

Use of cannabinoid CB1 receptor antagonists for the treatment of metabolic disorders

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SUMMARY (Max 150 words : 150)

Abdominal obesity is associated with numerous metabolic abnormalities including insulin resistance, impaired glucose tolerance/type 2 diabetes, and atherogenic dyslipidaemia with low HDL cholesterol, high triglycerides and increased small dense LDL cholesterol. Part of these metabolic disorders may be attributed to increased endocannabinoid activity. The selective CB₁ receptor antagonist rimonabant has been shown to reduce body weight, waist circumference, insulin resistance, triglycerides, dense LDL, CRP and blood pressure, and to increase HDL and adiponectin concentrations in both non-diabetic and diabetic overweight/obese patients. Besides an improvement of glucose tolerance in non-diabetic subjects, a 0.5-0.7% reduction in HbA1c levels was consistently observed in various groups of patients with type 2 diabetes. Almost half of metabolic changes could not be explained by weight loss, supporting direct peripheral effects of rimonabant. Ongoing studies should demonstrate whether improved metabolic disorders with CB₁ receptor antagonists (rimonabant, taranabant, ...) would translate in less cardiovascular complications among high-risk individuals.

1. Introduction

The discovery of the endocannabinoid (EC) system represents a hallmark not only in neuroscience, but also in metabolic research [1]. There is considerable evidence that EC system plays a significant role in appetite drive and associated behaviours, as well as in endocrine and metabolic regulation and energy balance [2-5]. Indeed, cannabinoid (CB) receptors, especially CB1 receptors, participate in the physiological modulation of many central and peripheral functions [2-5]. The tremendous increase in the understanding of the molecular basis of CB activity [6,7] has encouraged many pharmaceutical companies to develop synthetic CB analogues and antagonists (rimonabant, taranabant, ...), leading to an explosion of basic research and clinical trials, especially in the field of metabolic disorders associated to abdominal obesity [1,8,9].

CB1 receptors are found not only in the central nervous system [10], but also in the adipose tissue [11,12], the gut [13], the liver [14], the skeletal muscle [15] and the pancreas [11,16], all organs playing a key-role in energy balance [3,4] as well as in glucose [17-19] and lipid metabolism [12]. Interestingly, whereas antagonism of CB1 receptors acutely reduces food intake, the long-term effects on weight reduction and metabolic regulation rather appear to be mediated by stimulation of energy expenditure and by peripheral effects [3,4]. Therefore, it is reasonable to hypothesize that the attenuation of EC system overactivity characterizing abdominal obesity, by using selective CB1 receptor antagonists, would have therapeutic benefit in treating metabolic disorders related to excessive visceral adipose tissue [20-24].

Considering that (1) most overweight/obese patients with abdominal adiposity have glucose and lipid disorders leading to a high incidence of cardiovascular complications and (2) various organs playing a key-role in glucose and lipid metabolism contain both ECs and CB1 receptors, the therapeutic CB1 modulation deserves much attention in the management of metabolic disorders associated with abdominal obesity in order to reduce the so-called cardiometabolic risk [20-24]. The aim of the present review is to analyze the currently available human data from randomised controlled trials having investigated the potential role of CB1 receptor antagonists, especially rimonabant, on glucose and lipid disorders in both non-diabetic and diabetic overweight/obese patients. The metabolic effects of CB1 receptor antagonists in various animal

models have been reviewed recently in several other papers [2-5] and will not be considered here. Finally, safety concern of CB1 receptor antagonists, especially psychological adverse effects, has also been debated in recent review papers [25,26] and will only be briefly mentioned in the conclusion of the present article.

2. EC system overactivity and metabolic abnormalities in abdominal obesity

There is increasing evidence in humans for overactivity of the EC system during conditions of unbalanced energy homeostasis, i.e. obesity (especially abdominal obesity) and type 2 diabetes, and for its causative role in these disorders [3-5]. Circulating levels of 2-arachidonoyl glycerol (2-AG), one major EC, were significantly correlated with body fat, visceral fat mass, and fasting plasma insulin concentrations, but negatively correlated to glucose infusion rate during an hyperinsulinaemic clamp (gold standard method to measure insulin sensitivity - [27]) [28]. Obese subjects had a reduction in adipose tissue FAAH (fatty acid amide hydroxylase, a key-enzyme in EC degradation) gene expression compared with lean individuals, and FAAH gene expression was negatively correlated with visceral fat mass and with circulating 2-AG [29]. Higher levels of 2-AG in the serum and visceral, but not subcutaneous, fat of obese subjects were also reported [11]. In untreated asymptomatic men, plasma 2-AG levels correlated positively with body mass index (BMI), waist girth, intra-abdominal adiposity, fasting triglycerides and insulin levels, and negatively with HDL cholesterol and adiponectin concentrations [30]. Recent animal data suggested that insulin-resistant adipocytes fail to regulate EC metabolism and decrease intracellular EC levels in response to insulin stimulation [31]. These novel observations offer a mechanism whereby obese insulin-resistant individuals exhibit increased concentrations of ECs.

All together, these findings suggest that intra-abdominal fat accumulation is a critical correlate of peripheral EC system dysregulation and that the EC system may represent a primary target for the treatment of abdominal obesity and associated metabolic changes, including type 2 diabetes and atherogenic dyslipidaemia [20-24].

