Educational Forum
International Journal of Medical and Dental Sciences, *Vol 11(2), DOI: 10.18311/ijmds/2022/636, July 2022*
ISSN (Print) : 2454-8952
ISSN (Online) : 2320-1118

Tirzepatide: Revolutionary Drug in Management of "Diabesity"

Vansh Chouhan[1], Simran Spal[1] and Rakesh Kumar[2*]

[1]MBBS Final Prof., Punjab Institute of Medical Sciences, Jalandhar - 144006, Punjab, India; vanshchouhan70@gmail.com, simranspal2k@gmail.com
[2]Professor, Department of Pharmacology, Punjab Institute of Medical Sciences, Jalandhar - 144006, Punjab, India; bagharakesh@gmail.com

Abstract

Tirzepatide, a glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor agonist has recently been approved by FDA for type 2 diabetes in adults as a single dose weekly. Tirzepatide is in phase 3 development for adults with obesity or overweight with weight-related comorbidity. Tirzepatide is also under evaluation for treatment of non-alcoholic steatohepatitis, heart failure and obstructive sleep apnea.

Keywords: GIP Agonist, GLP–1 Agonist, Incretin, Obesity, Type 2 Diabetes Mellitus

1. Introduction

Tirzepatide is a GIP (Glucose-dependent Insulinotropic Polypeptide) receptor and GLP-1 (Glucagon-like Peptide-1) receptor agonist. This drug was approved by FDA as a treatment for adults with type 2 diabetes and is in phase 3 development for adults with obesity or overweight with weight-related comorbidity. Tirzepatide is now being evaluated in different clinical trials around the world for its safety and efficacy as an anti-obesity drug.

2. Mechanism of Action

Tirzepatide, a dual GIP/GLP-1 receptor agonist, is a new incretin-based therapy for type 2 diabetes. Under hyperglycemic conditions, glucose-dependent insulinotropic polypeptide stimulates the release of insulin, thereby lowering glucagon levels, and under euglycemic or hypoglycemic conditions, glucagon levels are increased[1]. GIP enhances both the postprandial lipid-buffering capacity of white adipose tissue and the sensitivity of adipose tissue to insulin, which may prevent ectopic fat deposition[2,3]. Hence tirzepatide has high glucose lowering and weight loss potential (Figure 1).

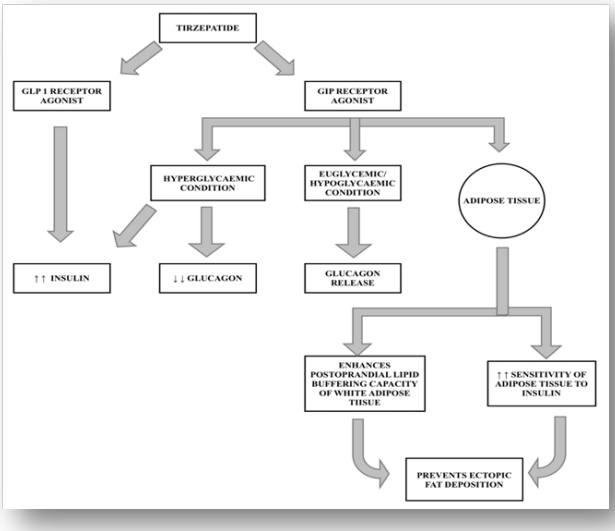

Figure 1. Mechanism of action of tirzepatide.

2.1 The SURPASS Clinical Trials

SURPASS randomized, phase 3, double-blind trials compared the effect of tirzepatide to five different drug therapies in patients with type 2 diabetes mellitus. SURPASS clinical trials compared safety and efficacy of

*Author for correspondence

Tirzepatide, as mono therapy to placebo in adults with type 2 diabetes inadequately controlled with diet and exercise alone in SURPASS 1, to injectable Semiglutide in adults with type 2 diabetes inadequately controlled with metformin ≥ 1500 mg/day alone in SURPASS 2, to Insulin Degludec in adults with type 2 diabetes treated with metformin with or without an SGLT-2 inhibitor in SURPASS 3, to Insulin Glargine in adults with type 2 diabetes inadequately treated with at least one and up to three oral antihyperglycemic medications in SURPASS 4, to placebo in adults with type 2 diabetes inadequately controlled with Insulin Glargine with or without metformin in SURPASS 5.

