Study Protocol Systematic Review

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Effectiveness and safety of sotagliflozin adjuvant therapy for type 1 diabetes mellitus

A protocol for Systematic review and Meta-analysis

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Abstract

Background: Type 1 Diabetes Mellitus (T1DM) has long required insulin treatment. Sotaglifl flozin (SOTA), as a dual SGLT-1/2 inhibitor, has the potential to be the first oral antidiabetic drug (OAD) to be approved for T1DM in the US market. It is important to evaluate the effectiveness of SOTA for T1DM.

Methods: Web of Science, PubMed datebase, Cochrane Library, Embase, Clinical Trials, and CNKI will be searched to identify randomized controlled trials (RCTs) exploring SOTA adjuvant therapy for T1DM. Strict screening and quality evaluation will be performed on the obtained literature independently by 2 researchers; outcome indexes will be extracted. The bias risk of the included studies will be evaluated based on Cochrane assessment tool. Meta-analysis will be performed on the data using Revman 5.3 software.

Result: We will provide practical and targeted results assessing the efficacy and safety of SOTA for T1DM patients, to provide reference for clinical use of SOTA.

Conclusion: The stronger evidence about the efficacy and safety of SOTA for T1DM patients will be provided for clinicians.

Trial registration number: PROSPERO CRD42019133099.

Abbreviations: CI = confidence interval, CNKI = China National Knowledge Infrastructure, CSII = continuous subcutaneous insulin injection, DKA = diabetic ketoacidosis, HbAlc = glycosylated hemoglobin, MD = mean difference, MDIs = multiple daily injections, OAD = oral antidiabetic drug, PROSPERO = international prospective register of systematic reviews, RCTs = Randomized Controlled Trials, RR = relative risk, SOTA = Sotagliflozin, T1DM = Type 1 Diabetes Mellitus, T2DM = Type 2 Diabetes Mellitus, TDD = total daily insulin dose.

Keywords: meta-analysis, randomized controlled trials, SGLT-1 inhibitors, SGLT-2 inhibitors, sotagliflozin, type 1 diabetes mellitus

1. Introduction

Type 1 diabetes mellitus, or insulin-dependent diabetes, is most common in children and adolescents, affecting millions of people worldwide.[1] Owing to insufficient insulin production, patients have to use multiple daily injections (MDIs) of insulin or continuous subcutaneous insulin injection (CSII); otherwise, blood glucose cannot be well controlled.[2] The incidence of T1DM is much lower than that of T2DM, but T1DM is more dangerous. Individuals with T1DM are prone to serious complications that can sometimes be life-threatening such as severe hypoglycemia, hypertonic coma, diabetic ketoacidosis, etc.[3] For the treatment of T1DM, there are few noninsulin-assisted therapies; sodium-dependent glucose transporter-2 (SGLT-2) inhibitors are one of the popular topics in the research of diabetes drugs in recent years.[4] SGLT-2 regulates blood glucose through the excretion function of the kidneys in addition to the metabolic pathway of glucose in the body by means of increasing the excretion of glucose by the kidneys.[5] Sotagliflozin is a novel SGLT-1/ SGLT-2 dual inhibitor. Relying on its unique hypoglycemic mechanism, it reduces the absorption of glucose in the gastrointestinal tract by inhibiting SGLT-1 and increases the excretion of glucose by the kidneys by inhibiting SGLT-2.[6] Studies have found that SOTA can not only treat T2DM but can also treat T1DM.[7] Currently, SOTA has completed phase iii clinical trials (inTandem1, inTandem2, inTandem3).[8] The purpose of this meta-analysis is to analyze the therapeutic effect and safety of SOTA on T1DM, thereby providing evidence for the treatment of T1DM by SOTA.

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2. Methods

2.1. Design and registration

A meta-analysis will be conducted to evaluate the effectiveness and safety of SOTA adjuvant therapy for T1DM. This protocol has been registered on the international prospective register of systematic reviews (PROSPERO), registration number: CRD42019133099 (https://www.crd.york.ac.uk/PROSPERO). No ethical approval is required since this study used data that were already in the public domain.

2.2. Study selection

2.2.1. Study type. Randomized Controlled Trials (RCTs).

2.2.2. Study object. Type 1 diabetic patients who rely on insulin to control their glucose using MDIs or CSII to inject insulin, excluding individuals with other serious underlying diseases.

2.2.3. Intervening measure. Patients received treatment for a period of time to stabilize their blood glucose and glycosylated hemoglobin (HbAlc) prior to the experiment. In the case of normal insulin therapy, SOTA tablets or placebo should be taken once a day.

2.2.4. Outcome indicator. The following outcomes will be assessed compared with the effects of the placebo:

(1) differences in HbAlc,
(2) differences in the total daily insulin dose (TDD),
(3) differences in weight,
(4) differences in fasting blood glucose,
(5) differences in 2-hour postprandial blood glucose,
(6) differences in the rate of well-controlled diabetes (HbAlc < 7 after the end of the study, and no serious complications),
(7) differences in the probability of severe hypoglycemia,
(8) differences in the probability of diabetic ketoacidosis (DKA),
(9) differences in the probability of genital mycotic infections, and
(10) differences in the probability of urinary tract infections.

2.2.5. Exclusion criteria. Literature whose data cannot be extracted or utilized, literature on animal experiments, literature reviews, etc.

2.3. Data sources and searches

We will search English and Chinese language publications through July 2019 using the following databases: Web of Science, PubMed, Cochrane Library, Embase, Clinical Trails, and the China National Knowledge Infrastructure (CNKI). Search terms were "sotagliflozin", "Type 1 Diabetes Mellitus", "T1DM", "LX4211" and so on. Here, we use the PubMed database as an example (see Fig. 1).

