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Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study

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Summary:

Background

In animal models, cannabinoid-1 receptor (CB_1) blockade produces a lean phenotype, with resistance to diet-induced obesity and associated dyslipidaemia. We assessed the effect of rimonabant, a selective CB_1 blocker, on bodyweight and cardiovascular risk factors in overweight or obese patients.

Methods

1507 patients with body-mass index 30 kg/m^2 or greater, or body-mass index greater than 27 kg/m^2 with treated or untreated dyslipidaemia, hypertension, or both, were randomised to receive double-blind treatment with placebo, 5 mg rimonabant, or 20 mg rimonabant once daily in addition to a mild hypocaloric diet (600 kcal/day deficit). The primary efficacy endpoint was weight change from baseline after 1 year of treatment in the intention-to-treat population.

Findings

Weight loss at 1 year was significantly greater in patients treated with rimonabant 5 mg (mean -3 · 4 kg [SD 5·7]; p=0·002 *vs* placebo) and 20 mg (-6·6 kg [7·2]; p<0·001 *vs* placebo) compared with placebo (-1·8 kg [6·4]). Significantly more patients treated with rimonabant 20 mg than placebo achieved weight loss of 5% or greater (p<0·001) and 10% or greater (p<0·001). Rimonabant 20 mg produced significantly greater improvements than placebo in waist circumference, HDL-cholesterol, triglycerides, and insulin resistance, and prevalence of the metabolic syndrome. The effects of rimonabant 5 mg were of less clinical significance. Rimonabant was generally well tolerated with mild and transient side effects.

Interpretation

CB_1 blockade with rimonabant 20 mg, combined with a hypocaloric diet over 1 year, promoted significant decrease of bodyweight and waist circumference, and improvement in cardiovascular risk factors.

Introduction

The prevalence of obesity continues to increase, with more than 50% of Europeans currently classified as overweight and up to 30% as clinically obese.[1,2] WHO has estimated that, yearly, about a quarter of a million deaths in Europe and more than 2·5 million deaths worldwide are weight-related, with cardiovascular disease as the leading cause.[3] Because few safe and effective drugs are available, the treatment of obesity remains one of the greatest unmet clinical needs of our time.

The newly discovered endocannabinoid system contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects.[4-6] This system consists of endogenous ligands and two types of G-protein-coupled cannabinoid receptors: CB_1, located in several brain areas and in a variety of peripheral tissues including adipose tissue, the gastrointestinal tract, the pituitary and adrenal glands, sympathetic ganglia, heart, lung, liver, and urinary bladder;[7,8] and CB_2, in the immune system.[9] The endocannabinoid system is overactivated in genetic animal models of obesity[5] and in response to exogenous

stimuli such as excessive food intake.[10] Preclinical studies implicate the endocannabinoid system in the modulation of food intake and adipogenesis,[11-13] through peripheral mechanisms. The system might provide a possible treatment target for high-risk overweight or obese patients. Insights into the endocannabinoid system have been derived from studies in animals with genetic deletion of $CB_{1:}$ which have a lean phenotype and are resistant to diet-induced obesity and associated insulin resistance produced by a highly palatable high-fat diet.[14] Further evidence comes from investigation of pharmacological blockade of CB_1 receptors with the selective CB_1 blocker rimonabant, which produces weight loss and ameliorates metabolic abnormalities in obese animals.[10,15] Preclinical findings support the role of the CB_1 receptor in both central and peripheral regulation of energy balance and body weight,[5] providing a mechanistic basis for the clinical development of rimonabant for the management of obesity and associated cardiovascular risk factors.

We undertook a large, multicentre, multi-national, randomised, placebo-controlled trial—the RIO (Rimonabant In Obesity) Europe trial—to assess the efficacy and safety of rimonabant in reducing body weight and improving cardiovascular risk factors in overweight or obese patients.

Methods

Patients

Men and women aged 18 years or older, with body-mass index (BMI) 30 kg/m^2 or greater, or BMI greater than 27 kg/m^2 with treated or untreated hypertension or treated or untreated dyslipidaemia, were recruited from 60 sites in Europe and the USA between October, 2001, and April, 2002. Although RIO-Europe was planned to be done in Europe only, difficulties in meeting recruitment targets led to the extension of the study to 20 sites in the USA with an enrolment, of 276 US patients.

Eligible patients had less than 5 kg variation in body-weight within the 3 months before study entry. Exclusion criteria included clinical disorders, such as substantial endocrine disease, diabetes mellitus, cardiovascular or pulmonary disease, hepatic and renal disorders, or substantial neurological or psychological illness. Patients were also excluded if they had a history of depression necessitating hospitalisation, two or more recurrent episodes of depression, or suicide attempt. Previous history of surgical procedures for weight loss (eg, stomach stapling, bypass) was also an exclusion criterion. Concomitant use of medications known to alter bodyweight or appetite, including anti-obesity drugs, corticosteroids, antidepressants, neuroleptics, non-selective systemic antihistamines, nicotine substitutes, and antidiabetic drugs, was not permitted. No change in hypolipidaemic medication was allowed. To avoid metabolic effects due to altered smoking habits, patients who indicated their intention to stop smoking were not included. Marijuana and hashish users were excluded from the study.

