C-Peptide Levels in Latent Autoimmune Diabetes in Adults Treated With Linagliptin Versus Glimepiride: Exploratory Results From a 2-Year Double-Blind, Randomized, Controlled Study

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Latent autoimmune diabetes in adults (LADA) is a slowly progressing form of immune-mediated diabetes often misdiagnosed as type 2 diabetes because of its typical clinical presentation, i.e., an adult without weight loss or ketoacidosis not initially requiring insulin (1). Prior to insulin dependence, pharmacological options for reducing hyperglycemia comprise the oral glucose-lowering drugs used in type 2 diabetes; however, none has been established as the drug of choice in LADA because of the scarcity of evidence for or against the various agents (2).

This study was a prespecified, exploratory analysis of a large (n = 1,519) trial in which patients diagnosed with type 2 diabetes and HbA_{1c} of 6.5–10.0% (48–86 mmol/mol) on metformin were randomized to additional once-daily linagliptin 5 mg or glimepiride 1−4 mg for 2 years (NCT00622284) (3). Fasting plasma samples taken during the study were tested for autoantibodies against GAD 65-kDa isoform (GAD65), islet cell cytoplasm, tyrosine phosphatase IA-2 (IA-2A), or insulin (IAA), and patients were classified as having LADA if positive for one or more autoantibody. Fasting C-peptide and HbA_{1c} levels were obtained at baseline and weeks 26, 52, and 104. Antibodies to GAD65 were detected using radioimmunoassay (Oslo University Hospital in-house assay using translation-labeled GAD); an antibody index of ≥0.05 was considered positive and provided a sensitivity of 82% and specificity of 99% (Diabetes Autoantibody Standardization Program 2010).

Plasma samples from 1,505, 862, 436, and 327 patients were tested for GAD, islet cell cytoplasm, IA-2A, and IAA, respectively, and 118 (7.8%) were identified as having LADA. GAD65 was the most prevalent autoantibody (99 patients, 6.5%). At baseline, GAD65-positive linagliptin patients with C-peptide measurements at weeks 28, 52, and 104 compared with glimepiride-treated patients were slightly younger (mean age 59–62 vs. 63–68 years) with lower C-peptide levels (821–944 vs. 1,326–1,425 pmol/L), whereas HbA_{1c} levels were similar (Table 1).

In GAD65-positive patients, fasting C-peptide levels increased from baseline at weeks 28, 52, and 104 in patients treated with linagliptin but decreased in glimepiride-treated patients; between-group differences were significant at weeks 28 and 52 (Table 1). Mean HbA_{1c} decreased to a similar extent with glimepiride and linagliptin.

This exploratory analysis suggests that over a 2-year disease trajectory in LADA patients, treatment with linagliptin may, at least, have attenuated the rate of decline in C-peptide levels. The lack of a greater HbA_{1c} reduction with linagliptin suggests that reducing glucotoxicity was not responsible for the observations. Mechanisms that could explain a potential attenuation of decline in C-peptide levels with linagliptin include a β-cell–protective effect through elevation of endogenous glucagon-like peptide 1 (GLP-1) (4), and/or non-GLP-1–related mechanisms through modulation of peptides involved in cell signaling and autoimmunological pathways (5).

The current study, although limited by its exploratory nature, between-group difference in baseline C-peptide levels, lack of information on C-peptide after drug washout, small sample size, and lack of inert comparator, adds to the currently sparse evidence on the effects of oral glucose-lowering drugs in LADA patients (2). Potential further long-term clinical benefits of linagliptin in LADA patients will be further examined in a

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Table 1—Change in fasting C-peptide and HbA_{1c} in GAD65-positive (GAD+) patients treated with linagliptin or glimepiride for up to 2 years

	28 weeks		52 weeks		104 weeks	
	Linagliptin GAD+	Glimepiride GAD+	Linagliptin GAD+	Glimepiride GAD+	Linagliptin GAD+	Glimepiride GAD+
n	21	17	14	14	9	9
Baseline fasting C-peptide (pmol/L), mean ± SD	821 ± 485	1,326 ± 819	835 ± 522	1,425 ± 875	944 ± 627	1,374 ± 697
Follow-up fasting C-peptide (pmol/L), mean ± SD	917 ± 379	1,221 ± 316	978 ± 380	1,246 ± 320	1,146 ± 606	1,345 ± 401
ΔC-peptide (pmol/L)	+96*†	−105	+143*†	−179	+202*	−29
Baseline HbA_{1c} (%/mmol/mol), mean ± SD	7.6 ± 0.9/59 ± 10	7.8 ± 0.8/61 ± 9	7.4 ± 0.9/58 ± 10	7.5 ± 0.5/58 ± 5	7.3 ± 1.0/56 ± 11	7.4 ± 0.4/57 ± 4
ΔHbA_{1c} (%/mmol/mol)	−0.25/3	−0.75/9	−0.49/5	−0.52/5	−0.41/4	−0.49/5

Differences in mean change from baseline in C-peptide levels were assessed using Kolmogorov-Smirnov test (between treatment groups) and signed rank test (within treatment groups). *$P < 0.001$ vs. baseline. †$P < 0.01$ vs. glimepiride.

substudy of the ongoing CAROLINA trial (NCT01243424).

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