



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
National Institutes of Health

National Institute of Diabetes and  
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December 12, 2002

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Dear Dr. Goldkind, .

I am writing you in regard to the cases of presumed leflunomide (Arava) hepatotoxicity that you sent me for my opinion regarding their status. I received from you four different groupings: acute liver failure/death from the United States; serious liver injury from the United States; acute liver failure (International); and hepatotoxicity (Australia).

As we discussed on the telephone, identification of hepatotoxicity ascribable to a single drug is often (usually) problematic and difficult to identify with certainty even in the best of circumstances, such as when an authoritative physician is personally involved in evaluating the situation. It is, of course, far more difficult when one has to rely on sparsely accumulated data gathered by persons not necessarily expert in the needed analysis and particularly when only minimal or even negligible data are provided.

As you are well aware, in order to achieve some degree of certainty, it would be ideal to have, at a minimum, information on the following:

1. A baseline panel of liver test results before initiating treatment;
2. Regular (at least 1-2 monthly) screening of liver chemistries after initiation of treatment over the course of at least one year;
3. Preferably the use of only a single drug;
4. Once liver test abnormalities or suggestive clinical symptoms develop, careful sequential screening of the liver chemistries are needed;
5. Withdrawal of the drug, if possible, and follow-up of the liver chemistries to determine the effect of drug withdrawal
6. Complete evaluation of patient for other sources of liver dysfunction (viral serology; evaluation for autoimmune hepatitis, iron overload, obesity and diabetes; the use of over-the-counter drugs, herbal products or vitamin supplements; non-hepatic causes such as congestive cardiac failure, etc)
7. A liver biopsy or, if relevant, an autopsy.

Clearly, even under ideal circumstances, relatively few of these items are satisfied. The greatest likelihood that these items will be made available is if the affected person is evaluated by a physician with knowledge and preferably expertise in this area (internist, gastroenterologist, hepatologist). More often than not, this is not the case, and time elapses before an appropriate

evaluation is undertaken or a diagnosis is reached without full consideration of the possibilities.

This long preamble is made simply to underscore the difficulties entailed in trying to squeeze an

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accurate diagnosis from a series of reports that rarely contain the complete information needed, that involve persons who are receiving multiple other drugs, some known to have potential hepatotoxic effects, and who often have diseases that themselves can lead to liver dysfunction. Critical in the analysis, of course, is the fact of the temporal relationship of the use of the drug to the beginning evidence of liver dysfunction, plugging in all drugs administered. Complete information will facilitate defining the "incubation period" to development of hepatotoxicity and help define the mechanism responsible for causing the injury.

As you know better than I do, the information found in the MedWatch report often suffers from these omissions and lacks the needed information so critical to reaching a comfortable and accurate diagnosis. This is not meant as an excuse on my part, but simply underscores the challenges posed in reaching even the lowest degree of certainty.

All that having been said, I will present to you my views on what these forms provide in determining whether, and with what frequency, leflunomide causes liver damage as well as its severity. It is highly probable that, even among a group of "experts," there will be differences of opinion. I will say that with the information provided, I am unable to determine with absolute certainty that these reports contain any instance of unequivocal hepatotoxicity. There are, however, many instances of possible hepatotoxicity that can be attributable to leflunomide.

A. Acute liver failure/death, USA

Among the 18 reports in this section, I assess that in 11 of them (1,2,4,5,6,10,12,13, 16,17,18), leflunomide might have been responsible for causing liver damage, but in some of them, there were other drugs taken that could also be incriminated. In a further 5 instances (3,8,9,14,15), the information was insufficient to draw any conclusions, and in 2 cases (5, 11), the diagnosis was uncertain.

