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CB1 Receptor Blockade and its Impact on Cardiometabolic Risk Factors: Overview of the RIO Programme with Rimonabant

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Abstract : Rimonabant, the first selective CB_1 receptor antagonist in clinical use, has been extensively investigated in the Rimonabant in Obesity (RIO) programme, comprising four 1-2 year placebo-controlled randomised clinical trials recruiting more than 6600 overweight/obese patients with or without co-morbidities. Rimonabant 20 mg daily consistently reduced body weight, waist circumference, triglycerides, blood pressure, insulin resistance and C-reactive protein levels, and increased HDL cholesterol concentrations in both non-diabetic and type-2 diabetic overweight/obese patients. Adiponectin levels were increased, an effect that correlated with HDL cholesterol augmentation, while small dense LDL cholesterol levels were decreased in patients receiving rimonabant 20 mg compared with those receiving placebo in RIO Lipids. Furthermore, in RIO Diabetes, a 0.7% reduction in glycated haemoglobin (HbA1c) levels was observed in metformin- or sulphonylurea-treated patients with type-2 diabetes, an effect recently confirmed in the 6-month SERENADE (Study Evaluating Rimonabant Efficacy in drug-NAïve DiabEtic patients) trial in drug-naïve diabetic patients. Almost half of metabolic changes occurred beyond weight loss, in agreement with direct peripheral effects. The positive effects observed after 1 year were maintained after 2 years. Rimonabant was generally well-tolerated, but with a slightly higher incidence of depressed mood disorders, anxiety, nausea and dizziness compared with placebo. In clinical practice, rimonabant has to be prescribed to the right patient, i.e. overweight/obese subjects with cardiometabolic risk factors and with no major depressive illness and/or ongoing antidepressive treatment, in order to both maximise efficacy and minimise safety issues. New trials are supposed to confirm the potential role of rimonabant in patients with abdominal adiposity, atherogenic dyslipidaemia and/or type-2 diabetes, i.e. at high cardiometabolic risk.

Key words: endocannabinoid system ; cardiometabolic risk ; CB1 receptor ; obesity ; rimonabant ; type 2 diabetes.

There is now considerable evidence that the endocannabinoid (EC) system plays a significant role in appetite drive and associated behaviours, but also in endocrine and metabolic regulation and energy balance (1). Indeed, cannabinoid (CB) receptors, especially CB_1 receptors, are present not only in the brain, but also in many peripheral organs, i.e. adipose tissue, gut, liver, skeletal muscle and pancreas (1-3). They participate in the physiological modulation of many central and peripheral functions (1-3), and thus the EC system is a new target for pharmacological modulation (4, 5).

EC system overactivity has been demonstrated in human obesity, especially in the visceral adipose tissue (6,7), which is closely related to a high risk of type-2 diabetes and cardiovascular disease (CVD) (8, 9).
A multitargeted strategy is recommended to reduce the CVD risk of abdominally obese patients, especially in the presence of type-2 diabetes (10-13). The presence of the EC system and CB_1 receptors in several organs that play an important role in metabolic disturbances offers a great opportunity for new pharmacological approaches (4,5).

The diarylpyrazole derivative SR141716A (rimonabant) is the first selective CB_1receptor antagonist extensively investigated both in sophisticated research in animals and in large clinical trials in humans (14-17). It is the only one already commercialised in many countries for the management of abdominal obesity associated with multiple cardiometabolic risk factors, especially atherogenic dyslipidaemia and type-2 diabetes (18).

The aims of the present review are as follows: (i) to briefly describe the efficacy results obtained in randomised controlled trials (RCTs) with rimonabant in non-diabetic overweight/obese individuals and in patients with type-2 diabetes; (ii) to summarise the safety profile of rimonabant in the RIO programme, completed with a recently updated analysis; and (iii) to describe the benefit/risk profile of rimonabant and provide advice to target the right patient in clinical practice.

