Review Article

Rimonabant: Boom to ban

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Abstract

Rapidly rising prevalence of obesity and health care cost of its complications necessities need for highly efficacious and safe antiobesity drugs. As most old antiobesity drugs had moderate efficacy, severe toxicity and some of them very costly. Rimonabant, CB1 receptor antagonist was introduced with high expectations. Rimonabant has multiple beneficial effects, apart from significant weight loss it increases HDL and reduces triglycerides, Hb A_{1C} level, prevalence of metabolic syndrome. This wide spectrum of effects helps in comprehensive management of obesity and associated complications. Cost of rimonabant (generic Rs.5-8 per tablet) is also much lesser than the only other commonly used antiobesity drug orlistat around Rs. 40 per tablet. During trials rimonabant apart from nausea had neuropsychiatric side effects. EMEA approved rimonabant in June 2006 with concern over its psychiatric side effects. In 2007 EMEA contraindicated rimonabant in patients of depression or taking antidepressants. Further analysis in 2008 concluded that the incidence of psychiatric side effects was higher in clinical practice compared to controlled trials also few cases of suicide became a major safety concern, finally leading to suspension of its sale by EMEA in Oct 2008. USFDA never approved rimonabant over safety concerns, while India banned it shortly thereafter as precautionary measure. Present paper deals with the various events during the rapid rise and fall of rimonabant which was widely considered as blockbuster diet pill but was suspended over serious neuropsychiatric side effects.

Key words: Rimonabant, obesity banned, withdrawn

INTRODUCTION

The problem of being obese (body mass index[BMI] >30) and overweight (BMI >27) has already assumed an epidemic proportion worldwide. The International Obesity Task Force estimates that more than 300 million individuals worldwide are obese and an additional 800 million are overweight. The rapidly increasing prevalence of obesity is associated with an increased incidence of comorbidities like hypertension, dyslipidemia, and type 2 diabetes mellitus thus substantially rising the health care cost. Efforts to reverse this trend by dietary or behavioral counselling to maintain optimum weight, although possible in some individuals, has limited success and current methods of lifestyle modification (alone) as a treatment of obesity are widely regarded as inadequate. Thus, pharmacotherapy becomes an important adjunctive to lifestyle modification.[1]

Worldwide, the market for obesity drugs is rapidly expanding not only for cosmetic purposes but also because of the increased awareness about obesity as a medical disorder with severe complications. The Indian obesity market is estimated to be US $50 million, which is growing annually by almost 50%.

Despite the tremendous progress in understanding the intricacies of energy balance regulation in the body and the assured big returns from the market, antiobesity drug development and their presence in the market in the long run have not been very impressive.

Need was always felt for an ideal antiobesity drug that could induce clinically significant weight reduction and maintain

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it, have a favorable and significant effect on common comorbidities associated with obesity, like hypertension, diabetes, and dyslipidemia,. have a high tolerability with acceptable short-term side-effects, and ensure affordability and availability.

But not even one drug has been even closer to being ideal. Most of the older drugs either have severe toxicity or are withdrawn; till recently, in the market, only two drugs were available. Sibutramine is a centrally acting monoamine reuptake inhibitor that mainly acts to increase satiety.[2] It has been associated with a small increase in blood pressure and pulse rate, leading to concerns about potential cardiovascular toxic effects, which may not be suitable for patients with uncontrollable hypertension, pre-existing cardiovascular disorder, or tachycardia, as a significant proportion of obese patients may have one of these disorders, not all the obese patients can be given sibutramine. In 2002, the sales of sibutramine in Italy were suspended over reports of cardiovascular events and two deaths,[3] but the European Medical Agency (EMEA) independent review led to its reinstatement.[4] Recently, in Jan 2010, the EMEA has recommended suspension of sibutramine sales,[5] followed by a ban in India in Nov 2010.

Orlistat is a gastric and pancreatic lipase inhibitor that reduces dietary fat absorption by around 30%.[6] Orlistat, although devoid of cardiovascular and central nervous system (CNS) side-effects, has socially embarrassing gastrointestinal side-effects like oily spotting and fecal urgency.[7] What is equally deterrent is its high cost. Its standard dose of 120 mg t.i.d. costs about 120/day, which may not be affordable to all socioeconomic strata.

