Manage Abdominal Obesity, Manage Cardiometabolic Risk

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Introduction

For decades ‘classical’ risk factors such as elevated LDL-cholesterol, hypertension and elevated blood glucose have played important roles in the pathogenesis of cardiovascular disease. Though various treatments have been used to reduce individual risk factors, cardiovascular disease remains the leading cause of death worldwide. The MRC/BHF Heart Protection Study showed a majority of cardiovascular risk remains unaffected after effective statin treatment.1 Almost 20% of patients in the statin group had a major cardiovascular event during the 5-year follow-up period.1 Therefore, in spite of therapeutic advances, cardiovascular disease has more impact on mortality rates than other major sources of mortality, such as cancer, respiratory disease, accidents or diabetes.

Intra-abdominal Adiposity and Cardiometabolic Risk

The cluster of risk factors, including hypertension, high LDL-cholesterol, low HDL-cholesterol, smoking, and intra-abdominal adiposity (IAA) are known as the cardiometabolic risk and are the underlying cause of type 2 diabetes and cardiovascular disease (Figure 1a).2-3 In particular, IAA, as measured by waist circumference, is associated with insulin resistance, hyperglycaemia, dyslipidaemia, hypertension, and prothrombotic/proinflammatory states (Figure 1b).4-6 Excess IAA typically is accompanied by elevated levels of C-reactive protein (CRP) and free fatty acids (FFAs), as well as decreased levels of adiponectin. Elevated levels of CRP are considered to be predictive of cardiovascular disease and insulin resistance.4-5 It has been suggested that elevated FFAs and intracellular lipids inhibit the insulin signalling mechanism, leading to decreased glucose transport to muscle. FFAs also play a mediating role between insulin resistance and β-cell dysfunction, indicating that a reduction in FFA level could be a desirable therapeutic target. Adiponectin is an adipose tissue-specific circulating protein which is involved in the regulation of lipid and glucose metabolism.4-6 Adiponectin has been shown to be reduced in adults with obesity and type 2 diabetes.4-6 In non-diabetics, hypertriglyceridaemia and low HDL-cholesterol have been shown to be associated with low plasma adiponectin concentrations.4-6 All of these components help to explain why excess abdominal adiposity is considered to be a great threat to cardiovascular and metabolic health.

Given this association of metabolic and cardiovascular diseases with IAA, it is logical to presume that improvement in abdominal obesity would diminish risk factors and alleviate complicating disease. Several landmark trials have shown that treatments targeting individual risk factors such as hyperlipidaemia significantly reduce the risk of cardiovascular events.7 Yet cardiovascular disease remains the leading cause of death worldwide. A more comprehensive pharmacotherapy focusing on improving the metabolic risk profile of abdominally obese patients might therefore be required.
The Endocannabinoid System
The newly discovered endocannabinoid system (ECS) contributes to the physiological regulation of energy balance, food intake, and lipid and glucose metabolism through both central and peripheral effects.\(^8\)\(^-\)\(^10\) This system consists of endogenous ligands and two types of G-protein coupled cannabinoid receptors: CB1 and CB2. CB1 receptors are located in several brain areas\(^8\),\(^10\)-\(^13\) and in a variety of peripheral tissues including adipose tissue\(^8\),\(^10\)-\(^13\), the gastrointestinal tract\(^14\), skeletal muscle\(^15\) and liver\(^16\); whereas CB2 receptors can be found in the immune system.\(^17\) Overactivation of the ECS is associated with multiple cardiometabolic risk factors, such as intra-abdominal adiposity, dyslipidaemia, and insulin resistance (Figure 2).\(^12\),\(^15\)-\(^18\),\(^19\)

Three lines of pre-clinical evidence support the modulation of the ECS for the treatment of obesity. Firstly, feeding lowered, and fasting raised, hypothalamic, but not cerebellar, levels of endocannabinoids.\(^20\) Secondly, CB1-receptor deletion or pharmacological blockade blunted re-feeding activity in fasted animals (with no added effect of CB1 blockade in CB1 knock-out mice).\(^10\) Thirdly, local injection of endocannabinoids into the hypothalamus stimulated feeding activity in satiated animals, and this was blocked by CB1-receptor antagonist.\(^21\) These observations implicate the ECS as a homeostatic feedback system regulating acute feeding activity, i.e. increased ECS activity stimulates feeding behaviour and feeding behaviour inhibits ECS activity. The ECS might therefore provide a possible treatment target for high-risk overweight or obese patients.

