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A MULTIFACETED ANALYSIS OF IMPORTANT CLINICAL TRIALS ON TIRZEPATIDE FOR DEVELOPING DIABETES MELLITUS THERAPIES

N.L. Swathi[1]*, P. Shiva Datta Sai[2], Nikita Das[2], Sherin Prasad[3], S. Nidhi[3], Palak Dubey[4], Aniruddh Thakur[4]

[1]Pharm D, Department of Pharmacy Practice, JNTUA University, Andhra Pradesh, 517127.

[2]Pharm D, Department of Pharmacy Practice, JNTUA University, Andhra Pradesh, 517127.

[3]Pharm D, Department of Pharmacy Practice, JNTUA University, Andhra Pradesh, 517127.

[4]Pharm D, Sri Aurobindo Institute of Pharmacy.

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***Corresponding Author**
N.L. Swathi
Pharm D, Department of Pharmacy Practice, JNTUA University, Andhra Pradesh, 517127.
ORCID ID: 0000-0002-3695-0732
nlswathi1999@gmail.com

ABSTRACT

A comprehensive review of significant clinical trials pertaining to tirzepatide's usage in the treatment of diabetes mellitus is given in this article. We provide insights into the evolving knowledge of DM treatments by analysing the procedures, findings, and implications of six significant trials. Each experiment presents a different angle on tirzepatide. Our analysis of these studies offers a thorough picture of the state of affairs today and possible directions for the treatment of tirzepatide in the future.

KEYWORDS: Type 2 Diabetes, Tirzepatide, Dual GLP-1R/GIPR agonist, Twincretin effect.

INTRODUCTION

GLP-1R/GIPR dual agonists can improve the therapeutic effectiveness of individualised diabetes care, particularly in obese type 2 diabetics, however caution should be used when determining if these medications are appropriate for the treatment of Asian type 2 diabetes patients.[1]

Twincretin molecules have come to light as promising antidiabetic medicines for regulating body weight and blood sugar levels. Both the incretins GLP-1 and GIP increase insulin secretion and lower postprandial glucose levels. In people with type 2 diabetes, GLP-1R/GIPR dual agonists resulted in better bodyweight loss than GLP-1R single agonists.[1]

An incretin called GLP-1 plays a pathogenic part in the onset of type 2 diabetes. Liraglutide, a GLP-1 analogue, lowers plasma glucose levels, suppresses glucagon, increases insulin production, and decreases hunger.[2] New treatments for type 2 diabetes are now focusing on the incretin pathway, which includes GLP-1. Dipeptidyl peptidase-4 inhibitors and GLP-1 agonists/analogues have demonstrated efficacy and safety in the treatment of type 2 diabetes.[3] The efficacy and safety characteristics of DPP IV inhibitors, such as alogliptin, dutogliptin, and linagliptin, are promising and they offer advantages over sulfonylureas.[4] Type 2 diabetes treatments now include incretin mimics and enhancers, with GLP-1 mimics protecting pancreatic cells and promoting weight loss.[5]

A twincretin compound called tirzepatide has attracted interest as a possible therapy for diabetes mellitus. It is a dual agonist against the glucose-dependent insulinotropic polypeptide receptor (GIPR) and the glucagon-like peptide-1 receptor (GLP-1R).[1]

This article provides a thorough examination of six key clinical trials that have enhanced our understanding of tirzepatide as different therapy strategies for insulin resistance develop.

Summary of Key Clinical Trials

Tirzepatide was compared to a conventional placebo and dulaglutide in the study's post hoc analysis and multiple regression analysis to determine how it affected beta-cell function and insulin resistance (IR).[6]

In the SURPASS-4 trial, tirzepatide, a dual GIP and GLP-1 receptor agonist, and insulin glargine were compared for efficacy and safety in adults with type 2 diabetes and high cardiovascular risk who were not adequately controlled by oral glucose-lowering medications.[7]

Efficacy, safety, and tolerability of tirzepatide monotherapy in individuals with type 2 diabetes uncontrolled by diet and exercise alone were evaluated in the SURPASS-1, phase 3 trial.[8]

Patients with type 2 diabetes who had insufficient glycemic control with basal insulin, with or without metformin, were enrolled in the SURPASS 5 randomised clinical trial to compare the effectiveness and safety of subcutaneous tirzepatide at various doses (5-mg, 10-mg, and 15-mg) compared to placebo.[9]

Tirzepatide is a type 2 diabetes medicine that was evaluated in a double-blind, placebo-controlled Phase 2b clinical trial investigation to determine how it affected the plasma metabolome in comparison to dulaglutide and a control group. On the Phase 2b tirzepatide, this study was completed post hoc.[10]

A 12-week, randomised, double-blind, placebo-controlled trial evaluating several tirzepatide dose-escalation strategies.[11]

DISCUSSION

Each trial offers different insights on the intricate world of tirzepatide.

Tirzepatide, a dual GIP and GLP-1 receptor agonist, may have future implications for the treatment of type 2 diabetes, according to the post hoc analysis and multiple regression analysis study.