Over such background introduction, any new molecule for obesity would obviously receive much hype and attention by health care professionals, patients and media. That is what happened with rimonabant introduced by Sanofi Aventis, a French pharmaceutical giant. Rimonabant is a selective antagonist of Cannabinoid receptor (CB1), and it is the first member of a novel class of compounds that target the endocannabinoid system that is involved in the regulation of food intake and CNS rewarding system.[8]

THE RISE

The endocannabinoid system includes two major receptors, CB_1 and CB_2, and two major ligands, anandamide and 2 arachidonoyl-glycerol.[9,10] They have been implicated in many biological responses, including counteracting stress stimuli such as food deprivation, pain, and aversive memories. CB1 receptor is extensively expressed in the CNS and in areas concerned with the control of food intake.[11] Endocannabinoids interact with several anorexic and orexigenic pathways within the CNS, including central melanocortin and mesolimbic, increasing motivation to eat and stimulating food intake[11-14] Ability of the recreational marijuana to reliably stimulate appetite generated interest in the use of endogenous cannabinoid agonist and antagonist for weight-related disorders.[15]

Rimonabant is a potent CB1 selective antagonist with a 1000-fold greater affinity than CB2. It is metabolised in the liver and excreted in the bile. It has a larger peripheral volume of distribution and half-life of 6–9 days, which is longer in obese patients (16 days).[16] In Europe, it was indicated for use in conjunction with diet and exercise for patients with a BMI >30 kg/m^2 or with BMI >27 kg/m^2 with associated risk factors, such as type 2 diabetes mellitus or dyslipidemia.

PRE-CLINICAL STUDIES

Rimonabant produces a dose-dependent reduction in food intake in various rodent models,[17, 18] effects that seem to be both central and peripherally mediated. Central effects are mediated through blockade of CB1 receptors. Potential peripheral mechanisms include enhanced thrmogenesis via increased oxygen consumption,[19] augmentation of Adiponectin concentration,[20] promotion of vagally mediated cholecystokinin-induced satiety,[11,21] inhibition of preadipocyte proliferation, and increased adipocyte maturation without lipid accumulation.[22]

Tetrahydrocannabinod (THC) is known to impair short-term memory. It was therefore hypothesised that rimonabant may improve the short-term memory. Indeed, in animal studies, it significantly improved the performance of rats to encode information in short-term memory.[23]

CLINICAL STUDIES

With the knowledge of various involvements of the endocannabinod system in humans, rimonabant was thought to be effective in weight reduction, have a favorable effect on the lipid profile, reduce the blood sugar level, be effective in smoking cessation, and reduce cocaine, opioid, and ethanol addiction. Multiple clinical trials were started in support for each effect.

For weight reduction, four randomized controlled double-blind trials were conducted under the programme RIO (Rimonabant In Obesity),[24-27] comparing rimonabant 20 mg or 5 mg with placebo, and the 20 mg dose was found to be significantly better than placebo. As compared with placebo, rimonabant treatment resulted in a greater

weight reduction of 4.7 kg on an average after a year-long treatment [Table 1]. Individuals receiving rimonabant were five-times more likely to achieve at least 10% weight loss (as a general guideline for quantifying the efficacy of any intervention in weight reduction programme, the NIH has recommended 10% weight loss as the threshold).

In the RIO-NA study, after 1 year of treatment with rimonabant, when the patients were rerandomised to placebo in the second year of the study, they regained weight, whereas those who continued with rimonabant maintained their weight loss.[26]

The rimonabant-treated group showed significant reduction in waist circumference (which is a marker of abdominal obesity, a major independent risk factor for cardiovascular disorders and a primary target for the treatment of metabolic syndrome), with improvement in the triglyceride and high-density lipoprotein (HDL) cholesterol level. Even though there was no significant change in the low-density lipoprotein (LDL) cholesterol level, RIO-LIPID showed that the size of the LDL particles was increased so as to make them less atherogenic.

Across the trials, blood pressure was mostly unchanged or slightly reduced. The prevalence of metabolic syndrome (defined by NCEP ATP III) was reduced significantly as compared with the placebo. In RIO-LIPID, there was a significant rise in the serum adiponectin levels. High adiponectin level is reported to be predictive of a reduced risk of diabetes and cardiovascular events.[25]

In RIO-DIABETES, the rimonabant treatment group had a placebo-subtracted reduction in HbA_{1C} level by 0.7%, of which only 0.3% could be attributed to weight loss and 0.4% was an independent effect of rimonabant. In patients with HbA_{1C} level >7%, in the rimonabant-treated group, 52.7% patients could achieve HbA_{1C} level <7% compared with 26.8% in the placebo group.

