

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 31 January 2005

FROM: John R. Senior, M.D., Associate Director for Science, Office of Pharmaco-epidemiology and Statistical Science (OPSS), HFD-030

TO: Renata Albrecht, M.D., Director, Division of Special Pathogen and Immunologic Drug Products (DSPIDP), HFD-590
Mary Singer, M.D., Medical Reviewer, HFD-590

VIA: Mark Avigan, M.D., Director, Division of Drug Risk Evaluation (DDRE), HFD-430; Office of Drug Safety (ODS), HFD-400
Paul Seligman, M.D., Director, (OPSS), HFD-030

SUBJECT: ODS consultation #D040713 regarding hepatotoxicity possibly induced by use of micafungin (MYCAMINE, Fujisawa) for treatment of esophageal candidiasis (NDA 21-754)

Documents reviewed:

- 1) Consultation request from HFD-590 to OPSS/ODS/DDRE dated 26 October 2004, assigned #D040713 for desired completion date of 25 January 2005
- 2) Packages of material (37 volumes) from Fujisawa Pharmaceuticals providing:
 - a) 120-day safety update to NDA 21-754 submitted 24 August 2004: 17 volumes
 - b) Response to September 10 request for information, submitted 22 September: 3 volumes
 - c) Clinical protocols for 8 studies for NDA 21-506 and 21-754: 2 volumes
 - d) Response to October 13 request for information, submitted 25 October: 1 volume
 - e) Response to October 20 request for information, submitted 29 October: 1 volume
 - f) Response to October 27 request for information, submitted 12 November: 1 volume
 - g) Response to December 14 request for information, submitted 22 December: 12 volumes
- 3) Medical literature (PubMed) on echinocandin toxicity 21 January 2005
- 4) DSS, DFS listings for reviews entered to 21 January 2005 for micafungin, NDA 21-754
- 5) Additional two cases of possible micafungin-induced injury received by fax 24 January 2005

In view of the huge amount of material submitted in the 37 volumes cited above, plus the original New Drug Application (NDA) submission, I asked Dr. Mary Singer what critical questions I should address in this consultation. She suggested on 13 January 2005 that it would be most helpful for me to focus my attention on the cases that were reviewed by a special panel of experts. Division 590 on 27 October 2004 had requested Fujisawa to have a panel of external expert hepatologists review all deaths due to hepatic failure and serious events of hepatic failure in the safety database. That panel included Drs. _____

_____ They were asked to review 19 cases of "liver damage" and "hepatic failure" to assess the relation of the adverse event to study drug administration. Of the 19 patients, 14 had been treated with micafungin, 4 with fluconazole, and 1 with neither ("placebo"),

but panelists were blinded to what treatment the patients had. They were asked to assess whether the adverse hepatic events were not related, possibly related, or related to study drug, as follows:

- | | |
|------------------|---|
| Not Related | Adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has much more likely alternative etiology). |
| Possibly Related | Adverse event has a strong temporal relationship to study drug and another etiology is equally or less likely. |
| Related | Adverse event has a strong temporal relationship to study drug or recurs on rechallenge, and another etiology is unlikely or significantly less likely. |

Fujisawa assembled information on the 19 cases, including for each a patient profile and narrative, plus laboratory, radiology, liver biopsy and autopsy reports if available. Treatment with micafungin, fluconazole, or neither was not stated. The 19 cases, along with a copy of the current Investigator Brochure, were sent to each of the panelists during the week of 8 November. They reviewed the cases individually, and then “met” by telephone conference on 23 November 2004 to discuss each of the cases and to reach their consensus on the association of study drug with the occurrence of the hepatic events, with their reasons for arriving at the decisions. Their final report of the review was sent to the sponsor that day by Dr. — who said that, from their review and deliberations, there appeared to be no clear signal of hepatotoxicity from micafungin, but they emphasized that the underlying medical conditions in these patients were extraordinarily complex. The patients were receiving many other types of medications, were immuno-compromised, and had serious underlying diseases including AIDS, malignancies, and pre-existing end-stage liver disease. Of the 19 cases, they felt that 13 were not related, 6 possibly related, and none probably related to study drug. The report of the external panel of expert hepatology reviewers was then forwarded to HFD-590 on 1 December 2004, which then requested on 14 December additional information, including as item 10 a request for a copy of the package of information given to the expert panel, exactly as sent, with the data on the 19 patients and the Investigator Brochure. Fujisawa responded on 22 December, and sent the material requested as volume 8 of a total of 12 volumes.

Comment: The accurate attribution of causality of adverse events as drug-induced has been one of the most difficult problems in medicine to resolve, despite many attempts over the past 35 years or so. Most of the initial attempts considered the problem in general, for any drug-induced adverse reaction (Irey, 1971; Feinstein, 1974; Karch and Lasagna, 1975; Kramer, et al., 1979; Naranjo, et al., 1981), but special efforts were subsequently undertaken in France (Danan, et al., 1987, 1988; Bénichou, et al., 1990, 1993) to address the question of drug-induced liver injury (DILI), and soon after in other European countries (Maria and Victorino, 1997; Aithal, et al., 2000; Lucena, et al., 2001). More recently, with the formation of the Drug-Induced Liver Injury Network (DILIN) funded by the National Institutes of Health (NIH) in 2003, particular attention has been aimed at moving beyond simply opinion-based overview decisions as to the quantitative likelihood of drug-induced causality of the liver reactions. It has been recognized for many years (Goodman, 2002) that there are no pathognomonic histologic changes to make a certain diagnosis that an hepatic disorder is caused by exposure to a drug, as opposed to being caused by a non-drug or disease etiology. At most it can be said that a given set of findings on liver biopsy or autopsy may be “compatible with”

or “consistent with” drug causation. There are no laboratory tests that are diagnostic, either. The diagnosis of DILI therefore is one of exclusion, requiring that other possible causes be ruled out, before concluding that it may have been the drug that caused the problem. Time relationships of exposure to drug are critical, for the reaction must follow the exposure, although by how much time is still debatable. Generally, it is widely believed that if the reaction subsides when exposure to drug is stopped (dechallenge), that is some evidence in favor of drug-causation; even stronger evidence is reappearance of the reaction if drug administration is resumed (rechallenge), but that is less and less frequently done intentionally because of the danger of a more severe, irreversible reaction, as well as for ethical and legal liability reasons. To go beyond what the expert panel of hepatologists did when reviewing the 19 cases, let us consider in more detail the semi-quantitative methods developed initially in France, and now widely used throughout the world (Lee, 2000; Kaplowitz, 2001; Kaplowitz, et al., 2003) and under active investigation by the DILIN group.

French investigators (Danan and Bénichou, 1987-1993) worked for years to develop national and international consensus on what information would be needed and how to weight that information to make a reasonably certain diagnosis of DILI. They developed a method for typing a given liver reaction as principally hepatocellular or cholestatic, or mixed, based on the ratio (R) of relative rise in serum activity of alanine aminotransferase (ALT) to alkaline phosphatase (ALP) at the time of onset of the hepatic reaction, or first set of clearly abnormal laboratory findings, both expressed as multiples of the upper limit of the normal range for each measure.

DETERMINING THE TYPE OF ACUTE LIVER INJURY

International Consensus (1990), *J Hepatol* 11: 272-6.

<i>Ratio (R) of serum activities of ALT/ ALP, in xULN, measured together at time liver injury first recognized</i>	
Hepatocellular	$R \geq 5$, OR (ALT >2xULN and ALP in normal range)
Cholestatic	$R \leq 2$, OR (ALP > 2xULN and ALT in normal range)
Mixed	$2 < R < 5$ AND (ALT > 2xULN and ALP > ULN)

Note: ALT, alanine amonotransferase; ALP, alkaline phosphatase; xULN, multiples of the upper limit of the normal range.