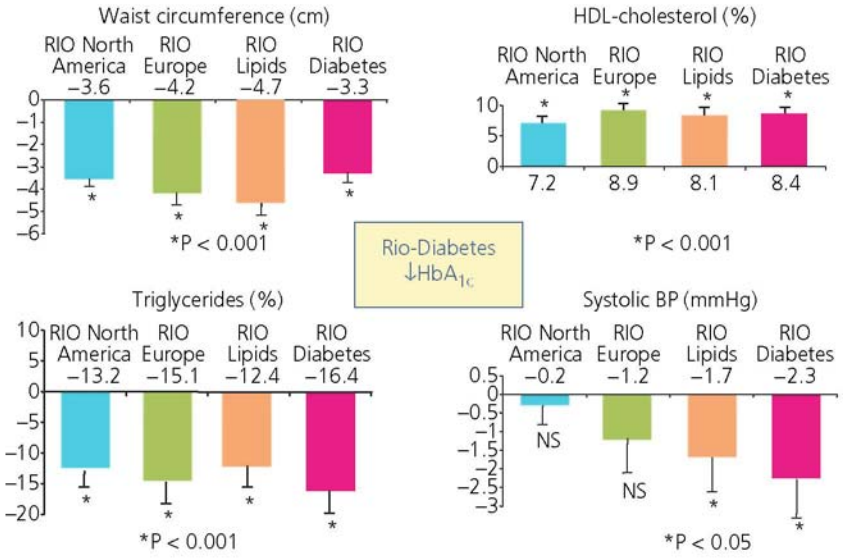
Efficacy of rimonabant

Cardiometabolic effects in overweight/obese non-diabetic patients

The selective CB1 receptor blocker rimonabant has been carefully evaluated in the phase III RIO (Rimonabant In Obesity) programme involving more than 6600 overweight/obese patients (14-16). This programme comprised three large placebo-controlled RCTs in overweight/obese non-diabetic patients, comparing rimonabant 5 mg and

20 mg with placebo: two 2-year RCTs (RIO Europe and RIO North America) (19-21) and one 1-year RCT (RIO-Lipids) specifically devoted to patients with untreated dyslipidaemia (22). These three RCTs led to remarkably consistent results (Fig. 1). After 1 year of follow up, rimonabant 20 mg has been shown to produce significant weight loss (-4.7 to -5.4 kg) and waist circumference reduction (-3.6 to -4.7 cm) compared with placebo, when combined with diet and exercise advice. In addition, improvements in multiple cardiovascular and metabolic risk factors were noticed. In particular, consistent significant reductions in triglyceride (TG) levels (-12.4 to -15.1%) and increases in HDL cholesterol (HDL-C) levels (+7.2 to +8.9%) were observed in overweight/obese patients treated with rimonabant 20 mg compared with placebo (19, 21). These improvements persisted after 2 years, with placebo-subtracted differences almost similar to those after 1 year for changes in body weight, waist circumference, TG and HDL-C levels (20, 21). If the treatment was interrupted after 1 year, however, which happened for some patients in RIO North America, body weight progressively increased to reach, after 2 years, the body weight measured in patients receiving placebo throughout the 2 years of the study, and the positive effects associated to initial weight loss progressively disappeared with weight regain (21). Therefore, obesity, as all chronic diseases, requires a long-term pharmacological intervention.

Fig. 1. *Consistent metabolic effects of rimonabant 20 mg compared with placebo in the 4 RIO trials. Results are expressed as placebo-subtracted after 1 year (mean ± SD; ITT and LOCF analysis). ITT, intent to treat; LOCF, last observation carried forward.*



The data of RIO Europe and RIO North America were further confirmed in overweight/obese patients with untreated dyslipidaemia in RIO-Lipids (22). Interestingly, part of these metabolic improvements (especially HDL-C increment) could be attributed to a significant increase in plasma adiponectin levels with rimonabant 20 mg (22). Adiponectin, a hormone specifically secreted by adipo-cytes, has been shown to improve insulin sensitivity and metabolic profile (23), and to exert favourable effects on endothelial dysfunction and arterial wall inflammation (24). The levels of LDL cholesterol were not affected by rimonabant, but the drug was associated with a shift to a lower proportion of small-dense LDL particles, the most atherogenic lipoproteins (22). A post-hoc analysis demonstrated that the positive effects of rimonabant on metabolic dyslipidaemia (low HDL-C and high TG levels) were almost similar in patients receiving or not receiving a cholesterol-lowering therapy with statin (25). This is an important observation, because prescription of statin is now recommended in all type 2 diabetic patients with high cardiovascular risk. A moderate reduction in systolic and diastolic blood pressure, related to weight loss, was also observed in the rimonabant group compared with the placebo group, and such a reduction was greater and highly significant in patients with elevated blood pressure at baseline (26). Fasting plasma insulin concentrations and HOMA (Homeostasis Model Assessment) insulin resistance index were significantly decreased in patients receiving rimonabant 20 mg compared with placebo. The prevalence of the metabolic syndrome, as defined using the National Cholesterol Educational Program - Adult Treatment Panel III (NCEP-ATP III) criteria, was significantly reduced in all three RIO trials performed in non-diabetic individuals. Finally, the levels of plasma C-reactive protein, a biological marker of silent inflammation and an independent CVD risk marker, were also diminished (-25%) in the rimonabant-treated group of the RIO-Lipids trial compared with the placebo-treated group (22).

