

The Voice of the Board

Primum non nocere in immunopreventive trials in diabetes

I would like to share with you some of my concerns regarding intervention trials among patients with autoimmune type 1 diabetes. Among diabetologists, who deal with type 1 diabetes, there is still a need for an effective preventive therapy for the patients with persisted residual insulin secretion and individuals who are genetically at risk of developing diabetes. Many clinical intervention trials were performed using for instance cyclosporine, insulin, antiCD3 and CD20 antibodies and GAD vaccine as immunomodulating agents. Some time ago also Polish group from Gdansk applied in the clinic the protocol of immunopreventive trial using expanded autologous CD4+CD25^{high}CD127⁻ T regulatory cells (Tregs). This study has indicated that the administration of Tregs is able to prolong the clinical remission in DM1 children but the clinical improvement persists as long as increased Tregs numbers are present in peripheral blood. The other recent trials showed also beneficial outcomes in preserving residual beta-cell function in new onset type 1 diabetes subjects but these effects were not long lasting. This is disappointing not only for medical community but especially for patients and family members seeking for a cure of autoimmune diabetes. Participation in the preventive trials might be even harmful for the patients since they could lose a motivation for further standard insulin treatment. Thus, this should be also considered during recruitment procedures. Another population for immune interventions is a group individuals who are genetically at risk of developing diabetes and who are positive for multiple

anti-islet antibodies. For this goal the TrialNet initiative has recently modified definition of the autoimmune type diabetes adding two preclinical phases as a target population for immune intervention. During the last the ADA meeting in San Diego highly visible session on type 1 diabetes immune intervention trials took place. Prof. Desmond Schatz presented results of the TrialNet oral insulin trials showing significantly more than one-year delay in clinical manifestation of diabetes among subjects who were treated with insulin. Two other papers revealed some mild beneficial effects of imatinib and GAD-vaccine. However, infant genetic screening for type 1 diabetes raises parent anxiety when the child is at increased risk. Persistence of anti-islet antibodies results heighten parent anxiety, and parents faced with two or more types of autoantibodies results may experience considerable anxiety for longer periods. This is an additional possible injurious outcome of the intervention trials in diabetes. Drawing the conclusion based on the ADA session, this has been attributed to an incomplete understanding of the complex etiopathogenesis of the disease. Many have also suggested that monotherapeutic agents, as has been the norm in most of the recent clinical trials, may not be as efficacious as synergistic combinations of immunotherapeutic agents targeting multiple keypoints of the immune system. However, beneficial effects on the course of diabetes of the trials should also consider psychological aspects, which might be harmful of the individuals with type 1 diabetes and their families.

On behalf of the Board
Prof. Wojciech Młynarski, MD, PhD

