News and Views from the Literature

Obesity

Rimonabant Trials Confirm Benefit

Reviewed by Norman E. Lepor, MD, FACC, FAHA

The David Geffen School of Medicine,
Cedars-Sinai Medical Center, Los Angeles, CA
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Effect of Rimonabant, a Cannabinoid-1 Receptor Blocker, on Weight and Cardiometabolic Risk Factors in Overweight or Obese Patients: RIO-North America: A Randomized Controlled Trial.

Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al.

JAMA. 2006;295:761-775.

Obesity is an epidemic: approximately two thirds of all Americans are overweight, defined as a body mass index (BMI) ≥ 25, or obese, defined as a BMI ≥ 30.[1] (BMI = weight[kg]/height^2 [meters].) An assessment of BMI should be made with every new patient interaction (Table 1).

Because obesity is associated with a host of risk factors, including diabetes and dyslipidemia, and weight is an important component of the metabolic syndrome, efforts to modify weight have always been a cornerstone of cardiovascular risk-reduction strategies. Unfortunately, the words of encouragement that we use to counsel our patients on the need to reduce calories and increase activity to lose weight rarely lead to significant weight loss. Thus far, pharmaceutical treatments have been limited. Use of one current option, sibutramine, is restricted because it can elevate blood pressure, particularly at higher doses.[2] Orlistat, a lipase inhibitor, is commonly associated with gastrointestinal side effects and, with long-term use, fat-soluble vitamin deficiencies.[3]

The endocannabinoid system plays a key regulatory role in energy homeostasis through cannabinoid-1 receptors (C-1R), which are located both centrally and in peripheral tissues, including that in muscle, fat, the liver, and the gastrointestinal tract. Activation of central C-1Rs stimulates lipogenic pathways in the liver and adipose tissue while it decreases activity of these pathways in muscle tissue. Activation of central C-1Rs also stimulates the desire to eat. Peripheral C-1R activation leads to decreases in adiponectin production. Adiponectin levels are related to insulin sensitivity and inversely related to parameters of inflammation (C-reactive protein). In preclinical trials, rimonabant, a selective C-1R blocker, has been shown to increase adiponectin gene expression, which leads to its greater production in adipose tissues,[4] increased insulin-mediated glucose uptake in muscle, and decreased lipid accumulation in response to the intake of high-fat foods.

Table 1
Body Mass Index (BMI) Chart*

	BMI	25	26	27	28	29	30	31	32	33	34	35	40
		WEIGHT (lbs)											
	4'10"	119	124	129	134	138	143	149	153	158	163	167	191
	4'11"	124	128	133	138	143	148	154	158	164	169	173	198
	5'	128	133	138	143	148	153	159	164	169	175	179	204
	5'1"	132	137	143	148	153	158	165	169	175	180	185	211
	5'2"	136	142	147	153	158	164	170	175	181	186	191	218
H	5'3"	141	146	152	158	163	169	175	181	187	192	197	225
	5'4"	145	151	157	163	169	174	181	187	193	199	204	232
E	5'5"	150	156	162	168	174	180	187	193	199	205	210	240
	5'6"	155	161	167	173	179	186	192	199	205	211	216	247
I	5'7"	159	166	172	178	185	191	198	205	211	218	223	255
	5'8"	164	171	177	184	190	197	204	211	218	224	230	262
G	5'9"	169	176	182	189	196	203	210	217	224	231	236	270
	5'10"	174	181	188	195	202	207	216	223	230	237	243	278
H	5'11"	179	186	193	200	208	215	222	230	237	244	250	286
	6'	184	191	199	206	213	221	228	236	244	251	258	294
T	6'1"	189	197	204	212	219	227	236	243	251	258	265	302
	6'2"	194	202	210	218	225	233	241	250	258	265	272	311
	6'3"	200	208	216	224	232	240	248	256	264	272	279	319

*A BMI of 25 to 29 is considered overweight; a BMI of 30 or higher is considered obese.

In a recently published double-blind trial by the Rimonabant in Obesity-Lipids Study Group, 1036 overweight or obese men and women (BMI 27 to 40) with untreated dyslipidemia (identified by triglyceride levels at 150 mg/dL to 700 mg/dL, or a ratio of cholesterol to high-density lipoprotein cholesterol [HDL-C] of $>$ 4.5 among women and $>$ 5 among men) received either placebo or rimonabant, at a dosage of 5 mg/d or 20 mg/d, for 12 months.[5] In addition, subjects followed a low-calorie diet that would yield a deficit of 600 kcal/d from that required to maintain body weight. The primary endpoint was weight loss; secondary endpoints included lipid levels, insulin levels (both fasting and during a glucose tolerance test), levels of leptin and adiponectin, and prevalence of the Adult Treatment Panel III criteria for the metabolic syndrome.