B. Serious liver injury, USA

Among the 38 reports in this section, the diagnosis of leflunomide hepatotoxicity seems possible in 23 (1,6,7,9,11,13,15,18,19,20,21,22,24,25,26,27,28,29,30,33,34,36,38), although in some, the data are sparse while in many others, other drugs might be held responsible. An additional 12 (2,3,4,5,8,10,17, 23,31,32,35,37) have insufficient data with which to draw any conclusion, while among the remaining three, one (12) seems unlikely to be a consequence of leflunomide, another (14) is probably hepatitis C, and the third (16) has such sparse data that it is difficult to clearly implicate leflunomide

Among the above two groups, over two thirds are female and in four, no gender is shown. The duration between drug institution and recognition of potential hepatotoxicity is variable (ranging from weeks to over a year), and the liver disease manifestation ranges from hepatocellular injury, though a mixed pattern, to overtly cholestatic liver disease.

C. Acute liver failure (International)

Among the 13 cases in this section, leflunomide hepatotoxicity is possible in 9 (3,4,5,6,7,8,11,12,13), while the available data are insufficient to reach any conclusions in the remaining four (1,2,9,10). Again, when I indicate that hepatotoxicity is possible, I mean that it cannot be ruled out but in many instances is far from certain.

D. Hepatotoxicity (Australia)

This group has the least reported data. A diagnosis of possible leflunomide hepatotoxicity can be eked out in about 6 cases but other drugs could also possibly be implicated. In most of the rest of the cases, the data are insufficient or entirely lacking with regard to reaching

any diagnosis.

In summary, there are clearly instances of definitive liver disease among many patients receiving

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leflunomide, but in most instances, other drugs are also being taken; principally methotrexate, prednisone, and celebrex. The question I would have is whether there are a similar number of reports to MedWatch regarding liver disease among recipients of anti-rheumatic drugs of the same class and in the same population who are not taking leflunomide. If the numbers are far fewer, it would support the probability that leflunomide itself, or perhaps in combination with the other drugs, is responsible for the many instances of reported hepatotoxicity.

Finally, although I know that this is unlikely, it would be preferable in reviewing these cases to have access to more complete data from the actual sources in order to attempt to better define the temporal association and the sequential laboratory values.

I hope that this is a useful exercise. Please let me know if you wish to have the actual forms shipped back to you.

Sincerely,



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November 21, 2002

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RE: Leflunomide Review

Dear Dr. Goldkind:

Thank you for requesting my review of the database on leflunomide (Arava) hepatotoxicity. I have completed my review which encompasses the materials that I received from your office including, by my count, 18 United States cases mentioning acute liver failure or death; 38 cases of serious adverse events with respect to the liver from the United States; 13 cases of acute liver failure from international sources and 18 cases of hepatotoxicity from Australia.

Following my assessment of all of these cases, my opinion is that the overall quality of the case reports leaves much to be desired and for many of these cases there was insufficient and often inadequate material to assess causality. Nearly all of these cases were highly confounded with patients receiving many other drugs including methotrexate and other agents that in their own right are associated with hepatic injury. Moreover, the underlying diseases being treated (rheumatoid arthritis, systemic lupus, etc.) are all associated with hepatic abnormalities in the absence of drug treatment.

I did not list any case as probably or definitely related from this database given the quality of the information, as well as the fact that I did not feel that any case was so unambiguous that no other possibility existed except leflunomide as a cause of liver injury. Nor did I classify any

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death as probably related to leflunomide. No chronic injury or cirrhosis was felt to be related to leflunomide in any of these cases. In fact, overall, there were so few cases where I felt comfortable in having the minimum requisite information in order to carry out causality assessment that no obvious or specific injury pattern could be discerned for the cases that were deemed possibly related. All of these cases, considered possibly related, were highly confounded and the designation of "possibly related" does not exclude the fact that other causes including drugs, might have been responsible for the injury.

As a result of my review of these cases, I do not feel that serious hepatic injury has been demonstrated to the degree that would warrant a change in the drug's current package labeling. I do not feel that there is sufficient evidence to warrant any restrictions on the use of this medication. I would certainly be happy to review any additional information that you receive, but would hope that the quality of spontaneous post-marketing reports would be improved over the information contained in the majority of these reports. For many of these cases, only a review of the complete medical record might suffice to truly determine causality of the liver injury reported; and that assumes that all of the appropriate studies were done to exclude other causes of hepatotoxicity. In my experience it is unusual that any of these spontaneous reports contain sufficient information to make the claim that all other causes have been reasonably ruled out.

