

MEMORANDUM

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

DATE: November 7, 2002

FROM: Renan A. Bonnel, Pharm.D., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation, HFD-430

David J. Graham, M.D., M.P.H.
Associate Director of Science, Office of Drug Safety, HFD-400

THROUGH: Julie Beitz, M.D., Director
Division of Drug Risk Evaluation, HFD-430

Victor Raczkowski, M.D., M.Sc., Director
Office of Drug Safety, HFD-400

TO: Lee Simon, M.D., Director
Division of Anti-inflammatory, Analgesics and Ophthalmic Drug Products
HFD-550

SUBJECT: Office of Drug Safety- Postmarketing Safety Review (PID # D020157)
Drug: Leflunomide (Arava®, NDA 20-905)
Reaction: Severe Hepatotoxicity and Liver Failure

Confidential: Contains IMS data; not to be used outside of the FDA without clearance from IMS.

EXECUTIVE SUMMARY

On March 28, 2002, a citizen petition was filed to FDA by the consumer advocacy group, Public Citizen, requesting Arava (leflunomide; Aventis®) be withdrawn from the market citing liver failure as the primary safety concern. Following the citizen's petition, the Division of Anti-inflammatory, Analgesics and Ophthalmic Drug Products (DAAODP, HFD-550) requested a review of post-marketing data for serious hepatic events and liver failure since approval of leflunomide. The following report summarizes the activities of the Office of Drug Safety and its evaluation of domestic reports of acute liver failure (ALF) and serious hepatotoxicity with the use of leflunomide.

Since approval (September 1998) through August 25, 2002, we identified a total of 102 U.S cases of serious hepatic events with leflunomide in FDA's AERS database, of which 48 were excluded as being unrelated to leflunomide use. We identified 54 cases of serious hepatic injury that were temporally associated with the use of leflunomide. The series included 38 reports of serious hepatic injury including hepatitis, jaundice/cholestasis and 16 reports of acute liver failure. There were 9 deaths.

Eight deaths were due to liver injury and one was due to interstitial lung disease. One patient underwent liver transplantation. The typical pattern of severe liver injury with leflunomide was hepatocellular or mixed in nature. Acute liver failure was unrelated to age, dose, or duration of therapy. Two-thirds of acute liver failure cases occurred in female patients.

Epidemiologic analysis found that the month-specific risk of developing ALF or other severe acute liver injury remained persistently elevated for as long as leflunomide was used. The cumulative risk for the development of ALF, expressed as number needed to harm, was estimated to range from 388 to 685 after 15 months of leflunomide use, adjusted for underreporting. For the combined outcome of ALF or other severe acute liver injury, the estimated number needed to harm ranged from 107 to 188. A sensitivity analysis for ALF yielded estimates of number needed to harm ranging from 428 to 1318.

Review of literature on hepatotoxic risks with methotrexate, another drug commonly used to treat RA, found that the major risk was the development of fibrosis, which was usually mild in degree, with no serious adverse clinical implications.

We reviewed the experience with existing risk-management modalities and found that the available evidence indicates these are largely ineffective. To rely upon methods that have been shown to be ineffective, or for which there is not supportive evidence showing they are effective, raises ethical concerns. In addition, the occurrence of ALF is not preventable with currently available risk management strategies.

Examination of risks and benefits of leflunomide found an absence of documented long-term benefit based on objective indices of functional ability/disability or delayed mortality. The primary measure of efficacy from pre-approval clinical trials, “%ACR20 response,” was found to be based primarily on subjective criteria that are highly correlated. The risks of leflunomide greatly exceeded its benefits. We recommend that leflunomide be withdrawn from the market.

BACKGROUND AND PRODUCT LABELING¹

Leflunomide (Arava®, Aventis Pharma) was approved on September 10, 1998. It is indicated for the treatment of rheumatoid arthritis to reduce signs and symptoms and to retard structural damage as evidenced by x-ray erosions and joint space narrowing. Leflunomide is an isoxazole immunomodulatory agent which inhibits dihydroorotate dehydrogenase (an enzyme involved in de novo pyrimidine synthesis) and has antiproliferative activity.

On March 13, 2001, the European Agency for the Evaluation of Medicinal Products (EMA) issued a public statement regarding very rare liver injury, that may be fatal, during treatment with Arava. These warnings and urgent safety restrictions are available on the EMA website:

<http://www.emea.eu.int/pdfs/human/press/pus/561101en.pdf>

On March 27, 2001, Michael Johnston R.Ph. (ODS, DDRE) documented hepatic failure (U.S-5) and fatal hepatitis (U.S-1) cases associated with leflunomide. He made a recommendation to DAAODP to include jaundice, hepatitis and liver-related fatalities into the current Arava label.

On March 28, 2002, a citizen petition was filed to FDA by the consumer advocacy group, Public Citizen requesting Arava be withdrawn from the market citing liver failure as the primary safety concern.

Several parts of the labeling contain the pertinent information related to hepatotoxicity and elevation of liver enzymes (see below). Serious liver injury including fatal hepatitis and fatal liver failure are not mentioned in leflunomide labeling. DAAODP had requested these be added to the label however, labeling negotiations with regard to these events have been put on hold pending this review.

Warnings

Hepatotoxicity. In clinical trials, ARAVA treatment was associated with elevations of liver enzymes, primarily ALT and AST, in a significant number of patients; these effects were generally reversible. Most transaminase elevations were mild (≤ 2 -fold ULN) and usually resolved while continuing treatment. Marked elevations (>3 -fold ULN) occurred infrequently and reversed with dose reduction or discontinuation of treatment. The following table shows liver enzyme elevations seen with monthly monitoring in clinical trials US301 and MN301. It was notable that the absence of folate use in MN302 was associated with a considerably greater incidence of liver enzyme elevation on methotrexate.

Table 1. Liver Enzyme Elevations >3-fold Upper Limits of Normal (ULN)								
	US301			MN301			MN302 *	
	LEF	PL	MTX	LEF	PL	SSZ	LEF	MTX
ALT (SGPT)								
>3 -fold ULN	8	3	5	2	1	2	13	83
(n %)	(4.4)	(2.5)	(2.7)	(1.5)	(1.1)	(1.5)	(2.6)	(16.7)
Reversed to ≤ 2 -fold ULN:	8	3	5	2	1	2	12	82
Timing of Elevation								
0--3 Months	6	1	1	2	1	2	7	27
4-6 Months	1	1	3	--	--	--	1	34
7-9 Months	1	1	1	--	--	--	--	16
10-12 Months	--	--	--	--	--	--	5	6
AST (SGOT)								
>3 -fold ULN	4	2	1	2	0	5	7	29
(n %)	(2.2)	(1.7)	(0.6)	(1.5)	--	(3.8)	(1.4)	(5.8)
Reversed to ≤ 2 -fold ULN:	4	2	1	2	--	4	5	29
Timing of Elevation								
0--3 Months	2	1	--	2	--	4	3	10
4-6 Months	1	1	1	--	--	1	1	11
7-9 Months	1	--	--	--	--	--	--	8
10-12 Months	--	--	--	--	--	--	3	--
*Only 10% of patients in MN302 received folate. All patients in US301 received folate.								

At minimum, ALT (SGPT) should be performed at baseline and monitored initially at monthly intervals then, if stable, at intervals determined by the individual clinical situation.

Guidelines for dose adjustment or discontinuation based on the severity and persistence of ALT elevation are recommended as follows: For confirmed ALT elevations >2 -fold ULN, dose reduction to 10 mg/day may allow continued administration of ARAVA. If elevations >2 but ≤ 3 -fold ULN persist despite dose reduction, liver biopsy is recommended if continued

treatment is desired. If elevations >3-fold ULN persist despite dose reduction, ARAVA should be discontinued and cholestyramine should be administered (see [PRECAUTIONS -- General -- Need for Drug Elimination](#)) with close monitoring, including retreatment with cholestyramine as indicated.

Rare elevations of alkaline phosphatase and bilirubin have been observed. Trial US301 used ACR Methotrexate Liver Biopsy Guidelines for monitoring therapy. One of 182 patients receiving leflunomide and 1 of 182 patients receiving methotrexate underwent liver biopsy at 106 and 50 weeks respectively. The biopsy for the leflunomide subject was Roegnik Grade IIIA and for the methotrexate subject, Roegnik Grade I.

Pre-existing Hepatic Disease. Given the possible risk of increased hepatotoxicity, and the role of the liver in drug activation, elimination and recycling, the use of ARAVA is not recommended in patients with significant hepatic impairment or evidence of infection with hepatitis B or C viruses.

Drug Interactions Section

Hepatotoxic Drugs. Increased side effects may occur when leflunomide is given concomitantly with hepatotoxic substances. This is also to be considered when leflunomide treatment is followed by such drugs without a drug elimination procedure. In a small (n=30) combination study of ARAVA with methotrexate, a 2- to 3-fold elevation in liver enzymes was seen in 5 of 30 patients. All elevations resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. A >3-fold increase was seen in another 5 patients. All of these also resolved, 2 with continuation of both drugs and 3 after discontinuation of leflunomide. Three patients met "ACR criteria" for liver biopsy (1: Roegnik Grade I, 2: Roegnik Grade IIIa). No pharmacokinetic interaction was identified (see [CLINICAL PHARMACOLOGY](#)).

Adverse Reactions Section

Gastrointestinal- diarrhea, elevated liver enzymes (ALT and AST).

MEDICAL LITERATURE

A MEDLINE and EMBASE search of the medical literature found one foreign article related to hepatotoxicity². The English translation provides a summary of the European experience with leflunomide and EMEA's public statement related to hepatotoxicity of leflunomide. Two other case reports were recently published, describing a fatal and non-fatal case of liver injury with the drug.^{3,4} Neither of these cases was included in our case series because one did not meet the criteria for inclusion (see case definition below) and the other was a foreign case.

CASE DEFINITIONS⁵⁻⁷

The following case definitions were used to categorize the extent of liver injury.

Category 1: Non-fatal but severe and potentially life threatening liver injury

- Jaundice reports not requiring hospitalization.
- Liver injury requiring hospitalization. This includes reports of hepatitis NOS with no lab data and reports of elevations in transaminases. Reported clinical symptoms might include jaundice, coagulopathy, or elevated bilirubin.

Category 2: Acute liver failure (ALF), fatal or non-fatal

- Interval from the development of liver-related signs or symptoms or jaundice to any of the following within a period of 3 months or less: hepatic encephalopathy; placement on a liver transplant list; or liver transplantation; or death in the setting of acute liver injury. In some reports,

specific information on timing was not provided and classification was based on the case report narrative suggesting a rapid time course.

- Acute liver failure includes elevated transaminases, bilirubin or jaundice which may be accompanied by coagulopathy or reduced renal function or renal failure.
- This category will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data.

SELECTION OF CASE SERIES

We conducted a search of FDA's Adverse Event Reporting System (AERS) and the published medical literature from September 10, 1998 through August 25, 2002. All cases in this review occurred before May 31, 2002 and the event dates coincide with IMS Health Data. The cases were identified using the following terms:

- *Hepatic and Hepatobiliary disorders (HLGT), hepatobiliary investigations (HLGT), liver transplant (PT)*- This search included outcomes of death, hospitalization, disability, life-threatening, and congenital anomaly. These outcomes were defined as "serious".
- *Jaundice cholestatic (PT); Jaundice hepatocellular (PT) and Jaundice NOS (PT)*- This search included "other" outcomes to capture the "jaundice" reports that were not retrieved under "serious" outcomes. Cases with jaundice where outcomes were not marked as hospitalization, death etc. on AERS reports were also retrieved.

There were a total of 262 (US and foreign) reports for leflunomide (crude count) in AERS. We combined 23 duplicate reports and excluded 137 foreign reports from further analysis. One hundred two cases remained. Of those 102 cases reviewed, the drug causality assessment for suspected adverse events was performed based on the following criteria adapted from World Health Organization (WHO).⁸ Intensive efforts were made to obtain follow-up from reporters and/or their health care providers.

Probable/likely:

- Hepatic event, including lab test abnormality, occurring in a plausible time relationship to drug administration;
- The event is unlikely attributed to concurrent disease or other drugs; and
- Positive dechallenge and rechallenge is not required.

Possible:

- Hepatic event, including lab test abnormality, occurring in a plausible time relationship to drug;
- There are other factors present that could plausibly have contributed to liver injury, but were not the most likely explanation for the adverse event, and
- Dechallenge or rechallenge information is not required.

Unlikely:

- Hepatic event, including lab test abnormality are not temporally related to drug.
or
- Other medications or underlying disease provide more likely explanation for the adverse events.

