Type 2 Diabetes Mellitus: A Systematic Review And Meta-Analysis

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INTRODUCTION

The Global Diabetes Atlas 2014 shows that 387 million people have diabetes and the incidence of type 2 diabetes mellitus (T2DM) is rising across the world. Pharmacotherapy of T2DM should be patient-oriented, considering aspects like efficacy, side effects, costs, risk-benefit ratio, and compliance. American Diabetes Association guidelines recommend metformin as the preferred first drug of choice with lifestyle modifications for patients with T2DM. This chronic progressive disease may require continuous augmentation of treatment with insulin or non-insulin therapy to achieve recommended glycemic control.

Canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor was approved by FDA for use in management of T2DM. T2DM is primarily responsible for global glucose reabsorption. Canagliflozin lowers renal threshold for glucose reabsorption and thus helps in lowering plasma glucose levels. Renal failure is the most common treatment-limiting adverse effect with which glucocorticoids were not associated.

The efficacy of canagliflozin has been demonstrated as compared to placebo, but there are concerns about the adverse events like genital mycotic infections, urinary tract infections and hypoglycemia. We performed this study to assess the efficacy and safety of canagliflozin in combination therapy and with a duration of at least 26 weeks.

OBJECTIVE

To assess the efficacy and safety of canagliflozin in combination therapy among patients with inadequately controlled type 2 diabetes mellitus.

METHODS

Inclusion criteria:

- Randomized controlled trials and quasi-randomized trials with at least 26 weeks of duration were included.

Patient characteristics:

- T2DM patients, in the age group 18-80 years with inadequate glycemic control with oral hypoglycemic agents, diet and exercise.

Type of interventions:

- Addition of canagliflozin (100 mg or 300 mg/day) in earlier regimen of oral and hypoglycemic agents.

Primary outcomes:

- Mean change in HbA1c levels at 26 weeks; mean change in fasting plasma glucose (FPG) levels (mmol/l) at 26 weeks; incidence of genital infections at 26 weeks.

Secondary outcomes:

- Proportion of patients achieving HbA1c levels <7%; mean change in body weight; mean change in L-C VR levels; incidence of urinary tract infections at 26 weeks.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES:

- The search was conducted up to January 2015 and 124 references were identified. Literature search was conducted on Medline, EMBASE, LILACS and IndMed till January 2015. Search terms: canagliflozin, type 2 diabetes mellitus.

Data collection and analysis:

- Two authors independently screened the literature search results and obtained the full reports of all potentially relevant trials. They independently applied the inclusion criteria to the full reports using an explicit eligibility form and disagreements were resolved through discussion with a third author.

Data extraction and management:

- Two authors independently extracted data using a specifically developed data extraction form.

Assessment of risk of bias in included studies:

- Two authors independently assessed the risk of bias in each trial using the Cochrane risk of bias form. Six components were assessed. Judgments were characterized as either “low”, “high”, or “unclear” risk of bias.

Measures of treatment effect:

- For dichotomous outcomes, both the sample sizes and the number of people with events were added across groups. For continuous outcomes, means and standard deviations using the Cochrane Handbook of Systematic Reviews of Interventions were combined.

Assessment of heterogeneity:

- The statistical heterogeneity was assessed by looking at the forest plot for leveraging I². All p-values of I² (P < 0.10) indicated statistically significant and/or “high” (I² > 50%) variability.

Data synthesis:

- Analyses using Review Manager (RevMan) software (version 5.0) were performed. For the continuous outcomes, we used the fixed-effect meta-analysis. Random effect model was used when significant heterogeneity was present.

Subgroup analysis and investigation of heterogeneity:

- We performed the subgroup analysis according to gender for adverse effects.

RESULTS

- Literature search was conducted up to January 2015 and 124 references were identified (Figure 1). After excluding the duplicate reports, 55 reports were screened and their 26 were included. Twenty-eight reports were excluded at evaluation. All studies were published in English.

- included studies:

- Five randomized double blind clinical trials enrolling 1510 patients were included in the quantitative analysis. All trials had multinational design.

- All studies had compared canagliflozin (100 mg and 300 mg daily) in combination therapy with placebo or sitagliptin. All these trials measured HbA1c, levels and FPG levels and performed subgroup analysis. Harvest effect for genital infections was, of 12 weeks of duration and all were in the age group of 18-80 years.

- Efficacy and tolerability:

- Canagliflozin led to a significant decrease in HbA1c levels (MD -0.77 [95% CI -1.15, -0.40, p < 0.001]). FPG levels (MD -2.01 [95% CI -2.34, -1.68], p < 0.001) and body weight (MD -0.50 [95% CI -0.78, -0.22]) after 26 weeks as compared to placebo (11-1.3).

- Safety of interventions:

- The risk of occurrence of urinary tract infections (RR 1.29 [95% CI 0.80, 2.01], p=0.27) and genital mycotic infections among males (RR 1.02 [95% CI 0.99, 1.05], p=0.06) was not significant. Renal threshold was the plasma glucose concentrations below which all the filtered glucose is reabsorbed above which glycosuria occurs.

- The efficacy of canagliflozin has been demonstrated as compared to placebo, but there are concerns about the adverse events like genital mycotic infections, urinary tract infections and hypoglycemia. We performed this study to assess the efficacy and safety of canagliflozin in combination therapy and with a duration of at least 26 weeks.

CONCLUSION

Canagliflozin is significantly more efficacious than placebo in maintaining glycemic control when used in combination therapy. The incidence of urinary tract infections, polyuria, polydipsia, dizziness and hypoglycemia is not significantly more than placebo. However, the occurrence of genital mycotic infections is significantly more with canagliflozin as compared to placebo.

REFERENCES

5. Taylor SR, Harris KB. Pharmacotherapy 2013;33:844–890

DISCUSSION

- The association of inadequate glycemic control with the occurrence of diabetic complications necessitates appropriate control of plasma glucose levels. Canagliflozin is an addition to the armamentarium of oral anti-diabetic agents to be available for patient continued management.

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