Compared with placebo, rimonabant, 20 mg, was associated with a significant ($P < .001$) mean weight loss (-5.4 ± 0.4 kg), reduction in waist circumference (-4.7 ± 0.5 cm), increase in HDL-C ($+8.1 \pm 1.5\%$), and reduction in triglycerides ($-12.4 \pm 3.2\%$). Rimonabant at 20 mg increased plasma adiponectin levels (46.2%; $P < .001$), a change that was partly independent of weight loss, reduction in leptin, fasting insulin, C-reactive protein, and blood pressure. It also significantly reduced apolipoprotein B/A-1, low-density lipoprotein cholesterol (LDL-C)/HDL-C, and the proportion of small LDL particles. The prevalence of the metabolic syndrome fell to 26% among subjects receiving 20 mg of rimonabant compared with 41% among subjects receiving placebo ($P < .001$).

The RIO-North America trial randomized 3045 obese or overweight patients with untreated hypertension or dyslipidemia to either placebo or rimonabant, at a dose of 5 mg/d or 20 mg/d, for 1 year. Patients were excluded if they had a body weight fluctuation of more than 5 kg in the previous 3 months; clinically significant cardiac, renal, hepatic, gastrointestinal tract, neuropsychiatric, or endocrine disorders; drug-treated or diagnosed type 1 or type 2 diabetes; use of medications that alter body weight or appetite; current substance abuse; or changes in smoking habits, including cessation, within the previous 6 months. Patients were instructed to follow a diet that would yield a 600 kcal deficit per day. After 1 year, the

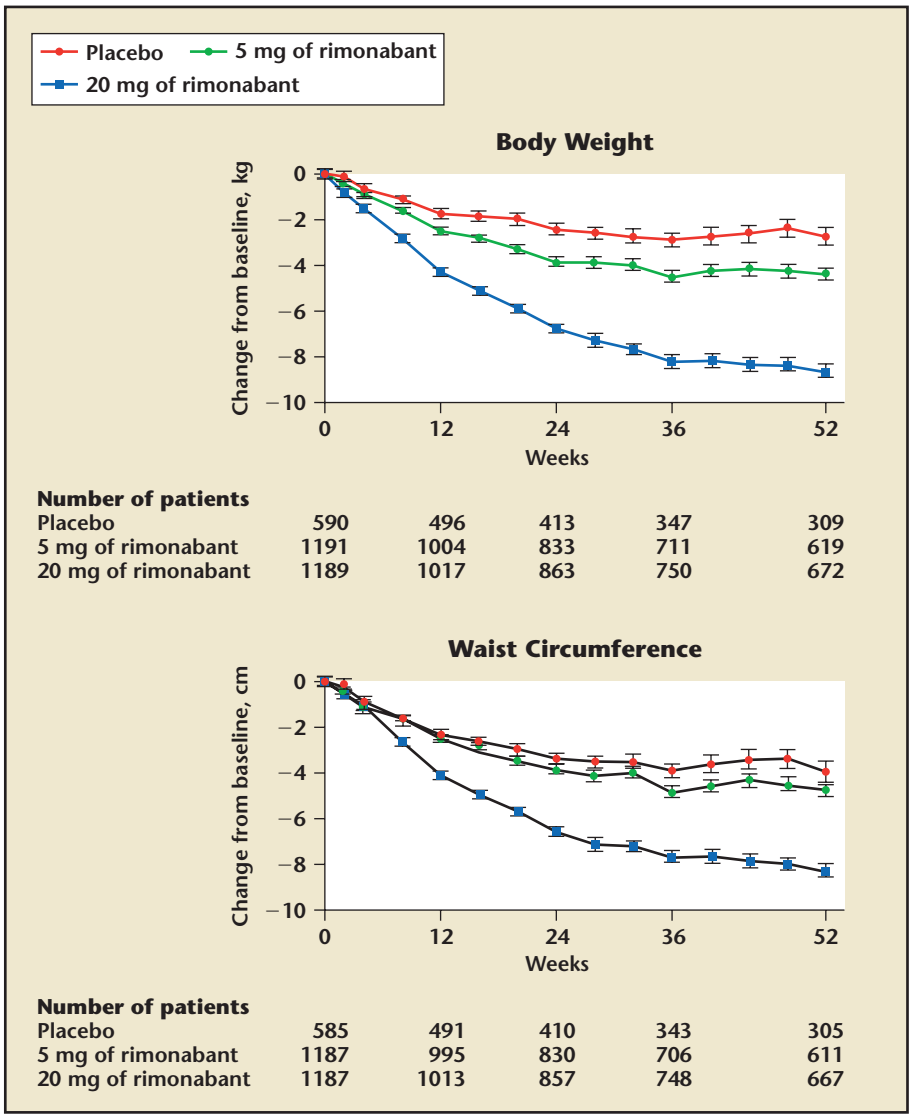

Figure 1. *Change in weight (kg) and waist circumference (cm) in year 1. Adapted with permission from Pi-Sunyer FX, et al.* JAMA. *2006;295:761-775.*

rimonabant-treated patients were randomized to receive placebo or the same rimonabant dose for an additional year, while the placebo group continued receiving placebo for an additional year. The primary endpoint was weight change over 1 year and prevention of weight regain during year 2. Secondary endpoints included changes in waist circumference, plasma lipid levels, and other cardiometabolic risk factors, including fasting glucose and insulin levels.