To quantify to what extent the improvements in cardiometabolic risk factors are attributable to a direct effect of rimonabant, prespecified analyses were performed using 1-year pooled data (27) from patients in RIO Europe (19), RIO North America (21), RIO Lipids (22) and RIO Diabetes (28). Changes from baseline in cardiometabolic variables (body weight, lipids, fasting glucose and insulin) at year 1 were analysed using analysis of covariance, with weight loss as a covariate. In year 1, almost half (between 45% and 57%) of the overall treatment effect on HDL-C, TG levels, fasting insulin and insulin resistance was owing to a direct effect not attributable to weight loss (Table 1). Weight-loss-adjusted improvements in all factors were significantly better with rimonabant than with placebo ($P < 0.001$ for HDL-C and TG, $P < 0.02$ for fasting insulin and insulin resistance, assessed using the HOMA method). These results were supported by further analysis using weight loss category showing that greater metabolic improvements were observed for the same weight reduction when comparing subgroups treated with rimonabant 20 mg to corresponding subgroups receiving placebo. These findings were confirmed at year 2 in RIO North America (21) and in RIO Europe (20). These improvements in cardiometabolic risk factors beyond weight loss are possibly caused by a direct pharmacologic effect of rimonabant in peripheral tissues, in agreement with increasing evidence from animal observations (1-3). It is not known, however, which peripheral organ plays the major role in the overall metabolic improvement, even if adipose tissue seems to exert a key role, as suggested by the EC system overactivity shown in human visceral adipose tissue (6, 7) and the significant increase of adiponectin levels observed with rimonabant in both rodents and humans (22).

Table 1. *Weight-Attributable and Weight-Independent Effects of Rimonabant 20 mg Versus Placebo in a Pooled Analysis of the 1-year Data of the Four Trials of the RIO Programme (27). Results are Expressed by the Mean Values (27). P < 0.001 Except for (*) Where P = 0.018.*

Variable	Treatment effect of rimonabant 20 mg		
	Overall effect (mean difference versus placebo)	Effect beyond weight loss alone (mean difference versus placebo)	% of the overall effect not attributable to weight loss alone
HDL-Cholesterol (%)	+8.0	+3.6	45%
Triglycerides (%)	-14.0	-6.5	46%
Fasting insulin à (µIU/ml)	-2.74	-1.34 0(*)	49%
Adiponectin (µg /ml)	+ 1.5	+0.85	57%
HbA1c (%)	-0.67	-0.37	55%

HDL-C and triglycerides: four RIO trials; Fasting insulin: RIO-North America, RIO-Europe and RIO-Lipids; Adiponectin: RIO-Lipids; HbA1c: RIO-Diabetes.

To determine whether rimonabant improves glucose tolerance in overweight/obese non-diabetic patients, data were pooled from the 2 studies involving oral glucose tolerance tests (OGTTs) at baseline and 1 year (RIO Lipids and RIO Europe) (29). After 1 year, rimonabant 20 mg produced significantly greater reductions than placebo in plasma glucose (-0.64 versus -0.37 mmol/l, $P < 0.01$) and insulin (-15.2 versus -1.8 µlU/ml, $P < 0.001$) levels at 120 min post-OGTT. Rimonabant 20 mg also significantly reduced both glucose and insulin area under the plasma concentration-time curve (AUC) values compared with placebo (both $P < 0.001$). Furthermore, rimonabant 20 mg significantly improved the distribution of glucose tolerance status at 1 year in the pooled intent-to-treat population ($P < 0.01$), with an increased proportion of patients who improved from impaired glucose tolerance or diabetes at baseline to normal glucose tolerance at 1 year (64.9 versus 51.8%, $P < 0.05$) and a decreased proportion of patients who deteriorated from normal glucose tolerance to impaired glucose tolerance or diabetes (5.1 versus 9.3%, $P < 0.05$) (28). These favourable effects on glucose tolerance status persisted after 2 years, despite a weight stabilisation from year 1 to year 2, as shown in the RIO Europe trial (20).

