

RIMONABANT: A NOVEL BUT CONTROVERSIAL AGENT

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Abstract: The treatment strategies for obesity and overweight include increased physical activity, low caloric diet and low fat diet, increased intake of dietary fibers, pharmacological and surgical treatment. Pharmacological management comes very late in the management of obesity. Most of the times this mode is used as an adjunct to diet and exercise. Currently three drugs are being used in the management of obesity: Sibutramine, Orlistat and Rimonabant. Intake of cannabis has been seen to be associated with an increase in appetite. Rimonabant is the first of the new class of agents that act by selectively blocking cannabinoid -1 receptors with resultant central and peripheral metabolic effects. It has a higher affinity for central receptors as compared to peripheral receptors. The drug has a long duration of action and good oral bioavailability. It reduces food intake and increases energy expenditure. The most frequent side effects are nausea, dizziness and upper respiratory infections. The drug has a favorable effect on lipid profile by increasing HDL-C and decreasing LDL-C. In addition to weight loss, Rimonabant has seen to improve HbA1c levels and therefore may be helpful in diabetes. It also prevents weight gain in persons who are quitting smoking and some but not all studies show an increased rate of smoking cessation. Future research and results of ongoing trials are required to establish its long-term therapeutic implications and safety profile.

INTRODUCTION

The treatment strategies available for obesity and overweight include increased physical activity, low caloric and low fat diet, increased intake of dietary fibers, and other life style modification, pharmacological as well as surgical treatment.

There is no doubt that weight control and weight reduction can reduce the risk of developing diabetes in subjects with impaired glucose tolerance, as shown both by lifestyle interventions^{1,2,3} and by use of drugs such as orlistat^{4,5}, acarbose⁶, and rosiglitazone⁷. However, the feasibility and benefits by weight reduction in established type 2 diabetes is less well documented and also sometimes hard to achieve if most antidiabetic drugs act by increasing weight, with metformin being the only exception.

The pharmacological intervention comes very late in the management of obesity. It is used in those patients where lifestyle modification and dietary modification have failed to achieve desired reduction in weight. Most of the time this mode of therapy is adjunctive to dietary and regular exercise regimens. Currently three drugs are being used in the management of obesity; these are Sibutramine, Orlistat and Rimonabant

THE ENDOCANNABINOID SYSTEM

Traditionally in India, there is usage of cannabis in various forms like 'BHANG', 'GANJA' on occasions like 'Holi' festival. It has been observed that after having cannabis there is marked increase in the appetite and thirst along with euphoria and altered behavior. Moreover in ancient India there are references to saints (SADHU) to using marijuana in various forms.

Cannabis sativa is a shrub that abundantly grows in India, being used as source of marijuana. The use of cannabis or hashish as a psychoactive substance reached Europe and the Americas through the Arab world in the 19th century. During the same period, cannabis extracts had gained widespread use for medicinal purposes until 1937, when concern about the dangers of abuse led to the banning of marijuana for further medicinal use in the United States. It has also been noted that cannabis abuse was associated with weight gain.

The active component of marijuana is tetrahydrocannabinol. The endocannabinoid system have several locally produced agonists which act through these receptors, these are anandamide, monoacyl glycerol, 2-arachidonylglycerol and other fatty acid ethanolamides. All these compounds are produced post-synaptically and act on pre-synaptic regions by realizing the neurotransmitters.

Rimonabant is the first in a new class of agents that act by selectively blocking the cannabinoid-1 receptors with resultant central and metabolic peripheral effects, thereby decreasing food intake. Evidence currently exists for two types of cannabinoid receptors: CB1 and CB2. CB1 receptors are present both in the CNS as well as in certain peripheral tissues. The areas in which CB1 receptors are most dense are thought to deal with cognition, motor function and movement. Rimonabant is reported to possess a 1000-fold higher affinity for the CB1 receptor than CB2 receptor. It shows high affinity for the centrally located cannabinoid receptor, while displaying low affinity for the peripherally located receptor. Additionally, it has little or no affinity for non-cannabinoid receptors.

CHEMICAL STRUCTURE

Rimonabant (SR141716) is a neurokinin-3 antagonist and selective cannabinoid (CB1) receptor antagonist. The chemical name is N-piperino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide⁸.

Pharmacokinetics: Rimonabant has demonstrated a long duration of action (8 hours) and good oral bioavailability⁹.

