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Liver Function Tests in F508del Homozygous Paediatric Patients with Cystic Fibrosis Taking Lumacaftor/Ivacaftor Combination Therapy

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Abstract

Aims
In clinical trials, elevated liver transaminase levels in patients taking lumacaftor/ivacaftor therapy were reported. Our aim was to assess in clinical practice, whether F508del homozygous paediatric CF patients had a derangement of liver functions tests (LFTs) while on lumacaftor/ivacaftor therapy.

Methods
A retrospective chart review audit in a single CF centre.

Results
Thirty-nine (43%) patients out of 91 CF clinic patients met criteria to start treatment. We observed a statistically significant decrease in ALT, ALP, GGT and total bilirubin levels, and no change in AST levels during first 3 months of treatment. In two patients (5%) AST levels rose to greater than three times the upper limit of normal (ULN) during treatment, however, these levels then decreased with continued use. A similar trend of improved LFTs was seen in a subgroup of patients with pre-existing liver disease (6/15.4% of patients). No patients died or experienced hepatic encephalopathy.

Conclusion
Our results were unexpected and encouraging. They suggest that, although the clinical trials report a risk of derangement of LFTs, the risk appears to be low.

Keywords
Cystic fibrosis, liver disease, CFTR modulators, adverse events, therapy

Introduction

Cystic Fibrosis (CF) is a genetic, multi-system condition, with progressive lung disease resulting in early death[1]. Ireland has the highest incidence of CF in the world and one in 19 people carry a defective gene[2]. The most common Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) variant is F508del and in Ireland 55% of patients are F508del homozygous[2].

The combination of lumacaftor (a CFTR corrector) and ivacaftor (a CFTR potentiator) is licensed for the treatment of patients with CF who are homozygous for the F508del mutation. It became available in Ireland to patients 12 years and older in 2017, and to patients aged 6-11 years in early 2018. Prior to this, select patients, with advanced disease, were able to receive the drug on a "managed access programme" (MAP). In clinical trials, serious adverse reactions related to elevated liver transaminase levels were reported [3-5]. Consequently, it is recommended that serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin are monitored prior to initiating the drug, and every three months for the first year of treatment, then annually. In patients with raised LFTs at baseline, more frequent monitoring is recommended, but not defined. Patients with significant liver disease were excluded from the original clinical trials[3-5]**.** The aim of this study was to ascertain if F508del homozygous paediatric CF patients had a derangement of LFTs while on lumacaftor/ivacaftor therapy in the first year after treatment, in the "real world" setting of a paediatric CF clinic.

Methods

This study was conducted at the University Hospital Limerick (UHL) Paediatric CF unit. This is a retrospective chart review performed as an audit process in July 2018. Homozygous F508del patients attending the unit, who fulfilled the criteria to start lumacaftor/ivacaftor combination therapy, were identified from the clinic patient database, and their medical notes were reviewed.

The following variables were extracted from the medical records for each patient: date of birth, gender, date and age at initiation of treatment, cohort (12 years and older, 6-11 years old), dose cohort. Patients aged 12 years and older started on the higher dose (lumacaftor 200mg/ ivacaftor 125mg, two tablets twice daily) and patients aged 6-11 years started on the lower dose (lumacaftor 100mg/ivacaftor 125mg two tablets twice daily). In an effort to reduce the risk of chest discomfort and transient decrease in lung function at the initiation of treatment, we instigated a local policy of starting with one tablet twice daily for the first week, increasing to two tablets in the morning, and one in the evening for the second week, before increasing to the final, steady state dosing of two tablets twice daily from the third week onwards. The LFTs included: AST, ALT, alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and bilirubin. Results at baseline, three, six, nine and 12 months of treatment were extracted. At the time of our study, none of our patients had been on treatment for longer than a year. To aid comparisons across time, blood levels taken within six weeks of a set time point were included in that time point (ie. three months +/- six weeks).