In 48 cases, hepatotoxicity could not be attributed (unlikely category) to leflunomide use. They were excluded for the following reasons:

- Primary event was unrelated to hepatotoxicity (i.e., pancreatitis; Stevens Johnson Syndrome/TEN, vasculitis, pyelonephritis, nephrotic syndrome, class III CHF, cholangiocarcinoma, fulminant myositis, acute respiratory failure with sepsis, mesenteric venous occlusion, and supraventricular tachycardia)
- Enbrel related hepatitis
- Bone marrow hyperplasia/dysfunction
- Advanced cirrhosis unrelated to leflunomide
- Cholelithiasis report with no clinical information

In the remaining 54 cases, the serious hepatic event was attributed to leflunomide and leflunomide was the primary suspect drug.

SUMMARY OF CASES

Table 2. Demographic and clinical characteristics of 54 leflunomide reports with hepatotoxicity.

Age (n= 47):	Mean 56.6; median 55 (range 28-80) years
Gender :	Female-38; male-14 ; unk-2
Duration of treatment (n=41):	Mean: 137 days; median: 91 days; range 3-693 days (ALF: mean: 135 days, median 91 days, range 4 days-436 days) (Severe liver injury: mean: 139 days, median: 84 days, range: 3 days-693 days)
Loading dose:	Received-21; not reported-33
Daily dose (n=37):	10mg-5; 20mg-30; 100mg-2
Jaundice at diagnosis:	52 % (28/54)
Liver function tests:	ALT- range 31-2,706 U/L ; mean-797 U/L (n=33) AST-45-6016 U/L; mean 1104 U/L (n=36) Total bilirubin 0.5-26 mg/dL ; mean 10.2 mg/dL (n=20) Alkaline phosphatase 91-2,707 U/L; mean 407 U/L (n=33)
Hepatic injury category:	Severe, non-fatal potentially life-threatening liver injury-38 (27-probable, 11-possible) Liver failure –16 (12-probable, 4-possible)
Dechallenge:	Positive-19 Negative-2 Unk-33

Outcome: Death- 9
Liver transplant- 1
Alive- 14
Unk: 30

Report type: 15-day-39; direct- 7; Periodic-8
Report year: 1999-12; 2000-20; 2001-15; 2002-7

The series included 38 cases of non-fatal severe hepatic injury including hepatitis, jaundice/cholestasis and 16 cases of acute liver failure. There were 9 deaths. Eight deaths were liver-related and 1 was due to concurrent severe interstitial lung disease.

The mean age of patients was 56.6 years with patients ranging from 28 to 80 years of age. About 73 % of patients (38 of 52) were females. The most frequently reported dose was 20 mg daily. About 39 % of the cases (21/54) received the recommended 100-mg loading dose.

Liver biopsies were reported in five patients. The results of the biopsies were reported as follows: submassive hepatic necrosis, centrilobular necrosis with portal inflammation and hepatic necrosis with drug reaction; moderate portal triaditis and mild hepatocellular fibrosis; fatty liver; hepatitis, and one case reported unspecified liver injury.

Data on the duration of leflunomide therapy prior to onset of liver injury was available for 13 patients with acute liver failure and 28 patients with non-fatal serious liver injury. Three patients were known to continue leflunomide therapy beyond the documented onset of liver injury. In two of the three, the patients developed mild transaminase elevations and were monitored while continuing therapy for 3 and 17 days, at which time the drug was stopped and the patients were hospitalized for progressive liver injury. In one other case, the physician continued leflunomide for 9 days beyond the onset of jaundice.

Liver injury usually occurred within the first six months of therapy but occurred after a year or more of therapy in 15.4 % (2/13) of ALF reports and in 10.7 % (3/28) of non-fatal severe liver injury reports. Positive dechallenge was reported in 19 cases. Two patients reported negative dechallenges. The dechallenge information was unknown in the remaining 33 cases. Rechallenge was not reported in any case.

Transaminase levels were reported in 39 cases (ALT (n=33), AST (n=36) and alkaline phosphatase values were reported in 33. The mean ALT and AST levels were 797 U/L (range 31-2706 U/L) and 1104 U/L (range: 45-6016 U/L), respectively. The mean alkaline phosphatase level was 407 U/L (range 91-2707 U/L). Total bilirubin levels were available in 20 patients and ranged from 0.5-26 mg/dL with a mean of 10.2 mg/dL. Liver injury was classified by us using International Consensus criteria as hepatocellular in 19 (19/54, 35 %), cholestatic in 7 (7/54, 13 %) and mixed in 9 (9/54, 17 %).⁵ Insufficient information was provided to classify 35 % (19/54) of reports.

Twelve patients (12/54, 22 %) presented with signs or symptoms of an allergic reaction such as rash, unexplained fever or eosinophilia that suggest a hypersensitivity component to liver injury. Twenty-eight (28/54, 52 %) patients had jaundice at diagnosis. Nine had prior medical history of autoimmune

liver disease (1), hepatitis A (2), hepatitis B (2) hepatitis C (1), concurrent herpes virus infection (1), Epstein-Barr infection (1), portal hypertension/esophageal varices (1), adult-onset Still's disease (1), and alcohol abuse/dependency (4). Some cases had more than one factor.

Forty patients were receiving medications concomitantly that are labeled for hepatotoxicity. These medications included naprosyn (2), oral contraceptive (1), conjugated estrogens (6), methotrexate (13), celecoxib (4), acetaminophen (7), sulfasalazine (3), ibuprofen (1), simvastatin (1), halothane (1), gatifloxacin (1), tramadol (1), clinoril (1), methyl dopa/levodopa (1), etodolac (1), atorvastatin (1), gabapentin (1), piroxicam (1) and amiodarone (1). Some cases reported more than one hepatotoxic concomitant medication. In six of the 54 cases, methotrexate (2), acetaminophen (1), celecoxib (1), atorvastatin (1) and amiodarone (1) were listed as second co-suspect medications. Some of these drugs are rarely or never are associated with acute liver failure. We recognize that acetaminophen overdose and halothane inhalations have been associated with severe acute/subacute liver injury. However in the cases presented here, these latter drugs do not appear to have been responsible for the acute hepatic event, or leflunomide was as likely to be the causative agent.

In 39 (39/54, 72 %) of reports, liver injury was probably caused by leflunomide per our causality assessment. Concurrent disease or other drugs were unlikely to have played a role in the development of serious liver injury. In the remaining 15 cases, the causal role of leflunomide was considered to be possible since other factors including concomitant medications and prior medical history could reasonably have contributed to the liver injury.

Nine patients died. Eight deaths were liver-related and 1 was due to concurrent severe interstitial lung disease. One patient underwent liver transplantation. Fourteen patients are known to have recovered, and for 30 (55 %), the outcome was unknown.

Sixteen of the 54 patients in this series experienced acute liver failure. Below is the demographic and clinical information on these cases. A line listing and case summary information of the acute hepatic failure cases is attached (Attachment 1).

Table 3. Demographic and clinical characteristics of acute hepatic failure cases (n=16)

Age (n=14):	Range 29-76 years old, median-58
Gender:	Female- 10; Male-5; unk-1
Duration of treatment:	Mean- 135 days , median- 91 days, range 4 days-436 days (n=13)
Daily dose:	20mg- 10; 10mg- 1; 100mg-1; unk-4
Loading dose:	100mg- 5
Dechallenge:	Positive-4
Cholestyramine:	Received-9
Outcome:	Died-8; Transplant-1; Recovered-2; Unknown-5
Report type:	15 day-13; direct- 3
Report year:	1999-3; 2000-4; 2001-4; 2002-5

All liver failure cases were temporally associated with leflunomide. Duration of use ranged from 4 to 436 days (n=13). The median age was 58 years old, and 10 (10/16, 62%) were female.

Most patients received the recommended daily dose of 20 mg. One patient received 100-mg daily dose (overdose) for 87 days, developed complete liver failure, but recovered. Dosing information was not available in four cases. Five patients received the recommended 100-mg loading dose. One patient with ALF continued to receive leflunomide 9 days beyond the onset of jaundice.

One patient had a history of hepatitis C infection and another had hepatitis A. One patient had evidence of chronic liver disease (esophageal varices) upon which was superimposed acute liver injury and failure. One patient had a possible syncopal episode and another had recent cardiopulmonary arrest, but in this case, the acute liver injury (hyperbilirubinemia and elevated transaminase levels) preceded the event.

Of the 16 reports of acute liver failure, 9 (56%) were hepatocellular, 2 (13%) were cholestatic (pronounced elevation of alkaline phosphatase / total bilirubin with minimal transaminase elevation) and 5 (31%) were of unknown type because of insufficient data. Liver biopsies were performed in four patients. They described submassive hepatocellular necrosis, centrilobular necrosis with portal inflammation and hepatic necrosis; fatty liver, or fibrosis and marked canalicular cholestasis.

One case (# 2, Attachment 1) presented with rash and fever suggesting a possible hypersensitivity component to the liver injury.

Of 16 cases of ALF, 8 died, 1 received a liver transplant, two recovered and the outcome was unknown for the remaining five cases. Two patients died while awaiting liver transplantation. Six of eight fatal cases received cholestyramine washout procedures. Because leflunomide serum levels were not available, the benefit of cholestyramine washout could not be determined in these cases.

EPIDEMIOLOGIC ASSESSMENT

Drug Use Data

The National Prescription Audit Plus (NPA, online), from IMS, a commercial health information company, indicated that approximately 1,872,000 prescriptions were dispensed for Arava® tablets from initial marketing through May 2002.

Table 4 summarizes the projected number of total prescriptions dispensed by independent, chain, food store, and mail order in the U.S from the time period indicated above. **This information is not to be used outside of the FDA without prior clearance by IMS Health.**

Table 4. US prescriptions for leflunomide, 1998 through May 2002.

Drug	1998*	Total 1999	Total 2000	Total 2001	Jan-May 2002	Total Rx
Arava	43,000	412,000	532,000	618,000	267,000	1,872,000

* 1998 totals reflect approximately three months of marketing (product approved on 9/10/1998)

Using CDER’s Cooperative Agreement Program in Pharmacoepidemiology, we obtained data on persistency of leflunomide use from two separate databases. Tennessee Medicaid/Tenn Care (TN) covers 1.5 million persons (20% of the state’s population). UnitedHealth Group (UHG) is a large, national health care company that maintains a research database covering 3 million persons within 12 different health plans located in 10 geographically dispersed states.

Demographic factors of leflunomide users within both databases are summarized in Table 5. Age and gender distributions were generally similar in each database.

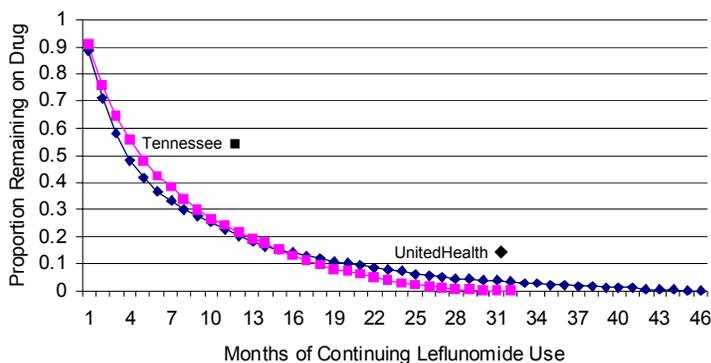
Table 5. Demographic characteristics of patients treated with leflunomide within the UnitedHealth and Tennessee Cooperative Agreement databases between September 1998 and June 2002.

	UnitedHealth	Tennessee
Patients (n)	2,295	1,262
Rxs (n)	16,875	14,118
% women	70.5	75.9
Age (%)		
0-44	29.8	23.8
45-64	58.2	56.5
≥ 65	13	19.7

Persistency of leflunomide use in each population is shown in Figure 1. The pattern of longitudinal use was virtually identical in TN and UHG. The median duration of leflunomide use was 4-5 months, with 19% continuing for greater than 1 year, 6% for greater than 2 years, and less than 1% for greater than 3 years.

Figure 1.

Comparison of Persistency of Leflunomide Use,
Tennessee Medicaid/TennCare and UnitedHealth Group,
1998-2002



In an effort to explore whether there were secular trends in longer-term leflunomide use, we analyzed the longitudinal use of the drug among patients receiving their first leflunomide prescription during the months of January or February for the years 1999-2002. Figures 2 and 3 display our findings. While there is some difference in the level of persistency by year between the inception cohorts from the two databases, a similar overall pattern is seen with both. With each successive year, the persistency of leflunomide use among new patients initiating therapy has declined. These data do not provide an explanation for this observation.

Figure 2.

