1307
PF-03491390 INHIBITS LIVER FIBROSIS IN PATIENTS WITH CHRONIC HEPATITIS C VIRUS INFECTION VIA SUPPRESSION OF PRO-APOPTOTIC CASPASE-ACTIVATION.

Gary Burgess[1], Peter Colman[1], Emanuel Engmann[1], Heike Bantel[2], Paresh N. Soni[3]; [1]Pfizer Ltd, Sandwich, United Kingdom; [2]Department of Gastroenterology, Hepatology and Endocrinology, Hanover Medical School, Hanover, Germany; [3]Pfizer Ltd, New London, CT

Background: In patients with chronic HCV infection, the pan-caspase inhibitor, PF-03491390 minimises hepatocellular damage, as reflected by reductions in elevated ALT and AST levels. As caspase activation plays a pivotal role in inflammatory and fibrotic liver injury in HCV-infection, we investigated caspase activation and a range of inflammatory and fibrotic serum biomarkers during therapy with this agent. **Methods**: 204 patients with chronic HCV infection and liver fibrosis were randomized to receive placebo or PF-03491390 5 mg, 25 mg, or 50 mg orally twice daily for 12 weeks in a placebo-controlled, double-blind, parallel-group study. If ALT and AST levels remained elevated at Week 10, the dose of study drug was doubled to Week 12. Changes in serum markers of inflammation, fibrosis and apoptosis are reported. **Results**: At Week 12, compared with placebo, PF-03491390 therapy was associated with decreases in serum levels of transforming growth factor (TGF) β1, α-2 macroglobulin, caspase-mediated cytokeratin-18 fragments (M30-Antigen), active caspases 3/7 and α-fetoprotein. PF-03491390 therapy was also associated with increases in serum levels of haptoglobulin and Fas ligand, at Week 12, compared with placebo. PF-03491390 therapy had no apparent impact on serum levels of the other measured biomarkers (Table 1). **Conclusions**: In patients with chronic HCV infection, 12 weeks of PF-03491390 therapy appears to inhibit liver inflammation and fibrosis via suppression of pro-apoptotic caspase-activation. Long-term studies are required to assess the mechanism of action and effects of PF-03491390 in patients with liver fibrosis.

Table 1: Median absolute change of serum markers of inflammation, fibrosis and apoptosis from baseline at Week 12

Serum marker	Placebo	PF-03491390		
		5 mg bid	25 mg bid	50 mg bid
Fibrosis	N=47-50	N=49-53	N=48-50	N=44-57
M30-Antigen (U/L)	-17.0	-114.5	-93.0	-105.0
Active caspases 3/7 (RLU)	-46.0	-292.0	-285.0	-464.0
TGFβ1 (ng/ml)	0.22	-0.95	-0.13	-0.33
α-2 macroglobulin (mg/dl)	2.00	-4.00	-0.50	-10.00
Haptoglobin (mg/dl)	-0.50	9.00	4.00	5.00
Apolipoprotein A1 (mg/dl)	0.50	-3.00	0.50	-4.00
Inflammation	N=48-51	N=49-55	N=46-50	N=43-48
Tumor necrosis factor-α (pg/ml)	0.00	0.10	0.00	0.00
C-reactive protein (mg/dl)	0.00	0.00	0.00	0.00
α-fetoprotein (ng/ml)	0.00	-0.60	-0.70	-0.40
Interleukin-6 (pg/ml)	0.00	0.20	-0.25	-0.20
Interleukin-8 (pg/ml)	-0.20	0.00	-0.60	-1.00
Fas ligand (pg/ml)	-0.30	2.10	2.40	1.70
Mechanism of Action	N=25	N=28	N=29	N=20
Interleukin-1β (pg/ml)	0.00	0.00	0.00	0.00

Disclosures:

