Efficacy and Safety of Ultra-Rapid Lispro Versus Lispro in Patients with Type 1 and 2 Diabetes: Indian Subpopulation Analyses of the PRONTO-T1D and PRONTO-T2D Trials

Sir,

Although advances have been made in the treatment of both type 1 and 2 diabetes, many patients still do not achieve sufficient glycaemic control.[1] The reasons behind this are multifactorial, but post-prandial hyperglycaemia is likely an important contributing factor.[1-4] Insulin formulations with a more rapid onset of action, along with appropriate timing of insulin use and post-prandial glucose (PPG) monitoring,[2,4] may offer potential options to improve PPG levels. A novel formulation of insulin lispro, ultra-rapid lispro (URLi), was studied in two randomized, double-blind, multicentre, international phase 3 trials: PRONTO-T1D, in patients with type 1 diabetes (T1D), and PRONTO-T2D, in patients with type 2 diabetes (T2D).[5,6] URLi was shown to be superior to insulin lispro for 1- and 2-h PPG control during mixed-meal tolerance tests when dosed at mealtime, despite similar haemoglobin A1c (HbA1c) and hypoglycaemic events after 26 weeks of treatment using a multiple daily injection regimen in combination with basal insulin.

Basal-bolus insulin is not commonly used by clinicians managing patients with T2D in India, and many persist with various combinations of premixed insulin or basal plus one or two doses of bolus insulin in addition to oral antihyperglycaemic medication (OAM).[7,8] As data for the use of basal-bolus therapy in India are lacking, we performed post-hoc analyses of the efficacy and safety of URLi versus lispro in patients with T1D and T2D in India, based on the Indian subpopulations from the PRONTO-T1D and PRONTO-T2D trials. As both trials recruited relatively small numbers of patients from India, a report of data from these two subpopulations is presented.

Of the 1222 patients randomized in PRONTO-T1D[5] and the 673 patients from PRONTO-T2D,[6] 52 and 100, respectively, were recruited in India. In the Indian subpopulation of PRONTO-T1D, 20 patients with T1D were randomized to lispro, 18 to mealtime URLi and 14 to post-meal URLi. In PRONTO-T2D, 49 patients with T2D in India were randomized to lispro and 51 patients to URLi. In PRONTO-T1D, the mean age of the Indian population was 27.77 years, and 60% were male; the mean duration of diabetes was 11.04 years, and baseline HbA1c was 7.55%. The mean age of the Indian population in PRONTO-T2D was 56.2 years, and 60% were male; the mean duration of diabetes was 14.21 years, and baseline HbA1c was 7.57%. For each of the trials, characteristics were generally similar between the treatment groups; in PRONTO-T1D, the mean body mass index was statistically significantly ($p = 0.033$) lower in the post-meal URLi group (20.4 kg/m^2) than in the mealtime URLi group (23.2 kg/m^2), and—although baseline HbA1c did not differ between groups—HbA1c at study entry was lower in the post-meal URLi group than in the mealtime URLi ($p = 0.008$) and mealtime lispro ($p = 0.013$) groups (7.99% vs 8.61% and 8.56%, respectively). In PRONTO-T2D, the duration of diabetes was shorter in the lispro group than in the URLi group (12.45 vs 15.89 years; $P = 0.026$).

In PRONTO-T1D, baseline HbA1c was 7.65%, 7.44% and 7.55% in the lispro, mealtime URLi and post-meal URLi groups, respectively. HbA1c levels generally improved in all treatment groups during the lead-in period and remained stable up to week 26 [Figure 1a]. At week 26, the least-squares mean (LSM) change from baseline in HbA1c in the lispro, mealtime URLi and post-meal URLi groups were − 0.33%, − 0.42% and − 0.20%, respectively. In the mealtime URLi group, within-group statistically significant decreases in LSM HbA1c from baseline were observed from week 4 and continued until week 26. In the mealtime lispro group, within-group statistically significant decreases in LSM HbA1c were observed at weeks 4, 12 and 26. No within-group statistically significant decreases in LSM HbA1c were observed in the post-meal URLi group. There were no statistically significant differences between the groups at any time point. In PRONTO-T2D, baseline HbA1c was 7.50% and 7.63% in the lispro and URLi groups, respectively. HbA1c levels generally improved in both treatment groups during the lead-in and titration periods; they remained stable up to week 26 in the lispro group and increased marginally (but remained below baseline levels) in the URLi group from week 12 to 26 [Figure 1b]. At week 26, the LSM change from baseline in HbA1c in the lispro and URLi groups was − 0.42% and − 0.24%, respectively. In the URLi group, within-group statistically significant decreases in LSM HbA1c from baseline were observed from week 4 and continued until week 12. In the lispro group, within-group statistically significant decreases in LSM HbA1c were observed from week 4 to week 26. There were no statistically significant differences between the two groups at any time point.

