HEPATITIS C MEDICATIONS:
ANALYSIS OF ADVERSE DRUG EVENTS AND POOR PATIENT OUTCOMES

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OBJECTIVES

1) TO COMPARE THE PRE-APPROVAL SAFETY PROFILES OF NEW HEPATITIS C MEDICATIONS TO THEIR POST-MARKETING ADVERSE EVENT (AE) REPORTS.

2) TO ESTIMATE DOWNSTREAM DIRECT MEDICAL COSTS RELATED TO AES AND POOR PATIENT OUTCOMES ASSOCIATED WITH THESE DRUGS.

BACKGROUND

IT IS A WIDELY ACCEPTED CONCEPT THAT PRE-APPROVAL DRUG CLINICAL TRIAL PROGRAMS OFTEN FAIL TO UNCOVER SERIOUS AND LIFE-THREATENING AES.

MANY AES ONLY BECOME EVIDENT WELL AFTER REGULATORY BODY APPROVALS.

THEREFORE, GIVEN SIMILAR CURE RATES AND ACQUISITION COSTS, THE QUESTION OF REAL WORLD TOLERABILITY FOR THE CURRENT CLASS OF HEPATITIS C MEDICATIONS IS OF GREAT INTEREST.

METHODS

PRE-APPROVAL DATA:

- XML FILES FROM CLINICALTRIALS.GOV WERE IMPORTED FOR BOTH PHASE II AND III INTERVENTIONAL AND OBSERVATIONAL HUMAN STUDIES

POST-APPROVAL DATA:

- ALL "PRIMARY SUSPECT" CASE REPORTS FOR EACH DRUG WERE COLLECTED FROM FDA'S ADVERSE EVENT REPORTING DATABASE (FAERS)

- DISPROPORTIONAL REPORTING WAS ASSESSED WITH THE REPORTING ODDS RATIO (ROR) AND 95% CONFIDENCE INTERVALS

POST-APPROVAL COST ESTIMATES:

- AE AND OUTCOME-SPECIFIC MEDICAL COSTS WERE OBTAINED FROM AHRQ

- ICD-9 CODES WERE MAPPED TO MEDDRA TERMS BY THE USE OF BIOPORTAL AND ICD9DATA.COM

- FOCUS WAS LIMITED TO EUDRAVIGILANCE IMPORTANT MEDICAL EVENTS

- IN CASES WITH MORE THAN ONE AE, ONLY THE LARGEST INDIVIDUAL COST WAS SELECTED

- IN CASES WITH NO ELIGIBLE AE, BUT WITH A LISTED OUTCOME, ONLY THE LARGEST OUTCOME COST WAS USED

- COSTS WERE SUMMED FOR EACH DRUG AND THEN DIVIDED BY EXPOSURE RATES OBTAINED FROM EVALUATE PHARMA TO CALCULATE DOWNSTREAM COSTS PER PATIENT.

IT SHOULD BE NOTED THAT UNDER REPORTING MAY RESULT IN UNDER ESTIMATION OF PROJECTED DOWNSTREAM COSTS.

DISCLAIMER / FINANCIAL

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RESULTS

TABLE 1: PRE-APPROVAL ADVERSE EVENT PROFILES

HCV TREATMENT[1]	SERIOUS COUNT	SERIOUS N	SERIOUS RATE	OTHER COUNT	OTHER N	OTHER RATE
SOFOSBUVIR	20	1062	1.88%	828	936	88.46%
LEDIPASVIR; SOFOSBUVIR	12	763	1.57%	466	763	61.07%
DASABUVIR; OMBITASVIR; PARITAPREVIR; RITONAVIR	44	2,484	1.77%	1,761	2,484	70.89%

[1] PATIENTS WITH GENOTYPE 1 CHRONIC HEPATITIS C WITHOUT CIRRHOSIS, RENAL DISEASE, HIV CO-INFECTION, OR LIVER TRANSPLANTATION. DATA IS FOR 12 WEEK TREATMENTS. SOFOSBUVIR DATA INCLUDES COMBINATION TREATMENTS WITH SIMPEPREVIR, DACLATASVIR, AND PEG/RBV. VPAK DATA INCLUDES SINGLE TREATMENT WITH VPAK AND COMBINATION TREATMENTS WITH RBV.

TABLE 2: POST-MARKETING ADVERSE EVENTS REPORTS (FDA DATABASE)

DRUG NAME	FAERS DATA	TOTAL PRIMARY SUSPECT COUNTS
SOFOSBUVIR	12/6/2013 – 12/31/2015	4,946
LEDIPASVIR; SOFOSBUVIR	10/10/2014 – 12/31/2015	4,852
DASABUVIR; OMBITASVIR; PARITAPREVIR; RITONAVIR	12/19/2014 – 12/31/2015	4,073

TABLE 3: DISPROPORTIONAL REPORTING (ROR RANGE & CASE COUNTS)

