Effect of Rimonabant on Glycemic Control in Insulin-Treated Type 2 Diabetes
The ARPEGGIO Trial

Short title: Effect of rimonabant in insulin-treated type 2 diabetes

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Additional information for this article can be found in an online appendix at http://care.diabetesjournals.org

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**Objective** — To examine the efficacy and safety of rimonabant, a selective cannabinoid receptor type-1 antagonist, in patients with type 2 diabetes receiving insulin monotherapy.

**Research, design and methods** — Patients (n = 368; HbA1c ≥ 7%) were randomized to rimonabant 20 mg/day or placebo in this 48-week, double-blind, placebo-controlled multicenter trial. Change in baseline HbA1c to Week 48 (primary outcome), and changes in body weight, waist circumference, and lipid levels (secondary outcomes) were assessed.

**Results** — Rimonabant significantly reduced baseline HbA1c vs. placebo (-0.89% vs. -0.24%; \( P < 0.0001 \)), and significantly greater improvements were observed in cardiometabolic risk factors. More rimonabant patients achieved >10% reduction in mean total daily insulin dose vs. placebo (\( P = 0.0012 \)) and fewer required rescue medication (\( P < 0.0001 \)). Hypoglycemia, nausea, dizziness, anxiety, and depression were more frequent with rimonabant.

**Conclusions** — Rimonabant improved glycemic control and cardiometabolic risk factors in patients with type 2 diabetes receiving insulin.

ClinicalTrials.gov identifier: (NCT00288236)
The increasing prevalence of obesity is contributing to a type 2 diabetes epidemic (1). Current standard of care of type 2 diabetes targets control of lipid and blood pressure levels, as well as glucose control (1–3). Most classes of antidiabetic agents are associated with weight gain, spurring research into therapeutic agents that improve both weight and glycemia, along with favorable effects on other co-morbidities (4).

The endocannabinoid system contributes to energy homeostasis, and lipid and glucose metabolism regulation (5). Treatment with the selective cannabinoid type 1 (CB1) receptor antagonist rimonabant improves multiple cardiometabolic risk factors in overweight/obese patients (6–10), as well as glycemic control in patients with drug-naïve type 2 diabetes (SERENADE study) (11) or disease suboptimally controlled on sulfonylurea/metformin (RIO-Diabetes study) (8).

ARPEGGIO evaluated once-daily rimonabant 20 mg on glycemic control in patients with type 2 diabetes inadequately controlled on insulin monotherapy (a population considered therapeutically challenging). It should be noted that the clinical development of rimonabant has stopped and the compound withdrawn from the market.

**RESEARCH DESIGN AND METHODS**

Eligible patients were ≥18-years-old with type 2 diabetes, screening HbA1c ≥7%, and receiving insulin monotherapy for ≥3 months (≥30 U/day for ≥4 weeks). Type 1 diabetes was excluded with C-peptide < 1.0 ng/dl. Patients with a history of depression and/or past/current antidepressant treatment were included.

Institutional Review Boards and Independent Ethics Committees at each center approved the protocol. The study was conducted in accordance with the Declaration of Helsinki. Patients provided written informed consent.

Following a 14-day screening period, patients were randomized (1:1; stratified by HbA1c level) to placebo or rimonabant 20 mg (oral, once daily before breakfast) for 48 weeks.

Patients were advised to follow a controlled diet and increase physical activity. The total daily dose of insulin was to be maintained at a stable level (<10% increase/decrease of baseline dose). Use of rescue medication (increased insulin dose, oral medication) was at the investigator's discretion if the patient met certain criteria; such patients remained in the study.

Primary endpoint was the change from baseline to study end (Day 336) in HbA1c. Secondary endpoints included changes in glycemic parameters (FPG; patients meeting HbA1c <7% and <6.5% targets; introduction of rescue medication; change in mean total daily insulin dose [MTDID]); proportion of patients with decreased total daily insulin dose (>10% of baseline dose); lipid parameters (high-density lipoprotein cholesterol [HDL-C], triglycerides, low-density lipoprotein cholesterol [LDL-C], total cholesterol, total cholesterol:HDL-C ratio); body weight; waist circumference. In addition to standard safety assessments, a scripted neurological and psychiatric questionnaire was completed at each visit (see online appendix at http://care.diabetesjournals.org).

**RESULTS**
In total, 366 patients were randomized (n = 179, rimonabant; n = 187 placebo), and 284 completed treatment (134 [74.9%], rimonabant; 150 [80.2%] placebo). Demographic and baseline clinical characteristics were similar across groups (Supplementary Table 1, online appendix).