SERENADE (Study Evaluating Rimonabant Efficacy in Drug Naive Diabetic patients) and ARPEGGIO (evaluation of rimonabant in type 2 diabetic patients inadequately controlled with insulin monotherapy) concluded that rimonabant improved glycemic control and cardiometabolic risk factors in diabetic patients.[28]

Trials performed to determine the effect on cardiovascular diseases included STRADIVARIUS (Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant - The Intravascular Ultrasound study), which failed to provide any evidence of efficacy in the prevention of adverse cardiovascular outcome.[29] CRESCENDO (Comprehensive Rimonabant Evaluation Study of cardiovascular ENDpoints and Outcomes) had to be terminated the by sponsor after the EMEA halted its marketing authorization.[30]

Cohen *et al.*[31] studied the nicotine-seeking behavior in rats. Rats that were given rimonabant displayed decreased nicotine-conditioned behavior, as demonstrated by decreasing the self-administration of nicotine and dopamine turnover in the nucleus accumbens after nicotine stimulation. Balerio *et al.*[32] reported that pre-treatment with rimonabant in mice decreased the anxiety-reducing effects of nicotine in mice that had been previously exposed to nicotine. This study supports the link between the endocanabanoid system and nicotine's anxiety-like behaviors. For smoking cessation, Sanofi conducted STRATUS (Studies with Rimonabant and Tobacco Use). The company presented STRATUS-US as one of the largest smoking cessation trial ever conducted in the US. The results of STRATUS-US were very encouraging as, with smoking cessation, it also reduced the weight gain associated with cessation. STRATUS-EU and STRATUS-WW results did not show significant difference between the groups (unpublished Anthennelli 2005, niaura 2005); in 2006, the US-FDA notified Sanofi that rimonabant was not approvable for smoking cessation.

All these trials supported the fact that rimonabant, along with a significant reduction of weight, also improves the lipid profile, blood sugar control and reduces the incidence of metabolic syndrome.

Rimonabant is the only antiobesity drug with such a wide spectrum of beneficial effects, which would be of help in the comprehensive management of obesity and related disorders.

In India, the generic version of rimonabant was launched in May 2007 and, since then, 17 companies have been

Table 1: Placebo-subtracted improved outcome with rimonabant therapy[15]

Study	Weight reduction (kg)	Waist circumference reduction (cm)	HDL increase (%)	Triglyceride reduction (%)
RIO-EU	4.8 (3.9–5.7)	4.1 (3.1–5.1)	9 (6–12)	15 (10–21)
RIO-LI	5.4 (4.6–6.2)	4.7 (3.7–5.7)	8 (5–1)	12 (6–19)
RIO-NA	4.7 (4.1–5.4)	3.6 (2.9–4.3)	7 (6–9)	13 (9–18)
RIO-DIA	3.9 (3.2–4.6)	3.3 (2.4–4.1)	8 (6–11)	16 (10–23)

making generic rimonabant. Relatively low cost has also been a big advantage on its part. With such a portfolio, rimonabant was once regarded as the biggest weight loss hope after Fen-Phen: few years ago, it seemed destined to be the newest blockbuster diet drug.

THE FALL

Rimonabant trials saw an average 60% study completion rate, similar to orlistat and sibutramine trials. Rimonabant caused more adverse events than placebo and 1.4-times more serious adverse events. The FDA report about safety of rimonabant reported that 26% of the people given rimonabant 20 mg versus 14% of those given placebo had developed psychiatric symptoms, while 9% patients on rimonabant and 5% on placebo developed depression. The FDA further reports that the overall relative risk of psychiatric adverse effects in the rimonabant-treated group was 1.9, while the odds ratio for suicide was 1.9.[8]

The most common adverse drug reactions (ADRs) noted across the RIO trials are nausea, URTI, dizziness, and diarrhea. Trial discontinuation rates were similar in the rimonabant and in the placebo group, but, in the rimonabant 20 mg group, more patients discontinued because of adverse reactions, the most common being nausea, mood alteration with depressive symptoms, depressive disorders, and anxiety.[24-26]

Because patients with mental illness were excluded from the RIO studies, these estimates of potential psychiatric side-effects of rimonabant were considered conservative.[8]

The EMEA approved rimonabant as Acomplia in June 2006.[33] Psychiatric side-effects were identified as the main safety issue at the time of approval. Doctors were warned that rimonabant is not recommended for patients with uncontrolled serious psychiatric illness such as major depression.

As a part of its continuous monitoring of safety, all available data on safety till July 2007 were analyzed by the EMEA, concluding that the benefit of rimonabant continues to overweigh its risk, except in patients of major depression and patients taking antidepressants, for whom rimonabant was contraindicated.[34]

Further analysis in the mid-2008 by EMEA concluded that the psychiatric side-effects were more common in clinical practice as compared with what was seen at the time of approval. Also, the reporting rate for depressive disorder had markedly increased and, despite the contraindication issued in 2007 for patients taking antidepressants, it was found that 6–20% of the patients taking rimonabant were concomitantly taking antidepressants. This represented a safety concern.[33]

Even though depression as a side-effect occurred mostly in patients with concurrent and past history of depressive disorder, it could also occur in patients who have no obvious risk factors. Also, patients who may be at highest risk of psychiatric reactions cannot be identified reliably, and, therefore, further restrictions on the use of rimonabant would have been unlikely to reduce the risk to an acceptable level.[30]