3. Pharmacological modulation of EC system : CB1 receptor antagonists

EC system overactivity may result from increased EC synthesis, CB (mainly CB1) receptor overexpression and/or decreased EC degradation. Conversely, pharmacological modulation to correct overactivity of EC system may theoretically involve reduction of EC production, blockade of CB1 receptors and/or enhancement of EC degradation [1]. The most advanced pharmacological approach targets C1 receptors [32]. There are different possible mechanisms by which CB1 receptor antagonists produce their effects on the CB1 receptor. The ligands can be pure competitive antagonists of CB1 receptor activation by endogenously released ECs (neutral antagonists), or they can act as inverse agonists and modulating constitutive CB1 receptor activity by shifting it from an active “on” to an inactive “off” state [33,34].

SR141716 (rimonabant) was the first selective CB1 receptor antagonist reported and extensively investigated [34-36]. Rimonabant is a selective CB1 receptor antagonist, with little or no affinity for other receptors, including CB2 receptors. Some evidence suggests that rather than acting as a pure (neutral) antagonist, rimonabant might function as an inverse agonist, i.e. have intrinsic activity opposite to that of agonists or inhibit constitutive CB1 receptor activity [33,34]. Rimonabant is the only CB1 receptor antagonist already commercialized in numerous European countries and worldwide (but not in the United States) with the following indication : “as an adjunct to diet and exercise for the treatment of obese patients (BMI ≥ 30 kg/m²), or overweight patients (BMI > 27 kg/m²) with associated risk factor(s), such as type 2 diabetes or dyslipidaemia” [37].

In addition to rimonabant, several other CB1 receptor antagonists have been synthesized and many are under development but, at present, little is known about them, although some recent data are available concerning the CB1 receptor inverse agonist taranabant [38]. In a 12-week weight-loss study, taranabant induced statistically significant weight loss compared to placebo in obese subjects over the entire range of evaluated doses (0.5, 2, 4, and 6 mg once per day) ($p < 0.001$) [39]. Mechanism-of-action studies suggested that engagement of the CB1 receptor by taranabant leads to weight loss by reducing food intake and increasing energy expenditure and fat oxidation [39]. However, the results from long-term RCTs with taranabant in non-diabetic or diabetic overweight/obese patients are not available yet. Therefore, the present review paper will be essentially devoted to the results obtained with rimonabant, which has been

carefully evaluated in the phase III RIO (“Rimonabant In Obesity”) programme comprising over 6,600 patients [26,40]. This programme included three large placebo-controlled randomised clinical trials (RCTs) in overweight/obese non-diabetic patients with or without comorbidities : two 2-year RCTs (RIO-Europe and RIO-North America) [41-43] and one 1-year RCT (RIO-Lipids) specifically devoted to patients with untreated dyslipidaemia [44]. The fourth trial, RIO-Diabetes, focused on patients with type 2 diabetes treated either with metformin or sulfonylureas [45]. After this impressive phase III trial, both the efficacy and safety of rimonabant were further evaluated in numerous RCTs, some of them being already completed (SERENADE, ARPEGGIO, STRADIVARIUS, ADAGIO-Lipids) while other being still underway (numerous RCTs in the population with type 2 diabetes, plus VICTORIA, AUDITOR, CRESCENDO, ...) (see below) [46].

4. CB1 receptor antagonists and glucose metabolism

The presence of CB1 receptors in the pancreatic islets, including beta cells (which also contain CB2 receptors), with a possible effect on insulin secretion [16], and the evidence that CB1 receptor inhibition increases adiponectin production [11,44], an adipocyte-derived hormone that seems to play a key-role in insulin sensitivity [47], are fundamental arguments in favour of a potential influence of CB1 receptor antagonists on glucose metabolism [19,46,48]. We will first describe the available data in non-diabetic subjects, mainly fasting glucose and insulin data allowing the calculation of the so-called HOMA (“HOmeostasis Model Assessment”) insulin resistance index [28] and glucose tolerance assessed during an oral glucose tolerance test (OGTT). Afterwards, we will focus on individuals with type 2 diabetes among whom rimonabant 20 mg has been compared to placebo on top of various antidiabetic therapies (diet alone, monotherapy with metformin or sulfonylureas, or insulin).

4.1. Glucose tolerance in non-diabetic patients

The three large RCTs of the RIO programme performed in non-diabetic overweight/obese individuals led to remarkably consistent results [25,26,40]. After one year of follow up, rimonabant 20 mg has been shown to produce significant weight loss (placebo-subtracted : -4.7

to -5.4 kg in the various studies; $p < 0.001$) and waist circumference reduction (-3.6 to -4.7 cm; $p < 0.001$) as compared to placebo, when combined with diet and exercise advices. These changes persisted after two years of follow up in the two trials where such long-term assessment was performed [42,43]. In addition, significant improvements in parameters of glucose metabolism were noticed after one and two years of treatment with rimonabant 20 mg as compared to placebo [19,46,48].

4.1.1. Fasting assessment

As fasting plasma glucose levels were normal at baseline in this selected non-diabetic population, only mild and non significant reductions in basal glucose concentrations were observed after 1 or 2 years of drug therapy in RIO-Europe, RIO-North America and RIO-Lipids [41-44]. However, fasting plasma insulin levels, a crude marker of insulin resistance [28], were significantly reduced in the rimonabant-treated groups as compared to the placebo-treated group. A statistical analysis of the pooled data of the RIO programme demonstrated that 49 % of the reduction in fasting plasma insulin levels could not be explained by weight loss alone, suggesting a direct effect of the drug on insulin sensitivity [26]. The HOMA insulin resistance index, derived from a model based on both glucose and insulin fasting concentrations [28], was significantly decreased in patients receiving rimonabant 20 mg compared to placebo. However, there is no experimental data in humans that investigated the effects of the CB1 receptor antagonist rimonabant on insulin sensitivity with more sophisticated techniques such as the euglycaemic hyperinsulinaemic glucose clamp, the gold standard method [28].

