Cannabinoid-1 Receptor Blockade in Cardiometabolic Risk Reduction: Efficacy

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Intra-abdominal fat mass, or central adiposity, and cardiovascular risk are strongly correlated. Adipose tissue is an endocrine organ that secretes hormones and cytokines influencing appetite, energy metabolism, and atherosclerosis. National Heart, Lung, and Blood Institute (NHLBI) guidelines recommend that if dietary and lifestyle interventions fail to produce favorable outcomes in individuals with a body mass index >27 and weight-related comorbidities, as well as those with a body mass index >30, treatment plans may include weight loss medication. The endocannabinoid system has recently emerged as a viable target for the pharmacologic treatment of obesity and cardiometabolic risk factors. This article provides an in-depth review of efficacy results from clinical trials of rimonabant, a selective cannabinoid-1 receptor. (Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in further studies.) Compared with placebo, rimonabant 20 mg significantly decreased body weight and waist circumference measurements. In addition, rimonabant was associated with favorable changes in several other cardiometabolic risk factors, including significant increases in serum levels of high-density lipoprotein cholesterol and adiponectin, as well as reductions in serum levels of triglycerides, small, dense low-density lipoprotein particles, C-reactive protein, insulin resistance, and glycosylated hemoglobin. **(Am J Cardiol 2007;100[suppl]:18P–26P)**

Obesity prevalence continues to reveal an upward trend, with national data collection representative of US citizens estimating that 66.3% aged >20 years are overweight or obese.[1] Increased fat mass is associated with an increased risk for developing numerous life-threatening, chronic, and debilitating illnesses.[2] Of particular concern is the association of increased fat mass with cardiovascular disease (CVD) risk.[3] A recent comprehensive report published by the American Heart Association (AHA) estimates that 1 in every 3 US adults has CVD.[4] It is estimated that in 2007, 700,000 people in the United States will have a new heart attack and 500,000 will have a recurrent attack. The direct and indirect costs of CVD are estimated at $431.8 billion.[4] The need to reduce CVD risk in the United States is obvious.

Intra-abdominal fat mass, or central adiposity, can be conveniently assessed via waist circumference and is strongly correlated with CVD risk.[5,6] Once thought to be inactive tissue, adipose tissue is now recognized as an endocrine organ that secretes hormones and cytokines that influence health as well as disease initiation and progression.[2] Secretions from adipose tissue influence appetite and energy metabolism. Leptin, a hormonal secretion from fat cells, is produced in amounts proportional to total fat mass.[7,8] Leptin crosses the blood–brain barrier to bind to its receptor in the hypothalamus, where it activates signals that inhibit food intake and increase energy expenditure.[7] Adipokines secreted by adipose tissue such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-6, IL-8, plasminogen activator inhibitor-1, angiotensinogen and resistin are associated with proinflammatory and prothrombotic processes.[9,10] The secretion of these factors, along with free fatty acids, reduces insulin sensitivity and contributes to endothelial dysfunction.[11] Adipose tissue also secretes adiponectin, a cytokine that has anti-inflammatory actions.[11] Adiponectin positively influences the vasculature by many mechanisms, some of which include enhancement of endothelium-dependent and -independent vasodilation, suppression of atherosclerosis, reduction in TNF-α levels and suppression of TNF-α effects on the endothelium, inhibition of effects of oxidized low-density lipoprotein (LDL) on endothelial cells, enhanced production of nitric oxide, and stimulation of angiogenesis.[11]

Weight gain leading to reductions in adiponectin secretion as well as increases in proinflammatory cytokines may

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lay the path for the development of dysglycemia, hypertension, and dyslipidemia, currently referred to as cardiometabolic risk factors. The presence of cardiometabolic risk factors increases the risk of developing overt CVD.[11,12]

The Metabolic Syndrome and Cardiometabolic Risk Factors

The metabolic syndrome—a cluster of metabolic abnormalities believed to increase the risk for CVD—includes obesity, elevated blood pressure, impaired fasting glucose, and dyslipidemia.[12] Some experts have recently questioned the clinical usefulness of identifying this syndrome in individuals.[13] Subtle differences in diagnostic criteria from the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III), the International Diabetes Federation (IDF), and the World Health Organization (WHO), have contributed to the debate over the usefulness of this syndrome.[14] However, in a recent joint report by the American Diabetes Association (ADA) and the AHA, the organizations state that the importance of identifying and treating the core set of risk factors in the development of CVD "cannot be overstated." The "core set of factors" is identified as comprising prediabetes, hypertension, dyslipidemia, and obesity.[12] Recent estimates report that approximately 47 million people in the United States meet the NCEP ATP III criteria for the metabolic syndrome, with prevalence ranging from a low of 6.7% in individuals aged 20–29 years to a high of 43.5% in those aged 60–69 years.[4]