The EMEA also observed that till the mid-2008, in the finalised clinical studies, the incidence of suicidal ideation was similar in the rimonabant and in the placebo group; however, in ongoing trials (CRESCENDO), few cases of suicide attempts and completed suicide occurred, raising serious safety concerns.[35] Rimonabant has a beneficial effect on HDL-cholesterol, triglycerides, and HbA_{1C} level, which could be an advantage as prevention of cardiovascular diseases should be based on a multifactorial approach. However, the available data from real-life usage of rimonabant indicated that the patients take it only for a short duration, which may not be sufficient enough to prevent cardiovascular diseases.[33]

All these findings led to a conclusion by the EMEA in Oct 2008 that the beneficial effects of rimonabant no more overweighed the risk associated with it and, thus, suspended its sales in all member countries.[33] Approval of drug was officially withdrawn by the EMEA in Jan 2009. The US-FDA never approved rimonabant, citing concerns over its psychiatric side-effects. Even though there are no reports of severe psychiatric side-effects reported from India, rimonabant was banned in India shortly thereafter as a precautionary measure.

DISCUSSION

If a genome-wide association study had been done to establish what sequence variants are linked with suicides, suicide attempts, or significant neuropsychiatric side-effects, endocannabinoid blocker rimonabant could have proven viable by excluding those patients. One such finding in a study is single nucleotide variants in a tyrosine kinase receptor gene (NTRK2) involved in neurotrophic signalling, which were associated with more than four-fold increased risk of suicide.[35] Also, the low absolute risk of neuropsychiatric effects led to the termination of the trials by the regulatory authorities in multiple participating countries, suggesting that the tolerance for risk of new molecular entities is considerably lower now than a decade or two ago.

Further focused research in subtyping of the CB1 receptor would be helpful in differentiating the weight loss effect from the neuropsychiatric effects, and then a rationally designed new congener of the rimonabant molecule might be introduced with only a favorable clinical profile. Similarly, by chemical alterations of the structure of rimonabant, new congeners can be produced and screened for the expected clinical effect.

In India, there have been no reports of any serious neuropsychiatric side-effects, but rimonabant was banned following EMEA. Among the various possible reasons, non-reporting of the ADR stands at the first place. As the drug was launched in Europe almost a year before its launch in India, it may be probable that Indian physicians were well aware of the possible neuropsychiatric side-effects and they screened patients thoroughly before starting them on rimonabant. As the Indian population is very heterogeneous in genetic composition, one more possibility is the less or non-susceptibility of the Indian population to dreaded adverse events of this drug. All these questions could have been answered with large randomised controlled trials in India.

Why it concerns India? In India, obesity is a rising health problem, particularly in urban areas, paradoxically coexisting with under nutrition. Almost 30–65% of the adult urban Indians are either overweight or obese, or have abdominal obesity. It has a direct correlation with the increasing prevalence of comorbidities; hypertension, metabolic syndrome, dyslipidemia, type 2 diabetes mellitus, and cardiovascular diseases.[36] Also, the recently revised reduced cut-off of the BMI for the Indian population drastically increases the percentage of patients falling in the category needing treatment for obesity or overweight. In such a situation, a very effective, low-cost drug like rimonabant would have been a very valuable addition to therapeutic life style changes like healthy dietary habits and exercise.

Now, the focus should be returned to motivating patients to control their caloric intake and increasing their physical activity. Although cumbersome, this approach is causal and safe.

CURRENT STATUS

Further continued research in animals has come up with various unexpected and a wide variety of beneficial effects apart from those already known. To mention a few important effects, rimonabant inhibits Acyl coenzyme A: cholesterol acyltransferase (ACAT), which play key roles in the pathophysiology of atherosclerosis, and ACAT inhibition retards atherosclerosis in animal models, retarding macrophage foam cell formation.[37]

In another study, rimonabant improved the systolic and diastolic heart function and decreased the arterial stiffness in rats 6 weeks after myocardial infarction. Reduced inflammation in the heart may contribute to cardiac protection by rimonabant.[38] Rimonabant had anti-inflammatory effects on endothelial cells and inhibited TNF-α-induced IKKα/β phosphorylation, IκB-α degradation, and IL-6 production in human umbilical vein endothelial cells. This effect was related to CB1 antagonism and protein kinase A PKA activation.[39]

To summarise, rimonabant, once projected as the biggest blockbuster diet pill with many desirable qualities, was banned because of unacceptable side-effects, leaving orlistat as the sole weapon in the armament against obesity, necessitating the need of deeper and broader research against the epidemic of obesity.

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