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Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study

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Summary

Background Rimonabant, a selective cannabinoid type 1 receptor blocker, reduces bodyweight and improves cardiovascular and metabolic risk factors in non-diabetic overweight or obese patients. The aim of the RIO-Diabetes trial was to assess the efficacy and safety of rimonabant in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylureas.
Methods 1047 overweight or obese type 2 diabetes patients (body-mass index 27-40 kg/m^2) with a haemoglobin A_{1c} (HbA_{1c}) concentration of 6•5-10•0% (mean 7•3% [SD 0•9] at baseline) already on metformin or sulphonylurea monotherapy were given a mild hypocaloric diet and advice for increased physical activity, and randomly assigned placebo (n=348), 5 mg/day rimonabant (360) or 20 mg/day rimonabant (339) for 1 year. Two individuals in the 5 mg/day group did not receive double-blind treatment and were thus not included in the final analysis. The primary endpoint was weight change from baseline after 1 year of treatment. Analyses were done on an intention-to-treat basis. This trial is registered at ClinicalTrials.gov, number NCT00029848.
Findings 692 patients completed the 1 year follow-up; numbers in each group after 1 year were much the same. Weight loss was significantly greater after 1 year in both rimonabant groups than in the placebo group (placebo: -1 · 4 kg [SD 3•6]; 5 mg/day: -2•3 kg [4•2], ρ=0•01 *vs* placebo; 20 mg/day: -5•3 kg [5•2], ρ<0•0001 *vs* placebo). Rimonabant was generally well tolerated. The incidence of adverse events that led to discontinuation was slightly greater in the 20 mg/day rimonabant group, mainly due to depressed mood disorders, nausea, and dizziness.
Interpretation These data indicate that 20 mg/day rimonabant, in combination with diet and exercise, can produce a clinically meaningful reduction in bodyweight and improve HbA_{1c} and a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes inadequately controlled by metformin or sulphonylureas.

Introduction

Type 2 diabetes frequently co-exists with a cluster of other cardiovascular and metabolic risk factors including abdominal obesity, low HDL-cholesterol concentrations, high triglyceride concentrations, and raised blood pressure,[1] and is considered to be a cardiovascular disease risk equivalent.[2,3] A recent population-based retrospective cohort study showed that diabetes confers an equivalent cardiovascular risk to ageing 15 years in people aged 40 years or older.[4] The treatment of multiple cardiovascular and metabolic risk factors is central to the management of type 2 diabetes.[5]

Being overweight or obese—in particular, abdominally obese—increases the risk of type 2 diabetes and cardiovascular disease,[6,7] yet those with diabetes often have more difficulty in losing weight[8] and experience weight gain associated with most antidiabetic medications.[5]

The endocannabinoid system, consisting of the cannabinoid type 1 (CB_1) receptor and endogenous lipid-derived ligands,[9] seems to modulate energy homoeostasis as well as glucose and lipid metabolism,[10-12] both through central orexigenic effects and peripheral metabolic effects in adipose tissue, liver, and skeletal muscle.[13-15] Patients with obesity or hyperglycaemia caused by type 2 diabetes exhibit higher concentrations of endocannabinoids in visceral fat or serum, respectively, than the corresponding controls.[16]

In non-diabetic overweight or obese patients, 20 mg daily of the selective CB_1 receptor blocker rimonabant has been shown to produce substantial weight loss and waist circumference reduction (a key marker of intra-

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abdominal adiposity), and improvements in multiple cardiovascular and metabolic risk factors.[17,18] These data were further confirmed in overweight or obese patients with untreated dyslipidaemia.[19] Part of these metabolic improvements could be attributed to a moderate, but significant, increase in plasma adiponectin levels.[19]

This multicentre randomised controlled trial was designed to assess the efficacy and safety of rimonabant in combination with a mild hypocaloric diet and advice for increased physical activity in overweight or obese patients with type 2 diabetes who were already on metformin or sulphonylurea monotherapy.

Methods

Patients

This randomised, double-blind, placebo-controlled study was done in 159 centres in 11 countries (in Europe, North America, and South America) between October, 2001, and May, 2004. Patients aged 18-70 years with type 2 diabetes who had been treated with metformin or sulphonylurea monotherapy for at least 6 months (stable dose for at least 3 months), but who remained inadequately controlled, were recruited. Inclusion criteria were body-mass index of 27-40 kg/m^2, a haemoglobin A_{1c} (HbA_{1c}) level of 6•5-10•0%, and a fasting glucose concentration of 5•55-15•04 mmol/L. Exclusion criteria were unstable bodyweight (defined as more than 5 kg variation within the past 3 months), any clinically significant disorder (including severe microvascular or macrovascular complications of diabetes), systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 95 mm Hg, pregnancy or lactation, recent or planned changes in smoking status, use of anti-obesity drugs within the past 3 months, or use of any medication known to affect bodyweight (eg, antidepressants). Written informed consent was obtained from all patients.

The protocol was approved by the Institutional Review Board/Ethics Committee for each centre. The study was done in full compliance with the Declaration of Helsinki, with an independent, unblinded data safety monitoring board.[17-19]

Procedures

The protocol has been described previously[17-19] A 2-week screening period preceded a 4-week, placebo run-in period, followed by randomisation to double-blind treatment. A randomisation code list, with a block size of three, was generated centrally by the sponsor. Treatments were allocated to patients with an interactive voice response system in accordance with the predefined randomisation list (1/1/1 ratio for placebo, 5 mg/day rimonabant, or 20 mg/day rimonabant, respectively). The interactive voice response system ensured that the randomisation of treatment was balanced within all centres and was stratified on the basis of bodyweight loss (≤2 kg or >2 kg) during the run-in period and class of antidiabetic medication. All patients were put on a mild hypocalorific diet and were advised on increased physical activity during the run-in period and until the end of the study.

Standardised assessments of bodyweight, waist circumference, and vital signs were done at screening, twice during the run-in period, at baseline (randomisation), and post-randomisation at week 2, week 4, and monthly thereafter for 1 year. Glycaemic and lipid variables were measured at screening, baseline, week 12, 24, and 36, and at 1 year. Insulin resistance was calculated by use of the homoeostasis model assessment (HOMA-IR).[20] The diagnosis of metabolic syndrome was assessed in accordance with National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria.[2]

The primary endpoint was weight change from baseline at the last observation carried forward (LOCF). Secondary endpoints included changes in HbA_{1c}, HDL cholesterol, triglyceride, fasting glucose, fasting insulin, high-sensitivity C-reactive protein (hsCRP), and leptin concentrations, prevalence of metabolic syndrome,[2] waist circumference, and blood pressure. Measurements of HbA_{1c}, glucose, insulin, total cholesterol, LDL and HDL cholesterol, triglyceride, leptin, and hsCRP were done at central laboratories (ICON Laboratories, Farmingdale, NY, USA and Dublin, Ireland), together with laboratory safety measurements in accordance with standard procedures.[17-19] HbA_{1c} was measured by ion exchange high-pressure liquid chromatography (Bio-Rad variant, Bio-Rad Laboratories, Hercules, CA, USA) with Diabetes Control and Complications Trial reference values.