They then assembled teams of experts from Europe and the Unites States to define terminology, establish standards and definitions, and decide what clinical information was critical to making the best decisions about drug causality. The time of drug exposure and course of the hepatic reaction were agreed to be essential factors, with positive weight for reaction following drug exposure, then subsiding when exposure was stopped, and reappearance if drug exposure was resumed. Negative weights were applied if the timing was wrong. Other possible causes for acute liver injury were important to determine, including acute viral hepatitis A or B (much less often acute hepatitis C), ischemic hepatitis following shock or heart failure, recent heavy alcohol consumption, acute cholelithiasis, autoimmune hepatitis, and less often other disease causes such as acute onset of Wilson’s disease, infections with other viruses (cytomegalic, herpes simplex, Ebstein-Barr). Also considered were other drugs that might have been taken concomitantly, and the known history of hepatotoxicity of the drugs, both the one in question and the concomitant medications. Weights for each factor, ranging from +3 to -3 points were assigned, by consensus of the experts, resulting in a total score that could range from -8 to +14. Scores of 0 or less were taken to exclude the possibility of drug-induced injury, 1 or 2 unlikely, 3-5 possible, 6-8 probable, and 9-14 as highly probable.

Because both Danan and Bénichou at that time were employed by the pharmaceutical firm of Roussel-Uclaf, the system of scoring was called "RUCAM," Roussel-Uclaf Causality Assessment Method. The simplified RUCAM scoring system, as published in 1993 (Danan, et al.; Bénichou, et al.), and still in use ten years later (Danan, 2003):

Criteria for Causal Assessment of Drug-induced Hepatocellular Liver Injury

1. Temporal relationship of start of drug to start of illness	
Initial treatment: onset in 5-90 days; subsequent treatment course: 1-15 days	+2
Initial treatment <5 or >90 days; subsequent treatment course: > 15 days	+1
After stopping drug: onset within 15 days, or within 15 days after subsequent treatment	+1
Otherwise	0
2. Course	
ALT decreases \geq 50% from peak within 8 days	+3
ALT decreases \geq 50% from peak within 30 days	+2
If the drug is continued or decrease \geq 50% from peak >30 days, or inconclusive	0
Against causative role for drug	-2
3. Risk factors	
Alcohol use, 1; No alcohol use, 0	0 or 1
Age \geq 55 years, +1; Age < 55 years, 0	0 or 1
4. Concomitant drug	
No concomitant drug administered	0
Concomitant drug with suggestive or compatible time of onset	-1
Concomitant known hepatotoxin with suggestive or compatible time of onset	-2
Concomitant drug with positive rechallenge or validated diagnostic test	-3
5. Non-drug causes: Six are primary: recent hepatitis A, B, or C, acute alcoholic hepatitis (AST \geq2x ALT), biliary obstruction, recent hypotension (especially if heart disease). Secondary group: Underlying other disease; possible CMV, EBV or HSV infection	
All primary and secondary causes reasonably ruled out:	+2
All 6 primary causes ruled out	+1
4 or 5 primary causes ruled out	0
Fewer than 4 primary causes ruled out (maximum negative score for items 4 and 5: -4)	-2
Non-drug cause highly probable	-3
6. Previous information on hepatotoxicity of the drug in question	
Package insert or labeling mention	+2
Published case reports but not in label	+1
Reaction unknown	0
7. Rechallenge	
Positive (ALT doubles with drug in question alone)	+3
Compatible (ALT doubles with same drugs as given before initial reaction)	+1
Negative (Increase in ALT but \leq 2 X ULN, same conditions as when reaction occurred)	-2
Not done, or indeterminate result	0

Total (range of algebraic sum: -8 to +14)

Note: Item 4 and 5 cannot exceed a score of -4

Interpretation: Highly probable, >8; Probable, 6-8; Possible, 3-5; Unlikely, 1-2; Excluded, \leq 0

Applying the RUCAM to a given case still requires experience and skill, as well as a consistent approach to how the items are defined. One of the problems in scoring the likelihood that a given hepatic abnormality is a DILI has been the amount and quality of information available to whomever is attempting to judge possible causality. This led the DILIN Causality Committee to list information that is needed in order to exclude non-drug causes of a given hepatic reaction. Items felt to be critical were:

DILIN DATA COMPLETENESS CHECKLIST
CRITICAL INFORMATION FOR DECIDING ON CAUSE OF LIVER INJURY

- | | | | |
|----|---|--------|----------------|
| 1 | Were details of drug exposure including dose, drug start and stop date recorded? | No ___ | Yes ___ |
| 2 | Was lifetime history of medication use from the same therapeutic class of agents recorded? | No ___ | Yes ___ |
| 3 | Was timing of clinical liver disease recorded? | No ___ | Yes ___ |
| 4 | Were key history and PE data present? | No ___ | Yes ___ |
| 5 | Was assessment for prior liver disease performed? | No ___ | Yes ___ |
| 6 | Were doses, start and stop dates of competing prescription medications recorded? | No ___ | Yes ___ |
| 7 | Were doses, start and stop dates of OTC and complementary/alternative agents recorded? | No ___ | Yes ___ |
| 8 | Was baseline EtOH history known? | No ___ | Yes ___ |
| 9 | Was baseline ALT recorded? | No ___ | Yes ___ |
| 10 | Were serial ALT values recorded? | No ___ | Yes ___ |
| 11 | Was baseline total bilirubin recorded? | No ___ | Yes ___ |
| 12 | Were serial total bilirubin values recorded? | No ___ | Yes ___ |
| 13 | Was baseline AP recorded? | No ___ | Yes ___ |
| 14 | Were serial AP values recorded? | No ___ | Yes ___ |
| 15 | Was baseline PT (INR) recorded? | No ___ | Yes ___ |
| 16 | Were serial PT (INR) values recorded? | No ___ | Yes ___ |
| 17 | Were data for anti-HAV IgM recorded? | No ___ | Yes ___ |
| 18 | Were data for HBsAg recorded? | No ___ | Yes ___ |
| | <i>If HBsAg was positive for >6 months, please be sure to also answer questions 30 and 31.</i> | | |
| 19 | Were data for anti-HBc IgM recorded? | No ___ | Yes ___ |
| 20 | Were data for HCV RNA recorded? | No ___ | Yes ___ |
| | <i>If HCV RNA was positive for >6 months, please be sure to also answer question 32.</i> | | |
| 21 | Were data for autoimmune hepatitis (ANA, immunoglobulins) recorded? | No ___ | Yes ___ |
| 22 | Was serum ceruloplasmin, if under 50, recorded? | No ___ | Yes ___ |
| 23 | Was history of hypotension or CHF recorded? | No ___ | Yes ___ |
| 24 | Were liver ultrasound, CT, or MRI data recorded? | No ___ | Yes ___ |
| 25 | Was ERCP performed, and if so, are data available? | No ___ | Yes ___ |
| 26 | Were liver biopsy data present? | No ___ | Yes ___ |
| 27 | Were data on rechallenge available? | No ___ | Yes ___ |
| | <i>Data related to chronic HIV, HBV or HCV:</i> | | |
| 28 | If the patient had a history of HIV disease, was baseline CD4 recorded? | No ___ | Yes ___ NA ___ |
| 29 | If HIV was positive, were serial CD4 and HIV RNA values recorded? | No ___ | Yes ___ NA ___ |
| 30 | If HBsAg positive >6 months, prior HBV DNA, HBeAg, anti-HBe, treatment recorded ? | No ___ | Yes ___ NA ___ |
| 31 | If HBsAg was positive for >6 months, were data on anti-HDV available? | No ___ | Yes ___ NA ___ |
| 32 | If HCV RNA positive >6 months, were prior HCV RNA, ALT, and treatment recorded? | No ___ | Yes ___ NA ___ |

Note: PE, physical examination; ALT, alanine transaminase, ; ALP, alkaline phosphatase; ; PT, prothrombin time; INR, international ratio; Serious = hospitalized, disabling, life threatening, or fatal; HAV, hepatitis A virus; IgM, immunoglobulin M; HBV, hepatitis B virus; ; HCV, hepatitis C virus; RNA, ribonucleic acid assay for HCV; ANA, antinuclear antibodies; EtOH, , ethanol; CHF, congestive heart failure; CT, computed tomography; MRI, magnetic resonance imaging.

