Tirzepatide Frequently Asked Questions

Dosage and Dose Escalation

How is tirzepatide administered and what are the available doses?

- Tirzepatide is administered once weekly by subcutaneous injection using a single-dose prefilled auto-injector pen with a pre-attached hidden needle. There are six dose strengths: 2.5 mg, 5 mg, 7.5 mg, 10 mg, and 15 mg per 0.5 mL.

At what dose is tirzepatide initiated and how is the dose adjusted?

- The recommended starting dose of tirzepatide is 2.5 mg injected subcutaneously once weekly. The 2.5-mg dosage is for treatment initiation and is not intended for glycemic control.
- After 4 weeks at the once-weekly 2.5-mg dose, it should be increased to 5 mg once weekly. If additional glycemic control is needed, the dose can be increased in 2.5-mg increments after at least 4 weeks on the current dose. The maximum dose is 15 mg subcutaneously once weekly.

What kind of follow-up is required?

- As with any change in a patient's therapeutic regimen, the patient should be monitored for glycemic response as well as any issues with tolerability to the medication. Follow-up should be individualized depending on patient characteristics, but the patient's glycemic response should be followed closely, as dose escalation of tirzepatide after the 5-mg dose should be based on the patient's individualized glycemic goals and their response to tirzepatide.

Using Tirzepatide with other Treatments for T2D

Is tirzepatide prescribed as an adjunct therapy only, or can it be prescribed as a monotherapy?

- Tirzepatide can be prescribed as monotherapy. It is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes (T2D). Clinical trial results support its use as the only pharmacological therapy (monotherapy) and also as an adjunct to other antidiabetic medications, including insulin.

How should the metformin dose be changed if used with tirzepatide?

- As with the addition of any antihyperglycemic agent for a patient who is treated with a regimen that includes metformin, the metformin dose should not generally be changed when tirzepatide is added. In clinical trials assessing tirzepatide in patients with T2D using metformin, the metformin dose was not changed.

How is tirzepatide prescribed along with insulin therapy?

- Concomitant use of tirzepatide with an insulin secretagogue, such as a sulfonylurea, or insulin may increase the risk of hypoglycemia. For this reason, reducing the dose of the insulin secretagogue or insulin should be considered, and patients should be educated on the signs and symptoms of hypoglycemia and on its treatment.

Measuring Success

Is A1c the primary measure of success in patients taking tirzepatide?

- Tirzepatide is indicated to improve glycemic control as an adjunct to diet and exercise in adults with T2D. As such, measurement of glucose levels and attainment of individualized glucose targets are the primary measures of success and the basis of dose escalation if needed. These measures may include self-monitored glucose, continuous glucose monitoring, and/or A1c.

How soon after beginning tirzepatide will improvement in A1c be seen?

- In the tirzepatide Phase 3 clinical trials, improvement in glucose as measured by A1c was seen as soon as 4 weeks after initiation of tirzepatide and continued to improve thereafter. These clinical trial results may vary for individual patients.

Weight Change with Tirzepatide

Does weight loss due to tirzepatide vary if the patient is also on metformin or insulin?

- There is no head-to-head study assessing the effect of tirzepatide on body weight loss in patients with T2D treated with metformin versus patients treated with insulin. In clinical trials assessing tirzepatide as add-on therapy to metformin or as an add-on to basal insulin, tirzepatide at 5 mg, 10 mg, and 15 mg resulted in significant weight reduction from baseline at 40 and 52 weeks. Results in individual patients may vary from average results observed in clinical trials.

If weight change is a secondary endpoint for tirzepatide, is this treatment safe for people with T2D who are not overweight or obese?

- Tirzepatide is indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D. Although in clinical trials weight loss was achieved in tirzepatide-treated patients, patients in need of improved glycemic control who are not overweight or obese may use tirzepatide. From a clinical perspective in a patient like this, weight can be monitored and dose de-escalation (reduction) may be considered if excessive weight loss occurs.

Will weight loss due to tirzepatide eventually taper off?

- In the clinical trials assessing patients with T2D, weight loss at the highest dose of tirzepatide (15 mg) plateaued around 52 weeks (1 year).

How soon after discontinuing tirzepatide is weight regained?

- This has not been assessed in clinical trials, and so it is not currently known.

Effects on Dyslipidemia

Can patients on tirzepatide also take statins?

- Yes, patients taking tirzepatide can also be on statins, and there is no need to adjust the statin dose in a patient initiating tirzepatide.

Does tirzepatide improve dyslipidemia in patients?

- In clinical trials, tirzepatide has been shown to improve patients' lipid profiles, including a reduction in triglyceride levels and an increase in HDL cholesterol levels.

Is there any comparison between GLP-1 RAs and tirzepatide in improving dyslipidemia?

