**Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e70;** doi:10.1038/psp.2013.46

www.nature.com/psp

PERSPECTIVE

# Opinion: The Pharmacometrics of Infectious Disease

**GR Davies[1], W Hope[2] and S Khoo[2]**

**The application of pharmacometric principles to the treatment of infectious diseases must address important biological issues across the diversity of pathogenic organisms. Recent applications of pharmacometric tools in this therapeutic area have had important translational impact not only in drug development but on real-world clinical practice. The fruitful fusion of preclinical and population methodologies promises increasingly personalized and mechanistic approaches.**
*CPT: Pharmacometrics & Systems Pharmacology* (2013) **2**, e70; doi:10.1038/psp.2013.46; published online 28 August 2013

## STILL WITH US

Even in the 21st century, infectious diseases continue to exact a heavy toll on humanity, despite the development and availability of highly effective therapies. A child dies from severe malaria every minute in Sub-Saharan Africa, whereas worldwide, tuberculosis (TB) claims another life every 20 s. In addition to these visible acute illnesses, the hidden burden of chronic viral infections such as HIV and hepatitis B and C is sobering, affecting at least 1 in 20 persons globally. Even in industrialized countries, the growth of intensive care medicine, hemato-oncology, and transplantation have ensured that the risk of serious and unusual opportunistic infections can never be ignored. Many of the current agents used to treat these infections have their origins in venerable and serendipitous advances that predated modern methods of drug discovery and development. Consequently, the anti-infective armamentarium still includes many drugs with challenging absorption, disposition, metabolism, and excretion characteristics for which little reliable dose-ranging pharmacokinetic (PK) or pharmacodynamic (PD) data exist. Many of these drugs clearly require further optimization or repurposing to maximize their potential impact beyond the limited scope of their original development programes. On the other hand, remarkable recent advances in antiviral and antifungal drug discovery have led to the development of completely new classes of better, safer drugs, some of which have been successfully deployed for public health purposes on a global scale. With nearly 9 million HIV-positive people now on daily antiretroviral therapy worldwide, the demand for efficacious, safe, and simply administered anti-infective drugs has never been greater.

## INFECTION IS DIFFERENT

Unlike other therapeutic areas, the pharmacology of anti-infective agents must consider the effect on two distinct organisms, the pathogen and the host. Despite the huge diversity of phylogenetically distinct target organisms, antimicrobial drug development and therapy are guided by some common principles. Almost uniformly, the problem of resistance to treatment has to be taken seriously because under the selective pressure induced by single or multiple drugs, infectious organisms evolve at an individual and population scale, sometimes very rapidly, to reduce their susceptibility to treatment. Therefore, licensing and therapeutic decisions have an impact not just on the infected host but also on their personal microbiota and potential contacts, with possible longer-term consequences beyond the individual receiving treatment. To prevent resistance emerging, combination therapy is now routine in many areas of infectious diseases such as treatment of malaria, TB, and HIV. In HIV-TB co-infection in particular, antimicrobial therapy is routinely tailored to individuals according to the resistance patterns of the organisms with which they are infected. The complexity of combination therapy is further compounded by the need to predict, recognize, and manage drug–drug interactions, and develop treatment regimens for co-infections such as HIV-TB and HIV-hepatitis C virus which are mutually compatible. Effective treatment relies not only on rapid elimination of organisms from clinical specimens but also on effectively supporting or complementing the natural immune response of the host for complete eradication of the invading organisms. Cure may be difficult to achieve in immunosuppressed patients, making assessment of length of therapy difficult and sometimes necessitating secondary prophylaxis and/or adjuvant immunotherapy. In addition, the presence of inaccessible sanctuary sites for residual organisms in many infections and the limits of detection of the most sensitive assays for many organisms may leave some doubt as to whether eradication has been achieved.

