β-cell function over 2 years in individuals with recent-onset T1DM [Orban T et al. *Lancet* 2011]. Tihamer Orban, MD, Joslin Diabetes Center, Boston, Massachusetts, USA, presented 1-year follow-up data from the previous 2-year study [NCT00505375].

The primary study was a multicenter, double-blind, randomized, controlled trial in which subjects (n=112) aged 6 to 45 years (mean 14 years) who were recently diagnosed with T1DM were randomly assigned (2:1) to receive abatacept (10 mg/kg, maximum 1000 mg per dose) or placebo infusions intravenously on Days 1, 14, and 28 and monthly thereafter for a total of 27 infusions over 2 years. Dr. Orban reported on the effects of discontinuing costimulation modulation with abatacept on preservation of β-cell function in patients from this study who were followed for 1 year after infusions were stopped.

The follow-up analysis included 93 subjects (64 from the abatacept group and 29 from the placebo group). C-peptide 2-hour AUC means, adjusted for age and baseline C-peptide, at 36 months were 0.215 (95% CI, 0.168 to 0.265) and 0.135 (95% CI, 0.0692 to 0.205) nmol/L for the abatacept and the placebo groups, respectively (p=0.033). This difference was similar to the difference observed during the treatment phase of the trial. The C-peptide decline from baseline remained parallel with an estimated 9.5-month delay with abatacept. HbA1C was lower in abatacept-treated patients (p<0.001), with no difference in insulin use. A treatment effect was observed only for race and CDR3 status.

Data from this follow-up study indicate that costimulation modulation with abatacept slows the decline in β-cell function in recent-onset T1DM beyond drug administration and leads to lower HbA1C levels. These results suggest that abatacept may be useful in prevention studies in individuals who are at high risk of T1DM and/or as a component in studies that use a combination of different treatment strategies. Further trials are needed to test whether or not a shorter course of abatacept treatment would be sufficient to achieve similar beneficial effects.

Explaining the UKPDS Legacy Effect

Written by Phil Vinall

Ten years of follow-up observations from the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated virtually identical HbA1C levels in subjects who were randomly assigned to 2 different glucose control strategies (intensive or conventional). However, subjects who received intensive glucose control remained at a significantly lower risk of diabetic complications. This continuing benefit of earlier improved glucose control has been termed the type 2 diabetes legacy effect [Chalmers J, Cooper ME. *N Engl J Med* 2008], an influence that is similar to the metabolic memory that has been described for type 1 diabetes [Stumvoll M et al. *N Engl J Med* 1995]. Marcus Lind, MD, University of Gothenburg, Gothenburg, Sweden, presented data that examined the degree to which historical HbA1C values contribute to later reductions in the risks of myocardial infarction (MI) and all-cause mortality. An additional aim was to elucidate the time-dependent impact of earlier HbA1C values on a year-by-year basis.

Continuous hazard functions for death and MI from diagnosis of type 2 diabetes in relation to age, sex, HbA1C, and original treatment assignment (intensive/conventional) were estimated in 3849 individuals from UKPDS. These data were then evaluated for different HbA1C levels during a preceding time interval to determine the degree to which they might explain the death and MI legacy effects.

Older age, male sex, and HbA1C, but not treatment group, were all found to be significantly (all p<0.001) related to MI and death. The model was used to estimate the impact of a 1% reduction in HbA1C from each of 2 time periods (at diagnosis and 10 years after diagnosis) on the risk of death and MI. For all-cause mortality, the results indicate the reduction in risk from the legacy effect is almost 3 times stronger when the HbA1C reduction is achieved early (at diagnosis) compared with later (after 10 years), and this effect is mostly because of the lower HbA1C levels at the earlier time points. The pattern is similar, but the effects of early reduction are somewhat less potent for MI.

The model was used to predict the relative reduction in the probability of death for a 50-year-old man with newly diagnosed type 2 diabetes and an HbA1C of 8% in 2 different scenarios: immediate (at diagnosis) reduction of HbA1C by 1% and waiting 10 years for the same HbA1C reduction. Reducing the HbA1C by 1% (to 7%) at diagnosis will result in an 18.6% risk reduction for death compared with only a 6.6% risk reduction if the HbA1C reduction is delayed for 10 years. Similar relationships in risk reduction and timing of the HbA1C reduction were seen when the model was applied to MI and to women.

Statistical modeling of UKPDS data confirmed that earlier HbA1C levels continue to contribute to the risk of diabetic complications, as seen in the Diabetes Control and Complications Trial [The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993]. The long-term impact of achieved HbA1C levels explains to a large extent the sustained reductions in the risk of death and MI that were seen in the UKPDS post-trial monitoring period. Thus, early intensive, optimal, glycemic control is essential to minimize the long-term risk of diabetic complications.