Response to Bell: Industry Perspective

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D avid S.H. Bell’s letter in the March issue of Diabetes Care (1) raises important and timely concerns about the ethics of conducting placebo-controlled trials for regulatory approval of compounds for the treatment of type 2 diabetes. Standard pivotal trial design involves withdrawal of patients from current therapy and comparison of the investigational drug with an inactive placebo rather than with current therapy (active placebo) to evaluate efficacy. Bell argues that the use of inactive placebo for 6-month regulatory trials is unethical because of the inherent, potentially detrimental exposure to exaggerated hyperglycemia in placebo-treated patients.

Two competing concerns are at play. The valid concern over the ethics of this traditional, placebo-controlled trial approach is counterbalanced by the equally worrisome potential of missing the actual therapeutic potential of a drug candidate by comparing it with active placebo rather than placebo. At least two general trial designs come to mind for active placebo: The investigational drug could either be added to or substituted for current therapy. In the former situation, the investigational drug would be deemed effective only if effects beyond those achieved with current therapy alone were observed. However, even if no added benefit were observed, the compound might still be effective as monotherapy. For example, there may be no beneficial effect on glycemic end points of adding a meglitinide to a sulfonylurea, yet the former may be efficacious as monotherapy. Moreover, the addition of an agent creates the possibility for negative drug-drug interactions not observed with monotherapy.

To evaluate effectiveness as monotherapy, an investigational drug could be substituted for current therapy, but this approach has its own complexities. Is the candidate immediately substituted for current therapy, is there a washout period (during which glycemic control will deteriorate), or is the candidate drug first added (with the complexity discussed above) and then, after a period of time, the current therapy removed? In the case where the candidate is substituted for current therapy, equivalent efficacy rather than superiority should be the requirement. In either alternative scenario, regulatory standards will need to be firmly established in which equivalency with respect to efficacy or failure to demonstrate statistical differences between the current therapy and the investigational drug would be accepted as evidence of efficacy. This would be similar to the approach currently used for antibiotic and antihypertensive drugs.

In the management of type 2 diabetes, the true value of a novel drug may not necessarily be reflected in a change in HbA1c, alone but in a combination of effects that on balance provide an overall improvement in diabetes control. For example, insulin lispro may not be any more effective than regular insulin at reducing HbA1c but it may do so with a lesser incidence of hypoglycemia. Conversely, a drug may lower HbA1c but do so at the expense of diabetes covariates, such as excessive hypoglycemia, weight gain, and deterioration of lipid profiles. It is perhaps timely to consider the use of a “diabetes control index” (DCI) as a unique end point that reflects HbA1c reduction along with other important covariates to better assess and compare the effect of different therapies on overall diabetes control. Drugs such as sulfonylureas and metformin may have equivalent potential to reduce HbA1c, but the latter may exhibit a higher DCI value by virtue of its lesser potential for weight gain and hypoglycemia and its beneficial effects on lipids. Conversely, although exogenous insulin is the undisputed champion at lowering HbA1c, its effects on hypoglycemia and weight gain may limit its DCI. More discussion along these lines needs to occur within a consortium of academic, pharmaceutical, and regulatory communities.

Acknowledging the ethical value of avoiding placebo-controlled studies in type 2 diabetes, what are the potential pitfalls and difficulties of this approach? A change to active-placebo comparisons likely would not result in inappropriate approval of drugs but rather may result in a process that fails to recognize a beneficial drug or understates its value. If an investigational drug has a novel mode of action yet fails to achieve equivalency compared with current therapy, this may not signify that it has no added therapeutic value but may signify that the investigational drug needs to be combined with another drug to optimize its potential. This could create difficulties in the design of pivotal trials. It is unlikely that one could a priori know the right combination of drugs, and performing all permutations of possible combinations is unrealistic. Additionally, head-to-head trials of established and investigational drugs within the same class would create the potential for unjustified marketing claims with respect to efficacy and side effects (perhaps because the dose was suboptimal). These are only some of the potential pitfalls of doing away with placebo-controlled studies.

From a regulatory perspective, claims currently established for approved drugs may be difficult or impossible to reconcile with claims for new drugs approved through a revamped approval process. This could necessitate retrospective, burdensome, and costly rectifying regulatory measures.

In brief, although the question regarding the ethics of the current process for approval of new drugs for the treatment of type 2 diabetes is important, valid, and timely, there are no easy one-size-fits-all solutions. Shortening the du-

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Abbreviations: DCI, diabetes control index.
ration of trials may reduce the glycemic insult, but does it truly address the ethical issue? Is 3 months more ethical than 6 months of poorly controlled diabetes? Drug approval on a case-by-case basis within an established framework that does not mandate the exclusion of placebo-controlled trials may be a prudent approach. A nonactive placebo–controlled trial may be appropriate in patients with early type 2 diabetes whose HbA1c is <7.5%, whereas a similar trial in patients on oral agents with HbA1c of 11% is clearly not. Regardless of the approach, patients with the latter characteristics should not be allowed to have further worsening of their diabetes during a trial. In all cases, safety and ethical considerations served by the regulatory process should take priority.

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References