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Rimonabant

A Viewpoint by Uberto Pagotto

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Rimonabant is the first of an increasing number of emerging drugs that act as selective cannabinoid type 1 (CB-1) receptor blockers. The anecdotes regarding the orexigenic properties of *Cannabis sativa* have been substantiated by a number of studies that make it possible to include the endocannabinoids in the large family of orexigenic signals. The synthesis of rimonabant in 1994 and the following large spectrum of experiments conducted with this drug, first in animals and later in humans, provided an enormous contribution to the understanding of the multiple mechanisms of action, not solely limited to the CNS, of the endocannabinoids in the regulation of energy balance. The extensive clinical use of rimonabant as a novel approach to tackling obesity and related disorders may shed further light on the mechanisms of action of endocannabinoids in relation to the development and progression of obesity. Moreover, the presumable widespread use of this drug will, at the same time, allow scientists and physicians to acknowledge this fascinating and so far neglected system.

The time has also come for intensive research on the pharmacotherapy of obesity, in particular the visceral phenotype and its associated metabolic alterations. Rimonabant will presumably provide new strength and emphasis in this field, contributing to a better definition of the strategies for managing the development and progression of this disease. Obesity, and in particular the abdominal type, has been neglected for too long or, even worse, has not been recognised as one of the pathogenetic mechanisms leading to cardiovascular events. The entry of this class of drugs into the market may allow us to begin considering the possibility of individually targeting therapeutic strategies according to phenotype characteristics and to the pathophysiological mechanisms that give rise to the disease. In fact, the clinical data provided by the RIO phase III programme showed that the majority of patients responded to therapy, but a minor proportion seemed to be resistant to this pharmacological treatment. Therefore, it seems conceivable that future studies will be aimed at identifying the phenotypic characteristics of the responder population to rimonabant treatment. However, until more robust data are provided, it is not possible to recommend CB-1 receptor blockers for a particular fixed phenotype of patients. Despite this, from the first human studies we can speculate that CB-1 receptor blockers may be useful for the selective treatment of visceral obesity, when increased amounts of visceral fat are associated with a single altered metabolic parameter, such as low high-density lipoprotein-cholesterol and/or mildly high triglycerides and/or high fasting glucose level. In fact, according to the European Medicines Agency (EMEA), the drug should be recommended for obese or overweight patients with associated risk factors such as type 2 diabetes and dyslipidaemia. However, it must emphasised that the EMEA also stated that rimonabant therapy should always be associated with lifestyle intervention programmes, clearly indicating that a change in lifestyle still remains the milestone in the treatment of obesity.

One matter of concern is related to the use of CB-1 receptor blockers in patients with a previous history of anxiety or depression. Monitoring for on-treatment anxiety and depression will be necessary to ensure the safe use of this important new class of drugs.

Finally, the data provided by the RIO phase III programme in humans have confirmed that part of the metabolic effect, such as the improvement in lipid and glycaemic profiles, may not be solely explained by the bodyweight reduction due to the anorectic effect induced by rimonabant, but may also be caused by targeting the organs involved in the metabolic processes. This evidence was statistically deduced by the analysis of covariance. It is conceivable that, in the future, more stringent evidence will be provided to support this conclusion in order to clarify the contribution of each individual organ in reducing bodyweight and in improving the metabolic profile. ▲