These results demonstrate that rimonabant 20 mg can reduce the progression of glucose intolerance in overweight/obese patients. Therefore, the CB_1 receptor antagonist rimonabant may have the potential to prevent type-2 diabetes; this effect is currently under investigation in the Rimonabant in Prediabetic Subjects to Delay Onset of Type 2 Diabetes (RAPSODI) trial in overweight/obese individuals with impaired fasting glucose and/or impaired glucose tolerance (30).

Cardiometabolic effects in type-2 diabetes

Metformin- or sulphonylurea-treated patients: RIO Diabetes trial

The RIO Diabetes trial investigated the efficacy and safety of rimonabant in overweight/obese patients with type-2 diabetes (28). Therefore, 1047 overweight/obese type-2 diabetes patients (BMI 27-40 kg/m^2) with a

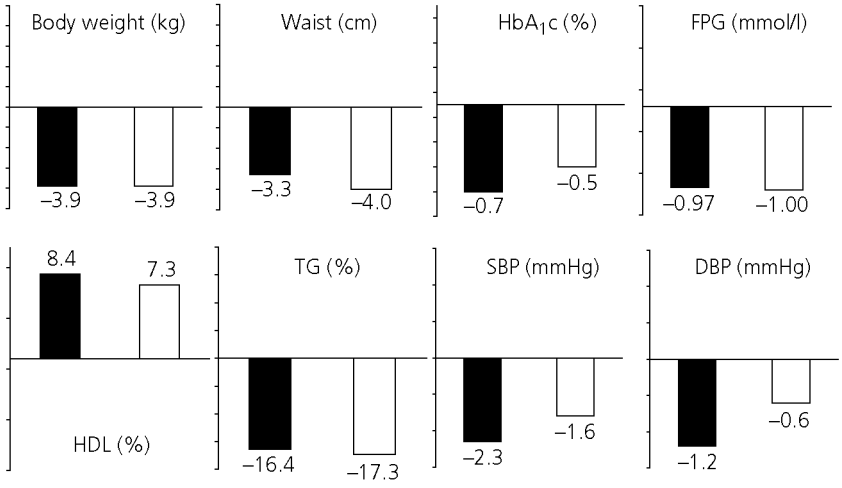
glycated haemoglobin (HbA1c) level from 6.5 to 10.0% already on metformin or sulphonylurea monotherapy were given a mild hypocaloric diet and randomised to placebo or rimonabant (5 or 20 mg) for 1 year. As in the three RIO trials in nondiabetic patients, the primary endpoint was weight change from baseline after 1 year of treatment. Secondary endpoints included changes in waist circumference, HbA1c, HDL cholesterol and TG levels (Table 1). Almost two-thirds of the diabetic population received metformin as monotherapy, the oral antidiabetic drug considered as first choice in the management of type-2 diabetes.

Weight loss in the intention-to-treat population was significantly greater after 1 year with rimonabant 20 mg (-5.3 ± 5.2 kg; $P < 0.001$) than with placebo (-1.4 ± 3.6 kg). Rimonabant 20 mg improved HbA1c (considered as secondary endpoint in this trial: -0.6 ± 0.8% versus +0.1 ± 1.0% for placebo; $P < 0.001$) in patients with only slightly elevated levels at randomisation (baseline HbA1c of 7.3 ± 0.9%). Treatment with rimonabant 20 mg enabled a greater number of patients to attain the HbA1c American Diabetes Association (ADA) target (HbA1c < 7%: 67.9% versus 47.6% with placebo) and the HbA1c International Diabetes Federation (IDF) target (HbA1c < 6.5%: 42.9% versus 20.8% with placebo). Improvements in blood glucose control were almost similar in patients with type 2 diabetes treated with metformin or sulphonylurea at baseline. In patients with higher HbA1c levels (> 8%) at baseline, greater reductions of 0.3% and 1.1% were observed in the placebo and rimonabant 20 mg treatment groups, respectively ($P = 0.001$ between groups).