Patients with pre-existing CF liver disease (CFLD) were also identified. These patients had been assessed for, and diagnosed with, CFLD at the national CFLD specialist centre, at Our Lady's Children's Hospital Crumlin (OLCHC), Dublin. This sub-group had more frequent monitoring in the initial weeks after initiation of treatment. As the medication product leaflet does not describe a monitoring system for patients with CFLD, a local protocol was devised with the following time intervals: at baseline, then at the two, four, six and 12 weeks, and, if stable, patients were followed as per the standard recommendations of every third month, until 12 months and then annually.

Data was analyzed using SPSS. Excel was used to graph the data. Distribution was determined using a combination of histogram and box-plot analysis and the Shapiro-Wilk test for normality (p-value <0.05). If the data had a skewed distribution, then it was compared using the Wilcoxon signed-rank non-parametric test for related data, with each patient compared to their previous level. If the data were normally distributed, then a paired samples t-test was used to compare the data. A p-value <0.05 was deemed statistically significant. The UHL Audit Office reviewed the protocol and endorsed the study.

Results

From a total clinic of 91 paediatric patients with CF we identified 42 (46%) who were F508del homozygous and over six years of age. Three children did not start treatment (7%); one (2%) was post lung transplant, one was listed for liver transplant (2%), and one was recruited into a tezacaftor/ivacaftor clinical trial (2%).

There were 39 patients who fulfilled the criteria to start treatment at time of study in July 2018. See Table 1 for patient demographics. All 39 initiated, and continued, treatment during the study period. No patients died, and none experienced liver failure, hepatic encephalopathy or jaundice during the study. Two patients received treatment as part of the MAP (5%). The patients aged 12 years and older were started on the higher dose (lumacaftor 200mg/ ivacaftor 125mg) and the patients aged 6-11 years were started on the lower dose (lumacaftor 100mg/ivacaftor 125mg). Prior to initiation of treatment, all patients had LFTS checked, however, two patients (5%) had no AST level reported due to lab error. There were 34 patients (87%) who had completed three months of treatment, 18 (46%) completed six months, 16 (41%) completed nine months and 13 (33%) completed 12 months at data collection.

Table 1: Demographics of CF patients at UHL Paediatric CF clinic. CFLD: Cystic Fibrosis Liver disease.

	All patients (n=39)	CFLD (n=6)
Average age (years)	11.1	12.3
Male sex	21 (54%)	4 (67%)
>12yo	18 (46%)	4
6-11yo	20 (51%)	2

Figure 1 displays the median levels for AST, ALT, ALP, GGT at each timepoint. AST, ALT, GGT all remained steady and within the normal reference range, with ALP having an overall graphical trend towards normalization of values.

Figure 1: AST, ALT, ALP, GGT median levels graphed at each time point. Median was used due to skewed distributions. Normal values: AST (5-34 IU/L), ALT (10-55 IU/L), ALP (47-175 IU/L), GGT (9-36 IU/L).

