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Interferon blockade:

could it be a good strategy for the prevention of type 1 diabetes?

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by the progressive destruction of insulin-producing β cells due to the attack of the immune system itself. To date, there is no treatment capable of definitively restoring endogenous insulin production in people with T1DM. For this reason, for more than a century the only treatment available after disease onset has been the exogenous administration of insulin. This limitation has driven the development of therapeutic strategies aimed at preventing the onset of the disease or delaying its progression during the preclinical stages. Achieving this objective would have a positive impact both on patients' quality of life and on the sustainability of health care systems, given the high cost of treatment and the complications associated with T1DM.

ROLE OF INTERFERONS IN T1DM

Before discussing the possible prevention of T1DM, it is useful to review the stages of the disease. There is a consensus classification that divides T1DM into 3 stages: **stage 1**, in which patients show the first signs of autoimmunity, characterized by the presence of autoantibodies against proteins typical of β cells but without metabolic abnormalities; **stage 2**, in which abnormalities in glucose regulation appear, known as dysglycemia; and **stage 3**, in which patients develop the classic symptoms following the clinical onset of the disease.

T1DM is a multifactorial disease resulting from the interaction between an individual's genetic background and environmental factors. In addition, increasing evidence indicates that the β cell is not merely a passive target of the immune system but plays an active role in its own destruction. Among the different hypotheses proposed to explain the initiation of the disease, the one currently supported by the strongest evidence suggests that a viral infection early in life could lead to a mild but persistent infection. This infection would initiate stage 1 by triggering an immune response directed against β cells. In the early stages of the disease, an increase in inflammatory mediators is observed, particularly type I **interferons** (IFNs), such as IFNα and IFNβ, and chemokines produced by the islet cells themselves. Due to this inflammatory environment, β cells increase the expression of major histocompatibility complex class I proteins, making them more easily recognized by autoreactive T lymphocytes. The resulting immune attack promotes the release of additional antigens and the activation of other immune cells, such as B lymphocytes and CD4+ T lymphocytes. This process leads to a persistent inflammatory environment in the pancreatic islet known as **insulitis**. During this phase, there is a transition in immune signaling toward a progressive predominance of type II interferons (IFNγ) and other proinflammatory cytokines, such as interleukin-1β and tumor necrosis factor α (produced by immune cells), characteristic of stage 2. Ultimately, after several years, this process culminates in the third and final stage, characterized by the destruction of a significant proportion of β cells and the appearance of the clinical symptoms of the disease (1, 2).

From a physiological perspective, IFNs are part of the body's defense mechanisms against potentially harmful agents, both of exogenous origin (eg, viruses) and endogenous origin (eg, tumor cells). IFN-mediated signaling begins after binding to specific receptors: **the type I IFN receptor (IFNAR)** and the **type II IFN receptor (IFNGR)**. Because both receptors lack intrinsic kinase activity, their activation depends on association with cytosolic kinases of the **Janus kinase (JAK)** family. Specifically, IFNAR primarily associates with the proteins JAK1 and tyrosine kinase 2 (TYK2), whereas IFNGR associates with JAK1 and JAK2. Activation of these proteins leads to phosphorylation of proteins belonging to the **STAT** family *(signal transducer and activator of transcription)*, which act as transcription factors and induce the expression of the so-called interferon-stimulated genes responsible for many of the proinflammatory effects associated with this signaling pathway ***(Figure 1)***.

In the context of T1DM, persistent activation of the IFN pathway in β cells is associated with processes that promote antigen presentation, the recruitment of immune cells to the pancreatic islet, and increased vulnerability of β cells to apoptosis, thereby contributing to the establishment and progression of the autoimmune process. Because IFN signaling participates in key stages of the pathogenesis of T1DM, this pathway has »