Persistency of Leflunomide Use by Time-Specific Inception Cohort, Tennessee Medicaid and TennCare, 1999-2002

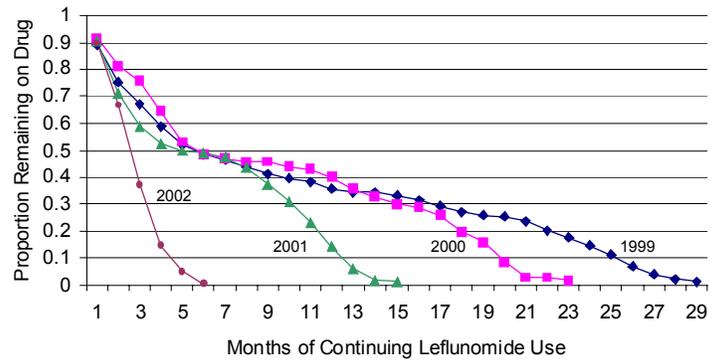
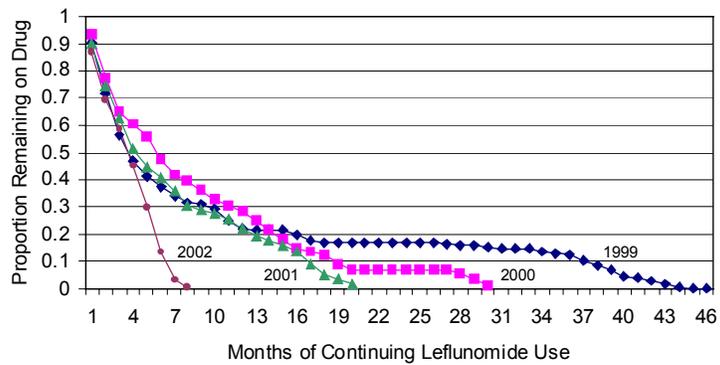


Figure 3.

Persistency of Leflunomide Use by Time-Specific Inception Cohort, UnitedHealth, 1999-2002



Reporting Rates

We identified 16 cases of ALF and 38 cases of other severe acute liver injury (hospitalization (29), jaundice without mention of hospitalization (9)) reported in association with leflunomide use. These were used as numerator events in subsequent analyses. There were 1.87 million leflunomide prescriptions during the study period, with an estimated mean duration ranging from 17.6 days (TN data) to 32.4 days (UHG data). This yielded an estimated population exposure time of 90,266 to 166,172 person-years. Reporting rates per million person-years of leflunomide exposure are summarized in Table 6. Reporting rates are shown based on case reports classified as probable or possible, and probable only. The overall reporting rate of ALF ranged from 73 to 177 per million person-years and that of other severe acute liver injury from 162 to 421 per million person-years.

Table 6. US reporting rates of acute liver failure and other severe liver injury with leflunomide, per million person-years of leflunomide use.

	Acute Liver Failure (x10 ⁻⁶ person-years)		Other Severe Liver Injury (x10 ⁻⁶ person-years)	
Probable or possible	(n=16)	96-177	(n=38)	229-421
Probable only	(n=12)	73-133	(n=27)	162-299

Survival Analysis⁸⁻¹³

Using data from the Cooperative Agreement databases on the mean number of leflunomide prescriptions per patient, and the total number of US prescriptions from IMS, we estimated the number of patients treated with leflunomide between September 1998 and May 2002. This number ranged from 153,442 (based on TN data) to 271,304 (based on UHG data). Persistency data from these databases (see Figure 1) was used to estimate the number of patients remaining on leflunomide through different lengths of time. This was combined with case reports data to perform survival analysis. Using this method, we calculated the cumulative risk, expressed as the number needed to harm (NNH) (the number of treated patients needed to produce a report of ALF or other severe liver injury), and the month-specific reporting hazard rate for these same outcomes. Table 7 presents NNH_{ALF} based on cases of ALF reported to FDA and exposed population estimates using TN and UHG data.

Table 7. Number needed to harm (produce 1 case report of ALF) at 6 and 15 months of continuing leflunomide use.

	At 6 months		At 15 months	
	(n=271,304)	(n=153,442)	(n=271,304)	(n=153,442)
Probable or possible (n=16)	10,957	6,197	6,853	3,876
Probable only (n=12)	13,979	7,907	9,632	5,448

Depending upon whether the analysis was based on probable and possible case reports combined, or only on probable ones, the NNH_{ALF} ranged from 6,197-13,979 at 6 months of leflunomide use and from 3,876-9,632 at 15 months of continuing use. For example, considering probable and possible

case reports together and basing the analysis on the larger exposed population estimate derived from UHG data, 1 case of ALF was reported to FDA for every 6,853 patients who remained on leflunomide for 15 months or longer. These analyses are not adjusted for underreporting (see below). A similar analysis of other severe liver injury reports is presented in Table 8.

Table 8. Number need to harm (produce 1 case report of other severe acute liver injury) at 6, 15 and 23 months of continuing leflunomide use.

	At 6 months		At 15 months		At 23 months	
	(n=271,304)	(n=153,442)	(n=271,304)	(n=153,442)	(n=271,304)	(n=153,442)
Probable or possible (n=38)	5,501	3,117	3,529	2,708	2,594	1,819
Probable only (n=27)	6,786	3,838	5,366	3,035	3,962	2,241

At 23 months of continued leflunomide use, NNH_{Other} ranged from 1,819 to 3,962. Combining ALF and other severe acute liver injury, NNH_{ALF+} ranged from 1,065 to 2,808 at 23 months (Table 9).

Table 9. Number need to harm (produce 1 case report of ALF or other severe liver injury) at 6, 15 and 23 months of continuing leflunomide use.

	At 6 months		At 15 months		At 23 months	
	(n=271,304)	(n=153,442)	(n=271,304)	(n=153,442)	(n=271,304)	(n=153,442)
Probable or possible (n=54)	3,667	2,074	2,330	1,318	1,882	1,065
Probable only (n=39)	4,569	2,584	3,446	2,062	2,808	1,662

Hazard Rates

With estimates of the number of patients treated with leflunomide during each successive month of continuing therapy, an estimate of the total person-time of leflunomide exposure during each month of increasing duration of use was obtained. Case reports of ALF and other severe liver injury were categorized by the duration of leflunomide use at the time of liver injury, and month-specific hazard (reporting) rates were calculated, using the more conservative (larger number of exposed patients) UHG estimates. Data are presented on a log scale with the point estimate of the hazard rate symbolized by the number of case reports received by FDA. Ninety-five percent confidence intervals are also shown. Figure 4 shows month-specific hazard rates of ALF, with known duration in 13 and unknown duration of use in 3. These 3 cases were distributed in proportion to those with known duration. Figure 5 shows the same information for ALF and other severe acute liver injury (28 known duration; 10 unknown).

Figure 4.

Month-Specific Hazard Rate of Reported Acute Liver Failure (Probable and Possible) by Duration of Leflunomide Use

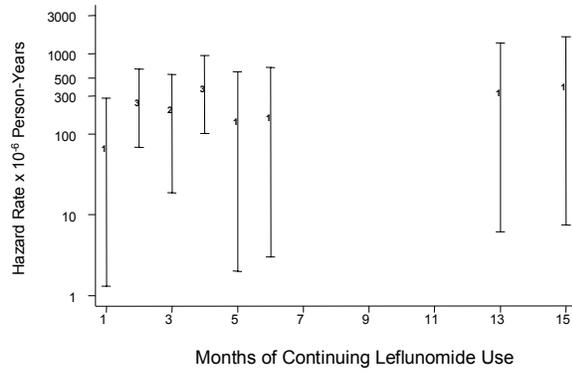
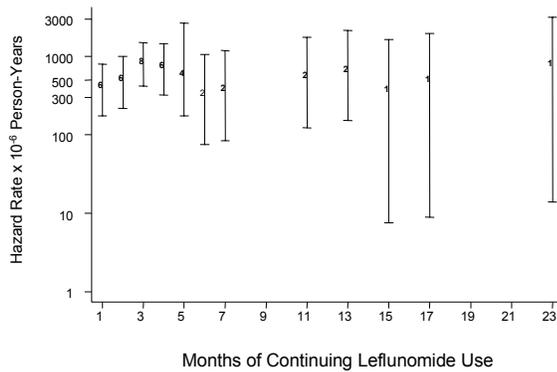


Figure 5.

Month-Specific Hazard Rate of Reported Acute Liver Failure and Other Severe Acute Liver Injury (Probable and Possible) by Duration of Leflunomide Use



Cases were not reported after every possible month of use. For the months in which cases were reported, the month-specific reported hazard rate varied between 62 and 363 per million person-years for ALF and between 314 and 813 per million person-years for ALF or other severe liver injury. Of note, the lower bound of the 95% confidence interval for ALF excluded 1 per million person-years, which is the estimated background rate of ALF in the general US population (see below). Also, the

data show that serious liver injury was reported even after extensive periods of time on drug. These data suggest that the hazard does not diminish with prolonged leflunomide use.

Adjustment for Underreporting¹⁴⁻²⁹

The analyses presented here were based on voluntary (spontaneous) case reports submitted to FDA. Such reports suffer from two major limitations.¹⁴ The most important from an analysis perspective is underreporting, that is, most serious adverse reactions are not reported.¹⁴⁻²⁹ Fatal and life-threatening reactions are reported to the FDA only about 1-10% of the time.¹⁶⁻²⁶ With longer-term drug use, even greater underreporting probably occurs because physicians become less likely to attribute serious reactions to a drug that has been used successfully for months or years.²⁷ An analysis comparing liver-related hospitalization and jaundice rates observed in pre-approval clinical trials for troglitazone with that reported postmarketing found that only about 5% of the expected number of cases were reported to FDA.²⁸ The implication of underreporting is that all our estimates of risk (hazard rates, NNH) greatly underestimate the actual risk experienced by patients using leflunomide. The reporting rate and cumulative risk estimates should realistically be multiplied by 4 (25% reporting), 10 (10% reporting) and 20 (5% reporting) to understand the magnitude of the problem we have described. Likewise, NNH should be divided by 4, 10 and 20.

Table 10. Estimates of overall incidence rates and number needed to harm (produce 1 case of ALF) among leflunomide users, after adjustment for underreporting of cases to FDA.

	Rate x 10 ⁻⁶ person-years			Number needed to harm @ 15 months		
	<u>Reporting Efficiency</u>			<u>Reporting Efficiency</u>		
	<u>5%</u>	<u>10%</u>	<u>25%</u>	<u>5%</u>	<u>10%</u>	<u>25%</u>
Prob+poss	1920-3540	960-1770	384-708	194-343	388-685	969-1713
Prob only	1460-2660	730-1330	292-532	273-482	545-963	1362-2408

Table 11. Estimates of overall incidence rates and number needed to harm (produce 1 case of ALF or other severe acute liver injury) among leflunomide users, after adjustment for underreporting of cases to FDA.

	Rate x 10 ⁻⁶ person-years			Number needed to harm at 23 months		
	<u>Reporting Efficiency</u>			<u>Reporting Efficiency</u>		
	<u>5%</u>	<u>10%</u>	<u>25%</u>	<u>5%</u>	<u>10%</u>	<u>25%</u>
Prob+poss	4580-8420	2290-4210	916-1684	54-94	107-188	266-471
Prob only	3240-5980	1620-2990	648-1196	83-141	166-281	416-702

Tables 10 and 11 present data from Tables 6, 7 and 8 after adjustment for a range of plausible degrees of underreporting. Even under the assumption that 25% of cases were reported, the “incidence” rate for leflunomide-associated ALF would range from 292 to 708 per million person-years. The NNH_{ALF} would range from 969 to 2408 at 15 months of continuing leflunomide use. Under the more likely scenario of 10% or lower reporting, NNH_{ALF} with leflunomide ranged from 388 to 963 at 15 months of continuing use. For the combined outcome of ALF or other severe acute liver injury, the overall

“incidence” rate would range from 648 to 1684 per million person-years and NNH_{ALF+} from 266 to 702 at 23 months of continuing leflunomide use, assuming 25% reporting efficiency.

The other important limitation of spontaneous case reports is the potential for incomplete information. Depending on the pharmaceutical company involved, the number of cases reported, the intensity of case follow-up, and other factors, the quality of case reports can vary greatly. Our overall assessment of leflunomide case reports of ALF and other severe liver injury was that they were generally of poor quality. There appeared to be little or no effort at follow-up for most of the cases reported. Associated with this, many case reports lacked important laboratory data as well as information relating to ultimate patient outcome. This combination imposed a significant handicap on risk assessment efforts.