Figure 1: *Trial profile *Including run-in period*

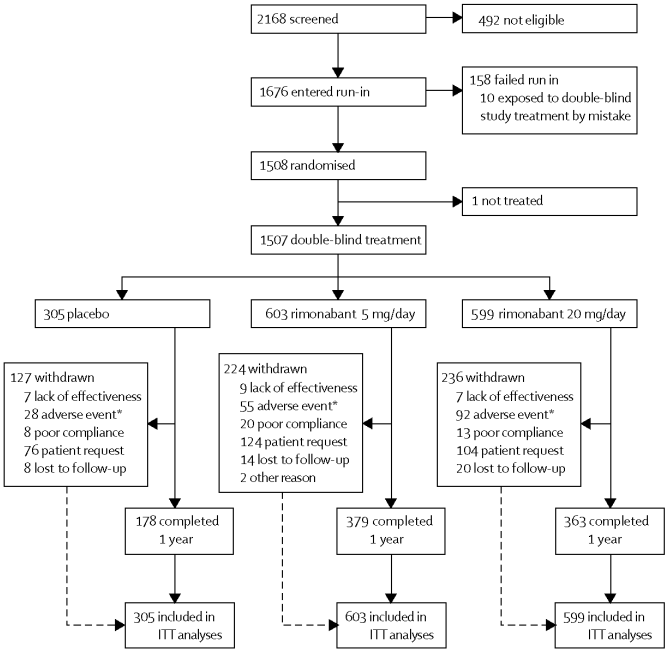

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Table 1: *Baseline characteristics*

	Placebo (n=305)	Rimonabant 5mg(n=603)	Rimonabant 20mg(n=599)
Race (white)*	290(95·1%)	565 (93·7%)	555(92·7%)
Sex (female) *	244(80·0%)	476 (78·9%)	478 (79·8%)
Age (years)†	45·0(11·6)	45·4(11·2)	44·6(11·9)
BMI (kg/m^2)†	35·7(5·9)	36·0(5·9)	36·2 (5·8)
Weight (kg) †	100·0(20·3)	100·9 (19·8)	101·7(19·5)
Waist (cm)†	107·7(13·8)	108·4(14·3)	108·8(14·1)
Hypertension (%)*	116(38·0%)	264(43·8%)	237 (39·6%)
Dyslipidaemia (%)*	189(62·0%)	371 (61·5%)	355 (59·4%)
Metabolic syndrome (%)*	121(40·6%)	243 (40·8%)	251(42·4%)
Current smokers (%)*	60 (19·7%)	136(22·6%)	102 (17·0%)

*Data are number (%). †Data are mean(SD).

Procedures

The study was approved by the local ethics committees and done in accordance with the Declaration of Helsinki and ICH Good Clinical Practice between October, 2001, and June, 2004. RIO-Europe was a 2-year randomised, double-blind, placebo-controlled, parallel group, fixed-dose, multicentre study, with a 2-week screening period and 4-week single-blind, placebo run-in period. For the double-blind treatment period, the randomisation code list, with a block size of five, was generated centrally by the sponsor. Treatments were allocated to patients using the interactive voice responding system according to the predefined randomisation list (1: 2: 2 ratio for placebo, 5 mg rimonabant, and 20 mg rimonabant, respectively). A central laboratory (ICON Laboratories, Farmingdale, USA, and Dublin, Ireland) ensured that the randomisation of treatment was balanced within each centre and was stratified based on the loss of bodyweight (≤2 kg or >2 kg) recorded during the run-in period, per protocol. During the double-blind period, patients were seen every 14 days during the first month and thereafter every 28 days until the end of the study.

Basal metabolic rate was estimated with the Harris Benedict formula, and 600 kcal were subtracted by a dietician to calculate a recommended daily energy intake for each patient. At each visit, patients received dietary counselling and were encouraged to increase physical activity.

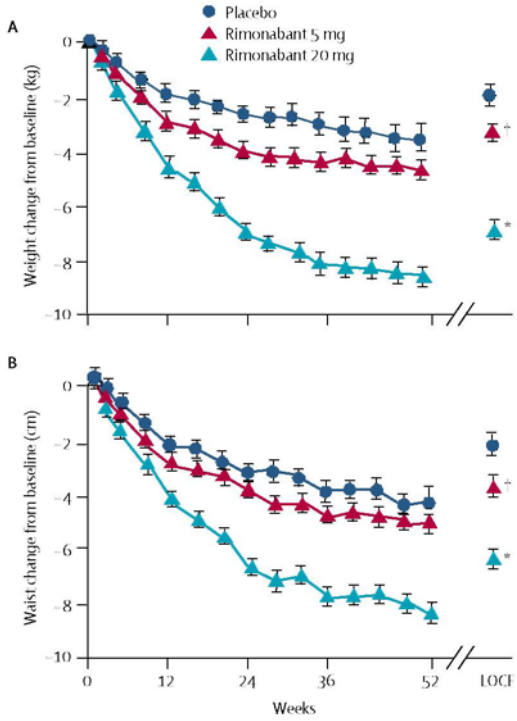
Bodyweight, waist circumference, and blood pressure were measured at screening, at randomisation, and at every treatment visit, whereas lipid profile, fasting glucose, and insulin were measured every 3 months by use of standard procedures in the central laboratory (ICON Laboratories).[16] Hypertension was defined as systolic/diastolic blood pressure of 140/90 mm Hg or greater. Dyslipidaemia was defined as LDL-cholesterol 3·36 mmol/L or greater, HDL-cholesterol less than 1·03 mmol/L, and triglycerides 1·69 mmol/L or greater. The prevalence of the metabolic syndrome was assessed at screening, baseline, and 12 months, according to the criteria of the National Cholesterol Education Program Adult Treatment Panel III.[17] An oral glucose tolerance test (75 g glucose) was done at baseline and at 1 year.

The primary efficacy endpoint was the absolute weight change from baseline (randomisation) at the end of year 1 in the intention-to-treat (ITT) population. Another weight-related criterion was the proportion of patients who achieved weight loss of 5% or more and 10% or more. Secondary efficacy endpoints were waist circumference (as a marker of change in abdominal obesity), concentrations of glucose and insulin in serum when fasting, HDL-cholesterol and triglycerides, and the prevalence of the metabolic syndrome. Additional efficacy endpoints were changes in concentrations of total cholesterol and LDL-cholesterol in serum and changes in insulin resistance, derived from the HOMA-IR (homoeostasis model assessment), calculated as fasting insulin (μU/mL) x fasting glucose (mmol/L)/22·5.[18] Analysis of quality of life and dietary assessment were also done at baseline and after 1 year (data still under analysis).