Waist circumference, HDL-cholesterol, TG levels, fasting glucose levels, HOMA-estimated insulin resistance, systolic blood pressure, metabolic syndrome prevalence, and C-reactive protein levels also improved significantly with rimonabant 20 mg versus placebo (Figs 1 and 2). These favourable effects on multiple cardiovascular risk factors are important in order to improve the overall cardiovascular prognosis in this population (10-13). These results confirmed in overweight/obese patients with type-2 diabetes what was previously observed in the non-diabetic population (19-22). Again, the HbA1c, HDL-C and TG improvements with rimonabant 20 mg were approximately twice those expected from the observed weight loss alone (Table 1).

In RIO-Diabetes, rimonabant 20 mg/day reduced liver enzymes, especially alanine transferase (ALT) levels, the best marker of fatty liver, in addition to improving cardiometabolic risk factors in overweight/obese patients with type 2 diabetes (31). These observations are in agreement with previous reports showing that endocannabinoids promote hepatic lipogenesis and steatosis through CB_1 receptors (32). This might be an important feature, because fatty liver is strongly associated with insulin resistance in overweight/obese patients with type-2 diabetes (33) and might progress toward liver fibrosis in some patients (32).

Fig. 2. *Effects of rimonabant 20 mg in overweight/obese patients with type-2 diabetes: comparison of the results (placebo-subtracted differences) in the 1-year RIO Diabetes trial (black columns) and in the 6-month SERENADE trial (white columns) (mean; ITT and LOCF). $P < 0.001$ for all parameters except for systolic blood pressure (SBP, $P = 0.02$ in RIO Diabetes, NS in SERENADE) and diastolic blood pressure (DBP, $P = 0.06$ in RIO Diabetes, NS in SERENADE). FPG, fasting plasma glucose. NS, non-significant*



Drug-naive patients: SERENADE trial

The favourable effects of rimonabant in type 2 diabetes have been recently confirmed in SERENADE, a 6-month placebo-controlled trial in overweight/obese with recent-onset diabetes treated with diet alone (34). HbA1c (primary endpoint in this trial) decreased by 0.8% in the group receiving rimonabant 20 mg compared with 0.3%

in the group receiving placebo (P = 0.0002; mean baseline HbA1c: 7.9%). These differences were almost similar to those observed after 6 months in RIO-Diabetes (27). In patients with higher HbA1c levels (> 8.5%) at baseline, impressive reductions of 0.7% and 1.9% were observed in the placebo and rimonabant 20 mg treatment groups, respectively (P < 0.001). Similar to the changes observed in RIO Diabetes, significant reductions in body weight, waist circumference and TG levels were observed, whereas a significant increase in HDL-C was noticed with rimonabant 20 mg compared with placebo (Fig. 2). Whereas LDL cholesterol level was similar between the treatment groups, LDL particle size was slightly increased with rimonabant, reflecting a reduction in small-dense LDL cholesterol particles (P = 0.0008 versus placebo), as previously shown in RIO Lipids in non-diabetic individuals with non-treated dyslipidaemia (22). Rimonabant also decreased HOMA insulin resistance index and significantly increased plasma adiponectin levels, as already reported in the non-diabetic population of RIO-Lipids (22). After adjustment for body weight, rimonabant 20 mg significantly increased adiponectin and HDL-C levels. Again, almost half of the metabolic improvement occurred beyond weight loss (57% for HbA1c reduction) (34). These data further support the use of rimonabant in the management of patients with type-2 diabetes (30, 35, 36). Indeed, abdominal obesity plays a central role in the pathophysiology of type-2 diabetes (8, 10), and weight loss is crucial to prevent the development or improve the control of type-2 diabetes (37). Unfortunately, weight gain is generally observed with most of glucose-lowering drugs (sulphonylureas, glitazones, insulin) (38). An ambitious development programme is ongoing in type-2 diabetes, essentially to demonstrate the efficacy of rimonabant 20 mg on top of the first-choice drug metformin, compared not only with placebo but also with other oral glucose-lowering agents (glimepiride or sitagliptin) (30).

