PERSPECTIVE

Questioning the Design of Non-Inferiority Trials: The Strange Case for Therapeutic Drug Monitoring Absence in Phase III Trials

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Anti-infective experimental drugs seeking approval to first-line treatment were frequently compared with a reference drug in non-inferiority clinical trials. While the reference drug often demonstrated high pharmacokinetic variability and a clear exposure–response relationship, therapeutic drug monitoring, a strategy aiming at optimizing drug exposure by measuring drug concentration and adjusting drug dosage, is surprisingly lacking in recent pivotal trials. This create a breach in the equipoise principle, which should be addressed by the regulatory agencies.

In recent years, phase III clinical trials comparing experimental drugs seeking approval to first-line treatment have been published in the era of anti-infective drugs. This includes isavuconazole, an antifungal agent evaluated in aspergillosis infections, maribavir and letermovir, two newer agents for the treatment of cytomegalovirus (CMV) infection or dalbavancin, a long half-life antibiotic tested in complicated skin and soft-tissue infections.[1] Designs of these phase III studies were non-inferiority compared with the drug of reference despite the equipoise principle was certainly not ensured in the opinion of a biological pharmacologist. For example, Limaye *et al*. evaluated letermovir, a newly approved CMV terminase inhibitor, vs. ganciclovir, the actual standard of care for prophylactic CMV treatment in CMV seronegative kidney transplant recipients receiving a CMV seropositive organ.[2] In their study, the authors showed that CMV disease through week 52 was not different between the letermovir and ganciclovir arms with 30 patients (10.4%) meeting the primary end point in the experimental arm vs. 35 patients (11.8%) in the control arm. Moreover, in the safety analysis, more leukopenia, neutropenia, and finally more treatment discontinuations due to drug-related adverse events were reported in the ganciclovir arm. These results may appear at first look as very positive for letermovir. However, we would like to point that the ganciclovir arm may possibly have been disadvantaged by the trial design. Ganciclovir efficacy and safety in solid organ transplant recipients is actually related to its exposure.[3] The drug has also a wide inter-individual pharmacokinetic variability and in our ongoing clinical trial study GANEX (NCT03088553), where patients received ganciclovir for preemptive or curative indications, the coefficient of variation of the drug trough concentrations was 90%, while 30% of patients showed low exposure (trough concentrations <1 mg/L) despite having a dosage adjustment based on renal function like in Limaye study (authors' personal data). These findings confirm what has already been reported in the literature.[4] Thus, a large part of patients might be under-exposed to ganciclovir in this study, therefore disadvantaging the control arm. On the other side, patients in the ganciclovir arm presented with more hematological adverse events. These events are known to be concentration-dependent and again, ensuring a proper exposure to the drug may have prevent part of them.[3,5] Failing to include therapeutic drug monitoring (TDM) of ganciclovir in a comparative trial might then preclude adequately evaluating the drug effect.

Such a flaw in trial design has already been seen in the SECURE study aiming at comparing isavuconazole and voriconazole for the treatment of aspergillosis, where the latter drug did not benefit from a TDM-driven strategy despite years of demonstration of the high variability and exposure–response of voriconazole[6] and high level of evidence for voriconazole TDM. In this study, isavuconazole treatment demonstrated non-inferiority regarding

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all-cause mortality from the first dose of the study drug to day 42 in the intent-to-treat population of patients included (19% vs. 20%; 95% confidence interval −7.8 to 5.7%). Of note, while the rate of treatment-emergent adverse events was not different between the two drugs, there were more permanent discontinuation due to drug-related adverse events for voriconazole (14%) than for isavuconazole (8%). The well-known variability of voriconazole exposure and its well-described exposure–response relationship may largely explain these results. Indeed, the same leading author has reported a higher mortality rate in patients with the highest quartile of voriconazole exposure in a study aiming at evaluating the exposure–response analysis of a double-blind randomized study of posaconazole and voriconazole for treatment of invasive aspergillosis.[7] The 39% mortality in the group of patients with voriconazole trough concentrations above 4,502 ng/mL, compared with the 6–8% in the other exposure groups, was attributed to the fact that it might be more seriously ill patients treated with the intravenous formulation. We can also hypothesize, and this was the conclusion of the SECURE trial as well, that patients with the highest exposure may be exposed to more adverse drug reactions and more treatment discontinuations finally leading to a higher risk of treatment failure. Eventually, TDM-driven voriconazole therapy strategy has been directly compared in a randomized controlled trial (RCT) with a non-TDM approach mainly in the case of an aspergillosis infection.[8] Treatment success in probable or proven infections was more frequent in the TDM group than in the non-TDM group (86 vs. 66%, $P = 0.04$). Treatment discontinuations due to adverse events also favor the TDM group with only 4% discontinuing voriconazole compared with 17% in the non-TDM group ($P = 0.02$). TDM vs. non-TDM RCT represents the highest level of evidence for the implementation of a TDM strategy in clinical practice. One can therefore legitimately question the rationale of a trial comparing voriconazole to an experimental drug without the use of such a strategy in the control arm. Moreover, we may also question the ethical nature of such approaches. Is it acceptable to run the risk of low or over-drug exposure in patients when the nature of the exposure–response relationship is well characterized, and to jeopardize possible consequences of a biased pivotal trial regarding individual patients' care as well as on public health perspective?