Functional in vitro and in vivo studies have shown that Rimonabant is able to antagonize the pharmacologic effects induced by cannabinoid receptor agonists¹⁰. It powerfully reduces food intake and increases energy expenditure. It modulates the rewarding properties of food by inhibiting the action of endogenous cannabinoids at specific mesolimbic areas. It alters the variety of signals of peripheral origin (leptin, ghrelin and adiponectin) which modulate the neurochemical activation of hypothalamic neurons and the state of relative energy balance. Rimonabant also inhibits the enzymes involved in lipogenesis¹¹. Many rodent model studies have demonstrated a memory enhancing effect due to Rimonabant use¹².

ADVERSE EFFECTS

The results of early human trials with rimonabant treatment showed

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an excellent tolerance among patients, except for some mild gastrointestinal adverse effects at the highest dose administered. Some adverse effects on mental function have been noticed in some patients, and that is why this drug should not be prescribed to patients with a medical history of depression or pronounced mental symptoms. Safety data from the preliminary results of the RIO-Lipids, RIO-Europe, RIO-North America and STRATUS-US trials revealed that Rimonabant is well tolerated among patients^{13,14,15}. The most frequently reported adverse effects are nausea, dizziness and upper respiratory infections. Diarrhea was seen most commonly in the RIO-Europe trial (2.3%, 5.8% and 7% for placebo, Rimonabant 5 mg/day and 20 mg/day, respectively).

ADVANTAGES

Rimonabant is reported to increase HDL-C and decrease atherogenic LDL-C levels. The unique property of this drug may, in turn, improve cardiovascular risk factors and metabolic syndrome.

In addition to weight loss, rimonabant is reported to produce improvement in HbA1C levels and may be helpful in diabetes.

It also prevents weight gain in persons who are quitting smoking.

Evidence: Clinical studies in obese subjects have documented weight loss, improved glucose metabolism, and lipid control, as well as reduced blood pressure in patients with type 2 diabetes^{16, 17, 18}. Other effects seen in some but not all studies include increased rates of smoking cessation. It is important that Rimonabant is currently being evaluated for effects on cardiovascular morbidity and mortality end points versus placebo in a randomized controlled study, the Comprehensive Rimonabant Evaluation Study of Cardiovascular End Points and Outcomes (CRESCENDO) study, with expected results in 2011¹⁹. This trial is recruiting patients with inclusion criteria: waist circumference >102 cm (40 inches) in males, >88 cm (35 inches) in females, with one coronary heart disease equivalent or two major risk factors for CVD.

CONCLUSION

Rimonabant, the selective blocker of CB1 receptors, may normalize the activity of the endocannabinoid system, resulting in weight loss, reduced waist circumference, improvement in lipid and glucose metabolism in obese people and may prevent weight gain associated with smoking cessation along with medical nutritional therapy and increased physical activity. The positive effects may, in turn, improve cardiovascular and metabolic risk factors. Future research and the

results of ongoing clinical trials of this exciting drug are required to establish its long-term therapeutic implications and safety profile.

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NOBLE PRIZE IN MEDICINE

Three European scientists who discovered virus that causes cervical cancer and AIDS share this year's Noble prize in Medicine. A German virologist, **Harald zur Hausen**, will receive half the award for discovery of HPV, the human papilloma virus, according to the announcement made on Monday by the Karolinska Institute in Stockholm. The discovery led to the development of a vaccine against cervical cancer, the second most common cancer in women. The institute said the other half of the award will be shared equally by two French virologists, **Francoise Barre-Sinoussi** and **Luc Montagnier**, for their discovery of virus of AIDS. Since its discovery in 1981, AIDS has rivaled the worst epidemics in the history.

An estimated 25 million more are living with HIV. Dr. Zur Hausen of the University of Heidelberg was cited for discovering the first HPV, Type 16, in 1983 from biopsies of woman who had cervical cancer. A year later, Dr. Zur Hausen cloned HPV 16 and another type, 18. The two HPV types are consistently found in about 70% of cervical cancer biopsies throughout the world, the institute said. Of the more than 100 human papilloma viruses now known, about 40 infect the genital tract, and 15 of them put women at the high risk for cervical cancer. Papilloma viruses account for more than 5% of all cancers worldwide. Discovery of HIV led to Blood tests to detect the infection and the infection and to anti-retroviral drugs that are effective in prolonging the lives of the patients. The discovery has also led to an understanding of the natural history of HIV infection, which ultimately lead to AIDS unless treated. "Never before has the science and medicine been so quick to discover, identify the origin and provide treatment for a viral infections," the Karolinska Institute said.