Developing and Using Therapeutics for Emerging Infections

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This issue of *Clinical Pharmacology & Therapeutics* focuses on emerging infections. The outbreaks of the vaccine-preventable diseases (e.g., measles) and the emerging pathogens (e.g., Ebola) show us how small the world has become. These outbreaks also show the pressing need for effective public education and development of novel therapies. This issue covers various aspects of relevant therapeutic topics ranging from preclinical models, pharmacokinetics, pharmacodynamics, pharmacogenomics, and clinical trial results, to education efforts in this area. Pharmacokinetic/dynamic modeling had an appreciable role in reducing the morbidity and mortality associated with human immunodeficiency virus and hepatitis C virus, recent emerging infections. However, these gains could be lessened by poor adherence to therapies, which has contributed to the development of multidrug-resistant tuberculosis. We must not forget lessons from previous infections, or they may reemerge.

The rapid diagnosis and effective treatment of patients afflicted with infectious disease(s) is one of the greatest medical advances of the past century,[1] with cardiovascular disease and cancer now the most common causes of death in the US. The ongoing (as of publication) outbreaks of the Ebola filovirus and Middle East Respiratory Syndrome coronavirus (MERS-CoV), however, demonstrate the need for continued innovation in the diagnosis and treatment of infectious diseases. *Clinical Pharmacology & Therapeutics (CPT)* serves as the global forum at the nexus of diverse communities focused on the discovery, development, reg-

ulation, and utilization of therapeutics.[2] As such, the *CPT* audience is uniquely poised to accelerate the response to emerging infections. The articles in this "Emerging Infections" issue address therapeutics for infections from emerging pathogens as well as those pathogens well known to impact human health.

Over the recent decades, it has become clear that the threat from serious infectious diseases persists, and human mortality attributed to infection is projected to remain at current levels (13–15 million deaths annually) until at least 2030.[3] Successes in eradicating diseases, as with

smallpox, are unfortunately isolated events[3] although there is hope that polio and measles can be eradicated as well.[4] Newly emerging infectious agents, however, represent ongoing challenges. Examples include human immunodeficiency virus (HIV) and hepatitis C virus (HCV) in the 20th century, and more recently, severe acute respiratory syndrome (SARS), West Nile Virus, drug-resistant pathogens, novel influenza A strains, and the ongoing Ebola virus and MERS-CoV outbreaks.[3] Global challenges for disease prevention and control are influenced by several factors, including increasing antimicrobial resistance, human connectivity, population growth, urbanization, and environmental and land-use changes, as well as changing human behavior. Mathematical models offer valuable tools for understanding epidemiological patterns and for developing and evaluating evidence for decision-making in global health.[3] Complementing these mathematical models of epidemiological patterns, population pharmacokinetic models,[5] and immune response models[6] can contribute to pharmacokinetic/dynamic modeling to optimize therapeutics of patients with an infectious disease.

Another strategy that enables drug development for some infectious diseases is the use of animal models to support development of therapies for which a traditional drug development pathway may not be logistically possible, such as an emerging infection.[7] Dr. Bergman explains how the "Animal Rule" provides a mechanism for a therapy to obtain marketing approval based on adequate and well-controlled animal studies when it is not ethical or feasible to conduct human efficacy studies. As explained by Dr. Bergman,[7] the US Food and Drug Administration (FDA)'s revised draft Guidance for Industry entitled "Product Development Under the Animal Rule" explains the necessary clinical pharmacology information to select an effective human dose.[8] First, one or more animal species is identified whose pathophysiology (natural history) of the disease or condition is comparable to that of humans, as this species reactions are expected to be predictive for humans. Subsequently, an effective dose is chosen based on integration of: 1) pharmacokinetic information from healthy animals and humans; 2) pharmacokinetic and pharmacodynamic knowledge gained from diseased animals selected for the efficacy studies; and 3) any known pharmacodynamic characteristics in humans. The process of integrating the three factors listed above requires identification of the "fully effective dose" in animals. Because the similarity of exposure–response in humans and animals is often not clear, the 2014 Draft Guidance emphasizes the importance of achieving concentrations in humans that exceed, preferably by several-fold, the concentrations associated with efficacy in animals. Although the recently revised draft guidance of the Animal Rule is nascent enough that it has yet to be used to achieve FDA approval for a drug, it offers a scientific and practical approach to identify and develop therapies for emerging infections.