As shown by Wunderink *et al*., ensuring an optimized exposure of the control-arm drug is possible. This group conducted a comparative study between linezolid and vancomycin in 448 adult patients with hospital-acquired or healthcare-associated Methicillin-Resistant Staphylococcus Aureus (MRSA) pneumonia. This RCT showed the superiority of linezolid over vancomycin on clinical cure in the *per-protocol* population with 57.6 vs. 46.6% of patients cured in the linezolid and vancomycin arms, respectively ($P = 0.04$). In this study, the vancomycin dose was adjusted based on trough concentration measurements, as recommended at the time. As a result, the vancomycin exposure was optimized with the median trough concentration being 12.3 µg/mL on day 3, increasing to 14.7 µg/mL on day 6, limiting, therefore, a possible bias due to drug low exposure.[9] Such a design, including TDM as a tool to ensure sufficient and similar drug exposure within participants, strengthens the level of evidence of the clinical trial results. In addition, while renal failure, the main adverse drug reaction concern with vancomycin, was more frequent in patients treated with vancomycin (7.3%) when compared with patients treated with linezolid (3.7%), the rate of nephrotoxicity in the vancomycin arm appears to be relatively low in this severe population of patients (mean APACHE II score = 17). In light of recent guidelines, a TDM based on area under the curve of vancomycin might have even further optimized the treatment and further decreased the risk of renal failure. As for linezolid, there is a clear exposure–toxicity relationship, and studies showed that controlling the drug exposure allows using the drug without toxicity/discontinuation even for a prolonged duration.[10]

Of course, planning a TDM-driven RCT presents some challenges. For example, the blinding of the study is hardly achievable, multicenter studies of that kind require similar quality standards in the analytical process, and in the case of anti-infective drugs, a sufficiently rapid turn-around time is needed. Nevertheless, some of these hurdles can be overcome. For example, Wunderkink *et al*. in their aforementioned study on linezolid vs. vancomycin study ensure clinicians' blinding regarding the drug and the dosage adjustment after TDM with the help of unblended pharmacists in charge of intravenous drug preparation. All other staff remained blinded to study medication.[9] Similarly to the control arm, one can question the absence of exposure adjustment for the experimental arm given the fact that some of the drug candidates may also present some important pharmacokinetic variability. While, the exposure–response of an experimental drug may be less well characterized, a negative bias related to an inadequate drug exposure cannot be ruled out. However, we also acknowledge that the pharma industry has to deal with constraints and that most of the drugs entered the market without TDM due to the fact that large trials evaluating TDM benefits cannot be easily planned during the pre-approval steps. We also acknowledge that the level of evidence for TDM should be improved for some drugs including (val) ganciclovir by conducting TDM vs. non-TDM RCTs.

Finally, one could also question the rationale of a non-inferiority design setting in the case of very expensive drugs. Coming back to letermovir, given the potential medico-economic impact of the drug (the cost is 323€ per day in France), it should probably have to show a clear superiority to enter clinical practice rather than just a non-inferiority. Regulatory agencies should probably include altogether: strict rules regarding appropriate intervention to prevent negatively biasing control arms, notably TDM for highly variable pharmacokinetic drugs, and medico-economic approaches to evaluate the cost-effectiveness of expensive experimental drugs seeking approval.

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