Relationship of autoantibodies to glutamic acid decarboxylase (GADA) to deterioration of glycamic control assessed by therapy progression in latent autoimmune diabetes in adults (LADA) in the UKPDS

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Background and Aims: Autoantibodies to glutamic acid decarboylase 65 (GADA) are markers of islet autoimmunity present at diagnosis in patients with type 1 diabetes (T1D) and latent autoimmune diabetes in adults (LADA). GADA persist after diagnosis in T1D for longer periods than other islet autoantibodies. However, the role of GADA in disease progression as a marker for β-cell failure in autoimmune diabetes is unclear. The aim of this study was to determine the persistence of GADA post-diagnosis and the relationship of GADA titre to disease progression in LADA.
Materials and Methods: GADA titres were determined in plasma samples from 242 subjects initially diagnosed with Type 2 diabetes in the United Kingdom Prospective Diabetes Study (UKPDS), (aged 25-65 yrs, ketonuria <3 mmol/l, no immediate insulin requirement) who were later found to be antibody-positive (ICA/GADA) and were defined as LADA patients. Subsequently, the same therapy decisions were made for antibody-positive patients as antibody-negative patients, defined by UKPDS protocol (diet → oral agents → insulin). GADA titres (WHO units) were measured at 0.5, 3 and 6 years post-diagnosis (p.d) by radiobinding assay. Deterioration of glycaemic control (>15 mmol/l) was assessed by progression within the therapy protocol; for this analysis, patients were termed as ‘progressors’ or ‘non-progressors’ at each of the three time-points.
Results: GADA positivity persisted until at least 6 yrs post-diagnosis. Median titres (IQR) of GADA were as follows: 0.5 yrs p.d, 331 (134-674); 3 yrs p.d, 199 (96-318); and 6 yrs p.d, 284 (107-518).
The proportion of patients by each timepoint on diet : oral agent : insulin therapy was follows: 0.5 yrs, 20% : 41% : 39%; 3 yrs, 6% : 29% : 65%; 6 yrs, 4% : 19% : 74%. GADA titre was not found to be significantly different between the patients in the therapy groups at any time-point.
By the 0.5 yr time-point, 23% of patients were ‘progressors’ and had higher GADA titres than ‘non-progressors’ ($p<0.05$); at diagnosis, ‘progressors’ were younger ($p<0.025$) and had higher fasting plasma glucose values ($p=0.001$).
Progression within the protocol by 3 and 6 yrs p.d. was not significantly related to GADA titre at either time-point; the median (IQR) titre of ‘progressors’ vs ‘non-progressors’ (between 0.5 - 3 yrs) was 184 (91, 316) vs 192 (81, 318), and between 3 - 6 yrs, 312 (93, 847) vs 250 (104, 464).
Conclusion: GADA postivity was maintained in LADA throughout the 6 yr follow-up period studied. Elevated GADA titres are predictive of requirement for more intensive therapy early in the course of disease but not at later time-points.