# Potential role of the endocannabinoid receptor antagonist rimonabant in the management of cardiometabolic risk: a narrative review of available data

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**Abstract:** The endocannabinoid system (ECS) is an endogenous physiological system composed of two cannabinoid receptors and several endogenous ligands. The ECS is intimately involved in appetite regulation and energy homeostasis, which makes it an intriguing target for pharmacological treatment of obesity, diabetes, and the metabolic syndrome. Rimonabant is the first cannabinoid receptor (CB-1) antagonist being studied and utilized to treat obesity (it is approved in Europe but is currently under review in the United States). Large randomized trials with rimonabant have demonstrated efficacy in treatment of overweight and obese individuals with weight loss significantly greater than a reduced calorie diet alone. In addition, multiple other cardiometabolic parameters were improved in the treatment groups including increased levels of high density lipoprotein cholesterol, reduced triglycerides, reduced waist circumference, improved insulin sensitivity, decreased insulin levels, and in diabetic patients improvement in glycosylated hemoglobin percentage. There was an increase in the adverse effects of depression, anxiety, irritability, and nausea in rimonabant-treated groups. This novel medication may become an important therapeutic option in the fight to reduce cardiovascular disease worldwide through its unique action on cardiometabolic risk.

**Keywords:** rimonabant, endocannabinoid, metabolic syndrome, obesity

## Introduction

Despite important therapeutic advances, cardiovascular disease (CVD) remains the number one cause of death worldwide (World Health Organization 2006a). Traditional risk factors for cardiovascular disease include hypertension, dyslipidemia, smoking, family history of coronary disease, and aging. Major efforts have been made to identify and treat these risk factors with varying degrees of success. Most of the pharmacological advances that have been made in reducing cardiovascular risk are designed to treat individual traditional risk factors.

Over the past decade, increasing evidence has implicated a number of emerging risk factors that also appear to independently identify patients at risk for CVD. The ever increasing list of emerging risk factors includes elevated triglycerides (TG), small low density lipoprotein cholesterol (LDL-C) particle size, insulin resistance and glucose intolerance, proinflammatory (as measured by high sensitivity c-reactive protein and other assays) states, and prothrombotic states (Grundy et al 2004). Many of these risks factors tend to cluster in individual patients compounding their risk of developing CVD. These same metabolic abnormalities also appear to predict the development of type 2 diabetes mellitus (T2DM). Both the National Cholesterol Education Program's (NCEP) Adult Treatment Panel III and the World Health Organization (WHO) have recognized this clustering of risk factors in their definitions of the

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metabolic syndrome (MetSyn) (Alberti 1998; Expert Panel 2001). While considerable debate has developed surrounding the exact definition and utility of MetSyn, it appears clear that these risk factors do indeed cluster in patients who are overweight and/or exhibit significant insulin resistance, and that this clustering increases the risk of both CVD (Lakka et al 2002) and T2DM (Lorenzo et al 2003), often referred to as "cardiometabolic risk."

Despite increased physician and patient awareness, the prevalence of obesity, MetSyn, and T2DM are increasing in the United States (Ford et al 2004) and worldwide (WHO 2006b). While lifestyle modification, including heart-healthy eating, caloric restriction, and increased physical exercise, remain key to stemming this epidemic of cardiometabolic risk, novel pharmacological options that affect weight, insulin resistance, and other cardiometabolic risk factors simultaneously could have considerable clinical potential. Unfortunately, our current guidelines tend to focus on treating individual risk factors, and most of our current pharmacological interventions do not simultaneously address the multiple risk factors associated with increased cardiometabolic risk.

Concomitant with increased awareness of the importance of MetSyn, our understanding of the role the adipocyte plays in the development of T2DM and CVD has also evolved. Traditionally, adipocytes have been thought of as mere storage depots for energy; however, there is now an increased understanding that the abdominal adipocyte is a metabolically active endocrine and paracrine organ that plays an important role in mediating lipogenesis, glucose homeostasis, and inflammation, most likely through effects on the synthesis of leptin, adiponectin, free fatty acids, tumor necrosis factor alfa, and plasminogin activation inhibitor-1 (Kershaw and Flier 2004). Pharmacological interventions that could affect adipocyte function could have a potentially beneficial role in the modification of cardiometabolic risk.

## Role of the endocannabinoid system in cardiometabolic risk

Over the last 15 years, there has been considerable research involving the endocannabinoid system (ECS), an endogenous physiological system important in the regulation of feeding behavior, lipid metabolism, and energy balance. The system is composed of two G-protein cannabinoid receptors (CB-1, CB-2) and their associated endogenous ligands (De Petrocellis et al 2004). Anandamide (ADA) and 2-arachidonylgycerol (2-AG) are the most studied of the endogenous ligands.

