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Acute liver failure during Pirfenidone treatment triggered by co-medication with Esomeprazole

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Introduction

Prifenidone is an antifibrotic agent for the treatment of Idiopathic Pulmonary Fibrosis (IPF) that improves the outcome of patients and is recommended by guidelines [1]. In few patients however, Pirfenidone can cause liver enzyme elevations according to LiverTox [2], with one case report describing acute liver failure [3]. We here present a patient in whom co-medication with Esomeprazole triggered iDILI. Moreover, we have used a novel *in-vitro* test with Monocyte-derived Hepatocyte-like (MH) cells [4] to investigate possible interactions *in vitro*.

Case Report

A 75 year old Caucasian male with IPF started Pirfenidone treatment (Week 1: 267mg TID; week 2: 534mg TID, week 3 and onwards: 801mg TID). Three months later he developed light sensitivity that was managed by pausing the treatment for 2 weeks. Liver enzymes were monitored regularly and were normal. One year later, elevated transaminases were detected. The only co-medication was Esomeprazole 40mg/day, introduced due to gastroesophageal reflux symptoms 3 days prior to diagnosis of liver injury. Despite discontinuation of Pirfenidone and Esomeprazole, the patient developed jaundice, pruritus, nausea and fatigue accompanied by further increase in transaminases leading to hospitalization (Bilirubin 17.3mg/dl, [normal <1.0mg/dl], ALT 1.421 U/l [normal <50U/l] and INR 1.4].

The patient's past medical history was notable for Prostate cancer in remission after radiation therapy 9 years earlier, seasonal Pollinosis (requiring no treatment) and IPF diagnosed 2 years earlier. The history was negative for chronic liver disease, smoking, alcohol/substance abuse or intake of over-the-counter or herbal medications and drug allergies (except from Pirfenidone induced light sensitivity).

The diagnostic work-up showed negative serologies for hepatitis A, B, C, E, Epstein-Barr Virus and Cytomegalovirus. Peripheral eosinophilia was not present. Imaging studies (Ultrasound, Magnetic Resonance Imaging and Computed Tomography) did not indicate extra- or intrahepatic cholestasis. Liver biopsy on the 8^{th} day after admission showed predominant eosinophilic portal infiltration, favouring DILI over Autoimmune Hepatitis. The condition of the patient worsened (Table 1) and the patient expired due to *Escherichia coli* sepsis, lactic acidosis and multi-organ failure 12 days after hospitalization. The RUCAM score of 6 implied a “probable” causality for both, Pirfenidone and Esomeprazole.

After inclusion in our clinical study (ClinicalTrials.gov: NCT 02353455), blood samples were obtained on day 7 after admission to generate MH cells, which then were exposed to Pirfenidone and Esomeprazole. MH cells derived from the patient showed increased toxicity caused by the combination of both drugs, whereas the effect of the single drugs did not differ from controls (Figure 1). This finding supports an increased susceptibility of the patient towards the combination of Esomeprazole and Pirfenidone.

Discussion:

Co-medications may play a role in Pirfenidone-induced liver failure by alteration of drug metabolism and accumulation of toxic metabolites [3]. Moreover, drug-drug interactions with Pirfenidone-therapy are to be expected [5]. In our patient, acute liver failure was triggered within three days after starting Esomeprazole. Esomeprazole is known to be an inducer of CYP1A2 as well as a substrate for CYP2C19 according to LiverTox [2]. Both pathways are important in Pirfenidone metabolism. A drug-drug interaction as trigger of iDILI in this patient, as suggested by the time course, is supported by the MH cell test, a novel *in vitro* tool [4]. Our case highlights the importance to monitor co-medications and especially Proton-Pump-Inhibitors - which are recommended for regular use in the clinical treatment guideline [1] - in IPF-patients treated with Pirfenidone.

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Table 1: Time course of events and laboratory parameters

