

The Katrina Aftermath  
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Modifying the Type I Diabetes Process

Jay Skyler presented a seminar on this topic on the morning of the last day. This topic could encompass the entire summary plus perhaps two or three others because of the amount of work that is going on. I just wanted to briefly skim over some of the points that were made. Please remember this is not a full summary whatsoever. He first talked about the efforts to preserve insulin production in the new-onset diabetics. These were studies that used interventions to keep c-peptide production intact (c-peptide is a marker for insulin release). He mentioned the earlier studies done with Cyclosporine in France and Canada that had too much toxicity and ultimately did not succeed. He mentioned the studies by Dr. Harold with anti-cd3. There was increased insulin production at six months but again it was not fully sustained. He also mentioned vaccination with GAD-65. Even here there was still progressive decline in insulin production. He felt that the studies indicated that we must approach these children earlier and very likely before they can be fully diagnosed as diabetic. He mentioned the Trial Net studies which evolved from the earlier DPT-1 study (Diabetes Prevention Trial-1) in which many of you participated several years ago. The MMTI-MMT-DZD study showed no prevention of diabetes. The Rituximab (cd-20) study still showed a decline in c-peptide production in the second six months although the patients did have a lower Hgb A1c and lower insulin dose. The Abadacett study has enrolled their patients now but we have no data yet and they are currently enrolling patients in the GAD Alum study. It is not important to know what these various medications are. The point I want to make is that there are a good many studies going on looking to help patients with new-onset diabetes perhaps preserve some beta cell function. He also mentioned a study that is not part of Trial Net using Etanercept. This is an anti-inflammatory which also improved c-peptide preservation. His feeling is that there will need to be a combination of several of these approaches if we hope to succeed. He feels that each individual approach alone will probably not succeed but perhaps in combination they could. He mentioned that it could be a combination of an anti-inflammatory (for instance an anti-TNF), plus an immunomodulator (? CD-20), an antigen specific treatment (GAD?), an immunologic expander (T regulators) and a beta cell mass expander (Extenetide). It may take a combination of all of these if we are to succeed. Obviously there is a good deal of study still to go on. He emphasized that the DPT-1 predictions of development of diabetes were correct. The number of antibodies present in the serum very much predicted who would develop diabetes and who would not. Likewise the age mattered with children under 18 developing diabetes much faster. Neither the parenteral or oral insulin worked but the oral insulin used in patients with the highest antibody titers caused a five to ten year delay in the onset of diabetes. Thus information is coming and ultimately there is hope that we may prevent the onset of Type I diabetes. He emphasized that there can be no cure without prevention. Dr. Matthias Von Herrath reported on antigen based therapies. He said that the hypothesis is that viruses trigger or enhance Type I diabetes. He pointed out that there is little evidence that viruses directly infect and lyse beta cells or cause molecular mimicry, leading antibodies to attack both the virus and the beta cells.

He thinks that viruses probably are more involved in the "fertile field hypothesis". The viruses unmask the beta cells for interferon destruction. He is hoping that ultimately this approach will eliminate auto-aggressive T cells and achieve long-term tolerance with the use of antigen specific therapy. Dr. Lucienne Chatenoud reported on the European CD-3 trial. This study is using immunomodulation with CD-3 monochromal antibodies to restore T cell function. The Hgb A1c level was no different at 48 months with treatment but the insulin needs were still lower when compared with controls. The slope of the curve, however, is parallel at 48 months and so the question is if the antibodies are losing their effect. The patients that responded best had the most beta cell mass. *We seem to be getting this message from several studies which again indicates that we need to pick up these patients very early in the diabetic process.* There were also safety problems with cytokine release, Epstein-Barr virus reactivation and anti-idiotypic antibodies. *If this summary sounds very confused it is because I am. This is the forefront of research and looking at ways to modify the diabetic process early on in its course. It is extremely experimental and highly biological rather than clinical. The average clinician knows very little about this work because it cannot be translated to clinical practice at this time. The immunology involved is mind-boggling. These studies are extremely important, however, if we are going to prevent the development of diabetes and full insulin dependence in our future generations. With our children getting older and reaching reproductive age, it should strike home.* There were two oral abstract presentations that pertained to this subject. Jonny Ludvigsson from Sweden presented a study looking at GAD<sub>65</sub>-alum treatment in children with Type I diabetes. He noted that GAD<sub>65</sub>-alum treatment may preserve residual insulin secretion in Type I diabetes. In mice the beta cell protective effect of GAD-65 had been associated with the induction of high titers of GAD specific IGG antibodies (GADA). The development of these antibodies, however, was associated with significant side effects. They did a study looking at 70 Type I diabetic patients 10 to 18 years of age who developed diabetes within the previous eighteen months. They measured GADA at baseline and also at the completion of the study. The GAD<sub>65</sub>-alum treatment significantly increased GADA titers in the treatment patients after three months. The levels remained higher even after thirty months. The patients with the best c-peptide preservation (remember this means the most insulin production) had higher levels of GADA before treatment was started. There were no signs of neurological or other adverse events. Their conclusion was that GADA<sub>65</sub> treatment induced a long-lasting GADA production but no adverse clinical events. Although there was not a significant c-peptide production advantage with it's use, the study was really designed to show that there were no adverse events. Then there was a study from Florida looking at autologous umbilical cord transfusion in very young children with Type I diabetes. Twenty-three patients underwent a single intravenous infusion of the patient's umbilical cord blood that had been collected at birth. Intensive insulin regimens were utilized to optimize glycemic control both in these patients and the control patients. Fifteen of 23 patients have completed one year of post infusion follow-up. The mean age at the time of infusion was 5.7 years with the post diagnosis time at infusion of ½ year. One year post infusion, the Hgb A1c was 7.0%, the insulin dose was 0.67 U/kg/day and the peak c-peptide production was 0.5 ng/mL. The historical control group matched for age and duration of diabetes had a Hgb A1c of 7.6% and insulin requirement of 0.73 U/kg/day and they did not report c-peptide production in these patients. They concluded that autologous umbilical cord blood transfusion is safe and may slow rates of decline of endogenous insulin production in children with Type I diabetes. They felt that their study mandates prolonged follow-up and additional efforts to determine if specific cell populations derived from the umbilical cord blood elicit direct or indirect immunomodulatory effects and if umbilical cord blood cells can be used as part of safe and effective therapies for Type I diabetes. *This is a very interesting study and requires*

*that we follow the progress of these patients very closely. If it proves that the early use of umbilical cord blood really does make a difference long term (and this study is only one year old and has a long way to go before it can be considered long term) then we might be wise to start collecting umbilical cord blood in infants born to parents with diabetes or in families that have diabetes. It is an expensive proposition and the study does not call for universal use by any means. It is the first step to see if it really will make a difference.*