Comment: Several of these items contain two or more questions, which cannot be well answered by a simple yes or no, and the quality of information for each is not assessed, just whether or not some information was available or recorded. Nevertheless, it is valuable for scoring the RUCAM to have as much information as possible. It may be unlikely that many cases will have all the information listed above, but it is perhaps useful to make some effort to quantitate how much information was indeed available for each of the cases to be adjudged. It has been the experience of all who attempt

to use spontaneously reported data, such as reports to MedWatch, that there is much information missing. The DILIN group recently (January 2005) called Dr. Danan, now working at Aventis in Paris, to resolve some questions of definition, so that in the future they can apply the method to scoring putative DILI cases in both retrospective review of cases associated with drugs known to cause hepatotoxicity of different types (isoniazid, phenytoin, Augmentin: clavulanic acid + amoxicillin), and valproic acid), and to prospective study of DILI cases from any drug. Use of the RUCAM is still something of an art, and obtaining accurate and reproducible results both within raters at different times and between raters at any time is still a work in progress. Proper use of the RUCAM requires that considerable amounts of good information be gathered. Simple failure to rule out 3 or more of the 6 primary disease causes of acute liver injury generates a -2 score for item 5, which will negate a +2 score for initial onset within 5-90 of first drug exposure. If nothing is known about the course after stopping the drug (dechallenge), and if there are no risk factors of age 55 or more or use of alcohol, no rechallenge is done, no concomitant drug likely to have caused the reaction was known to have been given, and no labeling or literature information available, then a RUCAM score of 0 will be generated, which is taken as excluding DILI. The RUCAM demands that adequate information be obtained, and allows an interpretation of "excluded" simply by failing to gather and record adequate information. This will need to be borne in mind as we proceed.

Finally, after assessing the quantity of information available, and using that information to score the likelihood that a DILI has occurred, a global assessment can be attempted, using a five-point scale:

Based on your assessment of the information available and RUCAM scoring, how likely do you assess the hepatic abnormalities to be drug-induced?

- | | | |
|--------------------------|-------------|---------------|
| <input type="checkbox"/> | Definite | More than 95% |
| <input type="checkbox"/> | Very likely | >75-95% |
| <input type="checkbox"/> | Probable | >50-75% |
| <input type="checkbox"/> | Possible | 25-50% |
| <input type="checkbox"/> | Unlikely | <25% |

Therefore, we shall try to apply these methods to assessing the apparent likelihood of causation of the selected cases as drug-induced injury, and then compare the findings to the consensus arrived at by the expert panel. As requested by Dr. Singer on 13 January 2005, we shall start by considering cases #1008, 10665008, 10745035, 063786, 262780, 262788, 287679, 0203501, and 474177, cases thought to be relatively less confounded, or in younger patients. Then, I shall consider the other 10 cases of the 19 reviewed by the special panel of experts.

In the tables below, I shall summarize patient identification information, acute liver disease, other concomitant or underlying diseases, concomitant medications, quantity and quality of information available, the RUCAM score, and my global assessment as an estimated percent likelihood that the drug may have caused the liver injury observed or diagnosed. This will not be an estimation of whether the drug may have caused the death of the patient, only the acute liver disease. I shall use the DILIN 32-question checklist of data completeness, and apply the information available in the patient profile and narrative provided for each case by the sponsor, as reviewed by the expert panel of external hepatologists. Finally, after reviewing all 19 cases, I shall compare the consensus report by Dr.  sent on 23 November 2004, and comment on agreements or disagreements.

Micafungin hepatotoxicity

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#1008 M48b — Pretoria, South Africa	Sday AST ALT ALP TBL -3 40 19 125 0.35 7 49 19 132 0.76 14 2068 322 122 0.76 hepatocellular injury nausea (7), vomiting (8), confusion (13), hepatorenal failure (13)	HIV: asthenia, diarrhea, cachexia. CD4 = 290/μL inv esophageal candidiasis. tuberculosis died — (15), of aggravated tuberculosis	micafungin — to — (14) cotrimoxazole betaclopramide loperamide flumazenil	9 + 20 – 3 NA very poor	+2 onset -2 <3 R/Os = 0 inadequate information	50%, possible

Comment: death may have resulted from the advanced underlying disease, but did micafungin cause the acute terminal liver failure?

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#10665008 F31b — Pretoria, South Africa	Sday AST ALT ALP TBL -1 47 28 103 0.29 7 49 22 163 0.23 16 44 15 128 0.76 21 4002 1274 294 3.74 hepatocellular injury nausea (16), anxiety (16), hepatic failure (21)	HIV: severe cachexia. CD4 = 34/μL inv esophageal candidiasis. reactivated tuberculosis died — (21), of pneumonia – Pneu. carinii	fluconazole — to — (21) Voltaren Panadol Cifran Rifafour Maxolon	8 + 21 – 3 NA very poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	30%, possible

Comment: death may have resulted from the tuberculosis, but did fluconazole or other drug cause the acute terminal liver failure?

Note: F, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#10745035 M34b — Pretoria, South Africa	Sday AST ALT ALP TBL -3 121 65 264 0.94 5 66 29 208 8.25 ?? alcoholic hepatic injury jaundice (5), severe hepatic failure (4-21)	HIV: lymphadenopathy, cachexia, diarrhea, anemia CD4 = 97/μL inv esophageal candidiasis. reactivated tuberculosis alcohol abuse died — (17), of reactivated tuberculosis	micafungin — to — (5), stop because liver failure Rifinah DS-24 Voltaren Bactrim herbal cough syrup	6 + 22 – 4 NA very poor	+2 onset -2 <3 R/Os +1 alcohol -1 other drug = 0 inadequate information	25%, possible

Comment: death may have resulted from tuberculosis, but did micafungin or other drug aggravate advanced alcoholic liver disease?

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#063786 M58c — location not stated	Sday AST ALT ALP TBL 1 158 102 332 30.5 7 266 132 472 43.0 ?? previous liver disease jaundice (5), severe hepatic failure (4-21)	end-stage liver disease, corticosteroid therapy invasive lung aspergillosis. died — (8), of hepatic failure from unknown liver disease	micafungin — to — (7) Solumedrol Prevacid Ambisome Haldol	7 + 20 – 5 NA very poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	15%, unlikely

Comment: death may have resulted from tuberculosis, but did micafungin or other drug aggravate advanced unknown liver disease?

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#262780 M4c — location not stated	Sday AST ALT ALP TBL 1 32 38 335 1.70 9 25 35 345 2.40 16 20 33 236 4.10 23 35 57 314 2.20 30 196 178 581 9.80 cholestatic liver disease nausea (5), vomiting (5), itch (18), bilirubin elevation (24), hepatic failure (27)	leukemia, bone marrow transplant invasive lung aspergillosis. died — (31), of interstitial pneumonia, with multiorgan failure	micafungin — to — (29) ABELCET itraconazole Tylenol Foscarnet Zithromax Actigall Many, many others	10 + 17 – 5 NA poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	25%, possible

Comment: death may have resulted from tuberculosis, but did micafungin cause or aggravate cholestatic liver disease?