Safety assessments, including physical examination, standard laboratory tests (haematology, liver enzymes, blood chemistry tests), and an ECG, were done at screening, at baseline, and at regular visits every 3 months. Adverse events were recorded at each visit. Mood was evaluated with the Hospital Anxiety and Depression (HAD) scale[19] at baseline and every 3 months. Patients who presented with a symptom of depression or an HAD score of 11 or greater had to be referred to a psychiatrist to ascertain the exact diagnosis of the clinical picture, and treatment if indicated. The HAD score is a short, self-report scale, which is easy to use in a primary-care setting to screen for the presence of mood disorders in different populations of patients, including obese

patients.[19] An independent Data Safety Monitoring Board was in place to ensure the safety of the patients by review and analysis of the unblinded safety data, on a regular basis.

Figure 2: *Change from baseline in bodyweight (A) and waist circumference (B).Data are mean (SE) values for patients completing each scheduled visit, and LOCF (values for the full ITT population with the last observations carried forward). *p<0·001 vs placebo. †p=0·002 vs placebo.*



Statistical analysis

For the primary endpoint, analysis was done in the ITT population using the last observation carried forward method and presented as mean and SD, unless otherwise stated. An analysis of variance (ANOVA) model, with treatment and randomisation strata as fixed effects, was used, followed by the modified Bonferroni procedure (Hochberg) to account for multiplicity of doses. For secondary endpoints, continuous variables were analysed by means of one-way ANOVA with treatment as fixed effect. Categorical variables were analysed with the χ^2 test. Each rimonabant dose group was compared with the placebo group.

Analysis of covariance (ANCOVA) and/or logistic regression models using weight loss as covariate were applied to investigate whether the observed effects on efficacy endpoints were independent of weight loss as reflected by the last weight measurement. All statistical tests were two-sided at the 5% significance level.

Role of the funding source

The study was designed by the steering committee, composed of the investigators of the RIO programme and a representative from the sponsor. The trial design and follow-up were assessed by the Trial Operational Committee. Data were collected by the pharmaceutical sponsor and were assessed jointly by the authors and the sponsor. The data were interpreted and the manuscript written by the authors. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

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Table 2: *Changes in metabolic and cardiovascular risk factors in ITT population*

	Placebo	**Rimonabant**		**p *vs* placebo**	
		5mg	20 mg	5mg	20 mg
Weight (kg)					
Baseline	99·9(20·2)	100·7(19·7)	101·7(19·4)		
1 year	98·1(20·9)	97·3(20·1)	95·1(20·6)		
Change	-1·8(6·4)	-3·4(5·7)	-6·6(7·2)	0·002	<0·001
Waist (cm)					
Baseline	107·7(13·8)	108·3(14·3)	108·7(14·1)		
1 year	105·3(14·3)	104·4(14·5)	102·2(15·4)		
Change	-2·4(6·9)	-3·9(6·3)	-6·5(7·4)	0·002	<0·001
SBP(mmHg)					
Baseline	126·8(13·7)	127·0(14·8)	127·0(14·1)		
1 year	127·0(13·6)	126·1(14·7)	126·0(14·1)		
Change	0·3(12·3)	-0·9(12·5)	-1·0(12·5)	ns	ns
DBP (mmHg)					
Baseline	79·7(8·5)	79·6(9·1)	79·4(8·8)		
1 year	79·8(8·7)	78·8(8·9)	78·5(8·6)		
Change	0·1(8·5)	-0·8(8·8)	-0·9(8·7)	ns	ns
TC(mmol/L)					
Baseline	5·29(1·00)	5·37(0·92)	5·37(1·00)		
1 year	5·37(1·01)	5·43(0·86)	5·42(0·98)		
Change	0·08(0·78)	0·06(0·70)	0·05(0·70)	ns	ns
HDL-C(mmol/L)					
Baseline	1·27(0·34)	1·27(0·32)	1·27(0·33)		
1 year	1·42(0·38)	1·46(0·37)	1·54(0·40)		
Change	0·15(0·23)	0·19(0·23)	0·26(0·26)	0·048	<0·001
TG(mmol/L)					
Baseline	1·45(0·87)	1·46(0·89)	1·45(0·85)		
1 year	1·43(0·78)	1·44(0·92)	1·25(0·72)		
Change	-0·01(0·68)	-0·02(0·77)	-0·20(0·64)	ns	<0·001
LDL-C(mmol/L)					
Baseline	3·13(0·82)	3·19(0·76)	3·21(0·81)		
1 year	3·30(0·88)	3·32(0·75)	3·29(0·83)		
Change	0·17(0·70)	0·13(0·62)	0·08(0·63)	ns	ns
Total/HDL-C ratio					
Baseline	4·42(1·28)	4·46(1·22)	4·44(1·21)		
1 year	3·99(1·15)	3·94(1·11)	3·72 (1·06)		
Change	-0·42(0·83)	-0·52(0·80)	-0·71(0·78)	ns	<0·001
Fasting glucose (mmol/L)					
Baseline	5·26(0·70)	5·30(0·62)	5·28(0·70)		
1 year	5·29(0·83)	5·26(0·73)	5·20(0·68)		
Change	0·03(0·77)	-0·05(0·68)	-0·09(0·65)	ns	0·026
Fasting insulin (mU/mL)					
Baseline	12·4(9·6)	12·7(9·2)	12·7(9·5)		
1 year	14·2 (13·1)	13·0(10·5)	11·7(8·3)		
Change	1·8(13·0)	0·3(11·2)	-1·0(8·8)	ns	<0·001
HOMA-IR (%)					
Baseline	3·0(2·6)	3·1(2·8)	3·1(2·5)		
1 year	3·4(3·5)	3·1(2·9)	2·8(2·3)		
Change	0·4(3·5)	0·0 (3·4)	-0·3(2·4)	ns	0·002

Data are mean (SD). Analyses for total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) were done on percentage changes from baseline, and those for cholesterol ratios were done on changes from baseline. SBP=systolic blood pressure. DBP=diastolic blood pressure, ns=not significant.