DISCUSSION

We identified 16 cases of leflunomide-related ALF (12 probable, 4 possible) and 38 cases of leflunomide-related other severe acute liver injury (27 probable, 11 possible). Based on an analysis of probably- and possibly-leflunomide associated, we obtained an overall reporting rate for ALF of 96-177 per million person-years, and for other severe liver injury, of 229-421 per million person-years. After adjustment for underreporting (10% efficiency), these rates ranged from 960-1770 (mean~1300) per million person-years for ALF and from 2290-4210 (mean~3000) per million person-years for other severe acute liver injury.

The monthly reported hazard rate for ALF and for other severe liver injury appeared to remain relatively constant with continued use of leflunomide.

The reported NNH_{ALF} ranged from 3876-6853 at 15 months of continuous leflunomide use, which after adjustment for underreporting, ranged from 388-685 (mean~540). For the combination of ALF and other severe liver injury, NNH_{ALF+} ranged from 107-188 (mean~150) at 23 months of continuous leflunomide use, adjusted for underreporting. These risks are extremely high.

Background rates of acute liver failure²⁸⁻³⁵ The background rate for idiopathic ALF in the general population has not been previously published. Two different approaches yielded estimates of less than 1 case per million person-years. Each year, about 2000 cases of ALF from all causes occur in the US, with 10% from unexplained causes.^{5,30} Using a US census estimate of 281 million,³¹ an estimated rate of unexplained ALF of 0.7 per million person-years was obtained for the US population. Using a second approach, 4 population-based epidemiologic studies of liver disease were pooled for a total of 12 million person-years of observation.³²⁻³⁵ Four cases of unexplained ALF were noted in these studies, yielding a rate estimate of 0.3 per million person-years.^{28,29} In similar fashion, the background rate of hospitalization for acute idiopathic liver injury (ALF + other acute liver injury) was found to range from 9 to 22 per million person-years in epidemiologic studies.^{32,34,36}

Based on these data, the estimated incidence rate of leflunomide-associated ALF was about 1300-fold above the expected background rate. Likewise, the estimated incidence rate of other severe liver injury (27 hospitalized, 9 jaundice without mention of hospitalization) was more than 100-fold greater than expected. Of note, RA itself has not been associated with an increased risk of ALF.

Sensitivity analysis. In the course of this review, two internal meetings were held so that the 16 ALF case reports could be reviewed and discussed by a group that included Drs. Steven Galson, Robert Temple, John Jenkins, Paul Seligman, Jonca Bull, Victor Raczkowski, Lee Simon, Julie Beitz, Lawrence Goldkind, Mark Avigan, John Senior, David Graham, and Renan Bonnel (non-voting). This arose because of sharp disagreement between the ODS and ODE V review staff regarding attribution of causality in the cases reported to FDA.

Table 12 presents the summary “votes” resulting from this process. Of note, in only 1 case (#8), did a majority of the group not involved in the primary safety assessment classify a case as unlikely. In 15 of 16 cases classified by the ODS authors of this report as either probably- or possibly-associated with leflunomide use, the larger group agreed. However, there were differences with respect to whether a case should be classified as probably- or possibly associated. To explore this further, we applied two different scoring systems to case reports as assessed by the larger group. In model A, probable received 5 points, possible 3 points and unlikely 0 points. In model B, unlikely was assigned a negative (-1) point. The scoring models were employed to assign some value to cases classified as “possibly-related,” because they were reported as due to leflunomide and were complete information available, some, perhaps all, would become “probable.” Of note, of the 16 reported cases of ALF, leflunomide was cited by the reporter as the only suspect drug in 12 (75%). In 4, leflunomide was suspected but a second co-suspect medication was also mentioned.

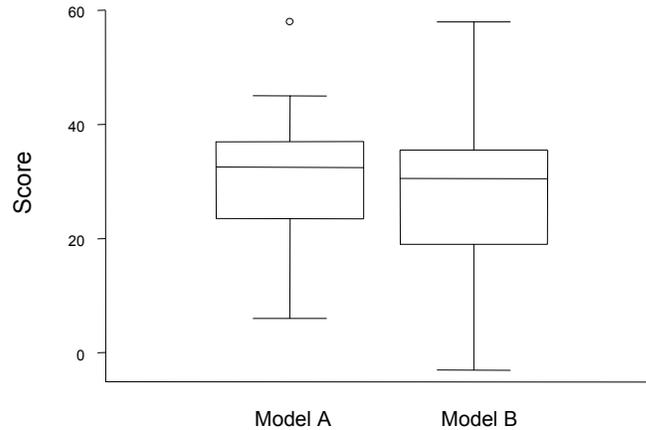
Table 12. Summary of Causality Assessment Counts and Scores Resulting from Group Discussion.

Case	Probable	Possible	Unlikely	Score A	Score B
1	4	5	2	35	33
2	11	1	0	58	58
3	3	5	3	30	27
4	2	7	2	31	29
5	3	8	1	39	38
6	4	5	3	35	32
7	0	7	4	21	17
8	0	2	9	6	-3
9	2	8	2	34	32
10	2	5	4	25	21
11	6	4	0	42	42
12	2	4	5	22	17
13	0	9	2	27	25
14	0	4	4	12	8
15	2	8	2	34	32
16	6	5	1	45	44

Exploratory data analysis of the scores suggested none of the case reports should be considered as unlikely. The 25th percentile score under model A was 23 and under model B, 19.

Figure 6.

Stem and Whisker Boxplot of Group Scoring of Leflunomide ALF Case Reports



A summary of the number of leflunomide ALF case reports meeting various threshold scores is shown in Table 13. The two scoring models yielded roughly similar results. The problem with model B is that it can yield negative scores, which would imply a protective effect of leflunomide.

Table 13. Distribution of Leflunomide ALF Case Reports by Summary Score.

Total Score	Model A	Model B
≥ 20	14	12
≥ 25	12	11
≥ 30	10	8

To help translate this information into a measure of patient risk, we calculated NNH_{ALF} based on the range of case report numbers shown above, adjusted for underreporting (Table 14).

Table 14. Estimated number needed to harm (cause 1 case of ALF), adjusted for underreporting.

	<u>Number of Case Reports Included in Analysis</u>			
	n=14	n=12	n=10	n=8
NNH_{ALF}	428-756	545-963	654-1156	756-1318

The sensitivity analysis, based on a wide range of cases included in the analysis suggested that NNH_{ALF} ranged between 428 and 1318 at 15 months of continuing leflunomide use. Expressed another way, for every 10,000 patients treated for 15 months or longer, 7.6 to 23.4 cases of ALF would occur. Qualitatively, these estimates are not substantially different from those we found in our primary analysis of the data (NNH_{ALF} 388-685; 14.6-25.8 cases per 10,000 treated for 15 months or longer). It is important to realize that because the month-specific hazard appears to be non-diminishing over time, the cumulative hazard will continue to rise with longer duration use.

This sensitivity analysis was performed in part, because of disagreement over whether the primary epidemiologic analysis of case reports should be based on “probable” plus “possible” reports combined, or on “probable” only reports. The perspectives expressed at the two internal meetings generally correlated with whether one’s background was primarily focused on NDA reviews or postmarketing safety. We believe that the most appropriate analysis is one based on the combination of “probable” and “possible” reports. 1) This approach is maximally protective of patients against drug-induced harm. If a drug has a true population benefit, it should exceed this threshold of harm. 2) The reason that most “possible” reports were classified as such is because clinical and laboratory information provided in the reports was incomplete. To exclude these reports would introduce a bias favorable to the drug and its manufacturer because were the missing information supplied, some proportion of these reports would be upgraded to the “probable” category. In essence, the population using leflunomide would be forced to unknowingly shoulder the burden of that additional harm. Also, excluding these reports presumes that leflunomide had no role in causation (which has not been shown) and would have the effect of rewarding poor quality reports. 3) The physicians who submitted these case reports believed that leflunomide was causally responsible or contributory.

In considering the risk of ALF and other severe acute liver injury with leflunomide, it is useful to consider the hepatotoxic risk of methotrexate (MTX) since it is used extensively in the same population as is treated with leflunomide.

Methotrexate and liver injury.³⁷⁻⁴⁶ Methotrexate has been used in the treatment of RA for many years. Hepatotoxicity, in the form of hepatic fibrosis, leading potentially to cirrhosis and eventually chronic liver failure, has been discussed at great length in the literature. We reviewed the literature to understand better the nature of hepatotoxicity with this drug. First, MTX has rarely, if ever, been causally associated with the development of acute or fulminant hepatic failure in the treatment of RA. We were unable to find a single report of this occurrence. On the other hand, there is extensive literature regarding the development of chronic fibrotic liver disease with MTX used in the treatment of psoriasis and RA. The severity and frequency of hepatic sequelae appear to be much greater with MTX use for psoriasis. We focused on MTX use in RA. A major limitation of the literature is that there are relatively few well-done longitudinal studies assessing histologic changes related to long-term MTX use. We identified several studies that were longitudinal in nature.

Two studies were performed in which RA patients about to begin MTX therapy underwent baseline liver biopsy as well as repeat biopsy at 2-year intervals while on drug.^{37,38} The methods in each study were similar. Although the authors did not perform a survival analysis, they presented sufficient data that permitted us to perform that analysis (see Table 15.) Of note, while both studies found that the prevalence of mild hepatic fibrosis increased with duration of chronic MTX use (68% @ 6 years; 13% @ 6 years), neither found evidence of progression to severe fibrosis or cirrhosis. Also, the presence of

mild fibrosis on liver biopsy was not associated with clinical hepatic impairment. Importantly, patients in the study reporting a 13% cumulative risk of mild fibrosis were repeatedly reminded and encouraged to keep alcohol consumption to a minimum.³⁸

Table 15. Cumulative risk of developing mild fibrosis on liver biopsy among RA patients treated with long-term MTX

Years	Kremer, 1989 (n=29) ³⁷		Weinblatt, 1992 (n=26) ³⁸	
	Cum MTX (mg)	Cum Risk (n)	Cum MTX (mg)	Cum Risk (n)
0	0		0	
2	1349±54	8% (26)	1082±104	0% (17)
4	2924±124	48% (15)	2006±193	6% (15)
6		68% (1)	3095±315	13% (10)

The predictive significance of hepatic fibrosis on liver biopsy in RA patients treated with MTX is poorly understood. Scully et al. performed 51 liver biopsies in 40 patients followed on MTX for up to 5 years.³⁹ Data from this paper was not presented in a format that permitted calculation of cumulative risk, but observation of changes in liver histology over time was possible for some patients. Pre-treatment liver biopsies were not performed (Tables 16, 17).

Of note, the authors' category IV (fibrosis) did not distinguish between mild fibrosis (Roenigk grade IIIA) and moderate/severe fibrosis (Roenigk IIIB). Nonetheless, cirrhosis was not observed in this cohort and evidence of regression or stability in histology was observed in most patients undergoing a second biopsy.³⁹

Table 16. Summary of liver biopsy data on 40 patients treated with MTX for RA, from Scully et al.³⁹

	1 st biopsy (n=40)	2 nd biopsy (n=16)	3 rd biopsy (n=1)
Years on MTX (mean ± SD)	2.7±.9 yrs	3.9±.6 yrs	4.8 yrs
Cumulative MTX Dose (mean ± SD)	1.3±.6 g	1.7±.4 g	2.6 g
<u>Biopsy Result</u>			
I (Normal)	8	2	
II (Fatty liver)	16	5	
III (Necrosis/inflammation)	6	2	1
IV (Fibrosis)	10	7	
V (Cirrhosis)	0	0	

Table 17. Summary of liver histology change in 16 patients with repeat liver biopsies, from Scully et al.³⁹

Regression		No Change		Progression	
II:I	1	II:II	3	I:IV	1
III:I	1	III:III	3	II:IV	1
IV:I	2	IV:IV	4		
Total	4		10		2

A study by Brick et al. is also interesting in this regard.⁴⁰ In this study, 96 patients underwent liver biopsies (62 before the start of MTX, 35 both pre- and post-MTX, and 34 post-MTX only). On pre-MTX liver biopsy, 3% (2/62) had Roenigk grade IV (cirrhosis) biopsies. In a separate analysis of patients with pre- and post-MTX biopsies, 1 patient with Roenigk grade IV on pre-biopsy also had a grade IV post-biopsy. Two patients (6%) had mild fibrosis on their post-treatment biopsy, but no patients progressed to grade IIIB or IV. In this same paper, the authors reviewed the literature on studies of post-MTX treatment liver biopsies without reference to longitudinality of follow-up or presence of a pre-treatment biopsy. Of 625 reported patients, 0% had cirrhosis and 11% (67) had some element of fibrosis.⁴⁰

Another study followed up on 25 patients with biopsy-proven cirrhosis attributed to MTX therapy for psoriasis.⁴¹ At a mean follow-up of 12 years (range 3-24 yrs) after the diagnosis of cirrhosis, 13 patients had died, 1 from liver failure and 12 from non-liver-related causes. The patient with liver failure died after continuing MTX for 8 additional years after the diagnosis of cirrhosis was first made. Among the 13 who died, the most recent liver biopsy preceding death was negative for cirrhosis in 8. Among the 12 patients still alive, the most recent liver biopsy was negative for cirrhosis in 4.