There was significant reduction in weight and HbA1c with different doses of tirzepatide when compared with placebo, semiglutide, degludec, glargine and placebo in SURPASS 1-5 respectively (Table 1).

2.2 The SURMOUNT Clinical Trial

SURMOUNT-1 is a multi-center, randomized, double-blind, parallel, placebo-controlled trial comparing the efficacy and safety of tirzepatide 5 mg, 10 mg and 15 mg to placebo as an adjunct to a reduced-calorie diet and increased physical activity in adults without type 2 diabetes who had obesity, or overweight with at least one of the following comorbidities: Hypertension, dyslipidemia, obstructive sleep apnea or cardiovascular disease in 2539 adults with a mean baseline body weight of 231lb (105 kg).

Tirzepatide was started in a dose of 2.5 mg once-weekly and then increased in a step-wise approach at four-week intervals to their final randomized maintenance dose of 5 mg (via a 2.5 mg step), 10 mg (via steps at 2.5 mg, 5 mg and 7.5 mg) or 15 mg (via steps at 2.5 mg, 5 mg, 7.5

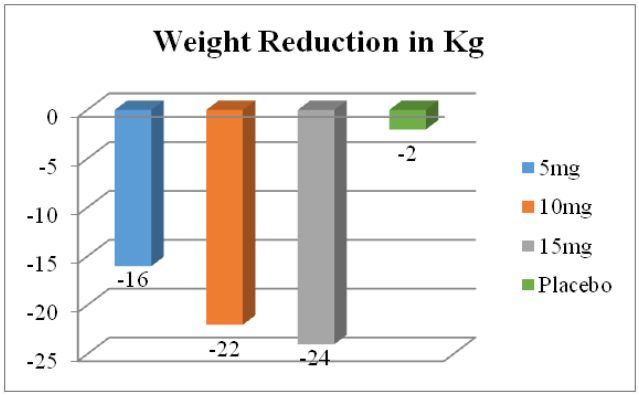

Figure 2. Weight reduction with different doses of Tirzepatide in Surmount 1 Clinical trial.

Table 1. Comparison of weight and HbA1c reduction of tirzepatide with different drug therapies in SURPASS clinical trials

Trials/Duration	Drug		HbA1c (%)	Weight (kg)
SURPASS 1 40 weeks	Tirzepatide	5mg	-1.87	-7.0
		10mg	-1.89	-7.8
		15mg	-2.07	-9.5
	Placebo		-0.04	-0.7
SURPASS 2 40 weeks	Tirzepatide	5mg	-2.1	-7.8
		10mg	-2.4	-10.3
		15mg	-2.5	-12.4
	Injection Semiglutide		-1.9	-6.2
SURPASS 3 52 weeks	Tirzepatide	5mg	-1.9	-7.5
		10mg	-2.2	-10.7
		15mg	-2.4	-12.9
	Insulin Degludec		-1.3	+2.3
SURPASS 4 104 weeks	Tirzepatide	5mg	-2.2	-7.1
		10mg	-2.4	-9.5
		15mg	-2.6	-11.7
	Insulin Glargine		-1.4	+1.9
SURPASS 5 40 weeks	Tirzepatide	5mg	-2.2	-6.2
		10mg	-2.6	-8.2
		15mg	-2.6	-10.9
	Placebo		-0.9	+1.7

Table 2. Common gastrointestinal side effects in SURPASS and SURMOUNT clinical trails

