GLP-1 analouges in Treatment of Type 2 Diabetes mellitus with Obesity : Liraglutide and Dulaglutide therapy in addition to SGLT-2 inhibitor and metformin treatment in Russia type 2 diabetics with Obesity: a real world retrospective observational study

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Introduction

The combination of Glucagon like Peptide Receptor Agonists (GLP-1RA) with a Sodium-glucose linked transporter inhibitor (SGLT2i) addresses many of the pathophysiological defects seen in Type 2 Diabetes (T2D), according to certain researchers. In the EDICT trial, using the strategy of treating T2D, using multiple agents addressing the pathophysiological defects of the disease (insulin resistance, beta-cell dysfunction and hyperglucagonaemia) was found to be superior to the traditional step wise approach to glycaemic control in terms of HbA1c reduction and reduction of hypoglycaemia. There have also been robust positive outcomes from the recent cardiovascular outcome trials (CVOT) with SGLT2i (empagliflozin and canagliflozin) and GLP-1 RA(liraglutide and dulaglutide), establishing cardiovascular benefits attributable to these agents . Hence there is a good scientific rationale for using them in combination.

The recent DURATION 5 study, testing the above rationale, demonstrated an additive effect on weight and systolic blood pressure reduction but not HbA1c reduction when exenatide LAR, a GLP-1 RA and dapagliflozin, a SGLT2i were used in combination as a co-initiation strategy . However multiple observational studies suggested that GLP-1 RA and SGLT2i are additive from a metabolic perspective as well, when SGLT2i was added to GLP-1 RA (sequential initiation instead of co-initiation) . This is contrary to a real world scenario where usually injectable are added only when oral drugs fail. This differing data therefore poses a conundrum for the physician as to whether to combine these drugs together or not, particularly keeping in mind that these drugs are very expensive. In a resource poor setting such as India where patients pay 'out-of-pocket', injectable therapies are usually used as a third-line agent when oral therapy fails. Hence, data on this combination mimicking a real-life setting i.e. oral therapy followed by injectable would be useful in guiding physician choices for intensification options in Type 2 diabetes.

We therefore designed this study to look into the sequential additive benefit of GLP-1 RA therapy to preexisting SGLT2i and Metformin therapy as well as comparing Dulaglutide with Liraglutide, in combination with SGLT2i and Metformin. The aim of this study is to evaluate real-life data from clinical practice using this combination of drugs and assess how the results compare with the available data from randomized controlled trials [1].

Description

A retrospective, real world observational study to evaluate the efficacy of triple-anti-hyperglycemic agent therapy namely metformin, sodium glucose co-transporter 2 Inhibitors (SGLT2i) and glucagon like peptide receptor agonists (GLP-1 RAs) for patients failing on a combination of full dose metformin 2000 mg/day and SGLT2ifor at least 3 months, was conducted in the outpatient clinics associated with two hospitals in Moscow, Russia, from May 2019 to October 2019.

After clearance from the local ethics committee (Nightingale Hospital ethics committee), the case notes of the first 30 consecutive patients who had been commenced on Metformin plus SGLT2i plus Dulaglutide, in addition to the first 30 patients who had been commenced on Metformin plus SGLT2i plus Liraglutide were collated after signing patient consent form to use their data for publication purpose. The ethics committee decided that consent of the patients was not required as this was a completely retrospective study of case notes with no intervention required.

Furthermore when the patients' data was entered into the

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database the patient could only be identified by a number; so there was no chance of the patients' confidentiality being compromised.After adequate counseling, patientswho couldaffordthis expensive combination of medications for at least 3 monthswere commenced on this therapy. The following inclusion and exclusion criteria decided by the two centres [2].

Family history of Medullary Thyroid cancer or MEN 2

Patients received treatment as per routine standard of care. All anti hypertensives, anti hyperlipidaemics and anti platelet agents and other preexisting medications (not related to diabetes) were continued as per the patients' requirements. All patients' records with respect to age, gender, height, body weight, body mass index (BMI), duration of diabetes, glycosylated hemoglobin (HbA1c), fasting plasma glucose, blood pressure and adverse effects were collected from the case note database. Blood glucose was measured by hexokinase method and HbA1c was measured by high performance liquid chromatographic (HPLC) method (Bio-RAD D-10, Bio-RAD, Hercules, CA, USA).

All 30 patients had been maintained on Liraglutide in a dose of 1.2 mg per day and all 30 patients on dulaglutide 1.5 mg dose once-weekly during the 13 weeks of the study period. Both the arms were well matched as far as baseline characteristics were concerned [3].

All 60 patients received either of the SGLT-2 Inhibitors namely dapagliflozin 10 mg/day (n =28), canagliflozin 100 mg/day (n =20), empagliflozin 10 mg/day (n =12), as per the treating physicians' decision. All patients were on Metformin 2000 mg per day. Other OADs had not been initiated [4, 5].

Conclusion

We have already accumulated more than a decade of experience in the successful use of GPP-1 receptor agonists in clinical practice. In addition to the predictable hypoglycemic effect, this class of drugs is attractive from the point of view of improving the cardiovascular prognosis. The results of thestudy strengthened the evidence base for GPP-1 receptor agonists. The use of dulaglutide reduced the risk of adverse cardiovascular events in patients with type 2 diabetes, both with confirmed atherosclerotic diseases and with risk factors for their development. Therefore, dulaglutide helps to solve the problems of primary and secondary prevention of CVD. The article is devoted to the actual problem of the medicine – the treatment of type 2 diabetes mellitus (DM). In recent years, the possibilities of therapy have significantly expanded due to the emergence of innovative classes of sugar-lowering drugs.It is known that patients with type 2 diabetes have a high risk of cardiovascular diseases development. To prevent atherosclerotic vascular complications, not only glycemia, but also other risk factors should be monitored. In particular, in type 2 diabetes, the effectiveness of endogenous incretins is reduced. It was found that glucagon-like peptide 1 (GPP-1) is one of the strongest stimulators of insulin secretion. In addition, it has protective and modulating cardiovascular effects.

Acknowledgement

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Conflict of interest

The author declares there is no conflict of interest in publishing this article.

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