OBESITY

Taranabant no longer developed as an antiobesity agent

The endocannabinoid system and its ability to regulate metabolism has held promise for the development of therapeutic agents to combat the growing epidemic of obesity.

Two randomized, placebo-controlled clinical trials, published in the *International Journal of Obesity,* assessed the safety and efficacy of the cannabinoid-1 receptor (CB1R) inverse agonist taranabant in patients with obesity (age ≥18 years, BMI 27–43 kg/m^2). Researchers of the low-dose study examined the effects of 0.5 mg, 1.0 mg and 2.0 mg of taranabant given orally once daily over 52 weeks, whereas the high-dose study assessed the effects of 2.0 mg, 4.0 mg and 6.0 mg per day over 104 weeks.

All analyzed doses led to a clinically meaningful, yet relatively modest, weight loss. Nevertheless, when compared with placebo, treatment with taranabant was associated with dose-related increases in the incidence of psychiatric adverse events, such as depression, anxiety, anger, aggression, mood change and irritability. The two highest doses of taranabant were even discontinued over the course of the trial owing to the high incidence of such adverse effects.

"The higher doses studied appeared to be at or near the top of the weight-loss efficacy curve, which could indicate that CB1R inverse agonists, as monotherapy, are not capable of delivering robust (that is, ≥10%) weight loss," says Louis J. Aronne (Weill-Cornell University Medical College, New York), lead investigator of the high-dose study.

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Even at the lowest doses tested, the incidences of adverse effects were increased, albeit not significantly, which according to Aronne could indicate that "the CB1 mechanism lacks a viable therapeutic window."

The risk–benefit profile of these regimented, controlled clinical trials, which included rigorous and frequent monitoring of the patients, would probably have been difficult to implement in clinical practice for the treatment of patients with obesity. As a result, and given its modest effects on weight-loss and the increased incidences of adverse events, Merck have discontinued the clinical development of taranabant as an antiobesity agent.

"While these findings have not been encouraging regarding the potential for the central CB1R as a target for the treatment of obesity, they do not necessarily represent the end of the road for the endocannabinoid system as a target for the pharmaceutical development in the area of obesity and metabolic disease," comments Aronne. "It has been hypothesized that neutral CB1R antagonists (as opposed to inverse agonists) might not be burdened by psychiatric side effects". Also, "preclinical studies have suggested that subtherapeutic doses of CB1R inverse agonists in combination with other agents might prove a viable therapeutic strategy". These possibilities, however, remain to be examined.

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Original articles Aronne, L. J. *et al.* A clinical trial assessing the safety and efficacy of taranabant, a CB1R inverse agonist, in obese and overweight patients: a high-dose study. *Int. J. Obes. (Lond.)* doi:10.1038/ijo.2010.21 | Proietto, J. *et al.* A clinical trial assessing the safety and efficacy of the CB1R inverse agonist taranabant in obese and overweight patients: low-dose study. *Int. J. Obes. (Lond.)* doi:10.1038/ijo.2010.38