Safety profile of rimonabant

The overall safety profile of rimonabant was generally good in the RIO programme. Adverse events (AEs) most frequently reported with rimonabant were gastrointestinal, neurological and psychiatric in nature, but serious adverse events were infrequent (14-16, 39). Overall AE rates were similar across treatment groups, but discontinuation from AEs occurred more frequently with rimonabant 20 mg compared with placebo during the first year (13.6% versus 7.7% in the non-diabetic population) (Table 2). The most commonly reported AEs were depressive disorders (1.9% versus 0.8%), anxiety (1.0% versus 0.3%) and nausea (1.4% versus 0.1%). Most AEs occurred during the first few weeks to months of rimonabant treatment. During the second year, overall discontinuation rate because of AEs was low and similar (4.7%) with rimonabant and placebo in a pooled analysis of RIO Europe and RIO North America trials.

Table 2. *Adverse Events Leading to Drug Discontinuation in the Four Trials of the RIO Programme, and Reported Depressive Disorders in the Extended Obesity/Diabetes Programme According to Baseline Patients Characteristics.*

	Patients with adverse events leading to drug discontinuation*	
RIO programme	Rimonabant 20 mg % (n exposed)	Placebo *%* (n exposed)
Non diabetic patients (1st year)†	13.6 (2164)	7.7 (1254)
Non-diabetic patients (2nd year)‡	4.7 (683)	4.7 (491)
Diabetic patients (1st year)§	15.0 (339)	5.5 (348)
	Patients with depressive disorders¶	
Extended Obesity/ Diabetes Programme	Rimonabant 20 mg % (n exposed)	Placebo *%* (n exposed)
All obese patients**	3.9 (2742)	1.7 (2474)
All diabetic patients††	2.5 (477)	1.4 (488)
Patients without depression antecedents‡‡	2.4 (2507)	1.1 (2282)
Patients with depression antecedents‡‡	19.1 (235)	8.9 (192)

*Among which depressive disorders.
†RIO-Europe, RIO-North America, RIO-Lipids.
‡RIO-Europe, RIO-North America.
§RI0-Diabetes.
¶Not necessarily leading to drug discontinuation.
**Four trials of the RIO-programme + EFC5031, EFC5745, ACT3801 trials.
††RIO-Diabetes + SERENADE.
‡‡Four trials of the RIO-programme + REBA, EFC5745, ACT3801 trials.

In RIO Diabetes, although overall discontinuation rates were similar, discontinuations owing to AEs were more frequent in the rimonabant 20 mg (15.0%) treated group compared with placebo treated (5.5%) (28). The most common AEs leading to premature study discontinuation in the rimonabant 20 mg group were depressed mood disorders, nausea and dizziness -similar AEs to those in the non-diabetic overweight/obese population. However, no serious AEs linked to psychiatric disorders were recorded in the rimonabant 20 mg group. Hypoglycaemia symptoms were uncommon, although slightly more frequent in the rimonabant-treated group than in the placebo group, essentially in diabetic patients receiving sulphonylureas. Overall, the safety profile of rimonabant 20 mg in SERENADE was comparable to that reported in RIO Diabetes and in other RIO trials (34).

The overall safety of rimonabant in the RIO programme has been extensively reviewed by the principal investigators of the 4 individual trials (39). A recently published independent meta-analysis of these 4 RIO trials confirmed that rimonabant caused significantly more adverse events than did placebo (odds ratio [OR] = 1.4; P = 0.0007) and more serious adverse events (OR = 1.4; P = 0.03) (40). In particular, patients treated with rimonabant 20 mg were 2.5 more likely to discontinue the treatment because of depressive mood disorders than were those given placebo (OR = 2.5; P = 0.01). Furthermore, anxiety caused more patients to discontinue treatment in rimonabant groups than in placebo groups (OR = 3.0; P = 0.03).