In mammals, CB-1 are found in the central nervous system, gastrointestinal organs, and adipose tissue. CB-2 are found almost exclusively in peripheral immune cells and are not thought to be involved in energy homeostasis (Howlett et al 2002).

In the central nervous system, the endocannabinoids (ADA and 2-AG) are produced on-demand (not stored in vesicles) from phospholipids or triglycerides on the post-synaptic membrane (Piomelli 2003). Once produced, these molecules are immediately released into the synapse where they are free to activate the pre-synaptic CB-1 receptor. Binding to the pre-synaptic CB-1 receptor then inhibits the release of other neurotransmitters stored there (Di et al 2003). This process, called retrograde signaling, appears to act as a modulatory feedback system controlling neurotransmitter release. After interacting with the CB-1 receptor these ligands are immediately degraded by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (Cravatt et al 1996; Dinh et al 2002).

In the brain, CB-1 are found primarily in the mesolimbic areas and the hypothalamus. Compared with lean control animals, in the obese mouse model, hypothalamic levels of both ADA and 2-AG were found to be higher (Di Marzo et al 2001). Interestingly, levels of these ECS ligands were significantly reduced when overweight and normal animals were subsequently administered the beneficial gut hormone leptin. In another experiment, levels of 2-AG and ADA were measured in the rat brain during fasting, feeding, and after satiation (Kirkham et al 2002). Levels of the endocannabinoids were very high in the mesolimbic area of the fasting animals but lower in the feeding animals, suggesting this area is involved in motivational behavior to find and consume food.

CB-1 receptors are also found in peripheral tissues including adipocytes, pancreas, gut, liver and muscle. Compared with lean controls, adipocytes from obese rats exhibited a greater than 3-fold upregulation in expression of CB-1, demonstrated by increased levels of messenger RNA (Bensaid et al 2003). Stimulation of CB-1 in adipose tissue induces lipoprotein lipase activity while blockade causes up-regulation of the protein adiponectin. Adiponectin increases free fatty acid oxidation and increased insulin sensitivity in skeletal muscle and liver, while decreasing vascular inflammation (Chandran et al 2003). In skeletal muscle, CB-1 stimulation reduces insulin-mediated glucose uptake (Liu et al 2005). In the liver, ECS activation leads to increases in de novo lipogenesis, a critical component in diet-induced obesity (Osei-Hyiaman et al 2005), and in the gastrointestinal tract, ADA levels increase during food deprivation suggesting a peripheral hunger signal (Gomez et al 2002).

Perhaps the most striking examples of the importance of the ECS in weight gain and glucose metabolism are demonstrated in experiments using CB-1 knock-out mice. These genetically engineered mice with absent CB-1 represent an experimental model of significantly decreased ECS activation. CB-1 knockout mice are leaner than wild type mice and consume less food (Cota et al 2003). When treated with the CB-1 antagonist rimonabant, wild type mice decrease food intake to the level of CB-1 knockout mice (Di Marzo et al 2001). Ravinet Trillou studied the differences in CB-1 knockout mice and wild type mice when both were given a choice of a very palatable high fat diet or standard diet (Ravinet Trillou et al 2004). Wild type mice fed the high fat diet exhibited a marked increase in weight compared with those fed the standard diet. However, in the CB-1 knockout mouse the difference in weight gain between high fat diet and standard diet was significantly attenuated (Table 1). Over the course of the study the hyperphagia in wild type mice diminished but the weight gain over controls continued. The CB-1 knockout mice also chose the high fat diet, but they did not eat excessively and remained lean. Additionally, compared with those fed a standard diet, wild type mice fed a high fat diet demonstrated a significantly increased glucose response to exogenous insulin injection (increased insulin resistance), while once again this effect was markedly attenuated in the CB-1 knockout mouse.

Multiple studies also indicate that the ECS is overactive in overweight and obese humans. Engeli et al demonstrated that obese women have elevated circulating levels of the endocannabinoids and reduced activity of the inactivating enzyme FAAH. These levels were not reversed with a 5% weight loss (Engeli et al 2005). Sipe et al showed that overweight and obese individuals have an approximately two-fold increased frequency of an abnormal FAAH gene, resulting in decreased activity of this endocannabinoid-inactivating enzyme and presumably higher levels of ECS activation (Sipe et al 2005).

**Table 1** Body weight of wild type mice (+/+) and CB1 knockout mice (-/-) fed a standard diet (SD) or a free choice of SD and high fat diet (SD/HFD) for 12 weeks

| Group | Body weight (g) |
|---|---|
| SD-/- | 31.8 ± 1.2 |
| SD/HFD-/- | 34.3 ± 2.4 |
| SD+/+ | 41.1 ± 1.6 |
| SD/HFD+/+ | 48.6 ± 1.6 |

Adapted from Ravinet Trillou et al (2004). Results reported as mean + standard error measure. $p < 0.05$ for SD-/- vs SD+/+; $p < 0.05$ for SD/HFD+/+ vs SD+/+.