The SF36 health survey questionnaire[21] and a patient's satisfaction scale were included in the study as exploratory secondary parameters. Patients completed the obesity-specific Impact of Weight on Quality of Life (IWQoL-Lite) exploratory secondary questionnaire at baseline and every 3 months for 1 year.[22,23] Food behaviour was also assessed by a Visual Analog Scale.[24]

Safety assessment was done regularly by an independent data safety and monitoring board and included standard adverse event reporting, vital signs, pulse-rate-corrected QT interval, and the Hospital Anxiety and Depression (HAD) scale.[25]

Statistical analysis

The sample size was calculated on the basis of the assumption that the SD of weight change at year 1 would be 10 kg. Thus 990 randomised patients (330 patients in every group) would provide 95% confidence to detect a 3 kg difference between both doses of rimonabant and placebo after 1 year. An α level of 0·025 was chosen to ensure an overall type error rate of 0·05 according to a modified Bonferroni procedure.

Analyses were done on a modified intention-to-treat basis. The modified intention-to-treat population consisted of all randomised patients who were exposed to at least one dose of study drug and had at least one post-baseline assessment and, when appropriate, a baseline assessment.

The primary endpoint was analysed with analysis of variance with the modified Bonferroni procedure (Hochberg) to adjust for multiple doses.[26] The three-way analysis of variance (ANOVA) model included terms for treatment and two randomisation strata (weight loss of ≤2 kg or >2 kg during the run-in period and antidiabetic therapy with metformin or sulphonylurea); both doses of rimonabant were compared with placebo. As an assessment of sensitivity, a post-hoc repeated measures approach was done for changes in weight from baseline, because this analysis includes all measurements gathered over time during the study, and thus might provide a better assessment in the presence of missing data.[27]

The repeated measures model included a number of fixed effects (randomisation strata, treatment, number of days from randomisation, and treatment-by-day interaction) and a random effect (the patient). Additionally, as another assessment of sensitivity, a more conservative method than LOCF for handling missing data was used. For dropouts with post-baseline efficacy, the last value was set to the baseline value—ie, baseline observation carried forward (BOCF)—and the change from baseline was set to zero.[28] Similar models, excluding randomisation strata, were applied to the secondary efficacy parameters.

Patients were classified as having a response of a 5% or 10% weight loss if they had a reduction in bodyweight from baseline at the LOCF of at least 5% or 10%. The incidences of patients who had a weight loss of 5% and 10% and of those with metabolic syndrome at LOCF were analysed with logistic regression models. The models for patients who had weight losses of 5% and 10% included terms for treatment and randomisation strata, and the model for the metabolic syndrome included terms for treatment and the status of the metabolic syndrome at baseline.

The effect of rimonabant independent of weight loss was tested with analysis of covariance (ANCOVA) with weight loss (change in weight from baseline to 1 year) as a covariate.[28] The statistical model for the weight-adjusted treatment effect is as follows: $Y=a+\beta T+\gamma W+e$ (ANCOVA model, weight adjusted) where Y is the efficacy variable, T is the treatment indicator, and W is weight loss. The weight-independent portion of the total treatment effect was calculated as the ratio of the weight-adjusted treatment effect, β, to the treatment effect in the overall unadjusted ANOVA model, β_1, determined from the ANOVA model: $Y=a+\beta_1 T+e_1$.[29] This ratio indicates the proportion of the total effect size that cannot be explained by weight loss.

All statistical tests were two-sided; all p values presented are unadjusted. Analyses were done with SAS software, version 8.2.

This trial is registered at ClinicalTrials.gov, number NCT00029848.

Role of the funding source

The sponsor participated in discussions regarding study design and protocol development and provided logistical support during the trial. Data were gathered by the sponsor and were assessed jointly by the authors and the sponsor. Data were interpreted and the manuscript written by the authors, with editorial support provided by the sponsor. The corresponding author had full access to all the data and takes responsibility for the integrity of that data and the accuracy of the data analysis. The corresponding author had final responsibility for the decision to submit for publication.

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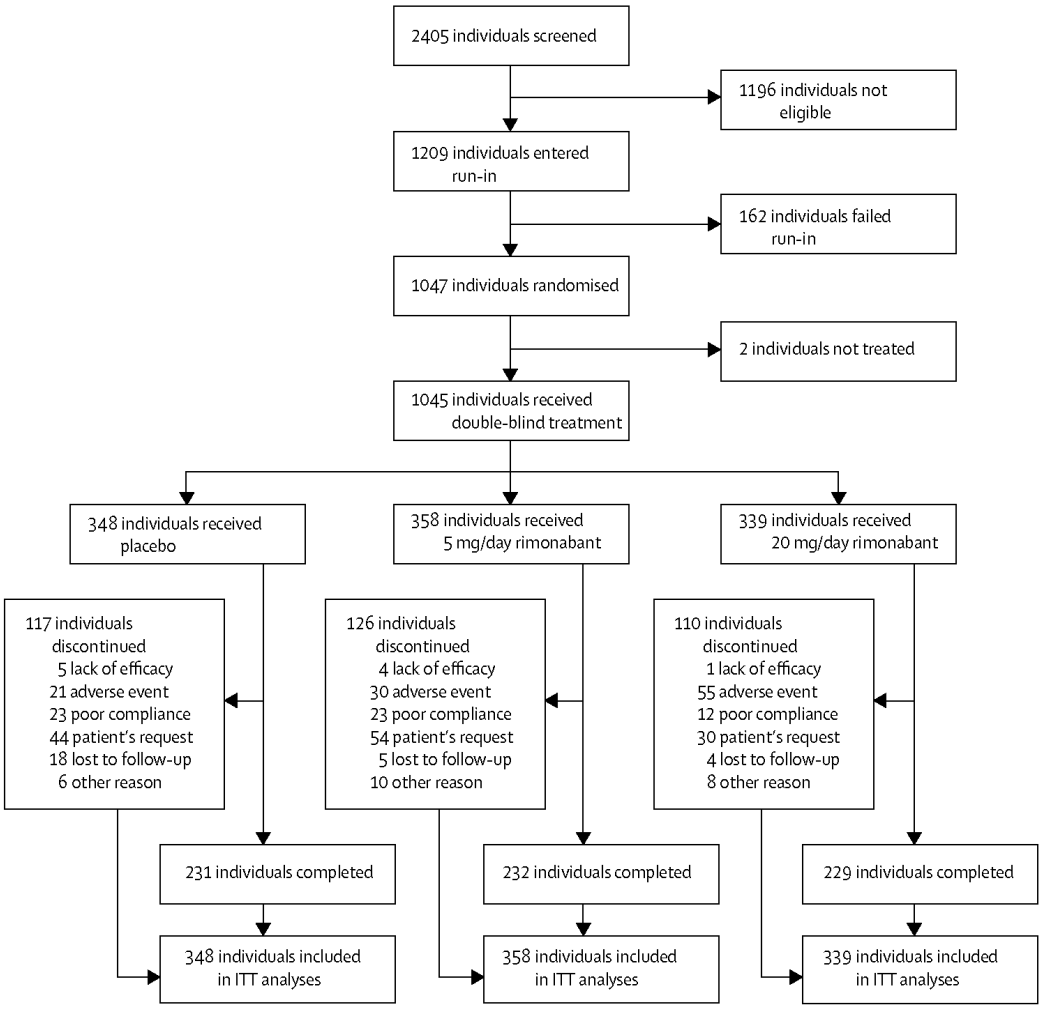
Figure 1: Trial profile



ITT=intention-to-treat.