I conducted my review of these cases much like I do any patient information as I would in a clinical practice setting. While I am aware of the regulatory definitions of probably related, possibly related, unlikely to be related and unrelated, there is often insufficient information provided for me to reach a definitive conclusion. As a result, I employ my clinical experience and judgement garnered over the past 24 years of reviewing such cases in order to make a clinical assessment. For me, possibly related implies that sufficient information is provided to exclude other reasonable causes, although it does not mean that causality has been proven. Probably related is obviously a stronger assessment that no other cause is likely to be responsible. Unlikely to be related means that I found other explanations that were more likely than leflunomide to have been responsible for the injury, including whether or not the injury pattern fit the relatively wide spectrum that is seen with other drug-induced hepatotoxins. Unrelated was assessed when there was a definitive reason for the injury that was not due to the medication.

The minimal information that was required for any type of causality assessment includes knowing the temporal relationship between the drug and the event, determining the latency (the time during which the patient was receiving the medication), being able to determine the biochemical injury pattern, determining a response to discontinuation of the medication (a positive dechallenge is defined as resolution of the abnormalities after the offending agent is withdrawn), and being able to determine that other common causes of hepatic injury including viral hepatitis, cholestatic syndrome, nonalcoholic steatohepatitis, as well as other causes and factors were excluded. The literature is replete with cases in which a drug has been alleged to cause injury, but the relationship has been called into question when additional information has

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been provided. I could only rely on the information available to me in this data set. Having said that, I am always willing to expand the spectrum of known hepatotoxins if the other factors seem to imply the drug was responsible. On the other hand, saying that a drug is possibly or probably related should be determined with great care so that other causes of toxicity are not overlooked. In addition, stating that a drug is possibly or probably the cause of toxicity implies that the drug will not be used again in that patient, which in some cases deprives individuals of useful medication for only circumstantial reasons.

My overall assessment of the four groups of cases is as follows:

1. Acute liver failure or death in US cases.

There were 18 such cases that I reviewed. I considered five to be possibly related, but all were confounded. One was a fatal case that I consider to be unrelated to any hepatic injury (death was from a perforated duodenal ulcer leading to septic shock from peritonitis). One of these possibly related cases involved possible exacerbation of underlying cirrhosis (which is a contraindication to the use of this medication). The three other possibly related cases I felt were unlikely to be related for various reasons including, one seemed much more likely to be related to shock liver and one included exacerbation of underlying a hepatitis B infection.

Four of these cases were considered unlikely to be related. I felt that there was clear-cut evidence of shock liver (ischemic hepatitis) in three of these cases. The fourth was highly confounded and I did not feel that leflunomide by itself could be labeled as causative. The remaining nine cases contained inadequate information for me to assess or draw any meaningful causality conclusions.

2. Serious liver injury in US cases.

There were 38 of these reports that I reviewed. Seven were considered to be possibly related, although two of these seven I felt were unlikely though still possible. There were eight cases that explanations other than leflunomide that I thought were more likely and therefore these were listed as unlikely to be related to leflunomide. Two instances were felt to be completely unrelated. There were 21 of the 38 cases that contained insufficient or adequate information to make a proper assessment. Even so, I felt that nine of these could be possibly related, six were unlikely to be related, and another six simply had inadequate information to assess.

Of the five cases that I considered possibly related with sufficient information in this group, four of the five were receiving methotrexate and several were also receiving other potential hepatotoxins including sulindac. In one of the possibly related cases there was only minimal evidence of hepatic injury. Two of the five had a reasonable response to withdrawing

leflunomide constituting a positive dechallenge.