More recently, a study was published summarizing the results of sequential liver biopsies in 94 patients from 3 separate cohorts treated with MTX for RA (Table 18).⁴² These patients underwent a total of 354 liver biopsies with an average interval between the first and most recent biopsy of 5±2.9 years. Within this group, there were no patients with Roenigk grade IIIB or IV histology, and only 7% (25/354) of biopsies showed grade IIIA histology (mild fibrosis).

Table 18. Number of patients and corresponding number of total liver biopsies in 94 patients treated with MTX for RA.⁴²

# liver biopsies	# patients
1	14
2	19
3	17
4	13
5	11
6	10

Another aspect of MTX use for the treatment of RA relates to long-term persistency of its use in patients. The table below summarizes findings from a number of different studies reporting on persistency of MTX use.^{38, 39, 43-46} As shown, it is common for MTX-treated patients to remain on drug for many years, with a range of estimates suggesting that 50% or more patients remain on drug for 6 years or longer (Table 19). The best single study may be that of Buchbinder et al., where 587 RA patients treated by community-based rheumatologists found 76% persistence at 6 years of MTX use.⁴⁵

Table 19. Tabulation of study estimates on the persistency of MTX use in patients with RA.

Years of continuing MTX use	Persistency of MTX use		
2	52% ³⁹	78% ³⁸	82% ⁴⁵
3	62% ⁴³	80% ⁴⁵	
4	39% ³⁹	62% ³⁸	72% ⁴⁶
5	58% ³⁸		
6	50% ³⁸	76% ⁴⁵	
7	46% ³⁸		
7.5	72% ⁴⁴		

Summary of leflunomide-associated ALF and other severe acute liver injury. Based on the above, several observations can be summarized. The background rates of idiopathic ALF and other severe acute liver injury are low, and RA is not associated with an increased risk of either. The cases of ALF and other acute severe acute liver injury reported to FDA in association with leflunomide suggest that the hazard (risk) of liver injury remains elevated for as long as patients remain on drug. This is without any adjustment for underreporting. Actual hazard rates are much higher than shown here. Also, cumulative risk is very high. Under the most likely scenario of 10% or less reporting efficiency, NNH_{ALF} was estimated to range from 388-685 (considering both probable and possible cases) and from 545-963 (considering probable cases only). For NNH_{ALF+} , the estimated ranges were 107-188 (probable+possible) and 166-281 (probable only). Even if the reporting efficiency were 25%, a level much higher than would be expected, NNH_{ALF} was estimated at 969-1713 (probable+possible) and at 1362-2408 (probable only). The corresponding estimates for NNH_{ALF+} were 266-471 and 416-702.

By comparison with leflunomide, MTX as used in RA is not associated with severe acute liver injury or failure. The main hepatotoxic risk with MTX use is liver fibrosis. However, the literature suggests that the level of fibrosis is usually mild, occurring after many years of treatment, and rarely progressing to cirrhosis, even after 6 years or longer use. Additionally, even if cirrhosis does develop, the long-term prognosis of such patients from a hepatic standpoint appears to be good if MTX is stopped. One potential limitation is that most sequential liver biopsy studies were based on relatively small numbers of patients. Nonetheless, a comprehensive review of the literature, covering 625 MTX-treated patients with liver biopsies, found no cases of cirrhosis.⁴⁰

Of note, while patient persistency on MTX is generally high (up to 82% at 2 years and 76% at 6 years), patient persistency on leflunomide is very low with only about 6% continuing leflunomide for more than 2 years. This lack of persistent use is important to recognize because it suggests that leflunomide is not well-tolerated (side effects), or else isn't very effective. Regardless of the reason, if patients do not remain on the drug for very long, no potential (if any) long-term benefit is, or can be, gained. At the same time, however, these patients are subject to all the hepatotoxic risks conferred by the drug. This leads us to now consider the benefits and risks of leflunomide.

Benefit-risk assessment of leflunomide. We turn now to an examination of the benefits of leflunomide. The following information was obtained from product labeling¹ because the medical officer's review and other supporting documents were neither posted on the FDA website nor available in DFS.

The leflunomide NDA approval was based on 816 patients studied in 3 clinical trials (US301 (182), MN301 (133), and MN302 (501)). Patients were followed for 6 to 12 months. The actual number of patients remaining on drug for varying lengths of time, was not stated and no life-table was presented. The study endpoints for efficacy were “% ACR20 Responder” and improvement in the Sharp score, a measure of slowing of radiographically identified structural damage to joints. The “ACR20 Responder” was defined as a patient who at the completion of the study had $\geq 20\%$ improvement in the number of swollen and painful joints plus $\geq 20\%$ improvement in 3 of the 5 following criteria: physician global assessment; patient global assessment; function/disability as measured by the Modified Health Assessment Questionnaire (MHAQ); visual analog pain scale; erythrocyte sedimentation rate or C-reactive protein.

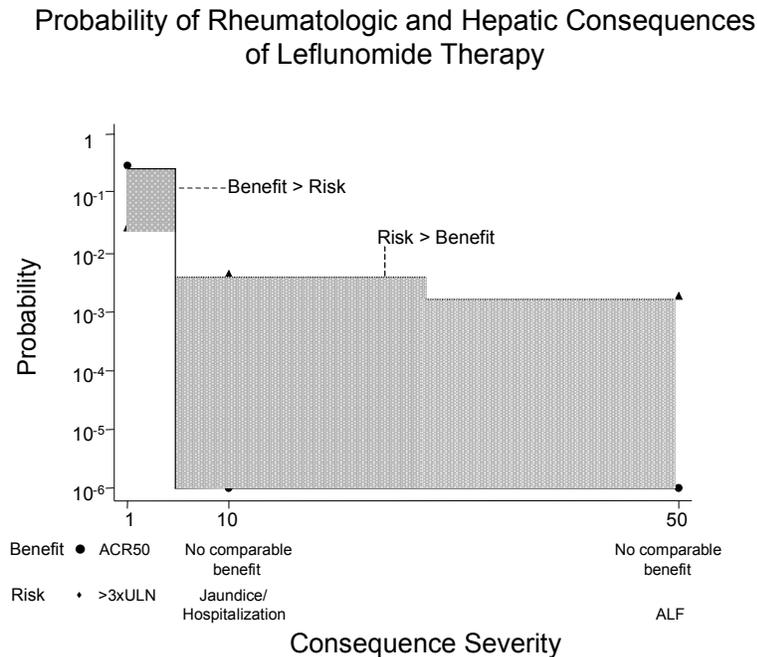
From Figure 1 of product labeling, ACR20 response ranged from 41% to 49% (weighted average: 44%). From Table 2, the ACR50 response ranged from 31% to 34% (weighted average: 32%) and the ACR70 response ranged from 10% to 20% (weighted average: 12%). These latter measures were based on “last observation carried forward,” a method that overestimates the true response rate. Importantly, leflunomide was not shown to be superior to MTX in terms of the efficacy measure used.

Of note, virtually all the endpoint measures upon which efficacy was based were subjective in nature and represent surrogates for what might be considered true benefit, such as delay/prevention of permanent loss of significant physical functioning, delay/prevention of serious disability, and delay in premature mortality. The value of subjective and surrogate measures in predicting true long-term benefit with leflunomide has not been established. Furthermore, if one examines the criteria for the ACR20, 50 and 70 responses, it can be seen that they are not independent. The first 4 of 5 secondary criteria are strongly correlated with the main criterion of swollen/painful joints.

Figure 7 (below) presents data on both benefit and harm from leflunomide. The y-axis is a \log_{10} scale of probabilities of experiencing a particular consequence (either beneficial or harmful). The x-axis represents the “Consequence Severity,” either beneficial or harmful. The units of scoring on this scale are intended to convey some sense of relative (comparative) value in terms of benefit and harm. Their purpose is to attempt to place various benefits and harms of comparable and relative intensity in appropriate reference to each other.

The figure shows that at the low end of the consequence scale, leflunomide has some “benefit” that exceeds the probability of experiencing the low-consequence harm of $>3\times$ ULN liver transaminase elevation. The use of the term “benefit” here must be qualified because a) it is based on subjective and surrogate measures, and b) it is related to short-term time intervals. As we move up the consequence severity scale, we find that there are no evidence-based metrics of benefit, obtained from objective and direct (as opposed to surrogate) endpoints, which demonstrate delay or prevention of disability or mortality. By contrast, we have estimates of harm derived from risk analysis of NNH_{Other} , NNH_{ALF} , and NNH_{ALF+} , all of which indicate that the risks of leflunomide greatly exceed its benefits.

Figure 7.



Effectiveness of existing risk management strategies. In the setting of particularly severe, potentially life-threatening adverse drug reactions, that occur at unacceptably high levels, the purpose of risk management efforts is to minimize this risk, and thereby restore the balance of benefit and risk to one that is maximally favorable to patients’ well-being. The methods used by CDER to address drug safety risks include: general labeling; labeled warnings with or without bolded lettering or a surrounding “black box”; “Dear Health Care Provider (HCP)” letters; recommendations to perform certain tasks prior to or during drug therapy (e.g., periodic liver enzyme monitoring, pregnancy testing); labeled contraindications; use as 2nd-line therapy only; restricted/registered distribution programs; and drug withdrawal.

A growing body of literature suggests that most of these strategies are ineffective in dealing with important drug safety problems. A study of the use of cisapride (withdrawn from the US market because of risks of QT prolongation and torsades de pointe) found that despite labeling efforts including bolded, boxed warnings, labeled contraindications, and “Dear HCP” letters, there was no change in the unsafe use of the drug.⁴⁷ Another study examined the performance of periodic liver enzyme monitoring in patients treated with troglitazone (withdrawn from the US market because of its high rate of causing ALF).⁴⁸ Despite bolded, boxed warnings, four “Dear HCP” letters and a nationally publicized open public FDA advisory committee meeting on the subject of troglitazone hepatotoxicity, the performance of periodic enzyme monitoring did not improve meaningfully.

More recently, a study of pemoline use found that despite being labeled as 2nd-line therapy for attention deficit hyperactivity disorder because of hepatotoxicity concerns, the drug continued to be used as 1st-line therapy in many children.⁴⁹ Also, periodic liver enzyme monitoring was not performed, despite bolded, boxed warnings in labeling and a “Dear HCP” letter recommending that monitoring be done.

Additional information regarding the effectiveness of various risk management strategies is provided by FDA’s experience with isotretinoin teratogenicity concerns and pregnancy exposure.^{50,51} Despite multiple FDA advisory committee meetings (at least 5), numerous “Dear HCP” letters, extensive bolded, boxed warnings in labeling, a number of company-sponsored educational campaigns, the use of a contraindications checklist in labeling, use of “signed informed consent”, and reliance on a nationally promoted “Pregnancy Prevention Program”, isotretinoin use more than tripled over a 10-year period (representing a marked increase in already extensive off-label, unapproved use), substantial numbers of pregnancy exposures continued to be reported (with many more not reported), and data from the sponsor’s Program showed that many women were not receiving pregnancy testing prior to initiating isotretinoin or monthly thereafter. Also, many patients treated with isotretinoin had one or more contraindications for its use. Recognizing the failure of previous risk management efforts, an FDA advisory committee unanimously recommended that a restricted distribution system be implemented for isotretinoin, with patient and physician registration and other safeguards designed to ensure that isotretinoin be used in as safe a manner as possible. The Agency did not follow this recommendation.

Restricted distribution programs have been implemented on several occasions in an effort to make drugs with significant toxicities available to a carefully selected subset of patients who may derive substantial medical benefit.^{52,53} Clozapine, an atypical anti-psychotic, was found to be beneficial in some patients with refractory schizophrenia. The drug also had a 1-2% risk of agranulocytosis. Clozapine was approved under a restricted/registered distribution program to ensure that weekly white blood cell/granulocyte counts were monitored as a pre-condition to receiving the medication. If blood counts fell below a certain threshold, no additional clozapine was given to the patient and the patient’s physician was informed of the lab results. Although little has been published about the clozapine experience, it is viewed as having been successful at substantially reducing the occurrence of agranulocytosis with the drug.

