area under the curve (AUC) targets, decision criteria for increasing, decreasing dose or recruiting more subjects at the same dose were implemented. PK sampling was minimized via optimal sampling.

Study 849 was also a Phase 1/2 study evaluating PK/safety/virology in infants less than year of age.[3] A provisional population PK (popPK) model derived from interim data from study 114 was used to assist in dose recommendations for the new trial.[3] Assumptions on the new formulation performance as well as remaining concerns on safety resulted in lower doses being evaluated in the youngest infants in this study.[3] Optimal sampling methods again supported limiting PK sampling.

Using modeling and simulation to inform dosing

The next component of the integrated pediatric clinical pharmacology strategy was establishing dosing in babies less than one year.[4] The approach involved three steps and required pooling the 114

and 849 studies. The first step was developing a popPK model to address the heterogeneity in the studies that might impact PK—different doses, formulations, and other developmental covariates.[4] The PK model was later reused to simulate both OC and OP exposures for infants less than one year. The second step was to provide due diligence around exposure response (ER) in infants. If ER was shown to differ between older children and adults, then dosing would be based on "infant specific" PK/PD and PK-safety relationships. If ER could not be demonstrated to differ in infants versus older children and adults, then this supported PK bridging to older children and adults to inform dosing. The final step was taking the information derived in step two, and using the popPK model to simulate candidate regimens that would be used to inform recommendations for doses for infants less than one year.

Developing a global filing strategy

The integrated clinical pharmacology strategy also informed the global filing strategy, including timing and sequence, data-packages and the scientific approach. The decision to file for the US was made despite the fact that the study 849 was still ongoing and was actually incomplete at time filing. The urgency to file Tamiflu was largely fuelled by unmet need.

The filing in EU occurred subsequent to that in the US. The general data-package and argumentation were similar, except they did not include any interim data. In addition, further quantitative pharmacology analyses were provided.

One important addition was incorporating novel toxicology information. Specifically, an adult and juvenile marmoset study was conducted and confirmed that CES activity was developmentally regulated. A physiologically-based pharmacokinetic (PBPK) model was developed to assist in bridging the data from both adult and juvenile marmosets in an iterative fashion with human adults and infants.[5]

Benefit

Optimized clinical studies

Innovative clinical pharmacology contributions were key to successfully designing and executing study 114. The study 114 popPK model derived simulations supported dose selection for study 849. This model also enabled a simplified, non-adaptive, parallel design trial that was easier to execute than study 114.

The popPK model built using pooled data from the two clinical studies yielded several important insights.[4] A three-compartment model accurately described the concentration-time course of OP and OC. Whilst allometric scaling using body weight adequately described OP PK alone, for OC, apparent clearance and volume of distribution also linearly increased with age. Despite exhaustive covariate exploration, no relevant impact of gender, ethnicity, race, or post-conceptual age could be detected. Ultimately, the PK model findings were plausible and consistent with the literature. Importantly, no study differences in bioavailability were detected.

The PK/PD and PK/safety evaluations across pooled studies uncovered no new information that would suggest a different ER relationship in infants versus older children or adults.[4]

Safe and effective dosing for infants

Simulations of OP and OC supported identifying a safe and effective dose for infants younger than one year.[4] A dose of 3mg/kg twice daily was considered necessary to ensure adequate OC exposures across all infants less than year of age, especially for those infants less than 1 month of age, where PK variability was highest.

The PBPK model developed by the Roche/Genentech team adequately simulated both OP and OC in both humans and marmosets for both adults and infants.[5] The additional PBPK model also supported the biological meaning behind the empirical observations from the popPK model.

The EMA drew reassurance from the PBPK model's evidence that human infants should have sufficient OP turnover to have adequate OC for efficacy and also acceptable safety margins for both OP and OC.[6]

Impact

This approach resulted in successful and harmonized approval for oseltamivir dosing in babies in Europe and the US.[7] Oseltamivir is the first medication indicated for the treatment of acute, uncomplicated influenza in patients two weeks of age and older. The case of Tamiflu illustrates how translational and quantitative pharmacology strategies in pediatric drug development can optimize clinical trial design and inform dosing.

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CS Nov 2016 v3 071818