HIV is a good example of the impact of therapeutics changing an emerging infection with relatively rapid morbidity and mortality to a chronic infection that can often be controlled with medications. Currently, early initiation of antiretroviral therapy (ART) is recommended in all patients with HIV regardless of their clinical stage or CD4 count.[9] Dickinson et al.[10] present the pharmacokinetic and pharmacodynamic comparison of two different efavirenz doses using data from the ENCORE1 (efficacy of 400 mg efavirenz vs. standard 600 mg dose in HIV-infected, antiretroviral-naïve adults) clinical trial in treatment-naïve HIV-infected patients. Consistent with historical data, HIV suppression was comparable between the two efavirenz doses despite a lower plasma exposure with the 400 mg

group, and efavirenz plasma exposure was similar between those patients with or without efavirenz-related toxicity.[10] The apparent oral clearance (CL/F) of efavirenz was associated with *CYP2B6* polymorphisms and weight. Notably, over 58% of the variability in CL/F was unexplained, potentially due to unidentified host genetic factors and potentially variable adherence. Low rates of medication adherence occur across a variety of long-term illnesses, including HIV.[11] Public health efforts are ongoing to support adherence to ART, as low ART adherence is associated with virologic failure.[12] Although ART has turned HIV into a chronic condition for many patients in the US, there is still a need for new therapies. Reeves *et al*.[13] review the current knowledge about mucosal dysfunction in the context of HIV infection. They describe potential avenues for therapeutic targets to enhance mucosal function and decrease morbidity and mortality in HIV-infected individuals.[13] The advances in HIV therapy have been substantive over the past 35 years but improvements are still needed.

Similarly, HCV is an example of how therapeutics can convert an emerging infection with substantial morbidity (i.e., cirrhosis and hepatocellular carcinoma) to an infection that can be cured in a majority of patients. HCV was identified in the late 1980s with the subsequent development of pegylated interferon-alpha (PEG) and ribavirin for 48 weeks as the standard of care for its treatment. Over the past 4 years, HCV treatment has shifted to a shorter course of direct-acting antivirals (DAAs) without PEG or ribavirin. Specifically targeting key viral proteins necessary for the HCV lifecycle, multiple DAAs have been tested in different combinations for variable durations ranging from 12 to 24 weeks.[14] These new DAA regimens are highly effective, much simpler to administer, safer, and more tolerable with minimal toxicity.[14] Sinha and colleagues discuss how the use of

a surrogate endpoint—virologic response at 12 weeks—was accepted as the primary efficacy endpoint for all HCV registration trials.[15] This change shortened the duration of clinical development and led to earlier approvals of the DAAs. The innovations in HCV treatment have arisen, in part, from mathematic models characterizing HCV RNA levels following treatment. Beginning with a foundational model of HCV RNA levels following interferon treatment, the model was modified to include hepatocyte turnover, resistant and wildtype virus, and intracellular viral replication, with the goal of improving the understanding of and describing observations from more recent regimens containing DAAs.

Despite the advances in therapy for HIV or HCV infections, the ongoing outbreaks of the Ebola virus and the MERS-CoV virus highlight the need for novel antiviral therapies. Antiviral therapies are approved to treat fewer than 10 viruses, although at least hundreds of viruses are known to cause human disease.[16] Developing therapies for individual viruses renders the drug development process expensive and slow, particularly when creating a new drug costs over $2 billion on average and takes 8–12 years to reach the market.[17] Developing therapies is further complicated by the unpredictable nature of virus emergence, raising concerns that the approach of developing therapies for one virus cannot provide adequate global health protection and national security preparedness.[16] The clinical needs resulting from emerging viruses will most likely be best met by a combinatorial approach that includes discovery of novel broadly acting direct acting antivirals and host-targeted therapies, as well as repurposing of already approved drugs. Emerging and reemerging pathogens with no specific, licensed treatments include the flavivirus dengue, the coronaviruses SARS and MERS-CoV, and the filovirus Ebola.[16] Readiness to treat future outbreaks of