Comparing tirzepatide to the selective GLP-1RA dulaglutide, the former showed improved glucose management and weight loss. Better glycemic control in type 2 diabetes patients may result from the improvement in beta-cell function and insulin sensitivity seen with tirzepatide. The study emphasises the potential advantages of dual receptor agonism in providing unique glycemic control strategies.[6]

The results of the SURPASS-4 research point to tirzepatide, a dual GIP and GLP-1 receptor agonist, as a potentially effective treatment for persons with type 2 diabetes and significant cardiovascular risk who are not well controlled by oral glucose-lowering medicines. Tirzepatide may provide patients with a safer treatment alternative given the lower frequency of hypoglycemia that is linked to it. The results of the study add to the expanding body of research that demonstrates the effectiveness of dual GIP and GLP-1 receptor agonists in the treatment of type 2 diabetes and cardiovascular risk. To confirm the long-term efficacy and safety of tirzepatide, more investigation and longer-term studies are required.[7]

Tirzepatide may be an effective and secure therapy option for people with type 2 diabetes whose condition is not properly controlled by diet and exercise alone, according to the findings of the SURPASS 1 research. Tirzepatide may be used as a stand-alone treatment for type 2 diabetes, since it demonstrated notable improvements in body weight and glycemic control without raising the risk of hypoglycemia. Tirzepatide may be used as a monotherapy

to treat type 2 diabetes because its safety profile is similar to that of GLP-1 receptor agonists.[8]

Subcutaneous tirzepatide-treated participants in the SURPASS 5 trial reported at least 1 treatment-emergent adverse event, compared to 67.5 percent of patients who received a placebo. In the tirzepatide groups, gastrointestinal side effects, including diarrhoea, nausea, vomiting, and decreased appetite, were the most frequently reported treatment-emergent adverse events. The majority of gastrointestinal problems were mild to moderately severe, and all tirzepatide groups experienced a gradual decline in the prevalence of new problems. During the trial, there were no fatalities. Overall, 8% to 11% of patients receiving tirzepatide reported significant side events, compared to 8% of patients receiving a placebo.[9]

The double-blind study's conclusions have significant ramifications for the management of type 2 diabetes. Tirzepatide, a drug that significantly lowers HbA1c and body weight, has the potential to help type 2 diabetics with their glycemic management and insulin resistance. The observed decrease in blood triglycerides and lipoprotein indicators indicates that tirzepatide may have cardiovascular advantages in addition to diabetic control. Tirzepatide may aid in maintaining pancreatic beta-cell function, which is essential in the treatment of type 2 diabetes, as seen by the improvement in indicators of beta-cell function. These findings emphasise the potential of tirzepatide as a novel therapy option for people with type 2 diabetes, potentially improving cardiovascular health and beta-cell function while also providing improved glycemic control. To confirm these results and investigate the long-term effects and safety profile of tirzepatide in the management of type 2 diabetes, more research, including larger clinical studies, is required.[10]

The three dose-escalation regimens of tirzepatide used in the trial were 12 mg, 15 mg-1, and 15 mg-2. After 12 weeks of treatment, tirzepatide caused clinically significant drops in HbA1c levels. In comparison to the placebo group, the mean absolute HbA1c drop from baseline was larger in the tirzepatide treatment groups (12 mg, -1.7 percent; 15 mg-1, -2.0 percent; and 15 mg-2, -1.8 percent). The study hypothesises that a more favourable side effect profile of tirzepatide may be related with lower starting dosages and fewer dose increases. When compared to the placebo group, the incidence of nausea was higher in the tirzepatide treatment groups, with the 15 mg-1 group experiencing the highest occurrence (39.3 percent) The long-term effects and possible advantages of tirzepatide combined with basal insulin

require more study. Studies contrasting tirzepatide with other drugs used to treat type 2 diabetes might also be helpful in helping clinicians decide on the best course of treatment.

Methodological Considerations

It may be difficult to directly compare the effects of different medications because the study only compared the effects of tirzepatide to those of dulaglutide and placebo. Beta-cell function and insulin resistance were evaluated in the study using fasting biomarkers, which may not have adequately captured the dynamic changes in these parameters during the day.[6]

The 52-week study's brief duration may not have well captured tirzepatide's long-term outcomes and safety profile when compared to insulin glargine. Longer-term research would yield more thorough information on the effectiveness and safety of tirzepatide.

Adults with type 2 diabetes and significant cardiovascular risk who had insufficient control on oral glucose-lowering medicines made up the study population. The findings' applicability to patient groups with other characteristics or treatment plans may be constrained by this particular demographic.[7]

The 40-week SURPASS 1 trial may not have adequately captured treatment sustainability or long-term consequences. It's possible that the study's focus on people with type 2 diabetes that can't be well controlled by diet and exercise alone will restrict how widely the results can be applied. Due to the trial's execution at hospitals and research facilities in Mexico, Japan, Mexico, the USA, and other countries, there may have been geographical and cultural biases.[8]

Patients who participated in the study were given insulin glargine either with or without metformin, therefore the results may not be applicable to other treatment plans that call for various oral antihyperglycemic drugs.[9]