Rimonabant - The First Selective CB1 Blocker
Rimonabant is the first selective CB1 receptor antagonist and was first described in 1994 by Rinaldi-carmona et al.\(^22\) The drug displays only a very low affinity for CB2 receptors.\(^22\) It is rapidly absorbed. Plasma concentrations of the drug reach a maximum approximately 1-2 hours after oral administration.\(^23\) Age, gender, body weight/BMI have no effect on exposure.\(^23\)

Rimonabant is also highly bound to proteins (>99%), and is extensively metabolised by CYP3A and amidohydrolase(s) (predominantly hepatic) pathways.\(^23\) It is mainly eliminated via metabolic/biliary pathways.\(^23\) The terminal half-life of rimonabant is about 9 days in non-obese subjects and 16 days in obese subjects.\(^23\)

The RIO Programme
The Rimonabant in Obesity (RIO) was a phase 3 programme of 4 randomised, double blind, placebo controlled clinical trials (Figure 3).\(^13\),\(^24\)-\(^25\),\(^27\) Results from all 4 studies consistently showed that rimonabant improved weight, waist circumference, HbA1c, HDL-cholesterol and triglycerides (p<0.001) in over 6,600 overweight/obese patients.\(^13\),\(^24\)-\(^25\)

Weight loss
After 1 year of rimonabant 20 mg treatment, there was a significant weight reduction of 8.6 kg (vs 3.6 kg in placebo).\(^13\) This was accompanied by a 8.5 cm reduction in waist circumference (vs 4.5 cm in placebo).\(^13\) In addition, a weight loss of 7.2 kg was maintained at 2 years (Figure 4).\(^26\) As maintaining weight loss for a long period of time is a difficult task, these results are encouraging for patients and is of great clinical significance.

Glycaemic control
In abdominally obese patients with type 2 diabetes, rimonabant 20 mg treatment for 1 year led to a 0.7% decrease in HbA1c.\(^27\) In addition, 42.9% patients, achieved the target HbA1c of <6.5% as recommended by
the International Diabetes Federation (IDF) (Figure 5). The 0.7% reduction in HbA1c levels is clinically relevant, since every 1% reduction in HbA1c is associated with a 21% risk reduction in any endpoint related to diabetes.

**SERENADE**

Similar to data of the RIO programmes, findings from the Study Evaluating Rimonabant Efficacy in Drug-Naive Diabetic Patients (SERENADE) showed that rimonabant was effective in the treatment of type 2 diabetes. SERENADE was the first trial of rimonabant in diabetics with HbA1c as a primary endpoint. It was a multicentre, randomised, placebo controlled study evaluating the effects of rimonabant 20 mg once daily on blood glucose control in treating naive type 2 diabetics not adequately controlled by diet alone.

At baseline, both the placebo and rimonabant groups had a HbA1c levels of 7.9%. By the end of the 6-month treatment, patients treated with rimonabant showed a significant 0.8% lowering of HbA1c from baseline, compared to 0.3% in placebo (p=0.002). In addition, those with levels of HbA1c of 8.5% or greater at baseline demonstrated a dramatic decline of 1.9% in HbA1c with rimonabant, compared to 0.7% with placebo (p<0.0009). Along with these improvements, rimonabant improved a range of other cardiometabolic risk factors as well, with the exception of blood pressure (Table I).