At Week 48, rimonabant produced significantly greater reductions in HbA1c and FPG levels versus placebo, and significantly more patients achieved target HbA1c levels (Supplementary Table 2, online appendix). HbA1c levels decreased continuously with rimonabant without plateau (Figure 1a). Within both groups, higher baseline HbA1c levels correlated with greater absolute HbA1c reductions; between-group differences favored rimonabant within all baseline HbA1c categories (Figure 1b). Rimonabant resulted in a significantly greater change in MTDID than placebo (mean difference -2.90; \( P = 0.0004 \)), and more patients reduced MTDID by >10%. Significantly fewer patients receiving rimonabant required rescue medication. Days with at least one non-symptomatic hypoglycemic event were greater with rimonabant than placebo (2.34 vs. 1.18 days, respectively; not significant).

Significantly greater improvements with rimonabant versus placebo occurred in body weight (Figure 1c), waist circumference, HDL-C, triglycerides, and total cholesterol:HDL-C ratio. No between-group differences were observed for total cholesterol or LDL-C changes.

The overall incidence of treatment-emergent adverse events (TEAEs) was similar between groups (Supplementary Table 3, online appendix); there were slightly fewer serious TEAEs with rimonabant versus placebo. TEAEs were mild to moderate in intensity, generally occurred early in treatment, and resolved without further corrective therapy. Metabolism/nutritional and psychiatric TEAEs occurred more frequently with rimonabant than placebo. Psychiatric disorders occurred in 31.3% of rimonabant-treated patients compared with 18.7% for placebo. Serious hypoglycemia was reported in four rimonabant patients versus two on placebo.

**CONCLUSIONS**

ARPEGGIO showed that rimonabant 20 mg significantly reduced HbA1c levels and improved multiple cardiometabolic risk factors in patients with type 2 diabetes receiving various types of insulin monotherapy, consistent with clinical trials of rimonabant in other type 2 diabetes populations (8, 11).

Similar to previous studies and diabetes pharmacotherapy in general, HbA1c reductions were greatest in patients with highest baseline HbA1c (12). ARPEGGIO was characterized by a higher mean baseline HbA1c than patients in the SERENADE and RIO-Diabetes studies (8, 11), and a larger fall in HbA1c may have been expected. The result may have been affected by weight loss (although significant, was less in this study and may have been mitigated by larger increases in glysuria) and reduced insulin dosing in the rimonabant group secondary to hypoglycemia.

Weight loss was less than that observed in other studies (8, 11). Weight gain is often associated with insulin therapy. In addition, patients in the ARPEGGIO study (mean diabetes duration, 14 years) were characterized by advanced \( \beta \)-cell loss and variable insulin resistance. Rimonabant-induced weight
loss occurs through central effects in reducing food intake and through peripheral metabolic pathways (altered substrate utilization, changes in adiponectin, changes in energy expenditure) (13). This study showed that rimonabant facilitates weight loss in patients receiving insulin and may independently impact glucose, but the absolute change may be attenuated compared with non-diabetic patients or those receiving oral agents.

The safety profile of rimonabant was concordant with studies in similar patient populations (8,11). Patients with a history of psychiatric illness (depression/anxiety) were not excluded. Few serious psychiatric AEs occurred (one case of suicidal ideation with rimonabant), consistent with previous studies involving patients with a psychiatric illness history (14).

ARPEGGIO further supports the endocannabinoid system as a therapeutic target for overweight and glycemia. Further evaluation of this system is needed to achieve effective and well-tolerated agents.

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Disclosure: Dr. Hollander has served on the advisory boards for sanofi-aventis, Pfizer, Novo Nordisk, and Merck; is a consultant for Orexigen, Sankyo, and Pfizer; is on the speakers bureau for Pfizer, Merck, and sanofi-aventis; has received research support only as part of multicenter clinical trials. Dr. Amod has received honoraria from sanofi-aventis and has served on the advisory boards for MSD, Eli Lilly, Servier, and Novartis. Dr. Litwak has served on the advisory boards for sanofi-aventis, Roche, Pfizer, Eli Lilly, Novo Nordisk, and Novartis; is a board member for Eli Lilly, and sanofi-aventis; has received research support from Roche, sanofi-aventis, and Novo Nordisk. Dr. Chaudhari is an employee of sanofi-aventis US.

Figure 1. (a) Change in HbA_1c over time; (b) change in HbA_1c according to baseline level; (c) change in body weight over time
REFERENCES
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(a) Mean (SEM) HbA1c (%)

Placebo (n)  Rimonabant (n)

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<th>Visit</th>
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(b) Change in HbA1c (%)

Baseline HbA1c category 7%–8.5% 8.5%–10% ≥10%

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(c) Mean (SEM) change in body weight (kg)

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