Gary Burgess - Employee: Pfizer

Peter Colman - Employee: Pfizer

Emanuel Engmann - Employee: Pfizer

Heike Bantel - Grant/Research Support: Pfizer

Paresh N. Soni - Employee: Pfizer

1308
DIFFERENTIATION OF EARLY VIROLOGIC RESPONSE (EVR) INTO RVR, COMPLETE EVR (CEVR) AND PARTIAL EVR (PEVR) ALLOWS FOR A MORE PRECISE PREDICTION OF SVR IN HCV GENOTYPE 1 PATIENTS TREATED WITH PEGINTERFERON ALFA-2A (40KD) (PEGASYS®) AND RIBAVIRIN (COPEGUS®)

Patrick Marcellin[1], Donald M. Jensen[2], Stephanos J. Hadziyannis[3], Peter Ferenci[4]; [1]Centre de Recherches Claude Bernard sur les Hépatites Virales, Hôpital Beaujon, Clichy, France; [2]Section of Hepatology, St. Luke's Medical Center, Chicago, IL; [3]Henry Dunant Hospital, Athens, Greece; [4]Department of Internal Medicine IV, Medical University of Vienna, Vienna, Austria

Background: Early on-treatment responses in HCV RNA at wks 4 & 12 post initiation of therapy are increasingly being used to predict those pts likely to achieve an SVR. Pts achieving an RVR (HCV RNA <50 IU/mL at wk 4 and maintained at wk 12) have a high rate of SVR irrespective of genotype. The standard definition of an early virologic response (EVR) had been defined as pts at wk 12 achieving either an undetectable HCV RNA (<50 IU/mL) or a ≥2 log drop in HCV RNA but still detectable. However, rates of SVR in pts achieving an EVR by this definition are heterogeneous. By further subdividing pts achieving early responses into RVR, complete EVR (cEVR or non-RVR but HCV RNA <50 IU/mL at wk 12) and partial EVR (pEVR or non-RVR but HCV RNA ≥2 log drop in HCV RNA at wk 12 but still detectable) it may be possible to improve the prediction of pts likely to achieve an SVR and may allow for tailoring of treatment duration. Here we performed a retrospective analysis of 2 large, multinational phase III studies of genotype 1 pts treated with peginterferon alfa-2a (40KD) in combination with ribavirin (RBV) (Fried et al. NEJM 2002 & Hadziyannis et al. Ann Intern Med 2004). **Methods:** 569 pts treated for 48 wks with 180 µg/wk peginterferon alfa-2a (40KD) and 1000/1200 mg/d RBV were included in the present analysis (ITT). Early responses were divided into 4 mutually exclusive categories as defined above: RVR, cEVR, pEVR and non-EVR (<2 log drop at wk 12). Rates of SVR were then calculated for each category. **Results:** 16% (90/569) pts were classified as achieving an RVR, 42% (240/569) pts a cEVR, 22% (128/569) pts a pEVR and 20% (111/569) non-EVR. Rates of achieving an SVR in these groups were 87% (78/90) for RVR, 68% (162/240) cEVR, 27% (34/128) pEVR and 5% (5/111) for non-EVR pts. **Conclusions:** Pts achieving an RVR have high rates of SVR and may benefit from shortened treatment duration (24 wks; also see Jensen et al. Hepatol 2006). Pts with a cEVR also have high rates of SVR but should be encouraged to remain on therapy for the standard duration of therapy (48 wks). Pts with a pEVR have lower rates of SVR with the standard 48 wks of therapy and may benefit from intensified treatment (72 wks; also see Sánchez-Tapias et al. Gastroenterol 2006) and pts that are non-EVR at wk 12 have a low chance of achieving an SVR and consideration should be given to change treatment strategy. Early on-treatment virologic responses in HCV RNA are highly predictive of achieving an SVR and subdividing early responses into RVR, cEVR and pEVR allows for a more precise prediction of achieving an SVR.

Disclosures:

Patrick Marcellin - Grant/Research Support: Roche; Consultant/Adviser: Roche; Speakers Bureau: Roche

Donald M. Jensen - Speakers Bureau: Roche; Consultant/Adviser: Roche

Stephanos J. Hadziyannis - Consultant/Adviser: Roche; Speakers Bureau: Roche