Compared with the placebo group, the 20-mg rimonabant group experienced greater weight loss—6.3 kg versus 1.6 kg ($P = .001$), and a larger decrease in waist circumference—6.1 cm versus 2.5 cm ($P < .001$) (Figure 1). The 20-mg rimonabant group also had a triglyceride reduction of 5.3 mg/dL versus the placebo group's increase of 7.9 mg/dL ($P < .001$), greater increase in HDL-C levels (+12.6 mg/dL versus +5.4 mg/dL, $P < .001$), and significant reductions in fasting insulin levels (Figure 2). Data from year 1 through year 2 showed that subjects re-randomized to 20-mg rimonabant maintained a mean weight loss from baseline of 7.4 kg as well as the reduction of waist circumference, whereas subjects re-randomized to placebo regained most of their previous weight and waist circumference loss (Figure 3). Rimonabant was well tolerated, with similar rates of trial withdrawal among the placebo, 5-mg rimonabant, and 20-mg rimonabant groups.

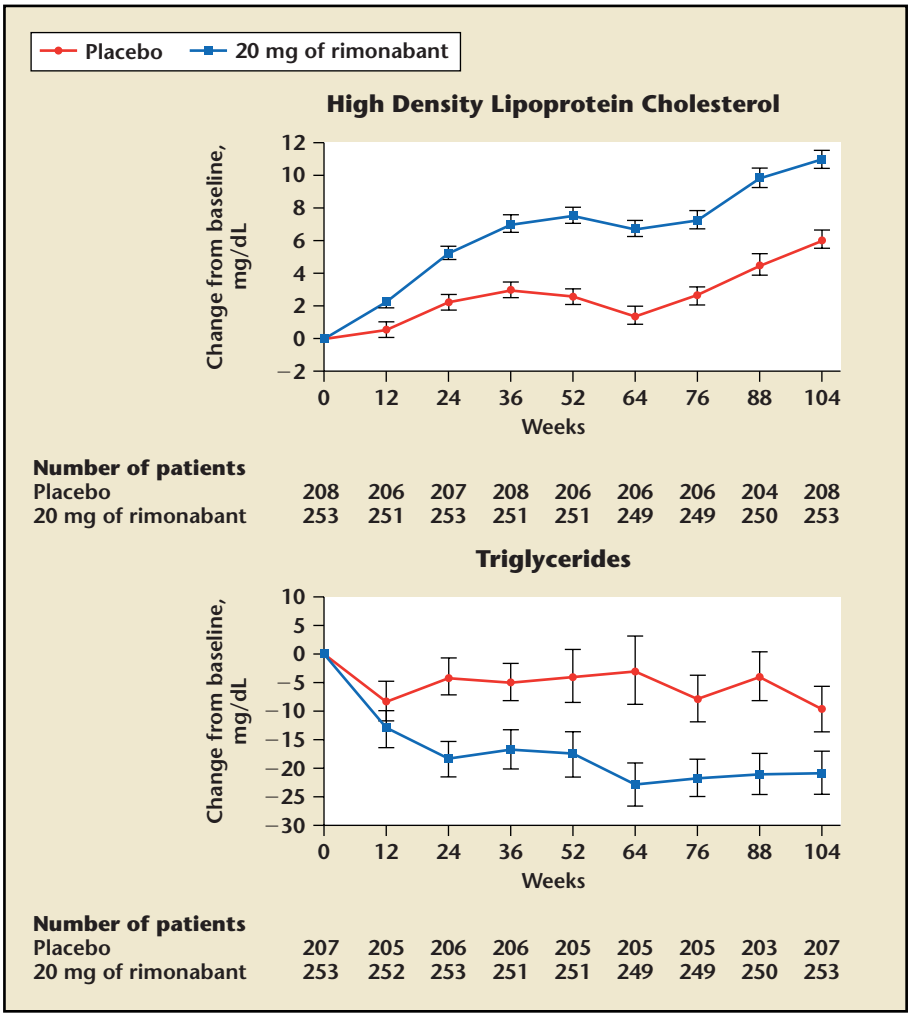

Figure 2. *Comparison of rimonabant and placebo in effects on high-density lipoprotein cholesterol and triglyceride levels. Adapted with permission from Pi-Sunyer FX, et al.* JAMA. *2006;295:761-775.*