One possible mechanism of the improvement of insulin sensitivity with rimonabant, independently of weight loss, may be attributed to an increase in adiponectin levels, an adipocyte-produced hormone known to promote insulin action [47]. Indeed, the RIO-Lipids showed a 46-57 % ($p < 0.001$) increase of plasma adiponectin levels in the rimonabant 20 mg group as compared to placebo. The increase in adiponectin levels correlated with weight loss in each treatment group; however, 57 % of the increase in plasma adiponectin levels observed in the group treated with rimonabant 20 mg could not be attributed to weight loss [44]. These data were recently confirmed in ADAGIO-Lipids (“An international study of rimonabant in

Dyslipidemia with AtheroGenic risk In abdominally Obese patients”) [49]. Indeed, a 19 % ($p < 0.0001$) increment in adiponectin levels was noticed in the group receiving rimonabant 20 mg as compared to that receiving placebo; only one third of this increase could be attributable to weight loss [49].

A pooled analysis from the three RIO trials performed in non-diabetic overweight/obese patients [41,43,44] was conducted on 1-year data from a subgroup of patients identified with prediabetes ($n=1290$) as defined by impaired fasting glucose (IFG > 5.5 - <7.0 mmol/l or > 100 - <125 mg/dl) [50]. A trend to reverse or retard the progression of IFG was reported as suggested by a numerically greater percentage of patients converting to normal fasting plasma glucose (≤ 5.5 mmol/l) and a lesser proportion of patients progressing to type 2 diabetes (≥ 7 mmol/l) in the rimonabant 20 mg group as compared to the placebo group. However, this post-hoc analysis was not properly powered to explore the role of rimonabant in the prevention of diabetes in individuals with prediabetes (see below).

4.1.2. Oral glucose tolerance tests

To determine whether rimonabant improves glucose tolerance in overweight/obese non-diabetic patients, data were pooled from the two studies involving OGTTs at baseline and 1 year (RIO-Lipids and RIO-Europe) [41,44], and 2 years (RIO-Europe) [42]. After 1 year, rimonabant 20 mg produced significantly greater reductions than placebo in plasma glucose (-0.64 vs -0.37 mmol/l, $p < 0.01$) and insulin (-15.2 vs -1.8 mIU/l, $p < 0.001$) levels at 120 minutes post-OGTT [51]. Rimonabant 20 mg also significantly reduced both glucose and insulin area under the plasma concentration–time curve values versus 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 with normal glucose tolerance and a decreased proportion of patients with impaired glucose tolerance or diabetes. Favourable effects on glucose tolerance status persisted after 2 years, despite a weight stabilization from year 1 to year 2 in the RIO-Europe trial [52].

These results demonstrated that rimonabant 20 mg could prevent or reverse progression of glucose intolerance in overweight/obese patients and suggest its potential to prevent type 2

diabetes. Such a prevention effect is currently tested in two prospective trials in overweight/obese patients with impaired fasting glucose and/or impaired glucose tolerance (RAPSODI and PRADO). As the CB1 receptor antagonist rimonabant targets a key factor in the pathophysiology of the disease, i.e. abdominal obesity and adiposopathy [53,54], one may speculate that this effect could be a true preventive effect rather than a delaying or masking effect as previously reported and discussed with various oral antidiabetic drugs [55].

4.2. Glucose control in diabetic patients

4.2.1. RIO-Diabetes in metformin- or sulfonylurea-treated patients

The RIO-Diabetes trial investigated the efficacy and safety of rimonabant, compared to placebo, in 1047 overweight/obese patients with type 2 diabetes already on either metformin (two thirds of the randomised population) or sulfonylurea (one third of the population), and insufficiently controlled with such monotherapy (HbA1c between 6.5 and 10 %) [45]. The primary endpoint was weight change from baseline after 1 year of treatment whereas HbA1c change was considered as a secondary endpoint. Weight loss (- 5.3 kg vs - 1.4 kg; $p < 0.001$) and waist reduction (- 5.2 cm vs - 1.9 cm; $p < 0.001$) in the intention-to-treat population were significantly greater after 1 year with rimonabant 20 mg than with placebo.

Rimonabant 20 mg improved HbA1c (-0.6% vs +0.1% for placebo; $p < 0.001$) in patients with mean baseline HbA1c of 7.3 % at randomisation. Treatment with rimonabant 20 mg enabled a greater number of patients to attain the HbA1c target proposed by the American Diabetes Association (HbA1c < 7% : 67.9% vs 47.6% with placebo; $p < 0.001$) and the HbA1c target proposed by the International Diabetes Federation (HbA1c < 6.5% : 42.9% vs 20.8% with placebo; $p < 0.001$). Improvements were almost similar in patients with type 2 diabetes treated with metformin or sulfonylurea at baseline (Table 2). Almost 55% of the HbA1c reduction observed with rimonabant 20 mg compared to placebo could not be explained by weight loss alone. In patients with higher HbA1c levels ($\geq 8\%$) at baseline, reductions of 0.3% and 1.1% were observed in the placebo and rimonabant 20 mg treatment groups, respectively ($p = 0.001$).

The 0.7 % observed reduction in HbA1c levels seen with rimonabant 20 mg vs placebo in the overall population of RIO-Diabetes appears to be greater than the corresponding reduction

observed with orlistat or sibutramine [56,57] and almost comparable to that reported with classical oral antidiabetic drugs (when adjusted for baseline HbA1c levels, as recommended) [58]. However, head-to-head comparative studies are still lacking. It is noteworthy, however, that at least two RCTs are ongoing, which will directly compare rimonabant 20 mg with glucose-lowering agents enhancing insulin secretion, in a population quite similar to the main group studied in RIO-Diabetes (treatment on top of metformin) (see below) [47].