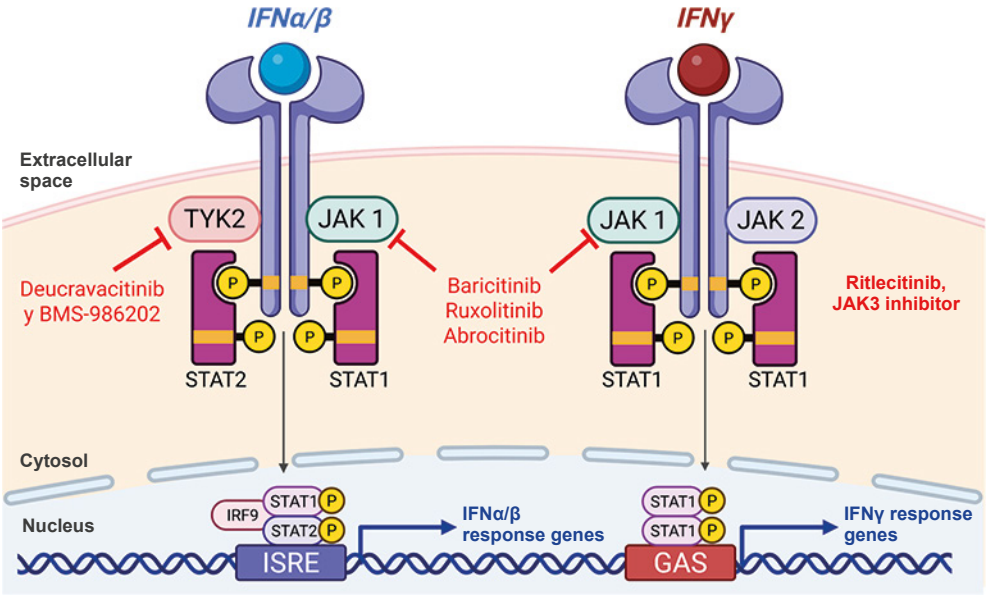

FIGURE 1. Interferon type I and type II signaling pathways and pharmacological blockade points in the JAK–STAT pathway. Schematic representation of intracellular activation induced by type I interferons (IFNα/β) and type II interferon (IFNγ). Binding of IFNs to their receptors activates JAK family proteins, leading to phosphorylation of STAT proteins that regulate gene transcription through interferon response elements. The main JAK inhibitors involved in these pathways are indicated, some of which are already approved for autoimmune diseases. The figure illustrates potential therapeutic intervention points for blocking the interferon response, relevant to their potential application in the prevention of T1DM.

INTERFERON SIGNALING CONTRIBUTES TO THE INDUCTION AND MAINTENANCE OF A PROINFLAMMATORY ENVIRONMENT IN THE PANCREATIC ISLET, MAKING IT A POTENTIAL THERAPEUTIC TARGET IN TYPE 1 DIABETES

» been proposed as a potential therapeutic target for the development of new strategies aimed at modifying the course of the disease.

JAK INHIBITORS

One approach for the development of preventive therapies in T1DM involves modulating signaling pathways involved in the autoimmune attack. As discussed above, IFN-mediated signaling plays a key role in the induction and maintenance of a proinflammatory environment within the pancreatic islet. In this context, interfering with IFN production or signaling emerges as a potential strategy to attenuate the pathological effects of these cytokines, limit immune activation directed against β cells, and ultimately prevent disease progression.

Among the proposed strategies to regulate IFN signaling pathways are, among others, the use of antibodies directed against IFNα or its receptor IFNAR. However, this article focuses exclusively on **JAK inhibitors**. These drugs are small nonbiological molecules that act directly on JAK proteins, interfering with signal transduction mediated by the JAK–STAT pathway. Most currently available JAK inhibitors, such as **ruxolitinib** (Jakafi or Opzelura), **baricitinib** (Olumiant), and **tofacitinib** (Xeljanz), act by binding to the catalytic domain of these proteins, which is responsible for their kinase activity and activation of the JAK–STAT signaling pathway. More recently, compounds targeting the pseudokinase domain, an allosteric regulator of JAK catalytic activity, have been developed to achieve more selective modulation of signaling, as in the case of **deucravacitinib** (Sotyktu).

These drugs are already used in several autoimmune diseases, such as psoriasis, systemic lupus erythematosus, and rheumatoid arthritis, in which multiple cytokines dependent on the JAK–STAT pathway are involved. Given this clinical background, and considering that JAK inhibitors block signaling induced by IFNs and other proinflammatory cytokines, their potential utility as a therapeutic strategy in T1DM has been proposed.

PRECLINICAL EVIDENCE IN T1DM

In the first *in vitro* studies, several broad-spectrum inhibitors such as ruxolitinib and baricitinib were evaluated in pancreatic β cells. These compounds, characterized by their ability to inhibit multiple members of the JAK family, significantly reduced the expression of genes associated with IFNα signaling, such as the chemokine CXCL10 and genes of the major histocompatibility complex class I. In addition, these inhibitors conferred protection against apoptosis induced by proinflammatory cytokines, suggesting a direct effect on β-cell survival (3).

The *in vitro* data obtained with broad-spectrum JAK inhibitors were supported by studies in animal models of T1DM. Among the drugs already mentioned, ruxolitinib demonstrated the ability to prevent disease onset in rats, reinforcing the idea that inhibition of the JAK–STAT pathway may modify the course of the disease (4). Similarly, other JAK inhibitors with different specificity profiles, such as tofacitinib, showed protective properties in murine models of T1DM, including delayed disease onset and modulation of the immune response (3).

Recently, research efforts have progressively shifted toward the development of more selective inhibitors targeting specific proteins within the JAK family. A notable example is deucravacitinib, a specific TYK2 inhibitor indicated for the treatment of moderate-to-severe plaque psoriasis. In *in vitro* studies in β cells, this inhibitor showed high efficacy, suppressing the expression of IFN-induced genes and providing nearly complete protection against the deleterious effects of proinflammatory cytokines (5). Importantly, these effects were observed at lower concentrations than those required for broad-spectrum inhibitors such as ruxolitinib or baricitinib, suggesting a potentially more favorable therapeutic window.