ADVERSE EVENT	SOFOSBUVIR	LEDIPASVIR; SOFOSBUVIR	DASABUVIR; OMBITASVIR; PARITAPREVIR; RITONAVIR
ASTHENIA	1.15 *(0.97-1.37)* (133)	0.72 *(0.58-0.89)* (82)	2.59 *(2.27-2.96)* (238)
DIARRHEA	0.89 *(0.75-1.07)* (129)	1.62 *(1.41-1.85)* (224)	2.23 *(1.97-2.54)* (255)
DYSPNEA	1.17 *(1.01-1.35)* (193)	0.59 *(0.48-0.72)* (98)	1.21 *(1.04-1.42)* (165)
FATIGUE	4.03 *(3.70-4.38)* (610)	5.17 *(4.78-5.59)* (742)	8.42 *(7.82-9.06)* (925)
NAUSEA	1.59 *(1.42-1.77)* (339)	1.33 *(1.18-1.50)* (282)	3.21 *(2.93-3.52)* (527)
PRURITUS	1.68 *(1.42-1.99)* (138)	0.78 *(0.61-1.00)* (64)	5.66 *(5.08-6.31)* (358)
RASH	2.08 *(1.80-2.42)* (184)	1.41 *(1.18-1.69)* (124)	2.98 *(2.59-3.42)* (213)
DIZZINESS	1.06 *(0.89-1.25)* (139)	0.98 *(0.82-1.17)* (127)	1.96 *(1.70-2.25)* (207)
EMOTIONAL DISORDER	1.42 *(0.88-2.29)* (17)	0.60 *(0.28-1.25)* (7)	2.86 *(1.97-4.15)* (28)
HEADACHE	2.57 *(2.33-2.85)* (411)	5.13 *(4.75-5.55)* (742)	3.47 *(3.14-3.83)* (443)
INSOMNIA	3.47 *(3.07-3.93)* (270)	3.16 *(2.77-3.59)* (242)	5.70 *(5.11-6.36)* (352)
MEMORY IMPAIRMENT	1.21 *(0.88-1.66)* (39)	1.27 *(0.93-1.73)* (40)	1.66 *(1.24-2.24)* (44)
OVERDOSE	2.45 *(2.04-2.95)* (116)	0.91 *(0.68-1.23)* (43)	0.15 *(0.07-0.34)* (6)
DRUG DOSE OMISSION	1.32 *(1.04-1.67)* (71)	0.96 *(0.73-1.27)* (51)	4.69 *(4.07-5.41)* (200)

TABLE 4: POST-APPROVAL ESTIMATED DIRECT MEDICAL COST BURDENS

DRUG NAME	TOTAL COSTS (2010-2015)	COSTED CASES	DOWNSTREAM COSTS PER RX
SOFOSBUVIR	$28,352,311	1,985	$71.65
LEDIPASVIR; SOFOSBUVIR	$24,579,021	1,824	$68.38
DASABUVIR; OMBITASVIR; PARITAPREVIR; RITONAVIR	$8,813,442	735	$212.62

CONCLUSIONS

- THESE DATA DEMONSTRATE THE OFTEN DISCREPANT SAFETY PROFILES OBSERVED DURING A DRUG'S PRE- VERSUS POST-MARKETING PHASES
- FOR EXAMPLE, DASABUVIR, OMBITASVIR, PARITAPREVIR, AND RITONAVIR APPEARED TO BE SAFER IN PRE-APPROVAL TESTING COMPARED TO REPORTED ADVERSE EVENTS AFTER FDA APPROVAL

- STRICT PATIENT ADHERENCE TO HEPATITIS C TREATMENT REGIMENS IS IMPORTANT FOR BOTH EFFICACY & COST
- ADHERENCE CAN BE SIGNIFICANTLY AFFECTED BY SIDE EFFECTS
- TABLE 3 INDICATES THAT MANY SIDE EFFECTS THAT COULD AFFECT PATIENT ADHERENCE ARE BEING REPORTED DIFFERENTLY BETWEEN THE 3 DRUGS

- TABLE 4 SUGGESTS THAT COST ESTIMATES BASED ON ADVERSE EVENTS ARE LOWER FOR LEDIPASVIR AND SOFOSBUVIR AND SOFOSBUVIR, WHEN COMPARED TO DASABUVIR, OMBITASVIR, PARITAPREVIR, AND RITONAVIR

LIMITATIONS

A NUMBER OF LIMITATIONS MUST BE CONSIDERED WHEN USING AND INTERPRETING THIS SYSTEM, INCLUDING REPORTING RATES AND POTENTIAL BIASES CONTAINED IN FAERS. THE "PRIMARY SUSPECT" DESIGNATION IN FAERS IS SUBJECTIVE AND THE INFLUENCE OF OTHER DRUGS OR FACTORS CANNOT BE RULED OUT FROM A GIVEN CASE REPORT. WHILE WE EXCLUDED OBVIOUS CASES WHERE A DISEASE-RELATED SYMPTOM WAS MISTAKENLY DENOTED AS AN AE, WE ASSUME THAT WE DID NOT CATCH ALL SUCH MISTAKES. OUR COST ESTIMATES COME FROM MAPPING AHRQ_HCUP COST SURVEY DATA TO MEDDRA TERMS FOUND IN FAERS. WHILE WE BELIEVE THIS IS APPROPRIATE, WE COULD NOT DETERMINE IF VARIATIONS BETWEEN FAERS PATIENT POPULATIONS AND THOSE USED FOR HCUP SURVEYS COULD INFLUENCE THE RESULTS PRESENTED HERE. FINALLY, LIMITATIONS IN BOTH THE ACCURACY OF MEPS DATA AND PATIENT EXPOSURE ESTIMATES USED HEREIN MAY CAUSE ARTIFICIAL INCREASES, OR DECREASES, IN CALCULATED DIRECT MEDICAL COSTS. WE VIGOROUSLY RECOMMEND THAT PATIENTS MUST HAVE A CONSULTATION WITH THEIR PRESCRIBING PHYSICIAN BEFORE TAKING ANY ACTION THAT RELATES TO FAERS OR THE DATA PRESENTED HERE.

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