Treating Obesity and Cardiometabolic Risk Factors

Practice guidelines for treating overweight and obesity have been outlined by the National Heart, Lung, and Blood Institute (NHLBI).[15] Recommendations include dietary and lifestyle interventions for overweight individuals (specifically, those with a body mass index [BMI] of ≥25–29.9).[15] The NHLBI recommends that if dietary and lifestyle interventions fail to produce favorable outcomes in persons with a BMI ≥27 and weight-related comorbidities, as well as those with a BMI ≥30, treatment plans may include weight loss medication.[15] To date, only 2 medications have received US Food and Drug Administration (FDA) approval for long-term treatment of obesity.[16] Sibutramine, a serotonin reuptake inhibitor, and orlistat, which reduces fat absorption by inhibiting pancreatic lipase, received FDA approval in 1997 and 1999, respectively.[16,17]

Not much success has been reported in the long-term maintenance of body weight loss through dietary and lifestyle interventions.[17–19] Multiple external factors in our "obeseogenic" environment have been identified as instigators of weight regain.[18,19] Maintenance of weight loss is also hampered by a redundant system of internal physiologic mechanisms designed to defend body fat mass as a survival measure.[7] Research combining the benefits of behavioral guidance with medication treatment show promise in increasing weight loss outcomes in obese individuals.[20]

Targeting mechanisms that enhance abdominal fat loss and influence hormonal and cytokine release to positively affect health outcomes presents a pharmaceutical challenge.[21] The endocannabinoid (EC) system has recently emerged as a viable target for the pharmacologic treatment of obesity and cardiometabolic risk factors.[17,22–26] This article briefly reviews the mechanisms of the ECS that influence body weight regulation and cardiometabolic risk factors and presents an in-depth review of the efficacy of the selective cannabinoid-1 (CB_1) blocker rimonabant* in treating obesity and cardiometabolic risk in clinical trials.

The Endocannabinoid System

The EC system influences body weight regulation along with many other physiologic functions.[23] It appears to act via the central nervous system as well as peripherally to modulate appetite, energy, lipid, and glucose metabolism.[22,25,27] The EC system consists of the cannabinoid receptors, their endogenous cannabinoid (EC) ligands, and the enzymes for EC biosynthesis and degradation.[22,23] Cannabinoid ligands bind with specific receptors and activate the EC system. Evidence points to overactivation of the EC system in obese individuals.[25,27]

In the 1990s, 2 cannabinoid receptors were identified and cloned: the CB_1 receptor and the cannabinoid-2 (CB_2) receptor. CB_1 receptors are located in many areas of the central nervous system, as well as in the gastrointestinal tract, the heart and lungs, the gonads, and in peripheral tissue, such as in adipocytes, hepatocytes, skeletal muscle, and endothelial cells.[22,23,25] CB_2 receptors appear to influence immune function and are found primarily in the thymus, spleen, and tonsils.[22,23,25] EC ligands that bind to and activate CB_1 receptors have also been identified and appear to influence body weight regulation and cardiometabolic risk factors.[22,25] These include *N*-arachidonoylethanolamine (anandamide or AEA) and 2-arachidonoylglycerol (2-AG). Elevated levels of AEA and 2-AG have been demonstrated in obese versus lean individuals,[27] an important finding that implicates EC system dysregulation in the pathophysiology of obesity. AEA is degraded by fatty acid amide hydrolase, and 2-AG is degraded by monoglycerol lipase.[23] Low levels of fatty acid amide hydrolase have been associated with increased body weight, pointing perhaps to AEA elevations secondary to lower degradation potential.[27]

Research in animal models has shown that blocking the actions of the EC system at the CB_1 receptor site with

* Recently, an FDA Advisory Committee recommended a delay in the approval of rimonabant because of safety issues that need to be addressed in further studies.