4.2.2. SERENADE trial in drug-naïve patients

The favourable effects of rimonabant 20 mg in type 2 diabetes have been recently confirmed in SERENADE (« Study Evaluating Rimonabant Efficacy in drug-NAive DiabEtic patients »), a 6-month placebo-controlled trial in overweight/obese individuals with recent-onset diabetes treated with diet alone (Table 2) [59]. HbA1c, selected as primary endpoint in this trial, decreased by 0.8 % in the group receiving rimonabant 20 mg compared to 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 [45]. In patients with higher HbA1c levels ($\geq 8.5\%$) at baseline, reductions of 0.7% and 1.9% were observed in the placebo and rimonabant 20 mg treatment groups, respectively ($p<0.001$). Rimonabant also decreased HOMA-IR insulin resistance index and significantly increased plasma adiponectin levels (+1.8 $\mu\text{g/ml}$, $p<0.0001$, as it was already reported in the non-diabetic population of RIO-Lipids [44]. Again, almost half of the metabolic improvement occurred beyond weight loss (57% for HbA1c reduction) [59].

4.2.3. ARPEGGIO trial in insulin-treated patients

The “ARPEGGIO” trial recently assessed the effect of rimonabant 20 mg in overweight/obese diabetic patients already treated with exogenous insulin [60]. In the intention-to-treat population, mean baseline HbA1c (9.1%) was reduced significantly more with rimonabant than with placebo (-0.89 vs - 0.24%; $p<0.0001$) at 48 weeks of follow up. Furthermore, more patients on rimonabant vs placebo had $>10\%$ reduction in mean total daily insulin dose (16.8% vs 5.8%; $p<0.0012$) and fewer received glucose-lowering rescue medication

(14.0% vs 34.9%; $p < 0.0001$). Despite this improvement of glucose control (leading to a reduction of glucosuria), there was significantly greater improvement in body weight (-2.5 kg vs + 0.1 kg; $p < 0.0001$) and waist circumference (- 2.8 cm vs + 0.2 cm; $p < 0.0001$) in the rimonabant group compared to the placebo group. Thus, the ARPEGGIO study of rimonabant in patients with advanced type 2 diabetes receiving insulin confirmed findings from previous studies where a clinically significant effect on glycaemic control (and other cardiometabolic risk factors) was shown.

4.2.4. STRADIVARIUS subgroup with type 2 diabetes

In the recently published STRADIVARIUS study [61], 248 out of the 839 patients with coronary disease had type 2 diabetes allowing a post-hoc analysis of this subgroup. After 18 months of follow up, the mean reduction in HbA1c averaged - 0.30% in the rimonabant group as compared to an increase of + 0.37% in the placebo group ($p = 0.0003$), starting from a baseline level of 6.7 %. The least-square means estimated HbA1c changes using a 2-way analysis of variance with terms for baseline value, treatment group, visit, and treatment x visit interaction were - 0.13% with rimonabant 20 mg and + 0.42% with placebo ($p < 0.001$).

4.2.5. Ongoing trials in patients with type 2 diabetes

All the available data in the diabetic population are consistent as far as the reduction in HbA1c associated to rimonabant 20 mg therapy is concerned, whatever this biological parameter was considered as a secondary or a primary endpoint. Numerous RCTs are ongoing to further demonstrate the efficacy of rimonabant in overweight/obese patients with type 2 diabetes. In all these new trials, HbA1c reduction has been chosen as a primary endpoint. The first set of RCTs will compare rimonabant 20 mg with placebo in patients treated with diet alone, with metformin, with sulfonylureas or alpha-glucosidase inhibitors, ... [47]. The second set of RCTs will compare rimonabant 20 mg against an active comparator, either a sulfonylurea (glipizide) or a dipeptidyl-peptidase-4 antagonist (sitagliptin), in patients already treated with metformin. These last two head-to-head trials are testing a non-inferiority hypothesis regarding HbA1c reduction when comparing rimonabant with the classical glucose-lowering agents, but with the expected

add-on benefits of greater weight loss and better improvement of lipid profile with the CB1 receptor antagonist.

These studies will broaden the spectrum of combined therapy with rimonabant in type 2 diabetes and, if conclusive, may support the role of rimonabant as a possible new antidiabetic agent in a near future [17,19,46,47,62].

5. CB1 antagonists and lipid metabolism

Patients at high risk of cardiovascular disease are treated with statins as recommended by most guidelines [63]. However, the residual risk remains high, especially in subjects with low HDL and high triglycerides levels [64], an atherogenic dyslipidaemia generally observed in individuals with abdominal obesity, especially in presence of type 2 diabetes [53,54,65].

5.1. Low HDL cholesterol and high triglycerides

In the RIO programme, consistent significant reductions in triglyceride levels (placebo-subtracted according to the various studies after one year of rimonabant 20 mg : -12.4 to -15.1 %) and increases in HDL cholesterol levels (+7.2 to +8.9 %) were observed in overweight/obese non-diabetic patients treated with rimonabant 20 mg [41,43,44]. These improvements persisted after 2 years despite no further weight reduction during the second year [42,43].