Approximately 57% of the improvements in HbA1c were independent of the weight loss achieved, suggesting a direct pharmacologic effect of rimonabant on blood sugar and further support the use of rimonabant as an add-on therapy in abdominally obese patients with type 2 diabetes.

**Lipid metabolism**

In abdominally obese patients with dyslipidaemia, rimonabant 20 mg treatment for 1 year significantly increased HDL-cholesterol by 23.4% and decreased triglycerides by 15.8%, but has no significant effect on LDL (Figure 6).

In addition to lipids and glycaemic control, rimonabant also increased adiponectin levels, an important adipocytokine involved in the regulation of insulin sensitivity and lipid metabolism, especially HDL-cholesterol.

**C-reactive protein**

Rimonabant 20 mg treatment also had a positive impact on C-reactive protein (CRP), an inflammatory biomarker considered to be a moderate predictor of cardiovascular disease. Compared to placebo, rimonabant 20 mg treatment for 1 year significantly reduced CRP level by 29%. This adds to all the above data that rimonabant is effective in lowering cardiometabolic risk.

**Weight-independent effect**

Furthermore, rimonabant improved multiple cardiometabolic parameters to a greater degree than could be attributed to body weight loss. After adjustment to body weight loss, regression analyses of the RIO data suggest that 50% of the overall treatment difference was accounted for by the direct CB1 inhibition of peripheral tissues by rimonabant (Figure 7). In other words, the antagonist property of rimonabant directly increased HDL-cholesterol and adiponectin levels, reduced triglycerides and improved HbA1c (diabetic patients) as well as fasting insulin (non-diabetic patients).
Clinical Safety
Safety assessment based on an extensive exposure of > 13,000 patients showed that rimonabant was safe and well-tolerated for up to 2 years.24 Most frequent reported adverse events were gastrointestinal, nervous system and psychiatric in nature (Figure 8).24 Adverse events usually occurred during the first months and were generally of mild to moderate intensity.

Though the use of rimonabant was associated with an increase in the incidence of depression-related events and anxiety, the overall incidence remained relatively low. Most adverse events were mild to moderate intensity and non-serious, and there was no evidence of increased suicidality. Long-term exposure did not identify new or increased risks. No adverse changes in laboratory variables, electrocardiogram variables or vital signs.

Right Patient Profile
Rimonabant is indicated as an adjunct to diet and exercise for the treatment of obese patients (BMI > 30 kg/m²), or overweight (BMI > 27 kg/m²) patients with associated risk factors, such as type 2 diabetes or dyslipidaemia.

The drug is best used in patients who are willing to embrace long-term treatment and concomitant lifestyle changes with BMI > 27 kg/m², abdominal obesity and type 2 diabetes or dyslipidaemia (low HDL-cholesterol and/or high triglycerides).

Rimonabant is contraindicated/not recommended in:
- Pregnant or breast-feeding women
- Children below age 18
- Patients with uncontrolled serious psychiatric illness such as major depression
- Patients receiving antidepressant medication, or have past history of depressive disorder.
- Patients with severe renal/hepatic impairment

Rimonabant should be used with caution in:
- Patients receiving potent CYP3A4 inhibitors
- Patients treated for epilepsy

Summary
In summary, obesity profoundly and severely increases our risk of developing cardiovascular disease and type 2 diabetes. Pre-clinical data in animal models showed that overactivation of the ECS is associated with abdominal obesity and provides the foundation for the use of CB1 antagonist to target obesity and reduce associated complications. The RIO programmes, which evaluated over 6,600 obese/overweight patients showed that the selective inhibition of the CB1 receptor by rimonabant significantly reduced weight and waist circumference as well as improved lipid and glucose metabolism in a weight-independent manner. Data from SERANADE further support the use of rimonabant as an add-on therapy in abdominally obese patients with type 2 diabetes. In addition, rimonabant was well tolerated and had a favourable safety profile for up to 2 years. All these data suggest that rimonabant is a promising agent for long-term management of obese or overweight patients with elevated cardiometabolic risk.

References
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