For Obesity Drugs, Safety Trumps Efficacy

Safety profiles to date bode well for two drugs in the pipeline: lorcaserin and liraglutide.

BY MITCHEL L. ZOLER

FROM THE INTERNATIONAL CONGRESS ON OBESITY

STOCKHOLM — With a scant number of obesity drugs on the worldwide market, new additions are eagerly sought but face tough safety scrutiny.

In July, a Food and Drug Administration advisory panel voted against approval of a new obesity formulation, Qnexa, which combines the weight-loss warhorse phentermine plus the epilepsy drug topiramate, because of safety concerns despite evidence of good efficacy. The same week the FDA panel made this recommendation, new findings on sibutramine, an effective agent many physicians rely on for treating obesity, came to light in a report on a 10,000-patient cardiovascular safety trial presented at the International Congress on Obesity. The findings showed sibutramine clearly boosted the risk for nonfatal myocardial infarction and stroke in patients with high cardiovascular risk.

That report helped heighten the attention paid to the safety of two other obesity formulations with trial results reported at the Congress: the glucagon-like peptide-1 (GLP-1) analog liraglutide, which is the focus of a 2-year, phase II trial with 564 patients on the active drug; and another combination of two well-seasoned drugs, naltrexone and bupropion, tested in a pair of 1-year, phase III trials with a total of more than 1,700 participants.

With liraglutide, which suppresses appetite, 'we know how it works because it mimics a natural hormone we have a lot of knowledge about.'

A third new weight-management agent, the selective serotonin 2C receptor agonist lorcaserin, was tested on nearly 1,600 obese patients in a 2-year, phase III study (N. Engl. J. Med. 2010;363:245-56).

"The combination formulations [phentermine plus topiramate, and naltrexone plus bupropion] are quite effective, but my concern is their safety," Dr. Arne Astrup said in an interview during the congress. "Based on our experience with rimonabant, withdrawn [in Europe in 2009] because of depression and suicide ideation, and with sibutramine, withdrawn [in Europe in January 2010] because of cardiometabolic risk, I think there will be a lot of focus on cardiovascular risk factors, blood pressure, and low-density lipoprotein cholesterol" when considering the safety of new agents. The two withdrawals by the European Medicines Agency meant that currently only one drug, orlistat, is approved for treating weight loss in Europe.

One-year results from the two phase III trials of naltrexone plus bupropion reported at the meeting showed that the combination led to a rise in LDL cholesterol over baseline that exceeded placebo, and a drop in baseline blood pressure that fell short of the BP decrease in the placebo groups of both studies.

The results "raise the question of how does this translate into reduced cardiometabolic risk? I think there will be a lot of focus on these risk factors," said Dr. Astrup, professor and head of the department of human nutrition at the University of Copenhagen. The safety threshold for obesity drugs has to be set higher than the threshold for agents that treat more immediately life-threatening disorders, he said.

"We need to see blood pressure levels during the first month of treatment, before weight loss, and we need to see a meta-analysis of all phase III trials [for a specific drug or combination] to get a much better idea of the safety profile. Ideally, we should see 5,000-10,000 patients on the drug" to judge safety, Dr. Astrup said.

Significant adverse effects "are not really justified when treating obesity," he added. "If you treat epilepsy or heart failure, you can use drugs with some adverse effects as long as the treatment does something good for the patient." But when treating obesity, the overall cardiometabolic outcome must show benefit in addition to weight loss, "or you must reserve the drug only for obese patients who are at high risk for serious outcomes," he said.

"We need long-term outcomes data. We've been in the situation before with molecules on the market [for treating obesity] that looked very promising but didn't stand the test of time," commented Dr. Tessa van der Merwe, a professor of endocrinology at the University of Pretoria (South Africa).

Although safety questions mean uncertain futures for the phentermine plus topiramate and the naltrexone plus bupropion combinations, better safety profiles may elevate the prospects for lorcaserin and liraglutide, Dr. Astrup said.