These data were further confirmed in overweight/obese patients with untreated dyslipidaemia and part of these metabolic improvements could be attributed to a significant increase in plasma adiponectin levels with rimonabant 20 mg. Indeed, changes in adiponectin levels produced by rimonabant 20 mg positively correlated with changes in levels of HDL cholesterol ($r=0.27$; $p<0.001$) and apolipoprotein A-I ($r=0.38$; $p<0.001$) [44]. The recent ADAGIO-Lipids trial essentially investigated the effects of rimonabant 20 mg on lipid profile and visceral adipose tissue in patients with abdominal obesity and atherogenic dyslipidaemia. This study confirmed the positive effect of rimonabant 20 mg on waist reduction and on HDL cholesterol and triglyceride levels, and demonstrated a significant reduction in visceral adipose tissue and liver fat content [49]. Interestingly, a post-hoc analysis of the data obtained in the RIO programme demonstrated that the positive effects of rimonabant on atherogenic dyslipidaemia (low HDL-C

and high triglycerides) were almost similar in patients receiving or not receiving a cholesterol-lowering therapy with statin [66].

A significant increase in HDL cholesterol and a significant reduction in triglyceride levels were also observed in the three available RCTs performed in overweight/obese patients with type 2 diabetes, whatever the baseline antidiabetic therapy (diet alone, metformin, sulfonylurea, insulin) (Table 2). As compared to what was noticed in the overweight/obese nondiabetic groups, the improvement in lipid profile was qualitatively and quantitatively similar in diabetic patients, a population more frequently characterized by atherogenic dyslipidaemia despite statin therapy.

In STRADIVARIUS [61], the only available study designed to assess whether rimonabant 20 mg is able to reduce the progression of coronary atheroma (see below), a significant improvement in the lipid profile was also observed in a large cohort of 839 patients (248 with diabetes) followed for 18 months. In the rimonabant vs placebo groups, HDL cholesterol levels increased by 22.4% vs 6.9% ($p < 0.001$) and median triglyceride levels decreased by 20.5% vs 6.2% ($p < 0.001$). Thus, these results confirmed in patients with coronary artery disease (82% being treated with statins) [61] the effects of rimonabant previously reported in the RIO programme [26].

5.2. LDL cholesterol and small dense LDL

The levels of LDL cholesterol were not affected by rimonabant, especially in the RIO-Lipids trial [44]. However, although there was no change in LDL cholesterol in the latter study, the distribution of LDL particles shifted toward larger size in the group receiving rimonabant 20 mg, as compared to placebo, with a 1.1 Å difference in LDL peak particle size ($p = 0.008$) and a 4.6% lower proportion of small LDL particles ($P = 0.007$). Such a shift may be favourable because small dense LDL are considered as the most deleterious particles for the arterial wall.

In the ADAGIO-Lipids trial, small dense LDL proportion was more reduced in the rimonabant group than in the placebo group (difference : - 6.5%; $p < 0.0001$), confirming the previous data of RIO-Lipids [44]. Interestingly, a more sophisticated analysis was performed concerning lipid subfractions (HDL subfractions) and apolipoprotein measurements (apoA1, apoB, apoCIII). The results will be detailed in the full paper of the ADAGIO-Lipids trial [49].

6. Cardiometabolic risk

6.1. Global risk assessment

In order to reduce the incidence of cardiovascular complications, most importantly in overweight/obese patients, it is important to target all parameters playing a role in the global risk associated with abdominal obesity [53,54,65,67,68].

Besides the already described positive effects of the CB1 receptor antagonist on glucose and lipid metabolism, a moderate reduction in systolic and diastolic blood pressure was observed in the rimonabant group as compared to the placebo group. In all RCTs, such a reduction was greater and significant in patients with elevated blood pressure at baseline, in non-diabetic and even more in diabetic individuals [69]. This pressure-lowering effect could be attributed to the greater weight loss induced by rimonabant as compared to placebo, without any intrinsic weight-independent pressure effect (in contrast to what was reported for metabolic improvements).

The prevalence of the metabolic syndrome as defined with the NCEP-ATP III (“National Cholesterol Education Program Adult Treatment Panel III”) criteria [63] was significantly more reduced with rimonabant 20 mg vs placebo after one year in all three RIO RCTs performed in non-diabetic patients : - 53% vs - 21% in RIO-Europe, - 39% vs - 8% in RIO-North America and - 51% vs - 21% in RIO-Lipids (all $p < 0.001$). In RIO-Diabetes, a significant reduction was also observed (-15% vs -6%; $p = 0.007$), although of lower magnitude because of the presence of hyperglycaemia (one of the 5 criteria of metabolic syndrome according to NCEP- ATP III).

Liver enzyme plasma concentrations were significantly reduced in overweight/obese patients treated with rimonabant 20 mg as compared to placebo, including in patients with type 2 diabetes of RIO-Diabetes [70]. This probably reflects a reduction in liver fat content as shown in various animal models [14], and recently demonstrated in humans in the ADAGIO-Lipids trial [49]. This metabolic improvement is important as steatosis is frequently observed in patients with abdominal obesity, especially when type 2 diabetes is present [71], and because a close relationship between fat liver content and insulin resistance, an independent marker of cardiovascular risk [72], has been reported [73]. The reduction in liver fat content after

rimonabant might be at least partially related to the increase in plasma adiponectin levels and the reduction in plasma leptin concentrations previously reported in RIO-Lipids [44].

Finally, abdominal adiposity is also associated with silent inflammation whose biological most popular marker is high sensitive C-reactive protein (hsCRP) [67]. This inflammatory protein has been shown to be an independent cardiovascular risk marker in various populations [74]. Several RCTs have demonstrated a significant greater reduction in CRP levels in the group receiving rimonabant 20 mg as compared to the group receiving placebo : - 25 % in RIO-Lipids [44], - 26 % in RIO-Diabetes [45], - 20 % in STRADIVARIUS [61], - 18 % in ADAGIO-Lipids [49].

