**Imeglimin Preserves β-cell Function and Mass in Male Zucker Diabetic Fatty Rats**

Sophie Hallakou-Bozec, Micheline Kergoat, Sébastien Bolze, Harold E. Lebovitz

*Poxel SA, 259–261 Avenue Jean Jaurès, 69007 Lyon, France; 2Metabrain Research, 4 Avenue Président F. Mitterand, 91380 Chilly Mazarin, France; 3State University of New York, Health Sciences Center, Brooklyn, NY, USA*

**Abstract**

**Aims**

Fragile insulin resistance and loss of β-cell function are the primary defaults in type 2 diabetes mellitus. Imeglimin has been shown to delay β-cell failure in vitro and in vivo, and has been shown to improve glucose homeostasis in type 2 diabetes mellitus patients with moderate hyperglycemia. The purpose of this study was to investigate the effects of Imeglimin on β-cell proliferation, apoptosis and islet architecture with a decrease in β-cell mass, appearance and proliferation were measured at the end of treatment.

**Methods**

7-week-old ZDF rats were treated with Imeglimin 150 mg/kg daily or 6 weeks of vehicle-treated control ZDF rats. Sections were immunostained with a monoclonal guinea pig anti-insulin antibody and, for each slice, the relative cross-sectional area of islet structure with a decrease in β-cell mass, appearance and proliferation were measured at the end of treatment.

**Results**

Imeglimin treatment significantly improved glucose tolerance (*p<0.05*) and increased insulin levels both in the basal state (+111%, *p<0.001*) and after OGTT (AUC insulin/T0). Urinary glucose was also significantly lower in the Imeglimin group. Overall, Imeglimin-stained β-cells, cells stained with both insulin and insulin were significantly increased in the treatment group compared with control ZDF rat pancreases, which demonstrated an irregular islet structure (*p<0.001*). In parallel, Imeglimin significantly increased the proportion of proliferating β-cells (+111%, *p<0.05*).

**Conclusions**

Imeglimin improved β-cell function and slowed down disease progression by preserving β-cell mass and function in a model of male diabetic rats. Imeglimin 150 mg/kg bid and 150 mg/kg bid increased the proportion of proliferating β-cells (+111%, *p<0.05*).

**Objectives**

The aim of this study was to investigate the pharmacological effects of Imeglimin treatment on the α-cell in Zucker diabetic fatty (ZDF) rats with a particular focus on the impact of Imeglimin on pancreas β-cells.

**Research Methods**

**Material and study design**

• Measurement of blood glucose and plasma insulin levels

**Statistical analysis**

- Student’s t-test was used to compare different groups.
- Analysis of variance (ANOVA) was used to compare different treatments.
- Dunnett t-test: *p<0.05 vs Control
- Dunnett t-test: **p<0.01 vs Control

**Results**

- **Figure 1a and b**
  - Imeglimin treatment significantly increased basal insulinemia by 72% (*p<0.05) and significantly increasing the proportion of proliferating β-cells (+111%, *p<0.001*).

- **Figure 2a**
  - AUC glucose // T0-

**Introduction**

Insulin resistance and β-cell dysfunction are the primary pathophysiological mechanisms underlying type 2 diabetes mellitus. Imeglimin is the first in a new tetrahydrotriazine-containing class of oral glucose-lowering agents, the Glimins. Imeglimin treatment preserved islet architecture and significantly increased β-cell mass, appearance and proliferation were measured at the end of treatment.

**Method**

To determine β-cell proliferation, sections were immuno-stained twice with a polyclonal rabbit anti-caspase 3 antibody and with a polyclonal guinea pig anti-insulin antibody; the number of cells stained with both antibodies was measured. Statistical analysis was performed using analysis of variance followed by a Dunnett t-test: *p<0.05 vs Control.

**Conclusion**

Imeglimin treatment preserves β-cell function and reduces β-cell apoptosis to delay the progression of pathophysiological mechanisms underlying type 2 diabetes mellitus in ZDF rats.