Present and Future of Insulin Therapy: Research Rationale for New Insulins

Current insulin analogues represent an important advance over human insulins, but clinically important limitations of these agents underlie ongoing efforts to develop new insulins. Differences in time-action characteristics present considerable clinical challenges with all currently available insulins. Neutral protamine Hagedorn (NPH) insulin is notable for its unpredictable uptake; the same dose in the same patient on 2 different days may peak and wash out at rates varying by hours. Glargine and detemir have more predictable time-action profiles and longer half-lives than NPH insulin. Often, this means that glargine and detemir can be dosed once daily, but some patients may need twice-daily dosing, which is less convenient and increases the number of daily injections.

Differences among rapid-acting insulin analogues also have important clinical consequences. In a 39-week randomized crossover study of aspart, glulisine, and lispro administered by continuous subcutaneous insulin infusion (CSII) in patients with type 1 diabetes mellitus (T1DM), the rate of hyperketonemia was higher with glulisine than with aspart (P = .01) or lispro (P = .02). No statistically significant differences in hypoglycemia or glycated hemoglobin (A1C) were observed.

Some studies demonstrated that improvements in glycemic control can be achieved with stepwise insulin intensification in type 2 diabetes mellitus (T2DM). A 36-week trial of the stepwise addition of aspart to basal detemir compared dosing with and without carbohydrate counting in patients who were unable to attain A1C < 7% after a 12-week run-in period on basal detemir. Patients who did not count carbohydrates adjusted their prandial insulin doses based on their estimate of the size of the meal. By the end of the study, approximately 77% of patients in both groups used basal-bolus therapy (BBT). Both groups experienced further reductions in A1C (no counting group: baseline A1C = 8.7%, ΔA1C = −1.1%; counting group: baseline A1C = 8.9%, ΔA1C = −1.3%). The average A1C reductions and hypoglycemia event rates did not differ between groups, but patients who counted carbohydrates gained less weight (2.0 kg) than patients who did not (2.7 kg; Figure 1). A 24-week study of patients with T2DM compared glargine and glulisine 3 times daily (TID) with and without carbohydrate counting in patients with baseline A1C = 8.16% (Figure 2). Patients who did not count carbohydrates split their total daily prandial dose 50%/33%/17% according to the size of their meals. This study found no statistically significant differences between treatment arms for glycemia, hypoglycemia, or weight gain, but total daily insulin doses were significantly lower with carbohydrate counting (P = .0002). Taken together, these studies suggest that stepwise addition of prandial insulin to a basal insulin protocol in T2DM can be effective and safe, that some patients will attain improvements in glycemic control with additional doses of prandial insulin, and that carbohydrate counting further increases efficacy and safety, although good results can be attained without carbohydrate counting.
Comparing 2 Methods for Adding Prandial Insulin in T2DM Over 36 Weeks—STEP-wise Trial

Figure 1.

Adjust-to-Target Trial: GLAR + GLU BBT in T2DM With Prandial Doses Adjusted According to Simplified Algorithm or Carbohydrate Counting

Figure 2.
Nevertheless, stepwise addition of prandial insulin does not bring a majority of patients to intensive targets in most clinical trials. Results from other randomized controlled trials highlight limitations in existing insulins and regimens. In a meta-analysis of 92 treatment arms from 53 randomized controlled trials targeting A1C < 7%, which included more than 32,000 patients, 4 common T2DM insulin regimens were evaluated: basal, premixed, prandial, and basal-bolus (Figure 3). The proportion of patients attaining glycemic targets ranging from 6.5% to 8.0% was measured. The results indicate that, on average, patients using BBT were more likely to attain a given glycemic target than patients using the other insulin regimens. However, fewer than half of patients participating in these trials were able to attain A1C < 7% on any regimen. Furthermore, one of the largest clinical trials of insulin therapy found that, on average, patients with baseline A1C of 8.6%-8.7% who did not attain A1C ≤ 7% after 6 months of twice-daily premixed insulin or once-daily basal insulin demonstrated no further improvement in A1C even if switched to BBT. Thus, some studies show that patients with T2DM unable to attain A1C ≤ 7% on their initial insulin regimens are unlikely to be able to attain A1C ≤ 7% with intensification of insulin therapy.

Figure 3.
Insulin demonstrating more consistent pharmacodynamics would represent a clinically important advance over current insulins. Clinical trials of insulin intensification strategies in T2DM have yielded conflicting results, with some trials finding further improvement of glycemic control with stepwise insulin intensification but others demonstrating no change; these findings suggest that improved prandial insulins are needed. In addition, it is desirable that basal insulins have a flat, peakless time-action profile and long duration of action to more closely mimic physiological basal insulin secretion and eliminate the need for twice-daily injection in some patients. Accordingly, several insulins that seek to improve upon current analogues are in development.

References