A restricted distribution program was also implemented for thalidomide.⁵⁴⁻⁵⁶ The primary safety concern here was the prevention of pregnancy exposure to a known teratogen. Currently, the program requires that all prescribers of thalidomide and all pharmacies distributing the drug must be registered centrally. There is also mandatory and confidential enrollment of all patients in a registry. Initial and follow-up survey forms must be completed by both the patient and prescribing physician. There are mandatory educational components and the requirement that informed consent be obtained (understood and a form signed) prior to beginning therapy. There is also mandatory periodic pregnancy testing with written test results in-hand prior to prescribing and filling a prescription. Under this program, there has been 1 reported documented pregnancy exposure that ended in miscarriage (personal communication: Sarah Singer, RPh, ODS Safety Evaluator).

Bosentan is another drug product recently approved with a restricted distribution program.⁵⁷⁻⁵⁹ The drug is indicated for an orphan condition, severe primary pulmonary hypertension, an ultimately fatal disease that often affects young women. Two safety concerns were identified prior to approval: hepatotoxicity (11% of patients with > 3xULN aminotransferase levels), and teratogenicity

(malformations and increased stillbirth rates in animal testing). The restricted distribution system involves patient and physician enrollment with a central clearinghouse and distribution of drug limited to 4 special distributors nationwide. There is monthly contact with every patient, both by postcard and by telephone. This serves as a means of identifying whether periodic liver enzyme testing and pregnancy testing are being performed. If enzyme monitoring is not being performed, the central clearinghouse contacts the prescribing physician. Bosentan came on the market in December 2001 and in the first 7 months of marketing, a total of 2341 patients had been registered with 1 reported documented pregnancy exposure. To date, there have been no reports of severe or fatal liver injury.

In general, restricted/registered risk management programs are used when there is a severe, clearly defined risk that has been shown to be preventable and for which a system can be engineered that greatly improves or guarantees that certain critical tasks will be performed. Additionally, such programs may serve to limit the number of patients exposed to the drug to that subset for which the balance of benefit to risk is maximized.

Withdrawal from the market effectively eliminates future harm due to the drug at the expense of its no longer being available.

Ethical considerations. Although it is a delicate topic, we believe there is an ethical dimension to risk-management considerations for leflunomide, and for other drugs, that requires discussion. Our intent is to surface and explore an issue we are concerned about. It is not our intent to criticize or question the motives or ethics of others.

The basic construct of the following discussion is: when CDER adopts and implements a risk-management strategy for a serious adverse consequence of a drug product's use, it is performing an experiment involving human subjects. The question for consideration is: when are such experiments ethical and when are they not? Typically, there is a serious or life-threatening drug-related harm that needs to be prevented or reduced to some "acceptable" level. We can view the drug-related harm as a "disease" that will be treated using a risk-management strategy. In this circumstance, the therapy (i.e., a risk management program) will be administered to the population using the drug. In a similar fashion, clinical trials usually involve some health disorder or disease for which a therapy (drug) is administered to a population of carefully screened and selected volunteers. Both scenarios represent experiments involving human subjects, a difference being that one experiment is uncontrolled while the other is controlled. We apply the word "experiment" to the risk-management setting because the methods (therapies) applied are for the most part, of unproven or unknown benefit or effectiveness, or else have evidence suggesting they are ineffective. Their use in addressing a serious safety concern should therefore be viewed as experimental in nature.

In the world of clinical trials, a number of ethical guidelines have been adopted, the purpose of which is first and foremost, protection of human subjects against harm.⁶⁰ These principles have been incorporated into regulations governing research in humans.⁶¹ Underlying all clinical trials is the premise that it is uncertain whether the experimental treatment will prove beneficial or not. This translates to an indifference on the part of the investigator and patient as to which treatment (experimental or placebo/standard) is better. This position of uncertainty or indifference has been referred to as equipoise.⁶² If equipoise does not exist, then randomization into a clinical trial is not justified.⁶³ Likewise, substituting unproven therapies for proven ones in the setting of serious or life-threatening circumstances is not ethical.⁶³

Three principles underlie the protection of human subjects.^{60,61} 1) Respect for persons necessitates an open, honest and transparent informed consent process. 2) Beneficence seeks to protect human subjects from harm (physical, psychological, social, legal or financial in nature), and requires that the probabilities and magnitudes of possible harm be compared with anticipated benefits. This principle also requires creation of institutional review boards (IRBs) to conduct an ethical and scientific review of the study protocol and informed consent. The purpose of this review is to determine if the rights and welfare of human subjects involved in research are adequately protected. Among many things, the IRB examines three questions: is there validation of the presuppositions upon which the research is based, is the research properly designed to answer the question being asked, and are the risks that subjects will be exposed to, justified? 3) Justice, requires fairness in access to participation in the study.

Applying these principles to leflunomide and severe hepatic injury, we make the following observations. Among the risk-management strategies that have been used in the past, none, except perhaps restricted distribution programs involving registration of physicians and patients, have been shown to be reliably effective. Setting restricted/registered programs aside for the moment, the *a priori* expectation is that none of the other strategies would be effective at minimizing the risks and maximizing the benefit:risk ratio of leflunomide. In several addresses to the CDER community, Dr. Woodcock has stated that labeling-related, educational, and “Dear HCP” letter strategies are not effective. That being the case, we believe that with respect to these strategies, equipoise does not exist, and that the evidence to date suggests that they are ineffective in addressing serious drug-related risks. From this perspective, reliance on these strategies to protect patients from the serious harm conferred by leflunomide is unethical.

Our experience with restricted distribution programs requiring patient, physician and in some cases, pharmacy (or other distribution center) registration, has not been critically evaluated. The clozapine registered distribution program has been successful,^{52,53} but we have not seen a critical epidemiologic evaluation of the programs for thalidomide and bosentan. In each of these situations, a specific severe and preventable adverse consequence of drug therapy was identified (potentially fatal agranulocytosis, teratogenic pregnancy exposure with congenital anomalies) and a program was engineered to minimize this risk. Because the conditions being treated (refractory schizophrenia; cancer (not the approved indication); primary pulmonary hypertension) could be viewed as imminently life-threatening, and because the therapies in question had substantial documented health benefit, a risk-management modality of last resort, registered/restricted distribution, was deemed appropriate. Finally, the number of patients registered and actively receiving drug within the program has been small in the case of thalidomide and bosentan.

Would a registered distribution program for leflunomide be appropriate and would it be effective? Such a program might be appropriate if at least two preconditions (there may be more) were met. The first precondition is that the documented medical benefits of the drug clearly exceed the harm that the drug would cause with the program in place. However, as shown above, there is no evidence of substantial long-term benefit from the drug, and even if there were one, patients do not remain on leflunomide for very long and so would not be expected to derive that benefit anyway. However, they would still be subject to the risks we have discussed. Returning to the three principles described above, the risks of exposure are not justified because no objective, substantial long-term benefit of clinical value comparable to that of being hospitalized or developing ALF or dying have been proven.

The second precondition is that there are proven means available whereby the harm caused by a drug can be prevented. We cannot identify a particular subset of patients to whom the risks are limited. We also have no means of predicting in advance who will develop severe acute liver injury or failure. The assertion that factors other than leflunomide are the cause of ALF (such as acetaminophen use at therapeutic doses, prior history of alcohol use or abuse, prior history of hepatitis B or C, or pre-existing liver disease caused ALF) in some of the cases reported to FDA is speculative and unproven. Such patients with potentially reduced hepatic reserve from whatever cause, are still at-risk of superimposed acute liver injury due to leflunomide use. The reporting of cases of ALF (US and foreign) where no potential risk factors or confounders are present also speaks to the intrinsic hepatotoxicity of leflunomide.

Most importantly, there is no evidence that ALF or other severe liver injury due to leflunomide is preventable. This being the case, use of periodic liver enzyme monitoring to prevent the occurrence of serious liver injury would be purely an experimental risk-management strategy of unknown or unproven effectiveness. We maintain that the *a priori* expectation of effectiveness for this approach must be low based on prior experience. With the anti-diabetic drug troglitazone, CDER implemented periodic liver enzyme monitoring as its central strategy for reducing the liver failure risks of the drug and keeping it on the market. This was done in the absence of any data to suggest that enzyme monitoring was effective or that physicians would comply with the recommendation to monitor. Our research found that enzyme monitoring was not performed to an appreciable degree and that monitoring did not prevent the occurrence of ALF.²⁹ We believe that in the absence of a demonstrated method of preventing the occurrence of severe liver injury, a registered distribution system for leflunomide is not justified and would be unlikely to protect patients against severe or fatal acute liver injury.

The remaining risk management strategy, market withdrawal, is effective at protecting patients against drug-induced harm. In our view, reliance on methods known to be ineffective or that are experimental in nature, is analogous to substituting unproven therapy for proven therapy or withholding proven therapy in the setting of serious or life-threatening circumstances.

CONCLUSIONS and RECOMMENDATIONS

Leflunomide use is associated with a high cumulative risk of ALF and other severe acute liver injury, which will likely increase further the longer a patient remains on drug because the risk of liver injury appears to persist for as long as a patient remains on therapy. The case reports were analyzed in a variety of ways (combining reports classified as “probably” and “possibly” causally related; “probable” only reports; and a sensitivity analysis) but each yielded a qualitatively similar result indicating substantial risk.

Methotrexate, another drug commonly used to treat RA has also been associated with liver injury. A review of the literature showed that the main hepatotoxicity with MTX was related to the development of fibrosis. This fibrosis was typically mild (Roenigk Grade IIIA) and the development of cirrhosis was uncommon, even after therapy lasting more than 6 years. Among patients who developed cirrhosis while taking MTX for psoriasis, long-term hepatic prognosis was good. From a risk perspective, the probability of liver failure or other severe acute liver injury with MTX for RA is very low, and if it occurs, is likely to do so after many years of treatment. By contrast, the hepatotoxic risks of leflunomide are much greater and more immediate.

We found that the criteria upon which leflunomide's efficacy were based are for the most part subjective in nature and surrogate measures for actual functional benefit. We were unable to find any objective and functionally important benefits of comparable value to the identified harms of hospitalization for acute liver injury or ALF. Combined with the magnitude of risk in terms of number needed to harm, we believe that the risks of leflunomide greatly exceed any documented benefit. In addition, even if we hypothesize some substantial, as yet undocumented long-term benefit due to leflunomide use, patients don't remain on the drug long enough to experience it. However, even under this hypothetical scenario, these patients would still be subject to the risks we have described. Further, it would be necessary to discount any hypothetical future benefit to present-day value because patients experience the "costs" of liver injury in the present.

Given that the risks of leflunomide use exceed its benefits, reliance on risk-management modalities short of market withdrawal are not justified. Were there a substantial long-term benefit approaching in value the magnitude and severity of hepatotoxic harm, reliance on labeling, education and similar efforts would not be justifiable because these approaches are not effective. The implementation of a restricted/registered drug distribution program is likewise not supportable because ALF from leflunomide is not a preventable condition and all patients who use the drug are at risk.

We recommend that leflunomide be removed from the market.

