European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-021-03272-0

LETTER TO THE EDITOR

Elevation of alkaline phosphatase and long-term drug therapy for cystic fibrosis

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Received: 20 October 2021 / Accepted: 28 December 2021

Keywords Cystic fibrosis · CFTR modulators · Azithromycin · Alkaline phosphatase

Dear Sir,

A 57-year-old man with a history of cystic fibrosis (CF) and grade 3b chronic renal failure was admitted for a rapidly progressive respiratory failure combined with the worsening of renal failure.

For CF, the patient received since April 2021 the combination tezacaftor/ivacaftor (100/300 mg/day), in addition to azithromycin (250 mg/day) that was started in 2015.

On July 20, azithromycin was increased from a daily dose of 250 to 500 mg, and elexacaftor/tezacaftor/ivacaftor replaced the previous association. Intermittent haemodialysis was daily performed.

Laboratory investigations revealed a rapid increase in serum alkaline phosphatase (ALP) (up to 2137 IU/l, reference 40–130), with no changes in serum transaminases and bilirubin, and only a modest elevation of gamma-glutamyl transferase (GGT) (Fig. 1). Genotyping for ATP-binding cassette B1 (ABCB1) and ATP-binding cassette C2 (ABCC2) gene showed that the patient was 3435/TT for ABCB1 and c.-24C > T for ABCC2. The list of the medications prescribed over the 2 weeks preceding ICU admission appears in Table 1. The abdomen ultrasound examination failed to reveal any abnormality of liver or biliary echostructure. Treatment with azithromycin was interrupted (August 2). Despite intensive care therapy and daily haemodialysis, the patient's condition worsened, and discontinuation of life-sustaining therapies was decided on ICU day 14 in agreement with the relatives.

Chronic azithromycin therapy is usually well tolerated in patients with CF, without significant changes in serum ALP levels over the time. Azithromycin is mainly excreted by the bile and no specific dosage adjustment is usually recommended in patients with end-stage renal failure or on haemodialysis. However, a study performed on eight patients on continuous ambulatory peritoneal dialysis (CAPD) showed that after a single dose of 500 mg azithromycin, the mean elimination half-life was increased to 84.55 h and plasma clearance was 21.93 L/h [1]. In a rat experimental model, renal clearance of azithromycin accounted for 14% of systemic clearance [2].

P-glycoprotein (P-gp, multidrug resistance protein 1 or MDR1, encoded by ABCB1) and multidrug resistance-associated protein 2 (MRP2, encoded by ABCC2) are both expressed on the canalicular membrane of hepatocytes and on the apical surface of the epithelial cells of small ductules of the pancreas and are playing a role in the elimination of various drugs. Azithromycin does not inhibit CYP3A4 but is both a substrate and a mild inhibitor of P-gp and a substrate of MRP2. Biliary and intestinal excretion of azithromycin is mediated by these two transporters [2]. While the c.-24C > T variant has been associated with increased diclofenac hepatotoxicity, its influence on azithromycin response is not known [3]. Ivacaftor is a weak inhibitor of P-gp, but is not a substrate of MRP2. While tezacaftor/ivacaftor does not affect exposure of CYP3A substrates in a clinically significant manner, its use may increase exposure of sensitive P-gp

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Published online: 15 January 2022

