ADAGIO-Lipids Gives Promises but Faces the Setbacks

Marja-Riitta Taskinen

The rapidly increasing global wave of obesity associated with cardiometabolic risk factors portends a daunting increase of cardiovascular disease. Consequently, the search for effective and safe drugs and new therapeutic avenues to fight obesity stands at the frontline because of a market with enormous opportunities. Rimonabant is a selective CB1 endocannabinoid receptor antagonist that was the first one authorized June 2006 by EMEA and marketed in 18 EU countries. The efficacy and safety of rimonabant had been evaluated in the extensive RIO program including more than 6000 overweight or obese subjects who received double-blind treatment with rimonabant 5 or 20 mg/d or placebo together with diet or lifestyle modification for 1 or 2 years.1–4 The results demonstrated the consistent and clear effects of rimonabant 20 mg/d not only on weight loss and reduced waist circumference but also on several markers of cardiometabolic risk especially on serum triglyceride and HDL cholesterol levels. Recently the efficacy of rimonabant was confirmed in the 2-year study of the RIO-Europe.5 The simultaneous improvement of several cardiometabolic risk factors by rimonabant raised enthusiasm and created expectations that have not been materialized. The promises were soon dimmed by concerns about its psychiatric side effects including depression, sleep disturbances, anxiety, and aggression. The FDA Advisory panel rejected the approval of rimonabant as a drug to treat obesity 2007. Growing concerns led EMEA to restrict the drug July 2007 in patients with depression or taking antidepressants. The final blow came October 2008 when EMEA concluded that the benefits of rimonabant did not outweigh its risk and recommended the suspension of the drug’s marketing authorization across the EU (http://www.emea.europe.eu EMEA/537/53/2008).

In the light of this development, from a promising success to the unexpected disaster, one asks what was going wrong.

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In this issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Despres et al report the results from the ADAGIO-Lipids study, which was a 1-year trial examining the effects of rimonabant 20 mg/d on multiple components of the atherogenic dyslipidemia, other cardiometabolic risk factors (C-reactive protein, adiponectin, and parameters of insulin resistance), as well as an intraabdominal fat and liver fat. The study randomized 803 patients (799 patients exposed to the study treatment) with abdominal obesity based on a waist circumference ≥102 cm (men) and ≥88 cm (women) and with the typical high triglyceride (≥1.69 mmol/L to ≤7.90 mmol/L) and low HDL cholesterol (≤1.04 mmol/L in men and ≤1.29 mmol/L in women) profile but no history of depression. The study was randomized, double-blind, placebo-controlled, parallel group study conducted in 14 different countries.

The coprimary end points were changes in HDL cholesterol and triglycerides over 12 months of the study duration. In rimonabant-treated patients HDL cholesterol increased by 7.4% (P<0.001) and triglycerides fell by 18.0% (P<0.0001) compared with placebo-treated patients. These favorable changes were reflected in positive shifts of both LDL and HDL mean particle sizes. Thus the proportion of small atherogenic LDL particles decreased while the proportion of large LDL particles increased without any change in LDL cholesterol concentration emphasizing the limitation of using only LDL cholesterol as a risk measure in patients with abdominal obesity. The data also confirmed the significant positive effects of rimonabant on lipoprotein markers of cardiovascular risk including apoA-I, apoB, and apoB/apoA-I ratio as well as hs-CRP (change −7%, P<0.01 compared with placebo) and adiponectin (change +18.9%, P<0.0001 compared with placebo). In addition the data showed beneficial effects on parameters of glycemic control and blood pressure.

For the first time a computed tomography (CT) substudy was conducted to examine whether antagonism of CB1 receptor in humans will reduce ectopic fat depots with reduction of liver fat and a preferential loss of visceral fat over subcutaneous fat. This concept was stimulated by metabolic profile of CB1 receptor knockout mice which were resistant to development of hepatic steatosis on a high-fat diet.5 This study also demonstrated the critical role of the ECS system in the activation of thesterol regulatory-element binding protein (SREBP-1c) and its regulated enzymes acetyl-CoA carboxylase-1 (ACCC1) and fatty-acid synthase (FAS) that are keyfactors for the stimulation of hepatic de novo lipogenesis. Recently Gary-Bobo et al showed that rimonabant prevented the development of hepatic steatosis in genetically obese Zucker rats (fa/fa). Additional evidence was provided by reports showing the overactivation of the ECS in subjects with excess visceral fat.5,10 The constellation of excess liver and visceral fat leading to increased production of large VLDL particles that is reflected in unfavorable changes of LDL and HDL species encompasses also hepatic insulin resistance.11 A recent study using mice with hepatocyte-selective deletion of CB1 receptors (LCB1−/− mice) demonstrated that hepatic CB1 receptor is required for development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance.12

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The ADAGIO-Lipids CT substudy demonstrated for the first time in humans that rimonabant indeed reduces liver fat and preferentially visceral fat loss over subcutaneous fat loss. Collectively the ADAGIO-Lipids study provides new knowledge on the metabolic effects of rimonabant and could have helped to position the drug in the clinical practice. Importantly, the ADAGIO-Lipids trial did not give any alarming signals of psychiatric adverse effects observed during the 1 year of treatment. The incidence was similar in the placebo and rimonabant group and fully consistent with that reported in the RIO program.13

The dual favorable effects of rimonabant on both atherogenic dyslipidemia and inflammation are highlighted in a recent study by Dol-Gleides et al.14 Importantly, rimonabant inhibited atherosclerosis in LDL receptor–deficient mice model fed a high-fat Western-type diet. The accompanying article by Pacher15 highlighted that these data strengthen the concept that CB1 antagonism may truly prevent atherosclerosis via multiple mechanisms, although the results of STRADIVARIUS were not unambiguous.16 Collectively, the available data together with ADAGIO-lipids results forecast selective targeting of peripheral CB1 receptors as an attractive rationale to develop CB1 blockers not able to cross the blood–brain barrier and thus to limit the CNS side effects for treatment of high cardiometabolic risk factors and prevention of atherosclerosis in abdominal obese patients.17,18

Unfortunately, the clinical relevance of the ADAGIO-Lipid study was passed when the benefit/risk ratio was evaluated by EMEA leading to the suspension of the drug from the market and also to the termination of the scientifically important and extensive research program by the company (www.sanofi-aventis.com). The main results of ADAGIO-Lipids were available to the company at the time of hearings to emphasize the appropriate use of the drug in the high risk patients with excess ectopic fat instead of the use as an “antiobesity blockbuster.” The question arises whether the safety data accumulated from the CRESCENDO assessing the efficacy of rimonabant on the long-term risk of CVD events were less favorable than from the RIO programs. The circumstances surrounding the decision to terminate the viable and extensive research program are not clear but will hamper the translation of the promises from the recent studies.6,14 Many burning and important questions may remain unresolved for a long time. Regrettfully the conclusion may be that a viable baby was drained with the washing water, but hopefully this is not the end of the line for CB1 receptor antagonists.

**Disclosures**

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**References**

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