Editorial: Treatment options in insulin-dependent diabetes and the developing paradigm shift from metabolic to immunologic therapy for new-onset type 1 diabetes

D. Mineo

Master School of Pediatric Endocrinology and Diabetology, "Tor Vergata" University of Rome and IRCCS "Bambino Gesù" Hospital of Rome, Rome, Italy.

Corresponding Author: Davide Mineo, MD, Ph.D; e-mail: davidemineo@tiscali.it

ABBREVIATIONS

CFM = cyclophosphamide; GCSF = granulocyte colony stimulating factor; ATG = anti-thymocyte globulin; IL1 = interleukin 1; TNFα = tumor necrosis factor alfa; LFA1 = lymphocyte function-associated antigen 1; GLP1 = glucagon-like peptide 1; DPP4i = dipeptidyl-peptidase-4 inhibitor.

Type 1 diabetes is a growing problem in the community since its incidence is increasing markedly in the last decades, at a percentage of more than 10%, accounting for 1-5% of all cases of diabetes, with an incidence in Europe in 2013 of 8-17/100.000, equal to 129,350 cases in children aged 0-14 years. Possible reasons for such increase appear to be the "epidemic" of obesity in childhood, that could deregulate the immune system together with metabolism, and an increased susceptibility to environmental injuries of the beta cells, that could depend on the insufficient maturation of the immune system to antigens, e.g. diet or toxins, so favoring the onset of autoimmune diseases[1].

The disease origins from an immune deregulation in genetically predisposed subjects encountering an environmental triggering stimuli, e.g. viral infections, that leads to a non-self-recognition of the own insulin-producing beta cells. Many immune cells and mediators are involved, mainly T and B lymphocytes, APCs and pro-inflammatory cytokines, recognizing and moving against some specific antigens of the pancreatic islets. This process finally leads to beta cells destruction and secondary insulin deficit with life-threatening hyperglycemia and ketoacidosis needing a life-long substitution therapy with exogenous insulin, and the development of organ-specific chronic complications[2].

Currently, the standard treatment for type 1 diabetes is primarily based on the substitution of the insulin deficiency derived from the autoimmune beta cells destruction. Exogenous insulin in a tight regimen (4-5 times/day) is then provided, but often does not allow for an optimal glucose control, even when using the current modern technological devices for insulin administration or glucose monitoring, and it does not prevent from developing severe diabetic complications with time. This approach is cumbersome for the patient facing practical difficulties and undergoing psychological stress with personal and social limitations often involving their family and by challenging doctors.

A paradigm shift in treating new-onset type 1 diabetes based on the autoimmune pathophysiology of the disease and not on its metabolic consequences, is required to block the complete beta cell destruction and to avoid the insulin deficiency. The rescued residual beta cell mass and preserved insulin secretion could then allow for better metabolic control with limited or no use of exogenous insulin, and also less associated complications and life limitations. Different immunological agents and/or facilitating immune cells have proved effective in several autoimmune disorders, dissecting the harmful immune/inflammatory process at different levels, limiting patients' side effects[3].

Several clinical trials have been performed in the last years and other are ongoing in attempting to block the autoimmune destruction of beta cells at disease's onset. Different immune-suppressive, immuno-modulatory and anti-inflammatory agents, specific vaccine-like antigens and facilitating immune cells were tested only singularly in different protocols achieving some promising but transient results; no specific attempt was done to favor beta

cells regeneration. Peculiar impediments to such approach are the recurrence of autoimmunity, the scarce ability of beta cells to regenerate, and the toxicity of the immune drugs, with concerns about safety of the treated young patients[4-9].

In this perspective, important lessons can also be learnt by the significant progresses achieved in the field of islet allo- and autotransplantation as an alternative therapeutic option for treating the most severe cases of long type 1 diabetes, or the metabolic consequences of chronic pancreatitis. In such settings, thanks also to the major improvements in pancreatic islets recovery from organ donors, different immunological agents have been positively tested, including immune facilitating cells, as well as novel metabolic drugs have been favorably incorporated, comprising beta-cell recovering molecules, overall with limited side effects, thus encouraging further studies[10-14].