The overall safety profile of the drug was assessed by the Food and Drug Administration (FDA), leading to a more extensive additional safety set of data (41). The main FDA concern was a higher incidence of suicidal ideation in rimonabant-treated patients compared with placebo-treated overweight/obese patients, although the levels remained very low (0.62 and 0.36%, respectively). In an updated (but as yet unpublished) analysis of the entire obesity clinical programme with rimonabant, depressive disorders were reported in 3.9% of patients in the rimonabant 20 mg group compared with 1.7% in the placebo group, while mood alterations with depressive symptoms were reported in 4.7% and 2.8% of the rimonabant- and placebo-treated patients, respectively (LF Van Gaal, AJ Scheen, JP Després, FX Pi-Sunyer, RM Anthenelli, unpublished data). Most importantly, there was a greater likelihood of developing depressive disorders among patients with a past history of depressive disorders than in patients with no past history. In patients with no such past history, the incidence of depressive disorders was 2.4% in the group receiving rimonabant compared with 1.1% in the group receiving placebo. By contrast, the incidence of depressive disorders in patients with a past history was 19.1% and 8.9% with rimonabant 20 mg and placebo, respectively (Table 2). Thus it is worth noting that the risk of depressive disorders was considerably lower in patients without past history of depression but receiving rimonabant 20 mg combined with diet and exercise advice than in patients with a past history of depression and receiving placebo and diet and exercise counselling. These observations lead to important recommendations for the use of rimonabant in clinical practice (see below).

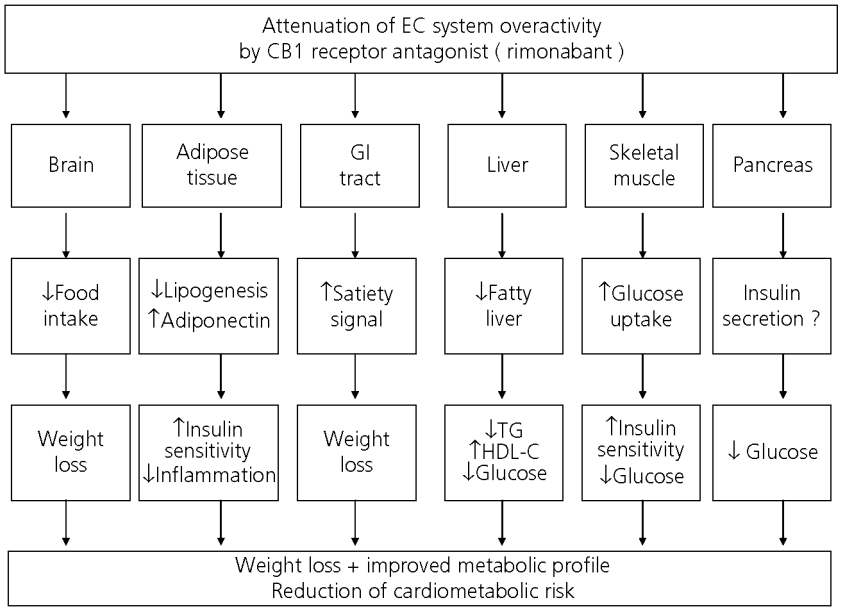
Anxiety and depression most probably result from the pharmacological CB_1 antagonist activity of the drug in the brain. Indeed, despite reporting of conflicting results, the pharmacological enhancement of the EC system activity at the CB_1 receptor level appears to exert an antidepressant-like effect in some animal models of depression. By contrast, a reduced activity of the EC system seems to be associated with an animal model of depression (42). With regard to clinical studies, several authors have reported an alteration of EC serum levels in depression (42). Therefore, it is highly probable that the psychological adverse effects reported with rimonabant will also be observed with other CB_1 receptor modulators (30). In a recent study, the acyclic CB_1 receptor inverse agonist taranabant was associated with a dose-related increased incidence of mild to moderate psychiatric adverse events (43).

