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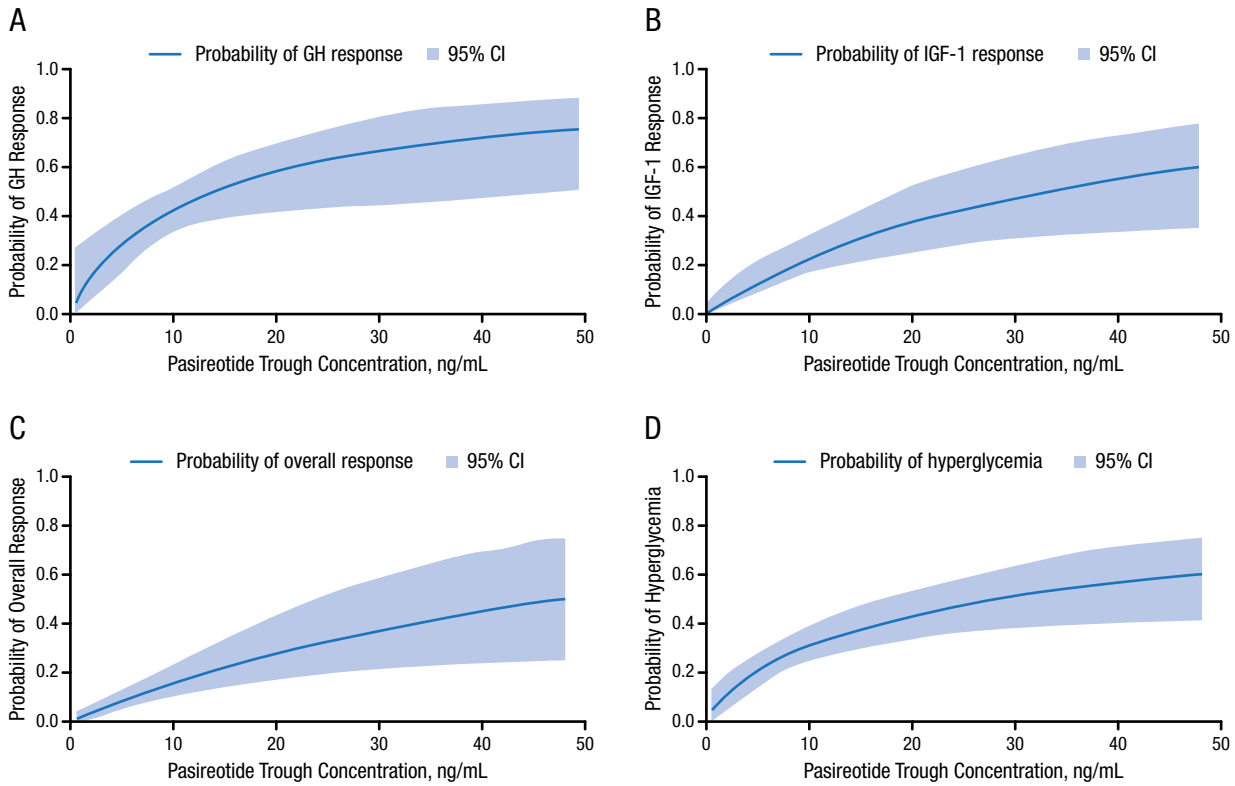
The PAOLA Study: Positive Benefit-Risk Profile for Pasireotide LAR for Acromegaly

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).

Figure 1. Pasireotide Trough Concentration Increases



GH, growth hormone; IGF-1, insulinlike growth factor.

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Pasireotide, a multireceptor-targeted SSA, was recently approved for use in patients with acromegaly. Earlier results from the PAOLA study found that pasireotide was able to produce biochemical disease control in patients who were not responsive to other agents, with an efficacy of 15.4% with pasireotide LAR 40 mg and 20.0% at 60 mg vs 0% with octreotide LAR 30 mg or lanreotide Autogel 120 mg [Gadelha MR et al. *Lancet Diabetes Endocrinol.* 2014].

Patients in the 2 treatment arms received double-blind pasireotide LAR 40 or 60 mg every 28 days (n = 65 in each group). Patients in the open-label, active-control treatment arm (n = 68) received either octreotide LAR 30 mg or lanreotide Autogel 120 mg every 28 days.

Within the dose range of pasireotide LAR 40 to 60 mg that was evaluated, the dose-exposure relationship of pasireotide LAR was approximately dose proportional. The concentration of pasireotide reached steady state after 3 consecutive monthly injections. Interpatient PK variability was moderate to high.

The PK covariate of sex suggested that female patients would have approximately 51% higher steady-state trough concentration of pasireotide than male patients with the same age and equal baseline bilirubin. However, since efficacy and safety profiles were similar between female and male patients, this PK difference was not considered clinically meaningful.

Levels of both GH and IGF-1 had a clear exposure-response relationship to pasireotide LAR concentration. The estimated maximum suppression of GH was 83.0%, which was relatively higher than the estimated maximum suppression of IGF-1 of 67.1%.