Results

513 men and 532 women were randomised to double-blind treatment. 692 patients (66·2%) completed the 1-year follow-up (figure 1). Two randomised patients were not exposed to treatment and 11 randomised patients were excluded from the analysis of weight (two for non-exposure and nine for missing post-baseline weight assessment). Baseline characteristics were much the same in the three groups (table 1), except smoking, which was slightly lower in the 20 mg/day rimonabant group (p=0·02), and fasting triglyceride concentrations, which were slightly higher in the 20 mg/day rimonabant group (p=0·03) At screening, mean weight was 96·3 kg (SD 14·7), mean waist circumference 109 cm (10·8), mean HbA_{1c} 7·3% (0·9), mean fasting plasma glucose concentration of 8·3 mmol/L (2·1), and mean prevalence of metabolic syndrome was 79%. Mean reductions in weight (-1·5 kg [1·8]), waist circumference (-1·4 cm [3·3]), HbA_{1c} (-0·24% [0·54]), fasting plasma glucose concentration (-0·52 mmol/L [1·87]), fasting plasma insulin concentration (-1·1 µIU/mL [10·5]), triglyceride concentration (-1·3% [35·3]), HDL-cholesterolconcentration (-1·9% [11·5]), and systolic blood pressure (-2·1 mm Hg [11·7]) were seen after the placebo run-in. 99·4% (338 of 340), 98·9% (349 of 353), and 99·1% (336 of 339) of the randomised and exposed patients for whom compliance data were available in the placebo, 5 mg/day, and 20 mg/ day groups, respectively, achieved compliance of 80% or more with the study medication.

Weight loss was significantly greater with both doses of rimonabant than with placebo, independent of age and sex (p=0·01 for 5 mg *vs* placebo, p<0·0001 for 20 mg *vs* placebo; table 2 and figure 2). The placebo-corrected weight loss after 1 year of treatment with 20 mg/day rimonabant was 3·9 kg (SD 0·3); placebo-subtracted losses were 4·3 kg (0·4) in patients treated with metformin and 3·1 kg (0·5) in those treated with sulfonylurea after 1 year of 20 mg/day rimonabant (p<0·0001 for both). The number of patients achieving weight loss of 5% or more

and 10% or more at the last follow-up visit was also significantly greater in both groups receiving rimonabant than in the placebo group (≥5% loss: p=0·02 for 5 mg and p<0·0001 for 20 mg; ≥10% loss: p=0·01 for 5 mg and p<0·0001 for 20 mg; table 2). Waist circumference was significantly lower with both doses of rimonabant than with placebo (p=0·02 for 5 mg, p<0·0001 for 20 mg; table 2 and figure 2B).

Table 1: Characteristics of participants

Demographics at screening*	Placebo group (n=348)	5 mg/day rimonabant group (n=358)	20 mg/day rimonabant group (n=339)
Age (years)	54·8(8·6)	55·9(8·6)	56·0(8·5)
Sex (% male)	159 (46%)	186 (52%)	168 (50%)
Race			
White (%)	308 (89%)	315 (88%)	302 (89%)
Black (%)	18 (5%)	20 (6%)	19 (6%)
Weight (kg)	97·5 (15·1)	98·7(15·1)	97·1 (14·4)
Waist (cm)			
Male	114·7 (10·6)	113·6(10·6)	112·9 (10·0)
Female	106·5 (10·1)	107·1(10·2)	107·0(10·2)
Body-mass index (kg/m^2)	34·2 (3·6)	34·4(3·6)	34·1(3·6)
HbA_{1c}(%)	7·5% (0·9)	7·5% (0·8)	7·5% (0·8)
Current smokers (%)	51 (15%)	43 (12%)	30 (9%)
Hypertension (%)†	206 (59%)	218(61%)	216 (64%)
Dyslipidaemia(%)‡	186 (53%)	202 (56%)	193 (57%)
Antidiabetic treatment			
Metformin	230 (66%)	230 (64%)	218 (64%)
Sulphonylureas	118 (34%)	128 (36%)	121(36%)
Efficacy at baseline			
Weight (kg)	96·0(15·1)	97·2 (14·8)	95·7(14·2)
Waist (cm)			
Male	113·7 (11·0)	112·0 (10·5)	111·3 (9·6)
Female	105·3 (10·6)	106·4(10·1)	106·0(9·9)
HbA_{1c}(%)	7·2% (0·9)	7·3% (0·8)	7·3% (0·8)
Fasting glucose (mmol/L)	8·2(2·2)	8·2 (1·8)	8·5(2·2)
Fasting insulin (µlU/mL)	16·0(13·3)	14·9(9·3)	15·5 (11·3)
HOMA-IR	5·8 (7·3)	5·3 (3·5)	5·9 (5·0)
Triglycerides (mmol/L) HDL cholesterol (mmol/L)	1·93 (1·05)	1·95 (1·01)	2·12(1·29)
Men	1·06 (0·23)	1·06 (0·22)	1·08 (0·22)
Women	1·26(0·28)	1·28(0·28)	1·24(0·28)
LDL cholesterol (mmol/L)	2·99(0·80)	2·98(0·80)	2·99(0·82)
Total cholesterol (mmol/L)	5·00(0·96)	499(0·97)	5·06 (0·97)
Total cholesterol/HDL cholesterol	4·48 (1·17)	4·46(1·20)	4·52 (1·19)
Non-HDL cholesterol (mmol/L)	3·83(0·92)	3·83(0·2)	3·89(0·95)
Metabolic syndrome§	271 (79%)	276 (80%)	267 (79%)
Supine systolic blood pressure (mm Hg)	128·7(13·1)	130·9 (13·4)	130·3 (12·5)
Supine diastolic blood pressure (mm Hg)	78·8 (7·8)	79·0(7·9)	79·0(7·8)
hsCRP (mg/L)	6·3 (8·1)	5·9 (7·3)	5·4(6·5)
Leptin (ng/mL)	16 (8·7)	16(9·3)	16(9·1)
Safety at baseline			
Heart rate (bpm)	67·0 (10·3)	64·8(9·8)	68·5 (10·6)
QTcF (ms)¶	406·0 (19·1)	406·0 (21·1)	407·4 (18·1)
HAD/depression‖	3·1(2·8)	2·8(2·6)	3·1(2·9)
HAD/anxiety‖	5·2 (3·4)	4·9(3·2)	5·1(3·6)