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Table 3: *Changes in selected metabolic and cardiovascular risk factors in patients who completed 1 year follow-up*

	Placebo	**Rimonabant**		**p *vs* placebo**	
		5 mg	20 mg	5 mg	20 mg
Weight (kg)					
Baseline	98·5(197)	100·1(19·6)	102·0(19·7)		
1 year	94·9(20·0)	95·4(19·8)	93·4(20·8)		
Change	-3·6(7·4)	-4·8(6·2)	-8·6(7·3)	0·042	<0·001
Waist (cm)					
Baseline	108·0(13·8)	109·0(14·2)	109·3(14·4)		
1 year	103·5(14·3)	103·7(14·7)	100·8(15·5)		
Change	-1·5(7·3)	-5·3(6·4)	-8·5(7·4)	ns	<0·001
SBP (mmHg)					
Baseline	127·1(13·8)	127·4(14·7)	127·8(14·1)		
1 year	126·7(13·7)	126·1(15·1)	125·8(13·5)		
Change	-0·4(12·7)	-1·3(12·2)	-2·0(12·6)	ns	ns
DBP(mmHg)					
Baseline	80·2(8·0)	79·6(9·3)	79·7(9·0)		
1 year	79·8(8·2)	78·2(9·0)	78·0(8·5)		
Change	-0·4(8·1)	-1·5(8·8)	-1·8(8·7)	ns	ns
LDL-C(mmol/L)					
Baseline	3·12(0·81)	3·22 (0·77)	3·18(0·79)		
1 year	3·33(0·87)	3·36 (0·75)	3·28(0·82)		
Change	0·21(0·70)	0·13(0·61)	0·10(0·63	ns	0·024
HDL-C(mmol/L)					
Baseline	1·28(0·37)	1·26(0·31)	1·27(0·33)		
1 year	1·48(0·41)	1·48(0·38)	1·59(0·41)		
Change	0·20(0·23)	0·23(0·23)	0·32(0·26)	ns	<0·001
TG(mmol/L)					
Baseline	1·41(0·84)	1·45(0·88)	1·44(0·80)		
1 year	1·37(0·69)	1·42(0·92)	1·18(0·60)		
Change	-0·04(0·68)	-0·03(0·80)	-0·26(0·60)	ns	<0·001
Fasting glucose (mmol/L)					
Baseline	5·29(0·76)	5·37(0·64)	5·31(0·71)		
1 year	5·30(0·93)	5·30(0·68)	5·20(0·68)		
Change	0·01(0·90)	-0·07(0·62)	-0·11(0·66)	ns	ns
Fasting insulin (mU/mL)					
Baseline	11·8(7·7)	12·7(10·3)	12·7(10·0)		
1 year	12·7(9·5)	12·5(8·2)	11·0(6·1)		
Change	1·0(8·7)	-0·3(10·2)	-1·7(8·8)	ns	0·002
HOMA-IR(%)					
Baseline	2·8(2·0)	3·1(3·2)	3·1(2·7)		
1 year	3·1(2·5)	3·0(2·3)	2·6(1·7)		
Change	0·3(2·2)	-0·1(3·3)	-0·5(2·4)	ns	0·005

Data are mean (SD). Analysesfortotal cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), and triglycerides (TG) were done on percentage changes from baseline. SBP=systolic blood pressure. DBP=diastolic blood pressure, ns=not significant.

Results

309 men and 1198 women were randomised to double-blind treatment. 920 patients (61%) completed the 1-year follow-up: 178 (58·4%) in the placebo group, 379 (62·7%) in the rimonabant 5 mg group, and 363 (60·6%) in the rimonabant 20 mg group (figure 1).

The treatment groups had similar demographic and baseline characteristics (table 1). 346 patients with a BMI of 40 kg/m^2 or greater were enrolled. At baseline, 617 (40·9%) patients had hypertension, 915 (60·8%) had dyslipidaemia, and 615 (41·4%) met the criteria for metabolic syndrome. During the 4-week run-in period, the mean decrease in weight across all groups was 1·9 kg (SD 2·2), with associated reductions of 1·5 cm (3·5) in waist circumference, 0·05 mmol/L (0·66) in triglyceride concentration, and 0·08 mmol/L (0·23) in HDL-

cholesterol concentration.

In the ITT population, change in bodyweight from baseline was significantly greater in the rimonabant 5 mg and 20 mg groups than in the placebo group (figure 2A and table 2). Table 3 shows differences between the groups in patients who completed the allocated treatment. Taking into consideration the mean weight loss during the run-in period of 1 · 9 kg, total cumulative weight loss ranged from 5 kg in the placebo group to more than 10 kg in patients on rimonabant 20 mg. Waist circumference changed significantly from baseline in the rimonabant 5 mg and 20 mg groups (figure 2B, tables 2 and 3).

Placebo-subtracted analysis showed that rimonabant 20 mg was associated with significant (all p<0·001) weight loss (mean -4·7 kg [SE 0·4] for ITT and -5·1 kg [0·6] for completers) and reduction in waist circumference (-4·2 cm [0·5] and -4·0 cm [0·6]; data not shown). In the ITT population, a significantly greater proportion of patients in the rimonabant groups achieved weight loss of 5% or greater from baseline compared with the placebo group (figure 3A). The proportion of completers who had 10% or more weight loss was also greater in the rimonabant 20 mg group than in the placebo group, but not different between the 5 mg group and placebo. A similar pattern of results was seen in completers (figure 3B).

In morbidly obese patients (BMI ≥40 kg/m^2), a similar effect on weight loss was recorded compared with the whole study population (data not shown). Results showed no interaction between sex and weight loss: no significant difference in changes was detected between men and women.

Changes in metabolic and cardiovascular risk factors in the ITT population are shown in table 2. In this population, treatment with rimonabant 5 mg and 20 mg increased HDL-cholesterol by 16·2% (SE 0·8; p=0·048 compared with placebo) and 22·3% (0·9; p<0·001), respectively, compared with 13·4% (1 · 1) in the placebo group (figure 4A). Triglyceride concentrations were reduced by 6·8% (SE 1·5; p<0·0001 vs placebo) in the rimonabant 20 mg group, compared with an increase of 5·7% (1·9) in the 5 mg group and 8·3% (2·6) in the placebo group, in the ITT population (figure 4B). Results in completers are presented in table 3.