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	Global
#262788 M16b Memphis, TN	Sday AST ALT ALP TBL -2 87 58 156 5.7 9 118 49 279 21.1 10 134 56 353 24.8 cholestatic liver disease bilirubin elevation (2), hepatic failure (2), renal failure (4)	acute myelogenous leukemia, allogenic marrow transplant invasive lung aspergillosis. probable liver candidiasis died (10), of respiratory distress syndrome autopsy confirmed	micafungin to (10) fluconazole Myccelex Ambisome many others	10 + 17 - 5 NA poor	-2 <3 R/Os -1 other drug = -3 inadequate information	<5%, very unlikely

Comment: death may have resulted from lung disease, but cholestatic liver disease preceded micafungin, so very unlikely M-DILI.

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#287679 F51c location not stated	Sday AST ALT ALP TBL 1 50 59 946 7.08 7 57 26 1217 9.65 14 134 63 2601 11.7 20 159 112 3188 19.6 cholestatic liver disease pre-existing disease; pain(13), ascites (19), jaundice (30)	pancreatic carcinoma Candida albicans septicemia. died (30), of hepatic failure secondary to spread of pancreatic cancer	micafungin to (19) amphotericin B vancomycin Panadol Tazocin others	11 + 16 - 5 NA fair	-2 <3 R/Os -3 panc. CA -1 other drug = -6 inadequate information	<1%, ruled out

Comment: death resulted from pancreatic cancer, and cholestatic liver disease preceded micafungin, so very unlikely M-DILI.

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#0203501 F36o U MN Minnea- polis MN	Sday AST ALT ALP TBL 1 37 43 81 0.9 4 27 37 65 0.6 12 20 17 69 1.5 16 5970 754 173 10.5 hepatocellular liver injury anorexia (6), liver large (10), confusion and renal failure (15), coagulation disorder (16), liver failure(16), cardiac arrest (17), GI bleed (18)	acute myelogenous leukemia, allogenic marrow transplant no fungal infection proved mitral regurgitation resistant bacteremia died (19), of gastro- intestinal hemorrhage, after liver failure with coagulation disorder	fluconazole to (15) IV heparin (?flush) acetaminophen Ativan Halcion tobramycin many others	13 + 14 - 5 NA fair	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	40% possible

Comment: death resulted from GI bleeding, but did fluconazole cause the acute liver failure and coagulation disorder?

Note: F, female; o, Oriental; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#474177 M40c mamz, Germany	Sday AST ALT ALP TBL 1 85 66 696 5.17 7 79 29 638 11.9 14 99 52 691 14.5 21 134 66 657 19.4 28 444 510 1680 25.0 34 419 381 1470 40.4 35 363 298 1442 41.8 cholestatic liver disease jaundice (5), pruritus (16), renal failure (33), shock, coma, hepatic failure (36),	leukemia, unspecified probable lung aspergillosis. alcohol abuse died (38), of leukemia	micafungin to (34) amphotericin B Distranervin cyclophosphamide Cytarabine Haldol Ambisome Caspofungin many others	10 + 17 - 5 NA poor	-2 <3 R/Os -1 other drug = -3 inadequate information	<5%, very unlikely

Comment: death may have resulted from terminal bleed, but cholestatic liver disease preceded micafungin, so very unlikely M-DILI.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

Comment: For these 9 cases, chosen by Dr. Mary Singer for me to review first, there are none that show a RUCAM score that suggests even possible drug causation of the liver disease, but mainly because the data available to insert into the RUCAM system are so inadequate. Without sufficient data, the RUCVAM can yield misleading interpretations that the likelihood of DILI is excluded. On

the other hand, the exercise of examining carefully just what information is and is not available may allow better-informed global assessments that may lead to different conclusions with higher levels of likelihood that the drugs in question may have at least aggravated severely any pre-existing liver disease or may have induced liver disease in otherwise very sick people. With these thoughts clearly in mind, let us now consider the other 10 cases of the 19 reviewed by the expert panel.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#384301 M52c Ottawa, ON CA	Sday AST ALT ALP TBL 1 25 33 163 17.9 4 24 23 387 25.8 7 45 28 188 21.5 8 66 33 134 24.2 cholestatic liver disease jaundice, liver failure (-??), hemorrhage (8), hepatic failure (9)	Hodgkin's lymphoma no fungal infection proved. renal insufficiency, Cr 3.15 sepsis, V tach (3), severe acidosis (6), Died (9), of hepatic failure. Autopsy confirmed dx	no antifungal agent ("placebo") 25Mar03 to 1Apr03 (8) cefotaxime vancomycin acyclovir Ativan many others	10 + 17 - 5 NA poor	onset before -2 <3 R/Os -3 other cause = not DILI incompatible inadequate information	<1%, not DILI

Comment: death resulted from lymphoma infiltration of the liver, preceding administration of "placebo", so not-DILI.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#2194007 M77c Stanford Palo Alto CA	Sday AST ALT ALP TBL 1 546 117 25 2.0 5 234 17 66 2.9 8 113 17 95 8.1 12 116 22 149 16.3 hepatocellular disease shocked liver failure (-??), hemorrhage (8), hepatic failure (9)	massive blood loss, aortic aneurysm repair (-1) no fungal infection proved. renal insufficiency, Cr 3, diabetes, respiratory distress, Died (9), in shock, with hepatorenal, respiratory failure	micafungin to (13) Kefzol midazolam dopamine insulin many others	10 + 17 - 5 NA poor	onset before -2 <3 R/Os -3 other cause = not DILI incompatible inadequate information	<1%, not DILI

Comment: death resulted from hypotensive shock, ischemic liver disease, preceding administration of micafungin, so not-DILI.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#20785 F30c U MN Minnea -polis MN	Sday AST ALT ALP TBL 8 32 30 236 0.7 15 35 38 257 0.7 28 35 26 257 0.6 54 16 12 150 2.5 66 66 27 203 3.4 80 44 244 34.6 93 64 844 51.3 cholestatic liver disease abd. pain (18), confusion (37) hepatic failure (78)	acute myelogenous leukemia, post marrow transplant probable lung aspergillosis. died (94), of veno occlusive disease, sepsis, liver failure, renal failure	micafungin to (77) amphotericin B itraconazole Percocet Tylenol Ativan Dilantin CellCept Many others	12 + 15 - 5 NA fair	+2 onset -2 <3 R/Os -1 other drug -3 other cause = -4 inadequate information	<10%, unlikely

Comment: death may have resulted from veno-occlusive disease, but did micafungin aggravate the terminal liver failure?

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#33885 F62b location not stated	Sday AST ALT ALP TBL -1 44 41 652 2.7 7 82 55 540 2.3 14 5836 783 1155 3.2 hepatocellular injury added ascites (6), confusion (14), vomiting (15), renal failure (15), hypotension (15)	duodenal carcinoid tumor septicemia, Candida glab. diabetes, cachexia, sepsis, pancreatitis, hypotension, renal failure, cholestatic liver disease from carcinoid died (15), sepsis, multiorgan failure	micafungin to (13) fluconazole APAP propoxyphen cefoxitin vancomycin many others	10 + 17 - 5 NA poor	+2 onset -2 <3 R/Os -1 other drug -3 other cause = -4 inadequate information	40%, possibly worsened

Comment: death may have resulted from sepsis, but did micafungin add hepatocellular injury to carcinoid liver disease?