Data are number (%) or mean (SD). *Screening data split into treatment groups retrospectively after randomisation, † Defined as systolic blood pressure ≥130 mm Hg or supine diastolic blood pressure ≥85 mm Hg, or both; overall 93% of patients with hypertension were treated. ‡Defined for men as LDL-cholesterol concentration ≥3·36 mmol/L, or H DL-cholesterol concentration <1·03 mmol/L for men and <1·3 mmol/L for women, or triglyceride concentration ≥1·69 mmol/L; overall 65% of patients with dyslipidaemia were treated. §Patients had metabolic syndrome as detected according to NCEP-ATP III.[2] Data on metabolic syndrome at baseline available for 342,347, and 337 patients in the placebo, 5 mg, and 20 mg groups, respectively. ¶QT interval corrected for heart rate. ‖HAD=Hospital Anxiety and Depression. The HAD scale consists of 14 items measuring the level of anxiety and depression in two separate subscales. Scale scores range from 0 (no symptoms) to 21 (maximum distress) for both depression and anxiety and is interpreted with the following cut points: 0-7= normal, 8-10=mild disturbance (probable case), ≥11=moderate to mood disturbance (definite case).

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Table 2: *Changes in weight and risk factors*

Weight	**Placebo**	**5 mg/day rimonabant**	**20 mg/day rimonabant**	**p value (5 mg vs placebo)**	**p value (20 mg vs placebo)**
Number of patients with data at last visit	345	355	336		
Change from baseline (kg)	-14(3·6)	-2·3 (4·2)	-5·3 (5·2)	0·01	<0·0001
≥5% weight loss	50 (14·5%)	77 (21·7%)	166 (49·4%)	0·02	<0·0001
≥10% weight loss	7(2·0%)	22(6·2%)	55 (16·4%)	0·01	<0·0001
Waist circumference					
Number of patients with data at last visit	344	355	336		
Change from baseline (cm)	-1·9 (5·5)	-2·9(5·6)	-5·2 (6·1)	0·02	<0·0001
HbA_{1c}					
Number of patients with data at last visit	317	330	315		
Change from baseline (%)	0·1% (1·0)	-0·1% (1·0)	-0·6% (0·8)	0·03	<0·0001
Patients that achieved HbA_{1c} <6·5%	66 (21%)	78 (24%)	135 (43%)	0·39	<0·0001
Patients that achieved HbA_{1c}<7%	151 (48%)	168 (51%)	214 (68%)	0·40	<0·0001
Change from baseline in patients taking metformin* (%)	0·1% (1·0)	-0·1% (1·1)	-0·6% (0·8)	0·19	<0·0001
Change from baseline in patients taking sulphonylureas† (%)	0·1% (1·1)	-0·1% (0·9)	-0·5% (0·8)	0·07	<0·0001
Fasting glucose concentration					
Number of patients with data at last visit	317	331	317		
Change from baseline (mmol/L)	0·33(2·32)	0·30(2·06)	-0·64(1·96)	0·86	<0·0001
Fasting insulin					
Number of patients with data at last visit	314	328	311		
Change from baseline (µlU/mL)	0·4(14·8)	0·7(9·0)	-0·7(9·9)	0·76	0·25
HOMA-IR					
Number of patients with data at last visit	308	319	309		
Change from baseline	0·6(8·9)	0·6(4·2)	-0·5 (5·7)	0·97	0·03
HDL cholesterol‡					
Number of patients with data at last visit	314	331	318		
Change from baseline (mmol/L)	0·07 (0·15)	0·11 (0·19)	0·17(0·20)	0·02	<0·0001
Change from baseline (%)	7·1% (13·5)	9·2% (15·8)	15·4% (17·4)	0·08	<0·0001
Triglycerides‡					
Number of patients with data at last visit	314	330	317		
Change from baseline (mmol/L)	0·04(0·87)	-0·01 (0·79)	-0·35 (1·28)	0·50	<0·0001
Change from baseline (%)	7·3% (43·0)	1·3% (35·1)	-9·1% (44·3)	0·07	<0·0001
Total cholesterol/HDL cholesterol ratio					
Number of patients with data at last visit	314	330	317		
Change from baseline	-0·16 (0·79)	-0·23 (0·80)	-0·51(0·82)	0·27	<0·0001
Change in non-HDL cholesterol‡					
Number of patients with data at last visit	314	330	317		
Change from baseline (mmol/L)	0·02 (0·85)	0·00 (0·75)	-0·13(0·80)	0·70	0·02
Change from baseline (%)	2·5% (22·5)	2·0% (21·1)	-1·8% (21·0)	0·75	0·01
Total cholesterol‡					
Number of patients with data at last visit	314	331	317		
Change from baseline (mmol/L)	0·10(0·88)	0·11 (0·76)	0·04(0·82)	0·90	0·36
Change from baseline (%)	3·3% (17·7)	3·3% (16·2)	2·0% (16·5)	0·98	0·32
LDL cholesterol‡					
Number of patients with data at last visit	314	331	317		
Change from baseline (mmol/L)	0·13 (0·76)	0·13 (0·66)	0·09 (0·79)	0·99	0·52
Change from baseline (%)	7·2% (26·3)	7·5% (26·8)	6·9% (34·5)	0·89	0·90
Metabolic syndrome					
Number of patients with data at last visit	316	331	318		
Improvement at 1 year	44/251 (18%)	57/260(22%)	66/252(26%)	0·21	0·02
Development at 1 year	25/65 (38%)	21/71 (30%)	18/66 (27%)	0·28	0·17
Supine systolic blood pressure					
Number of patients with data at last visit	345	355	336		
Change from baseline (mm Hg)	1·6(13·2)	-0·4(12·9)	-0·8(12·8)	0·04	0·02
Supine diastolic blood pressure					
Number of patients with data at last visit	345	355	336		

Change from baseline (mm Hg)	-0·7 (8·4)	-0·4(8·5)	-1·9(8·2)	0·70	0·06
hsCRP					
Number of patients with data at last visit	308	323	313		
Change from baseline (mg/L)	-0·0 (10·0)	-0·5 (5·8)	-1·4(5·2)	0·48	0·02
Leptin					
Number of patients with data at last visit	290	308	294		
Change from baseline (ng/mL)	3·1 (7·5)	1·9 (6·1)	-0·3 (6·0)	0·03	<0·0001

Data are mean (SD) or n/N (%), unless otherwise indicated. HOMA-IR=Homoeostasis Model of Assessment of insulin resistance. *n=211, n=209, and n=204 in the placebo, 5 mg/day, and 20 mg/day rimonabant groups, respectively, at the end of study. †n=106, n=121, n=111 in the placebo, 5 mg/day, and 20 mg/day rimonabant groups, respectively, at the end of study. ‡Analyses of cholesterol (total, LDL, HDL, and non-HDL) and triglycerides were done on percent changes from baseline.

