Learning About New Therapies: Phase 3 Clinical Studies—And Beyond

All new therapeutic agents, and updated versions of older ones, must be submitted for review by regulatory agencies. While this process is complex, its goals as stated by the U.S. Food and Drug Administration (FDA) are straightforward. The main aim is to determine "whether the drug is safe and effective in its proposed use(s), and whether the benefits of the drug outweigh the risks" (1). Additional concerns are the information provided in the package insert and assurance of quality and consistency of the manufacturing process. Phase 3 trials, which test the safety and efficacy of candidate drugs in moderately large cohorts of human subjects, lie at the center of the process. Properly done studies of this kind help determine whether a new product should be approved for clinical use and also provide some guidance regarding how best to use it in daily practice. However, phase 3 studies—as essential as they are to the regulatory process—have important limitations, which are the topic of this commentary.

Appearing in this issue of *Diabetes Care* is a good example of such a study. Gough et al. (2) report a comparison of a 200 units/mL (U200) formulation of degludec, a long-acting insulin analog, with U100 insulin glargine (Lantus). The study was well designed and well conducted. The investigators enrolled 457 participants with type 2 diabetes no longer well controlled with oral therapies alone (mean A1C ~8.2%), and randomized them to begin and titrate dosage of once-daily U200 degludec or U100 glargine using a typical treat-to-target scheme for 26 weeks. Efficacy of the new agent was assessed by the reduction of A1C from baseline, and its safety by, among other measurements, the frequency of hypoglycemic events. As in many studies, the main end point was noninferiority of glycemic improvement versus a well-known active comparator. The results were clear. Reduction of A1C and most other measures of glycemic control were equivalently improved with the two insulin formulations, and no significant difference in hypoglycemia (assessed either as percentage of participants affected or as total numbers of events) was evident. No other unwanted effects were detected. For navigating the regulatory process the reported results were helpful and positive: both safety and efficacy were established. These findings provide support for eventual approval of U200 degludec for clinical use. But from the standpoint of clinical practice, this study has important limitations.

Phase 3 studies conducted to examine efficacy of diabetes agents rely, by design, on short-term assessment of physiological end points, such as A1C levels, which are considered predictive of improved medical outcomes when followed over time. In addition, phase 3 studies are designed to observe safety in relatively modest numbers of individuals over just a 6- to 12-month interval. Hence, both long-term benefit and long-term risk are only partly assessed. In the case of degludec, including both U100 and U200 formulations, the FDA has been concerned with the problem of evaluating long-term benefits versus risks on the basis of phase 3 data and called for a longer-term study before approval (3). Judging long-term risks versus benefits is indeed a serious issue, but it is beyond the scope of this commentary. However, there is another difficulty, exemplified by but not limited to degludec: current preapproval clinical studies often fail to examine sufficiently the rationale for a new product and to define its best uses. As a result, they provide very little guidance on how, once approved for use, a new product actually should be used.

Turning to the specific example posed by the publication by Gough et al., consider the quality of currently available insulin products. These have been greatly improved over the crude, early preparations of bovine and porcine pancreatic extracts. Modern insulin formulations are less allergenic, well standardized, available in forms with varying duration of action, and extensively tested in clinical studies. Still, ways to improve them have been proposed. The rapid-acting analogs (aspart, glulisine, lispro) may not act as rapidly as desired in some settings, and versions with quicker onset are under study. Longer-acting analogs (detemir, glargine) may not have time-activity profiles that are as long, flat, and stable as needed for some patients. In addition, with increasing prevalence of obesity and insulin resistance, the high daily dosage of basal insulin required cannot be delivered by a single injection of a U100 formulation for a significant proportion of patients. Therefore, as mentioned in the report by Gough et al., U200 degludec, a more concentrated formulation of this quite long-acting insulin molecule (4), could have specific advantages. Differences between U200 degludec and U100 glargine might be demonstrated in at least two clinically relevant ways.