Table 1
Basic study design and measurements for the Rimonabant in Obesity (RIO) trials

Study Characteristic	RIO–North America[31]	RIO-Europe[32]	RIO-Lipids[33]	RIO-Diabetes[34]
BMI inclusion criteria	≥30 or >27 with treated or untreated hypertension or dyslipidemia	≥30 or >27 with treated or untreated hypertension or dyslipidemia	27–40 and triglycerides >1.69 mmol/L (150 mg/dL) to 7.90 mmol/L (700 mg/dL); and/or cholesterol/HDL-C ratio of >5 (men) or >4.5 (women)	27–40 with type 2 diabetes mellitus treated with metformin or sulfonylurea monotherapy for ≥6 mo; HbA_{1c} of 6.5–10%; fasting glucose 5.55–15.04 mmol/L (100–270 mg/dL)
Sex and age	Men and women ≥18 yr	Men and women ≥18 yr	Men and women 18–70 yr	Men and women 18–70 yr
No. of participants	3,045	1,507	1,036	1,047
Length of study	24 mo	12 mo	12 mo	12 mo
Primary outcome measurement	Body weight change over first yr Prevention of weight regain in second year	Body weight change over 1 yr	Body weight change over 1 yr	Body weight change over 1 yr
Secondary outcome measurements	Waist circumference HDL-C LDL-C Total C Triglycerides Fasting glucose Fasting insulin Insulin resistance (HOMA-IR) Blood pressure (diastolic and systolic) Presence of metabolic syndrome (NCEP ATP III criteria)	Waist circumference HDL-C LDL-C Total C Triglycerides Fasting glucose Fasting insulin Insulin resistance (HOMA-IR) Blood pressure (diastolic and systolic) Presence of metabolic syndrome (NCEP ATP III criteria)	Waist circumference HDL-C LDL-C Total C Triglycerides Fasting glucose Fasting insulin Blood pressure (diastolic and systolic) Presence of metabolic syndrome (NCEP ATP III criteria) Proportion of small LDL particles Peak size of LDL particles Adiponectin Leptin C-reactive protein	Waist circumference HDL-C LDL-C Total C Triglycerides Fasting glucose Fasting insulin Insulin resistance (HOMA-IR) Blood pressure (diastolic and systolic) Presence of metabolic syndrome (NCEP ATP III criteria) Change in HbA_{1c} Leptin C-reactive protein

BMI = body mass index; C = cholesterol; HbA_{1c} = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = homoeostasis model assessment for insulin resistance; LDL-C = low-density lipoprotein cholesterol; NCEP ATP III = National Cholesterol Education Program Adult Treatment Panel III.

SR141716 (rimonabant) promotes weight loss and increases energy expenditure.[22–29] In addition to reducing body weight and increasing energy expenditure, rimonabant administration was found to reduce plasma insulin, glucose, triglycerides, and LDL cholesterol levels, and to inhibit lipoprotein lipase in rodent models.[30] Findings from animal trials have provided encouragement for research leading to the investigation of CB_1 receptor blockers for the treatment of obesity and cardiometabolic risk factors in humans. Rimonabant has been studied in several phase 3 trials examining the safety and efficacy of this compound in >6,600 overweight and obese adults. These trials are summarized below.

Rimonabant in Obesity Trials

Study design and participant population: A total of 4 multisite Rimonabant in Obesity (RIO) trials have been completed: RIO–North America, RIO-Europe, RIO-Lipids, and RIO-Diabetes. These studies were conducted in centers throughout the United States, Canada, Europe, and South America. The 4 trials used a randomized, double-blind, placebo-controlled design.[31–34] The primary outcome of the RIO trials was to assess the effect on body weight in overweight and obese participants treated for 12 months with rimonabant 5 mg or 20 mg compared with placebo. RIO–North America also investigated the efficacy of rimonabant in preventing weight regain in year 2 of this 2-year trial. At year 2, all participants receiving placebo continued to receive placebo and those in the treatment groups were rerandomized to either receive the same dose as in year 1 or to receive placebo.[31] RIO-Lipids recruited overweight and obese participants with untreated dyslipidemia.[33] RIO-Diabetes included overweight and obese participants with type 2 diabetes mellitus receiving metformin or sulfonylurea as monotherapy.[34]

Secondary outcome measurements reported in the RIO trials include waist circumference, blood pressure, lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, LDL cholesterol, and triglycerides), fasting glucose and fasting insulin, as well as measures of insulin resistance and prevalence of the metabolic syndrome.[31–34] The RIO-Diabetes and RIO-Lipids trials measured serum CRP and leptin levels.[33,34] RIO-Lipids also measured serum

levels of adiponectin, the peak size of LDL particles, and the percentage of small, dense atherogenic LDL cholesterol particles.[33] RIO-Diabetes measured percent change in glycosylated hemoglobin (HbA_{1c}) in all participants.[34] Table 1 summarizes the study design and outcome measures for the 4 RIO trials.