2.4. Study screening, data extraction and risk assessment of bias

Data will be collected independently by 2 researchers. The unqualified studies will be eliminated, and the qualified ones will be screened out after reading the title, abstract and full text. Then, the research data were extracted and checked, and disagreements were discussed or a decision was made by the author. The extracted data included the following:

1. basic information of the study, including title, author and year of publication;
2. characteristics of the included study, consisting of study duration, sample size of test group and control group, and intervention measures;
3. outcome indicators and data included; and
4. collection of risk assessment elements of bias.

The risk of bias in the included studies will be assessed by using the RCT bias risk assessment tool recommended in the Cochrane Handbook for Systematic Reviews of Interventions (5.1.0).

2.5. Statistical analysis

Revman 5.3 software will be used for the meta-analysis. The dichotomous variables will be relative risk (RR) as effect indicators, the continuous variables are expressed as mean difference (MD) as effect indicators, and the estimated value and 95% confidence interval (CI) will be included as effect analysis statistics. A heterogeneity test will be conducted with the results of each study. The fixed effect model will be used for analysis if there was no statistical heterogeneity between the results ($I^2 \leq 50\%$). The sources of heterogeneity need to be analyzed if there was statistical heterogeneity between the results ($I^2 > 50\%$). After excluding the influence of obvious clinical heterogeneity, the random effect model will used for analysis. The significance level is set $\alpha = 0.05$.

2.6. Subgroup analysis

Subgroups will be established based on difference of oral dose (400 mg/day, 200 mg/day).

2.7. Assessment of publication bias

If more than 10 articles are available for quantitative analysis, we will generate funnel plots to assess publication bias. A symmetrical distribution of funnel plot data indicates that there is no publication bias, otherwise, we will analyze the possible cause and give reasonable interpretation for asymmetric funnel plots.

2.8. Confidence in cumulative evidence

GRADE system will be used for assessing the quality of our evidence. According to the grading system, the level of evidence will be rated high, moderate, low, and very low.[9]

3. Discussion

SOTA is a new generation SGLT inhibitor that can act on both SGLT-1 and SGLT-2. SGLT-1 is mainly expressed in the small intestine and kidneys and is responsible for transporting glucose and galactose in the small intestine and reabsorbing glucose in the proximal convoluted tubules. SGLT-2 is specifically located in the proximal convoluted tubules of the kidney and is responsible for the renal reabsorption of glucose in the urine and is responsible for approximately 90% of glucose reabsorption.[10]

At present, the therapeutic effect of SOTA on TIDM is satisfactory.[11] Literature supports that SOTA can reduce the HbAlc of T1DM patients, reduce the use of insulin does, and

#1
"(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(methylthio)tetrahydro-2H-pyran-3,4,5-triol" [Supplementary Concept]
#2 sotagliflozin OR LX4211 OR LX-4211
#3 #1 OR #2
#4 "Diabetes Mellitus, Type 1/therapy"[Mesh]
#5 Type 1 Diabetes Mellitus[Title/Abstract] OR Diabetes Mellitus, Type I[Title/Abstract] OR Type 1 Diabetes[Title/Abstract] OR Diabetes, Type 1[Title/Abstract] OR Diabetes Mellitus, Ketosis-Prone[Title/Abstract] OR Diabetes Mellitus, Ketosis Prone[Title/Abstract] OR Ketosis-Prone Diabetes Mellitus[Title/Abstract] OR Diabetes, Autoimmune[Title/Abstract] OR Autoimmune Diabetes[Title/Abstract] OR Diabetes Mellitus, Juvenile-Onset[Title/Abstract] OR Diabetes Mellitus, Juvenile Onset[Title/Abstract] OR Juvenile-Onset Diabetes Mellitus[Title/Abstract] OR Juvenile-Onset Diabetes[Title/Abstract] OR Diabetes, Juvenile-Onset[Title/Abstract] OR Juvenile Onset Diabetes[Title/Abstract] OR Diabetes Mellitus, Insulin-Dependent[Title/Abstract] OR Diabetes Mellitus, Insulin Dependent[Title/Abstract] OR Insulin-Dependent Diabetes Mellitus[Title/Abstract] OR IDDM[Title/Abstract] OR Diabetes Mellitus, Insulin-Dependent, 1[Title/Abstract] OR Insulin-Dependent Diabetes Mellitus 1[Title/Abstract] OR Insulin Dependent Diabetes Mellitus 1[Title/Abstract] OR Diabetes Mellitus, Brittle[Title/Abstract] OR Brittle Diabetes Mellitus[Title/Abstract] OR Brittle Diabetes Mellitus[Title/Abstract] OR Diabetes Mellitus, Sudden Onset[Title/Abstract] OR Sudden-Onset Diabetes Mellitus[Title/Abstract]
#6 #4 OR #5
#7 #3 AND #6

Figure 1. PubMed database retrieval strategy.

bring more patients to the standard.[12,13] However, SOTA may cause kinds of serious adverse events.[14] Among the common adverse reactions are urinary tract infection and genital infection. Meanwhile, SOTA may also increase the risk of diabetic ketoacidosis (DKA),[15] although some studies believe that these data are not reliable.[16] The comparison of benefits and losses in the treatment of TIDM by SOTA is still controversial.

This study will conduct a meta-analysis of related RCTs, and provide evidence on the efficacy and safety of SOTA in T1DM treatment, so as to better guide clinical practice.

Author contributions

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