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Tirzepatide Superior to Semaglutide for A1c Control, Weight Loss

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Antidiabetic drug tirzepatide (Mounjaro) shows superiority over semaglutide (Ozempic, Wegovy, and Rybelsus) in controlling blood glucose as well as in the amount of weight lost, results from a meta-analysis of 22 randomized controlled trials show.

"The results indicate tirzepatide's superior performance over subcutaneous semaglutide in managing blood sugar and achieving weight loss, making it a promising option in the pharmaceutical management of type 2 diabetes," first author Thomas Karagiannis, MD, PhD, Aristotle University of Thessaloniki, Thessaloniki, Greece, told *Medscape Medical News*.

"In clinical context, the most potent doses of each drug revealed a clear difference regarding weight loss, with tirzepatide resulting in an average weight reduction that exceeded that of semaglutide by 5.7 kg (12.6 pounds)," he said.

The study is being presented at the Annual Meeting of the European Association for the Study of Diabetes (EASD) in early October.

While a multitude of studies have been conducted for tirzepatide, a dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist, and semaglutide, a selective GLP-1 agonist, studies comparing the two drugs directly are lacking.

For a more comprehensive understanding of how the drugs compare, Karagiannis and colleagues conducted the meta-analysis of 22 trials, including two direct comparisons, the SURPASS-2 trial and a smaller trial, and 20 other studies comparing either semaglutide or tirzepatide with a common comparator, such as placebo, basal insulin, or other GLP-RA-1 drugs.

Overall, 18,472 participants were included in the studies.

All included studies had assessed a maintenance dose of tirzepatide of either 5, 10, or 15 mg once-weekly or semaglutide at doses of 0.5, 1.0, or 2.0 mg once-weekly for at least 12 weeks. All comparisons were for subcutaneous injection formulations (semaglutide can also be taken orally).

Blood Glucose Reduction

Tirzepatide at 15 mg was found to have the highest efficacy in the reduction of A1c compared with placebo, with a mean difference of -2.00%, followed by tirzepatide 10 mg (-1.86%) and semaglutide 2.0 mg (-1.62%).

All three of the tirzepatide doses had greater reductions in A1c compared with the respective low, medium, and high doses of semaglutide.

Karagiannis noted that the differences are significant: "An A1c reduction even by 0.5% is often deemed clinically important," he said.

Body Weight Reduction Comparisons

The reductions in body weight across the three drug doses were greater with tirzepatide (-10.96 kg [24.2 pounds], -8.75 kg [19.3 pounds], and -6.16 kg [13.6 pounds] for 15, 10, and 5 mg, respectively) compared with semaglutide (-5.24 kg [11.6 pounds], -4.44 kg [9.8 pounds] and -2.72 kg [6 pounds] for semaglutide 2.0, 1.0, and 0.5 mg, respectively).

In terms of drug-to-drug comparisons, tirzepatide 15 mg had a mean of 5.72 kg (12.6 pounds) greater reduction in body weight vs semaglutide 2.0 mg; tirzepatide 10 mg had a mean of 3.52 kg (7.8 pounds) reduction vs semaglutide 2.0 mg; and tirzepatide 5 mg had a mean of a 1.72 kg (3.8 pounds) greater reduction vs semaglutide 1.0 mg.

Adverse Events: Increased GI Events With Highest Tirzepatide Dose

Regarding the gastrointestinal adverse events associated with the drugs, tirzepatide 15 mg had the highest rate of the two drugs at their various doses, with a risk ratio (RR) of 3.57 compared with placebo for nausea, an RR of 4.35 for vomiting, and 2.04 for diarrhea.

There were no significant differences between the two drugs for the gastrointestinal events, with the exception of the highest dose of tirzepatide, 15 mg, which had a higher risk of vomiting vs semaglutide 1.0 (RR 1.39) and semaglutide 0.5 mg (RR 1.85).

In addition, tirzepatide 15 mg had a higher risk vs semaglutide 0.5 mg for nausea (RR 1.45).

There were no significant differences between the two drugs and placebo in the risk of serious adverse events.

Real World Applications, Comparisons

Karagiannis noted that the results indicate that benefits of the efficacy of the higher tirzepatide dose need to be balanced with those potential side effects.

"Although the efficacy of the high tirzepatide dose might make it a favorable choice, its real-world application can be affected on an individual's ability to tolerate these side effects in case they occur," he explained.

Ultimately, "some patients may prioritize tolerability over enhanced efficacy," he added.

Furthermore, while all three maintenance doses of tirzepatide analyzed have received marketing authorization, "to get a clearer picture of the real-world tolerance to these doses outside the context of randomized controlled trials, well-designed observational studies would be necessary," Karagiannis said.

Among other issues of comparison with the two drugs is cost.

In a recent analysis, the cost per 1% of body weight reduction was reported to be $1197 for high-dose tirzepatide (15 mg) vs $1511 for semaglutide 2.4 mg, with an overall cost of 72 weeks of therapy with tirzepatide at $17,527 compared with $22,878 for semaglutide.

Overall, patients and clinicians should consider the full range of differences and similarities between the medications, "from [their] efficacy and side effects to cost-effectiveness, long-term safety, and cardiovascular profile," Karagiannis said.

Semaglutide is currently approved by the US Food and Drug Administration for treatment of type 2 diabetes and obesity/weight loss management.

Tirzepatide has also received approval for the treatment of type 2 diabetes and its manufacturers have submitted applications for its approval for obesity/weight loss management.

Karagiannis reports no relevant financial relationships.

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