Investigator-initiated studies in infectious diseases

Märtson, Anne Grete; Alffenaar, Jan Willem C.

Published in:
Clinical Infectious Diseases

DOI:
10.1093/cid/ciab401

Publication date:
2021

Clinical Infectious Diseases

CORRESPONDENCE

Investigator-Initiated Studies in Infectious Diseases—Considerations for Pharmacokinetic-Pharmacodynamic Optimization

Anne-Grete Märtson,[1] and Jan-Willem C. Alffenaar[2,3,4]

[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [2]Sydney Pharmacy School, The University of Sydney, Sydney, New South Wales, Australia; [3]Westmead Hospital, Sydney, New South Wales, Australia; and [4]Marie Bashir Institute of Infectious Diseases and Biosecurity, The University of Sydney, Sydney, New South Wales, Australia

To the Editor—With great interest we read the viewpoint article by Paul and colleagues [1] published in the April issue of *Clinical Infectious Diseases*. Conducting studies in infectious diseases is an important topic and robust design of studies with appropriate planning is of great importance. We agree with the authors that investigator-initiated studies thrive due to dedicated investigators and collaborations. Furthermore, the inclusion and exclusion criteria are much stricter in industry trials as compared with investigator-initiated trials, which lead to studies in specific patient cohorts.

We think that an important difference between investigator-initiated and industry trials in infectious diseases is the incorporation of pharmacokinetic/pharmacodynamic (PK/PD) endpoints [2]. As rightfully mentioned in the publication, pharmaceutical companies are focused on the registration of new drugs. However, clinician-investigators often have an additional interest in how anti-infectives are used in clinical care and if dose optimization will benefit individual patients. It is therefore important to conduct PK/PD studies to investigate what could be the drivers of efficacy and/or toxicity. For instance, the efficacy target area under the curve/minimum inhibitory concentration (area under the curve/minimum inhibitory concentration) suggested for vancomycin is essentially the result of decades of investigator-initiated studies [3].

From a marketing point of view, a one-size-fits-all approach is preferred over a personalized approach requiring additional diagnostic procedures or therapeutic drug monitoring (TDM). As is often not well understood, a personalized dosing strategy is simply intended to let more patients benefit from an antimicrobial drug, as it aims to reduce the number of patients who are at risk for treatment failure or adverse effects [4]. A good example of an investigator-initiated study incorporating PK/PD indexes as endpoints is the DALI (Defining Antibiotic Levels in Intensive Care Unit Patients) study looking into B-lactam dosing in critically ill patients [5]. Although, investigator-driven studies aiming to optimize dosing strategies try to resolve the questions regarding dose optimization, the majority are only moderately successful [6]. One of the main reasons is that the investigator-driven trial has several limitations such as using surrogate endpoints instead of clinical endpoints, has a too small sample size, or does not use optimal TDM procedures with a short turnaround time or use of model-informed precision dosing [7].

Ideally, we would like to see that the pharmaceutical industry and investigators join forces and include PK/PD assessment in phase IIb/III trials leading to registration of the drugs [8]. The phase IIb/III studies typically include clinical endpoints and are of sufficient sample size to validate PK/PD targets for efficacy and threshold concentrations for toxicity. We believe that clinically relevant information coming from those trials would find its way into the summary of product characteristics/product inserts, providing clinicians and other professionals with a more detailed dosing profile in order to not only treat the average patient but also provide suggestions on what to do in case of slow response to treatment- or drug concentration–associated adverse effects.

Notes

Financial support. A.-G. M. reports grants from Marie Skłodowska-Curie Actions (grant agreement no. 713 660–PRONKJEWAIL–H2020-MSCA-COFUND-2015) during the conduct of the study.

Potential conflicts of interest. The authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References

1. Paul M, Harbarth S, Huttner A, et al. Investigator-initiated randomized controlled trials in infectious diseases: better value for money for registration trials of new antimicrobials. Clin Infect Dis **2021**; 72:1259–64.
2. Labreche MJ, Graber CJ, Nguyen HM. Recent updates on the role of pharmacokinetics-pharmacodynamics in antimicrobial susceptibility testing as applied to clinical practice. Clin Infect Dis **2015**; 61:1446–52.
3. Rybak MJ, Le J, Lodise TP, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Heal Pharm **2020**; 77:835–64.
4. Alffenaar JC, Gumbo T, Dooley KE, et al. Integrating pharmacokinetics and pharmacodynamics in operational research to end tuberculosis. Clin Infect Dis **2020**; 70:1774–80.
5. Roberts JA, Paul SK, Akova M, et al; DALI Study. DALI: Defining Antibiotic Levels in Intensive Care Unit Patients: are current β-lactam antibiotic doses sufficient for critically ill patients? Clin Infect Dis **2014**; 58:1072–83.
6. Märtson AG, Sturkenboom MGG, Stojanova J, et al. How to design a study to evaluate therapeutic drug monitoring in infectious diseases? Clin Microbiol Infect **2020**; 26:1008–16.
7. Wicha SG, Märtson AG, Nielsen EI, et al; International Society of Anti-Infective Pharmacology (ISAP); PK/PD Study Group of the European Society of Clinical Microbiology, Infectious Diseases (EPASG). From therapeutic drug monitoring to model-informed precision dosing for antibiotics. Clin Pharmacol Ther **2021**; 109:928–41.
8. Märtson A-G, Kim HY, Marais B, Alffenaar J-W. Pharmacokinetics/pharmacodynamics assessment should be included in randomized controlled 2 phase IIB/III tuberculosis treatment trials. Int J Tuberc Lung Dis **2021**; 25:336–9.

Correspondence: J.-W. C. Alffenaar, The University of Sydney School of Pharmacy Faculty of Medicine and Health S343, Pharmacy Building (A15), The University of Sydney, Sydney, NSW, 2006 Australia (johannes.alffenaar@sydney.edu.au).

Clinical Infectious Diseases® 2021;73(9):1742

DOI: 10.1093/cid/ciab401