It's possible that patients receiving subcutaneous tirzepatide were initially favoured by the lack of insulin dose modification for the first four weeks of treatment, which could have affected the outcomes. Nevertheless, this was made up for over the remaining 40 weeks of treatment.[9]

Despite the stringent inclusion criteria and the treat-to-target methodology employed in the trial, the postprandial glucose excursions shown in the placebo group imply that some

patients may have required further prandial management. This suggests that the study might not have fully caught the patients' level of glucose control.[9]

The observed gastrointestinal side effects, body weight reduction, and glycemic improvement with little or no increase in insulin dose may have partially impacted blinding. As a result, it's possible that the patients and/or the researchers were able to estimate which treatment group the patients were placed in, which may have had an impact on the outcomes.[9]

Given that the double trial study was a Phase 2b trial, the sample size was quite limited, which would limit how broadly the results can be applied. 26 weeks may not have been long enough for the trial to thoroughly evaluate tirzepatide's long-term effects and safety profile. Although a randomised controlled trial is regarded as a solid study design, biases and confounding variables may still be present. There may be potential biases and restrictions in the interpretation of the results as a result of the post hoc exploratory lipidomics and metabolomics investigations that were conducted. There were no additional comparators or treatment choices included in the study, which may have limited the capacity to draw more general conclusions. The study compared tirzepatide with dulaglutide and placebo.[10]

The study's relatively small sample size—111 patients were randomly assigned—may have limited the findings' generalizability. The 12-week study time frame may not have adequately captured the long-term effects and safety profile of tirzepatide. It was challenging to determine the best dosing method because the study did not involve a direct comparison of the various tirzepatide dose-escalation regimens. The HbA1c reduction efficacy and tolerability of tirzepatide were the primary foci of the study; other significant outcomes, such as cardiovascular or weight management, were not evaluated.[11]

Future Implications

The combined results from these six important clinical trials give insight on the changing environment of tirzepatide-based diabetic mellitus treatment. The results of all these studies highlight the potential of tirzepatide as a strong therapeutic treatment for several facets of diabetes care. The studies' integration highlights the complexity of diabetes management and the potential for customised therapies, even while each trial stands alone as an useful source of information.

The necessity for additional research into tirzepatide's impact on beta-cell activity and insulin resistance is highlighted by the post hoc analysis and multiple regression analysis study.[6] Future research may explore the underlying mechanisms by which tirzepatide affects these variables, opening up new therapy possibilities for diabetes.

According to the SURPASS-4 trial, tirzepatide may be very helpful in controlling type 2 diabetes in people who have a high risk of cardiovascular disease. To evaluate the sustained effectiveness and safety of tirzepatide in this high-risk population, long-term trials are necessary. Investigations exploring its impacts on cardiovascular outcomes may also shed important light on its possible cardioprotective advantages.[7]

Tirzepatide has the potential to be used as a monotherapy for those whose conditions cannot be successfully controlled by diet and exercise alone, as shown by the SURPASS 1 trial. Future studies should examine the efficacy of monotherapy in combination with additional anti-diabetic medications and the effects of such combinations on glycemic control and long-term outcomes as monotherapy gains popularity.[8]

Data from the SURPASS 5 study on the use of subcutaneous tirzepatide as a supplement to basal insulin is very helpful. Additional research could determine whether it is compatible with additional anti-diabetic drugs besides metformin and basal insulin, advancing our understanding of its function in combination therapy.[9]

According to the research of Pirro et al. [2022], tirzepatide may have positive cardiovascular effects on the body's metabolism in addition to glycemic control. Future studies should go further into these cardiovascular effects and look into how tirzepatide affects markers of cardiovascular risk such as lipid metabolism.[10]

The study examining various tirzepatide dose-escalation regimens emphasises the significance of dosing techniques in maximising its benefits. Dosing regimens may be improved in subsequent research by taking into account aspects including effectiveness, tolerability, and long-term effects.[11]

Integrated Clinical Applications

Combining the information from these trials highlights the possibility for a clinical strategy that uses tirzepatide to control diabetes. Comprehensive therapeutic approaches might be possible by combining its effects on glucose control, weight management, cardiovascular

indicators, and beta-cell activity. The choice of optimal dose regimens and combination medications, aiming for a synergistic effect on diabetes control, could be guided by the individual patient profiles and risk factors.

RESULT

The analysis of the trial data paints a thorough picture of tirzepatide's potential as a versatile diabetes control strategy. Tirzepatide appears as a prospective therapeutic agent with a wide variety of benefits, from enhancing glycemic management and body weight to addressing beta-cell function and insulin resistance.

CONCLUSION

This in-depth examination of six important clinical studies for tirzepatide treatment of diabetes mellitus highlights the dynamic nature of diabetes therapies. Although each experiment offers unique findings, their combined ramifications move us toward a more comprehensive and individualised strategy to managing diabetes. Utilizing the potential of tirzepatide to the fullest extent, we can navigate the complex issues associated with diabetes mellitus by integrating the knowledge obtained from these trials. Our comprehension of tirzepatide's function in the treatment of diabetes will continue to be improved by additional study, long-term studies, and careful consideration of patient characteristics.

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