emerging pathogens may be facilitated by off-label use of approved broad-spectrum antivirals.[16] The optimal drug dosing regimen and duration in subpopulations should be addressed for off-label use of an approved therapy, and anticipated early in drug development for therapies in clinical development. Pregnant women, who often have higher drug clearance, represent one such subpopulation.[18] Beigi and colleagues describe their work to determine the appropriate oseltamivir dose for pregnant women afflicted with H1N1 during the 2009 outbreak in the US.[19] This investigation was undertaken by the National Institutes of Health (NIH)'s Obstetric-Fetal Pharmacologic Research Unit (OPRU) Network using an "opportunistic study design" that involved enrolling pregnant women treated for H1N1 with oseltamivir. The physiologic changes of pregnancy produced an ~30% lower plasma exposure to the active metabolite relative to other populations, including nonpregnant women. These data suggested that altered dosing regimens are needed for pregnant women to achieve a plasma exposure comparable to their nonpregnant counterparts afflicted with the H1N1 virus. The H1N1 virus that caused the 2009 pandemic is now a regular human flu virus and continues to circulate seasonally worldwide. Although H1N1 is included in the flu vaccine, compliance rates with vaccination are insufficient for herd immunity, so continued vigilance is needed for optimal use of the available H1N1 therapies.

In contrast to the successes in treating HIV and HCV, the treatment of tuberculosis (TB)—a pathogen long known to impact health—still needs improvement. TB continues to be a leading cause of death in low- and middle-income countries despite the availability of effective treatments.[20] The World Health Organization currently recommends at least 6 months of treatment for active disease, and 12 months for latent TB.[20] It is difficult for patients to adhere to the long durations of treatment. Poor adherence can lead to relapse and even death in individuals, and also has important public health consequences, such as the transmission and development of multidrug-resistant TB (MDR-TB). Eglund et al.[21] describe how slow responses to TB medications may reflect low drug exposure. They indicate that maximizing drug exposure will increase the chance of developing an effective short-course regimen. Furthermore, they provide a thoughtful review regarding pharmacokinetic and pharmacodynamic modeling to optimize drug regimens to treat TB, including MDR-TB. Increased innovation is clearly needed for current TB therapies, such as the 6-month "short course" treatment that was developed from empiric evidence and has marginally changed in the last 40 years. Fortunately, momentum for practice changes is building with more studies of the pharmacokinetics/dynamics of TB drugs. Furthermore, immune response models of the cellular response to a pulmonary TB infection[6] can contribute to pharmacokinetic/dynamic modeling to optimize therapeutics of patients with TB. With continued efforts, the impact of mathematical modeling to TB treatment can follow the impact of such techniques applied to HCV treatment, as discussed above.

Successful treatment of infections relies on the development of novel therapies and effective utilization of existing therapies. Effective deployment of therapy requires an efficient educational system and nimble support of healthcare providers to address new emerging pathogens in addition to recalcitrant pathogens. In the Policy article, Pastakia et al. address ways to strengthen health systems, including education of healthcare providers to appropriately respond to outbreaks of emerging infections, particularly in low- to middle-income countries.[22] Therapeutic drug monitoring is used as a metaphor for this strategy, where the goal is to effectively use multiple

strategies—building local capacity, infrastructure, and systems—to maximize the total exposure of infected patients to the available therapies.

Finally, we must not forget lessons from previous infections, or they may reemerge. In the Macroscopy article, Dr. Pergam[23] reminds us that the need for rapid development of complex institutional systems and structures to address Ebola and other emerging pathogens must not come at the expense of transmittable infections that are already known to impact human health. The Ebola virus cases in the US in Autumn 2014 were temporally juxtaposed with cases of vaccine-preventable infections, such as the measles outbreak that started at Disneyland in late 2014. Widespread acceptance of vaccination is essential to maintain herd immunity and protect the community from diseases that still circulate.[24] Population-level data from 95,000 patients recently demonstrated that the effect of measles on host resistance extends over 2 to 3 years.[25] Thus, measles vaccination has a major role in preventing childhood mortality from other infectious diseases. Furthermore, the Disneyland measles outbreak prompted a discussion among pediatric organizations about how best to restrict vaccine exemptions.[24] Vaccination policy and practice must evolve to embrace contemporary factors that are actively shaping an age-old tension between personal choice and public health.[24] The outbreaks of the vaccine-preventable disease measles and the emerging pathogens Ebola and MERS-CoV show us how small the world has become and the need for effective therapies to treat these emerging pathogens.

DISCLAIMER

KSR is employed by the U.S. Food and Drug Administration. The views, opinions, and interpretation expressed in this article are those of the author and do not reflect either the policies or the position of the U.S. Food and Drug Administration.

