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 drugs’s marketing authorization across the EU (http://www.emea.europa.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 al6 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 metabolic profile of CB1 receptor knockout mice which were resistant to development of hepatic steatosis on a high-fat diet.7 This study also demonstrated the critical role of the ECS system in the activation of the sterol regulatory-element binding protein (SREBP-1c) and its regulated enzymes acetyl-CoA carboxylase-1 (ACC1) and fatty-acid synthase (FAS) that are keyfactors for the stimulation of hepatic de novo lipogenesis. Recently Gary-Bobo et al8 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.9,10 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 the RIO program.13

Refrain 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.

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