HbA_{1c} levels were lower with both doses of rimonabant than with placebo (p=0·03 for 5 mg and p<0·0001 for 20 mg; table 2 and figure 3A and B) with a sustained decline in the 20 mg/day rimonabant group (figure 3A). Treatment with metformin or sulphonylurea did not affect HbA_{1c} levels (table 2). More patients in the 20 mg/day rimonabant group reached an HbA_{1c} target of less than 6·5%[30] and less than 7%[31] than did those in the placebo group (p<0·0001 for both target levels; table 2). The observed effects of 20 mg/day rimonabant on Hb A_{1c} were about twice that attributable to concurrent weight loss alone after adjustment with ANCOVA (figure 3C). For example, of the observed placebo-subtracted 0·7% reduction in HbA_{1c} with 20 mg/day rimonabant, 0·4% (SD 0·1) remained after weight-loss adjustment, equivalent to 57% (10) of the overall response (p<0·0001). In the 20 mg/day rimonabant group more patients needed downward adjustment of their antidiabetic medication than did those in the placebo group (table 3).

Improvements in fasting glucose concentrations and HOMA-IR were greater in the 20 mg/day rimonabant group than in the placebo group (p<0·0001 and p=0·03, respectively; table 2). HDL cholesterol, triglyceride, and non-HDL-cholesterol concentrations also improved more with 20 mg/day rimonabant than with placebo (p<0·0001 for all; table 2 and figure 2C and D). The residual effect on HDL-cholesterol concentration of 20 mg/day rimonabant was 57% (14) of the observed effect after adjustment for weight loss (ρ<0·0001). The residual effect on triglyceride concentration after adjustment for weight loss was 36% (20) of the observed effect, which was not significant (p=0·08). The persisting prevalence of the metabolic syndrome was lower in the 20 mg/day rimonabant group than in the placebo group at 1 year (p=0·02; table 2). Supine systolic blood pressure was lower in both rimonabant groups than it was in the placebo group (p=0·04 for 5 mg, p=0·02 for 20 mg; table 2). However, the residual effect on supine systolic blood pressure after adjustment for weight loss was 48% (42) of the observed effect, which was not significant (p=0·30). The prevalence of hypertension in the 20 mg/day rimonabant group was much the same as that in the placebo group and it did not differ between baseline and 1 year of treatment (54·8% *vs* 53·9%, respectively, in the 20 mg/day group). The decrease in hsCRP levels was greater in the 20 mg/day rimonabant group than it was in the placebo group (p=0·02; table 2). Change in fibrinogen concentrations were much the same in all three groups (data not shown). Leptin levels—a marker of fat mass— were lower in the 20 mg/day rimonabant group than they were in the placebo group (p<0·0001; table 2).

Improvements were seen for all food behaviour parameters in the 20 mg/day rimonabant group at 1 year. Patients in the 20 mg/day rimonabant group reported less appetite (p<0·0001), easier to follow the diet (p<0·0001), less desire for high fat foods (p=0·0003), and less desire for sweets (p=0·04) than did those in the placebo group (data not shown). A number of exploratory secondary parameters were investigated as per protocol. A greater improvement in physical functioning (as assessed by SF36; p=0·012; data not shown) and a greater impairment in mental health score (p=0·022) were recorded at 1 year in the 20 mg/ day rimonabant group than in the placebo group (data not shown). Furthermore, more patients on 20 mg/day rimonabant reported being "very" or "exceptionally" satisfied at 1 year than did patients on placebo (p=0·001), as assessed by a patient's satisfaction scale (data not shown). Health-related quality of life was specifically assessed with IWQoL-Lite. A greater improvement at 1 year in the physical function (p=0·002) and self-esteem domains (p=0·004) and in the total IWQoL-Lite score (p=0·006) was noted in the 20 mg/day rimonabant group than in the placebo group (data not shown).

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Figure 2: *Changes in weight, waist, HDL cholesterol, and triglycerides (A) Mean (SE) change from baseline in bodyweight over 1 year; last observation carried forward (LOCF), baseline observation carried forward (BOCF), and repeated measures (RM), *p<0·001, †p=0·01, ‡p=0·03 vs placebo. (B) Mean (SE) change from baseline in waist circumference over 1 year; LOCF, BOCF, and RM. *p<0·001, †p=0·02, ‡p=0·03 vs placebo. (C) Mean (SE) percentage change from baseline in HDL-cholesterol concentration over 1 year; LOCF, BOCF, and RM. *p<0·001, †p=0·05 vs placebo. (D) Mean (SE) percentage change from baseline in triglyceride levels over 1 year; LOCF, BOCF, and RM. *p<0·001 vs placebo.*