A possible approach in new-onset type 1 diabetes, inspired by the trials since now conducted, could be a sequential, low-dose, multiple immune drugs plus own facilitating immune cells and specific vaccine-like antigens together with usual plus new beta cell metabolic and regenerative agents. Aims are to block the autoimmune insulitis, restoring immune tolerance to the own beta cells, and save and regenerate the beta cells itself, finally remaining free from immunosuppression and possibly from insulin. Critical points of this strategy have to be a minimal-dose and time-limited exposure to immune drugs in face of acceptable patient safety and better quality of life (Figure 1).

At disease's onset, the patients will receive their own hematopoietic stem cells, mobilized by bone marrow cell-depleting then -stimulating agents (CFM then GCSF), and extracted by leukapheresis. Next, both T and B lympho-depleting drugs will be given (ATG or anti-CD2 or anti-CD3 plus anti-CD20 antibody) followed by an anti-cytokine anti-inflammatory antibody (anti-TNFα or anti-IL1). Afterward, an immune-modulatory costimulatory blockade antibody (anti-CD80/86 or anti-LFA1) will be provided. Finally, according to the patient disease-specific auto-antibodies detected, a desensitization therapy with a modified antigen will be performed (oral insulin or GAD-alum). At 1 year, all the immunologic drugs will be weaned to verify the occurrence of immune tolerance without recurrence of autoimmunity. This approach could eliminate the defective auto-reactive immune clones and cells while rise of newly-formed normal ones, thus preserving the own beta cells, with limited protocol immune depression and patients' risk of infections. With a similar time-line, a complete metabolic substitution therapy with exogenous insulin analogs will be given initially to favor beta-cell sparing and resting and to optimize glucose control. After that, a beta-cell regenerative and stimulating drug will be given (long-acting GLP1 agonist), together with a double insulin-sensitizing treatment (pioglitazone plus metformin) since the beginning, thus favoring the peripheral action of circulating insulin and limiting glucose production and absorption. At 1 year, a DPP4 inhibitor instead of GLP1 agonist, and eventually a beta-cell secretagogue, will be added as per patient glycaemia.

The road toward a successful immunologic and metabolic treatment of new-onset type 1 diabetes is still long and full of obstacles; and many criticisms
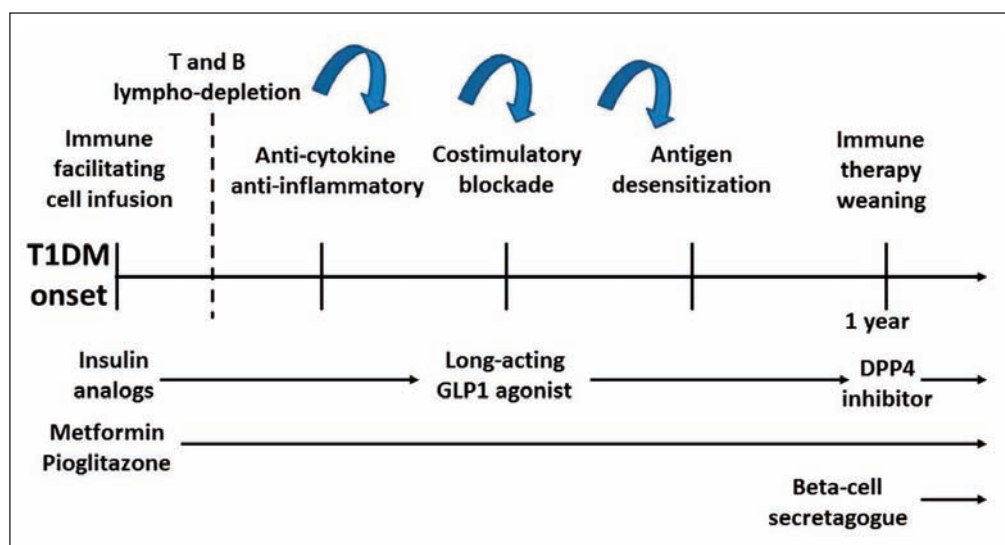
Figure 1. Possible immune-therapy protocol for new-onset type 1 diabetes.

have to be solved and preconceptions overcome. Hoping for a single-bullet therapy is difficult due to the complex mechanisms of the disease while a multifaceted approach may at least try to make it a type 2 diabetes phenotype. Scientists should be open to challenge all of this, by drawing continue inspiration from both research studies and pharmacological innovations, thus to be able to achieve finally a good balance between acceptable risks and benefits of the therapy and, even more, a satisfactory quality of life for the patients[15].

CONCLUSIONS

The Author declare that does have no conflict of interests.

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