1. Lewis, K. Platforms for antibiotic discovery. *Nat. Rev. Drug Discov.* **12**, 371–387 (2013).
2. Waldman, S.A. & Terzic, A. *Clinical Pharmacology & Therapeutics*: The next five years. *Clin. Pharmacol. Ther.* **97**, 2–6 (2015).
3. Heesterbeek, H. *et al*. Modeling infectious disease dynamics in the complex landscape of global health. *Science* **347**, aaa4339 (2015).
4. Roberts, L. Is measles next? *Science* **348**, 958–961 (2015).
5. Leeds, J.M. *et al*. Pharmacokinetic and pharmacodynamic modeling to determine the dose of ST-246 to protect against smallpox in humans. *Antimicrob. Agents Chemother.* **57**, 1136–1143 (2013).
6. Palsson, S. *et al*. The development of a fully-integrated immune response model (FIRM) simulator of the immune response through integration of multiple subset models. *BMC Syst. Biol.* **7**, 95 (2013).
7. Bergman, K.L. The animal rule: the role of clinical pharmacology in determining an effective dose in humans. *Clin. Pharmacol. Ther.* **98**, 365–368 (2015).
8. US Food and Drug Administration, HHS. Guidance for Industry; Product Development Under the Animal Rule (draft). <http://www.fda.gov/downloads/drugs/guidancecompliance regulatoryinformation/guidances/ucm399217.pdf>. Accessed June 16, 2015.
9. World Health Organization (WHO). Consolidated guidelines on HIV prevention, diagnosis, treatment and care for key populations. (World Health Organization (WHO) Geneva, Switzerland, 2014).
10. Dickinson, L. *et al*. Pharmacokinetic and pharmacodynamic comparison of once daily efavirenz (400 mg versus 600 mg) in treatment-naive HIV-infected patients: results of the ENCORE1 study. *Clin. Pharmacol. Ther.* **98**, 406–416 (2015).
11. Vrijens, B. & Urquhart, J. Patient adherence to prescribed antimicrobial drug dosing regimens. *J. Antimicrob. Chemother.* **55**, 616–627 (2005).
12. Ruperez, M. *et al*. Determinants of virological failure and antiretroviral drug resistance in Mozambique. *J. Antimicrob. Chemother.* (2015); e-pub ahead of print.
13. Reeves, K.R., Burgener, A. & Klatt, N.R. Targeting the GI tract to develop novel therapies for HIV. *Clin. Pharmacol. Ther.* **98**, 381–386 (2015).
14. Ghany, M.G. The ongoing debate of who to treat for chronic hepatitis C virus. *JAMA Intern. Med.* **175**, 169–170 (2015).
15. Florian, J. *et al*. Direct-acting antiviral drug for the treatment of chronic hepatitis c virus infection: interferon free is now. *Clin. Pharmacol. Ther.* **98**, 394–402 (2015).

16. Bekerman, E. & Einav, S. Infectious disease. Combating emerging viral threats. *Science* **348**, 282–283 (2015).

17. Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion. November 18, 2014. <http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study>. Accessed June 16, 2015.

18. Zhao, Y., Hebert, M.F. & Venkataramanan, R. Basic obstetric pharmacology. *Semin. Perinatol.* **38**, 475–486 (2014).

19. Beigi, R.H., Pillai, V.C., Venkataramanan, R. & Caritis, S.N. Optimizing the treatment of H1N1 influenza in pregnancy. *Clin. Pharmacol. Ther.* (this issue) 2015.

20. Karumbi, J. & Garner, P. Directly observed therapy for treating tuberculosis. *Cochrane Database Syst. Rev.* **5**, CD003343 (2015).

21. Egelund, E.F., Alsultan, A. & Peloquina, C.A. Optimizing the clinical pharmacology of tuberculosis medications. *Clin. Pharmacol. Ther.* **98**, 387–393 (2015).

22. Pastakia, S., Njugana, B., Le, P.V., Singh, M.K. & Brock, T.P. To address emerging infections, we must invest in enduring systems: the kinetics and dynamics of health systems strengthening. *Clin. Pharmacol. Ther.* **98**, 362–364 (2015).

23. Pergam, S.A. Addressing fear, fighting complacency. *Clin. Pharmacol. Ther.* **98**, 359–361 (2015).

24. Opel, D.J. & Omer, S.B. Measles, mandates, and making vaccination the default option. *JAMA Pediatr.* **169**, 303–304 (2015).

25. Mina, M.J., Metcalf, C.J., de Swart, R.L., Osterhaus, A.D. & Grenfell, B.T. Vaccines. Long-term measles-induced immunomodulation increases overall childhood infectious disease mortality. *Science* **348**, 694–699 (2015).