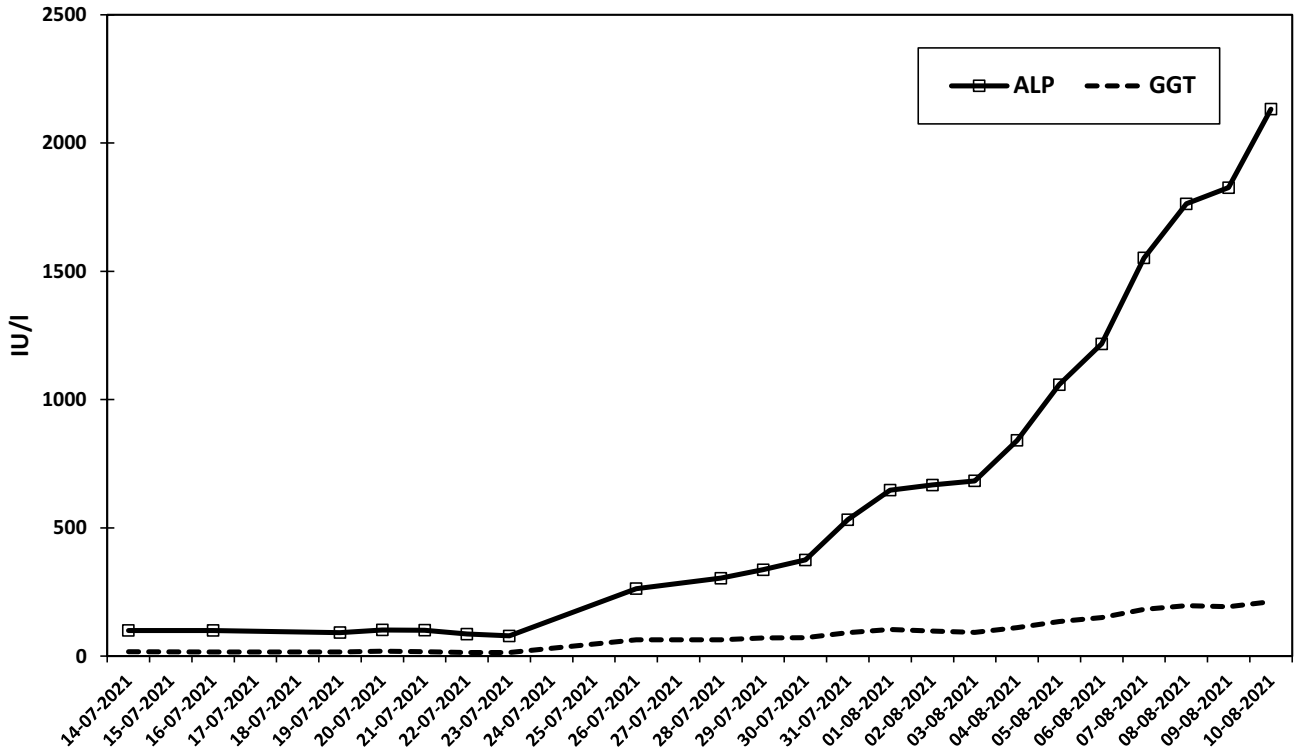

Fig. 1 Evolution of serum alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGT) over time

substrates, so caution and appropriate monitoring should be used [4]. The 3435/TT genotype is associated with a reduced expression of P-gp at least in the small intestine. The influence of this genotype on drug disposition remains controversial and in particular has not been investigated to date for ivacaftor. Renal excretion rate is only 6.6% for ivacaftor and 14% for tezacaftor, limiting the influence of renal clearance on pharmacokinetics. Mild or transient elevation of serum transaminases has been reported with lumacaftor/ivacaftor, tezacaftor/ivacaftor or elexacaftor/tezacaftor/ivacaftor therapy, but marked elevation of ALP seems exceptional [5]. While other causes of ALP elevation could not be definitely excluded in our observation, the combination of the progression of renal failure, increase of azithromycin dosage and genetic polymorphism on ABCB1 and ABCC2 could predispose to an unusual side effect of the association of azithromycin with tezacaftor/ivacaftor through the mechanism of MDR1 or MRP2-mediated transport.

Table 1 List of the recent medications

Drug	**Substrate (+)/inhibitor (−) CYP 450**	**Substrate (+)/inhibitor (−) P-gp**
Amlodipine	+3A4/5 (major)	+(minor)
Azithromycin	−(minor)	+/−(minor)
Aztreonam		
Bumetanide		
Chlortalidone		
Clonazepam	+3A4/5 (major)	
Colistimethate sodium		
Furosemide		
Pregabalin		
Spironolactone		
Tamsulosin	+3A5/5 (major)	
Teicoplanin		
Tezacaftor/Ivacaftor	+3A4/5 (major)/−(minor) (mainly ivacaftor)	+/−(minor) (mainly ivacaftor)

Data availability The authors confirm that the data supporting the findings of this study are available within the article or its supplementary materials.

Declarations

Ethical statement The patient's relatives gave written informed consent for publication of the case report.

Conflict of interest The authors declare no competing interests.

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