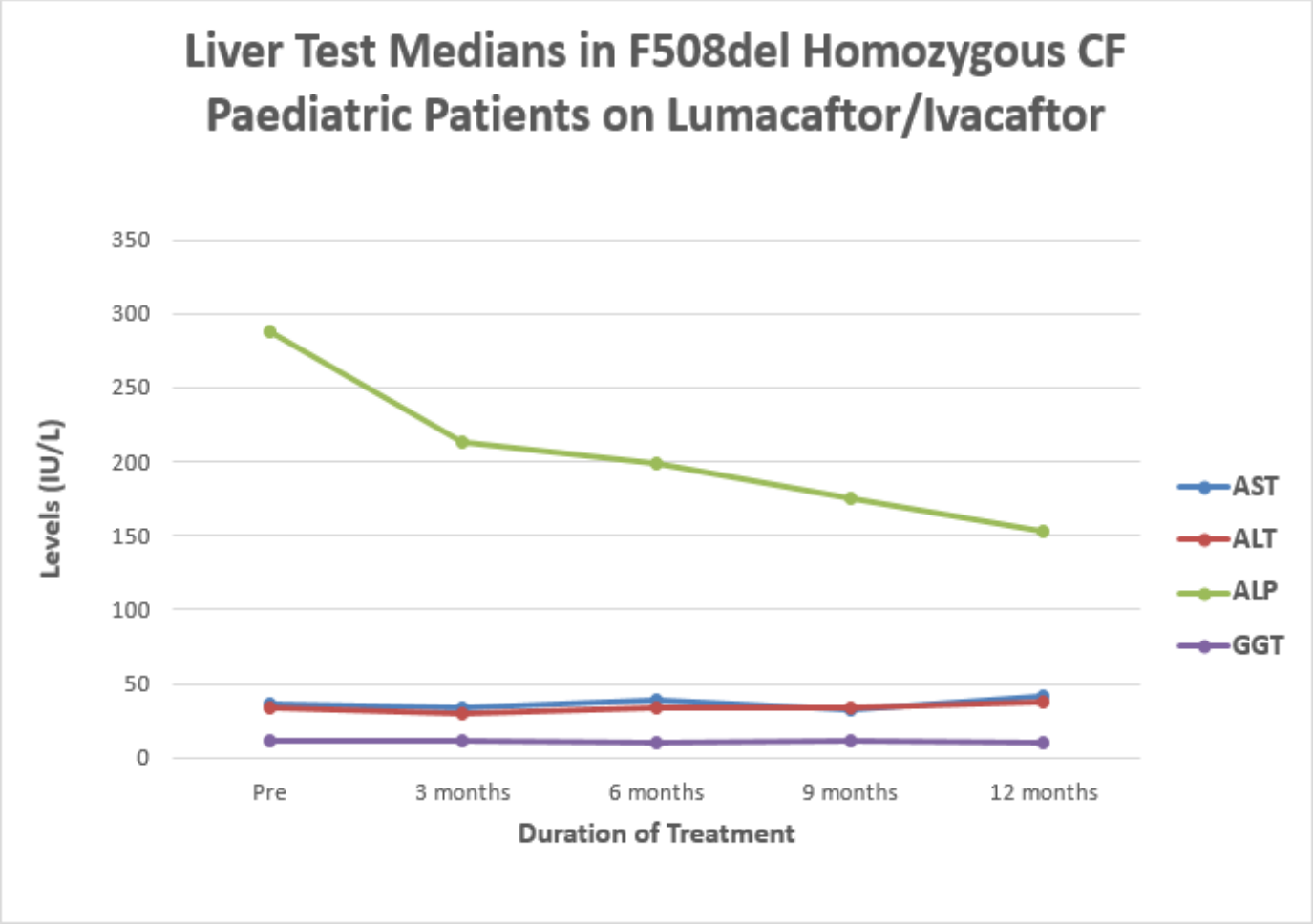