Initial screening of participants included physical examination, electrocardiography, clinical chemistry, thyroid function test, hematology, and urinalysis, as well as body weight, height, and waist measurements. Safety evaluations conducted during the study period included a physical examination with collection of vital sign and adverse event information. Hematology and serum chemistry were evaluated on a regular basis. The validated Hospital Anxiety and Depression Scale (HADS) was administered to evaluate mood and psychological traits at screening and throughout the study period. All study participants received instructions on a 600-kcal (1 kcal = 4.2 KJ) reduced diet and were encouraged to increase physical activity.[31–34] Study participants in the 3 treatment groups had similar baseline values. Table 2 lists baseline characteristics of the study participants.

Weight: The primary end point in the 4 RIO trials was the change in body weight during a 1-year period.[31–34] The RIO–North America trial continued for 2 years; during year 2, weight loss maintenance was evaluated.[31] In the 4 trials, weight losses in the rimonabant 5-mg and 20-mg groups were significantly greater than in the placebo groups,[31–34] as shown in Table 3. The ranges of weight loss in the rimonabant 20-mg groups (−5.3 to −6.9 kg) were significantly greater than in the placebo groups (−1.4 to −1.8 kg). The ranges of participants achieving ≥5% weight loss was significantly greater in the rimonabant 20-mg groups versus the placebo groups (48.6%–58.4% vs 14.5%–20%, respectively). A significantly greater range of participants in the rimonabant 20-mg groups achieved a weight loss of ≥10% of body weight compared with those in the placebo groups (16.4%–32.6% vs 2%–8.5%, respectively),[31–34] as shown in Table 4.

RIO–North America continued until the 2-year mark, with rerandomization of participants in year 2. Those in the intention-to-treat population who received rimonabant 20 mg during year 1 of the trial and who were rerandomized to continue with the same dose in year 2 maintained a mean weight loss of −7.4 kg at the end of year 2, whereas those who received rimonabant 20 mg during year 1 and were rerandomized to receive placebo in year 2 regained most of their previously lost weight. In addition, 40% of participants who continued to receive rimonabant 20 mg achieved a weight loss of ≥5% of body weight, whereas only 19% of those in the placebo group achieved this level of weight loss.[31]

Recent evidence shows that a loss of body weight of just 5%–10% can significantly improve health outcomes.[6,35] Pooled data from the 4 trials showed that the rimonabant 20-mg groups exhibited a mean placebo-subtracted weight loss of approximately 5%.[36] These data support the observation that rimonabant can effectively reduce body weight, suggesting that it may improve overall health outcomes.

Waist circumference: Waist circumference is a strong indicator of disease risk.[3,6] Therefore, reduction in waist measurement is a good marker for improvement in health outcomes. Rimonabant 20 mg was robust in reducing waist measurements. Results from the RIO–North America, RIO-Europe, RIO-Lipids, and RIO-Diabetes trials reported significant reductions in waist measurements (−6.1, −6.5, −7.1, and −5.2 cm, respectively), compared with measurements in the placebo groups (−2.5, −2.4, −2.4, and −1.9 cm, respectively).[31–34] Table 5 summarizes changes in waist measurements at 1 year in the 4 trials.

Participants in RIO–North America who remained on rimonabant 20 mg for 2 years had significantly reduced waist circumference measurements compared with those in the placebo group (−5.0 vs −2.2 cm, respectively; $p < 0.001$).[31]

Lipid profile end points: Low serum levels of HDL cholesterol and elevated levels of serum triglycerides help to define the dyslipidemia component of the metabolic syndrome.[12] Treatment with rimonabant 20 mg had a significantly favorable impact on several lipid measurements. There were significant increases in serum levels of HDL cholesterol in the rimonabant 20-mg groups compared with the placebo groups, in RIO–North America (12.6% vs 5.4%, $p < 0.0001$), RIO-Europe (20.5% vs 11.8%, $p < 0.0001$), RIO-Lipids (15.4% vs 7.1%, $p < 0.0001$), and RIO-Diabetes (19.1% vs 11.0%, $p < 0.0001$).[31–34] Investigators reported that 58% of the elevation in HDL cholesterol could not be attributed to the amount of fat mass lost.[31]