Thus, multiple lines of evidence in both human and animal models suggest that over-activity of the ECS is intimately involved in management of weight, energy, and metabolism. As such, interruption of ECS over-activity may provide an attractive therapeutic target for management of the increased cardiometabolic risk associated with overweight and obesity.

## Rimonabant, a selective CB-1 antagonist

Rimonabant, an orally available selective CB-1 antagonist, has shown promise in both animals and humans in the treatment of cardiometabolic risk, especially in patients who are overweight, obese, or have T2DM. It represents the first agent affecting the ECS to undergo extensive clinical development. Rimonabant has been approved for weight loss in overweight and obese persons in Europe, but at the time of this publication has not been approved in the US.

### Pharmacology and pharmacokinetics of rimonabant

In healthy human subjects, rimonabant shows linear pharmacokinetics in doses up to 20 mg, which is the maximum dose used in large-scale clinical trials (Turpault et al 2006). Median time to maximal plasma concentration in the obese patient is 2 hours. The half-life of rimonabant is 6–9 days in non-obese subjects; in obese subjects the half-life is approximately 16 days due to a larger area of distribution. Likewise, the time required to reach steady state is also increased in obese subjects (25.5 days) versus the non-obese (12.7 days). Gender does not affect pharmacokinetics. In vitro, rimonabant is metabolized in part by hepatic CYP3A enzyme pathways, leading to the potential for drug interactions with common CYP3A inhibitors such as ketokonazole, itraconazole, ritonavir, and clarithromycin, and inducers such as rifampin, phenytoin, phenobarbital, and carbamezapine (Gadde and Allison 2006). Further studies are needed to determine the clinical significance of these potential interactions.

### Animal data with rimonabant

Ravinet Trillou et al demonstrated that mice with diet induced obesity treated with 5 weeks of rimonabant were 20% lighter than those receiving placebo (Ravinet Trillou et al 2003). In addition, the weight loss in response to a 24-hour fast was greater in animals treated with rimonabant, suggesting that metabolic effects other than simple reduction of caloric intake contributed to the weight loss. The rimonabant treated mice also demonstrated a 50% decrease in plasma

insulin levels, a 53% decrease in leptin levels, a statistically significant decrease in non-esterified fatty acids, and statistically significant improvement in insulin sensitivity. When these experiments were repeated in CB-1 knockout mice rimonabant had no effect, indicating that the beneficial effect of rimonabant is mediated entirely through the CB-1 receptor. Interestingly, CB-1 knockout mice also appear to have a greater tendency towards anxiety-like responses and anhedonic state (Martin et al 2002).

In an obese rat model, Vickers et al showed that 4 weeks of treatment with rimonabant decreased food intake and weight. Discontinuation of rimonabant led to increased food intake and significant weight regain (Vickers et al 2003). This finding suggests that the effects of rimonabant on weight are reversible upon cessation of treatment.

Leptin is a beneficial adipose tissue derived neuropeptide that appears to be strongly associated with weight and metabolism (Kershaw and Flier 2004). Rats with genetically deficient leptin signaling are obese and are used as a research model of obesity. It appears that leptin modulates appetite at least in part by reducing levels of endocannabinoids in the hypothalamus (Di Marzo et al 2001). As mentioned above, Bensaid et al demonstrated that blockade of CB-1 by rimonabant increased levels of adiponectin in wild type mice and in obese rats with defective leptin signaling (Bensaid et al 2003). Adiponectin is a protein product of white adipose tissue and is beneficial in lipid and glucose metabolism. Some of the known effects of adiponectin include increasing skeletal muscle fatty acid transport and oxidation, improvement of hepatic insulin sensitivity, and decreasing vascular inflammation (Chandran et al 2003).

Together these animal studies demonstrate that by blocking CB-1, administration of rimonabant leads to sustained weight loss, decreased free fatty acid levels, and improvement in insulin sensitivity that is reversible upon discontinuation of the drug. These effects are likely mediated through multiple mechanisms including decreased energy intake and changes in metabolism related to increases in circulating levels of leptin and adiponectin.