To quantify to what extent the improvements in cardiometabolic risk factors are attributable to a direct effect of rimonabant, analyses were performed using pooled data [26] from patients in RIO-Europe [41], RIO-North America [43], RIO-Lipids [44], and also RIO-Diabetes [45]. Changes from baseline in cardiometabolic variables (body weight, lipids, fasting glucose and insulin levels at year 1) were analyzed by using analysis of covariance with weight loss as a covariate. Almost half (between 45% and 57%) of the overall treatment effect in year 1 on HDL-C, triglycerides, fasting insulin and insulin resistance was due to a direct effect not attributable to weight loss [26]. Weight-loss adjusted improvements in all factors were significantly better with rimonabant than placebo ($p < 0.001$ for HDL cholesterol and triglycerides, $p < 0.02$ for fasting insulin and HOMA-IR insulin resistance index). These results were supported by analysis using weight loss category [26]. These findings were confirmed at year 2 in RIO-Europe [42] and RIO-North America [43]. These improvements in cardiometabolic risk factors beyond weight loss are possibly due to a direct pharmacologic effect of rimonabant in peripheral tissues, in agreement with increasing evidence from animal data [2-5]. Thus, because of its pleiotropic effects, rimonabant should not be considered simply as an antiobesity drug [75].

6.2. Atherosclerosis and its complications

Metabolic abnormalities, such insulin resistance, impaired glucose tolerance or type 2 diabetes and dyslipidaemia, are important risk factors of atherosclerosis (besides other factors

such as smoking), and play a crucial role in the occurrence of cardiovascular complications [54, 65,67,68]. Of course life-style changes are the cornerstone in the management of high risk individuals [76]. Although it is important to demonstrate that a new compound has a positive impact on almost all the metabolic abnormalities associated with abdominal obesity (as already shown for rimonabant 20 mg), it is of course even more important to prove that the pharmacological approach is able to reduce atherosclerosis and to diminish the incidence of major cardiovascular events in a high-risk population.

Two studies aimed at assessing atherosclerosis using imaging techniques. The results of the first one (STRADIVARIUS), using the coronary intravascular ultrasound (IVUS) technique, were recently reported [61]. Treatment with the CB1 receptor antagonist rimonabant 20 mg for 18 months reduced body weight and waist circumference and improved lipid profiles, glycaemic measures, and hsCRP levels, but did not significantly reduce atherosclerosis for the primary efficacy parameter, change in percent atheroma volume (+0.25% with rimonabant vs +0.57% with placebo; p=0.13). However, rimonabant treatment did show a statistically significant favourable effect for a secondary IVUS endpoint (total atheroma volume : -1.95 mm³ with rimonabant vs +1.19 mm³ with placebo; p=0.02) and an additional exploratory endpoint (maximum atheroma thickness; p=0.01). Accordingly, this agent, presumably because of its pleiotropic effects on multiple metabolic disorders [74], may favourably influence the progression of atherosclerosis. The conclusion of the STRADIVARIUS trial was that this promise should, however, be explored in further clinical trials [61]. The second study, AUDITOR (“Atherosclerosis Underlying Development Assessed by Intima-Media Thickness in Patients on Rimonabant”), was a 24-month study of the effects of rimonabant on carotid intimal-medial thickness (IMT), another validated marker of atherosclerosis. However, the follow up was recently prolonged so that the AUDITOR study is still ongoing.

Besides these surrogate endpoints, it is of major interest to demonstrate that rimonabant is able to improve the overall cardiovascular prognosis of high risk patients. The ongoing CRESCENDO (“Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes”) RCT will assess whether rimonabant 20 mg, compared to placebo, can reduce the risk of major cardiovascular disease events in 17,000 abdominally obese patients with

clustering risk factors (at least half with type 2 diabetes) followed for 5 years [77]. This landmark trial (results expected in 2011) should provide the ultimate evidence of the efficacy of the CB1 receptor antagonist, rimonabant, as a cardioprotective agent, especially in patients with abdominal obesity.

9. Conclusions

Increasing evidence suggests that CB1 receptor inhibition is a novel therapeutic strategy that targets most of the metabolic disorders associated with abdominal obesity, including type 2 diabetes and atherogenic dyslipidaemia. Clinical results are already available for rimonabant at a daily dosage of 20 mg, but still remain to be published for taranabant. Despite the fact that the initial development of the first available CB1 receptor antagonist rimonabant was designed as an anti-obesity drug (weight reduction as primary endpoint in the RIO programme), available data showed that metabolic improvements, especially the reduction in HbA1c, the triglyceride decrease and the increase in HDL cholesterol levels, were almost twice that expected from the weight loss alone. These results are consistent with the direct peripheral metabolic effects of the drug demonstrated in various animal models and open new perspective for the management of overweight/obese patients whose residual cardiovascular risk remains high despite the use of other drugs such as statin and antiplatelet therapies. The recent results from the STRADIVARIUS trial confirmed the favourable impact of rimonabant on cardiometabolic risk profile and opened new hope in the possibility to reduce atherosclerosis progression with CB1 receptor antagonists. This should be confirmed in the ongoing CRESCENDO RCT with rimonabant 20 mg using hard cardiovascular outcomes. Furthermore, a huge investigation programme is ongoing to further confirm the favourable effects of rimonabant as a glucose-lowering agent, superior to placebo and non-inferior to well accepted glucose-lowering agents. In case of favourable results, a claim for a recognition of rimonabant as an antidiabetic agent may be asked in a near future.

Nowadays, 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 cholesterol and/or high triglycerides).

