Does dapagliflozin affect the metabolic response in patients with elevated alanine aminotransferase (ALT) and Type 2 diabetes?: the Association of British Clinical Diabetologists (ABCD) nationwide dapagliflozin audit

M.Yadagiri[1], P S Gupta[1], M L Cull[1], D Price[2], V Oguntolu[3], K Imtiaz[4], D Barnes[5], A Nugent[6], A Robinson[7], I W Gallen[8], K A Adamson[9], R E J Ryder[1], the ABCD nationwide dapagliflozin audit contributors[10]

[(1)]Sandwell and West Birmingham NHS Trust Hospital, Birmingham, UK;[(2)]Abertawe Bro Morgannwg University NHS Trust, Swansea, UK;[(3)]The Royal Wolverhampton NHS Trust, Wolverhampton, UK;[(4)]East Lancashire Hospitals NHS Trust, Chorley, UK; [(5)] Maidstone And Tunbridge Wells NHS Trust, Tunbridge Wells, UK; [(6)] Belfast City Hospital, Belfast, UK;[(7)] Royal United Bath Hospital, Bath,UK;[(8)]Berkshire West CCG, Reading, UK;[(9)] West Lothian NHS Trust, Livingston, UK;[(10)] Various Hospitals and health centres, various towns, UK

Aims

To evaluate the effect of :

(1) Dapagliflozin on metabolic response in type 2 diabetes patients with elevated alanine aminotransferase(ALT)

(2) Baseline ALT on metabolic response to dapagliflozin

Background

Liver disease is common in type 2 diabetes, mainly due to the high prevalence of non-alcoholic fatty liver disease(NAFLD). ALT levels tends to be elevated in those with more fatty liver and tends to fall when liver fat reduces.

Methods

Anonymised patient data was collected by an online password protected questionnaire contributed by practicing clinicians from both acute hospitals and GP surgeries in UK.

Only those with both baseline and follow up ALT values within a median of 6.0(4.0-9.0) months were included and excluded those who had bariatric surgery. Depending on baseline ALT, they were categorized into three groups: ALT<30U/l, ALT30-50U/l and ALT>50U/l.

Descriptive statistical analysis was performed. Changes in ALT, weight and HbA1c over time were calculated within and between ALT groups with Wilcoxon signed rank test. And spearman's correlation was used to derive the relationship between baseline variables including ALT and the metabolic response.

Results: Baseline Characteristics

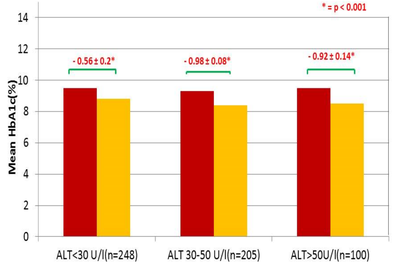
n(%)	ALT<30U/l n=250 (44.8)	ALT 30-50U/l n=209 (37.1)	ALT>50U/l n=101(18.1)	P value	Vs Combined Clinical Trials-Dapagliflozin
Males(%)	49.2	65.2	66.3	<0.001	
Age(yrs)	58.9±10.1	57.1±10.3	55.9±8.5	<0.001	
Diabetes of Duration(yrs)	12.0(7.0-17.0)	9.0(3.0-15.0)	6.0(4.0-12.5)	<0.01	
HbA1c(mmol)	79.2±16.9	78.1±17.5	79.2±16.7	<0.001	
HbA1c(%)	9.4±1.5	9.3±1.3	9.4±1.3	<0.001	7.96
BMI(Kg/m*)	35.8±8.4	36.2±9.9	35.7±6.7	<0.01	32.16
Weight(Kg)	99.2±21.9	103.3±24.1	103.1±19.6	<0.01	
ALT(U/l)*	21.0(17.0-25.0)	37.0(33.0-41.0)	63.0(57.0-73.5)	n/a	

In this ABCD nationwide audit of dapagliflozin in real clinical use, 147 contributors from 57 centres all over UK submitted data on 1725 patients. Of these, we have included 558 into this analysis with both a baseline and at least one ALT follow up measurement and categorized these into three groups.

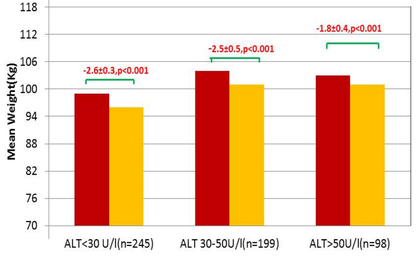
Baseline characteristics {(expressed as mean ± SD and*median (interquartile range)} shows that in higher ALT groups, there were more males who were much younger with a lower duration of type 2 diabetes.

In real clinical use, patients are more heavier and with much more poorer glycaemic control than in combined clinical trials of dapagliflozin.

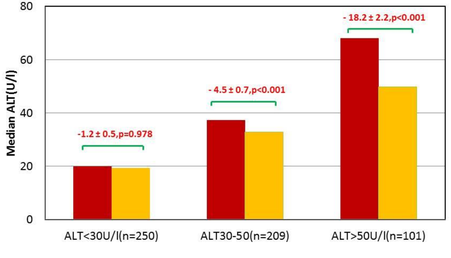
HbA1c Response to Dapagliflozin



Weight Response to Dapagliflozin



ALT Response to Dapagliflozin



Correlation

Change in ALT correlation with:	Spearman's Rank Correlation coefficient *	P-value
Change in HbA1c	0.1	<0.05
Change in weight	- 0.06	0.18
Baseline ALT	0.5	<0.01

Discussion

Apart from a positive impact on glycaemic control and weight, dapagliflozin has a clinically and statistically significant response on ALT reduction in type 2 diabetes patients with a high baseline ALT>30U/l. As discussed earlier, it may well be that those with higher ALT's are those with more fatty livers. It is possible that this is indicating some reduction in liver fat in those with high liver fat. Baseline ALT correlated with ALT fall, weakly with HbA1c fall and did not correlate with weight fall.

This result may have implications regarding the insulin resistance associated with fatty liver and non-alcoholic fatty liver disease.

Acknowledgement

We thank all the nationwide contributors for submitting data of patients on dapagliflozin.

The ABCD nationwide dapagliflozin audit is supported by an unrestricted grant from Astra Zeneca. The audit was independently initiated and performed by ABCD and the authors remained independent in the analysis and writing of this report.