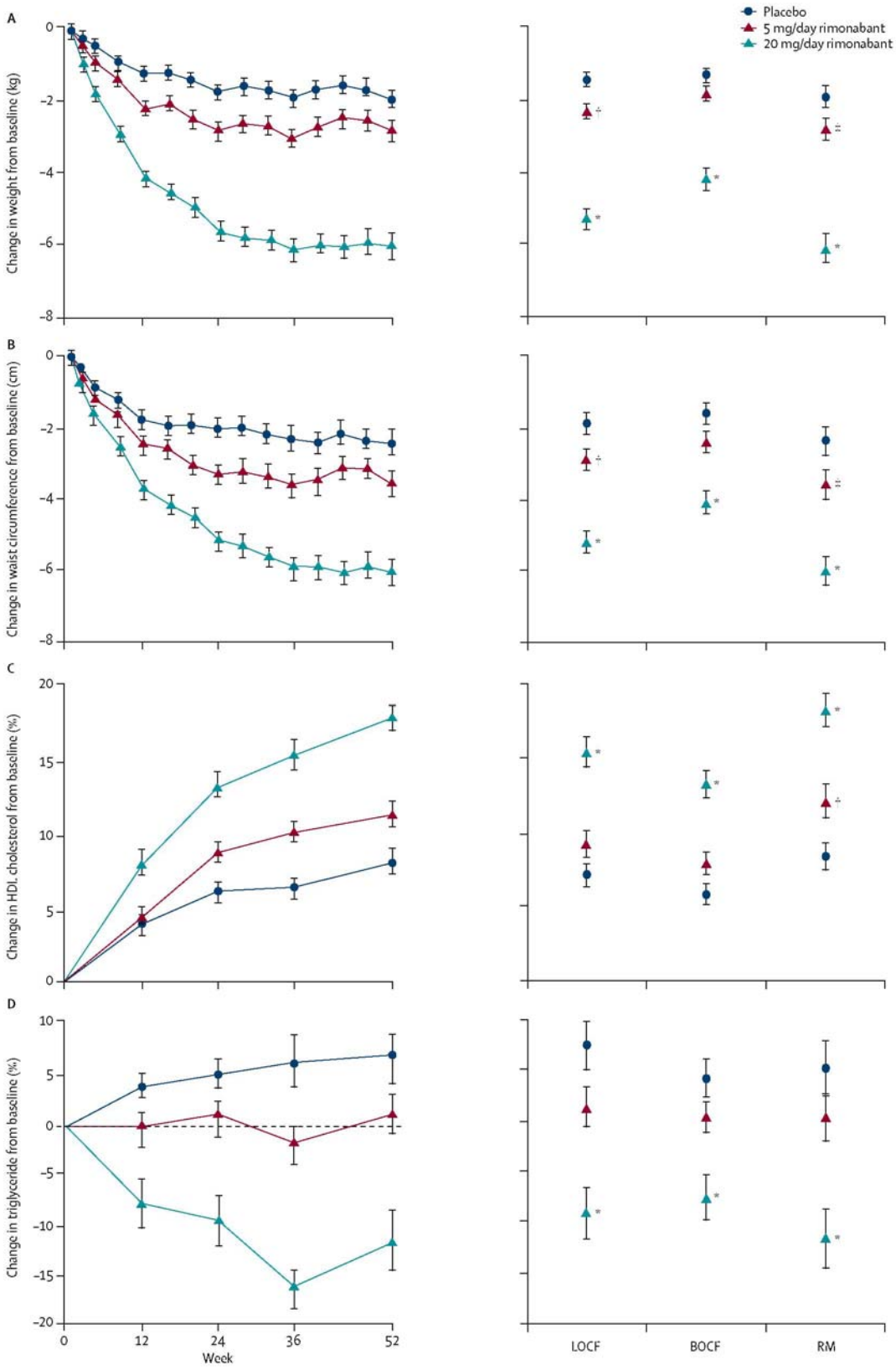

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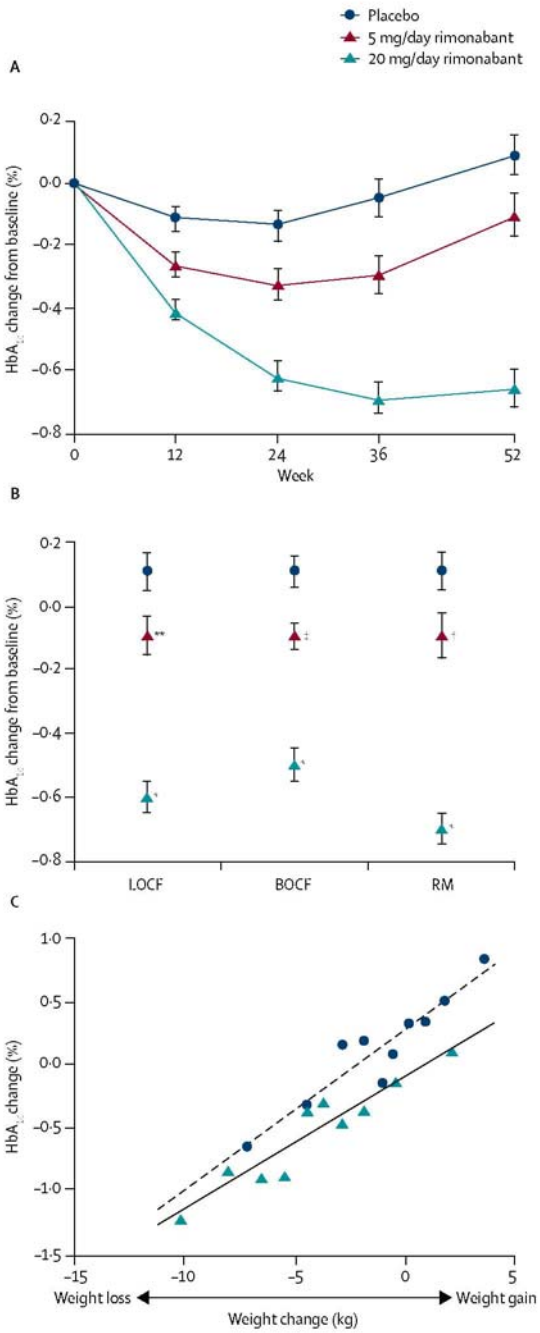
Figure 3: *Changes in HbA_{1c} levels* (A) Mean (SE) change from baseline in HbA_{1c} levels over 1 year. (B) Mean (SE) change from baseline in HbA_{1c} levels: last observation carried forward (LOCF), baseline observation carried forward (BOCF), and repeated measures (RM) *p<0·0001, †p=0·03, ‡p=0·04, §p=0·05 vs placebo. (C) Linear regression analysis between HbA_{1c} changes and bodyweight changes, excluding patients with extreme weight loss (≥11·2 kg), in patients receiving placebo or 20 mg/day rimonabant. The weight change data from lowest to highest was divided into ten groups with about equal sample size (deciles) and within each decile the mean weight change and the mean change in HbA_{1c} was calculated The pairs of mean changes (weight, HbA_{1c}) were plotted along with the regression line to illustrate the relation between weight loss and HbA_{1c}.



A slightly greater proportion of patients in the rimonabant treatment groups experienced adverse events than did those in the placebo group (table 4). The most common adverse events, occurring in 5% or more rimonabant-treated patients, were nausea, diarrhoea, vomiting, dizziness, hypoglycaemia, fatigue, and anxiety (table 4); these were generally mild or moderate, transient and self-limited, and seen early in the treatment period. In the 20 mg/day rimonabant group, hypoglycaemia was reported more frequently in diabetic patients treated with sulphonylureas than in those given metformin, but only one case led to treatment discontinuation.

Although overall discontinuation rates were much the same in all groups, discontinuations due to adverse events were more frequent in the 20 mg/day and 5 mg/day rimonabant groups than they were in the placebo group (table 4). Dropouts due to adverse events in the 20 mg/ day group were much the same in patients who lost weight (-5 kg or more) as in those who gained weight (≥0 kg)-10·6% (16 of 151 patients) and 12·8% (5 of 39 patients), respectively. The most common adverse events that led to premature study discontinuation in the 20 mg/day rimonabant group were depressed mood disorders, nausea, and dizziness (table 4). However, no serious adverse events linked to psychiatric disorders were recorded in either rimonabant group.

Cardiovascular safety endpoint measures and HAD depression and anxiety subscores were much the same across the three treatment arms at baseline and at 1 year (table 1 and table 4). Although there was a trend towards slight increases in both HAD scores in the 20 mg/day rimonabant group compared with the placebo group, the observed increases should be considered to be marginal.