At week 26, PPG excursions in PRONTO-T1D increased after meal initiation and decreased from 2 h after meal initiation in all treatment groups [Figure 2a]. PPG excursions were numerically lower in the two URLi groups, versus the lispro group, but there were no statistically significant differences in PPG excursions between treatment groups. In PRONTO-T2D, PPG excursions increased after meal initiation and decreased from 2 h after meal initiation in both treatment groups [Figure 2b]. LSM PPG excursions at week 26 were statistically significantly lower in the URLi group (versus the lispro group) at all time points from 30 min to 3 h [Figure 2b]. At week 26, no significant differences

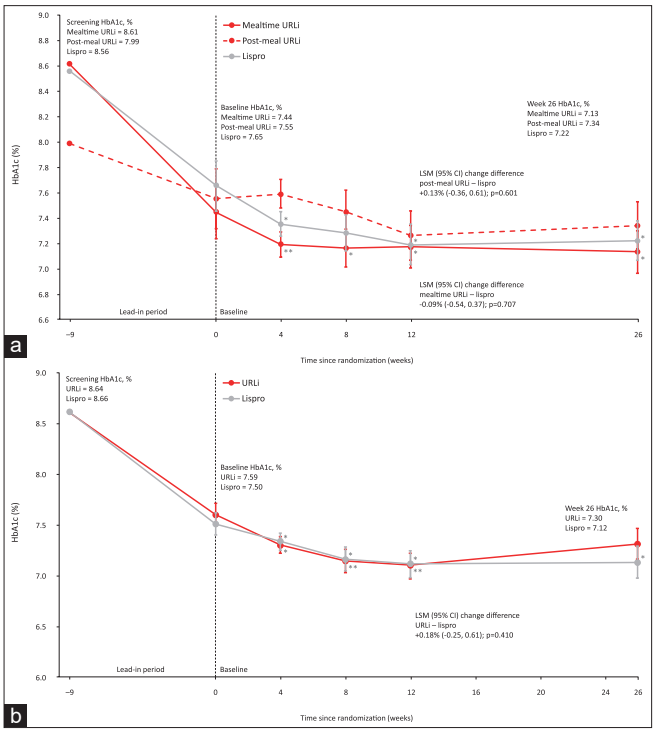

Figure 1: Haemoglobin A1c from study entry to week 26 in India. (a) PRONTO-T1D; (b) PRONTO-T2D. Data are mean at study entry and LSM ± SE at all other time points and based on the mixed-effects model for repeated measures analysis. Asterisks relate to within-treatment change from baseline for individual treatments at each time point: *$p < 0.05$, **$p < 0.001$. There were no statistically significant differences between the groups in either PRONTO-T1D or PRONTO-T2D at any time point. CI, confidence interval; HbA1c, haemoglobin A1c; LSM, least-squares mean; SE, standard error; URLi, ultra-rapid lispro

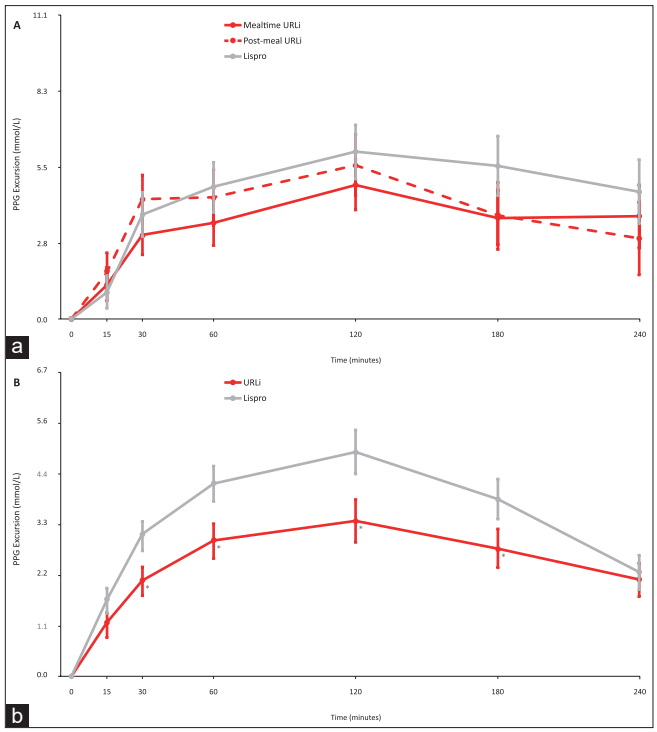

Figure 2: Post-prandial glucose excursions during a meal test at week 26 in India. (a) PRONTO-T1D; (b) PRONTO-T2D. Data are LSM ± SE. (a) There were no significant LSM differences of change in PPG excursion from baseline between the groups using an analysis of covariance model for endpoint measures: variable = baseline + pooled country + type of basal insulin during lead-in + prandial insulin dosing plan + baseline HbA1c stratum + treatment (type III sum of squares). Analysis of variance model for baseline measures: variable = treatment (type III sum of squares). (b) *$p < 0.05$ for between-treatment comparison. LSM PPG excursions at week 26 were statistically significantly lower in the URLi group (versus the lispro group) at all time points from 30 min to 3 h using an ANCOVA model for endpoint measures: variable = baseline + HbA1c stratum at baseline + number of bolus insulin injections at study entry stratum + type of basal insulin at lead-in stratum + treatment (type III sum of squares). ANOVA model for baseline measures: variable = treatment (type III sum of squares). CI, confidence interval; HbA1c, haemoglobin A1c; LSM, least-squares mean; PPG, post-prandial glucose; SE, standard error; URLi, ultra-rapid lispro

in LSM self-monitored blood glucose at any time point or daily glucose levels were observed between treatment groups in the Indian subpopulations of either PRONTO-T1D or PRONTO-T2D.

