PREVENTION

Neuropsychiatric adverse effects signal the end of the line for rimonabant

In November 2008, the European Medicines Agency requested that all clinical trials of the selective cannabinoid-1 (CB1) receptor antagonist rimonabant be terminated with immediate effect following reports of serious neuropsychiatric adverse effects. CRESCENDO was one such study. The CRESCENDO investigators have now published the initial findings of this trial in the *Lancet*. Data collected before termination of the study indicate that rimonabant did not reduce the incidence of major cardiovascular events when compared with placebo, but was indeed associated with an increased risk of anxiety, depression, and suicide.

Rimonabant was the first selective CB1 receptor antagonist to be approved and used in clinical practice. Blockade of the endocannabinoid system carried high hopes as a pharmacological strategy for the treatment of obesity, which is a pandemic risk factor for cardiovascular disease. Over the past 5 years, clinical studies of rimonabant have shown beneficial effects in terms of weight loss, reduction in waist circumference, increases in levels of HDL cholesterol, and reductions in triglyceride levels and total atheroma volume. However, none of these studies demonstrated reductions in blood pressure or levels of LDL cholesterol (both major determinants of atherosclerotic progression) and, as early as 2007, an increase in the risk of psychiatric disorders associated with the drug was reported. CRESCENDO was the first randomized, placebo-controlled trial designed with the aim of evaluating the long-term effects of rimonabant on hard clinical end points (a composite of cardiovascular death, myocardial infarction, and stroke).

CRESCENDO was conducted at 974 hospitals across 42 countries; a total of 18,695 participants were enrolled. Patients were eligible for inclusion in the trial if they had a waist circumference >88 cm in women and >102 cm in men, were aged older than 55 years, and had cardiovascular disease or at least two cardiovascular risk factors. Individuals with a medical history of serious psychiatric illness, those who had attempted suicide, and those whose obesity was secondary to an endocrine disorder, were excluded.

Patients were randomly assigned to receive rimonabant 20 mg per day or placebo. Neurological and psychiatric status were assessed at baseline and throughout the study. Patents who developed depressive or anxiety disorders were referred to a psychiatrist.

At termination of the study in November 2008 (mean treatment duration 13.8 months), there were no significant differences in the incidence of the composite end point between the two groups (hazard ratio 0.97, 95% CI 0.84–1.12, $P = 0.68$). The investigators argue, however, that early termination of the trial meant that the study was underpowered to detect a beneficial effect of rimonabant. The incidence of adverse gastrointestinal and psychiatric effects were significantly increased in the rimonabant group ($P < 0.0001$ for both). Of the five patients who committed suicide during the study, four were receiving rimonabant.

Professor Arne Astrup from the University of Copenhagen, Denmark, who first reported the link between rimonabant and depression/anxiety in 2007 and who was not involved in CRESCENDO, believes that "it was absolutely correct of the authorities to stop the trial ... three excessive suicides in healthy obese people is three too many." Professor Astrup goes on to explain that "in the future, we need a much better assessment of [the] risk–benefit ratio of weight-loss drugs before they reach the market."

Alexandra King

Original article Topol, E. J. *et al*. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* **376**, 517–523 (2010)