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LIRAGLUTIDE AND CARDIOVASCULAR OUTCOMES IN TYPE 2 DIABETES: A REVIEW

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ABSTRACT

BACKGROUND: The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown. **OBJECTIVE:** Asses the safety of Liraglutide over other oral hypoglycaemic agents in patient with Cardiovascular complications. **METHODS:** In this double-blind, placebo controlled trial, in which patients are arranged randomly into control and placebo according to their Glycated haemoglobin levels and their coexisting cardiovascular condition. Control receive liraglutide either 1.8 mg or matching placebo once daily as a subcutaneous injection in addition to standard care. The minimum planned follow-up was 42 months, with a maximum of 60 months of receiving the assigned regimen and the data were analysed for to find the confidence interval. **RESULTS:** The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group. **CONCLUSIONS:** In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

BACKGROUND

Type 2 diabetes is a complex metabolic disorder that is characterized by hyperglycemia and associated with a high risk of cardiovascular, microvascular, and other complications.

Although glycemic control is associated with reductions in the risk of microvascular complications, the macrovascular benefits of glycemic control are less certain. Furthermore, concern has been raised about the cardiovascular safety of antihyperglycemic therapies. Consequently, regulatory authorities have mandated cardiovascular safety assessments of new diabetes treatments.

Liraglutide, an analogue of human glucagon like peptide 1 (GLP-1), has been approved for the treatment of type 2 diabetes. Its efficacy in lowering glucose levels has been established, and it has been associated with slight reductions in weight and blood pressure. It has been associated with an increase in pulse rate. To assess the long-term effects of liraglutide on cardiovascular outcomes and other clinically important events, the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was initiated in 2010.

SUMMARY

It is a multicenter, double-blind, placebo-controlled trial conducted at 410 sites in 32 countries A total of 9340 patients underwent randomization from September 2010 through April 2012 and the study was conducted for a period of 4yrs. Patients with type 2 diabetes who had a glycated hemoglobin level of 7.0% or more were eligible if they an age of 50 years or more with at least one cardiovascular coexisting condition such as coronary heart disease, cerebrovascular disease, peripheral vascular disease, chronic kidney disease of stage 3 or greater, or chronic heart failure and not receive any hypoglycemic agents.

From a total of 9340 patients, 4668 patients were randomly assigned to receive liraglutide and 4672 to receive placebo. The median daily dose of liraglutide was 1.8 mg subcutaneous injection given to control in addition to standard care. But in placebo only give standard care during the trial period. The primary and exploratory analyses for the outcomes in the time-to-event analyses were based on a Cox proportional-hazards model with treatment as a covariate.

Death from cardiovascular causes occurred in fewer patients in the liraglutide group, 219 [4.7%] than in the placebo group, 278 [6.0%]. The frequencies of nonfatal myocardial infarction and nonfatal stroke were also lower in the liraglutide group than in the placebo group, but the differences were not significant.

Changes in the glycated hemoglobin values over time are shown a greater reduction in liraglutide group than the placebo with a range of 40%.

The cardiovascular risk factors including, weight loss, the systolic blood pressure show positive outcome. Even though the diastolic blood pressure, heart rate favour the placebo group.

The incidence of a composite outcome of renal microvascular complications were lower in the liraglutide group than in the placebo group. But reciprocal is seen in incidence of retinopathy were it is lower in placebo group.

The overall rates of benign or malignant neoplasms were higher in the liraglutide group than in the placebo group, but it varies. The incidence of Prostate cancer, leukaemia, acute pancreatitis, hypoglycaemia and medullary carcinoma were less in Control group. However there is a higher increase in the occurrence of pancreatic cancer, acute gall stone disease, elevation of serum amylase and lipase, and thyroid disorder than placebo. The major event that leads to permanent discontinuation of liraglutide therapy is its pertinent gastrointestinal disorders such as nausea, vomiting, diarrhoea, abdominal pain and discomfort.

CONCLUSION

In diabetes patients with cardiovascular events, it shows a greater reduction mortality and also it help to reduce the progression of risk factors than prone to such macrovascular complications. So it's a good choice for such indications. Because of its high incidence rate of adverse effects, it can only be used as a second choice of drug for diabetes. So further studies were necessary to state its indication as first line drug for diabetes.

RELEVENCE OF STUDY

Type 2 diabetes mellitus is a progressive multi-system disease in which individuals exhibit varying degrees of declining beta cell function, insulin resistance and a failure to suppress postprandial glucagon secretion. It is associated with an array of co-morbidities and potentially devastating complications. Currently available therapies do not adequately control glycaemia in the long term as they do not address the issue of declining beta cell function and do not impact positively on weight or cardiovascular concerns associated with the disease. Furthermore, such therapies often comprise complex treatment and titration regimens and can increase the risk of hypoglycaemia and undesirable effects such as oedema and weight gain.

Glucagon-like peptide-1 (GLP-1) is a naturally occurring incretin hormone with a wide range of physiological actions that make it a potent blood-glucose-lowering agent with the potential to modify the natural history of type 2 diabetes. In animal models, native GLP-1 stimulates beta cell proliferation, inhibits beta cell apoptosis and may have a number of cardiovascular and other benefits. The glucose-lowering actions of GLP-1 are glucose dependent, which limits the risk of hypoglycaemia. However, its very short half-life, consequent to its rapid metabolism by the enzyme dipeptidyl peptidase-4 (DPP-4), limits its therapeutic potential. Liraglutide is a once-daily human GLP-1 analogue with a high degree (97%) of amino-acid-sequence identity with native human GLP-1. The molecule has a half-life of 13 h making it suitable for once-daily subcutaneous administration.

Clinical data from this clinical trials demonstrate that liraglutide reduces blood glucose, bodyweight and systolic blood pressure (SBP). And it also help to reduce macro and microvascular complications of diabetes. Liraglutide is licensed for treatment of adults with type 2 diabetes mellitus in combination with metformin or a sulphonylurea in patients with insufficient glycaemic control despite maximal tolerated dose of monotherapy or with metformin or sulphonylurea or metformin and a sulphonylurea or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy. Further clinical trials were necessary to prove its indication as first line agent in Diabetes and other comorbidities.

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