Rimobanant is not a cosmetic drug and is not indicated for patients with a BMI < 27 kg/m² or for those with a BMI between 27 and 29.9 kg/m² but who have no associated cardiometabolic risk factor(s). It is noteworthy that patients with antecedent of severe depression or receiving antidepressant agents were excluded from the RIO programme and that mood disorders were more frequently (almost twofold increase of the incidence) observed with rimonabant 20 mg than with placebo in all clinical trials. Therefore, rimonabant is contraindicated in patients with uncontrolled serious psychiatric illness such as major depression, or patients receiving antidepressant medication. Monitoring for on-treatment anxiety and depression is mandatory to ensure the safe use of rimonabant or of any novel CB1 receptor antagonist. Further ongoing studies should confirm the long-term efficacy and safety of rimonabant, the first selective CB1 receptor antagonist, and of other compounds of the same pharmacological class. This is the case for taranabant, a CB1 receptor inverse agonist that is currently in late phase III development and should be available in clinical practice in a near future in case of favourable efficacy/safety profile.

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Conflict of interest : AJ Scheen is a consultant for sanofi-aventis, AstraZeneca, GlaxoSmithKline, and has received lecture fees from sanofi-aventis.

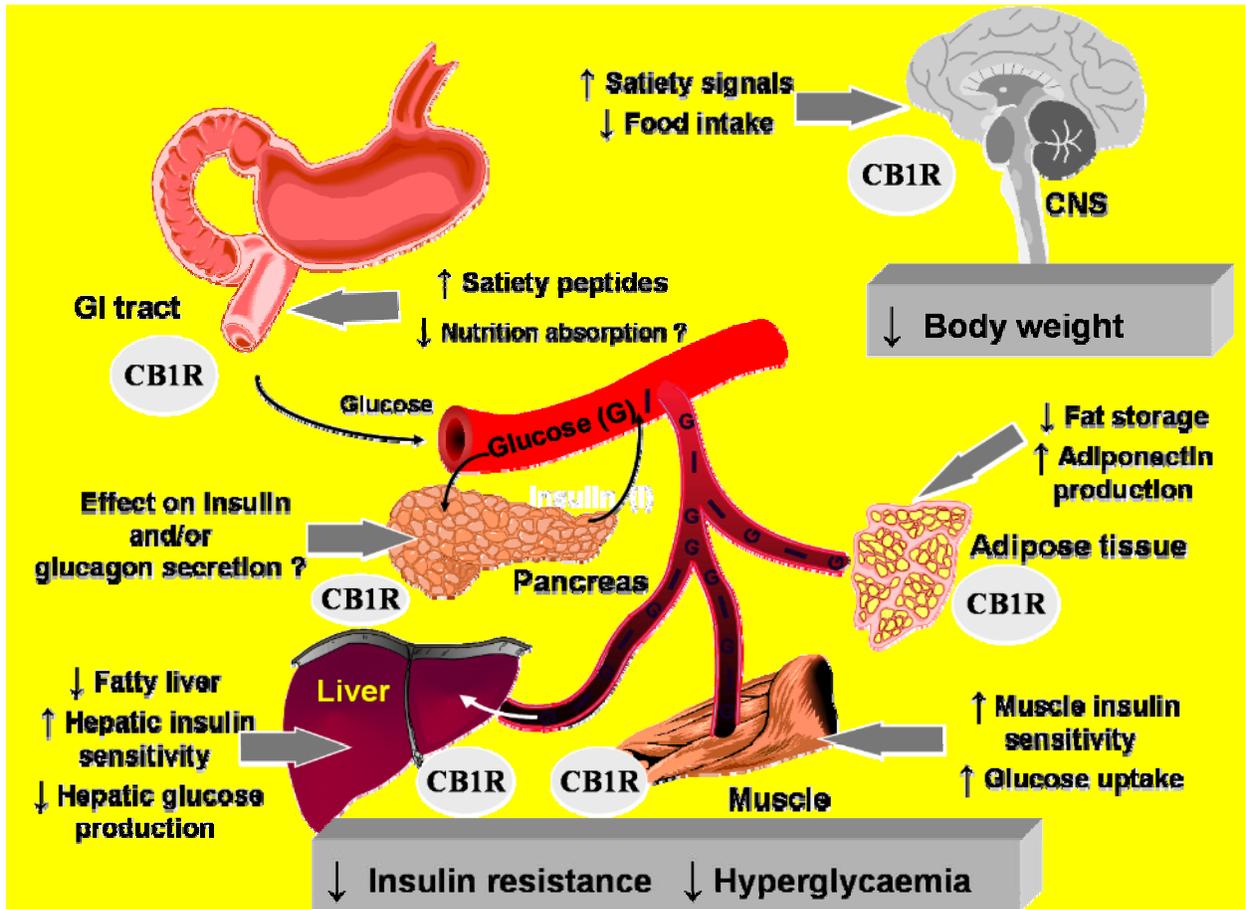


Figure 1 : Dual (central and peripheral) mechanisms of action of rimonabant, a selective cannabinoid type 1 receptor (CB1) antagonist, in the improvement of insulin sensitivity, glucose control (type 2 diabetes) and atherogenic dyslipidaemia in overweight/obese patients. ECS : Endocannabinoid system. CNS : Central nervous system.