In summary, based on the results of these evaluations, it would seem that we will finally have a patient-friendly pharmaceutical approach to modify the metabolic abnormalities that place our overweight and obese patients at high risk for coronary artery disease. Not only is rimonabant associated with weight loss, but also with positive changes in a variety of cardiometabolic parameters, including HDL-C and triglyceride levels, and increases in insulin sensitivity. The impact of these effects will be to make the metabolic syndrome itself the target of this therapy, reducing the incidence of the metabolic syndrome and, one hopes, the progression to diabetes. It is anticipated that rimonabant will become an important part of our armamentarium to modify cardiometabolic risk in overweight patients, in addition to the primary interventions of lifestyle modification, particularly diet and exercise. ■

References

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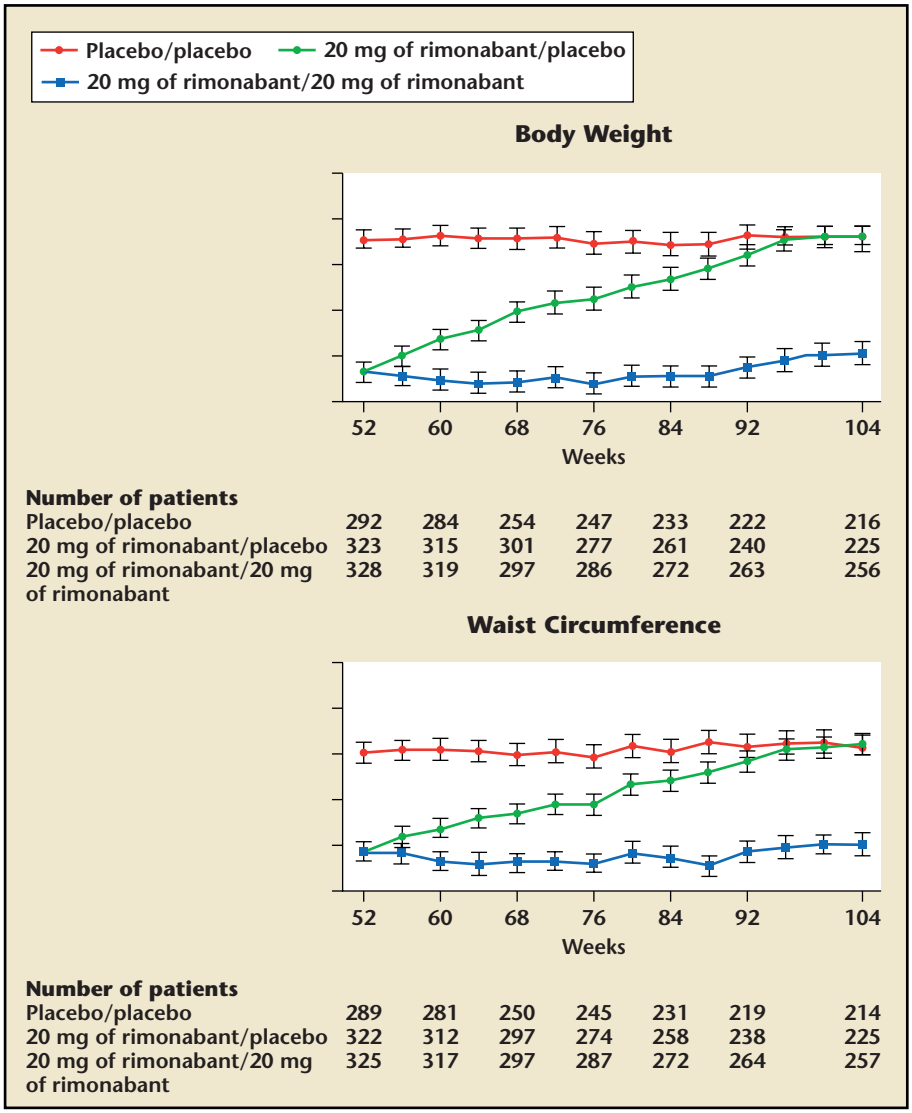

Figure 3. *Maintaining improvement in weight and waist circumference in year 2. Adapted with permission from Pi-Sunyer FX, et al.* JAMA. *2006;295:761-775.*

Atherosclerosis

The Role of C-Reactive Protein

Reviewed by Alan C. Yeung, MD
Stanford University School of Medicine, Stanford, CA
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C-reactive protein (CRP), a serum marker, has been shown to be a valuable marker for cardiovascular disease and its clinical sequelae. This predictive value seems to be independent of the low-density lipoprotein (LDL) cholesterol level and the Framingham 10-year risk score. Despite this epidemiological evidence, the pathophysiology behind the ways CRP confers risks is not well understood. Two new studies examine how CRP promotes atherosclerosis and what determines an individual's CRP level.