VIEWPOINT

Modern Drug Development
Which Patients Should Come First?

Muthiah Vaduganathan, MD, MPH
Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts.

Vinay Prasad, MD, MPH
Bloomberg School of Public Health, Johns Hopkins University, Baltimore, Maryland.

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Corresponding Author: Vinay Prasad, MD, MPH, Bloomberg School of Public Health, Johns Hopkins University, 615 N Wolfe St, Room W1015, Baltimore, MD 21205 (vprasad4@jhu.edu).

The goal of drug development is to expeditiously bring safe, effective medications to the patients who need them most. In parallel with the traditional phases of drug testing (1, 2, and 3), drug manufacturers must choose the patient populations and the indications for which drugs will first be studied. Historically, novel agents ordinarily have been introduced in patients with advanced disease states. If these trials were positive, approval was sought, whereas subsequent studies defined the role of the drug in less severe or earlier forms of the disease, in important subgroups, and even as chemoprevention. Recent trials in cardiovascular and cancer medicine, however, have challenged this approach; many novel drugs now seek to establish safety and efficacy in early disease settings.

The shift in initial target population raises questions regarding optimal protocol: Is the shift to early disease better for patients? Is the motivation for recent trends driven by a biological rationale or a desire by sponsors to capture a larger market share? Should regulators demand proof that a therapy works in advanced stages? In this Viewpoint, we consider the implications for novel agents being developed in early disease states.

Sacubitril in Heart Failure

Evaluating novel drugs in advanced disease settings has long been a model of drug discovery for patients with heart failure (eTable in the Supplement). During the last 2 decades, drug development programs for angiotensin-converting enzyme inhibitors, β-blockers, and mineralocorticoid receptor antagonists initially evaluated patients with poor functional status, eg, patients with New York Heart Association (NYHA) class III and IV heart failure symptoms.

Now consider the development of a novel medication for heart failure. In a recently completed phase 3 trial, sacubitril, a neprylisin inhibitor, improved overall survival when given in combination with valsartan compared with a control group receiving enalapril.[1] The trial was stopped early because a prespecified boundary for benefit of the study drug had been crossed during interim analyses.[1] However, stopping criteria appeared to have been driven by benefits seen primarily in patients with NYHA class II heart failure, because less than 1% of patients with NYHA class IV symptoms and less than 25% with class III symptoms were enrolled at the time of study termination.[1] In fact, interaction analysis revealed significant differences in the primary end point among patients with NYHA class III and IV symptoms, suggesting that these patients may not benefit similarly.[1]

Pertuzumab in Breast Cancer

The contrasting development of trastuzumab emtrancine (TDM-1) and pertuzumab illustrate the consequences of a drug manufacturer's decision of where to begin drug development. Both antibodies, developed contemporaneously by Roche/Genentech, target the *ERBB2* (formerly *HER2*) receptor. TDM-1 was originally tested as second-line therapy,[2] whereas pertuzumab was tested as first-line therapy for metastatic, *ERBB2*-positive breast cancer.[3] Pivotal trials leading to approval enrolled 991 patients (TDM-1) and 808 patients (pertuzumab). Because TDM-1 was developed in more advanced disease, the trial showed an overall survival benefit with a median follow-up of 19 months. Forty-five months elapsed from the date of first enrollment to the publication of results.

In contrast, pertuzumab was developed in an earlier disease setting. An overall survival advantage was not demonstrated until median follow-up of 30 months, and the trial publication reporting this outcome appeared 63 months after the first patient was enrolled. Although the pertuzumab study was started a year before the TDM-1 study, the report of survival results appeared only several months afterward. Progression-free survival benefits also occurred more quickly with TDM-1. It is unlikely that biological rationale justifies the decision to evaluate the drugs in different populations, because pertuzumab appears active even when used as second-line therapy.[4]

Maximizing Drug Benefit and a Biological Rationale for Trial Design

In general, patients with advanced disease states have the highest risk for poor outcomes such as death or relapse, despite receiving available therapies. This high-risk population is more likely to experience events of interest, diminishing the effects of competing risks. For example, in patients with NYHA class IV heart failure, cardiovascular causes are a major cause of death, whereas other competing causes of death play a larger role in milder disease. As such, focusing on high-risk patients may increase study power, allowing protocols to be completed on a faster timeline. Shortening the interval between drug discovery and use in clinical practice is a clear benefit and a stated goal of drug development. Traditional drug programs also follow a biologically consistent approach to validating drug targets. In heart failure, enhanced neurohormonal activation in patients with NYHA class III and IV heart failure makes this patient subset an attractive target for initial evaluation of novel therapies.

Maintaining Acceptable Toxicity Profiles

Broad inclusion criteria, like those in the neprilysin inhibitor trial, theoretically should capture a wide spectrum of patient profiles. However, despite best intentions, certain groups of patients may be underrepresented. At the site level, "sicker" patients may be more challenging to enroll, because they present more frequently with comorbid diseases. It is unknown whether these complex patients with advanced illness would experience the same adverse effect as those with milder disease. In a prior trial of neprilysin inhibitors in heart failure, lower systolic blood pressure, which is typically more common in patients with NYHA class III and IV symptoms, was a major determinant of frequency of adverse effects, including hypotension and renal failure.[5] Thus, although these large trials support drug safety in a general population of patients with heart failure, they fail to inform safety in those most vulnerable to adverse effects and attendant risks.

A Cost-Conscious Approach to Patient Prioritization

From a pragmatic standpoint, drug development programs conducted in broad populations poorly prioritize which patients should start therapy first. If provided regardless of risk, expensive new first-in-class agents may overwhelm health care budgets. In hepatitis C management, novel drug therapies broadly indicated for most patients with chronic hepatitis C, such as sofosbuvir, cost approximately $1000 per pill, presenting major cost challenges to drug implementation and distribution. In an effort to balance access and affordability, recent hepatitis C clinical practice guidelines have encouraged use of these agents primarily in the sickest subgroup of patients.[6] In the current financial environment, emerging clinical trials should consider selecting the groups at highest risk to guide an economically viable and practical approach to drug utilization.

Optimizing Future Clinical Trials

Ultimately, novel drugs entering the market must be tested in settings that closely reflect the general real-world population and important high-risk subgroups. Recent changes in Food and Drug Administration protocol[7] expect drug developers to augment inclusion of sicker patients with multiple comorbidities. If instead current trends continue, measures must be taken to ensure that trials inform the safety and efficacy in the sickest patients. In addition to an overall power analysis, recruitment targets must be established for important high-risk subgroups. Similarly, prior to early termination of a trial secondary to drug benefit, enough patients with advanced disease should have been recruited and exposed to the study drug. Robust programs are required to provide adequate safety data to justify exposure of patients with early-stage disease to the study drug.

Conclusions

Randomized clinical trials are the major test of novel therapeutics. Study drugs have traditionally been evaluated in the sickest patients and then developed stepwise in a more general population. Recent trends in study design, target populations, and drug labeling have deviated from this approach. Increasing interest in development of broad markets for first-in-class agents have raised new questions and concerns regarding the clinical applicability of these drugs. It is time to return to a patient-centric approach to drug development and offer novel, breakthrough therapies first to the patients who need them most.

ARTICLE INFORMATION

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