The first potential distinction lies in adherence to insulin dosing. If more than a single daily injection of basal insulin is needed, adherence may be inconsistent and hyperglycemia may persist for some people prescribed U100 insulin (5). This is the main rationale underlying increasing use of U500 regular human insulin (6–8). Use of U200 degludec might lead to improved adherence and better glycemic control by replacing two injections of any U100 insulin given by syringe (up to 100 units per injection) or by pen (up to 80 units) with a single daily injection of up to 160 units. However, the current study does not directly address this hypothesis. An adequately powered study of people taking high dosage of insulin is needed.

Another potential advantage of U200 degludec is a lower risk of hypoglycemia. Although the current study did not show less hypoglycemia than with U100 glargine, further studies of certain subpopulations might do so. Both the extended duration of action of the degludec molecule (4) and a flatter time-activity profile associated with a higher concentration of injected insulin (9) could lead to a very stable, flat profile of this formulation. Modest reductions of hypoglycemia, especially at night, have been reported in some (10,11) but not all (12) earlier studies comparing U100 degludec with U100 glargine. There is reason to believe that an advantage of degludec (or any especially long-acting insulin) over glargine might be most evident in people with lower insulin

requirements. In an analysis of data pooled from more than 2,200 individuals with type 2 diabetes who were treated with systematically titrated glargine, younger age, lower BMI, and lower basal insulin dose requirement all were independently associated with greater risk of confirmed hypoglycemia (13). Thus, younger, less obese individuals needing lower than average dosage of basal insulin might be another subgroup of interest for study of new basal insulin formulations such as U200 degludec.

Also, a strong case can be made that methods for examining hypoglycemia in clinical studies should be reevaluated. Many specific issues can be identified. Hypoglycemia is epidemiologically associated with increased risk of adverse medical outcomes of various kinds (14–16), but the extent to which this association is causal rather than due to shared physiological or behavioral factors remains unknown. In many studies of therapies for diabetes, hypoglycemia has been regarded as an adverse event identified only when reported by a participant, and thus many events are unrecognized. Recent studies often include hypoglycemia as an "event of interest," but there is lack of agreement on how events should be defined, ascertained, and analyzed. Various levels of plasma-referenced blood glucose have been used as thresholds for reporting, ranging from 4 mmol/L (72 mg/dL) to 2.8 mmol/L (50 mg/dL), and variously reported as associated or not associated with symptoms when measured. The relative importance of nocturnal versus daytime or total daily events remains uncertain. Nocturnal events are often emphasized in publications, although they are less common than daytime events, and the time interval that best defines "nocturnal" is not well defined. Finally, both the schedule prescribed for glucose testing in study protocols and the means of testing vary greatly. All these factors limit comparisons of hypoglycemia in different studies and prevent meaningful meta-analyses. A recent statement by a working group of the American Diabetes Association and The Endocrine Society directly addresses some of these questions, but more work toward improved definitions and methods is needed (17). Lack of consensus regarding hypoglycemia greatly complicates evaluating how methods of treating diabetes, including insulin, can be improved.

The several issues posed by consideration of the well-performed study by Gough et al. can be briefly summarized. U200 degludec appears as effective and safe as U100 glargine in the heterogeneous population in this phase 3 study. However, demonstrating equivalence of short-term efficacy and safety with a widely used comparator provides little insight into whether we need this or any other longer-acting or more concentrated insulin formulation in clinical practice. Evidence of better treatment adherence by individuals needing more basal insulin than can be administered in a single injection of U100 insulin would be of interest, but this is still lacking. Similarly, lower risk of hypoglycemia in a defined subpopulation at high risk with glargine or detemir—perhaps less obese, more insulin-sensitive individuals—would support use of longer-acting insulins such as degludec, but we have limited direct evidence for this. For the majority of insulin-requiring patients, whether we need new insulin formulations more than we need to improve behavioral tactics in use of existing insulin formulations remains an unanswered question. Finally, these observations may be generally applicable to studies of other new products. Well-designed and conducted phase 3 studies are essential for regulatory review, but they are not usually sufficient to guide clinicians in the use of new therapies. More effort to identify subgroups with the most favorable benefit-to-risk profiles, both before and after approval for clinical use, would greatly assist clinical providers.

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