Significant reductions in serum triglyceride levels were also reported in the rimonabant 20-mg groups versus the placebo groups in the 4 RIO trials. Favorable changes in the percentage of serum triglycerides in the rimonabant 20-mg groups versus the placebo groups, were reported in RIO–North America (−5.3% vs +7.9%, $p < 0.001$), RIO-Europe (−13.8% vs −0.7%, $p < 0.001$), RIO-Lipids (−9.1% vs +7.3%, $p < 0.001$), and RIO-Diabetes (−12.6% vs −0.2%, $p < 0.001$).[31–34] Researchers reported that 47% of the reduction observed in serum triglyceride levels was independent of weight loss.[31]

Rimonabant did not significantly reduce total cholesterol or LDL cholesterol levels in the RIO trials. However, evidence of a shift in the distribution of LDL particles toward a larger, less atherogenic size was reported in the RIO-Lipids study. The peak size of LDL particles at the 1-year mark in the RIO-Lipids trial revealed an increase in the percent peak size of LDL particles in the rimonabant 20-mg group (0.3%, $p < 0.001$) versus the placebo group (−0.9). In addition, the percent proportion of small, dense atherogenic LDL particles decreased significantly in the rimonabant

Table 2
Rimonabant in Obesity (RIO) trials: baseline patient population

Characteristic	RIO–North America[31]			RIO-Europe[32]			RIO-Lipids[33]			RIO-Diabetes[34]		
	Placebo (n = 607)	Rimonabant 5 mg (n = 1,214)	Rimonabant 20 mg (n = 1,219)	Placebo (n = 305)	Rimonabant 5 mg (n = 603)	Rimonabant 20 mg (n = 599)	Placebo (n = 342)	Rimonabant 5 mg (n = 345)	Rimonabant 20 mg (n = 346)	Placebo (n = 348)	Rimonabant 5 mg (n = 358)	Rimonabant 20 mg (n = 339)
Race/ethnicity (n)												
White	516	1,010	1,027	290	565	555	—	—	—	308	315	302
Black	67	140	132	—	—	—	—	—	—	18	20	19
Sex (n)												
Male	113	245	230	61	127	121	144	130	133	159	186	168
Female	494	969	989	244	476	478	198	215	213	189	176	171
Average age (yr)	44.8	44.4	45.6	45.0	45.4	44.6	47.0	48.1	48.4	54.8	55.9	56.0
BMI, mean	37.6	38	37.2	35.7	36.0	36.0	34.0	34.1	33.9	34.2	34.4	34.1
Weight, mean (kg)	105.0	105.5	103.0	100.0	100.9	101.7	97.0	96.0	95.3	97.1	98.7	97.1
Waist circumference, mean (cm)												
Both sexes	106.0	106.5	104.9	107.7	108.4	108.8	105.7	104.8	104.7	—	—	—
Men	—	—	—	—	—	—	—	—	—	113.7	112.0	111.3
Women	—	—	—	—	—	—	—	—	—	105.3	106.4	106.0
Hypertension (n)	168	367	390	116	264	237	—	—	—	206	218	216
Dyslipidemia (n)	388	767	749	189	371	355	—	—	—	186	202	193
Metabolic syndrome (n)	192	438	419	121	243	251	177	193	183	276	285	276

BMI = body mass index.

Table 3
Weight change* at 1 year in Rimonabant in Obesity (RIO) trial participants (intention-to-treat data)

Trial	Placebo	Rimonabant 5 mg	p Value	Rimonabant 20 mg	p Value
RIO–North America[31]	−1.6	−2.9	<0.001	−6.3	<0.001
RIO-Europe[32]	−1.8	−3.4	0.002	−6.6	<0.001
RIO-Lipids[33]	−1.5	−3.1	<0.001	−6.9	<0.001
RIO-Diabetes[34†]	−1.4	−2.3	0.01	−5.3	<0.001

* Values are given in kilograms.
† Based on modified intention-to-treat data (all randomized participants who received ≥1 dose of study drug).