Discussion

The main finding of the RIO-Diabetes trial is that 20 mg/day rimonabant for 1 year significantly reduced weight, waist circumference, and HbA_{1c} levels and improved a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes that was inadequately controlled by metformin or sulphonylurea. These results extend previous findings in non-diabetic overweight or obese patients to those with type 2 diabetes.[17-19] Patients with type 2 diabetes are characterised by resistance to weight loss,[8] overactivity of the endocannabinoid system,[16] and increased cardiovascular risk,[2,3] with obesity being deemed to be an additional and independent risk factor.[32]

Treatment with 20 mg/day rimonabant enabled a greater number of patients on monotherapy with metformin or sulphonylurea whose baseline HbA_{1c} levels were close to the American Diabetes Association recommended level (7%) to attain such a target.[31] The placebo-corrected reduction in HbA_{1c} levels of 0·7% seen with 20 mg/day rimonabant is clinically relevant, since every 1% reduction in HbA_{1c} has been shown to be associated with a reduction in risk of 21% for any endpoint related to diabetes.[33] For the purpose of comparison, in metformin-treated diabetic patients, treatment with twice-daily subcutaneous injection of 10 μg exenatide induced a 0·86% placebo-subtracted reduction in HbA_{1c} after 30 weeks, a decrease that is close to that recorded with 20 mg/day rimonabant with baseline HbA_{1c} levels above 8%.[34]

Improved glycaemic control has an important beneficial effect on the risk of microvascular and macrovascular complications related to diabetes.[33] Nevertheless, in recent years considerable emphasis has been placed on aggressive management of multiple cardiovascular and metabolic risk factors in type 2 diabetes patients.[35,36] 20 mg/day rimonabant improved atherogenic dyslipidaemia and diminished systolic blood pressure in diabetic patients, and also reduced the prevalence of metabolic syndrome,[37] as already reported in overweight dyslipidaemic non-diabetic patients.[19] Compared with placebo, 20 mg/day rimonabant also reduced hsCRP levels, an inflammatory biomarker considered to be a moderate predictor of cardiovascular disease.[38]

Table 3: *Distribution of dose changes in antidiabetic medications*

	Placebo (n=345)	**5 mg/day rimonabant (n=355)***	**20 mg/day rimonabant (n=336)†**
No change	268 (77·7%)	279(78·6%)	255 (75·9%)
Increase	44 (12·8%)	49(13·8%)	38 (11·3%)
Decrease	26 (7·5%)	22(6·2%)	40(11·9%)
Another drug added due to insufficient efficacy	7(2.0%)	3(0·8%)	0 (0%)
Another drug added due to other reasons	0 (0%)	2(0·6%)	3 (0·9%)

Data are number (%). *p=0·42 for all categories vs placebo. †p=0·005 for all categories vs placebo.

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Table 4: *Safety data at 1 year and adverse events in randomised and exposed patients*

	Placebo (n=348)	5 mg/day rimonabant (n=358)	20 mg/day rimonabant (n=339)
Safety data at 1 year			
Overall dropout rate	117 (34%)	126 (35%)	110 (32%)
Patients with any adverse event	276 (79%)	293 (82%)	288 (85%)
Patients with any serious adverse event*	15 (4%)	27(8%)	27(8%)
Discontinuations dueto adverse events	19 (5%)	28 (8%)	51 (15%)
Adverse events that led to study discontinuation†			
Psychiatric disorders			
Depressed mood disorders‡	3(0·9%)	0	11 (3%)
Anxiety	0	0	2 (0·6%)
Aggression	0	2(0·6%)	0
Nervous system disorders			
Headache	1 (0·3%)	1 (0·3%)	2 (0·6%)
Dizziness	0	0	3 (0·9%)
Paraesthesia	0	0	2 (0·6%)
Gastrointestinal disorders			
Nausea	1 (0·3%)	0	5 (1·5%)
Vomiting	0	0	2 (0·6%)
General disorders			
Chest pain	0	0	2 (0·6%)
Asthenia/fatigue	0	2(0·6%)	1 (0·3%)
Adverse events with an incidence of >5% in any group			
Nausea	20 (6%)	22(6%)	41 (12%)
Nasopharyngitis	74 (21%)	59 (16%)	41 (12%)
Dizziness	17(5%)	11 (3%)	31 (9%)
Arthralgia	28 (8%)	35 (10%)	30 (9%)
Headache	32 (9%)	29 (8%)	28 (8%)
Diarrhoea	23(7%)	22(6%)	25 (7%)
Back pain	24(7%)	22(6%)	24(7%)
Upper respiratory tract infection	33 (9%)	28 (8%)	23 (7%)
Vomiting	8(2%)	14 (4%)	20 (6%)
Hypoglycaemia	6(2%)	5(1%)	18 (5%)
Fatigue	13 (4%)	19 (5%)	18 (5%)
Anxiety	9(3%)	4(1%)	17(5%)
Safety endpoints			
Heart rate (bpm)‡			314
Number of patients with data at last visit	314	332	
Year 1	67·8 (10·8)	69·3 (10·1)	69·5 (11·4)
Change from baseline	0·8(8·8)	0·9(8·7)	1·0(10·2)
QTcF (ms)‡			
Number of patients with data at last visit	313	331	314
Last recorded value	403·9 (20·1)	404·4(19·8)	407·1 (19·4)
Change from baseline	-2·1(16·6)	-1·6(16·3)	-0·3(15·4)
HAD/depression‡			
Number of patients with data at last visit	279	286	262
Last recorded value	2·9 (3·0)	2·7(2·8)	3·3(3·3)
Change from baseline	-0·2 (2·6)	-0·1 (2·3)	0·3(2·9)
HAD/anxiety‡			
Number of patients with data at last visit	279	285	262
Last recorded value	4·9 (3·6)	4·7(3·6)	5·5 (4·0)
Change from baseline	-0·3 (3·2)	-0·1 (2·7)	0·4(3·4)

Data are number (%) or mean (SD), unless otherwise indicated.*There was one death during the placebo run-in period (cardiac arrest) and four deaths during the double-blind treatment period. One patient in the 5 mg/day rimonabant group died of septic shock 6 months after starting the study treatment, while in the 20 mg/day rimonabant group, one patient was a passenger in a traffic accident (more than 6 months after the start of study treatment) and two metformin-treated patients with multiple risk factors died of a cardiovascular disease (one death 2 months and the other 5 months after the start of study treatment). No causal relation to the study drug was suspected by the investigators for any death. In the overall RIO trial programme (n=6625; four studies), deaths were equally distributed across groups (four in the placebo group, three in the 5 mg/day rimonabant group, and four in the 20 mg/day rimonabant group), † According to MedDRA, in at least two patients in any rimonabant group and in main system organ class (≥1%). One patient can report several events. ‡Depressed mood disorders

corresponded to the MedDRA HLGT term "Depressed mood disorders and disturbances" and consist of depression, major depression, depressed mood, and depressive symptoms.

