Sandwell and West Birmingham Hospitals NHS Trust

1105-P
The Effect of Canagliflozin on Alanine Aminotransferase (ALT) Levels: Data from the Association of British Clinical Diabetologists (ABCD) Nationwide Audit Programme

Thomas SJ Crabtree, Suzanne M Phillips, Alison Evans, Devesh K Sennik, Anurita Rohilla, Alex Bickerton, Ken H Darzy, Peter Winocour, Melissa L Cull, Anna Strelecka, Rejeev P Raghavan, Ian W Gallen, Mahender Yadagiri, Robert EJ Ryder

with thanks to all ABCD audit contributors

ABCD
Association of British Clinical Diabetologists

Disclosures

- TSJC has received an educational grant from Novo Nordisk

The ABCD audit programme…

- Launched in **January 2016**
- The second sodium glucose link transporter 2 inhibitor (SGLT2) programme to launch in the UK

- Aims:
  - To collect anonymised routine clinical data for patients taking **Canagliflozin** in order to provide real-world data on it's use

- Data input:
  - Primary care – via the online audit tool
  - Primary care – via data submitted by clinical commissioning groups
  - Secondary care – via the online audit tool

What we know so far…

- Evidence from the ABCD audit programme for other members of the class suggests SGLT-2 inhibitor use is associated with significant reductions alanine aminotransferase (ALT) levels
  - ALT has been demonstrated to correlate with liver inflammation[1]
  - Although fairly specific for non-alcoholic fatty liver disease is not sensitive[1,2]

- Evidence from trials:
  - Small scale trials showed improvements in transient elastography ("Fibroscan" or equivalent) and liver biochemistry with dapagliflozin[3]
  - Evidence from Korea that SGLT2 + Metformin superior to Metformin + DPP+4 inhibitors[4]
  - Large Canadian real-world dataset showing reductions in ALT with SGLT2 inhibitor use, with reductions greatest in those with the highest baseline levels and independent of weight loss[5]

Methods

- Data were extracted from the ABCD audit tool
- Those with baseline and follow—up ALT levels at 12 months (6-18months) were included

- Those included (n=730) were stratified into groups using recognised gender specific reference ranges[6] as follows:
  - Female, normal ALT (≤19U/L)
  - Female, raised ALT (>19U/L)
  - Male, normal ALT (≤30U/L)
  - Male, raised ALT (>30U/L)

- Data were analysed using Stata 16
  - ALT followed a non-parametric distribution therefore Wilcoxon Signed Rank tests and Kruskal-Wallis (non-parametric ANOVA) were used

Baseline characteristics

Characteristic		Total n=730	Male, normal ALT	Male, raised ALT	Female, normal ALT	Female, raised ALT
Age, years ± SD		61.3 ± 10.8	64.2 ± 10.9	58.7 ± 9.6	64.4 ± 12.4	60 ± 10.2
Male, %		61.6	n/a	n/a	n/a	n/a
Median diabetes duration, year (IQR)		6.7 (1.6-11.8)	8.2 (1.2-12.8)	5.4 (1.4-10.9)	9 (2.6-14.2)	6.1 (1.6-10.5)
Mean Hba1C,	% ± SD	8.89 ± 1.56	8.83 ± 1.55	9.06 ± 1.61	8.47 ± 1.32	8.93 ± 1.58
	mmol/mol ± SD	73.6 ± 17.0	73.0 ± 16.9	75.5 ± 17.6	69.1 ± 14.4	74.1 ± 17.2
Mean BMI, kg/m2 ± SD		32.6 ± 6.5	31 ± 6.1	33.4 ± 5.9	32.4 ± 8.2	33.4 ± 6.6
Mean weight, kg ± SD		97.6 ± 22.2	98.9 ± 21.3	106.6 ± 20.8	87 ± 22.6	89.9 ± 19.9
Median ALT, U/L (IQR)		28 (20-39)	23 (18-26)	42 (35-55)	15 (14-17)	27 (23-37)
Mean eGFR, ml/min		76.7 ± 13.9	74.5 ± 14.1	80.1 ± 13.3	73.1 ± 14.3	76.9 ± 13.3
Mean Systolic BP, mmHg ± SD		133 ± 14.7	131 ± 12.2	135 ± 16.2	131 ± 16.7	132 ± 14
Mean Diastolic BP, mmHg ± SD		77.5 ± 9.5	76 ± 8.9	80 ± 9.3	74 ± 10.5	77 ± 8.9