	Drug		NAUSEA	DIARRHOEA	VOMITING	CONSTIPATION	DYSPEPSIA
SURMOUNT 1	Tirzepatide	5mg	24.6%	18.7%	8.3%	16.8%	—
		10mg	33.3%	21.2%	10.7%	17.1%	—
		15mg	31%	23%	12.2%	11.7%	—
	Placebo		9.5%	7.3%	1.7%	5.8%	—
SURPASS 1	Tirzepatide	5mg	11.6%	11.6%	3.3%	5.8%	9.1%
		10mg	13.2%	14.1%	2.5%	5.0%	6.6%
		15mg	18.2%	11.6%	5.8%	6.6%	5.8%
	Placebo		6.1%	7.8%	1.7%	0.9%	3.5%
SURPASS 2	Tirzepatide	5mg	17.5%	13.2%	5.7%	6.6%	7.2%
		10mg	19.2%	16.4%	8.3%	4.5%	6.2%
		15mg	22.1%	13.8%	9.8%	4.5%	9.2%
	Semiglutide	1mg	17.9%	11.5%	8.3%	5.8%	6.6%
SURPASS 3	Tirzepatide	5mg	11.5%	15.4%	5.9%		3.9%
		10mg	22.5%	16.4%	9.4%		8.9%
		15mg	23.7%	15.6%	10.0%		5.0%
	Insulin Degludec		1.7%	3.9%	1.1%		0.0%
SURPASS 4	Tirzepatide	5mg	11.9%%	12.5%	4.9%	5.2%	5.5%
		10mg	16.2%	19.8%	8.2%	4.3%	8.2%
		15mg	22.5%	21.9%	8.6%	4.1%	7.7%
	Insulin Glargine		2.3%	4.4%	1.5%	0.5%	1.3%
SURPASS 5	Tirzepatide	5mg	12.9%	12.1%	6.9%	6%	6.9%
		10mg	17.6%	12.6%	7.6%	6.7%	8.4%
		15mg	18.3%	20.8%	12.5%	6.7%	5.0%
	Placebo		2.5%	10%	2.5%	1.7%	1.7%

Table 3. Incidence of mild and severe side effects of tirzepatide in SURPASS 1-5 clinical trials

	DRUG		MILD/MODERATE ADR'S	SEVERE ADR'S
SURPASS 1	Tirzepatide	5mg	41.3%	4.1%
		10mg	45.5%	1.7%
		15mg	43.8%	0.8%
	Placebo		47.0%	2.6%
SURPASS 2	Tirzepatide	5mg	36.1%	7.0%
		10mg	39.9%	5.3%
		15mg	43.0%	5.7%
	Injection Semiglutide	1mg	36.7%	2.8%
SURPASS 3	Tirzepatide	5mg	34.6%	8.1%
		10mg	43.6%	5.6%
		15mg	49.9%	7.2%
	Insulin Degludec		18.3%	6.1%

SURPASS 4	Tirzepatide	5mg	34.0%	14.6%
		10mg	48.2%	16.5%
		15mg	54.4%	12.1%
	Insulin Glargine		19.2%	19.3%
SURPASS 5	Tirzepatide	5mg	44.8%	7.8%
		10mg	50.4%	10.9%
		15mg	55.8%	7.5%
	Placebo		48.3%	8.3%

mg, 10 mg and 12.5 mg). There was significant reduction in weight when compared with placebo at the end of 72 weeks (Figure 2).

2.3 Adverse Effects

Majority of adverse drug reactions were minor and majorly were gastrointestinal related in SURPASS 1-5 and SURMOUNT 1. The common side effects included nausea, vomiting, diarrhea, decreased appetite, indigestion, constipation, abdominal pain, nasopharyngitis, decreases appetite, hypertension and were mild to moderate in severity and usually occurred during the dose escalation period (Table 2).

The serious side effects include pancreatitis, hypoglycemia, hypersensitivity reactions, kidney disorders, eye disorders, hepatobiliary symptoms, diabetic retinopathy, cardiac symptoms and nervous system disorders. Mild to moderate adverse effects was reported in 36% to 55% and severe adverse effects was reported in 1% to 16% (Table 2, 3).

