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COMMENTARY

The Risk of Treating Populations Instead of Patients

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Many clinical questions today relate to precision medicine and individualized therapeutics. Clinical pharmacology, including pharmacometrics, aims to quantify sources of drug response variability to ensure safe, effective therapy for all individuals. Recently, Reuter *et al.*,[1] using a pharmacometric analysis, proposed less cost-prohibitive dosing for the antiviral palivizumab. This analysis integrated epidemiological-level and population-level information but lacked information regarding management of individual patients. Here, I identify shortfalls and propose a more patient-centered approach to clinical questions such as these.

ASKING QUESTIONS WITH PURPOSE AND CONTEXT

It is generally agreed that models (and the resulting solutions) should be fit for purpose and, although it may be implied, also fit for context.

Purpose pertains to the specific question being asked and what information is needed to provide an adequately informed answer: What is the deliverable one would like to obtain from the research question? What population will the answer apply to, and are there clinically relevant differences that are important? Does the time frame of interest warrant considering disease progression or other time-varying patient or environmental characteristics? If assumptions are made, what, if any, potential impact do they have on the question and resulting answers?

Context refers to the scenario in which a question is being asked. One might pragmatically divide these into a drug development (preapproval) context or postmarket context. In answering the big questions of whether a drug is safe and effective, scientific inquiries in a preapproval context will likely have the following aspects in mind: What leads should move forward to clinic? What should be the first-in-human dose/dosing regimen, and how should one dose escalate? What doses are optimal to show efficacy with an acceptable level of safety in proof-of-concept or phase III trials? How should the dosing regimen be adapted in special populations (i.e., organ impairment, pediatrics)?

For postmarket situations, the questions can take on a much wider scope, on which drug approval may not depend: How does one dose a drug in a special population not previously studied? Do certain groups respond better than others? What underlying factors are contributing to response heterogeneity, and how might these aspects be harnessed in therapeutic strategies? Both contexts (preapproval and postmarket) may be broken down further and, in reality, substantially overlap with each other, whereas the acceptable assumptions and margin for error may vary. Examples in the drug-development setting[2] and the clinic[3] have been described elsewhere.

PREAPPROVAL—POPULATION LEVEL

The market approval of drugs for most indications is based on an acceptable safety profile and efficacy when compared with placebo or active comparator. Efficacy is often established by comparing outcomes between groups receiving the test drug or comparator and thus is based on an overall (average, population-level) benefit. Statistical testing can confirm with a reasonable level of confidence that an identified benefit between groups is not the result of random chance. Although subpopulations of responders may be identified during the drug-development process, noninferiority or superiority of the test drug vs. the comparator is still the overall goal, just now in a subpopulation context. These approvals are designed to ensure the safe and effective treatment of a population of interest, and approval is often based on a population-level view.

POSTMARKET—PATIENT LEVEL

Almost inevitably, in a postmarket setting, more variability will be observed when broader, less-restricted patient populations are exposed and off-label use occurs. One might observe variability in response and exposure between patients or patient groups exhibiting differences in clinical characteristics, disease pathology, environmental factors, and adherence. Statistical and pharmacometric models may be used to identify these inconsistencies, find better doses, tailor doses to target treatment populations, or identify new potential indications. In this space, it is not always about proving a drug will work for a population but about addressing adequate treatment in subpopulations or individual patients based on differentiating characteristics. If a researcher only approaches the problem from a population level, they may not appropriately answer the question because they are not considering the building blocks of patient response: the disease pathology and progression, the patient's environment, his or her individual exposure and exposure/response relationship, adherence, and other clinical characteristics.

HOW A POPULATION-LEVEL ANALYSIS CAN MISS THE INDIVIDUAL PATIENT: AN EXAMPLE WITH PALIVIZUMAB

Palivizumab is an antibody used as prophylaxis to neutralize respiratory syncytial virus (RSV), thereby preventing

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infection in at-risk pediatric patients.[4] Typical dosing is 15 mg/kg/month throughout the RSV season based on preclinical *in vivo* targets of 40 mg/L. The phase III trials contributing to palivizumab's approval boasted a 55% reduction in preventing hospitalizations because of RSV disease.[5,6] It is clear that the drug bears substantial benefit for the population. Per Reuter *et al.*,[1] as a result of the prohibitive cost, many patients do not have access to palivizumab, and often clinicians attempt to modify the regimen to reduce the dose used. The authors also sought to define a modified regimen (with lowered drug burden) based on population pharmacokinetic and epidemiological disease prevalence data to define a new target and dosing.