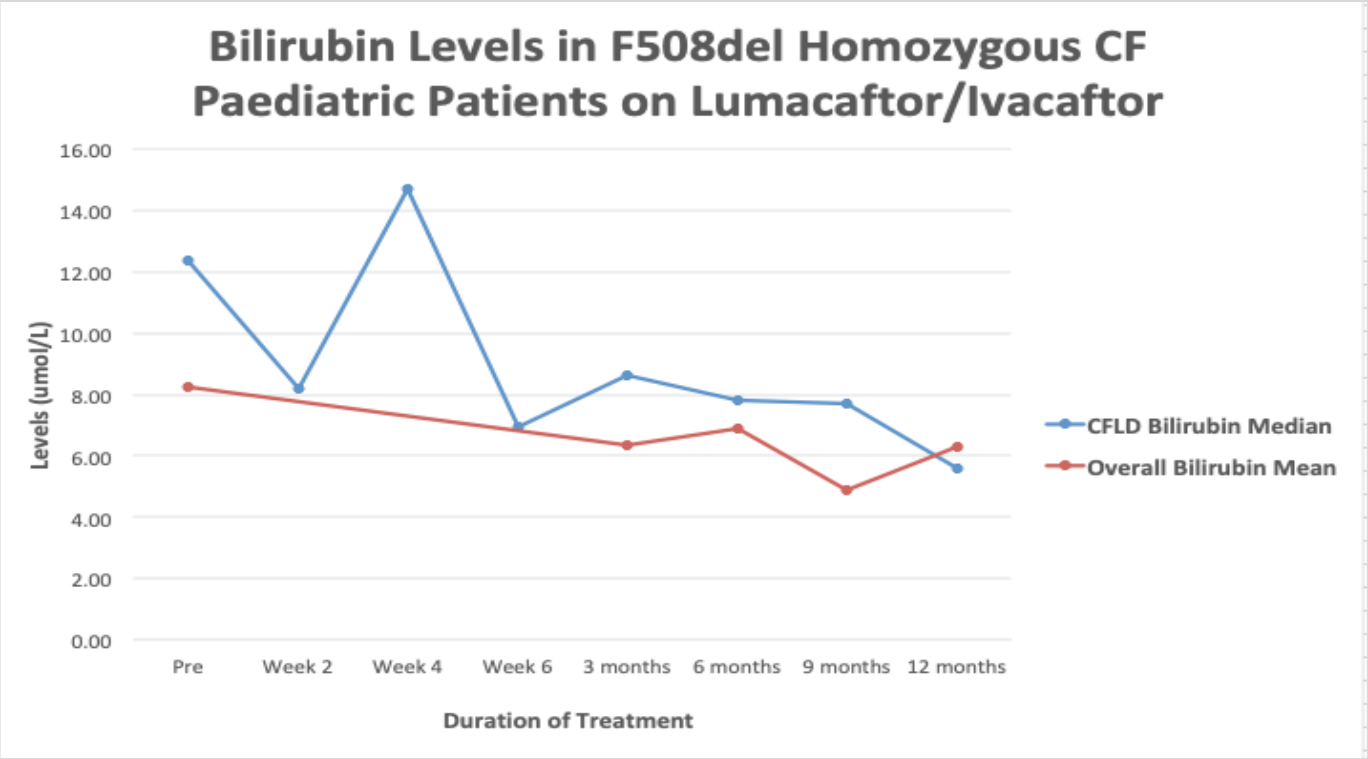