3. Acute liver failure cases reported internationally.

There were 13 such cases and four were felt to be possibly related. Of these four, one was unlikely as it involved shock and Lyell syndrome. Of the other three possibly related cases, one had only minimal elevations in liver enzymes, one occurred in the presence of the active hepatitis B and the third involved a patient with underlying cirrhosis who had a death that was not related.

There were three cases that I considered unlikely to be related and one that was considered unrelated. There were five cases including one undergoing a liver transplant that had insufficient information to fully assess. The liver transplant case was listed as possibly related, although the data were largely insufficient; three contained inadequate information and the fifth case in this group was considered insufficient, but unlikely to be related.

4. Review of the hepatotoxicity from Australia.

There were 18 such reports, although 14 of these 18 contained insufficient information. Of those, 11 had information that was completely inadequate to assess and three others were felt to be unlikely based on the limited information. There were three other cases that I felt were also unlikely to be related, and only one case of the 18 did I list as possibly related, although this case included only an incomplete dechallenge with very little follow-up information provided.

I will provide a brief summary of each case of alleged acute liver failure cases from the United States and my assessment. These cases follow:

1. Case Number 2001-10085. This involved a 29-year-old female with Still=s disease who was treated for two to three months and developed an AST of 1,574 and an ALT of 1,679 with a bilirubin of 31. She was taking several medications including what was felt to be a toxic dose of atovaquone, in addition to azithromycin, prednisone and OxyCodone. She developed severe hypotension and was felt to possibly have herpetic hepatitis. She required pressors to maintain her blood pressure and these liver enzymes certainly could be explained by ischemic injury. The issue of an overdose of atovaquone also entered into my assessment that it was unlikely to be related to leflunomide. She died prior to receiving a liver transplant.

2. Case Number 2002-20914. This involved a 51-year-old woman who took leflunomide for four to five months for rheumatoid arthritis. Her ALT and AST values rose to the 400-600 range with an alkaline phosphatase that was also elevated and a bilirubin of 17. She presented with rash, fever, and pleuritic chest pain, along with jaundice and was diagnosed with a left, lower lobe pneumonia. She was taking Celecoxib and prednisone. A liver biopsy revealed inflammation and central lobular necrosis consistent with a possible drug reaction. A bone

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marrow biopsy showed red cell aplasia. She developed a perforated duodenal ulcer leading to peritonitis and septic shock with liver enzymes that became markedly elevated. I listed this case as possibly related, though highly confounded, but I did not feel that the death was directly related to liver disease given the perforated ulcer.

3. Case Number 2000-11168. This involved a 53-year-old woman who took leflunomide over the course of one month and then later on over a three-month period who was taking other medications including Sulfasalazine, Cytotec, and prednisone. No liver enzymes were provided and we are told that her Aliver failure $\cong$  resolved after a liver biopsy. There was inadequate information to fully assess in this case.

4. Case Number 1999-20773. This involved a 55-year-old man who took leflunomide for approximately two months with a history of ethanol use who presents with ascites, jaundice and encephalopathy. Liver enzyme values are not provided. He is on several other medications, including allopurinol, a sulfamethoxazole trimethoprim, amitriptyline, lisinopril, heparin, prednisone and verapamil. I felt that this case was a possible exacerbation of underlying alcoholic cirrhosis, although it was officially recorded as inadequate information.

5. Case Number 1998-13621. This involved a 55-year-old woman who, by my reading, took leflunomide for approximately one week and presents with deep jaundice, with a bilirubin of 22, an AST of 288 and an ALT of 63. The alkaline phosphatase was markedly elevated at 766. There is a history of ethanol use, along with several other medications including Plaquenil, Naprosyn, Inderal, Synthroid, and Premarin. Although this was a fatal case, there was inadequate information to assess. I listed it as inadequate and unlikely in view of the information that I did have because of the short latency period.