## Efficacy of rimonabant in clinical trials of overweight and type 2 diabetes mellitus

In a 16-week phase IIb trial enrolling obese individuals, average weight loss was 1.1, 3.5, 3.9, and 4.4 kg for once daily doses of placebo, 5 mg, 10 mg, and 20 mg of rimonabant respectively (Di Marzo and Matias 2005). In the phase III clinical trial program doses of 5 mg and 20 mg daily were compared with placebo. Since the 20 mg dose is likely to be the most utilized in clinical practice, presentation of the results of these trials will focus on that dose. As part of this phase III program there have been four major completed, placebo-controlled, double-blind, randomized controlled trials of rimonabant in humans: Rimonabant in Obesity – Europe (RIO-EU), Rimonabant in Obesity – Lipids (RIO-Lipids), Rimonabant in Obesity – North America (RIO-NA), and Rimonabant in Obesity – Diabetes (RIO-DM) (Van Gaal et al 2005; Després et al 2005; Pi-Sunyer et al 2006; Scheen et al 2006). Participants in all trials were overweight (body mass index [BMI] $\geq$27 kg/m$^2$) or obese (BMI $\geq$30 kg/m$^2$) and were randomized to one of three groups, rimonabant 5 mg daily, rimonabant 20 mg daily, or placebo and followed for at least 1 year. All patients were asked to follow a hypo-calorie diet aimed at reducing caloric intake by approximately 600 kcal/day. In each study, prospective subjects underwent a 4-week placebo run-in, during which a number of patients were excluded; these patients were not included in subsequent intention-to-treat (ITT) analysis.

Exclusion criteria common to all four trials included clinically significant cardiovascular, endocrine, pulmonary, neurological, dermatological, gastrointestinal, hepatic, hematological, renal, and psychiatric diseases (including severe depression). In all but the RIO-DM trial diabetic patients were excluded. Common measured parameters included changes from baseline in weight, waist circumference, systolic blood pressure (SBP) and diastolic blood pressure (DBP), changes in levels of high density lipoprotein cholesterol (HDL-C), serum triglycerides (TG), fasting glucose, fasting insulin, and total cholesterol to HDL-C ratio. In each study, change from baseline in each parameter was calculated using ITT, last observation carried forward (LOCF) analysis. Detailed differences in methodology and the results of each trial are described below.

## Rimonabant in obesity – Europe (RIO-EU)

In RIO-EU 1507 obese patients (BMI $\geq$30 kg/m$^2$) or overweight patients (BMI $\geq$27 kg/m$^2$) with either hypertension or dyslipidemia were randomized to placebo, 5 mg or 20 mg of rimonabant daily (Van Gaal et al 2005). Eighty per cent of participants were female, 94% were white, and the mean age at baseline was 45 years. At baseline, 41% had hypertension, 61% had dyslipidemia, and 41% met criteria for the metabolic syndrome. The mean baseline weight was 101 kg. Only 61% of participants completed the trial. In the intention to treat (ITT) analysis with the last observation carried forward (LOCF) the 5 mg group decreased body weight 3.4 kg ($p = 0.002$ vs placebo) and the 20 mg group decreased 6.6 kg ($p < 0.001$ vs placebo). The proportions of

patients who lost at least 5% of their baseline weight after 1 year were 51%, 33%, and 19% in the 20 mg, 5 mg, and placebo groups respectively. Waist circumference decreased 3.9 cm ($p = 0.002$ vs placebo) in the 5 mg group and 6.5 cm ($p < 0.001$ vs placebo) in the 20 mg group.

Compared with placebo, 20 mg rimonabant led to statistically significant increases in HDL-C (+22.3% vs +13.4%; $p < 0.001$) and decreases in total cholesterol to HDL-C ratio, triglycerides (–6.8% vs +8.3%; $p < 0.0001$), fasting glucose, fasting insulin, and insulin resistance (measured by the homeostasis model assessment [HOMA]); effects with 5 mg rimonabant did not reach statistical significance compared with placebo except in HDL-C (+16.2% vs +13.4%; $p = 0.048$). Based on their statistical analysis, the investigators suggested that only approximately 50% of the effect on triglycerides and HDL-C could be explained by weight loss, adding support to a weight-independent metabolic effect of CB-1 blockade. No significant changes in systolic blood pressure, total cholesterol or LDL-C were apparent. In the 20 mg rimonabant group, the incidence of MetSyn decreased from a baseline of 42.2% to 19.6% after 1 year while only changing from 39.9% at baseline to 31.4% at 1 year in the placebo group. Table 2 illustrates the placebo subtracted change from baseline in the major metabolic variables measured at the completion of the study.

## Rimonabant in obesity – lipids (RIO-Lipids)

In RIO-Lipids 1036 obese or overweight patients (BMI 27–40 kg/m$^2$) with dyslipidemia (defined by elevated ratio of total cholesterol to HDL-C >4.5 in women or >5 in men or elevated triglyceride levels >1.69 to 7.90 mmol/L) were randomized to placebo, 5 mg or 20 mg of rimonabant daily for 1 year (Després et al 2005). Exclusion criteria were similar to the other trials but also included patients receiving pharmacological treatment for dyslipidemia in the 6 weeks preceding the trial. Approximately 60% of the participants were female and 62% completed the study. Race of the participants was not reported. Baseline mean age was 48 years, average weight was approximately 96 kg, and average BMI was about 34 kg/m$^2$.