Figure 2 displays the total bilirubin levels for all patients and those specifically with CFLD. Overall, the bilirubin levels remained within normal range throughout treatment.

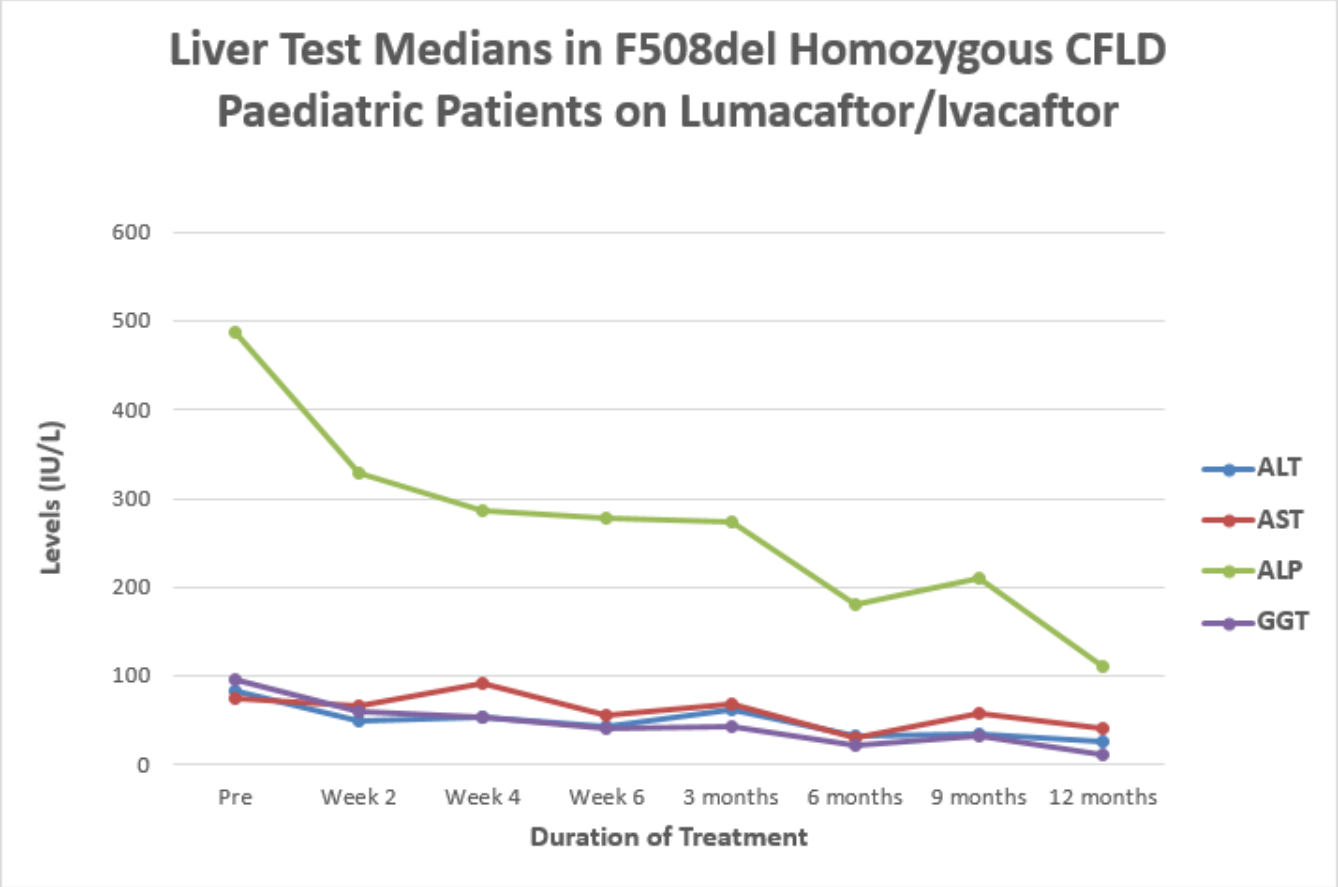
Figure 2: Bilirubin levels graphed at each timepoint. CFLD patients had closer LFT monitoring during the first 6 weeks of treatment. The remaining patients did not have levels checked during this time. Bilirubin levels from all patients had a normal distribution, thus the mean was used for analysis. The data for the 6 patients with CFLD was skewed, thus, the median was used. Bilirubin normal values: 3-21 umol/L.



We had adequate numbers of test results only at baseline and at three months for all patients to perform a statistical analysis. The ALT, AST, ALP and GGT data were determined to have a skewed distribution based on histogram and boxplot distributions and the Shapiro-Wilk test for normality. Thus, the data were compared using the Wilcoxon Signed Rank Test. The total bilirubin levels were determined to have a normal distribution, thus a paired samples t-test was applied. Overall, we found our patients had a statistically significant decrease in ALT, ALP, GGT and total bilirubin levels, and no statistically significant change in AST levels as follows; the median LFT values (IU/L) at baseline (pre-treatment) and at three months, respectively, were : ALT 34 and 30 (p-value 0.016), ALP 288 and 213.5 (p-value 0.001), GGT 12 and 12 (p-value 0.002), and AST 37 and 33.5 (p-value 0.076). The mean bilirubin levels (umol/L) at baseline (pre-treatment) and at three months on treatment for all patients was 8.26 and 6.36 respectively, (p value: 0.002). Two patients (5%) had increased AST levels during treatment > 3 x ULN, however, these levels then decreased with continued use. None of our patients had LFTs > 8 x ULN, or > 5 x ULN during treatment, and none had ALT, ALP or total Bilirubin levels > 3 x ULN during treatment.

The data for six patients with pre-existing CFLD were extracted and were also analyzed separately. See table 1 for demographic details. Results were similar to those without established CFLD. The median levels at each time point for bilirubin and AST, ALT, ALP, GGT are graphically depicted in Figures 2 and 3, respectively and demonstrate a clear graphical trend of improving LFTs across all parameters. We could not determine statistical significance in CFLD population due to the limited number of patients.