57% of placebo-subtracted effects of 20 mg/day rimonabant on HDL-cholesterol concentrations and HbA_{1c} levels were independent of weight loss, consistent with the direct peripheral metabolic effects of the drug.[13,15,17,18,39] Rimonabant increases the secretion of adiponectin,[19] an adipokine whose plasma concentrations correlates positively with insulin sensitivity, and levels of which are lower both in obese and type 2 diabetic patients than in lean healthy individuals.[40] Although low adiponectin levels have been deemed to be a predictor of cardiovascular disease, further studies are needed to confirm this association.[41] The blockade of CB_1 receptors might also inhibit hepatic fatty acid synthesis and hepatic lipid accumulation, which have also been implicated in insulin resistance and dyslipidaemia.[14]

Intentional weight loss in overweight or obese type 2 diabetes patients improves lipid profile, blood pressure, and diabetes control.[5] Weight loss has been shown to be associated with a reduced mortality risk in observational studies,[42] although such an association has not been recorded in randomised clinical trials yet. Although only moderate weight loss (5-10% of bodyweight) is required to improve glycaemic control, weight loss and maintenance of weight loss in patients with type 2 diabetes are generally more difficult than in non-diabetic individuals.[8,43] Furthermore, most antidiabetic medications (in particular sulphonylureas, thiazolidinediones, and insulin) produce concomitant weight gain.[5,31,44] In this study, a mean weight loss of 6·1 kg was noted in patients who completed the 1-year treatment with 20 mg/day rimonabant, much the same as that described in the Diabetes Prevention Program (DPP),[45] in which patients were treated with an intensive lifestyle intervention. However, lifestyle intervention in the DPP was highly demanding and applied to non-diabetic individuals, a population that has less difficulty in losing weight than diabetic patients.[8] In a study done on 114 obese patients with type 2 diabetes submitted to a 12-month follow-up after a 10-16-week behavioural weight-control programme, only 27 patients (24%) who succeeded in obtaining a prolonged weight reduction above 6-9 kg exhibited a significant reduction in HbA_{1c} levels after 1 year.[46] The authors of a recent consensus statement recognised that for most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain metabolic goals, either because of failure to lose weight, weight regain, progressive disease, or a combination of factors.[47]

In agreement with previous data,[8] the placebo-subtracted weight loss at 1 year of treatment with 20 mg/day rimonabant was 3·9 kg in the present study in patients with diabetes compared with 4·7 kg and 5·4 kg reported in patients without diabetes.[17-19] Due to its unique mode of action and because of the absence of head-to-head trials, comparison of the results obtained with 20 mg/day rimonabant with those reported with orlistat or sibutramine should be cautious. Nevertheless, this study shows greater weight loss and HbA_{1c} reduction than those reported in a recent meta-analysis of sibutramine or orlistat trials in patients with type 2 diabetes and similar demographic characteristics (ie, age, sex, and body-mass index), but higher baseline HbA_{1c} levels (9·1-9·3% instead of 7·3% in RIO-Diabetes).[48]

20 mg/day rimonabant improved health-related quality of life, especially physical functioning, which points to a positive effect of the drug on this health-related concept.[21] Rimonabant was well tolerated in this study, with adverse events that were generally transient and mild, and much the same as the safety profile reported in non-diabetic patients.[17-19] The most frequent adverse event that led to premature withdrawal in the 20 mg/day rimonabant group was the occurrence of self-reported depression. However, objective measures of depression and anxiety from the HAD scales[25] showed only slight and probably not clinically relevant changes in the 20 mg/day rimonabant group compared with the placebo group. Nevertheless, in this trial, as in other RIO-trials,[17-19] patients with severe psychiatric disorders or receiving antidepressants were excluded, so the safety of rimonabant in such individuals remains to be determined.

There are two limitations to our study. First, although consistent with that of previous 1-year studies in overweight or obese patients,[49] including those done in patients with type 2 diabetes,[48] the retention rate of about 66% in all treatment groups might be considered as rather low. One should note that the dropout rate in this study was lower than in previously reported studies with rimonabant in non-diabetic patients.[17-19] The discontinuation due to reasons other than adverse events was about threefold higher in patients who gained weight than in those who lost weight; this difference was noted in all three treatment arms. Nevertheless, dropouts due to adverse events in the 20 mg/day rimonabant group was much the same in patients who lost weight as in those who gained weight. To take into account the dropout rate, two additional sensitivity analyses, including a repeated measures approach and a BOCF approach, were done, and the results supported the conclusions of the LOCF analysis (figure 2). Second, RIO-Diabetes is a 1-year trial and long-term studies will be

needed to assess the effect on diabetes-related complications, especially cardiovascular outcomes.

The results of RIO-Diabetes show the therapeutic value of 20 mg/day rimonabant in patients with type 2 diabetes through effective weight loss, reduced abdominal adiposity, a clinically significant reduction in HbA_{1c} levels, and improvements in HDL-cholesterol, triglyceride, and hsCRP concentrations, and systolic blood pressure. The improvements in HbA_{1c} and HDL-cholesterol concentration levels were twice that expected from the weight loss alone, consistent with the direct peripheral metabolic effects of the drug. These findings support the use of 20 mg/day rimonabant, in addition to diet and exercise, as a new approach to improve glucose control and reduce a number of cardiovascular and metabolic risk factors in overweight or obese patients with type 2 diabetes that is inadequately controlled with metformin or sulphonylureas.

Contributors

A J Scheen, N Finer, and L F Van Gaal were involved in the study concept and design. All named authors participated in the study and contributed to the analysis and interpretation of data, and to the drafting, development, and critical revision of the manuscript. The final version of the manuscript was seen and approved by all authors.

Conflict of interest statement

A J Scheen is a consultant for sanofi-aventis, AstraZeneca, GlaxoSmithKline, and Merck-Santé, and has received lecture fees from sanofi-aventis. N Finer is a consultant for Novarris, Shionogi, Merck, Abbott, sanofi-aventis, Ajinomoto, and GlaxoSmithKline, and has received lecture fees from Abbott, sanofi-aventis, Roche, and Novo-Nordisk. He has also received grant support from Merck, Novarris, Roche, the EU Framework 6 'Diabesity' grant, Alizyme, Abbott Laboratories, and sanofi-aventis. P Hollander is a consultant for, and has received lecture fees from, sanofi-aventis and Pfizer. M D Jensen is a consultant for sanofi-aventis, Metabolic Pharmaceuticals, Novartis, MetaCure, Shionogi USA, and Merck, and has also received grant support from the US National Institutes of Health. L F Van Gaal is a member of advisory boards for sanofi-aventis, Abbott Pharma, and E Lilly and Co. He has received lecture fees from sanofi-aventis and Abbott Pharma, and has grant support from Fonds voor Wetenschappelfjk Onderzoek (Scientific Research Council, Flanders, Belgium).

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