REFERENCES

1. Arava® Product Labeling. Aventis , April 2000.
2. Severe liver damage with leflunomide. Translated from Prescrire International.2001 October, Oct; 10 (55): 149.
3. Legas A, Bergemen-Fouquet AM, Joville-Bera AP. Fatal hepatitis with leflunomide and itraconazole. *Am J Med* 2002; 113:352-4.
4. Weinblatt ME, Dixon JA, Falchuk KR. Serious liver disease in a patient receiving methotrexate and leflunomide. *Arthritis Rheum* 2000; 43:2609-11.
5. Lee William. Acute Liver Failure. *N Engl J Med* 1993; 329:1862-72.
6. Zimmerman HJ, Maddrey WC. Toxic and drug induced hepatitis. In: Schiff L, Schiff ER, eds. *Diseases of the liver*. Philadelphia: J.B. Lippincott, 1993: 707-83.
7. Larrey Dominique. Drug-induced liver diseases. *Journal of Hepatology* 2000; 32 (suppl 1.): 77-88.
8. Clayton D, Hills M. *Statistical models in epidemiology*. Oxford University Press: New York, NY, 1993;298-318.
9. Kelsey JL, Whittemore AS, Evans AS, Thompson WD. *Methods in observational epidemiology*. Oxford Press: New York, NY, 1996.
10. Kahn HA, Sempros CT. *Statistical methods in epidemiology*. Oxford University Press: New York, NY, 1989;168-225.
11. Hosmer DW, Lemeshow S. *Applied survival analysis: regression modeling of time to event data*. John Wiley & Sons, Ltd.: New York, NY, 1999;73-113.
12. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. *Ann Intern Med* 1997;126:712-720.
13. McAlister FA, Straus SE, Guyatt GH, Haynes RB, for the Evidence-Based Medicine Working Group. Users' guides to the medical literature, XX: integrating research evidence with the care of the individual patient. *JAMA* 2000;283:2829-2836.
14. Graham DJ, Ahmad SR, Piazza-Hepp T. Spontaneous reporting in the USA. In: Mann RD, Andrews EB, eds. *Pharmacovigilance*. John Wiley & Sons, Ltd., New York, 2002:109-124.
15. Meyboom RHB, Egberts ACG, Edwards RI, Hekster YA, de Kining FHP, Gribnau WJ. Principles of signal detection in pharmacovigilance. *Drug Safety* 1997;16:355-365.
16. Graham DJ, Waller PC, Kurz X. A view from regulatory agencies. In *Pharmacoepidemiology*, 3rd edition. Strom BL, ed. John Wiley & Sons, Ltd.: New York, NY, 2000;109-124.
17. Rogers AS, Israel E, Smith CR. Physician knowledge, attitudes and behavior related to reporting adverse drug events. *Arch Intern Med* 1988;148:1589-1592.
18. Scott HD, Rosenbaum SE, Waters WJ, Colt AM, Andrews LG, Juergens JP, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. *RI Med J* 1987;70:311-316.
19. Kessler D. MEDWatch: the new FDA medical products reporting system. *JAMA* 1993;269:2765-2768.
20. Warren JL, McBean AM, Hass SL, Babish JD. Hospitalizations with adverse events caused by digitalis therapy among elderly Medicare beneficiaries. *Arch Intern Med* 1994;154:1482-1487.
21. Faich GA. Adverse reaction monitoring. *N Engl J Med* 1986;314:1589-1592.
22. United States General Accounting Office. Adverse drug events: the magnitude of health risk is uncertain because of limited incidence data. GAO/HEHS-00-21, January 2000:1-47. Available from internet URL: <http://www.gao.gov>. Last accessed October 11, 2001.
23. Griffin JP, Weber JCP. Voluntary systems of adverse reaction reporting. Part II. *Adv React Ac Pois Rev* 1986;1:23-55.

24. Moride Y, Harambaru F, Requejo AA, Begaud B. Under-reporting of adverse drug reactions in general practice. *Br J Clin Pharmacol* 1997;43:177-181.
25. Alvarez-Requejo A, Carvajal A, Moride BB, Vega T, Arias L. Under-reporting of adverse drug reactions. Estimate based on spontaneous reporting scheme and a sentinel system. *Eur J Clin Pharmacol* 1998;54:483-8.
26. La Grenade L, Graham DJ, Nourjah P. Underreporting of serious adverse drug reactions due to over-the-counter drugs [research letter]. *JAMA* 2002;286:3081.
27. Leiper JM, Lawson DH. Why do doctors not report adverse drug reactions? *Neth J Med* 1985;28:546-550.
28. Graham DJ, Green L. Epidemiology of hepatotoxicity with troglitazone. FDA Metabolic-Endocrine Drugs Advisory Committee Meeting, Bethesda, MD. 1999; 26 Mar. Available from: US Food and Drug Administration via the Internet (www.fda.gov/ohrms/dockets/ac/99/transcpt/3499t1a.pdf; /3499t1b.pdf; /3499t1c.pdf; /3499t1d.pdf; /3499t1e.pdf). Accessed 8 January 2002.
29. Graham DJ, Green L. Final report: liver failure risk with troglitazone. Office of Postmarketing Drug Risk Assessment, Center for Drug Evaluation and Research, Food and Drug Administration. December 2000.
30. Schiodt FV, Atillasoy E, Shakil AO, et al. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transplant Surg* 1999;5:29-34.
31. US Census Bureau. Available at: <http://www.census.gov/population/cen2000/tab02.pdf>. Accessed 28 January 2002.
32. Beard K, Belic L, Aselton P, et al. Outpatient drug-induced parenchymal liver disease requiring hospitalization. *J Clin Pharmacol* 1986;26:633-7.
33. Garcia Rodriguez LA, Gutthann SP, Walker AM, et al. The role of nonsteroidal anti-inflammatory drugs in acute liver injury. *Br Med J* 1992;305:865-8.
34. Carson JL, Strom BL, Duff A, et al. Safety of nonsteroidal anti-inflammatory drugs with respect to acute liver disease. *Arch Intern Med* 1993;153:1331-6.
35. Garcia Rodriguez LA, Williams R, Derby LE, et al. Acute liver injury associated with nonsteroidal anti-inflammatory drugs and the role of risk factors. *Arch Intern Med* 1994;154:311-15.
36. Almdal TP, Sorensen TIA. Incidence of parenchymal liver disease in Denmark, 1981 to 1985: analysis of hospital registry data. *Hepatology* 1991; 13:650-5.
37. Kremer JM, Lee RG, Tolman KG. Liver histology in rheumatoid arthritis patients receiving long-term methotrexate therapy. *Arthritis Rheum* 1989; 32:121-7.
38. Weinblatt ME, Weissman BN, Holdsworth DE, Fraser PA, Maier AL, Falchuk KR, et al. Long-term prospective study of methotrexate in the treatment of rheumatoid arthritis: 84 month update. *Arthritis Rheum* 1992; 35:129-37.
39. Scully CJ, Anderson CJ, Cannon GW. Long-term methotrexate therapy for rheumatoid arthritis. *Semin Arthritis Rheum* 1991; 20:317-31.
40. Brick JE, Moreland LW, Al-Kawas F, Chang WWL, Layne RD, DiBartolomeo AG. Prospective analysis of liver biopsies before and after methotrexate therapy in rheumatoid patients. *Semin Arthritis Rheum* 1989; 19:31-44.
41. Zachariae H, Sogaard H, Heckendorff L. Methotrexate-induced cirrhosis. *Dermatology* 1996; 192:343-6.
42. Kremer JM, Furst DE, Weinblatt ME, Blotner SD. Significant changes in serum AST across hepatic histological biopsy grades: prospective analysis of 3 cohorts receiving methotrexate therapy for rheumatoid arthritis. *J Rheumatol* 1996; 23:459-61.

43. Weinblatt ME, Trentham DE, Fraser PA, Holdsworth DE, Falchuk KR, Weissman BN, et al. Long-term prospective trial of low-dose methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31:167-75.
44. Kremer JM, Phelps CT. Long-term prospective study of the use of methotrexate in the treatment of rheumatoid arthritis. *Arthritis Rheum* 1992; 35:138-45.
45. Buchbinder R, Hall S, Sambrook PN, Champion GD, Harkness A, Lewis D, et al. Methotrexate therapy in rheumatoid arthritis: a life-table review of 587 patients treated in community practice. *J Rheumatol* 1993; 20:639-44.
46. Weinblatt ME, Kaplan H, German BF, Merriman RC, Solomon SD, Wall B, et al. Methotrexate in rheumatoid arthritis: effects on disease activity in a multi-center prospective study. *J Rheumatol* 1991; 18:334-8.
47. Smalley W, Shatin D, Wysowski DK, et al. Contraindicated use of cisapride: impact of Food and Drug Administration action. *JAMA* 2000;284:3036-3039.
48. Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ. Liver enzyme monitoring in patients treated with troglitazone. *JAMA* 2001; 286:831-3.
49. Willy ME, Manda B, Shatin D, Drinkard CR, Graham DJ. A study of compliance with FDA recommendations for pemoline (Cylert). *J Amer Acad Child Adolesc Psychiatry* 2002; 41: 785-90.
50. Vega L. Accutane and pregnancy exposure. Dermatologic Drugs Advisory Committee meeting, Gaithersburg, MD, September 18, 2000. Available from internet URL: www.fda.gov/ohrms/dockets/ac/cder00.htm#Dermatologic and Ophthalmologic. Last accessed October 24, 2002.
51. Vega L. Engineering a risk management program. Dermatologic Drugs Advisory Committee meeting, Gaithersburg, MD, September 18, 2000. Available from internet URL: www.fda.gov/ohrms/dockets/ac/cder00.htm#Dermatologic and Ophthalmologic. Last accessed October 24, 2002.
52. Honigfeld G. Effects of the clozapine national registry system on incidence of deaths related to agranulocytosis. *Psychiatr Serv* 1996; 47:52-6.
53. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. *J Clin Psychiatry* 1998; 59(Suppl 3):3-7.
54. FDA approval of thalidomide. American Society of Health-System Pharmacists. Available from internet URL: <http://www.ashp.org/public/news/breaking/thalid01.html> Last accessed October 22, 2002.
55. System for Thalidomide Education and Prescribing Safety. Celgene Corporation. Available from internet URL: [http://www.celgene.com/images/pdf/\\$FILE/Balancing.pdf](http://www.celgene.com/images/pdf/$FILE/Balancing.pdf) Last accessed October 22, 2002.
56. Thalidomide information. Center for Drug Evaluation and Research. Available from internet URL: <http://www.fda.gov/cder/news/thalinfo/default.htm> Last accessed October 22, 2002.
57. Tracleer (bosentan) in pulmonary arterial hypertension. Cardiovascular and Renal Drugs Advisory Committee. Briefing package for advisory meeting, August 10, 2001. Available from internet URL: <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3775b2.htm> Last accessed October 22, 2002.
58. Open public meeting of the Cardiovascular and Renal Drugs Advisory Committee for bosentan. Bethesda, MD, August 10, 2001. Transcript available from internet URL: <http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3775t2.rtf> Last accessed October 22, 2002.

59. Patient and health professional information on bosentan. Actelion Pharmaceuticals US, Inc. Available from internet URL: http://www.tracleer.com/tracleer_website/default.asp Last accessed October 22, 2002.
60. Belmont report: Ethical principles and guidelines for the protection of human subjects. Fed Reg 79-12065. Available from internet URL: www.ohrp.osophs.dhhs.gov/humansubjects/guidance/belmont.htm Last accessed October 28, 2002.
61. Dunn CM, Chadwick G. Protecting study volunteers in research: a manual for investigative sites. CenterWatch, Inc. Boston, 1999.
62. Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987; 317:141-5.
63. Piantadosi S. Clinical trials: a methodologic perspective. John Wiley & Sons, Inc. New York, 1997; 29-60.

Attachment 1. U.S. Hepatic Failure Cases Associated with Leflunomide

ISR# (mfr)	Year	Location	Age/ Sex	Tx duration	Diagnosis	Concomitant Medications	Outcome/ Causality	Summary
1.3651386-7(200110085US)	2001	MA	29/F	90 days	Fulminant hepatic failure	Azithromycin, atovaquone, calcium, methylprednisolone, multivitamin, acetaminophen and infliximab	Died Probable	<p>The patient died of fulminant hepatic failure after approximately three months of leflunomide (20mg daily, unknown if loading dose was given) therapy for Still's disease. The past medical history included possible alcohol use, marijuana use, and immunosuppression. She was Hep A,B, C and HIV negative. After starting leflunomide, LFTs were found to be markedly elevated but it was also discovered that her dose of atovaquone (Mepron®) (antimalarial) was three times the prescribed dose due to medication error. Cholestyramine rescue was attempted but not completed due to patient non-compliance. She presented with jaundice and hospitalized. On admission her lab values included SGOT 1574, SGPT 1679, Alk Phos 153, amylase 103, bilirubin 31, lipase 426, and albumin 2.4. Cholestyramine was restarted and the patient developed coagulopathy (PTT 123; PT 32; INR 5), and DIC which clotted off hepatic blood supply. She had a rapid progressive downhill course. Blood cultures were negative, urine and sputum were positive for yeast, and peri-rectal hepatic lesions were noted. Liver biopsy was not done. She was transferred for evaluation for liver transplant but died before transplant of fulminant liver failure. At that time, liver enzymes were in the “2000 range”, creatinine 2.1, C0₂ 8.0 and albumin was 1. No autopsy was done. Progression to ALF within 3 months.</p>
2.3645714-6200020914US	2001	US	51/F	4-5 mo	Hepatic necrosis	Celecoxib Prednisone	Hosp Died Probable	<p>The patient developed hepatic necrosis and died after 4-5 months of leflunomide (20 mg daily after 100 mg loading dose) therapy for rheumatoid arthritis. The patient was initially hospitalized for rash, fever, and jaundice. At that time, leflunomide and celecoxib were discontinued and the patient started on cholestyramine. She had no history of alcohol use. The patient was discharged but returned to the hospital on an unknown date due to fever. During this second admission, she was noted to have atelelectasis, abnormal LFTs (ALT 600, AST 400, alk phos 270), PT 27.1, PTT 31.4, bilirubin 9.0, and albumin 2.2. Hepatitis panel was negative. Highest transaminases were >1000, alk phos >1400 and bilirubin 17. A liver biopsy showed centrilobular necrosis with portal inflammation and hepatic necrosis consistent with drug reaction. Bone marrow biopsy showed hypercellular activity with no evidence of malignancy. Bone marrow and liver biopsies were negative for TB. The patient was negative for Hepatitis A, B, and C. Despite a ten-day course of cholestyramine, leflunomide levels remained high. The patient was admitted a third time with GI bleeding, cholestyramine washout given again, and she was diagnosed with a duodenal ulcer. The patient eventually was able to take food orally but remained jaundiced as LFTs improved. She was transferred for liver transplant evaluation. While waiting for liver transplantation, she developed peritonitis, post-op complications, shock and died. No autopsy was performed.</p>
3.3486831-3200011168HMR I	2000	TX	53/F	87 days	Hepatic failure	Sulfasalazine misoprostol prednisone	Life-threat Recovered Probable	<p>A consumer reported receiving leflunomide 100-mg daily (overdose) for RA for 87 days. During therapy, although her LFTs were elevated, she was instructed to continue to take the drug at this dose. She developed tongue burning, weight loss and developed “complete liver failure” and coma. The patient received lactulose for several months following the events. The follow-up liver biopsy revealed resolution of liver damage and she recovered. Progression to ALF within 3 months.</p>