- Yes. In the SURPASS-2 study, assessing tirzepatide (5 mg, 10 mg, and 15 mg once weekly) versus semaglutide (1 mg once weekly) in patients with T2D treated with metformin, tirzepatide-treated patients had lower triglyceride and higher HDL cholesterol levels after 40 weeks of treatment than did semaglutide-treated patients.

Risk of Hypoglycemia

What are the risks of hypoglycemia with tirzepatide?

- Based on the mechanism of action of tirzepatide, the risk of clinically significant hypoglycemia is very low. The risk of clinically significant hypoglycemia is also low when used in conjunction with another antihyperglycemic agent with a low risk of hypoglyemia such as metformin or an SGLT2 inhibitor. The risk of hypoglycemia may increase in patients treated with an insulin secretagogue, such as a sulfonylurea, or insulin. For this reason, reducing the dose of the insulin secretagogue and/or insulin should be considered, and patients should be educated on the signs and symptoms of hypoglycemia and on its treatment.

What precautions should be taken to prevent hypoglycemia while taking tirzepatide?

- If tirzepatide is being added to a patient's regimen that includes an insulin secretagogue and/or insulin, a reduction in the dose of the insulin secretagogue and/or insulin should be considered. Additionally, patients should be educated on self-monitoring of blood glucose, on signs and symptoms of hypoglycemia, and on treatment of hypoglycemia should it occur.

If hypoglycemia occurs, should tirzepatide be titrated to a lower dose or should other adjunct therapies be reduced or changed?

- If clinically significant hypoglycemia occurs in a patient taking tirzepatide in combination with an insulin secretagogue and/or insulin, a reduction in the dose of the insulin secretagogue and/or insulin should be made. In a situation in which such as this, tirzepatide may increase the risk of insulin secretagogue- and/or insulin-induced hypoglycemia. For this reason, reducing the dose of insulin secretagogue and/or insulin is the most appropriate course of action.

Adverse Events

What are the most common adverse events that patients on tirzepatide may encounter?

- As with selective GLP-1RAs (eg, dulaglutide and semaglutide), the most common adverse events observed in clinical trials with tirzepatide were gastrointestinal in nature. These included nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal pain. In a pooled analysis of two placebo-controlled trials (SURPASS-1 and SURPASS-5), the incidence of gastrointestinal side effects in tirzepatide-treated patients was higher than that in patients receiving placebo and tended to increase with increasing tirzepatide dose.

Does tirzepatide have the same contraindications and warnings and precautions as GLP-1 RAs?

- Tirzepatide has the same contraindications as long-acting selective GLP-1RAs such as dulaglutide and semaglutide. It is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). It is also contraindicated in patients with known serious hypersensitivity to tirzepatide or any of the excipients in the medication. Warnings and precautions are generally similar to those of the selective GLP-1RAs, and include pancreatitis, hypoglycemia when used in combination with insulin secretagogues or insulin, hypersensitivity reactions, acute kidney injury, severe gastrointestinal disease, diabetic retinopathy, and acute gallbladder disease.

Do gastrointestinal side effects that occur with tirzepatide dissipate on their own?

- In clinical trials, if patients taking tirzepatide experienced gastrointestinal side effects, they tended to occur early in the course of therapy (during dose escalation), be mild or moderate in severity, and resolve over time. Relatively few patients had to stop tirzepatide because of gastrointestinal side effects. For example, in a pooled analysis of placebo-controlled clinical trials, discontinuation of treatment due to gastrointestinal side effects occurred in 3.0%, 5.4%, 6.6%, and 0.4% in patients treated with tirzepatide 5 mg, 10 mg, 15 mg, and placebo, respectively. From a clinical perspective, as with selective GLP-1RAs, it is important to proactively tell patients that they may experience gastrointestinal side effects and that these can generally be mitigated with dietary interventions and that they are generally self-limited and dissipate with time.

Precautions

Which patients is tirzepatide not indicated for?

- There are contraindications to the use of tirzepatide (see above). Additionally, tirzepatide is not indicated for use in patients with type 1 diabetes.

Are there any guidelines on retinopathy? What if a patient has mild retinopathy?

- The tirzepatide FDA label contains a warning/precaution related to retinopathy. It states that tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression, because of the well-known finding that rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients should follow standards of care with respect to diabetic retinopathy screening and follow-up and, as standard in clinical practice, should be monitored for progression of retinopathy.

Can tirzepatide be discontinued immediately or should it be tapered off?

- If needed, the dose can be stopped without tapering. If a patient is not tolerating a given dose, a dose reduction may improve tolerability. If tirzepatide is stopped or the dose reduced, as with any adjustment in antihyperglycemic regimen, glucose control should be more closely monitored.

Courtesy of Juan Pablo Frias, MD; Medical Director, Velocity Clinical Research, Los Angeles, CA.

For additional detail see:

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- Frías JP, et al. N Engl J Med. 2021;385:503-515.
- Ludvik B, et al. Lancet. 2021;398:583-598.
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- Dahl D, et al. J Amer Med Assoc. 2022;327:534-545.