Type 1 Diabetes Mellitus (T1DM) is a chronic autoimmune disease affecting millions of people worldwide. Immunoregulation may be achieved in many ways, one of the most promising is regulatory T cell therapy. Here will be discussed the numerous T1DM after-diagnosis therapies that are currently being involved in clinical trials or have proved to be effective in animal models.

**Keywords:** immunotherapy, regulatory T cells, Type 1 Diabetes Mellitus, autoimmunity

---

### 1 T1DM: THE DISEASE

**Type 1 Diabetes Mellitus (T1DM)** is a chronic autoimmune disease where insulin-producing pancreatic β cells are efficiently destroyed by autoreactive T cells, causing hypoglycemia and therefore uncontrolled hyperglycemia. It is a complex disorder in which many other effectors are involved such as macrophages, NK cells, dendritic cells and B cells.

The disease is divided in four different stages:

- **Triggering:** environmental (virus, microbiota, diet) and genetic (HLA class II genes DRB1, DQB1, DOQ1) factors.
- **Autoimmunity:** idet autoimmuneides are created against pancreatic antigens (insulin B chain, GAD65, HSP60).
- **Pre-Diabetes:** 6-cell mass start to be destroyed by autoreactive T cells.
- **Diabetes:** severe dysglycemia, symptomatic stage.

T1DM is mainly a children disease: 85% of the cases → 10-14 years old children.

The lowest incidences are found in China and South America, and the highest incidences in the Nordic countries, UK, Portugal, Canada and also New Zealand.

---

### 2 REGULATORY T CELLS

**Regulatory T cells** belong to a suppressive T cell lineage that regulate T cell responses, establish tolerance and regulate the effectors triggered during the immune response by expressing inhibitory cytokines, cytokis, metabolic disruption, competition or dendritic cell-targeting. There are two types of regulatory T cells:

- **Natural T reg (nTreg):** Thymus
- **Induced T reg (iTreg):** Periphery

- **Generation**
  - **Cytokine Signaling**
    - IL-2, IL-15, IL-7, TGF-β
- **Specificity**
  - **Self-antigens**
  - **Non-self antigens (diet, allergens...)**
- **Markers**
  - CD4+ CD25+ CD127+
- **Function**
  - Suppress immune responses, participate creating self-tolerance, and homoeostasis maintenance

There is a clear relationship between Treg cells and T1DM, with a functional alteration within this population that leads to the loss of self-tolerance. The equilibrium between Teff and T eff cells is unbalanced and might be therefore a causative effect.

---

### 3 T REG IMMUNOTHERAPY

**In vivo** administration of an antigen-based vaccine into the patient aiming to induce protective immunity and produce an efficient T cell proliferation that would restore tolerance. Based in a mainly autoantigen involved in the disease development.

**The antigens used for this therapies correspond to the first antigens against which autoantibodies are created:**

- **GadAlum:** Pancreatic enzyme antigen + Alum
- **DiaPeP27:** Insulin immunodominant antigen
- **GAD65** + Alum or HSP60 p277

**GLOBAL RESULTS**

- Shift the cytokine environment → anti-inflammatory
- Immunomodulatory cytokines (IL-5, IL-10, TGFβ)
- Blockade T cell function, proliferation and differentiation
- Treg induction
- Less insulin need
- Disease regression
- Clinical trials: Phase II
- Treg numbers
- Augment T reg numbers
- Augment C-peptide levels
- Less side effects
- Personalized
- More T reg numbers
- X Theraupetic dose?
- X After-diagnosis

**ADVANTAGES**/

- Easy to administer
- Global therapy
- After-diagnosis
- Well-studied
- Side effects

**DISADVANTAGES**/

**MODELS**

- **nTreg:** APC: artificial/dendritic cells + anti CD3/CD28 + IL-2
- **iTreg:** HLA class II tetramers (peptide-MHC complexes) + GILZ
- **In vivo vs Ex vivo**

**EX VIVO**

- Isolation can be achieved efficiently by FACs as described in Figure 1. Several methods have been described to specifically expand T reg cells:

**Isolation**

- Treg: Regulatory T cells
- Effector T cells: Effector T cells

**ADVANTAGES**/

- Less insulin need
- Disease regression

**DISADVANTAGES**/

- **Therapeutic dose?**
- X After-diagnosis

---

Since the Treg population is disbalanced in T1DM patients, immunotherapies increasing this population seem the fittest possibility for the disease reversion. Among all therapies discussed, only ex vivo T reg expansion has presented remarkable results and regulatory T cells are mainly found on guard and in higher numbers. The finding of a personalized treatment that could revert the disease represents the main objective of the diabetes scientific community.

---

**MAIN BIBLIOGRAPHY:**


---