PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Investigating the effect of verapamil on preservation of beta-cell function in adults with newly diagnosed type 1 diabetes mellitus (Ver-A-T1D): protocol for a randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial

Authors

Wych, Julie; Brunner, Martina; Stenson, Rachel; Chmura , Piotr Jaroslaw; Danne, Thomas; Mander, Adrian Paul; Mathieu, Chantal; Dayan, Colin; Pieber, Thomas R.

VERSION 1 - REVIEW

Reviewer **1**

Name **Cho, Kyu Yong**

Affiliation **Hokkaido University, Division of Diabetes and Obesity, Faculty of Medicine and Graduate School of Medicine**

Date **13-Aug-2024**

COI **None.**

Dear Authors,

I was pleased to review your submitted protocol for an RCT to investigate whether verapamil can counteract the decline in endogenous insulin secretion in adult patients with newly diagnosed T1DM. This is clinically intriguing and, given its relative affordability, could potentially contribute to future therapeutic approaches.

The protocol is well designed and incorporates relevant considerations for preventing or suppressing the progression of T1DM in recently published papers. The administration of verapamil itself is not inappropriate, given its use in studies of pediatric T1DM and reports in adults.

I have no specific questions or comments at this time. It is interesting to consider why verapamil has not been shown off to have this effect in daily use, given its widespread use in cardiovascular disease. However, this is simply my observation and does not require an answer.

Reviewer	**2**
Name	**Gastaldi, Giacomo**
Affiliation Medicine	**Geneva University Hospitals, Geneva, Switzerland.,**
Date	**18-Aug-2024**
COI	**I have no competing interests.**

A Randomised, Double-blind, Placebo Controlled, Parallel Group, Multi-centre Trial in Adult Subjects with Newly Diagnosed Type 1 Diabetes Mellitus Investigating the Effect of Verapamil on Preservation of Beta-cell Function (Ver-A- T1D).

Ver-A-T1D is a randomized, double-blind, placebo-controlled, multi-center Trial that addresses a key question about early T1D management. Shall we consider Verapamil as an adjunct treatment to insulin at the diagnostic phase ?

Verapamil is an old calcium blocker that lowers TXNIP expression on beta-cell wall. It has shown enthusiastic results on beta cell preservation in case of mouse models of diabetes and human auto-immune diabetes. The postulated mechanism is the capacity to prevent beta-cell destruction. Few side effects have been observed in human studies and verapamil can be easily taken (once a day at 24h intervals).

It is therefore of uttermost importance to determine if Verapamil as an adjunct treatment of insulin can improve early T1D management.

The protocol is concise, clear, well-structured and with high standards of written English.

The methodology is clear. The research protocol components are described with the utmost care.

I have only minor suggestions for the authors:

- To extend the age for inclusion (45 years old is quite young)

- To extend to 8 weeks of the date of first insulin injection. It was 3 months in the Ovalle et al study.

- To quantify “tobacco consumption” and “alcohol intake” in the list of visit items due to their impact on insulin needs and to add them in table 3 (assessments at study visits).

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1
Dr. Kyu Yong Cho, Hokkaido University
Comments to the Author:

Dear Authors,
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The protocol is well designed and incorporates relevant considerations for preventing or suppressing the progression of T1DM in recently published papers. The administration of verapamil itself is not inappropriate, given its use in studies of pediatric T1DM and reports in adults.
I have no specific questions or comments at this time. It is interesting to consider why verapamil has not been shown off to have this effect in daily use, given its widespread use in cardiovascular disease. However, this is simply my observation and does not require an answer.
We thank Dr Kyu Yong Cho for his time to review our manuscript and positive comments.

Reviewer: 2
Dr. Giacomo Gastaldi, Geneva University Hospitals, Geneva, Switzerland., Hirslanden Clinique des Grangettes

Comments to the Author:
A Randomised, Double-blind, Placebo Controlled, Parallel Group, Multi-centre Trial in Adult Subjects with Newly Diagnosed Type 1 Diabetes Mellitus Investigating the Effect of Verapamil on Preservation of Beta-cell Function (Ver-A- T1D).
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- To quantify “tobacco consumption” and “alcohol intake” in the list of visit items due to their impact on insulin needs and to add them in table 3 (assessments at study visits).
We thank Dr Giacomo Gastaldi for his time to review our manuscript and insightful comments. Given the trial has now closed to recruitment it is not possible to make the three changes suggested, but these points will be taken forward in any future trials and we appreciate your careful consideration of the trial design.