In ITT-LOCF analysis, the 5 mg group decreased weight by 3.1 kg ($p < 0.001$ vs placebo) and the 20 mg group decreased weight by 6.9 kg ($p < 0.001$ vs placebo). The proportion of patients who lost at least 10% of their weight after 1 year was 33% in the 20 mg group and 7% in the placebo group. Waist circumference in the 5 mg group decreased 3.5 cm ($p = 0.029$ vs placebo) and 7.1 cm ($p < 0.001$ vs placebo) in the 20 mg group. HDL-C increased 14.2% ($p = 0.025$ vs placebo) in the 5 mg group and 19.1% ($p < 0.001$ vs placebo) in the 20 mg group. The 20 mg group also showed significant beneficial changes in total cholesterol to HDL-C ratio, peak size of LDL-C particles, proportion of small LDL-C, triglycerides, and fasting insulin levels. Although there were no significant differences between groups, total cholesterol increased modestly and LDL-C increased by about 7% in all three treatment groups. Systolic and diastolic blood pressure demonstrated a modest statistically significant decrease in the 20 mg group compared with placebo. Subjects randomized to 20 mg rimonabant also demonstrated beneficial effects on leptin and adiponectin levels that were not seen with placebo. In the 20 mg rimonabant group, c-reactive protein decreased from 5.0 to 4.1 mg/dL ($p = 0.02$ vs placebo) compared with only a modest decrease from 5.3 to 4.9 mg/dL in the placebo group. The 5 mg group did not show statistically significant changes in any of these blood pressure, lipid, or neurohormonal parameters. Table 2 illustrates the placebo subtracted change from baseline in the major metabolic variables measured at the completion of the study.

## Rimonabant in obesity – North America (RIO-NA)

In RIO-NA 3045 obese or overweight subjects were randomized to placebo, 5 mg rimonabant or 20 mg rimonabant daily. Unique to RIO-NA following the first year of treatment, patients who received rimonabant were re-randomized to receive the same dose of rimonabant or placebo for a second year; subjects initially randomized to placebo remained on placebo for the full two years. Females composed 81% of the patients and 84% were white. Baseline average weight was approximately 105 kg and BMI was about 38 kg/m$^2$. Only 52.6% of participants completed the first year of the study. Results in this trial were reported as placebo subtracted changes rather than the absolute values reported in the other trials.

In the ITT-LOCF analysis, after one year placebo subtracted weight was reduced 1.3 kg ($p < 0.001$ vs baseline) in the 5 mg group and 4.7 kg ($p < 0.001$ vs baseline) in the 20 mg group. In the 20 mg rimonabant group 25% of subjects demonstrated at least a 10% weight loss compared with only 9% in the placebo group. The 20 mg group had statistically significant placebo subtracted improvements in waist circumference (–3.6 cm; $p < 0.001$) and triglycerides (–13.2; $p < 0.001$%). Placebo subtracted HDL-C improved 2.3% in the 5 mg group ($p = 0.01$ vs baseline) and 7.2% ($p < 0.001$ vs baseline) in the 20 mg group. Total cholesterol to HDL-C ratio also improved significantly in both treatment groups. Fasting insulin level decreased (1.7 μU/mL in the 5 mg group and 2.8 μU/mL in the 20 mg group) and insulin resistance as measured by HOMA improved (Table 2). Prevalence of

**Table 2** Selected placebo subtracted results from rimonabant in obesity (RIO) trials after 1 year. Only shown are those results that are statistically signficant

| Measure | RIO-EU | RIO-Lipids | RIO-NA | RIO-DM |
|---|---|---|---|---|
| Weight (kg) | –4.7 | –5.4 | –4.7 | –3.9 |
| Waist circumference (cm) | –4.2 | –4.7 | –3.6 | –3.3 |
| SBP (mmHg) | ns | –1.8 | ns | –2.4 |
| DBP (mmHg) | ns | –1.5 | ns | ns |
| HDL-C (% change) | 8.9 | 8.1 | 7.2 | 8.3 |
| TG (%change) | –15.1 | –12.4 | –13.2 | –16.4 |
| Total C:HDL-C ratio | –0.29 | –0.32 | –0.28 | –0.35 |
| Fasting glucose (mmol/L) | –0.06 | ns | ns | –0.97 |
| Fasting insulin (μU/mL) | –2.8 | –2.6 | –2.8 | ns |
| Peak size LDL-C particle (Å) | nr | 1.2 | nr | nr |
| Adiponectin (μg/ml) | nr | 1.5 | nr | nr |
| Leptin (ng/ml) | nr | –3.8 | nr | –3.4 |
| HOMA-IR (%) | –0.7 | nr | –0.8 | –1.1 |
| CRP (mg/L) | nr | –0.5 | nr | –1.4 |