Table 4
Achievement of 5% or 10% weight loss at 1 year in Rimonabant in Obesity (RIO) trial participants (intention-to-treat data)

Trial	Placebo	Rimonabant 5 mg	p Value	Rimonabant 20 mg	p Value
RIO–North America[31]					
>5% Loss	20%	26.1%	0.004	48.6%	<0.001
>10% Loss	8.5%	10.6%	NS	25.2%	<0.001
RIO-Europe[32]					
>5% Loss	19.2%	33.2%	<0.001	50.9%	<0.001
>10% Loss	7.3%	10.1%	NS	27.4%	<0.001
RIO-Lipids[33]					
>5% Loss	19.5%	NR	NR	58.4%	<0.001
>10% Loss	7.2%	NR	NR	32.6%	<0.001
RIO-Diabetes[34]					
>5% Loss*	14.5%	21.7%	0.02	49.4%	<0.0001
>10% Loss*	2.0%	6.2%	0.01	16.4%	<0.0001

NR = data not reported; NS = not statistically significant.
* Based on modified intention-to-treat data (all randomized participants who received ≥1 dose of study drug).

20-mg group (−1.5%, p = 0.002) and increased in the placebo group (3.2%).[33] Table 6 summarizes changes in lipid measurements and in the incidence of the metabolic syndrome at 1 year in the 4 RIO trials.

Compared with participants receiving placebo for 2 years, those who received rimonabant 20 mg for 2 years in the RIO–North America trial maintained significantly elevated HDL cholesterol (p <0.001) and reduced triglyceride (p <0.001) levels.[31]

Glucose metabolism in the RIO trials: Measures of glucose regulation were improved in the rimonabant-treated groups in the 4 RIO trials.[31–34] Insulin resistance was measured based on the homeostasis model assessment for insulin resistance (HOMA = IR), which is determined by multiplying fasting insulin by fasting glucose and dividing this value by 22.5.[31] These measurements were significantly reduced in the rimonabant 20-mg groups versus the placebo groups in RIO–North America (placebo-subtracted value, −0.6%; p <0.001), RIO-Europe (−0.3% vs 0.4%, respectively; p = 0.002), and RIO-Diabetes (−0.5% vs 0.6%, respectively; p = 0.03).[31,32,34] Researchers reported that 51% of the reduction in insulin resistance was independent of weight loss.[31]

Scheen and colleagues[34] monitored additional measures of glycemic control in a cohort of >1,000 individuals with type 2 diabetes in the RIO-Diabetes trial. Measurement of long-term glucose control was captured in serum HbA_{1c} values at baseline and at the end of 1 year. Change from baseline HbA_{1c} levels in the rimonabant 20-mg group was significantly improved compared with the placebo group (−0.6% vs 0.1%, respectively; p <0.0001). In addition, the percentage of participants who achieved the goal Hb_{A1c} level of <6.5% was significantly greater in the rimonabant 20-mg group than in the placebo group (43% vs 21%, respectively; p <0.0001). The percentage of participants achieving HbA_{1c} levels of <7% was also significantly greater in the rimonabant 20-mg group than in the placebo group (68% vs 48%, respectively; p <0.0001). The significance of the 0.7% placebo-corrected reduction in HbA_{1c} in the rimonabant 20-mg group is illuminated by data from the ADA showing that a 1% reduction in HbA_{1c} translates to a reduction in risk of 21% for any end point related to diabetes.[37]

The Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE): In another more recent trial investigating the efficacy of rimonabant in obese individuals with type 2 diabetes, researchers studied 278 obese, drug-naive patients with type 2 diabetes. SERENADE was a multicenter, randomized, placebo-controlled trial. Participants were randomized to receive rimonabant 20 mg or placebo. This trial was conducted for 6 months; those in the rimonabant 20-mg group had a significantly greater reduction in HbA_{1c} than those in the placebo group (−0.8% vs −0.3%, respectively; p = 0.002). Measurements of weight, waist circumference, and serum triglyceride levels were significantly reduced in the rimonabant 20-mg group com-

Table 5
Change in waist circumference measurements* at 1 year in Rimonabant in Obesity (RIO) trial participants (intention-to-treat data)

Trial	Placebo	Rimonabant 5 mg	p Value	Rimonabant 20 mg	p Value
RIO–North America[31]	−2.5	−3.1	0.08	−6.1	<0.001
RIO-Europe[32]	−2.4	−3.9	0.002	−6.5	<0.001
RIO-Lipids[33]	−2.4	−3.5	0.029	−7.1	<0.001
RIO-Diabetes[34†]	−1.9	−2.9	0.02	−5.2	<0.0001

* Values are given in centimeters.
† Data based on modified intention-to-treat data (all randomized participants who received ≥1 dose of study drug).