Attachment 1. U.S. Hepatic Failure Cases Associated with Leflunomide

ISR# (mfr)	Year	Location	Age/ Sex	Tx duration	Diagnosis	Concomitant Medications	Outcome/ Causality	Summary
4. 3344035-9 199920773HMRI	1999	NE	55/M	60 days	Hepatic failure	Allopurinol, Bactrim DS, amitypyyline, lisinopril, heparin, prednisone	Hosp Recovered Probable	The patient received leflunomide daily for unknown dose (unknown if loading dose was given) about 2 months. Medical history included alcohol dependency. The patient was hospitalized with increased PT/PTT/INR, ascites, jaundice, elevated liver enzymes, encephalopathy, respiratory decompensation, liver failure and required intubation. Leflunomide was discontinued. The patient received 18 doses of cholestyramine. As the time of this report, the liver enzymes were still elevated. FDA was unable to obtain more information.
5. 3242747-9 199813621HMRI	1999	CA	55/F	5 days	Fatal Hepatitis	Hydrochloroquin innaproxen, propranolol, conjugated estrogens	Died Probable	The patient died one month after starting leflunomide 100 mg x 3 days followed by 20 mg daily dose for 4 days. Past medical history was significant for alcohol abuse. She was evaluated for jaundice. The lab values revealed bilirubin: 22; AST 288; ALT 63, and alkaline phosphatase 766. The hepatitis screen was negative. The physician stated that leflunomide was related to the jaundice and liver injury. Progression to ALF within 3 months.
6. 3469221-9 200010080HMRI	2000	NJ	61/M	unknown	Liver failure	Methotrexate Atenolol, trazolan, verapamil, alprazolam	Hosp Probable	The patient presented to ER with elevated liver enzymes, lethargy, confusion, and respiratory failure after receiving leflunomide 10 mg twice daily for rheumatoid arthritis (unknown duration). The laboratory values were: LDH: 16,376/3009; AST 4595/2587; ALT 2215 ; total bilirubin 1.2 ; alk phos 123. Cholestyramine was given at 8 grams every 8 hours for 11 days. Follow-up labs included AST 74; ALT 422 and Alk Phos was 128. The event resolved after discontinuation of leflunomide
7. 3862570-1 200123598US	2002	FL	66/M	4 months	Hepatic failure	Methotrexate, rofecoxib, prednisone calcium	Hosp, life- threat Possible	The patient received 20-mg daily dose of leflunomide for RA. No loading dose was given. Medical history was significant for a recent viral illness, rheumatoid arthritis and smoking. About 4 months after starting leflunomide therapy, he developed gangrenous fingers and toes. He was admitted to hospital with liver failure, renal failure, and thrombocytopenia (platelet count is unknown). Leflunomide and methotrexate were discontinued. He received cholestyramine for 2 days, leucovorin, platelets, IV fluids and IVIG for 5 days. The creatinine decreased from 8.4 to 2.2 (baseline is not available). The final outcome was unknown.
8. 3651385-5 200022670US	2001	IL	66/F	3 weeks	Massive hepatic necrosis	Ibuprofen, prednisone, lansoprazole	Hosp Died Possible	The patient started on 20-mg daily leflunomide for RA. Three weeks after starting leflunomide, she developed severe diarrhea and cardiopulmonary arrest. On admission she had diarrhea with bleeding, metabolic acidosis, possible DIC and renal failure (required hemodialysis). Her liver enzymes were in thousands (supporting lab values were not provided). The baseline liver enzymes were normal (AST/ALT: 10-20). Liver biopsy showed fatty liver. The patient had no history of alcohol use. She was intubated, received charcoal and cholestyramine therapy. The patient died. Autopsy results were not completely available, with the exception that there was no evidence of coronary artery disease. The consulting physician felt that the leflunomide caused the diarrhea and hepatic necrosis. Progression to ALF within 3 months.

Attachment 1. U.S. Hepatic Failure Cases Associated with Leflunomide								
ISR# (mfr)	Year	Location	Age/ Sex	Tx duration	Diagnosis	Concomitant Medications	Outcome/ Causality	Summary
9.3859484-X 200210502US	2002	MN	67/F	4 months	Hepatic failure		Hosp Life- threat, Died Probable	The patient received 20-mg daily (unknown if the loading dose was given) leflunomide for rheumatoid arthritis. Significant medical history included hepatitis A, portal hypertension, gastritis, steroid induced diabetes, Grade III esophageal varices (unknown etiology) per EGD and allergies to aspirin, piroxicam and ibuprofen. She has used azathioprine and methotrexate in the past. Four months after starting leflunomide, she presented with jaundice (bilirubin: 19) and pulmonary infiltrates. Liver biopsy showed fibrosis and marked canalicular cholestasis suggestive of possible medication reaction per reporter. CT of abdomen showed "hepatic cirrhosis with varices". After discharge, she presented to a different hospital with diarrhea, weakness and jaundice. She continued to receive leflunomide for 9 days beyond the onset of jaundice. She was started on cholestyramine washout. The follow-up lab values included INR 1.5; total bilirubin 25/21/20.7; AST: 61/59/59; ALT 31/29/28, alkaline phosphatase 151/145/132. The patient declined liver transplantation. The family requested DNR and she died.
10.3720213-1 Direct	2001	IL	75/F	unknown	Acute liver failure	Prednisone, tramadol, venlafaxine, neurontin, aspirin, amiodarone, dicloxacillin, Vicodin, alendronate, rofecoxib	Hosp Probable	The patient was admitted with increased liver enzymes, change in mental status, confusion. Past medical history is significant for Hepatitis C secondary to blood transfusion, hypertension, osteoarthritis, A-fib, CHF, and interstitial lung disease. Baseline LFTs were within normal limits. (ALT/AST: 19/28). Following leflunomide, there was a rapid change in ALTA/ST: 999/1187. Ammonia level was 57 (normal: 9-33 µmol/L). The medications were discontinued and the patient improved. Hepatology consult assessed the case as liver failure secondary to drug-induced ischemic hepatitis.
11.3892731-7 200121594US Direct	2002	AZ	75/F	2 months	Acute liver failure	Furosemide, propofenone, coumadin, prilosec, premarin, hydrochloroquine, amiodarone	Hosp Died Probable	The patient with a history of cutaneous lupus and atrial fibrillation received leflunomide 20 mg daily for rheumatoid arthritis with a 5-year history. She had no history of alcohol intake, hepatitis or exposure to toxins. Two months after starting leflunomide, she was admitted to hospital with fast irregular heart beat (150/min). On admission, she was hemodynamically stable, her serum creatinine was 1.9 (baseline 0.8), WBC: 5.2, HCO ₃ :20, BUN: 53, albumin 2.5, INR:5.7 and LFT's were increased ~10 fold per reporting physician. She received 800-mg oral dose of amiodarone to convert cardiac rhythm. Later that morning, the labs indicated AST: 1186; ALT: 669, Alk Phos:58. Over the next 2 days, her condition worsened and she went into progressive liver failure. At that time, her lab values were: AST: 4682, ALT:2202, total bilirubin:3 and alk phos:92. She received cholestyramine without effect and died. Family refused autopsy. Progression to ALF within 3 months.

Attachment 1. U.S. Hepatic Failure Cases Associated with Leflunomide							Summary	
ISR# (mfr)	Year	Location	Age/ Sex	Tx duration	Diagnosis	Concomitant Medications	Outcome/ Causality	
12.3562186-0 Direct	2000	PA	76/F	366 days	Acute liver Failure	Duragesic, calcium, magnesium, Percocet, acetaminophen	Hosp Life-threat, Died Probable	The patient received leflunomide 20mg daily for rheumatoid arthritis for about a year. She was prescribed acetaminophen products (Percocet - 1 tab every 4 hours as needed and acetaminophen 650 mg four times daily as needed) for back pain resulting from fall injury. She had history of COPD, HTN, lumbar spine fusion. She had no history of alcohol use or liver disease. She presented with increasing confusion, hypotension, positive hemocult, AST : 5795, ALT: 1056, bilirubin: 2.4, alk phos: 195, PT>33, ammonia: 85 and albumin:2.8. Herpes, CMV and viral hepatitis titers were negative. Baseline LFTs were normal. She was provided supportive care and received N-acetylcysteine per hospital protocol. No acetaminophen levels were drawn. Her fu labs improved with AST: 62, ALT: 78, alk phos 102 and bilirubin 1. She had complicated hospital course with pneumonia, pancreatitis, emphysema, UTI and A-flutter and she died secondary to liver complications. The cause of death attributed to acute liver failure as result of leflunomide and acetaminophen.
13.348161-0 200010951HMRI	2000	SC	F	3 months	Acute liver failure		Hosp Died Possible	The patient received leflunomide 100mg x 3 and then 20-mg daily dose for RA for 3 months. Significant medical history includes interstitial lung disease. Three months after starting leflunomide, she presented to the emergency room with a near syncope episode and shock. She was hospitalized with liver failure, pancreatitis and interstitial lung disease and died. Arava was discontinued but she did not undergo a washout. FDA was unable to obtain more information from the reporter. Progression to ALF within 3 months.
14. 3424801-1 199922130HMRI	1999	NC	unk	unknown	Liver failure		Possible	Poorly documented report of hepatic failure, jaundice, elevated alkaline phosphatase and vasculitis. FDA was unable to obtain more information.
15.3923098-3 200214805US	2002	TX	55/M	15 months	Fulminant hepatic failure	None	Hosp Recovered Probable	Pt with scleroderma, on leflunomide for 15 months, with history of past EtOH use, admitted to hospital with possible pneumonia and ALT/AST > 200. Leflunomide stopped. Hepatitis studies were negative. Over subsequent 4 days, patient went into acute liver failure, with ALT/AST up to ~6000 and INR of 3.1. Discharged home after 2 weeks only to be readmitted to ICU with encephalopathy 4 days later. Peak total bilirubin 26 mg/dl. Gastroenterologist diagnosed as Arava-induced chemical hepatitis. During readmission, patient found to have ejection fraction of 10% by cardiac echo. Progression to ALF within 3 months.
16.3959092-6 200215633US	2002	MIN	49/M	6 weeks	Fulminant hepatic failure	MTX Infliximab ?INH?	Hosp Transplant Probable	Patient on leflunomide x 6 wks presented with jaundice after ~ 1wk of N/V, fever, chills and cough. ALT peaked at ~6000, total bilirubin @ 14.4 mg/dl, and INR @ 4.3. Transferred to another hospital where he underwent emergency liver transplantation. Time from onset of jaundice to transplant was 12 days. Liver pathology showed submassive hepatic necrosis “consistent with a toxic insult.” Patient is a Vietnamese, with HB _s Ag +, HB _s Ab +, and hepatitis A Ab (IgG) +. History of potential INH use is confusing. Narrative suggests that patient was started on INH when admitted for pneumonia because of fever, cough and apical infiltrates on CXR suggesting TB. Progression to ALF within 3 months.

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

/s/

Renan Bonnel
11/8/02 11:16:07 AM
PHARMACIST

Julie Beitz
11/8/02 11:30:07 AM
DIRECTOR

Victor Raczkowski
12/16/02 08:01:08 AM
MEDICAL OFFICER
Office Director's comments to follow in a separate memorandum