Logistic regression models and/or ANCOVA using weight loss as a covariate were applied to assess whether the effects of rimonabant 20 mg on both HDL-cholesterol and triglyceride at 12 months were partly independent of weight loss as reflected by the last weight measurement. The weight-loss-adjusted difference in HDL-cholesterol (expressed as the percentage change from baseline) between the placebo and rimonabant 20 mg groups was 3·6% (p=0·01 *vs* placebo), compared with an unadjusted difference of 8·9% (p<0·001 *vs* placebo); this value would translate to about 60% of the increase in HDL-cholesterol being accounted for by the observed weight loss in the ITT population. Similarly, the weight-loss-adjusted difference in the percentage change in triglyceride concentrations between placebo and rimonabant 20 mg was -8·3% (p=0·006 *vs* placebo) compared with the unadjusted difference of -15·1% (p<0·001 vs placebo) in the ITT population, corresponding to about 45% of the reduction being accounted for by the observed weight loss.

A significant decrease in non-HDL-cholesterol was observed in the rimonabant 20 mg group compared with placebo (4·3% [SD 16·1] *vs* -0·2% [18·3]; p<0·001) in the ITT population; no difference was noted between the rimonabant 5 mg and placebo groups. Changes in LDL-cholesterol and total cholesterol were not significantly different between the rimonabant and placebo groups.

In the ITT population, 1-year treatment with rimonabant 20 mg resulted in a significant reduction in fasting plasma glucose, compared with the placebo group (table 2). A similar pattern was observed for insulin concentration. A decrease from baseline in HOMA-IR was seen in the rimonabant 20 mg, whereas this index increased in the placebo group. No significant differences in fasting plasma glucose, fasting insulin, or HOMA-IR, were noted between the rimonabant 5 mg group and placebo. Results for completers are presented in table 3. The proportion of patients with impaired glucose tolerance or diabetes during the oral glucose tolerance test at baseline who improved their glucose tolerance status was not different between groups. The 2-h post-load glucose concentrations were not statistically significant between groups. However, rimonabant 20 mg was associated with a significant reduction in 2-h insulin (-11·0 μU/mL [SD 40·1] from baseline *vs* -2·3 μU/mL [38·5] with placebo; p=0·019), a marker of insulin resistance. There were no significant differences in post-load insulin concentrations between rimonabant 5 mg and placebo.

Overall, there were no interactions between sex and observed weight loss, changes in metabolic parameters, or reduction in waist circumference. Although the systolic and diastolic blood pressure were slightly reduced after 1 year of rimonabant 20 mg treatment, the changes were not significantly different from placebo.

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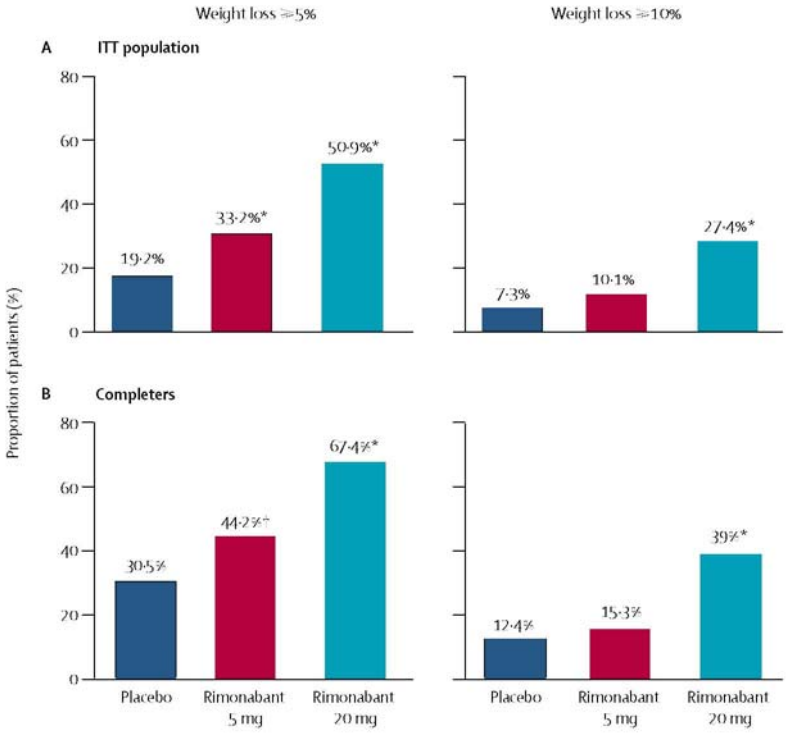
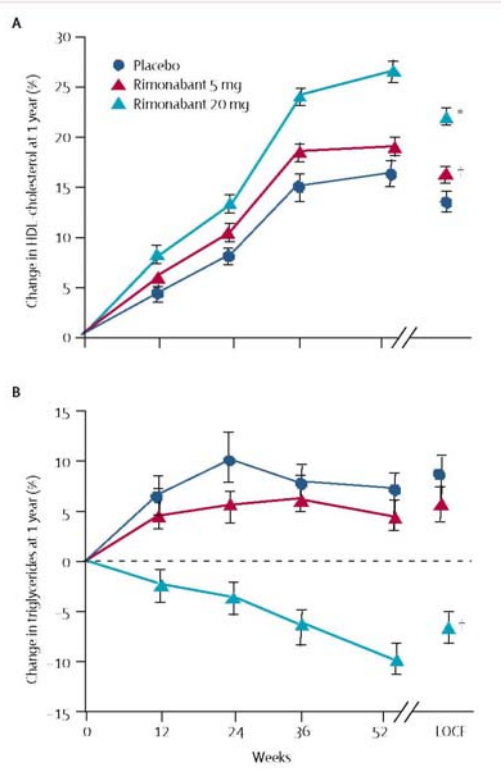
Figure 3: *Proportion of patients who lost ≥5% and ≥10% of baseline weight at 1 year*



*p<0·001 *vs* placebo. †p=0·002 *vs* placebo.