6. Case Number 2000-10080. This involved a 61-year-old man with rheumatoid arthritis who received leflunomide for an unspecified amount of time. He was on methotrexate and other medications, but had clear-cut evidence of significant hypotension and liver enzymes that were in keeping with shock liver, with an AST of 4,600 and an LDH of 16,000 and with a bilirubin that was essentially normal at 1.2. I listed this case as unlikely to be related given the fact that this was probably shock liver.

7. Case Number 1999-12102. This involved a 62-year-old man with rheumatoid arthritis who took leflunomide for about a five-month period and had liver enzymes that were mildly elevated with an ALT of 84 and an alkaline phosphatase of 131. He died following heart valve surgery, off of leflunomide and probably developed a shock liver picture. I listed this case as possibly related because of some improvement in his liver enzymes on a lower dose of leflunomide, but overall felt it was unlikely to be related.

8. Case Number 2001-23598. This involved a 66-year-old man with rheumatoid arthritis who

took leflunomide for about five months and presents with renal and hepatic failure along with gangrenous digits. He was on methotrexate among other medications and his treating physicians were concerned about a vibrio infection. His outcome is not stated and this case was insufficient to assess further.

9. Case Number 2000-22670. This involved a 66-year-old woman with rheumatoid arthritis who presents with acute liver failure after developing diarrhea and collapse with disseminated intravascular coagulation and a Coombs positive anemia associated with respiratory failure and a cardiopulmonary arrest. Her liver enzymes were in the 1,000's and this case was felt to be unlikely to be related to leflunomide and much more likely to be related to shock liver secondary to sepsis and other factors.

10. Case Number 2002-10502. This involved a 67-year-old woman with rheumatoid arthritis who presents with jaundice two to three months after starting leflunomide with a bilirubin of 9.5, but an AST of only 48 and an ALT of 27 with a mildly elevated alkaline phosphatase of 160. She was taking piroxicam and had a history of taking methotrexate and Imuran. She develops an acute pneumonic process and probably had underlying cirrhosis, very possibly due to her diabetes leading to non-alcoholic steatohepatitis. I listed this case as possibly related as an exacerbation of underlying cirrhosis, but more information would have been nice to have.

11. Case Number 143047. This involved a 25-year-old woman who was taking leflunomide for an unspecified indication at an unspecified dose and duration of therapy. We are only told that she had elevated liver enzymes and mental status changes. She was, however, hepatitis C positive and was receiving amiodarone among other drugs. I listed this as inadequate to assess.

12. Case Number 164596. This involved a 75-year-old woman with rheumatoid arthritis and systemic lupus who undergoes cardioversion for atrial fibrillation having been on leflunomide for about five months. Although her liver enzymes are reported to have been normal previously, in following the cardioversion the AST rises to 4,682 and the ALT to 2,202 and she has documented hypotension and a fatal outcome. I listed this case as unlikely to be related since it appeared that she developed shock liver following cardioversion.

13. Case Number 128229. This involves a 76-year-old woman with rheumatoid and osteoarthritis who develops acute liver failure after about 12 months of leflunomide therapy, in addition to prednisone, acetaminophen, and Percocet. She develops pneumonia and pancreatitis and is known to have hypotension with an AST greater than 4,500 and an ALT greater than 1,000. She was treated with an acetylcysteine. I rated this case as insufficient information to fully assess, but I considered it unlikely to be related to leflunomide and much more likely to be related to either shock liver or possibly even acetaminophen injury.

14. Case Number 2000-10951. This involved a patient of unstated age with rheumatoid arthritis

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who develops a near-syncopal episode three months after leflunomide is started. Concomitant medications are not stated, but there is a history of interstitial lung disease and hypotension is documented. This is a fatal case, but I considered it insufficient information to assess. It would be unlikely, if indeed, severe shock is demonstrated in the medical record.

15. Case Number 1999-22130. This involves a patient of unstated age and no stated indication of duration of therapy, where we are told that there is an elevated bilirubin, alkaline phosphatase, and acute liver failure in the setting of an underlying vasculitis. There was inadequate information to assess in this case.