Table 6
Rimonabant in Obesity (RIO) trials: change in lipid measurements and prevalence of metabolic syndrome at 1 year (intention-to-treat data)

Measurement	RIO–North America[31]		RIO-Europe[32]		RIO-Lipids[33]		RIO-Diabetes[34]	
	Placebo	Rimonabant 20 mg	Placebo	Rimonabant 20 mg	Placebo	Rimonabant 20 mg	Placebo	Rimonabant 20 mg
% Change in HDL-C level	5.4	12.6†	11.8	20.5†	7.1	15.4†	11.0	19.1†
% Change in triglycerides	7.9	−5.3†	−0.7	−13.8†	7.3	−9.1†	−0.2	−12.6†
Peak size of LDL-C	—	—	—	—	−0.9	0.3†	—	—
% Change in proportion of small LDL-C	—	—	—	—	3.2‡	−1.5‡	—	—
% Decline in metabolic syndrome incidence	8	39†	21.3	53.6†	24	52.2†	18	26‡

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.
*Based on modified intention-to-treat data (all randomized participants who received ≥1 dose of study drug).
† p <0.001, rimonabant 20 mg vs placebo.
‡ p = 0.02, rimonabant 20 mg vs placebo.

pared with the placebo group. Researchers reported that 57% of the improvement in HbA_{1c} values could not be explained by the amount of weight lost.[38]

Rimonabant and serum adipokine levels: The apparent detrimental effect of elevated levels of CRP on cardiovascular health has also been demonstrated. Recent data suggest that elevated levels of CRP may be a strong independent predictor of coronary artery disease.[10] CRP is synthesized mainly in the liver and appears to be regulated by circulating levels of IL-6, as well as IL-1 and TNF-α. CRP can initiate secretion of other proinflammatory adipokines, such as plasminogen activator inhibitor−1, which in turn creates a prothrombotic state.[10] CRP may directly influence the development of atherogenesis by modulation of endothelial function. There is a strong positive correlation between elevated serum CRP levels and obesity.[10]

CRP was measured at baseline and again at the end of the RIO-Lipids and RIO-Diabetes trials. CRP levels measured at the end of year 1 revealed favorable outcomes in the rimonabant 20-mg groups compared with the placebo groups. There was a significant reduction in serum CRP levels in the rimonabant 20-mg group versus the placebo group in RIO-Lipids (−0.9 vs −0.4 mg/L, respectively; p = 0.020) and RIO-Diabetes (−1.4 vs 0.0 mg/L, respectively; p = 0.020).[33,34]

Serum adiponectin levels were measured in the RIO-Lipids trial in a subgroup sample of 691 study participants, with benefit found in the rimonabant-treated group. Participants in the rimonabant 20-mg group had a significantly increased serum adiponectin level (2.2 μg/mL, p <0.001) compared with the placebo group (0.7 μg/mL). Researchers reported that 57% of the increase in adiponectin level was independent of the loss in fat mass.[33]

Reductions in the incidence of the metabolic syndrome: Rimonabant has been shown to favorably influence body weight, waist circumference, triglycerides, HDL cholesterol, LDL particles, insulin resistance, CRP, and adiponectin levels. Therefore, it is no surprise that the prevalence of the metabolic syndrome, according to the diagnostic criteria set forth by NCEP ATP III, was reduced more significantly in the rimonabant-treated groups in the RIO trials.

At the 1-year mark in the RIO–North America trial, the incidence of the metabolic syndrome was more significantly reduced from baseline measurement in the rimonabant 20-mg group (from 34.8% to 21.2%, p <0.001) than in the placebo group (from 31.7% to 29.2%).[31] The RIO-Europe trial reported a significant 53% (p <0.001) reduction in the prevalence of the metabolic syndrome in the rimonabant 20-mg group, whereas the placebo group experienced a reduction of only 21.3%.[32] The RIO-Lipids trial reported a baseline incidence of the metabolic syndrome in 54% of the participants. There was a reduction from this baseline prevalence to a 25.8% prevalence rate in the rimonabant 20-mg group. However, a reduction from 54% baseline to 41% prevalence in the placebo group was observed at study completion (p <0.001).[33] Data from the RIO-Diabetes trial show a significant decrease in the incidence of the metabolic syndrome in the rimonabant 20-mg group (26% decrease, p

= 0.002) versus that in the placebo group (18% decrease).[34] Table 5 shows changes in lipid values and in the prevalence of the metabolic syndrome.