Figure 3: AST, ALT, ALP, GGT median levels graphed at each time point for CFLD patients only (n=6). Median was used due to skewed distributions. Normal values: AST (5-34 IU/L), ALT (10-55 IU/L), ALP (47-175 IU/L), GGT (9-36 IU/L)



Discussion

We present the first "real world" study of the short-term effect of lumacaftor / ivacaftor combination therapy on the liver function status of children with CF. Our results were unexpected and encouraging. They suggest that, although the clinical trials raised a concern that commencing a child on this new CFTR modulator therapy came with a significant risk of derangement of LFTs, the risk appears to be low and therapy may actually help improve LFTs.

CFLD is a significant complication of CF primarily evolving in the school age years and can have a detrimental effect on morbidity and mortality [6, 7]. To date there has been no intervention which has demonstrated efficacy in altering the course of CFLD [6, 7]. Pre-existing CFLD was an exclusion criteria for the clinical trials, however it is not a contra-indication to prescribing lumacaftor / ivacaftor combination therapy. Although our numbers are small, with just six patients (15%) with significant CFLD, the trends observed are encouraging. Dempsey *et al*, found similar improvements in LFTs in a small number (n=7) of patients with CFLD, but did not assess the effect of lumacaftor / ivacaftor on those without CFLD[8]. Firstly, it appears these patients can tolerate the treatment safely. Secondly, and perhaps more encouragingly; this may represent the first evidence of an intervention that can improve LFTs in patients with CFLD. Further observation is required to ascertain if this is translated into improvements in liver synthetic function and the manifestations of portal hypertension, such as splenomegaly and oesophageal varices.

Similar to many other medications lumacaftor / ivacaftor combination therapy may indeed come with a risk of liver injury. Drug induced liver injury (DILI) is the most common reason for withdrawing an agent from the market, and / or issuing warnings and modifications for their use[9-11]. RUCAM (Roussel Uclaf Causality Assessment Method) is a well-established methodology to assess causality in suspected DILI[9, 12, 13]. DILI is defined as, the now familiar, ALT levels above 5 × ULN and/or ALP levels greater than 2 × the ULN[9, 12, 13]. In addition the Hy's law predicts a 10% mortality (range 5-50%) when hepatocellular DILI is associated with a serum bilirubin level of ≥ 3 ULN[14]. However, determining causality of DILI remains complex and challenging with the majority of cases classed as "idiosyncratic" – essentially unexpected and unexplained[10]. Relevant to this discussion is the fact that, in the liver, CFTR is not expressed in hepatocytes, but exclusively in cholangiocytes[15, 16]. Defective chloride channel function can result in inspissated secretions that obstruct biliary flow, peri-biliary fibrosis, and for some patients progression from focal to multilobular biliary cirrhosis[16-20]. Onset of clinically significant disease is typically during the first decade of childhood[21, 22]. One might speculate that there are two separate processes at play here. The medication may come with a risk of liver injury, by a mechanism yet to be clearly defined, but may also come with a marginal, but potentially important, improvement in CFLD by improving CFTR functioning at the apex of cholangiocytes lining the bile ducts. Consistent with this theory, Kutney *et al*, demonstrated, using magnetic resonance imaging proton density fat fraction analysis, that lumacaftor / ivacaftor therapy was associated with reduced hepatic steatosis. Interestingly, the study excluded patients with CFLD or persistently elevated liver enzymes[23].

Our study has several limitations. It is a single centre study, with a small sample size. We had adequate numbers to perform a statistically valid comparison of baseline and three-month data, however the ability of this dataset to make inferences about the wider CF population is limited, and the findings should be viewed with caution. Also, many of the time points have missing data. This illustrates the challenges of applying a stringent surveillance system for adverse events requiring frequent blood draws in a paediatric CF clinic. We continue to explore local policies to improve adherence to the surveillance policy.

Although the results of our study are encouraging, continued vigilance is required. On the basis of these findings we plan to expand our study to involve greater numbers, across multiple sites, and to include both adult and paediatric subjects.

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Declaration of Conflicts of Interest:
The authors have no conflicts of interest to declare.

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