Tirzepatide can cause tumors in thyroid, therefore contraindicated in patients with family history of medullary thyroid carcinoma and in patients who have MEN-2 syndrome. History of chronic or acute pancreatitis, diabetic retinopathy or maculopathy, acute/chronic hepatitis are also contraindications for the use of this drug[4–9].

Tirzepatide has the potential as an antiobesity drug and has already been approved as a once weekly dose in type 2 diabetes mellitus patients. It can be a revolutionary drug in management of diabesity i.e., obesity in type 2 diabetes mellitus patients. Only non serious adverse effects have been reported in various clinical trials. The long term safety of the drug is yet to be ascertained.

3. References

1. Christensen M, Vedtofte L, Holst JJ, Vilsbøll T, Knop FK. Glucose-dependent insulinotropic polypeptide: A bifunctional glucose-dependent regulator of glucagon and insulin secretion in humans. Diabetes. 2011; 60:3103-9. https://doi.org/10.2337/db11-0979 PMid:21984584 PMCid:PMC3219957
2. Yip RG, Boylan MO, Kieffer TJ, Wolfe MM. Functional GIP receptors are present on adipocytes. Endocrinology. 1998; 139:4004-7. https://doi.org/10.1210/endo.139.9.6288 PMid:9724057
3. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept. Mol Metab. 2018; 18:3-14. https://doi.org/10.1016/j.molmet.2018.09.009 PMid:30473097 PMCid:PMC6308032
4. A study of Tirzepatide (LY3298176) in participants with type 2 diabetes not controlled with diet and exercise alone (SURPASS-1)- study results [Internet]. A study of tirzepatide (LY3298176) in participants with type 2 diabetes not controlled with diet and exercise alone- Study Results- ClinicalTrials.gov. [cited 2022 Jul11]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03954834
5. A study of tirzepatide (LY3298176) versus semaglutide once weekly as add-on therapy to metformin in participants with type 2 diabetes (SURPASS-2)- study results [Internet]. A study of tirzepatide (LY3298176) versus semaglutide once weekly as add-on therapy to metformin in participants with type 2 diabetes- Study Results- ClinicalTrials.gov. [cited 2022 Jul11]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03987919?view=results
6. A study of tirzepatide (LY3298176) versus insulin degludec in participants with type 2 diabetes (SURPASS-3)- study results [Internet]. A study of tirzepatide (LY3298176) versus insulin degludec in participants with type 2 diabetes - Study Results - ClinicalTrials.gov. [cited 2022 Jul11]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03882970?view=results

7. A study of tirzepatide (LY3298176) once a week versus insulin glargine once a day in participants with type 2 diabetes and increased cardiovascular risk (SURPASS-4)- study results [Internet]. A study of tirzepatide (LY3298176) once a week versus insulin glargine once a day in participants with type 2 diabetes and increased cardiovascular risk- Study Results - ClinicalTrials.gov. [cited 2022Jul11]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT03730662?view=results
8. A study of tirzepatide (LY3298176) versus placebo in participants with type 2 diabetes inadequately controlled on insulin glargine with or without metformin (SURPASS-5) - study results [Internet]. A study of tirzepatide (LY3298176) versus placebo in participants with type 2 diabetes inadequately controlled on insulin glargine with or without metformin - Study Results - ClinicalTrials.gov. [cited 2022Jul11]. Available from: https://clinicaltrials.gov/ct2/show/results/NCT04039503?view=results
9. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, Kiyosue A, Zhang S, Liu B, Bunck MC, Stefanski A. Tirzepatide once weekly for the treatment of obesity. New England Journal of Medicine. 2022 Jun 4. https://doi.org/10.1056/NEJMoa2206038 PMid:35658024

How to cite this article: Chouhan, V., Spal, S. and Kumar, R. Tirzepatide: Revolutionary Drug in Management of "Diabesity". Int. J. Med. Dent. Sci. 2022; 11(2): 2046-2050.