

Insulin Antibodies Associated With Technosphere® Insulin

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Both liquid and powdered formulations of pulmonary human insulin have been shown to have enhanced immunogenicity over sc insulins but with no adverse clinical consequences. Technosphere® Insulin (TI) differs from previous formulations in particle structure, pharmacodynamics, and glucodynamics. Thus, the development of insulin antibodies (IABs) was studied from 3 to 24 months in multicenter trials of patients with type 1 or type 2 diabetes. IABs (IgG) were measured using a validated Kronus® RIA assay, which was quantitated using a proprietary antibody and is significantly correlated ($r=.66$) with a quantitative Esoterix assay. IAB levels were found to increase as early as 2 weeks upon TI initiation, rose over time, then plateaued or spontaneously declined after 10 to 18 months. IABs developed to a greater extent in TI subjects than in those on noninhaled antidiabetic regimens, regardless of diabetes type. This difference was more pronounced in type 1 vs type 2 patients. Type 1 patients taking TI showed a maximum median IAB increase of approximately 8-fold vs 2-fold for sc insulins. In type 2 patients, the maximum median IAB increase was <3-fold vs a 2-fold increase with sc insulins. Factors such as race, country, study, age, or A1C were not of predictive value for elevated IABs. No associations were noted between IAB levels and key clinical outcomes, such as A1C, fasting plasma glucose, hypoglycemia, insulin dose, adverse events (including allergic events), and changes in pulmonary function tests. Three months after discontinuation of TI, IABs returned to near-baseline values, indicating that the IAB response to pulmonary inhalation of TI is reversible. In conclusion, a greater IAB response was observed after pulmonary administration of TI vs sc insulins. This was expected as the lungs function as a port of entry for exogenous substances and contain a large concentration of immunoactive tissue. No clinical consequence of IAB elevation was observed.

Median Insulin Antibodies (Kronus® Units/ml)

Study No./ Diabetes Type	n	Baseline (U/ml)	Week 26 (U/ml)	Week 52 (U/ml)
009/type 1				
TI	283	7.2	58.6	48.2
sc insulin	260	6.6	8.2	8.7
102/type 2				
TI	300	6.1	14.9	14.5
sc insulin	309	5.6	8.9	8.7