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EDITORIAL

Status of type 1 diabetes mellitus prevention: promises and realities

Estado de la prevención de la diabetes mellitus tipo 1: promesas y realidades

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For more than 20 years, numerous resources have been dedicated to identifying interventions to prevent type 1 diabetes mellitus (T1DM), but so far, no significant progress has been made in its clinical application. The aim of this editorial is to discuss the current situation based on events from the past 5 years.

In January 2024, the European Medicines Agency (EMA) published an update to the guidelines for the study of drugs for the prevention and treatment of T1DM[1] recognizing the 3 stages of T1DM[2] and regulating the development of new drugs for its prevention, emphasizing the importance of conducting clinical trials (randomized and placebo-controlled) with safe drugs and focusing interventions on individuals at high risk of developing clinical diabetes. For immunosuppressive drugs, the need for long-term pharmacovigilance is stressed.[1]

Among the many interventions evaluated over the past 25 years, none have demonstrated a significant effect on the development of diabetes in individuals with a genetic risk for T1DM (primary prevention). Despite promising initial results, delaying exposure to cow milk protein in newborns with diabetes risk-associated HLA did not prove to delay the onset of beta-cell autoantibodies or the diagnosis of T1DM.[3] Among secondary prevention interventions (in individuals with beta-cell autoantibodies; stages 1 and 2 of the disease), to date, only teplizumab has shown some impact on disease progression.

In a small clinical trial with individuals at stage 2 (ie, with autoimmunity^{+} and dysglycemia; N = 44 in the active treatment group and 32 in the placebo group), Herold et al. demonstrated that although treatment with teplizumab did not prevent progression to stage 3, it did reduce the annual rate of clinical diabetes onset by half, with a median time to diagnosis of 48.4 months in the teplizumab group vs 24.4 months in the placebo group.[4] Most patients were siblings of individuals with T1DM, white, younger than 18 years, and positive for 3 autoantibodies. The median follow-up was 745 days (74–2,683). Although the number of patients included did not allow firm conclusions to be drawn from subgroup analyses, a heterogeneous response was observed based on

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HLA haplotype, autoantibody profile, age, initial C-peptide level, or beta-cell stress markers. After a median follow-up of 6.7 years, 72% of the teplizumab group and 87% of the placebo group had progressed to stage 3.[5] The most common side effects were lymphopenia (75%) and rash (36%). Among patients with detectable Epstein-Barr virus antibodies at baseline, viral DNA (reactivation) was detected after infusion in 50% of the teplizumab group and 0% in the placebo group.[4] These adverse effects, along with GI symptoms such as nausea and vomiting, were confirmed in a recent meta-analysis.[6]

Back in November 2022, the U.S. Food and Drug Administration (FDA) approved teplizumab for delaying the onset of clinical T1DM in individuals aged 8 and older at stage 2 of the disease,[7] which was described as a milestone in T1DM.[8] However, logistical, technical, and ethical challenges in screening to identify at-risk groups were raise,[9] as well as economic and equity issues associated with the drug cost, which exceeds $193,000 USD per treatment.[10] In addition, the toxicity of teplizumab, which requires premedication and close monitoring, and its administration method, involving 14 consecutive daily IV infusions, poses challenges.[11]

In April 2023, Sanofi acquired Provention Bio, Inc. (the company that developed teplizumab) for $2.9 billion USD[12] and launched a major campaign to promote its prescription in the United States.[13] As of this editorial's publication, teplizumab has not been not approved in Europe. On the other hand, the demonstration that an early intervention can slow the progression of T1DM has spurred multiple organizations to work on developing other interventions, and several European initiatives are worth mentioning.

The natural history studies of T1DM, which have provided greater understanding of factors related to its development and its heterogeneity, are now complemented by networked infrastructure aimed at identifying and testing new interventions to slow down the progression of the disease. INNODIA was established as a public/private consortium funded by the European Union. Since 2022, it has been a nonprofit entity whose mission is to facilitate the development of new cures and disease-modifying treatments for all individuals with T1DM.[14] Recently, several Spanish centers have joined the network.

Additionally, several screening programs have been launched to evaluate the most appropriate approaches regarding target populations (first-degree relatives or general population), screening age, sample collection methods, definition of antibodies to measure, determination methodologies, and strategies for positive follow-up. DiaUnion1.0, in Denmark, studies first-degree relatives of individuals with T1DM,[15] while TRIAD, in Sweden, includes the general population.[16] Both initiatives study antibodies vs pancreatic beta cells, and anti-transglutaminase and anti-thyroid antibodies. In Italy, the Senate passed a law in September 2023 regulating screening for T1DM and celiac disease in the general population.[17] In the United Kingdom, there is a child screening program,[18] where those who test positive are connected to the INNODIA network, and another program aimed at adult screening.[19] All these programs are in their early stages, and their results will be highly useful in defining their applicability in health care systems. To this end, they must follow WHO recommendations and meet the Wilson and Jungner criteria, which define an appropriate screening program: briefly, the disease must represent an important health problem, with effective treatments to mitigate, delay, or ideally cure it; and the detection process must be effective, acceptable, and affordable.[20]

In conclusion, although the new evidence generated in the past 5 years is limited, recent political/legislative developments and current programs under development are very promising. However, there is still much uncertainty in this field, with many questions yet to be answered.[21] We hope that these efforts will be rewarded with the identification of new, safe treatments that delay or prevent the onset of clinical T1DM, which has such a significant impact on the quality of life of affected individuals. Meanwhile, it is difficult to justify population-wide screening outside a research project, especially without a clear plan for addressing its results.

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