Note: F, female; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#585271 M73c — Warsaw, Poland	Sday AST ALT ALP TBL 1 36 19 112 0.72 5 29 16 8 439 118 928 2.18 mixed liver injury severe liver damage (8), renal insufficiency (8)	mantle cell lymphoma, chemotherapy pulmonary aspergillosis and candidiasis, pneumonia diabetes, coronary disease Die ^r (22), heart failure. Autopsy confirmed.	micafungin to — (8) metformin fluconazole Ambroxol many others	8 + 19 – 5 NA very poor	+2 onset -2 <3 R/Os -1 other drug -3 other cause = -4 inadequate information	<10%, unlikely

Comment: death resulted from cardiac failure, which may have caused ischemic liver injury

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#059777 M0.7h — Washing- ton, DC	Sday AST ALT ALP TBL -1 10 9 135 5.7 3 18 9 115 23.3 10 52 3 305 51.1 17 101 81 290 8.9 24 202 232 330 6.4 31 61 146 315 2.9 46 54 78 284 1.5 84 37 58 218 0.7 98 27 10 91 0.3 116 10 33 163 162 26 153 1.1 ?cholestatic liver injury jaundice, hepatomegaly (2), renal insufficiency (11), acute hemolysis? (9)	acute myelogenous leukemia, chemotherapy Klinefelter syndrome sinus aspergillosis, sinusitis fever, pancytopenia, failure to thrive, systolic murmur survived , recovered	micafungin 22Aug00 to 13Dec00 (114) Ambisome Nystatin Tylenol Ativan Midazolam Bactrim RBCs, platelets dopamine itraconazole many, many others	9 + 16 – 5 NA poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	25%, possibly made worse

Comment: infant, 8 months, with preexisting jaundice, possibly increased markedly by micafungin, but adapted and recovered

Note: M, male; h, Hispanic; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#287674 M48c — Capetown South Africa	Sday AST ALT ALP TBL 1 22 18 74 0.59 7 51 26 87 0.59 14 257 356 110 8.42 21 54 65 117 25.7 hepatocellular injury vomiting (3), jaundice (15), hepatic failure (14)	Lymphoma chemotherapy Candida rugosa septicemia hypotension (13), Afib (14), anemia and renal failure (14), pneumothorax (17), bleeding gastric ulcer, hematemesis, edema (28) died — (28), heart failure	micafungin — to — (27) warfarin (-4 to 14) Panadol Amphotericin B Mycostatin many others	10 + 17 – 5 NA poor	+2 onset -2 <3 R/Os -1 other drug = -1 inadequate information	30%, possible

Comment: death resulted from hypotensive shock, ischemic liver disease.

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#372501 M39c — Ontario Canada	Sday AST ALT ALP TBL 3 31 37 62 0.47 8 35 59 58 0.64 16 17 24 45 5.08 19 21 18 51 14.3 24 58 35 64 28.7 26 60 45 62 36.9 33 118 110 53.9 39 129 226 65.5 veno-occlusive disease jaundice (13), veno-occlusive disease (16), liver failure (32)	acute biphenotypic leukemia marrow transplant (6) HBsAg carrier possible fungal infection (26) persistent leucopenia, anemia, thrombocytopenia (21-35) renal insufficiency (27-43) died — (43), hepatic failure, venoocclusive disease	fluconazole — to — (26): LE cyclophosphamide ciprofloxacin methotrexate acyclovir ceftazidime vancomycin Abelcet (26-34) dopamine many others	14 + 15 – 3 NA fair	+2 onset -2 <3 R/Os -2 neg dechall -1 other drugs -3 other cause = -6 limited information	<1%, not F-DILI

Comment: death resulted from veno-occlusive liver disease, probably from chemotherapy; liver disease not from fluconazole

Note: M, male; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; LE, lack of efficacy; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#423004 F40c — Portland, Oregon	Sday AST ALT ALP TBL -1 39 55 177 0.6 3 122 289 171 0.7 6 91 134 120 1.6 12 110 110 81 1.6 17 33 25 111 2.4 hepatocellular injury abdominal pain, asthenia (7), anorexia (12), 'hepatic failure' (17), abnormal thinking (18-34)	chronic myelogenous leukemia marrow transplant pulmonary Candida albicans and Aspergillus sp. chest pain (8), lung edema (9) pericardial effusion (9), heart failure, congestive (10), renal failure (13), GVHD (32) died (34), pulmonary mycosis	fluconazole — to — (17): LE ursodiol cyclophosphamide Decadron acetaminophen ciprofloxacin methotrexate vancomycin Solumedrol dobutamine many others	10 + 17 – 5 NA poor	+1 onset -2 <3 R/Os -1 other drugs = -2 inadequate information	25%, possible
Comment: death resulted from cardiopulmonary disease, probably from chemotherapy; liver injury relatively mild (not liver failure)						

Note: F, female; c, Caucasian; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, alkaline phosphatase; TBL, total bilirubin; LE, lack of efficacy; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#3103 F26c “ — ” location not stated	Sday AST ALT ALP TBL -2 27 30 312 0.9 1 27 20 140 0.8 7 24 18 190 1.1 14 16 17 152 0.8 28 18 9 163 0.8 ? obstructive liver disease nausea (5), 'liver damage' (11), vomiting (16), liver biopsy, laparoscopy (42)	HIV, non-Hodgkins lymphoma esophageal Candida alb. fever, cough many liver abscesses(15), liver bx(42), non-Hodgkins lymphoma in hilar nodes survived	micafungin 3May02 to 16May02 (14) acetaminophen(-1 to 24) isoniazid (2-24) metronidazole ceftriaxone many others	9 + 18 – 5 NA very poor	incompatible excluded inadequate information	<1% not M-DILI
Comment: no significant liver disease; isolated elevated alkaline before micafungin given						

Note: F, male; c, Caucasian; Sday, days since first dose; AST, ALT, serum aspartate, alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; R/Os, diseases ruled out; (#), study day number; NA, not applicable.

Comment: In the majority of these cases (10 of the 19), there did not seem to be clear causation of the hepatic injury by the administered antifungal treatment, which in 8 of the cases was micafungin (#3103, 20785, 63786, 262788, 287679, 474177, 585271, 2194007), in 1 case was fluconazole (#372501) and in 1 case none (#384301). Nine other cases seem possibly to have had liver injury caused or aggravated by the drug, 6 by micafungin (#1008, 33885, 262780, 287674, and 10745035) and 3 by fluconazole #203501, 423004, 10665008). There were no cases in this series in which it can be stated with confidence that the antifungal drug definitely or even probably caused the liver injury, mainly because of multiple confounding possible other causes from underlying or concomitant diseases, or by the plethora of other drugs that were given. This was further made difficult by the generally inadequate provision of sufficient clinical information to make the differential diagnosis of drug-induced, as opposed to disease-induced, other drug-induced, and certainly no information at all on the possibilities of drug-drug interactions that might have caused the problems. Many of the patients considered were actually dying of terribly serious diseases when antifungal treatment was started, and there are almost no data on effects of withdrawing the drug to see if improvement in the liver injury might follow, and no patients were observed long enough for rechallenge effects to be observed.