## FROM THEORY TO PRACTICE

Though many of these features are not specific to infectious diseases, taken together they are responsible for a therapeutic landscape in infection that is uniquely complex and which continues to evolve rapidly. This presents challenges for both the development of new agents and their optimal use in the clinic. Processing and making effective use of all the pertinent information can be very difficult

[1]Department of Clinical Infection, Microbiology and Immunology, Institutes of Infection and Global Health and Translational Medicine, University of Liverpool, Liverpool, UK; [2]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK. Correspondence: GR Davies (gdavies@liv.ac.uk)
Received 29 March 2013; accepted 8 July 2013; advance online publication 28 August 2013. doi:10.1038/psp.2013.46

without the unifying framework that PK-PD theory provides. The quantitative foundations of infectious disease therapy have only recently begun to be appreciated. Simple laboratory methods relating the minimum inhibitory concentration *in vitro* to various measures of drug exposure in plasma or at the site of action in the host are routinely used to assess the likelihood of response to therapy in a clinical context. The development of laboratory animal and *in vitro* systems capable of mimicking the dynamic patterns of drug exposure found in the host; however, has allowed the underlying PK-PD relationships determining efficacy and controlling the emergence of resistance to be elucidated. By studying the PK-PD properties of drugs, rational clinical treatment targets can be developed and dosing strategies proposed to achieve them, with the promise of better clinical outcomes. To fully implement this approach practically and cost-effectively at the bedside, however, population PK models which quantify the extent of interpatient variability in drug exposure under routine conditions are required. The ability to obtain meaningful individual estimates of parameters using such sparse sampling strategies has facilitated the direct clinical application of the concepts generated in the laboratory. Today PK-PD considerations play a central role in infectious diseases therapy and the power of pharmacometric approaches to optimize treatment for individuals and populations during and beyond the development phase is increasingly recognized.

## RECENT ADVANCES

Identifying and hitting clinical PK-PD targets for efficacy was an early goal of pharmacometric approaches. A canonical example providing proof-of-principle of the impact of PK-PD approaches on clinical practice was that of fluoroquinolones for treatment of severe respiratory infections. The identification of an area under the curve/minimum inhibitory concentration threshold for efficacy in animal models of pneumococcal infection was confirmed in clinical studies of treatment of patients with community-acquired respiratory tract infections for five different members of the class.[1] This paradigm has proved to be of use in other bacterial infections. Alteration of the dosing schedule of daptomycin according to a PK-PD target enabled effective use of this unique drug while averting musculoskeletal toxicity,[2] whereas more recently an area under the curve/minimum inhibitory concentration target derived from the neutropenic mouse thigh model for vancomycin in staphylococcal bloodstream infections has been supported in large clinical cohorts.[3] In TB, re-evaluation of preclinical PK-PD findings has significantly influenced clinical development of the new drug PA-824[4] and in antifungal therapy, dosing predictions derived from preclinical models have been confirmed in fluconazole treatment of cryptococcal meningitis.[5] These concepts have also translated well in the field of antiviral therapy. For several HIV drugs, predicted or actual trough concentration is a strong predictor of subsequent virological failure and PK-PD targets analogous to those used in bacteriology have proved useful. In treatment-experienced patients, the genotypic or phenotypic inhibitory quotient has been proposed and supported as a predictor of individual outcome with HIV-protease inhibitors.[6] In hepatitis C virus therapy, early and cumulative exposure of ribavirin has been linked to sustained virological response[7] resulting in weight-based dosage recommendations to optimize outcome. In many infections, concern about emergence of resistance at a population level has led to pharmacometric approaches to optimize deployment of therapy in the face of declining efficacy. This has perhaps had the most impact in malaria where study of the emergence of resistance to common antimalarial drugs such as sulphadoxine-pyrimethamine led to the development of a PK-PD paradigm for development and deployment of new artemisinin combination therapies.[8]