Data are from ITT-LOCF analysis. Data are placebo subtracted from the 20 mg rimonabant treatment group.
**Abbreviations:** ns, not significant ($p > 0.05$); nr, not reported; SBP, systolic blood pressure; DBP, diastolic blood pressure; C, cholesterol; HOMA-IR, insulin resistance measured by homeostasis model assessment; CRP, C-reactive protein.

the MetSyn decreased from a baseline of 34.8% to 21.2% in the 20 mg group. Investigators used analysis of covariance (ANCOVA) to demonstrate that the effects in HDL-C, TG, fasting insulin, and insulin resistance were twice that attributable to the weight loss alone, once again pointing to a weight-independent effect of CB-1 blockade. Neither treatment group showed significant changes in fasting glucose, SBP, or DBP. Table 2 illustrates the placebo subtracted change from baseline in the major metabolic variables measured at the completion of the first year of the study.

During the second year of the study, subjects who continued to receive 20 mg of rimonabant maintained the weight loss achieved during the first year (placebo subtracted mean loss of 7.4 kg) and continued to show significant beneficial changes in HDL-C, triglycerides, total cholesterol to HDL-C ratio, waist circumference, fasting insulin, and insulin resistance. However, subjects who received rimonabant 20 mg the first year followed by placebo the second year slowly regained most of their previously lost weight and waist circumference. After completion of year two, subjects who received 1 year of rimonabant followed by 1 year of placebo had similar weight and metabolic parameters to those who received placebo for the full two years. Based on these results, it appears that chronic administration of rimonabant, at least longer than 1 year, may be necessary in order to maintain the beneficial clinical effect over the long term.

## Rimonabant in obesity – diabetes (RIO-DM)

Although the results of RIO-DM have been presented at multiple national meetings and have been widely disseminated, the results were not published as a complete manuscript in a peer-reviewed journal until fall 2006 (Scheen et al 2006). In RIO-DM 1045 overweight or obese patients with T2DM were randomized to daily doses of placebo, 5 mg, or 20 mg of rimonabant for 1 year in a fashion similar to the above-mentioned trials. Additional inclusion criteria for RIO-DM included monotherapy oral hypoglycemic treatment with either metformin or a sulfonylurea for at least 6 months, fasting glucose of 5.55–15.04 mmol/L (100–271 mg/dL), and hemoglobin A1C (HbA1C) between 6.5% and 10%. Exclusion criteria included any clinically significant microvascular or macravascular diseases related to T2DM, systolic BP >160 mmHg, or diastolic BP >95 mmHg, pregnancy, lactation, recent change in smoking status, or the use of anti-obesity drugs in the prior 3 months. In addition, subjects using concomitant medications known to affect weight, including antidepressants, were excluded. Patient demographics were roughly similar across the three treatment groups. Overall, 88.5% of participants were white and 50.1% were female. Average baseline weight was about 98 kg and mean baseline HgbA1C was 7.3%. The majority of patients were on metformin monotherapy at baseline. Sixty-six per cent of patients completed the 1-year follow-up.

In the ITT-LOCF analysis, the placebo group lost 1.4 kg body weight compared with a 2.3 kg loss ($p = 0.01$ vs placebo) for the 5 mg treatment group and a 5.3 kg loss ($p < 0.0001$ vs placebo) for the 20 mg group. Waist circumference decreased 1.9 cm in the placebo group compared with a decreases of 2.9 cm ($p = 0.02$ vs placebo) and 5.2 cm ($p < 0.0001$ vs placebo) respectively in the 5 mg and 20 mg groups. Beneficial effects

were also seen in fasting glucose, insulin resistance, HDL-C, total cholesterol to HDL-C ratio, triglycerides, and systolic BP. However, after adjusting for weight loss, the residual effects on triglycerides and systolic BP were not significant. Like in RIO-Lipids, all three randomized groups showed an increase in LDL-C of approximately 7%. Table 2 illustrates the placebo subtracted change from baseline in the major metabolic variables measured at the completion of the study.

Unlike the other studies, RIO-DM also examined change in placebo subtracted HbA1C. After one year of therapy, in the 20 mg group there was an absolute decrease in HbA1C of –0.6% compared with a change of only +0.1% with placebo ($p < 0.0001$). Additionally, 42.9% of the patients receiving 20 mg of rimonabant achieved a HbA1C of <6.5% compared with only 20.8% in the placebo group. According to the statistical analysis used by the investigators, the effects of rimonabant 20 mg on HbA1C were twice that attributable to weight loss alone. A similar side-effect profile was seen in this trial compared with the other RIO trials and is discussed in the following section.