Days from admission	AST (normal <50 U/l)	ALT (normal <50 U/l)	AP (normal <130 U/l)	GGT (normal <60 U/l)	TBL (normal <1.0 mg/dl)	INR (normal 0.8-1.2)
Day - 426	Start Pirfenidone					
Day - 332	Light sensitivity, Pirfenidone stop for 2 weeks, resumed full dose					
Day - 145	26	16	93	24	0,3	-
Day – 15	Start Esomeprazole 40mg/d					
Day – 12	613	716	301	462	2,76	-
Day – 10	Stop Pirfenidone and Esomeprazole					
Day – 7	863	973	379	507	6,4	-
Day -5	942	994	367	474	8,9	1,24
Day – 1	1080	997	283	326	11,8	-
Admission	1493	1421	344	307	17,3	1,4
Day 2	1477	1326	335	278	17,4	1,4
Day 5	1367	1185	290	215	17,6	1,5
Day 7	-	1525	316	222	21,4	1,7
Day 9	1905	1525	306	214	23	1,5
Day 10	-	1483	316	-	23,3	1,5
Day 11, 7 a.m.	Transfer to ICU due to progressive encephalopathy					
	889	1229	251	161	23,6	1,8
Day 11, 3.p.m.	519	914	265	135	18,5	2,7
Day 11, 7 p.m.	-	538	175	88	9,8	4,1
Day 12, 1 a.m.	death due to multi-organ failure (septicemia with *E. coli*)					

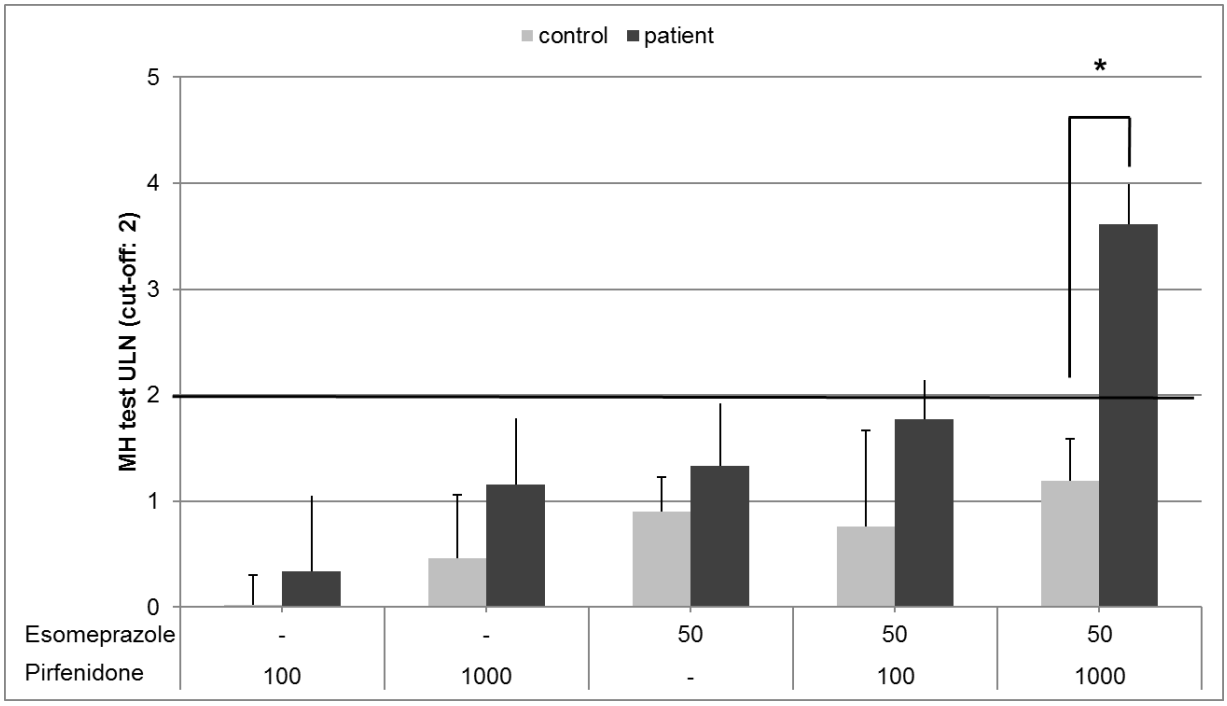

Figure 1: Effects of Esomeprazole (50µM) and Pirfenidone (100 and 1000µM) in MH cells. Toxicity in MH cells was determined by release of Lactate-Dehydrogenase after 48h drug treatment of the cells. The resulting toxicity was normalized on vehicle control (DMSO = 0%) and positive control (Lysis with TWEEN-100 = 100%). Toxicity observed in MH cells of each single donor was normalized to 2xSD of vehicle control to correct for possible seeding variability, resulting in the depicted ULN values. A ULN value of ≥2 is considered as a positive test result. Toxicity response of MH cells derived from 6 control donors (grey bars, mean±S.D. of the 6 donors; capped error bars) were compared to the effects in MH cells derived from the patient (black bars; mean±S.D. of triplicate measurements; uncapped error bars; *$p<0.05$ patient vs. controls).