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EDITORIAL

Advancing toward the aetiologic treatment of type 1 diabetes in the early stages: the dawn of a new era in its management

Hacia el tratamiento etiológico en fases tempranas de la diabetes tipo 1 en la edad pediátrica: el inicio de una nueva era en su abordaje

Roque Cardona-Hernández[a,1], Luis Antonio Castaño González[b,1], Enrique Palomo Atance[c], Itxaso Rica Echevarría[b,*]

[a] *Servicio de Endocrinología Pediátrica, Hospital Sant Joan de Déu, Esplugues de Llobregat, Barcelona, Spain*
[b] *Hospital Universitario Cruces, Universidad del País Vasco, IIS Biobizcaia, CIBERDEN, CIBERER, Endo-ERN, Baracaldo, Vizcaya, Spain*
[c] *Unidad de Endocrinología Pediátrica, Hospital General Universitario de Ciudad Real, Ciudad Real, Spain*

The treatment for type 1 diabetes (DM1) in children and adolescents has advanced considerably in the past few decades. Novel insulin analogues and the development of continuous glucose monitoring and automated insulin delivery systems have allowed a shift in the approach to its management. All of it has had a positive impact on the health of children and adolescents with T1D, but their lives are still partially limited due to the risk of complications of diabetes. It is important to avoid lapsing into optimistic complacency, as management is still based on replacement therapy, which is far from a curative or preventive strategy for the disease. Despite the advances, most paediatric patients do not achieve the blood glucose targets established by the International Society for Pediatric and Adolescent Diabetes, and the diagnosis of T1D in children under 10 years is associated with a decreased life expectancy.

Current treatment approaches with automated insulin delivery and continuous glucose monitoring systems optimise the management of diabetes and improves quality of life, but the application of these techniques is very heterogeneous. The benefits of these systems have been demonstrated in randomised controlled trials and they are expected to be corroborated in upcoming years with the publication of studies based in real-world practice. Long-acting insulin analogues, such as formulations for weekly injection, which are currently in the preclinical phase of development, may offer an alternative for those patients who choose not to use these technological systems in the future.

In parallel to advances in replacement therapy, for more than 3 decades, research has been conducted in pursuit of aetiological treatment strategies for T1D. We know that T1D is disease whose aetiology involves the interaction of a polygenic basis with poorly understood environmental factors that activate the autoimmune response against the islets of Langerhans resulting in the selective destruction of β-cells.

There are genetic factors that can constitute a risk or confer protection against the disease. Variants in more than 50 polymorphic genes have been associated with T1D and, more specifically, some polymorphisms in the HLA region

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* Corresponding author.
E-mail address: itxaso.ricaechevarria@osakidetza.eus (I.R. Echevarría).
[1] Both authors have contributed equally to the writing of the document.

account for more than 50% of the risk. The presence of the HLA DR3-DQ2 and/or HLA DR4-DQ8 haplotypes is associated with an increased risk, while the HLA DR2-DQ6 haplotype has a protective effect.

In the 1970s, Bottazzo discovered islet cell antibodies (ICA) in patients with T1D, giving rise to the autoimmune aetiology hypothesis, which was consolidated with the detection of other autoantibodies against specific β-cell antigens (insulin, GAD, IA2, ZnT8) and evidence that cyclosporin inhibited the destruction of pancreatic β-cells in children and adults with T1D. In the wake of these discoveries and based on evidence from studies of autoantibodies in first-degree relatives, the natural history of type 1 diabetes was defined. The current nomenclature classifies it into 3 stages:

- *Stage 1*: preclinical stage characterised by the presence of pancreatic autoantibodies and normal glucose levels (normal β-cell function).
- *Stage 2*: preclinical stage characterised by the presence of pancreatic autoantibodies with mildly raised blood glucose (β-cell dysfunction).
- *Stage 3*: clinical manifestations of diabetes that develop after a period of sustained hyperglycaemia and are secondary to an apparent β-cell failure.

The current knowledge on the environmental factors involved in the activation of the immune response is scarce. Different hypotheses have been proposed involving factors such as infectious agents, hygiene, infant feeding modality and vitamin D levels, among other, but none is yet fully supported by evidence. Thus, most *primary prevention* trials conducted in individuals with genetic risk before the activation of the immune response have failed.

Treatment with immunomodulating agents in the *early stages* once the autoimmune response is activated *(secondary prevention)* or at the onset of clinical symptoms (*tertiary prevention*) has shown encouraging results. Some clinical trials of drugs developed to halt the autoimmune process have achieved partial benefits. In the] DIAGNODE 2 trial,[1] the administration glutamic acid decarboxylase (GAD) (subcutaneous or intralymphatic) appeared to preserve endogenous insulin secretion after initiation of treatment in a subset of adolescents and young adults with T1D carrying a specific HLA haplotype. Monoclonal antibodies (anti-CD2, anti-CD3, anti-CD20, among others) and other immunosuppressive drugs have also been found to temporarily promote β-cell preservation, decrease insulin needs and even improve levels of glycated haemoglobin in recently diagnosed patients.[2–4]

In recent years, the United States Food and Drug Administration (FDA) and the European Medical Agency (EMA) have approved new biological therapies for use in different medical specialities that, through their action on the immune system, can modify the progression of different diseases and improve their prognosis. It is to be hoped that this new approach will also be applied to T1D. The first and sole biologic agent approved by the FDA for treatment of T1D is teplizumab, which has proven effective and safe in preventing progression of diabetes from stage 2 to stage 3 in patients aged less than 18 years.[2] Recently, the results of another clinical trial of teplizumab in stage 3 have become available, showing benefits in terms of the maintenance of C-peptide levels and lower insulin requirements over the 18-month follow-up.[5] The EMA is evaluating these data toward the potential authorization of the drug. Thus, we are witnessing the dawn of a new era and promising results are emerging in regard to the aetiological treatment of T1D, although there are still aspects that need to be defined better.

To understand what this therapeutic option entails, clinicians need to convey to families and patients the importance of maintaining residual insulin secretion to improve metabolic control and reduce the development of complications in the long term.

The possibility of halting the progression of T1D in the early stages poses the challenge of organising public health programmes for the early detection of individuals at preclinical stages of disease. Most changes in this regard have focused on first-degree relatives of patients with T1D, but this subset accounts for only 10% of new cases. To be more effective, these programmes should be expanded to the general population with an active immune response. This has been the approach in Italy, which recently approved the introduction of universal, nationwide screening for T1D in the paediatric population combined with screening for coeliac disease. Other European countries, such as Germany, Czech Republic, Denmark, Slovenia and Sweden and Israel are planning similar strategies. A second aspect that is required to guarantee the effectiveness of population-based screening is the availability of sensitive and specific markers for autoantibodies. The knowledge of certain genetic characteristics associated with an increased risk or protection against T1D can guide the selection of risk groups eligible for autoantibody testing.

To conclude, we trust that the EMA will soon authorize the use of teplizumab and, in the future, other drugs that will make it possible to prevent progression of T1D to stage 3. As clinicians, we must take on the challenge to collaborate in the development of effective and feasible strategies to identify patients who can benefit from this therapeutic option, the access to which should be universal and free.

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