## Safety and tolerability of rimonabant in the RIO clinical trials

As noted above, in each RIO study a large number of patients (34%–47%) did not complete the full year of study drug. While concerning, this high drop-out rate is similar to that seen in other trials of obesity treatment and there was no statistically significant difference in overall discontinuation rates between treatment groups. Although overall discontinuation rates were similar, discontinuations specifically due to adverse effects were greater in the rimonabant-treated groups. The most common reasons for discontinuation in treatment groups included the psychiatric disorders of depression, anxiety, and irritability, followed by nausea. Discontinuation rates due to psychiatric complaints and disorders for each of the RIO trials are shown in Table 3. Overall, nausea is the most common adverse event reported with rimonabant in these clinical trials. The incidence of adverse effects diminished over time suggesting either a degree of tolerance or that the majority of side-effects occurred fairly quickly after initiation of treatment.

All of the RIO trials screened for depression and anxiety throughout the studies with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith 1983). This scale contains 7 items assessing depression and 7 items assessing anxiety with each item scored from zero to three. Scores ≥11 usually require additional assessment. There were no reported differences in groups on this scale; however, exclusion criteria for each study specifically excluded patients with a known history of severe depression. Additionally, in three of the trials (RIO-Europe, RIO-NA, and RIO-DM) subjects taking either antidepressants or medications known to alter weight (including anti-depressants) were also excluded. Importantly, the number of patients in each group who scored ≥11 on the HADS and the number removed after subsequent psychiatric consultation have not been included in the published manuscripts (Gadde and Allison 2006).

Safety was also assessed by examining the effect of treatment on multiple other parameters including QTc intervals on electrocardiogram, hematological parameters, liver function, kidney function, and blood pressure. No significant incidence of adverse effects was seen in any of these parameters in any trials. In RIO-DM there was a higher incidence of hypoglycemia in the rimonabant 20 mg group compared with placebo (5% vs 2%) and this occurred more frequently in patients on concomitant sulfonylurea (but not on metformin) therapy.

## Future directions for research with rimonabant

The beneficial cardiometabolic effects of rimonabant have led to interest in further research in multiple areas. Ongoing trials include those examining the effects of rimonabant on cardiovascular events endpoints (myocardial infarction, stroke, or cardiovascular death), progression of atheroma, visceral fat accumulation, and prevention of diabetes in individuals with impaired glucose tolerance. Of these planned clinical trials, perhaps the Strategy to Reduce Atherosclerosis

**Table 3** Discontinuations during RIO trials due to any adverse event and due to psychiatric disorders

| | **Any adverse event** | | **Psychiatric disorders** | |
|---|---|---|---|---|
| | Placebo | Rimonabant 20 mg | Placebo | Rimonabant 20 mg |
| RIO-EU | 9.2% | 14.5% | 5.2% | 7.0% |
| RIO-Lipid | 7.0% | 15.0% | 2.4% | 7.6% |
| RIO-NA | 7.2% | 12.8% | 2.3% | 6.2% |
| RIO-DM | 5.5% | 15.0% | 0.9% | 3.6% |

Development Involving Administration of Rimonabant: the Intravascular Ultrasound Study (STRADIVARIUS) may be the most clinically meaningful. This long-term international effort will examine the effect of rimonabant therapy on an important surrogate endpoint, the progression of coronary atheroma as measured by intravascular ultrasound, using similar methodology to what has been done with other proven risk reduction strategies. Most of these trials are several years away from completion but will answer some important questions about the effects of rimonabant in managing cardiometabolic risk. These trials should also add important data on safety and tolerability in persons with important comorbid conditions.

Hopefully, future studies will also seek a more diverse patient population since the published trials to date have included predominantly white patients. It will also be important to study the effects of rimonabant in patients with a history of mild depression and other psychiatric conditions and in persons on pharmacological treatment for depression. The currently published trials specifically excluded these conditions yet many obese patients either have a diagnosis of or risk factors for depression (Herva et al 2006). It will also be important to study the effects of rimonabant with concomitant use of other weight loss medications such as orlistat and sibutramine as well as other lipid-lowering and hypoglycemic agents. Since rimonabant works through a unique mechanism, combination therapy may offer a cumulative effect on weight loss and other cardiometabolic endpoints.

In addition to effects on cardiometabolic risk, the central nervous system effects of rimonabant may be useful in other conditions such as tobacco or alcohol dependence. At least one large prospective randomized clinical trial investigating the use of rimonabant for smoking cessation has been completed. The Studies with Rimonabant and Tobacco Use—United States (STRATUS-US) was a 10-week trial where chronic tobacco users desiring to quit were randomized to either placebo, 5 mg rimonabant, or 20 mg rimonabant once daily (Anthenelli and Dale 2004). Patients in the 20 mg group were more successful at quitting smoking (36%) than the placebo group (21%). Nevertheless the US Food and Drug Administration (FDA) issued a letter to the manufacturer stating that rimonabant will not be considered for smoking cessation at this time (Sanofi Aventis 2006). Future studies should continue to look into this indication as well as usefulness in other addictive disorders such as alcoholism.

