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Effects of baricitinib, empagliflozin, linagliptin and telmisartan on CAN measures in type 1 diabetes: a sub-study of ROTATE-1 trial

Aim: The first objective of this study was to assess the effects of baricitinib, empagliflozin, linagliptin and telmisartan on standard deviation of the normal-normal intervals (SDNN) in participants with type 1 diabetes (T1D). The secondary outcomes were to evaluate changes on time and frequency domain indices of Heart Rate Variability (HRV) and on three cardiovascular autonomic reflex tests (CARTs).

Methods: Participants with T1D, UACR between 30 and 500 mg/g and eGFR>45 mL/min/1.73m^2, were enrolled in ROTATE-1 trial and received 4-week treatment in casual order with telmisartan 80 mg, empagliflozin 10 mg, linagliptin 5 mg, and baricitinib 2 mg to evaluate responses in UACR reduction. A long washout period of 4 weeks was incorporated between the treatment periods. At the end of the study period, each participant was re-exposed for other 4 weeks on his best-response treatment to confirm UACR response. In this substudy, the same participants underwent CAN evaluation using HRV indices and CARTs at baseline, after 4-weeks treatment (baricitinib, empagliflozin, linagliptin, telmisartan), and in conclusion with best drugs for SDNN by using Vagus Device and a five-min resting ECG recording.

Results: 26 participants (61±12 years, 70% male, 50% with CAN at randomization). Mean SDNN did not change after treatment with baricitinib, empagliflozin, linagliptin or telmisartan (p>0.59). With telmisartan, HF increased by 75% (p=0.01) with significant difference when compared with baricitinib and linagliptin but not with empagliflozin. With linagliptin, the Valsalva ratio decreased by 5% (p=0.04) with significant difference when compared with telmisartan but not with linagliptin or empagliflozin. Individual's best drug for SDNN was baricitinib (n=7), empagliflozin (n=7), linagliptin (n=3), telmisartan (n=7), missing (n=2). Compared with the best drug for albuminuria, there were 7 matches (27%). When considering individual best drug for SDNN, authors found a 31% increase in SDNN measures (p<0.01 vs baseline and p<0.05 vs other drugs).

C*onclusions*: Primary outcome of this trial was not achieved but considering a tailored-treatment approach, significant results on all time and frequency domain HRV indices were reached using individual best drug for SDNN. Individual's responses are now heterogeneous but with further investigations, it could be possible to select between different drugs considering individual characteristics to identify the best response in CAN measures.

Comments. This Research Letter shows the results of a substudy of ROTATE-1, a randomized, open-label, exploratory, crossover trial whose aim was to determine the individual response of four albuminuria-lowering drug classes in type 1 diabetes (Curovic VR et al *Diabetes Care. 2023;46(3):593-601*). This substudy uses the same innovative rotational approach to determine the effects of single-use of four different drugs on CAN measures. Authors have not already considered possible effects of combination therapies and this aspect could be interesting to investigate in a larger population.

Considering results on CAN measures, the study is not entirely conclusive but given the lack of available therapy for this complication, these findings could represent a first step to establish a possible individualized therapeutic approach.

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Reference. Laursen JC, Rotbain Curovic V, Kroonen MYAM, Jongs N, Zobel EH, Hansen TW, Frimodt-Møller M, Laverman GD, Kooy A, Persson F, Heerspink HJL, Hansen CS, Rossing P. Effects of baricitinib, empagliflozin, linagliptin and telmisartan on cardiovascular autonomic neuropathy in type 1 diabetes: An exploratory, randomized, open-label, crossover trial. Diabetes Obes Metab. 2023 Jun 29. doi: 10.1111/dom.15180. Epub ahead of print. PMID: 37385968.

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