Figure 4: *Mean percentage change from baseline in HDL-cholesterol (A) and triglycerides (B). Data are mean (SE) values for patients completing each scheduled visit, and LOCF (values for the full ITT population with the last observations carried forward).*



*p<0·001 *vs* placebo. †p=0·002 *vs* placebo.

The proportion of patients who fulfilled the criteria for the metabolic syndrome in the ITT and completer populations is shown in table 4. At 1 year from baseline, the proportion had decreased significantly more in the rimonabant 20 mg group than in the placebo group.

The frequency of adverse events was slightly higher in the rimonabant 20 mg group than in the rimonabant 5 mg and placebo groups. Table 5 provides an analysis of all the adverse events occurring in at least 5% of patients in any group. The most common adverse events occurring with rimonabant were: nausea, dizziness, arthralgia and diarrhoea, some patients exhibiting a higher incidence with rimonabant 20 mg. These events, however, were for the most part, mild to moderate in intensity and considered to be transient, based on the occurrence mainly during the first months of the study. There was more headache, fatigue, and upper respiratory infection in the placebo group.

Similar frequencies of serious adverse events were reported in all groups: except for psychiatric disorders, no differences between the treatment groups were observed (tables 5 and 6). Two deaths were reported: one in the placebo group (haemorrhagic cerebrovascular accident, about 2·5 months after randomisation, in a 63-year-old woman treated with phenprocoumon for an aortic valve prothesis), and one in the rimonabant 20 mg group (diagnosis of uterine adenocarcinoma 2 months after randomisation in a 55-year-old woman, resulting in death 3 weeks later due to complications).

Table 4: *Prevalence of the metabolic syndrome in the ITT and completer populations at baseline and after 1 year of treatment*

	Placebo (%)	**Rimonabant 5 mg(%)**	**Rimonabant 20 mg** (%)
ITT			
Baseline	108 of 271 (39·9%)	228 of 553 (41·2%)	228 of 540 (42·2%)
1 year	85 of 271 (31·4%)	158 of 553 (28·6%)	106 of 540 (19·6%)*
Change from baseline (%)	21·3%	30·6%	53·6%*
Completers			
Baseline	65 of 167(38·9%)	155 of 366 (42·3%)	159 of 354 (44·9%)
1 year	43 of 167 (25·7%)	101 of 366 (27·6%)	56 of 354 (15·8%)*
Change from baseline (%)	33·9%	34·8%	64·8%*

*p<0·001 rimonabant 20 mg vs placebo.

The discontinuation rate was similar between the groups, with more withdrawals due to adverse events in the rimonabant 20 mg group and a higher rate of discontinuation due to lack of effect in the placebo group (figure 1). The most common adverse events leading to study discontinuation were depressed mood disorders in all treatment groups; discontinuations due to nausea, vomiting, diarrhoea, headache, dizziness, and anxiety were more frequent in the rimonabant 20 mg group than in the other groups (table 7).

After 1 year, there were no significant changes in the HAD scale subscores for depression (placebo 2·7 [SD 2·9], rimonabant 5 mg 2·7 [2·7], and rimonabant 20 mg 3·4 [3·4]) or anxiety (4·4 [4·0], 4·5 [3·7], and 5·6 [4·1]). Similar proportions of patients with post-baseline depression subscores of 11 or greater were noted in the placebo (23, 8·5%), rimonabant 5 mg (40, 7·5%), and rimonabant 20 mg groups (41, 7·9%). No specific changes in laboratory parameters for haematology or kidney and liver functions were reported. No effect of rimonabant on blood pressure was noted (tables 2 and 3). Mean heart rate remained unchanged from baseline with rimonabant 20 mg, and QTcF decreased by 5·7 msec (SD 16·3) in the placebo group and 3·6 msec (16·9) in the rimonabant 20 mg group.

Discussion

In this study, treatment with rimonabant over 1 year led to sustained, clinically meaningful weight loss, reduction in waist circumference, and associated improvements in several cardiovascular and metabolic risk factors, including HDL-cholesterol and triglyceride concentrations, HOMA-IR, and prevalence of the metabolic syndrome. About half of the effect of rimonabant on HDL-cholesterol and triglycerides was independent of weight loss. Despite a significant effect on bodyweight, rimonabant 5 mg had an effect of limited clinical interest on metabolic variables. More than 67% of patients who completed treatment with rimonabant 20 mg achieved 5% or more weight loss, and 39% achieved 10% or more weight loss; the target of 5-10% weight loss, which is

judged to be standard in the field of conventional obesity treatment, could be achieved.[20,21] The pattern of weight loss observed in this study with rimonabant appears to be sustained up to 36-40 weeks. How this finding would translate into prolonged weight loss in clinical practice has to be determined. The decrease in waist circumference, a measure of abdominal obesity, is known to be associated with improvements in cardiovascular disease risk factors,[22,23] including atherothrombotic and proinflammatory metabolic abnormalities.[24] The weight loss observed in 39% of patients treated with rimonabant 20 mg was associated with a concomitant reduction in waist circumference by about 9 cm, a value that could be associated with a 30% decrease in intra-abdominal adiposity.[24]

Rimonabant treatment was associated with significant improvements in lipid and glycaemic variables. Importantly, the improvements in HDL-cholesterol and triglycerides observed in this study could not be fully explained by the observed weight loss alone; this statement is supported by the changes over time in these metabolic variables compared with bodyweight. The marked increase of HDL-cholesterol among placebo-treated patients can partly be explained by the fact that, during the run-in period, HDL-cholesterol decreased by about 6% (data not shown) as a logical consequence of the negative energy balance during that period. Irrespective of this effect, the placebo-subtracted benefit in HDL-cholesterol increase with rimonabant reached about 10%. In view of the knowledge that a 1% increase in HDL-cholesterol might lead to a 2% reduction in cardiovascular risk, these findings seem to be promising.[25]

The endocannabinoid system is a neuromodulatory system that plays a role in many physiological processes, including the regulation of food intake and energy homoeostasis.[5] Over the past decade, understanding of endocannabinoid biology has progressed substantially with the identification of two G protein-coupled cannabinoid receptors, CB_1 and CB_2,[26,27] and their endogenous ligands. CB_1 receptors are located in the central nervous system and in various peripheral tissues.[28] CB_2 receptors are located in the immune system and do not seem to have a role in energy homoeostasis.[29] Rimonabant is a selective CB_1 blocker that suppresses tonic endogenous activation of the endocannabinoid system centrally[4,6] and peripherally[8,30] (figure 5).