The defined target trough of 40 mg/L is based on *in vivo* preclinical models where this exposure conferred at least a 100-fold decrease in RSV titers.[6] This target is a pharmacodynamic threshold that may be linked to efficacy (prevention of disease) given that a certain concentration of palivizumab neutralizes a particular amount of virus. The investigators aimed to match the percentage of patients achieving this exposure threshold (in trough measurements) to be congruent with disease prevalence. The authors justified lowered dosing given that the same percentage of the population could attain the target trough later in the season when compared with earlier in the season with lower doses (prevalence was similar earlier and later in the RSV season). The authors have approached this from a population standpoint and in the context of the approval. Their reasoning relies on the assumptions that a lower disease prevalence in a population means less virus is present in a patient's environment, so the viral inoculum to which a patient is exposed is lower, and therefore less drug is required during low-prevalence time periods. Following are the assumptions broken down:

- Assumption: lower disease prevalence = less virus in the environment.
  - Comment: Prevalence infers the number of cases of RSV infection per a population. A multitude of factors may lead to differences in RSV prevalence, better known to viral epidemiologists. It does not imply that an individual has less risk of being exposed to disease but potentially just that fewer individuals are being exposed overall and presenting with clinical manifestation of the infection. In addition, several studies have documented asymptomatic RSV episodes in children and adults,[7,8] which would not be captured by prevalence metrics.
- Assumption: lower prevalence = lower viral inoculum.
  - Comment: Overall prevalence is not a marker of viral density (the authors do not cite literature evidence supporting otherwise). When an individual patient is diagnosed clinically, it is because RSV was present in a certain density, and the concentration of palivizumab and their own immune defenses could not prevent clinical infection. Just because RSV is less prevalent overall does not mean that all individuals are exposed to low viral inoculum. Studies have established that asymptomatic disease is often associated with lower viral loads[7] and that viral load may vary across groups (i.e., viral load is higher in caregivers when compared with other adults[8])—both epidemiological characteristics not captured by prevalence.

The authors justify revised dosing that leads to a lower percentage of patients achieving target concentrations later in the season compared with the current regimen by implying that disease prevalence and hence equivalent risk to earlier in the season may allow for a lower percentage of individuals to reach target concentrations without compromising efficacy. On the contrary, the original dosing may have provided added protection from higher drug exposures later in the season (which may have substantially contributed to clinical benefit). In this way, the authors' approach advocates to potentially put more patients at risk later in the season given that this risk is equivalent to that earlier in the season. Thinking on a more individual level, one might advocate that 100% of patients should reach the target levels of 40 mg/L all season to ensure maximum protection for all patients, but this would not serve to reduce drug costs.

This population-level approach will, by design, fail some individual patients. If incidence is so low, why give any drug at all? If optimizing to treat a therapeutic target, why aim for lower than 100% of individuals achieving that target? Although a lower percentage of individuals attaining the target during preapproval trials was adequate to establish efficacy vs. placebo, in postmarket the goal is efficacy and safety in individual patients, not the overall population—so why use the same bar?[9] Pure disease prevalence cannot serve as justification that being below target is not potentially harmful to the individual's clinical outcome, as epidemiological data do not necessarily dictate that individual virus exposure is lower in those who were exposed during low prevalence periods. These targets should rather be supported by what we know about patient-level, disease-level, and environmental-level characteristics that may make a patient more or less at risk for disease. Furthermore, this would be a great situation in which our field can find support from epidemiologists.

Perhaps alternatively, if some hospitals have low RSV infections, palivizumab may not be needed or only needed for the highest-risk individuals. Consider if even lower viral inoculum was as likely or more likely to cause infection in higher-risk groups (e.g., because of lowered immune function). A stratified approach to dosing based on risk factors that incorporated relevant epidemiological information could provide a more cost-effective alternative when compared with the standard regimen. However, if we forget the individual in our approaches in improving therapy, we are treating averages and doing a disservice to patients who deviate from "typical values." This is the opposite of precision therapeutics. From an epidemiological, disease-control, and population-level standpoint, it is pivotal to find approaches that optimize protection, minimize risk, and allow for access to care, but we should use what we know about individual patient risk to improve population outcomes.

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