The relevance of these findings has been reinforced by *in vivo* studies. In several murine models, treatment with deucravacitinib was associated with both a reduction in classical T1DM markers in β cells and attenuation of the proinflammatory profile of immune cells, ultimately preventing disease development. Similarly, treatment with BMS-986202, a molecule similar to deucravacitinib, showed additional protective effects, including reduced systemic and tissue inflammation, prevention of β-cell death, and delayed onset of T1DM (3, 6). »

JAK INHIBITORS ARE USED IN AUTOIMMUNE DISEASES AND CURRENT RESEARCH FOCUSES ON THE DEVELOPMENT OF MORE SELECTIVE INHIBITORS

» CLINICAL EVIDENCE IN T1DM

Although evidence in humans remains limited, it is beginning to emerge from isolated clinical observations and from the first clinical trials specifically designed to evaluate the impact of JAK–STAT pathway blockade in T1DM. Among these observations is the clinical case of a 17-year-old patient with T1DM who presented a gain-of-function mutation in one of the components of the IFNα signaling cascade, leading to excessive activation of this pathway. Treatment with ruxolitinib progressively reduced inflammation, resulting in a decreased requirement for exogenous insulin and ultimately complete withdrawal of insulin therapy.[7] However, this represents an exceptional situation linked to a specific genetic alteration.

Regarding **clinical trials**, the **BANDIT** program (Bariciti- »

THE FIRST CLINICAL DATA ON BLOCKADE OF THE JAK–STAT PATHWAY IN TYPE 1 DIABETES MELLITUS ARE PROMISING, BUT MORE RESULTS ARE NEEDED BEFORE WIDESPREAD CLINICAL APPLICATION

» nib in New-onset Type 1 Diabetes; NCT04774224) and the JAKPOT T1DM study (JAK Inhibitors Newly Diagnosed Study; NCT05743244) currently represent the main lines of investigation in this field.

The BANDIT trial is one of the first systematic approaches to the use of JAK inhibitors in patients with T1DM. It is a phase 2, multicenter, randomized, double-blind, placebo-controlled clinical trial that evaluated daily oral administration of baricitinib for 48 weeks in patients diagnosed with T1DM within the previous 100 days. Participants were between 10 and 30 years of age, had at least one T1DM-associated autoantibody, and had detectable C-peptide during the mixed-meal tolerance test. The primary objective was preservation of β-cell function, quantified as C-peptide preservation at 48 weeks. Secondary outcomes included HbA1c levels, insulin dose, glycemic profile »

» measured by continuous glucose monitoring, and adverse events. The results showed that treatment with baricitinib was associated with improved glycemic control. Participants receiving baricitinib maintained higher mean levels of stimulated C-peptide and required less exogenous insulin than the placebo group (8).

Based on these results, 2 new approaches have been designed under the name BARICADE (9).

BARICADE-DELAY (phase 3; NCT07222137) will investigate whether daily administration of baricitinib in individuals at preclinical stages (stage 2 T1DM) can prevent or delay the onset of clinical disease (stage 3) over a 5-year follow-up.

BARICADE-PRESERVE (phase 3; NCT07222332) will evaluate whether the same treatment in newly diagnosed patients can preserve residual β-cell function, measured through C-peptide secretion, over approximately one year.

Both trials are randomized, double-blind, placebo-controlled studies designed to confirm and extend the effects observed in BANDIT in terms of preservation of insulin secretion and metabolic control.

The **JAKPOT T1DM** study, promoted by the TrialNet group, is a phase 2 randomized double-blind placebo-controlled clinical trial evaluating the use of abrocitinib and ritlecitinib to preserve insulin production in patients with T1DM diagnosed within the previous 3 months. In this study, 78 participants aged 12 to 35 years will be assigned to 3 groups (26 abrocitinib, 26 ritlecitinib, and 26 placebo). Participants will receive a daily tablet of one of the drugs for one year, followed by an additional year of follow-up to evaluate residual β-cell function using standardized tests, including the mixed-meal tolerance test and other metabolic measures. The primary endpoint is to determine whether any of these compounds attenuate β-cell damage and whether this preservation translates into improved glycemic control and reduced insulin requirements (19). D

CONSLUSIONES

The data reviewed suggest that blockade of IFN signaling through JAK inhibitors may represent a promising strategy for the prevention and early treatment of T1DM. Both preclinical models and the first clinical trials in humans indicate a protective effect on β cells and a possible preservation of insulin secretion in stages close to disease onset. However, long-term safety and efficacy profile, and the optimal way to integrate these treatments—either as monotherapy, in combination with other immunomodulators, or alongside cell-based therapies—remain unresolved questions that must be addressed in future studies. Therefore, although preliminary results are encouraging, it will be necessary to await the results of ongoing clinical trials before considering widespread clinical implementation of this strategy.

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