We are stuck, therefore, with relying upon opinions as to whether the hepatic injuries seen were related to drug administration or not, and even experts do not always agree, as we have seen, and will now consider more closely. After considering independently the data provided, I rated each case for adequacy of information to make a diagnosis of DILI, an estimate of the RUCAM score, and my estimated likelihood that the hepatic reaction was drug induced, before looking at the panel consensus ratings. In the following table, I list my ratings and the expert panel's:

COMPARISON OF CAUSALITY ATTRIBUTION RATINGS BY JRS AND THE EXPERT PANEL

Note: M, micafungin; F, fluconazole; N, neither; NR, not related; P, possibly related; R, related; U, unlikely

Case #	Underlying diseases	Liver Disease/Injury	Drug	JRS	Panel
# 1008, M48b, South Africa	HIV cachexia, tuberculosis; Esophageal candidiasis	Hepatocellular injury without jaundice, 14 days, moderately severe	M	P 50% concur	PR
# 3103, F26c, location not stated	Non-Hodgkin's lymphoma Esophageal candidiasis	Obstructive liver disease, hilar lymphoma, elevated ALP before micafungin given	M	U <1% concur	NR
# 20785, F30c, Minneapolis MN	Acute myelogenous leukemia; Probable lung aspergillosis	Cholestatic liver disease, before drug given, but worse after 80 days, ?leukemic infiltrate	M	U <10% concur	NR
# 33885, F62b, location not stated	Duodenal carcinoid tumor; Candida septicemia	Hepatocellular injury, at 14 days, added to carcinoid cholestatic disease	M	P 40% disagree*	NR
<i>*Comment: Panel thought NR, but JRS noted preexisting liver disease, probably worsened by micafungin</i>					
# 59777, M 0.7h Washington DC	Acute myelogenous leukemia; Sinus aspergillosis ; survived	Cholestatic liver injury, transient, aggravating mild preexisting abnormality, recovered	M	P 25% disagree*	NR
<i>*Comment: Panel thought data inadequate, but JRS noted preexisting liver disease, probably worsened by micafungin.</i>					
# 63786, M58c location not stated	End-stage liver disease ???; Invasive lung aspergillosis	Previous liver disease of unknown type, with slight increase in jaundice, 7 days	M	U 15% concur	NR
# 262780, M4c location not stated	Leukemia, marrow transplant; Lung aspergillosis	Cholestatic liver injury or aggravation, some preexisting cholestasis	M	P 25% concur	PR
# 262788, M16b Memphis TN	Acute myelogenous leukemia; Lung aspergillosis; liver C alb	Cholestatic liver injury aggravation, 9 days, some preexisting cholestasis	M	U <5% concur	NR
# 287674, M48c, South Africa	Lymphoma chemotherapy; Candida rugosa septicemia	Hepatocellular injury with jaundice, 14 days, Liver tests normal before	M	P 30% concur	PR
# 287679, F51c location not stated	Pancreatic CA, metastases; Candida alb septicemia	Cholestatic liver disease, pre-existing, before drug given	M	U <1% concur	NR
# 474177, M40c Mainz, Germany	Leukemia, NOS Probable lung aspergillosis	Alcoholic liver disease, with cholestasis, somewhat worsened after 21 days on drug	M	U <1% disagree*	PR
<i>*Comment: Panel thought PR, but JRS noted preexisting liver disease, probably worsened by drugs given for leukemia.</i>					
# 585271, M73c Warsaw, Poland	Mantle cell lymphoma Lung aspergillosis & candida	Mixed liver injury, probable tumor in liver, preexisting before micafungin given	M	U <10% concur	NR
# 2194007, M77c Palo Alto CA	Massive blood loss, aneurysm Repair; no fungal infection	Hepatocellular disease, probably ischemic liver injury	M	U <1% concur	NR
#10745035, M34b South Africa	HIV cachexia, tuberculosis; Esophageal candidiasis	Aggravation of prior alcoholic liver disease, with jaundice and hepatic failure, 5 day	M	P 25% concur	PR
FLUCONAZOLE CASES					
# 203501, F36o Minneapolis MN	Acute myelogenous leukemia; No fungal infection proved	Hepatocellular injury with jaundice, 16 days coagulation disorder, gastrointestinal bleeding	F	P 40% disagree*	NR
<i>*Comment: Panel divided, maybe aggravation, but data unreadable; JRS thought fluconazole may have caused liver failure</i>					
# 372501, M39c, Ontario, Canada	Acute biphenotypic leukemia Possible fungal infection	Veno-Occlusive disease, from chemotherapy, with progressive liver failure	F	U <1% concur	NR
# 423004, F40c, Portland OR	Chronic myelogenous leukemia Pulmonary aspergillus sp.	Hepatocellular injury, perhaps added to Leukemic infiltrate before drug	F	P 25% disagree*	NR
<i>* Comment: Panel thought NR; JRS thought quite possibly fluconazole-induced aggravation, not liver failure</i>					
#10665008, F31b South Africa	HIV severe cachexia, tbc; Esophageal candidiasis	Hepatocellular injury with jaundice, 21 days Severe	F	P 30% concur	PR
NEITHER MICAFUNGIN OR FLUCONAZOLE					
# 384301, M52c Ottawa, Canada	Hodgkin's lymphoma No fungal infection proved	Cholestatic liver disease before drug given, due to tumor in liver, not DILI	N	U <1% concur	NR

Comment: It may be seen that my independent assessments concurred with the consensus of the panel of experts in 5 of 6 cases in which they thought the liver abnormalities were possibly related to administration of study drug. The exception was #474177, the 40-year-old German man with a history of alcohol abuse who had significantly abnormal liver tests before starting on micafungin, and then slowly progressed to worsening of all his liver tests as he died of leukemia complications

or the many antineoplastic and other drugs he received. Micafungin was stopped after 34 days, and he lived only 4 days more, so not "dechallenge" effects could be observed. My estimates also were in concurrence in 9 of the 13 cases in which the panel thought the liver reactions were unrelated to study drug, with disagreements for cases #33885, 59777, both of whom received micafungin, and for cases #203501 and 372501 who received fluconazole. It was my thinking in all 4 cases that the antifungal treatment had added to or aggravated pre-existing liver disease, with some degree of likelihood, but insufficient information to be more certain.

The concept of drug-induced injury adding to or aggravating pre-existing liver disease was seen in some of the cases in which there was concurrence of our thinking (#262780), although this is not a widely held view. There is considerable controversy about whether or not a relatively uncommon or unpredictable ("idiosyncratic) hepatic injury is more likely to occur in patients with previous liver disease, or whether it simply appears so because such people are less well able to withstand or to recover from additional liver injury if it is induced by a drug.

Another point that was noted in review of these cases was that there were several cases of serum bilirubin elevations that seemed out of proportion to the serum enzyme indicators of liver injury, often in cases in which there was underlying liver disease not likely caused by micafunfin (e.g., see cases #63786, 262788, 474177, 384301, 2194007, 20785, 59777, 287674, and 372501 among the 19 cases summarized above). All of the echinocandins were plagued by some degree of red blood cell hemolysis problems during their development, and molecular manipulations were used to find less hemolytic antifungal compounds. Merck found that L-671,329 was less hemolytic than was aculeacin (Frompting and Abruzzo, 1989); and L-743,872 (MK-0991, (later called caspofungin) less hemolytic than amphotericin B (Bartizal, et al., 1997). Efforts in the Fujisawa laboratories in which FR131535 was found less hemolytic than FR901379 (Fujie, et al., 2001), led to FK-463 (micafungin). In evaluating the cases of possibly micafungin-induced hepatotoxicity, whether in a previously normal liver, or in aggravation of some underlying liver disease, a contribution of micafungin-accelerated hemolysis should be considered as at least partly responsible for rises in serum total bilirubin concentrations.

The finding of significant but rare hepatotoxicity associated with caspofungin, a recently approved member of this new class of echinocandin agents, is of interest and possible pertinence to this consideration of micafungin. The class of echinocandins (caspofungin, anidulafungin, micafungin) all have a central, large, cyclic hexapeptide nucleus with N-terminal fatty acyl and an amino group connecting the 3-OH-proline moiety to the δ -amino- γ -hydroxyornithine to form the ring. The three new drug agents differ mainly in their patterns of hydroxylations, which is extensive and confers the water solubility of the compounds (Wiederhold and Lewis, 2003), and in their α -aminoacyl side chains. The agents were developed to be safer than earlier antifungal agents that caused collateral damage to host cells (amphotericin B) and drug interactions (the -conazoles). Caspofungin (CANCIDAS, Merck) is a large, complex, semisynthetic molecule that inhibits 1,3- β -D-glucan synthase required for fungal cell wall synthesis, approved in January 2001 for treatment of invasive aspergillosis. It is of interest that although 8 cases of caspofungin hepatotoxicity have been reported to AERS, only one case is even mentioned in the published literature, in an acute leukemic patient who had moderate but reversible hepatotoxicity (Aliff, et al., 2003). No cases of micafungin-induced liver injury have been reported as yet.