"The weight-loss efficacy of lorcaserin is slightly less than or equivalent to that of orlistat, and slightly less than that of sibutramine. … However, safety and adverse event profiles seem to be better with lorcaserin than with orlistat or sibutramine. … Phase III studies will be required to confirm these initial findings in larger populations of patients," Dr. Astrup wrote in an editorial that accompanied the lorcaserin report (N. Engl. J. Med. 2010;363: 288-90).

After reporting at the congress on 2-year follow-up of 238 obese patients treated with liraglutide, which showed the drug's safety and tolerability, Dr. Astrup also gave liraglutide a tentative thumbs-up.

"I think for the pharmaceutical management of obesity, we need tailor-made molecules where we know exactly how they're working."

When treating obesity, the cardiometabolic outcome must improve in addition to weight loss.

DR. ASTRUP

With liraglutide, which suppresses appetite, "we know how it works because it mimics a natural hormone we have a lot of knowledge about," Dr. Astrup said. He also praised liraglutide's route of delivery, a once-daily subcutaneous injection, as another safety plus for the drug rather than a logistical drawback.

"I think an injectable drug will help prevent abuse. It requires a certain commitment from the patient and the physician. The vast majority [of patients in the phase II study] thought it was an easy way to take the drug; it's a kind of hormone replacement therapy for glucagon-like peptide-1."

The 2-year results on liraglutide he reported involved patients who completed a 20-week, dose-ranging study that also randomized patients to placebo or to orlistat (Lancet 2009;374:1606-16). After completing 52 weeks on their initially assigned medication and dosage, all patients in the four liraglutide arms and the placebo group switched to a 3-mg/day dosage, while patients in the orlistat arm remained on that agent.

In the 2-year, last-observation-carried-forward analysis, average weight loss on liraglutide was 5.3 kg and average loss with orlistat was 2.3 kg.

The most common adverse effect with liraglutide was nausea, which was transient and dose-related.

Treatment with liraglutide also led to a substantial drop in systolic blood pressure and a greater change in lipid levels than seen with orlistat, which Dr. Astrup characterized as a "very positive cardiovascular disease profile," along with "completely clean" outcomes for psychiatric adverse effects.

The good safety profile for liraglutide contrasted with questionable findings reported for the naltrexone plus bupropion combination, which was the focus of one phase III study with 584 patients treated with 32 mg of sustained-release naltrexone daily plus 360 mg of sustained-release bupropion daily, and a second phase III study with more than 1,100 participants randomized to either of two dosages of naltrexone, 16 mg or 32 mg daily, plus 360 mg/day bupropion. The combined medication regimen showed good efficacy, with 32 mg/day naltrexone plus bupropion producing a 9% average weight loss when used with behavior modification (in the single-dosage study) and a 6% average weight loss (in the two-dosage study), compared with average placebo-group losses of 5% (also with behavior modification) in the first study and 1% in the second.

But at 1 year in the single-dosage 32-mg naltrexone plus 360-mg bupropion study, systolic blood pressure fell an average of 4 mm Hg in the placebo group and an average of 1 mm Hg in the active-drug arm. Average diastolic pressure fell by 3 mm Hg in the placebo arm and 1 mm Hg in the active arm, reported Dr. Dennis Kim, senior vice president for medical affairs at Orexigen Therapeutics, the company developing a fixed-dose naltrexone and bupropion combination (Contrave).

Blood pressure drops were greater with placebo, even though these patients lost less weight than those in the active-drug group. In the other trial of this combination, patients on 32 mg/day naltrexone and bupropion experienced a 2–mm Hg rise over baseline in acute systolic blood pressure during the first 8 weeks, followed by a fall after 12 weeks to an average systolic pressure 1 mm Hg below baseline, according to a poster at the Congress.

Dr. Astrup's study was sponsored by Novo Nordisk, which is developing liraglutide.

Dr. Astrup has received honoraria as a speaker for and adviser to Novo Nordisk and Neurosearch, as well as research grants from both companies; he has also received honoraria as an adviser to Merck and Co. Dr. van der Merwe had no disclosures. ■