Food behavior and quality-of-life measures: Indicators that food-related behavior was improved in the rimonabant-treated group were reported in the RIO-Diabetes trial. Improvements were seen in all food behavior parameters in the rimonabant 20-mg group. Participants in the rimonabant 20-mg group reported a lower appetite ($p < 0.0001$), greater ease in following the diet ($p < 0.0001$), less desire for high-fat foods ($p = 0.0003$), and less desire for sweets ($p = 0.04$) than those in the placebo group.[34]

In addition to improvements in food behavior, data collected via a patient satisfaction scale in the RIO-Diabetes trial revealed that more participants in the rimonabant 20-mg group reported being "very" or "exceptionally" satisfied at 1 year than did those in the placebo group ($p = 0.001$). Participants also completed the obesity-specific Impact of Weight on Quality of Life Health (IWQOL-Lite) questionnaire at baseline and every 3 months thereafter for 1 year. A significantly greater improvement was found at 1 year in the rimonabant 20-mg group for the physical function ($p = 0.002$) and self-esteem ($p = 0.004$) domains and for the total score ($p = 0.006$) on the IWQOL-Lite questionnaire, compared with the placebo group.[34]

Discontinuation from study and treatment side effects: Overall percentages of discontinuation from the RIO trials were similar in the placebo and rimonabant groups. Discontinuation rates were 33.6%–49.1% in the placebo groups and 32%–44.9% in the rimonabant groups.[31–34] Relatively high discontinuation rates are not uncommon in weight loss trials. Rimonabant was reported as generally well tolerated. However, there was an increased rate of adverse events reported in the rimonabant 20-mg groups versus the placebo groups. In addition, an increase in the rates of discontinuation from the study because of adverse events was observed in the rimonabant 20-mg group (12.8%–15%) compared with the placebo group (5%–9.2%).[31–34] The most commonly reported adverse events in the RIO trials included central nervous system–related complaints, such as dizziness (5.6%–10.4%), insomnia (5.8%–6.4%), anxiety (5%–6.4%), and depressed mood (5.2%). The most common gastrointestinal adverse events reported were nausea (11.2%–12.9%) and diarrhea (5.3%–7.2%).[31–34]

Conclusion

Compared with placebo, rimonabant 20 mg significantly decreased body weight and waist circumference measurements. In addition, rimonabant reduced several other cardiometabolic risk factors. Significant increases in serum levels of HDL cholesterol and adiponectin, as well as reductions in serum levels of triglycerides, small, dense LDL particles, CRP, HOMA-IR, and HbA_{1c} in subjects with diabetes were reported in the rimonabant 20-mg groups compared with the placebo groups in the 4 RIO trials. Dropout rates were similar to those observed in clinical trials of other weight loss agents. Rimonabant was generally well tolerated, with dizziness, insomnia, anxiety, depressed mood, nausea, and diarrhea as the most frequently reported adverse events.

The EC system presents a novel pathway to target in the treatment of obesity and cardiovascular risk factors. The mechanisms underlying the EC system are complex and continue to be revealed. To investigate long-term efficacy and safety of rimonabant in the treatment of cardiovascular risk, several studies are currently under way.[39–42] The Comprehensive Rimonabant Evaluation Study of Cardiovascular Endpoints and Outcomes (CRESCENDO) trial is currently investigating the effect of rimonabant on myocardial infarction, stroke, and cardiovascular death in 17,000 high-risk obese study participants taking rimonabant or placebo for 4–5 years.[43]

Rimonabant targets a novel pathway that improves weight outcomes in obese and overweight individuals with comorbidities and that reduces cardiometabolic risk factors. The sustained weight loss conferred by rimonabant combined with its ability to reduce cardiometabolic risk factors makes this compound promising in the battle against obesity.

Author Disclosure

The authors who contributed to this article have disclosed the following industry relationships:

Louis J. Aronne, MD, is a member of the Speakers' Bureau for Pfizer Inc, and sanofi-aventis; serves as consultant to Amylin Pharmaceuticals Inc., Genaera Corporation, Merck & Co., Inc., Orexigen Therapeutics Inc., and sanofi-aventis; and has received research/grant support from Amylin Pharmaceuticals Inc., Arena Pharmaceuticals, Medtronic Inc., Merck & Co., Inc., Metacure Ltd. Obecure Ltd., Orexigen Therapeutics Inc., Pfizer Inc, sanofi-aventis, and VIVUS Inc.

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