In addition to the 19 cases discussed above that had been selected for special review, Dr. Mary Singer found two more, patients who had died after being treated with micafungin, and whose test results suggested acute liver injury. She sent copies of the narratives and patient profile summaries of data by fax on 24 January, and requested my opinion about them, in brief for the planned meeting at 4 p.m. that day, and more fully thereafter. On cursory inspection, both cases appeared to show acute rises in serum tests of liver injury and function, and of renal function, after starting treatment with micafungin. The information provided for the two cases is summarized below, in similar format to that used for the 19 cases previously reviewed above.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#10745031 M34b — South Africa	Sday AST ALT ALP TBL -3 101 85 217 1.05 7 649 305 519 4.27 hepatocellular injury not stated; lab tests suggest acute liver injury (7)	HIV: no retroviral therapy, CD4 = 148/ μ L inv esophageal candidiasis, anemia, renal insufficiency renal failure worsened (7) died — (10), of acute renal failure	micafungin — to — (9) Bactrim Immodium Lasix others	8 + 21 – 3 NA very poor	+2 onset -2 <3 R/Os = 0 inadequate information	50%, possible

Comment: death may have resulted from renal failure, but did micafungin cause the acute terminal liver injury also?

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

patient	acute liver disease	underlying diseases	medications	information	RUCAM	global
#10445008 M45c — Brazil	Sday AST ALT ALP TBL -1 50 74 547 0.41 8 179 227 646 0.82 14 43 81 741 1.18 26 5670 1760 249 4.05 hepatocellular injury mild transient injury (8), then more severe acute liver injury (26) when tbc therapy started	HIV: no retroviral therapy, cachexia, CD4 = 13/ μ L inv esophageal candidiasis, neurotoxoplasmosis disseminated tuberculosis; died — (26), of reactivated tuberculosis	micafungin — te — (14) Cisapride (3) Oxaciline (13) Riphampacine (20) Isoniazide (20) Pyrazinamide (20) many, many others	8 + 21 – 3 NA very poor	-1 onset? -2 <3 R/Os = -3 inadequate information	15%, unlikely

Comment: death may have resulted from tuberculosis, but did micafungin cause mild liver injury, anti-tbc therapy severe injury?

Note: M, male; b, Black; Sday, days since first dose; AST & ALT, serum aspartate & alanine aminotransferase; ALP, serum alkaline phosphatase; TBL, total bilirubin; HIV, human immunodeficiency virus; CD4, lymphocyte clustered domain 4; R/Os, diseases ruled out; (#), study day number.

Comment: The first case (#10745031) had findings 3 days before micafungin was started of modest serum ALT, AST, and ALP elevations but top-normal serum bilirubin, plus definite evidence of renal insufficiency (both UN and creatinine were elevated). After 7 days of micafungin, the renal indicators had worsened, but the serum AST, ALT, ALP and TBL were dramatically increased. It seems likely that the patient had some degree of tuberculous infiltrate in his liver, and that it is quite possible that micafungin induced an acute aggravation of the mild underlying liver problem, which clinically seemed overshadowed by the renal failure to which his death was attributed by the clinical staff. The data are insufficient for any more probable attribution of the acute liver injury to micafungin administration. The second case (#10445008) is interesting in the timing of the treatments. After micafungin was started, he showed a moderate mixed hepatocellular and cholestatic liver injury without rise in serum bilirubin, which subsided except for the cholestasis by Day 14 when the micafungin was stopped. After treatment with Oxaciline for phlebitis on Day 13, and initiation of anti-tuberculosis therapy with isoniazide, rifampin, and pyrazinamide on Day 20, he showed a dramatic rise in the serum transaminase activities suggesting acute superimposed hepatocellular injury with probable jaundice (bilirubin 4.05 mg/dL) on Day 26. Either the Oxaciline or the anti-tuberculosis regimen were more likely responsible for the severe hepatocellular injury noted on Day 26, 2 days before his death. The information available is inadequate to infer more.

Recommendations:

1. These cases in which there appear to be possible causation of liver injury following use of micafungin cannot be entirely dismissed, even though many of the cases can be "thrown out" as not related. As noted by the expert panel, these are extremely difficult cases to assess and there were many confounding factors, both other drugs and concurrent diseases. To make matters worse, drug-induced liver injury is a diagnosis of exclusion, and lack of good information to exclude other causes is not proof that they may be excluded.
2. Other cases must be looked for in patients treated with this micafungin, as well as the other two echinocandins, caspofungin and anidulafungin. Systemic fungal diseases usually occur in otherwise very sick patients who are on other therapies and have underlying problems, which may make them more vulnerable to or less able to recover from additional liver injury that may be caused by agents such as micafungin.

3. The labeling should indicate that some cases have been observed,

— / / / / — /

4. It may be shown that more patients are saved by micafungin treatment of their fungal infections than are injured, and the echinocandins may be safer than the previously available agents, but they should not be considered totally safe. Physicians should weigh carefully the relative benefits and risks of them, in managing these extremely serious and complex diseases.

John R. Senior, M.D.

cc: ODS PID#D040163
M. Avigan, ODS/DDRE
P. Seligman, OPSS
S. Birdsong, DDRE
M. Truffa, DDRE
R. Albrecht, HFD-590
M. Singer, HFD-590

References

- Aithal PG, Rawlins MD, Day CP. Clinical diagnostic scale: a useful tool in the evaluation of suspected hepatotoxic adverse drug reactions. *J Hepatol*. 2000 Dec;33(6):949-52. [PMID: 11131457]
- Aliff TB, Maslak PG, Jurcic JG, Heaney MI, Cathcart KN, Sepkowitz KA, Weiss MA. Refractory *Aspergillus pneumonia* in patients with acute leukemia: successful therapy with combination caspofungin and liposomal amphotericin. *Cancer*. 2003 Feb 15;97(4):1025-32. [PMID: 12569602]
- Barrett D. From natural products to clinically useful antifungals. *Biochim Biophys Acta*. 2002 Jul 18;1587(2-3):224-33. [PMID: 12084464]
- Bartizal K, Gill CJ, Abruzzo GK, Flattery AM, Kong L, Scott PM, Smith JG, Leighton CE, Bouffard A, Dropinski JF, Balkovec J. In vitro preclinical evaluation studies with the echinocandin antifungal MK-0991 (L-743,872). *Antimicrob Agents Chemother*. 1997 Nov;41(11):2326-32. [PMID: 9371328]
- Bénichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990 Sep;11(2):272-6. [PMID: 2254635]
- Bénichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. *J Clin Epidemiol*. 1993 Nov;46(11):1331-6. [PMID: 8229111]
- Carver PL. Micafungin. *Ann Pharmacother*. 2004 Oct;38(10):1707-21. [PMID: 15340133]
- Chiou CC, Groll AH, Walsh TJ. New drugs and novel targets for treatment of invasive fungal infections in patients with cancer. *Oncologist*. 2000;5(2):120-35. [PMID: 10794803]
- Danan G, Bénichou C, Begaud B, Biour M, Couzigou P, Evreux JC, Lagier G, Berthelot P, Benhamou JP. Critères d'imputation d'une hépatite aiguë à un médicament. Résultats de réunions de consensus. [*Criteria of imputation of acute hepatitis to a drug. Results of consensus meetings.*] *Gastroenterol Clin Biol*. 1987 Aug-Sep;11(8-9):581-5. [PMID: 3308618]
- Danan G. Causality assessment of drug-induced liver injury. Hepatology Working Group. *J Hepatol* 1988 Aug;7(1):132-6. [PMID: 3053889]
- Danan G, Bénichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol*. 1993 Nov;46(11):1323-30. [PMID: 8229110]
- Danan G. Atteintes hépatiques aiguës médicamenteuses. Qu'apportent les échelles diagnostiques ? [*Drug-induced acute hepatic injury. What is the value of diagnostic scales?*] *Gastroenterol Clin Biol*. 2003 May;27(5 Suppl):B21-5. [PMID: 12843933]
- Denning DW. Echinocandin antifungal drugs. *Lancet*. 2003 Oct 4;362(9390):1142-51. [PMID: 14550704]
- Feinstein AR. Clinical biostatistics. 28. The biostatistical problems of pharmaceutical surveillance. *Clin Pharmacol Ther*. 1974 Jul;16(1):110-23. [PMID: 4843239]