Rimonabant reduces the excessive consumption of palatable food or drinks in rats and marmosets.[31,32] The mechanism by which rimonabant regulates food intake is probably centrally mediated,[15] but recent results suggest an additional peripheral action. Indeed, endocannabinoids derived from the gastrointestinal tract appear to be able to modulate feeding behaviour by acting on CB_1 receptors located on capsaicin-sensitive sensory terminals.[11] In diet-induced obese mice, rimonabant treatment leads to a marked and sustained reduction of bodyweight and adiposity that could not be explained by the transient reduction of food intake observed. When compared with food restriction in a pair-feeding protocol, rimonabant treatment induced a greater bodyweight loss in diet-induced obese mice,[10] indicating that the effects of rimonabant on bodyweight are partly independent of food intake. It seems likely that CB_1 receptors expressed on adipocytes might be one of the effectors of the possible peripheral metabolic action of rimonabant.

Table 5: *Patients reporting adverse events (≥5% in any treatment group)*

	Placebo (n=305)	**Rimonabant 5 mg (n=603)**	**Rimonabant 20 mg (n=599)**
Any adverse events	257 (84·3%)	498(82·6%)	522 (87·1%)
Nasopharharyngitis	48 (15·7%)	87 (14·4%)	93 (15·5%)
Influenza	32 (10·5%)	51(8·5%)	54(9·0%)
Gastroenteritis	24(7·9%)	40 (6·6%)	51(8·5%)
Upper respiratory tract infection	23 (7·5%)	43(7·1%)	33 (5·5%)
Bronchitis	16(5·2%)	34(5·6%)	34(5·7%)
Sinusitis	17 (5·6%)	27 (4·5%)	26 (4·3%)
Headache	41 (13·4%)	58 (9·6%)	59 (9·8%)
Dizziness	15 (4·9%)	42 (7·0%)	52 (8·7%)
Nausea	13 (4·3%)	31(5·1%)	77(12·9%)
Diarrhoea	9 (3·0%)	36 (6·0%)	43(7·2%)
Arthralgia	21(6·9%)	58 (9·6%)	47 (7·8%)
Back pain	26 (8·5%)	56 (9·3%)	55(9·2%)
Fatigue	17 (5·6%)	24(4·0%)	25(4·2%)

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Table 6: *Serious adverse events by system organ class during the double-blind period of the trial*

	Placebo (n=305)	**Rimonabant 5 mg (n=603)**	**Rimonabant 20mg(n=599)**
Any serious adverse event	23 (7·5%)	45 (7·5%)	52 (8·7%)
Respiratory disorders	0	0	2 (0·3%)
Psychiatric disorders	1 (0·3%)	2 (0·3%)	9 (1·5%)
Nervous system disorders	3 (1·0%)	7(1·2%)	3 (0·5%)
Ear disorders	0	0	1(0·2%)
Cardiac disorders	0	2 (0·3%)	2 (0·3%)
Vascular disorders	0	2 (0·3%)	3 (0·5%)
Gastrointestinal disorders	3 (1·0%)	3 (0·5%)	2 (0·3%)
Hepatobiliary disorders	3 (1·0%)	5 (0·8%)	1(0·2%)
Musculoskeletal and connective disorders	6(2·0%)	13(2·2%)	10 (1·7%)
Renal and urinary disorders	0	2 (0·3%)	2 (0·3%)
Reproductive system and breast disorders	1 (0·3%)	2 (0·3%)	3 (0·5%)
Investigations	1 (0·3%)	0	1(0·2%)
Injury, poisoning, and procedure complications	4(1·3%)	5 (0·8%)	4 (0·7%)
Neoplasms: benign, malignant, and unspecified	2 (0·7%)	5 (0·8%)	7(1·2%)
General disorders	0	0	1(0·2%)

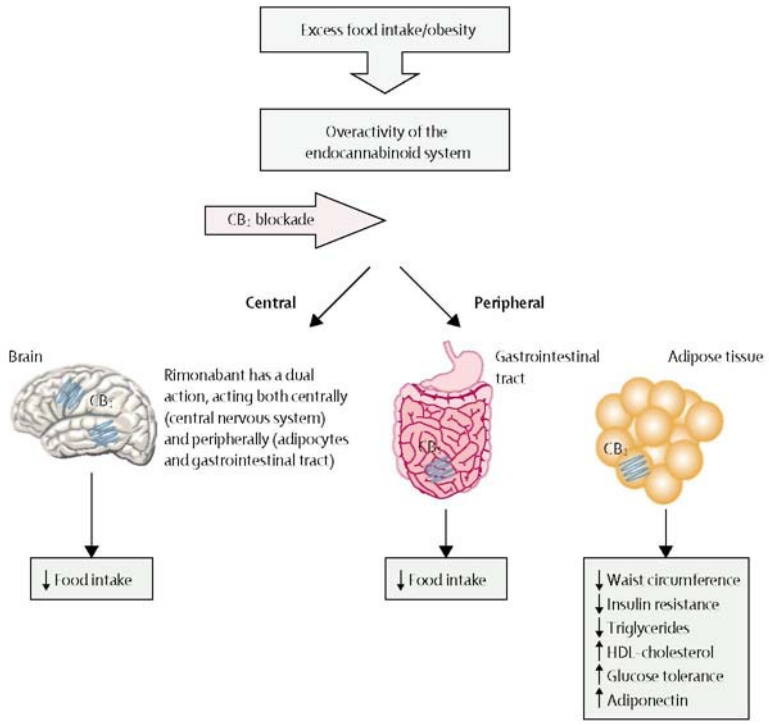
Data are proportions of patients with at least one serious event.