## THE FUTURE

The future of pharmacometrics in infectious diseases may well lie in adopting more mechanistic approaches capable of incorporating important system information relevant to PD. The availability of different classes of drugs for chronic viral infections with differing targets within the relatively simple life cycle of these viruses has resulted in the development of simple semi-mechanistic models representing the life cycle of pathogens and/or their location in the host.[9] Such models have been successfully fitted to data and can be made identifiable by technologies capable of measuring the distinct stages of infection corresponding to the putative model structure. Similar examples can be found in *in vitro* models designed to detect enrichment of resistance during treatment of bacterial infections and models reflecting the stage specificity of the action of antimalarial drugs which have helped to explain patterns of parasite clearance observed in clinical studies of quinine and artemisinin-based compounds.[10] Inherently, the additional insight that these models bring enhances the value and accuracy of their predictions. Although much effort has been focused on optimization of dosing at the population level, pharmacometric techniques have also begun to be used to truly individualize therapy as opposed to more traditional therapeutic drug monitoring approaches. Adaptive control and Bayesian forecasting methods have been applied successfully to dosing of a number of drugs and these approaches are capable of being incorporated into simple decision support software that could be used in the laboratory or clinic.[11] In addition to optimal dose selection, incorporation of technologies and programs that facilitate adherence and accurate timing of doses could also greatly reduce the interpatient PK variability implicated as a factor in poor treatment outcomes.[12] Ultimately, it is the fusion of the principles and techniques derived from *in vitro* and *in vivo* PD with modern population PK-PD methods that has resulted in these advances and the powerful toolkit that they provide for clinically oriented infectious diseases specialists and pharmacologists will be the underpinning for the progression to more fully rational therapy across the spectrum of infections.

**Conflict of interest.** The authors declared no conflict of interest.

1. Ambrose, P.G., Grasela, D.M., Grasela, T.H., Passarell, J., Mayer, H.B. & Pierce, P.F. Pharmacodynamics of fluoroquinolones against Streptococcus pneumoniae in patients with community-acquired respiratory tract infections. *Antimicrob. Agents Chemother.* **45**, 2793–2797 (2001).
2. Arbeit, R.D., Maki, D., Tally, F.P., Campanaro, E. & Eisenstein, B.I.; Daptomycin 98-01 and 99-01 Investigators. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. *Clin. Infect. Dis.* **38**, 1673–1681 (2004).
3. Kullar, R., Davis, S.L., Levine, D.P. & Rybak, M.J. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. *Clin. Infect. Dis.* **52**, 975–981 (2011).
4. Diacon, A.H. *et al.* Phase II dose-ranging trial of the early bactericidal activity of PA-824. *Antimicrob. Agents Chemother.* **56**, 3027–3031 (2012).
5. Longley, N. *et al.* Dose response effect of high-dose fluconazole for HIV-associated cryptococcal meningitis in southwestern Uganda. *Clin. Infect. Dis.* **47**, 1556–1561 (2008).
6. Gonzalez de Requena, D. *et al.* Comparative evaluation of seven resistance interpretation algorithms and their derived genotypic inhibitory quotients for the prediction of 48 week virological response to darunavir-based salvage regimens. *J. Antimicrob. Chemother.* **66**, 192–200 (2011).
7. Jin, R., Fossler, M.J., McHutchison, J.G., Howell, C.D. & Dowling, T.C. Population pharmacokinetics and pharmacodynamics of ribavirin in patients with chronic hepatitis C genotype 1 infection. *AAPS J.* **14**, 571–580 (2012).
8. Stepniewska, K. & White, N.J. Pharmacokinetic determinants of the window of selection for antimalarial drug resistance. *Antimicrob. Agents Chemother.* **52**, 1589–1596 (2008).
9. Dixit, N.M. & Perelson, A.S. Complex patterns of viral load decay under antiretroviral therapy: influence of pharmacokinetics and intracellular delay. *J. Theor. Biol.* **226**, 95–109 (2004).
10. Saralamba, S. *et al.* Intrahost modeling of artemisinin resistance in Plasmodium falciparum. *Proc. Natl. Acad. Sci. U.S.A.* **108**, 397–402 (2011).
11. Hope, W.W. *et al.* Software for dosage individualization of voriconazole for immuno-compromised patients. *Antimicrob. Agents Chemother.* **57**, 1888–1894 (2013).
12. Parienti, J.J. *et al.* Adherence profiles and therapeutic responses of treatment-naive HIV-infected patients starting boosted atazanavir-based therapy in the ANRS 134-COPHAR 3 trial. *Antimicrob. Agents Chemother.* **57**, 2265–2271 (2013).