Rimonabant in clinical practice

Rimonabant is recognised in the international literature as a promising drug for the management of abdominal obesity and high cardiometabolic risk (16, 44, 45), particularly because of its pleiotropic effects (46) (Fig. 3). Therefore, rimonabant should not be considered as simply an anti-obesity drug (47, 48); it might positively influence the so-called adiposopathy (49), as suggested by the increase in adiponectin concentrations and the decrease in C-reactive protein levels. Rimonabant (Acomplia®, 20 mg, sanofi-aventis, Paris, France) has been approved by the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMEA) *'as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m^2), or overweight patients (BMI > 27 kg/m^2) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia'* (18). Furthermore, the Committee recognised that half of the observed improvements in several metabolic parameters (HbA_{1c}, HDL-C and TG) in patients who received 20 mg rimonabant were beyond those expected from weight loss, in agreement with direct peripheral metabolic effects. However, the EMEA labelling clearly stated that *'rimonabant is contraindicated in patients with uncontrolled serious psychiatric illness such as major depression, or patients receiving antidepressant medication'* (18). After the decision by the Endocrinologic and Metabolic Drugs Advisory Committee of the FDA to postpone the launch of rimonabant in the United States because of safety concerns (41), the EMEA recently confirmed the benefit : risk ratio of the drug in well-selected overweight/obese individuals (50). However, the post-hoc extensive analysis regarding depression (see above)

led to the recent revision by the EMEA of the product label, which now states that *'In patients with a history of depressive disorder rimonabant should not be used unless the benefits of treatment are considered to outweigh these risks in an individual patient* (50).

Fig. 3. *Central and peripheral metabolic effects of CB_1 of rimonabant, a selective CB_1 antagonist.*



Patients most likely to benefit from rimonabant are those with multiple cardiometabolic risk factors known to be improved by the drug, such as abdominal obesity, type-2 diabetes and atherogenic dyslipidaemia (low HDL-C and/or high TG) (14-16, 42-45). The CRESCENDO (Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes) trial will further support the use of rimonabant to reduce the incidence of CVD complications in high-risk patients (30). Rimonabant is not a cosmetic drug and is not indicated for patients with a BMI < 27 kg/m^2 or for those with a BMI between 27 and 29.9 kg/m^2 but who have no associated cardiometabolic risk factor(s). Rimonabant is contraindicated for pregnant or breast-feeding women and is not recommended for children below 18 years of age. Moreover, it should not be given to patients with severe renal/hepatic impairment. Because patients with antecedent depression or those receiving antidepressant agents were excluded from the RIO programme and because mood disorders were more frequently observed with rimonabant than with placebo in all clinical trials, rimonabant is contraindicated in patients with uncontrolled serious psychiatric illness such as major depression, or patients receiving antidepressant medication, and should be used with caution in patients with a history of depression. Careful monitoring for anxiety and depressive disorders that might occur during treatment with rimonabant is also recommended, and caution recommends the interruption of rimonabant in the presence of such new psychological symptoms.

Conclusions

The widespread EC system does provide an opportunity to develop therapeutic agents, probably not with magic-bullet-like specificity but more likely with multiple actions targeting different facets of the system. This might be a great opportunity in the management of multifaceted diseases such as abdominal obesity and the metabolic syndrome or type-2 diabetes where overactivity of the EC system has been demonstrated.

The findings of the RIO-programme support the use of rimonabant 20 mg, a selective CB_1 receptor antagonist, as a new approach for the management of overweight and obesity associated with atherogenic dyslipidaemia and/or type-2 diabetes, in addition to diet and exercise. Indeed, multiple favourable effects have been consistently reported, with greater weight loss, reduced abdominal adiposity, lowering of HbA1c levels, and improvements in levels of HDL-C, TG, C-reactive protein, blood pressure and insulin resistance. Most metabolic improvements, especially the reduction in HbA1c and the increase in HDL-C levels, were almost twice those expected from weight loss alone, consistent with the direct peripheral metabolic effects of the drug reported in numerous animal models.

An extensive clinical research programme, more specifically devoted to type-2 diabetes, is going to further

support this new strategy and aims to demonstrate that rimonabant is able not only to reduce CVD risk factors, but also the progression of atherosclerosis and the incidence of major CVD events in high-risk individuals. In clinical practice, rimonabant has to be prescribed to the right patient, i.e. overweight/obese subjects with cardiometabolic risk factors but with no major depressive illness and/or ongoing antide-pressive treatment, in order to both maximise efficacy and minimise safety issues.

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Conflicts of interest

AJ Scheen is a consultant for Sanofi-Aventis, AstraZeneca, GlaxoSmithKline, and has received lecture fees from Sanofi-Aventis.

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