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Clinical trial data validate the C-peptide estimate model in type 1 diabetes

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The area under the curve of meal-stimulated C-peptide (CP_{STIM}) is most commonly used as the primary outcome for clinical trials of immune therapy in recent-onset stage 3 type 1 diabetes [1]. However, because CP_{STIM} requires repeated venous blood sampling over 2 to 4 h, it is burdensome to participants and its laboratory analysis is costly. Moreover, it is not convenient in the routine clinical setting, where interest in assessing beta cell function continues to grow given recent advances in immune therapy for type 1 diabetes [2, 3].

To simplify assessment of beta cell function, we developed a formula, 'CP_{EST}', that estimates CP_{STIM} using six single-time-point measures: disease duration, insulin dose, BMI, HbA_{1c}, fasting plasma glucose and fasting plasma C-peptide [4]. In the original publication, CP_{EST} reliably identified treatment effects in three trials of immune therapy in recent-onset

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Contribution statement

All authors contributed to the conception and design of the study. MJH oversaw data collection for the TN19 study. JMW and NGB performed data analyses and interpretation. JMW drafted the manuscript, which all authors edited. Each author approved the submitted manuscript. JW is the guarantor of this work and takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

Duality of interest

The authors declare that there is no duality of interest associated with this manuscript.

type 1 diabetes, suggesting it could be used as a simpler, less burdensome primary outcome measure. However, half of the data in these analyses had been used to develop the CP_{EST} model and the model needed to be tested further by applying it to new data.

The recent availability of data from the TrialNet TN19 anti-thymocyte globulin (ATG) and pegylated granulocyte colony stimulating factor (G-CSF) trial (NCT02215200) [2] allows definitive testing of the utility of CP_{EST} as a clinical trial outcome measure. TN19 compared, in children and young adults (age range 12 to 43 years) with recent-onset type 1 diabetes, the effects of ATG (2.5 mg/kg i.v. over 2 days) followed by G-CSF (6 mg s.c. fortnightly for 6 doses), ATG followed by placebo, and placebo followed by placebo. The primary endpoint was CP_{STIM} at one year, assessed using an ANCOVA model adjusted for baseline age, baseline $\log_e(CP_{STIM}+1)$ and sex [2].

TN19 data were supplied with participant age rounded to the nearest year. We excluded two participants with incomplete data, resulting in 28, 29 and 30 participants in the ATG/G-CSF, ATG/placebo and placebo/placebo groups, respectively. Statistical analyses were performed using R software (www.r-project.org).

Based on 432 measurements obtained from the 87 trial participants over the first year, CP_{STIM} correlated strongly with CP_{EST} (Spearman's R=0.911, 95% CI 0.892, 0.926). The correlation between CP_{STIM} and insulin dose-adjusted HbA_{1c} (IDAA1c), another proposed single-time-point measure based on HbA_{1c} and insulin dose [5], was significantly weaker (Spearman's R −0.555, 95% CI −0.619, −0.484).

Figure 1 presents the ATG/G-CSF trial primary outcome according to measured (CP_{STIM}) and modelled (CP_{EST}) beta cell function. Overall, the values and trajectory of each treatment group using CP_{STIM} and CP_{EST} were similar. The *p* values for the month 12 outcomes for placebo/placebo vs ATG/placebo and placebo/placebo vs ATG/G-CSF were 0.0007 and 0.0851, respectively, for CP_{STIM}, and 0.0034 and 0.376, respectively, for CP_{EST}; the *p* values for IDAA1c (not shown in the figure) were 0.021 and 0.105, respectively.

These findings provide further evidence that CP_{EST} is a reasonable substitute for CP_{STIM} and is more accurate than IDAA1c for approximating beta cell function using single-time-point measures. The ability of CP_{EST} to accurately identify treatment effects in a fully independent dataset supports the notion that it could be used as a primary outcome measure in future clinical trials in recent-onset stage 3 type 1 diabetes. Perhaps more compelling may be the suggestion that it could be used as a simple measure that incorporates readily available clinical and demographic information and fasting laboratory data to monitor the response to immune therapies when they are approved for clinical use.

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Data availability

Data used for this study can be obtained through TrialNet (www.trialnet.org).

Abbreviations

ATG	Anti-thymocyte globulin
CP_{EST}	Estimated CP_{STIM}
CP_{STIM}	Meal-stimulated C-peptide
G-CSF	Pegylated granulocyte colony stimulating factor
IDAA1c	Insulin dose-adjusted HbA_{1c}

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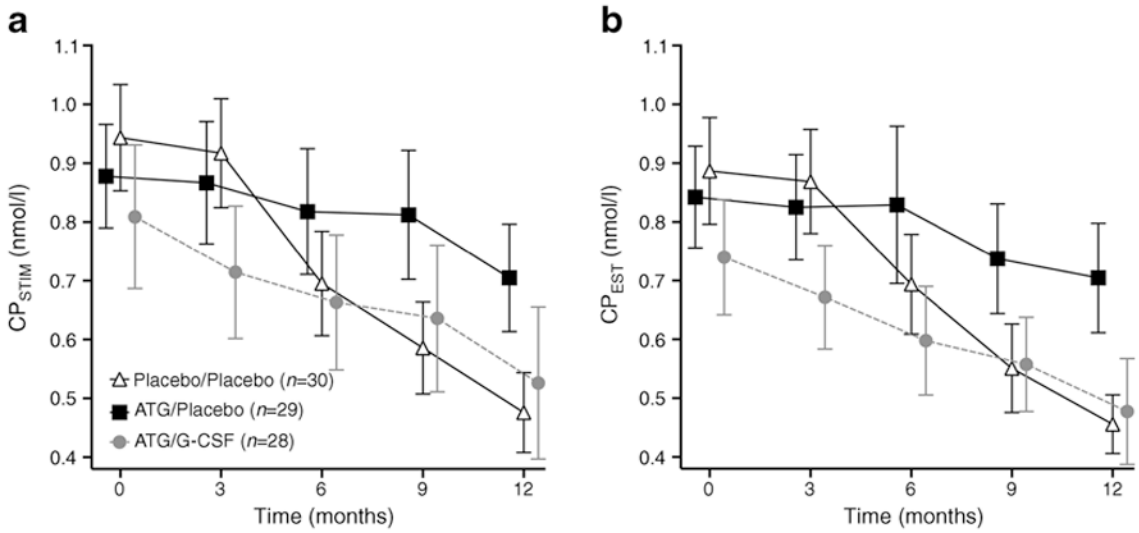

Fig. 1.

TN19 outcomes according to (**a**) measured (CP_{STIM}) and (**b**) modelled (CP_{EST}) beta cell function. Data presented are mean ± SEM. Measurements were taken at the same time points but have been offset to prevent overlap and enable better comparisons of the groups. Group comparisons were performed using an ANCOVA model adjusted for baseline age, baseline $\log_e(CP_{STIM}+1)$ and sex. The *p* values for the month 12 outcomes for placebo/placebo vs ATG/placebo and placebo/placebo vs ATG/G-CSF were 0.0007 and 0.0851, respectively, for CP_{STIM}, and 0.0034 and 0.376, respectively, for CP_{EST}