Optimal Dosing and Titration of U-500R Improve Glycemic Control

Written by Rita Buckley

Transitioning from U-100 to recombinant human regular U-500 insulin (U-500R) can improve glycemic control and reduce the number of daily injections in patients with inadequately controlled type 2 diabetes mellitus (T2DM). To study initiation and titration of U-500R, Robert C. Hood, MD, Endocrine Clinic of Southeast Texas, Beaumont, Texas, USA, conducted a randomized, controlled clinical trial, the Study of Human Regular U-500 Insulin in Adult Participants With Type 2 Diabetes [NCT01774968], a 24-week, open-label, parallel-arm trial in 325 patients taking 201 to 600 units per day of U-100 insulin therapy, with or without oral anti-hyperglycemic agents.

Patient demographics (means ± standard deviations) included the following: age, 55.4 ± 9.8 years; duration of diabetes, 15.2 ± 7.4 years; body mass index, 41.9 ± 7.5 kg/m^2; HbA_{1c}, 8.7% ± 1.0%; and U-100 insulin dose, 287.5 ± 80.5 units administered in a median of 5 injections per day (range, 2 to 10).

Patients were randomized to either thrice-daily (TID; n = 162) or twice-daily (BID; n = 163) dosing of U-500R after a 4-week lead-in period. The transition formula from U-100 insulins to U-500R reduced the total daily dose (TDD) by 20% for those with baseline $HbA_{1c} \leq 8.0\%$ or a mean pre-meal self-monitored plasma glucose (SMPG) < 183 mg/dL; otherwise, a 1:1 transition was used. Initial U-500R proportions were 40:30:30 (breakfast:lunch:dinner) for TID and 60:40 (breakfast:dinner) for BID. Both algorithms adjusted the TDD at each visit up to +30% (–20% for hypoglycemia) to achieve SMPG of 71 to 130 mg/dL.

After 24 weeks, both treatments demonstrated significant and comparable reductions in HbA_{1c} from baseline (TID, –1.12%, HbA_{1c} 7.53% ± 1.1%; BID, –1.22%, HbA_{1c} 7.41% ± 1.0%; $P < .001$ for both). The difference (BID vs TID) was –0.10% ($P = .37$; 95% CI, –0.33% to 0.12%), demonstrating clinical equivalence between treatments at the noninferiority margin of 0.4%.

Proportions of patients reaching HbA_{1c} target values were similar between the 2 regimens.

Comparable increases in U-500R TDDs were observed for the TID and BID arms (242.7 to 343.1 units and 249.0 to 335.0 units, respectively). Severe hypoglycemia was uncommon and occurred with similar incidence: 3 patients (1.9%) TID and 6 patients (3.7%) BID. The incidence and rate of documented symptomatic hypoglycemia (≤ 70 mg/dL) were lower for TID compared with BID ($P = .003$ and $P = .02$, respectively). Weight gain was similar between the regimens (5.4 ± 0.4 kg TID and 4.9 ± 0.4 kg BID).

Initiation and titration of U-500R using either algorithm (BID or TID) improved glycemic control effectively and safely, with fewer injections in patients with T2DM than in those on high-dose/high-volume U-100 insulin. These results provide clinicians with a practical approach for using U-500R in severely insulin-resistant patients with suboptimally controlled T2DM.

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The PAOLA Study: Positive Benefit-Risk Profile for Pasireotide LAR for Acromegaly

Written by Kathy Boltz, PhD

Pasireotide long-acting release (LAR) showed a positive relationship between exposure and the efficacy end point of growth hormone (GH) and insulinlike growth factor (IGF-1) in patients with acromegaly in the phase 3 PAOLA study [NCT01137682]. In this pharmacokinetic (PK) and pharmacodynamic (PD) analysis, researcher Guoxiang Shen, PhD, Novartis Pharmaceuticals, East Hanover, New Jersey, USA, and colleagues found that treatment with pasireotide LAR has a positive risk-benefit profile for patients whose acromegaly is inadequately controlled by first-generation somatostatin analogs (SSAs).