ALT, alanine aminotransferase; BMI, body mass index; BP, blood pressure

eGFR, estimated glomerular filtration rate

IQR, interquartile range; SD, standard deviation

Results

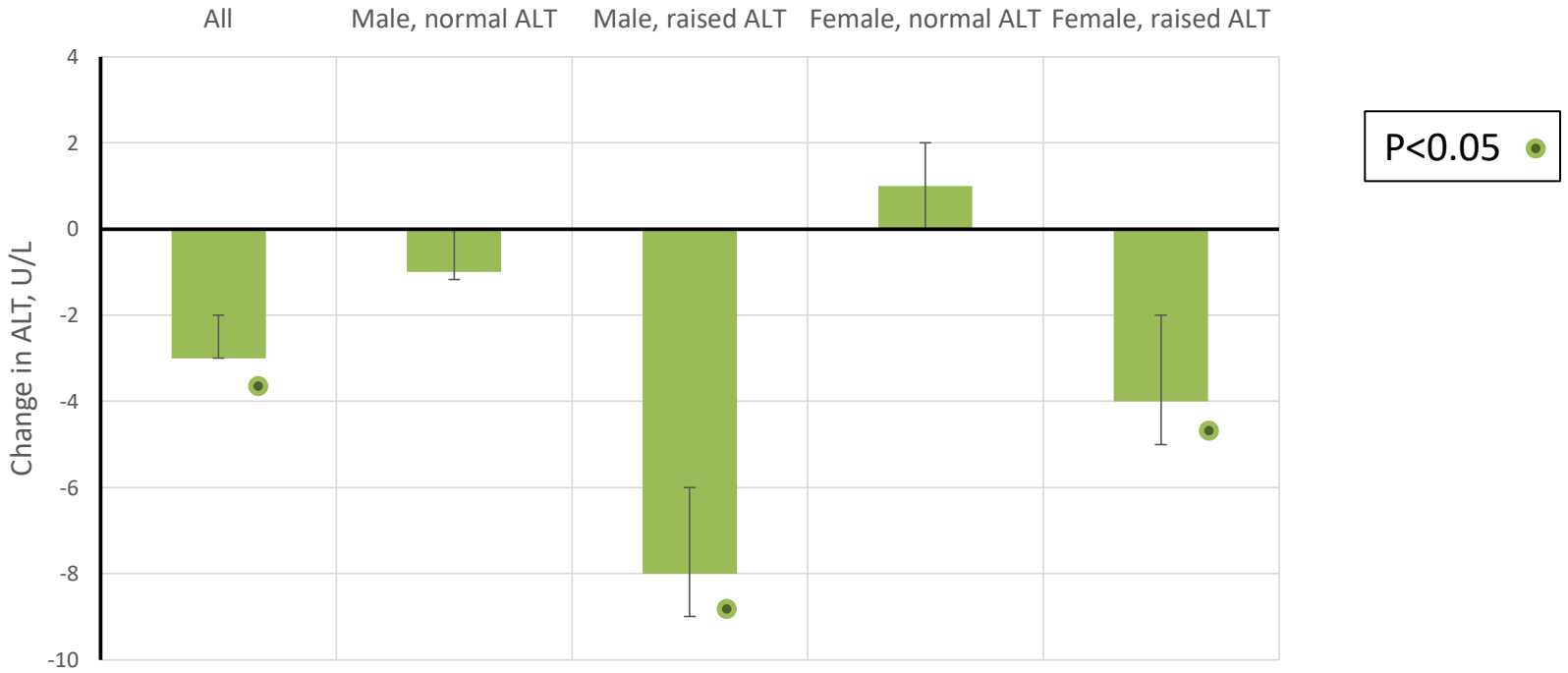
- Significant reductions in ALT were noted across the entire population
  - When stratified by gender and raised/normal:
    - Those with normal baseline ALT measurements did not have statistically significant changes in ALT
    - Those with elevated ALT levels at baseline had statistically significant decreases in ALT

- Regression analysis:
  - Elevated levels of ALT at baseline predicted larger decreases in ALT at follow-up (R 0.38, $P<0.0001$)
  - Due to multiplicity of measurements not other baseline factors predicted ALT decrease with dapagliflozin in this cohort

- Change in weight showed no correlation with change in ALT, suggesting a possible weight-loss independent mechanism of ALT reduction ($P=0.68$)

Figure

Changes in ALT from baseline following dapagliflozin treatment in patients from the ABCD audit program, error bars showing CI 95% at P<0.05 level. Difference between stratified groups P<0.0001 (Kruskal Wallis)



Discussion

- Canagliflozin use is associated with statistically significant reductions in ALT
- These reductions are of a significantly great magnitude in those with raised ALT levels at baseline
- Reductions in ALT appear to be independent of weight-loss
- Limitations: unable to correct for some confounders including alcohol use
- Further work: to include multiple parameters and assess the impact of SGLT2s at improving Fib4 score or similar validated NAFLD scoring system

Thank you for taking the time to read this presentation

References

1. Suzuki A, Lymp J, St Sauver J, Angulo P, Lindor K. Values and limitations of serum aminotransferases in clinical trials of nonalcoholic steatohepatitis. Liver Int 2006;26(10):1209–16.
2. Rinella ME. Nonalcoholic fatty liver disease: a systematic review. JAMA 2015;313(22):2263–73. https://doi.org/10.1001/jama.2015.5370 5 https://doi.org/10.1111/j.1478-3231. 2006.01362.x 8
3. Shimizu M, Suzuki K, Kato K, et al. Evaluation of the effects of dapagliflozin, a sodium-glucose co-transporter-2 inhibitor, on hepatic steatosis and fibrosis using transient elastography in patients with type 2 diabetes and non- alcoholic fatty liver disease. Diabetes Obes Metab 2019;21(2):285–92. https://doi.org/10.1111/dom.13520
4. Choi DH, Jung CH, Mok JO, Kim CH, Kang SK, Kim BY. Effect of dapagliflozin on alanine aminotransferase improvement in type 2 diabetes mellitus with non-alcoholic fatty liver disease. Endocrinol Metab (Seoul) 2018;33(3):387–94. https://doi.org/10.3803/EnM.2018.33.3.387
5. Bajaj HS, Brown RE, Bhullar L, Sohi N, Kalra S, Aronson R. SGLT2 inhibitors and incretin agents: associations with alanine aminotransferase activity in type 2 diabetes. Diabetes Metab 2018;44(6):493–9. https://doi.org/ 10.1016/j.diabet.2018.08.001
6. Prati D, Taioli E, Zanella A, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;137:1–9.