16. Case Number 2002-14805. This involves a 55-year-old man with scleroderma who develops an AST and ALT in the 6,000 range, two to three months after starting leflunomide. There is a history of alcohol use, pulmonary fibrosis from his scleroderma, congestive failure and cardiomyopathy with a markedly diminished ejection fraction of 10%. He presented with a cough and hemoptysis when his liver enzymes were found to be in the 200 range and leflunomide was discontinued. He was described as improving off of leflunomide. I listed this case as possibly related, although I felt it to be unlikely given the very high nature of the transaminases later in the course of the hospitalization which are more compatible with shock liver and/or severe hepatic congestion with shock.

17. Case Number 169376. This involves a 55-year-old man with rheumatoid arthritis and scleroderma taking leflunomide for approximately one year with a history of alcohol use, who was admitted for pneumonia and sepsis treated with antibiotics. There are no preadmission liver enzymes available and we are told his ALT rises to 1,850 and his AST rises to greater than 6,000. I listed this case as unlikely to be related and more likely to be associated with shock liver given the height of the AST and history of sepsis.

18. Case Number 2002-15633. This involved a 49-year-old man with rheumatoid arthritis being treated with Infliximab, isoniazid, prednisone and methotrexate which were discontinued after one month of taking leflunomide. After approximately six weeks he is noted to have an AST and ALT, both greater than 6,000. He is hepatitis B surface antigen positive, although his viral load was undetectable. There was a concern about reactivation of tuberculosis. A liver biopsy shows submassive necrosis and ischemia changes of his gallbladder. He undergoes liver transplant. While I listed this as possibly related, it was highly confounded as the height of the liver enzymes are certainly out of the range of idiosyncratic drug injury. The hepatitis B and his other medications also make it extremely difficult to assess causality.

In conclusion, as I mentioned at the beginning of this report, the quality of the spontaneous reports is often inadequate to fully assess causality of leflunomide. Of the cases that I considered even possibly related, all were confounded with other possible reasons in existence. Therefore,

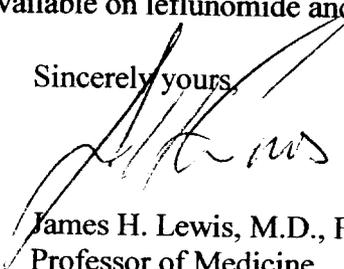
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this database does not constitute sufficient concern about the post-marketing experience thus far on the basis of these reports. Patients receiving leflunomide often have serious underlying disorders related to their rheumatoid arthritis and other rheumatologic conditions and are taking other potentially hepatotoxic medications. As a result, I believe that the benefit/risk ratio of leflunomide is well maintained in favor of the drug and I have no recommendations to revise or strengthen the current package labeling. It already calls for baseline and monthly liver enzyme monitoring with adequate information as to how to handle elevations in ALT, if they occur, including a liver biopsy which should be done. There are adequate stopping criteria. It is already listed that the drug is not recommended for use in patients with preexisting hepatic disease since it has not been adequately studied in this group. The use of cholestyramine, which was given in many of these cases to help eliminate the drug, is also mentioned in the prescribing information. There is still a question of whether there could be additive hepatic enzyme elevations in patients on methotrexate or Sulfasalazine. In the clinical trials, elevations in the aminotransferase values were seen in a frequency was often very similar to the comparative drugs including methotrexate and Sulfasalazine. Most of these enzyme elevations were less than twice-normal and resolved while treatment continued. Values later greater than three times normal were infrequent, but did reverse when the dose was reduced or the drug was discontinued. Recommendations that patients receive folic acid supplements are based on an increased risk of liver enzyme elevations, especially when receiving methotrexate.

It is clear that many of the individuals described in this data set were either not following the prescribed liver enzyme monitoring schedule and many had underlying liver disease. Nevertheless, I feel that the current labeling is sufficient as written.

I will be happy to discuss my opinions and conclusions with you and would be happy to review any additional information that becomes available on leflunomide and potential hepatic injury.

Sincerely yours,



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