Fromtling RA. Micafungin sodium (FK463). *Drugs Today (Barc)*. 2002 Apr;38(4):245-57. [PMID: 12532193]

Fromtling RA, Abruzzo GK. L-671,329, a new antifungal agent. III. In vitro activity, toxicity and efficacy in comparison to aculeacin. *J Antibiot (Tokyo)*. 1989 Feb;42(2):174-8. [PMID: 2647704]

Fujie A, Iwamoto T, Sano B, Muramatsu H, Kasahara C, Furuta T, Hori Y, Hino M, Hashimoto S. FR131535, a novel water-soluble echinocandin-like lipopeptide : synthesis and biological properties. [PMID: 11212120].

Goodman ZD. Drug hepatotoxicity. *Clin Liver Dis*. 2002 May;6(2):381-97. [PMID:12122862]

Higashiyama Y, Kohno S. Micafungin: a therapeutic review. *Expert Rev Infect Ther*. 2004 Jun;2(3):345-55. [PMID: 15482200]

Hutchinson TA, Leventhal JM, Kramer MS, Karch FE, Lipman AG, Feinstein AR. An algorithm for the operational identification of adverse drug reactions. II. Demonstration of reproducibility and validity. *JAMA*. 1979 Aug 17;242(7):633-8. [PMID: 449003]

Irey NS. Registry of tissue reactions to drugs. *Mil Med*. 1971 Apr;136(4):346-8. [PMID: 5005419]

Irey NS. Tissue Reactions to Drugs. Teaching Monograph, American Journal of Pathology 1976; 82:617-47.

Irey NS. Diagnostic problems in drug-induced diseases. *Ann Clin Lab Sci*. 1976 May-Jun;6(3): 272-7. [PMID:942185]

Irey NS. When is a disease drug induced? Chapter 1 *in* Pathology of Drug-Induced and Toxic Diseases, R. H. Riddell, ed., Churchill Livingstone, New York, 1982.

Jarvis B, Figgitt DP, Scott LJ. Micafungin. *Drugs*. 2004;64(9):969-84. [PMID: 15101786]

Kaplowitz N. Causality assessment versus guilt-by-association in drug hepatotoxicity. *Hepatology*. 2001 Jan;33(1):123-3. [PMID: 11124850]

Kaplowitz N, Lewis JH, Watkins PB. Did this drug cause my patient's hepatitis? [letter] *Ann Intern Med*. 2003 Jan 21;138(2):159-60. [PMID: 12529106]

Karch FE, Lasagna L. Adverse drug reactions. A critical review. *JAMA*. 1975 Dec 22; 234(12):1236-41. [PMID: 1242749]

Karch FE, Smith CL, Kerzner B, Mazzullo JM, Weintraub M, Lasagna L. Adverse drug reactions - a matter of opinion. *Clin Pharmacol Ther*. 1976 May;19(5, Part 1):498-92. [PMID: 1277705]

Kramer MS, Leventhal JM, Hutchinson TA, Feinstein AR. An algorithm for the operational identification of adverse drug reactions. I. Background, description, and instructions for use. *JAMA*. 1979 Aug 17;242(7):623-32. [PMID: 449002]

Lee WM. Assessing causality in drug-induced liver injury. [editorial] *J Hepatol*. 2000 Dec;33(6): 1003-5. [PMID:11131436]

Lee WM, Senior JR. Recognizing drug-induced liver injury: current problems, possible solutions. *Toxicol Pathol.* 2005 Jan;33(1):155-64. [PMID: pending]

Leventhal JM, Hutchinson TA, Kramer MS, Feinstein AR. An algorithm for the operational identification of adverse drug reactions. III. Results of tests among clinicians. *JAMA.* 1979 Nov 2;242(18):1991-4. [PMID: 480646]

Lucena MI, Camargo R, Andrade RJ, Perez-Sanchez CJ, Sanchez de la Cuesta F. Comparison of two clinical scales for causality assessment in hepatotoxicity. *Hepatology.* 2001 Jan;33(1): 123-30. [PMID: 11124828]

Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. *Hepatology* 1997 Sep;26(3):664-9. [PMID: 9303497]

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther.* 1981 Aug; 30(2):239-45. [PMID: 7249508]

Petratis V, Petraitiene R, Sarafandi AA, Kelaher AM, Lyman CA, Casler HE, Sein T, Groll AH, Bacher J, Avila NA, Walsh TJ. Combination therapy in treatment of experimental pulmonary aspergillosis: synergistic interaction between an antifungal triazole and an echinocandin. *J Infect Dis.* 2003 Jun 15;187(12):1834-43. [PMID: 12792859]

Petratis V, Petraitiene R, Groll AH, Rousillon K, Hemmings M, Lyman CA, Sein T, Bacher J, Bekersky I, Walsh TJ. Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. *Antimicrob Agents Chemother.* 2002 Jun;46(6):1857-69. [PMID: 12019101]

Schaffner F, Raisfeld IH. Drugs and the liver: a review of metabolism and adverse reactions. *Adv Intern Med* 1969;15:221-51. [PMID: 4908619]

Senior JR. ODS consultation #D040163 regarding hepatotoxicity possibly induced by use of anidulafungin for treatment of esophageal candidiasis. 25 March 2004. *in* CDER Document File System, N 021632.

Sivak O, Bartlett K, Risovic V, Choo E, Marra F, Batty DSJr, Wasan KM. Assessing the antifungal activity and toxicity profile of amphotericin B lipid complex (ABLCL; Abelcet) in combination with caspofungin in experimental systemic aspergillosis. *J Pharm Sci.* 2004 Jun;93(6):1382-9. [PMID: 15124198]

Van Burik JA, Ratanatharathorn V, Stepan DE, Miller CB, Lipton JH, Vesole DH, Bunin N, Wall DA, Hiemenz JW, Satoi Y, Lee JM, Walsh TJ. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation, *Clin Infect Dis.* 2004 Nov 15;39(10):1407-16. [PMID: 15546073]

Wiederhold NP, Lewis RE. The echinocandin antifungals: an overview of the pharmacology, spectrum and clinical efficacy. *Expert Opin Investig Drugs.* 2003 Aug;12(8):1313-33. [PMID: 12882619]

Yokote T, Akioka T, Oka S, Fujisaka T, Yamano T, Hara S, Tsuji M, Hanafusa T. Successful treatment with micafungin of invasive pulmonary aspergillosis in acute myeloid leukemia, with renal failure due to amphotericin B therapy. *Ann Hematol.* 2004 Jan;83(1):64-6. [PMID: 14661114]

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

John Senior
1/31/05 05:49:15 PM
MEDICAL OFFICER