Increasing pasireotide trough concentration by 1.5-fold corresponds to dose increases from 40 to 60 mg. This 1.5-fold increase resulted in increased odds of GH responses by 44%, of IGF-1 responses by 51%, and of GH + IGF-1 responses by 54% (Figure 1). Also, a 1.5-fold increase in pasireotide concentration increased the odds of having hyperglycemia by 36%.

The change from baseline for both QTcF and QTcB had a relatively flat relationship with pasireotide concentrations based on data up to week 24, suggesting no clinically significant effect. Also, pasireotide exposure up to week

24 had no clinically significant effect on liver function tests, which included aspartate aminotransferase, alanine aminotransferase, total bilirubin, γ-glutamyltransferase, alkaline phosphatase, and albumin.

This PK/PD analysis found an approximately dose-proportional relationship for pasireotide LAR dose-exposure over the 40- to 60-mg range that was evaluated. Efficacy end points of GH and IGF-1 suppression had a positive relationship with pasireotide exposure, with greater response rates at the higher dose of 60 mg.

Biochemical Control of Acromegaly Continued in PAOLA Trial Extension

Written by Kathy Boltz, PhD

Monica R. Gadelha, MD, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, presented a preliminary analysis of the phase 3 PAOLA study [NCT01137682] that showed that biochemical control continued through extension week 28. The intent within this extension phase was to assess pasireotide long-acting release (LAR) in patients with acromegaly over an extended period of time.

Dr Gadelha and colleagues examined data through extension week 28 of the extension phase of the 24-week, randomized, phase 3 PAOLA study, which enrolled patients with inadequately controlled acromegaly [Gadelha MR et al. *Lancet Diabetes Endocrinol*. 2014]. The 24-week, phase 3 study had found that biochemical control, defined as growth hormone < 2.5 μg/L and normalized insulinlike growth factor 1 (IGF-1), was achieved by significantly more patients who received pasireotide LAR 40 mg (15%; n = 10/65; $P = .0006$) or 60 mg (20%; n = 13/65; $P < .0001$) than those who received octreotide LAR or lanreotide Autogel (0%; n = 0/68). The most common adverse events in the phase 3 trial were hyperglycemia, diabetes, and diarrhea. Serious adverse events were reported in 6 patients receiving pasireotide 40 mg, 2 receiving pasireotide 60 mg, and 3 in the active control group.

The patients who were in the control group continued to receive the same doses in the extension phase from week 24 through a 4-week bridging phase. Next, patients from the control group who were not biochemically controlled received open-label pasireotide LAR 40 mg, and their dose was increased to 60 mg if their disease became uncontrolled. These were the crossover group.

The patients who were not in the control group remained on pasireotide LAR at 40 or 60 mg during the 4-week bridging phase. If they had not achieved biochemical control, they received open-label pasireotide LAR 60 mg beginning at extension week 4. These patients, the treatment groups, received a total of 52 weeks of treatment with pasireotide LAR for this analysis.

At extension week 28, biochemical control was achieved by 18% of the patients in the pasireotide LAR 40-mg group (n = 9/49; 95% CI, 9 to 32) and by 33% in the pasireotide LAR 60-mg group (n = 15/45; 95% CI, 20 to 49). Among the crossover group, 20% achieved biochemical control (n = 10/50; 95% CI, 10 to 34).

All 3 groups had a drop in IGF-1 levels during the extension time. At week 28, normal IGF-1 was obtained in 33% of the patients receiving pasireotide LAR 40 mg, in 38% receiving pasireotide LAR 60 mg, and in 24% of the crossover group. Growth hormone levels of < 2.5 μg/L were achieved by 39% of the patients receiving pasireotide LAR 40 mg, 47% of those receiving pasireotide LAR 60 mg, and 42% of the crossover group.

The safety profile was very similar to that of the core study. This longer-term treatment identified no new treatment-emergent safety signals.

Pasireotide may be a viable, long-term treatment option for patients with acromegaly that is inadequately controlled with first-generation somatostatin analogues.

Early Initiation of Low-Dose Levothyroxine After Radioactive Iodine Appears Safe

Written by Kathy Boltz, PhD

Spyridoula Maraka, MD, Mayo Clinic, Rochester, Minnesota, USA, reported on results from an interim safety analysis, which found that initiating low-dose levothyroxine at 4 weeks after patients received radioactive iodine (RAI) for Graves' disease (GD) appears safe and shows no increased incidence of hyperthyroidism.

Most patients with GD are treated with RAI and reevaluated 2 to 3 months later; the majority are hypothyroid by that time, and some have related troublesome symptoms and possible development or worsening of Graves' orbitopathy.

This randomized double-blind controlled trial [NCT01950260] was designed to determine whether early treatment with levothyroxine after RAI therapy for GD would prevent overt hypothyroidism. This interim analysis for safety was performed after the first 17 patients were enrolled, with 11 patients receiving levothyroxine, 25 μg QD, and 6 receiving placebo in a single tablet at 4 weeks after RAI therapy. At 6 weeks after RAI therapy, the levothyroxine dose was increased to 50 μg QD and the placebo to 2 tablets per day. At 8 weeks after RAI therapy, the