## Perspective and conclusion

Rimonabant has recently received approval for marketing as a weight management drug in Europe with the precaution that it should not be used in patients with serious uncontrolled psychiatric illnesses like major depression or who are receiving anti-depressant medication. In the US, the FDA issued an "approvable" letter for rimonabant as a weight loss agent, but at the time this manuscript was written it has not yet received final approval for marketing in the US (Sanofi Aventis 2006).

Assuming that rimonabant will soon be available to practitioners and their patients worldwide, it will be interesting to see how this unique therapeutic agent is used clinically. Although the absolute magnitude of the effect on weight loss is similar to other available pharmacological agents, the overall effect on weight is relatively modest, especially compared with the effect that can be attained with bariatric surgery or medically supervised very low calorie diets in motivated individuals. The placebo-corrected reduction in weight of about 5 kg seen with rimonabant 20 mg daily in the RIO trials, while certainly clinically meaningful, represents only a small fraction of the excess weight many overweight and obese individuals need to lose in order to significantly improve their health and quality of life.

Although regulatory agencies have so far offered indications for rimonabant as a weight management drug only, the true potential benefit of this novel pharmacological approach lies in its ability to positively affect multiple cardiometabolic risk factors simultaneously. Since statistical analysis suggests that only approximately 50% of the affect on HDL-C, triglycerides, and HgbA1C (in subjects with DM) can be attributed to weight loss alone, presumably rimonabant should offer additional benefit in reducing cardiometabolic risk over and above other similarly effective weight loss strategies. It should be noted that in keeping with the design of the RIO studies all the results cited in this review use ITT-LOCF analysis. Given the high rate of non-completers in these clinical trials, these results underestimate the benefits of those who completed 1 year of therapy. At least in RIO-EU, subjects who remained on rimonabant for the full year demonstrated significantly more favorable results than those who did not complete the study.

Nonetheless, it should be noted that the changes in lipid parameters seen in RIO-Lipids and other studies are relatively modest compared with other available therapies such as nicotinic acid, fibrates, and even high dose omega 3s, and importantly there is no apparent effect on LDL-C, the primary target of intervention for patients with dyslipidemia according to the US National Cholesterol Education Program. As patients on previous lipid lowering agents were excluded from RIO-Lipids, it is also unclear whether

the effect rimonabant has on lipids will be additive to that of other agents, including statins. In patients with diabetes the reduction in HgbA1C seen with rimonabant 20 mg daily is once again no greater in magnitude than that seen with other available oral hypoglycemic agents; however, again the effect on other metabolic parameters appears to offer a unique benefit in reducing cardiometabolic risk. Although all the efficacy data currently available demonstrates considerable benefit in a number of cardiometabolic parameters, determining the true magnitude of reduction in cardiometabolic risk will require long-term clinical trials (like STRADIVRIOUS) examining the effect on more clinically relevant endpoints than lipid parameters and levels of neurohormones.

Of course, as with all pharmacological interventions, the demonstrable benefit of rimonabant must be balanced against its safety and tolerability profile. In the >6600 subjects in the RIO studies, rimonabant proved be generally safe and well tolerated. However, practitioners must keep in mind that this was a highly selected population carefully screened to exclude subjects who would be most prone to the psychiatric adverse events seen more commonly with rimonabant than with placebo. Given the high prevalence of mood and other psychiatric disorders among overweight and obese patients, pending further trials practitioners will need to be especially vigilant in screening for symptoms of depression before initiation of and during treatment with rimonabant. One final potential limitation of rimonabant as a useful clinical tool was also seen in RIO-NA where patients who discontinued rimonabant for the second year of the trial had substantial weight regain and reversal of previous improvements in lipid parameters. As such, it appears that treatment for well past 1 year may be needed to achieve sustainable reductions in cardiometabolic risk.

In sum, based on its unique mechanism of action, reasonable safety and tolerability profile, and the beneficial improvements in weight, waist circumference, HDL-C, triglycerides and other factors seen in the RIO trials, in patients who are not at risk for significant depression rimonabant appears to be a potentially important therapeutic agent in helping reduce cardiometabolic risk in overweight and obese individuals, especially those with concomitant metabolic syndrome or T2DM. Its overall clinical effectiveness in reducing the progression of surrogate measures of atherosclerosis and the incidence of T2DM and CV events remains to be determined, as does its incremental benefit when added to other risk reduction strategies and its position in our current treatment paradigms.

## Disclosures

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