The cardiometabolic drug rimonabant: after 2 years of RIO-Europe and STRADIVARIUS

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This editorial refers to ‘Long-term effect of CB1 blockade with rimonabant on cardiometabolic risk factors: two year results from the RIO-Europe Study’† by L.F. Van Gaal et al., on page 1761

The prevalence of obesity and associated metabolic/cardiovascular disease has reached epidemic proportions in industrialized and developing countries. Dietary and behavioural approaches are insufficient to maintain weight loss and to fight this trend. Therefore, effective and safe new pharmacological therapies are absolutely required to overcome this obesity burden. One promising new strategy is the blockade of the endocannabinoid system which is involved in the regulation of energy balance, food intake, and lipid/glucose metabolism.1

Rimonabant is a first-in-class, selective cannabinoid receptor type 1 (CB1 receptor) antagonist, which has been shown to reduce body weight consistently in obese and overweight individuals.2–5 Data from the Rimonabant in Obesity (RIO) trial programme revealed that 1-year therapy with rimonabant results in a 4.7 kg greater mean weight loss than placebo.6 In addition, rimonabant treatment has been shown to exert beneficial actions on metabolic risk factors, with an increase in high-density lipoprotein (HDL)-cholesterol, a decrease in triglycerides, and an improvement of insulin sensitivity parameters (e.g. HOMA-IR index).2–5 With the exception of the RIO-North America study, most results were documented over a 1-year study duration, and long-term clinical efficacy and safety data have been limited. In RIO-North America, rimonabant-treated patients were re-randomized after 1 year to receive placebo or to continue to receive the same rimonabant dose for the second year.3 The 1-year placebo group continued on placebo for the second year. Due to high rates of discontinuation after 1 year in all groups (placebo, 49%; rimonabant 5 mg, 49%; rimonabant 20 mg, 45%), total patient numbers after the second year were limited (placebo n = 214, rimonabant 20 mg continued n = 257, rimonabant 20 mg followed by placebo n = 225), and have to be taken into account when interpreting the data. However, RIO-North America demonstrated that the patients treated with rimonabant in year 1 + 2 maintained their reduced body weight in the second year of treatment. Consistently, the improvement in metabolic risk factors such as HDL-cholesterol and triglycerides was maintained. In contrast, patients who were switched from rimonabant to placebo regained most of their previous weight loss. Taken together, the only previously published long-term 2-year clinical study with rimonabant confirmed maintenance of its beneficial clinical actions observed in the first year of treatment.

The other side of the ‘rimonabant coin’ comprises its side effect profile, in particular its adverse psychiatric effects. In a recent meta-analysis of the 1-year data of the four trials in the RIO programme, an increased rate of depression and depressive symptoms has been documented.6 Psychiatric adverse effects have resulted in a revised product label for rimonabant by the European Medicines Agency (EMEA), and in a recommendation against rimonabant approval by the US Food and Drug Administration (FDA) in 2007. Up to now, 2-year data for long-term clinical safety in the RIO trial programme were only available from the RIO-North America study. In RIO-North America, the 1-year rate of discontinuation because of depressed mood disorders including depression, major depression, depressed mood, and depressive symptoms was higher in patients receiving 20 mg rimonabant (27/1219) compared with placebo (8/607). Interestingly, the 2-year data revealed no major difference for the rate of depressed mood disorder-related discontinuation among the treatment groups, suggesting that adverse events with rimonabant occur mainly in the first year after initiation of drug therapy. Together, these safety concerns have to be taken into consideration when treating patients with rimonabant, and recommendations in the product information should be strictly followed. This includes the contra indication in patients with ongoing major depression or treatment with antidepressants, and immediately stopping the drug if a patient develops depression.

Van Gaal and colleagues have now presented the second set of long-term results from the RIO-trial programme.7 The 2-year results of the RIO-Europe study are presented from 168 patients
in the placebo group and 355 in the rimonabant 20 mg group in the intention-to-treat (ITT) population. Regarding the efficacy analysis, weight reduction achieved during the first year was almost fully maintained after 2 years, with a mean difference between placebo and active treatment of −4.2 kg in favour of rimonabant. Along this line, beneficial changes of risk factors such as an increase in HDL-cholesterol, lowering of triglycerides, and improvement of insulin resistance were also present after 2 years of therapy. These data are consistent with the 2-year results of the RIO-North America study, and confirm the long-term efficacy of this therapy. Analysis of adverse effects also revealed results consistent with previously published data. In particular, the overall rate of depressed mood disorders leading to discontinuation substantially decreased in the second year, with 1/168 (0.6%) in the placebo group [year 1: 9/305 (3%)3] and 4/355 (1.1%) in patients treated with 20 mg rimonabant [year 1: 22/599 (3.7%)].5 However, overall numbers continued to be higher in the rimonabant group.

How do the 2-year results from RIO-Europe help in evaluating the efficacy–safety profile of rimonabant? The results providing additional long-term data for rimonabant treatment are reassuring concerning the desired metabolic effects seen in the RIO-North America study. Rimonabant maintains its beneficial actions on body weight and metabolic risk factors over 2 years, and adverse actions such as depressive mood disorders decrease during long-term treatment. Therefore, these data definitively help in supporting a more positive efficacy–safety profile in the second year of treatment.

However, the final assessment of efficacy and safety of a ‘cardiometabolic’ drug requires the answer to an additional question: does the improvement of metabolic risk factors translate into cardiovascular protection which may overcome the safety concerns? The recently published STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study) trial aimed to address this question.6 In this randomized, double-blind, placebo-controlled trial, the effect of rimonabant on progression of coronary atherosclerosis was assessed in 839 patients with visceral obesity and coronary artery disease. Patients were treated with either placebo or rimonabant 20 mg, and atherosclerosis was evaluated by intravascular ultrasound (IVUS) prior to randomization and after 18 months. Consistent with previously published studies, rimonabant significantly lowered body weight and resulted in an improvement of metabolic and inflammatory risk factors. The primary end-point of this study, i.e. change in percentage atheroma volume measured by IVUS, was negative, but significant favourable effects were detected for the secondary end-point, total atheroma volume. Multiple reasons may account for the absence of a pronounced beneficial action of rimonabant in STRADIVARIUS, including the imaging technique, the tested surrogate end-point, the patient population, and the limited duration of therapy in the trial. Nevertheless, these data show that the translation of risk factor improvement into beneficial vascular actions of drugs appears to be highly complex. In the case of rimonabant, STRADIVARIUS could not provide a definitive answer as to whether the drug exerts cardiovascular protective actions or not.

Taken together, after publication of the 2-year RIO-Europe study and the STRADIVARIUS trial, the evaluation of rimonabant’s efficacy–safety profile still contains some open questions. Rimonabant provides an efficacious anti-obesity drug therapy comprising long-term weight reduction and improvement of metabolic risk factors. At present, uncertainty about its safety might be overcome by strictly following the recommendations of the current product information including the contraindication in patients with ongoing major depression or treatment with antidepressants, and immediately withholding the drug if a patient develops depression.

Studies such as the 2-year RIO-Europe and STRADIVARIUS contribute substantially to our understanding of the actions of rimonabant in patients, but finally to solve the question on cardiovascular risk reduction and safety we have to await the results from ongoing outcome trials with rimonabant such as CRESCENDO.

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