Table 7: *Patients reporting adverse events leading to discontinuation*

	Placebo (n=305)	**Rimonabant 5 mg(n=603)**	**Rimonabant 20 mg(n=599)**
Any adverse event leading to discontinuation	28(9·2%)	50 (8·3%)	87 (14·5%)
Psychiatric disorders	16(5·2%)	18 (3·0%)	42 (7·0%)
Depressed mood disorders	9 (3·0%)	14(2·3%)	22 (3·7%)
Anxiety	1 (0·3%)	0	6(1·0%)
Agitation	2 (0·7%)	0	3 (0·5%)
Sleep disorders	0	2 (0·3%)	1(0·2%)
Nervous system disorders	2 (0·7%)	8 (1·3%)	10 (1·7%)
Headache	0	2 (0·3%)	4 (0·7%)
Dizziness	0	2 (0·3%)	2 (0·3%)
Hypoaesthesia	0	0	2 (0·3%)
Gastrointestinal disorders	0	5 (0·8%)	21(3·5%)
Nausea	0	1 (0·2%)	14(2·3%)
Vomiting	0	0	4(0·7%)
Diarrhoea	0	0	3 (0·5%)
Dyspepsia	0	0	2 (0·3%)
Flatulence	0	2 (0·3%)	0
Cardiac disorders	3 (1·0%)	2 (0·3%)	5 (0·8%)
Palpitations	1 (0·3%)	0	2 (0·3%)

According to the Medical Dictionary for Regulatory Activities in at least two patients in any treatment group (one patient may report several events). Only main system organ classes are presented.

Figure 5: *Hypothetical model of role of central and peripheral components of endocannabinoid system in regulation of food intake and peripheral metabolism. CB_1 receptors are enriched in regions of the brain and in gastrointestinal system implicated in the regulation of food intake, and in adipose tissue. CB_1 receptor blockade might contribute to decreased food intake and exert direct metabolic effects.*



A possible explanation for the potential weight-independent effect of rimonabant on HDL-cholesterol and triglycerides might be related to the observation that rimonabant enhances the mRNA expression of adiponectin, an adipokine secreted by fat cells and reported to have a role in the regulation of hyperglycaemia, hyperinsulinaemia, and fatty acid oxidation,[33-36] at the peripheral adipocyte level.[8] Thus, improved fat-cell function may be postulated as a key peripheral effect of rimonabant leading to bodyweight reduction and improvement in metabolic parameters, including lipids and beneficial changes in adiponectin and C-reactive protein. Further studies of the in-vivo effects of the increased adiponectin production induced by rimonabant treatment are needed to elucidate possible metabolic effects of rimonabant in adipose tissue.

Rimonabant treatment was well tolerated during this trial, with a similar overall drop-out rate in all treatment groups. The most common adverse events experienced with rimonabant 20 mg, such as nausea and diarrhoea, were found to be mild and generally occurred in the first few months of the treatment. Gastrointestinal side-effects might be explained by the mechanism of action of the drug, since it is known that CB_1 receptors are present in the gut and likely to be involved in gastrointestinal motility. Serious adverse events did not seem to occur more frequently in the patients treated with rimonabant than in those on placebo. Mood disorders were more frequent in the rimonabant 20 mg treatment group than in the other groups, but the discontinuation rate due to this adverse event was similar between rimonabant 20 mg and placebo in this study.

The RIO-Europe trial was designed to reflect a real-life clinical setting in which we assessed parameters indicative of the metabolic syndrome and relevant clinical endpoints, such as waist circumference, in patients with a range of pre-existing risk factors. The 1-year results emphasise that blockade of the CB_1 receptor clearly targets several causes of cardiovascular risk, including obesity and the metabolic syndrome, along with its associated parameters such as waist circumference, HDL-cholesterol, and insulin resistance. The prevalence of the metabolic syndrome, compared with baseline, was reduced by more than half in the ITT population and by almost two-thirds in completers. There has been an increased awareness of the importance of this syndrome and its relation to cardiovascular disease in recent years. The large number of patients treated with CB_1 blockade who achieved the 10% target for weight loss or had a marked improvement in the top risk factors established by the world-wide INTERHEART study,[37] suggests that rimonabant can be considered as a valuable adjunct therapy for weight and waist reduction in patients at high cardiovascular risk.

The finding of a significant reduction in the incidence of the metabolic syndrome after 1 year of treatment with rimonabant 20 mg could have further implications, since the metabolic syndrome has been shown to be an important predictor of the development of type 2 diabetes and coronary heart disease.[38,39] However, the long-term benefits of weight loss and treatment of the metabolic syndrome on the prevention of cardiovascular events and mortality have yet to be confirmed by long-term outcomes studies.

In conclusion, the results of the RIO-Europe trial indicate that modulating the activity of the endocannabinoid system by blocking its CB_1 receptors holds therapeutic promise as an approach to the treatment of obesity and associated risk factors. Treatment with rimonabant was associated with clinically meaningful weight loss and additional improvements in waist circumference, lipid concentrations, and insulin resistance, and had a favourable safety profile.

Contributors

L Van Gaal and A J Scheen were involved in the study design and study follow-up as members of the RIO Operational Committee. Data and final analysis were reviewed and validated by all authors, who then wrote the manuscript. L Van Gaal had full unrestricted access to the complete set of data and wrote the initial draft of the paper. All the named authors participated in the study and contributed to interpretation of data and revision of the manuscript. The final version was written by L Van Gaal and A J Scheen, and was seen and approved by all authors.

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Conflict of interest statement

LVG, AMR, SR, AJS, and OZ have received travel awards and honoraria from Sanofi-Aventis for the purposes of attending RIO-Europe scientific committee meetings or presenting RIO-Europe trial results.

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