In the Indian subpopulation of PRONTO-T1D, there were no significant differences between treatment groups in the basal insulin dose given at baseline. Baseline bolus and total insulin doses were significantly higher in the mealtime URLi group than in the lispro and post-meal URLi groups, but there were no significant differences in the bolus: total insulin ratio. At week 26, no statistically significant differences between treatment groups were observed in the basal, bolus or total insulin doses, or in the bolus: total insulin ratio. In PRONTO-T2D, there were no statistically significant differences between treatment groups in the basal, bolus or total insulin doses, or in the bolus: total insulin ratio at baseline or week 26.

In PRONTO-T1D, there were no statistically significant differences in the proportion of Indian patients achieving HbA1c ≤6.5% or <7% between the URLi and lispro groups at any visit. There were no statistically significant treatment differences in the proportion of patients achieving HbA1c ≤6.5% between the post-meal URLi and the lispro or mealtime URLi groups. Statistically significantly fewer patients achieved HbA1c <7% in the post-meal URLi versus mealtime URLi group at week 4 (14.3% vs 38.9%, $P = 0.048$), but not at any other time point. In PRONTO-T2D, there were no statistically significant differences in the proportion of Indian patients achieving HbA1c ≤6.5% or <7% between treatment groups at any visit.

Incidence of all documented hypoglycaemia (blood glucose <3.0 mmol/L [54 mg/dL]) from baseline to week 26 was similar among the groups for the Indian subpopulations in both trials (PRONTO-T1D: mealtime lispro, 18 [90.0%], mealtime URLi, 15 [83.3%]. post-meal URLi, 13 [92.9%]; PRONTO-T2D: lispro, 43 [87.8%], URLi, 37 [72.5%]). No severe hypoglycaemic events were observed in PRONTO-T1D. One patient (4.0%) in the PRONTO-T2D URLi group experienced severe hypoglycaemia; no severe hypoglycaemic events were observed in the lispro group. In PRONTO-T2D, rates of post-meal hypoglycaemia were statistically significantly higher in the URLi versus lispro group at 0–1 h (relative rate versus lispro, 3.80 [1.43–10.12]; $P < 0.01$), 0–2 h (4.24 [1.64–10.92]; $P < 0.01$),

and 0–4 h (3.03 [1.41–6.52]; $P < 0.01$). However, there were no statistically significant differences in incidences of post-meal hypoglycemia between treatment groups at any time point.

No deaths in the Indian subpopulations were reported in either study. No discontinuations from the study or study treatment due to adverse events were reported for the PRONTO-T1D trial in India. Two serious adverse events (SAEs) were reported, both in the lispro group. One treatment-emergent adverse event (TEAE) in the lispro group was considered related to the study treatment. In PRONTO-T2D, one patient in the lispro group discontinued the study because of an adverse event. Three patients reported SAEs (one in the lispro group and two in the URLi group). Three patients (6.1%) in the lispro group and four (7.8%) in the URLi group had TEAEs considered to be related to the study treatment.

In conclusion, although underpowered for the Indian subpopulations, these post-hoc subanalyses showed that treatment effect and safety trends observed for the PRONTO-T1D and PRONTO-T2D Indian subpopulations were similar to those observed for the global populations, and suggest no evidence of clinically significant country-specific differences for patients in India versus the global populations.

Author contribution statement

Arpandev Bhattacharyya has made substantial contributions to the analysis of data, the interpretation of data and the drafting and critical revision of the manuscript. Indranil Bhattacharya has made substantial contributions to the conception of the work, the analysis of data, the interpretation of data and the drafting and critical revision of the manuscript. Vaishali Deshmukh has made substantial contributions to the acquisition of data and critical revision of the manuscript. Viswanathan Mohan has made substantial contributions to the acquisition of data and critical revision of the manuscript. Erik Spaepen has made substantial contributions to the conception of the work, the interpretation of data and the drafting of the manuscript.

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Conflicts of interest

Arpandev Bhattacharyya and Vaishali Deshmukh have no conflicts of interest to declare. Indranil Bhattacharya is an employee and minor shareholder of Eli Lilly and Company. Viswanathan Mohan has acted as a consultant and speaker, received research or educational grants from Eli Lilly and Company, Astra Zeneca, Novo Nordisk, MSD, Novartis, Boehringer Ingelheim, USV, Dr. Reddy's Laboratories, Lifescan J & J, Sanofi-Aventis, Roche Diagnostics, Abbott and from several Indian pharmaceutical companies. Erik Spaepen is a paid freelance consultant for Eli Lilly and Company.

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