Table 1 : Baseline characteristics and effects of rimonabant 20 mg (placebo-subtracted differences) on cardiometabolic risk factors in non-diabetic overweight/obese patients (ITT : intention to treat).

| | RIO-Europe | RIO-NA | RIO-Lipids | STRADIVARIUS | ADAGIO |
|-----------------------|------------|--------|------------|--------------|--------|
| N on rimonabant 20 mg | 599 | 1219 | 346 | 422 | 404 |
| N on placebo | 305 | 607 | 342 | 417 | 305 |

Baseline data

| | | | | | |
|--------------------------|-------|-------|-------|-------|-------|
| Sex ratio (% men) | 20.5 | 19.3 | 39.4 | 65.0 | 46.4 |
| Age (years) | 45.0 | 45.0 | 47.8 | 57.7 | 49.6 |
| Body weight (kg) | 101.0 | 104.4 | 94.1 | 103.5 | 103.7 |
| BMI (kg/m ²) | 36.0 | 37.6 | 33.3 | 35.3 | 36.2 |
| Waist circumference (cm) | 108.4 | 105.8 | 105.0 | 117.4 | 113.6 |
| % Metabolic syndrome | 41.3 | 34.7 | 54.0 | 92.9 | NA |
| Follow-up (months) | 12 | 12 | 12 | 18 | 12 |

Delta vs placebo (ITT)

| | | | | | |
|--------------------------|--------|--------|--------|--------|--------|
| Body weight (kg) | - 4.7 | - 4.7 | - 5.4 | - 4.2 | - 3.6 |
| Waist circumference (cm) | - 4.2 | - 3.6 | - 4.7 | - 3.7 | - 2.8 |
| HDL cholesterol (%) | + 8.9 | + 7.2 | + 8.1 | + 15.5 | + 7.4 |
| Triglycerides (%) | - 15.1 | - 13.2 | - 12.4 | - 14.3 | - 18.0 |
| Fasting glucose (mmol/l) | - 0.11 | - 0.04 | - 0.02 | - 0.59 | NA |
| Fasting insulin (μU/ml) | - 2.8 | - 2.8 | - 2.6 | - 3.6 | NA |
| Systolic BP (mm Hg) | - 1.2 | - 0.2 | - 1.7 | - 2.2 | - 3.3 |
| Diastolic BP (mm Hg) | - 1.0 | + 0.2 | - 1.6 | - 2.0 | - 2.4 |

BP : blood pressure. NA : not available

Table 2 : Baseline characteristics and effects of rimonabant 20 mg (placebo-subtracted differences) on cardiometabolic risk factors in overweight/obese patients with type 2 diabetes (ITT : intention to treat). SU : sulfonylurea.

| | RIO-Diabetes | RIO-Diabetes | SERENADE | ARPEGGIO |
|-------------------------------|--------------|--------------|------------|----------|
| Antidiabetic treatment | Metformin | SU | Diet alone | Insulin |
| N on rimonabant 20 mg | 218 | 121 | 138 | 179 |
| N on placebo | 230 | 118 | 140 | 186 |
| Baseline data | | | | |
| Sex ratio (% men) | 49 | 50 | 53 | 55 |
| Age (years) | 55.3 | 57.3 | 57.8 | 57.4 |
| Body weight (kg) | 97.8 | 95.7 | 96.6 | 97.6 |
| BMI (kg/m ²) | 34.4 | 33.5 | 34.4 | 35.0 |
| Waist (cm) | 110.6 | 108.6 | 108.7 | 112.3 |
| HbA _{1c} (%) | 7.3 | 7.4 | 7.9 | 9.1 |
| Follow-up (months) | 12 | 12 | 6 | 11 |
| Delta vs placebo (ITT) | | | | |
| Body weight (kg) | - 4.4 | - 3.1 | - 3.9 | - 2.6 |
| Waist (cm) | - 3.5 | - 2.9 | - 4.0 | - 3.0 |
| HbA _{1c} (%) | - 0.7 | -0.6 | - 0.51 | - 0.65 |
| Glucose (mmol/l) | - 1.0 | - 1.0 | - 1.0 | - 0.9 |
| HDL cholesterol (%) | + 8.6 | + 6.3 | + 7.3 | + 10.4 |
| Triglycerides (%) | - 14.9 | - 19.4 | - 17.3 | - 11.6 |
| Systolic BP (mm Hg) | - 1.9 | - 2.9 | - 1.6 | NA |
| Diastolic BP (mm Hg) | - 1.2 | - 1.2 | - 0.6 | NA |

Practice points

- Rimonabant, the first commercialized selective CB1 receptor antagonist, improves various metabolic disorders associated with abdominal obesity, especially insulin resistance, glucose tolerance or glucose control, and lipid abnormalities (low HDL cholesterol, high triglycerides).
- A key target population for the use of CB1 receptor antagonists is represented by patients with type 2 diabetes because they cumulate numerous metabolic disorders, they are confronted to a high risk of cardiovascular complications and they have already been successfully treated with rimonabant in large randomized clinical trials.
- There is hope that the improvement in metabolic disorders consistently reported with rimonabant will translate in a significant reduction in major cardiovascular events; however, ongoing trials should still support this statement.
- Rimonabant, because of its antagonist action on central CB1 receptors (and thus taranabant as well), is associated with a higher risk of anxiety and depressive disorders, especially in patients with antecedents of such psychological disturbances.
- Therefore, rimonabant should only be prescribed in overweight/obese patients who have an expected greater cardiovascular risk without rimonabant than the potential psychological risk with rimonabant

Research agenda

- Better assess the role of CB1 antagonists on insulin sensitivity using gold standard methods such as the hyperinsulinaemic glucose clamp.

- Better evaluate the metabolic improvement due to direct effects beyond weight reduction, avoiding the criticism of evidence in humans only supported by statistical analysis.
- Better identify individuals who may be good responders in terms of weight reduction and metabolic improvement, for instance by screening patients with the most important EC system overactivity
- Confirm the long-term efficacy (metabolic improvement) and safety (low incidence of psychological disorders) of rimonabant.
- Demonstrate the favourable effect of rimonabant on cardiovascular hard outcomes as should do the ongoing CRESCENDO trial