Leflunomide (Arava) and severe liver injury

FDA is adding information on severe liver injury to the Boxed Warning of leflunomide (Arava), a drug used to treat rheumatoid arthritis - to highlight the risk of severe liver injury in patients using this drug and how this risk may be reduced.

FDA conducted an updated review of severe liver injury and leflunomide in 2009 based on continued reports of severe liver injury, and identified 49 cases between 2002 and 2009, 36 of which required hospitalization. Of the 49 cases, there were 14 deaths. An additional 5 patients required a liver transplant and 9 patients experienced a life-threatening event. Major presenting symptoms included jaundice, coagulopathy, encephalopathy, vomiting, rash and or itching, abdominal pain, and fever. 17 cases reported normal liver enzymes prior to starting leflunomide. The estimated duration of leflunomide treatment before the occurrence of severe liver injury ranged from 9 days to 6 years, with the majority of patients having severe liver injury within the first 6 to 12 months of treatment. 46 of the 49 patients were also taking other medications that have been associated with liver injury, including methotrexate, TNF-α blockers, hydroxychloroquine, acetaminophen, non-steroidal

anti-inflammatory drugs, and statins. In addition, 14 patients had pre-existing liver disease such as active or chronic hepatitis, and/or a history of alcohol abuse. FDA concluded that use of leflunomide was associated with the development of severe liver injury in these patients.

Healthcare professionals should be aware of the risk for severe liver injury with leflunomide and ensure appropriate patient selection and monitoring.

- Cases of severe liver injury, including fatal liver failure, have been reported in patients using leflunomide.
- Only patients for whom the anticipated therapeutic benefit is expected to outweigh the risk of severe liver injury should be considered for leflunomide treatment.
- Patients with pre-existing liver disease (acute or chronic infection with hepatitis B or C virus), or those with serum ALT greater than 2 times the upper limit of normal before initiating treatment, should not be treated with leflunomide. Caution should be used when leflunomide is given with other drugs that have the potential to cause liver injury.
- ALT levels should be monitored at least monthly for three months after starting leflunomide and at least quarterly thereafter. If the ALT rises to greater than 2 x the upper limit of normal while the patient is being treated with leflunomide, leflunomide should be stopped, cholestryamine washout begun, and follow-up liver function tests conducted at least weekly until normalization.

Patients should be informed that severe liver injury is a rare, but serious side effect of leflunomide. Patients who experience signs of severe liver injury including itching, yellow eyes or skin, dark urine, loss of appetite, or light-colored stools should contact their healthcare professional immediately.

Vitamin D dosing error

The Food and Drug Administration (FDA) of the United States alerted parents and caregivers that overdose of liquid Vitamin D supplement to infants may occur with inaccurate dosing method on June 15 2010.

Vitamin D deficiency is associated with rickets, osteomalacia, osteopenia, and abnormal immune function with greater susceptibility to acute infections and other long-latency disease states. In a lactating mother supplemented with 400 IU/day of vitamin D, the vitamin D content of her milk ranges from 25 to 78 IU/L. On the other hand, all infant formulas sold in the United States must have a minimum vitamin D concentration of 40 IU/100 kcal (258 IU/L of a 20 kcal/oz formula) and a maximum vitamin D3 concentration of 100 IU/100 kcal (666 IU/L of a 20 kcal/oz formula).

The American Academy of Pediatrics (AAP) has recommended that

1. Breastfed and partially

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breastfed infants should be supplemented with 400 IU/day of vitamin D beginning in the first few days of life. Supplementation should be continued unless the infant is weaned to at least 1 L/day or 1 qt/day (~946ml) of vitamin D–fortified formula or whole milk. Whole milk should not be used until after 12 months of age. In those children between 12 months and 2 years of age for whom overweight or obesity is a concern or who have a family history of obesity, dyslipidemia, or cardiovascular disease, the use of reduced-fat milk would be appropriate.

2. All nonbreastfed infants, as well as older children who are ingesting < 1000 mL/day of vitamin D–fortified formula or milk, should receive a vitamin D supplement of 400 IU/day. Other dietary sources of vitamin D, such as fortified foods, may be included in the daily intake of each child.
3. Adolescents who do not obtain 400 IU of vitamin D per day through vitamin D–fortified milk (100 IU per 8-oz serving) and vitamin D–fortified foods (such as fortified cereals and eggs [yolks]) should receive a vitamin D supplement of 400 IU/day. (Pediatrics 2008;122:1142–1152.)

The vitamin D drop product commercially available in Hong Kong is in the strength of 8,000 international units per ml. As a supplement for healthy infants the recommended dose of 400 international units should be given as 0.05ml. A mere discrepancy in measuring the minute dose may result in a significant dosing error. Therefore, it is recommended that:

- A calibrated oral syringe is preferred to an oral dropper that is supplied with the vitamin D drop in measuring an accurate dose.
- Pharmacists should also actively provide demonstration of measuring vitamin D drops to parents and caregivers who are to give their children vitamin D drops for their first time.
- Pharmacists should advise parents and caregivers on the signs and symptoms of vitamin D overdose, which include nausea and vomiting, loss of appetite, excessive thirst, frequent urination, constipation, confusion and fatigue.

An English version of consumer update "Infant Overdose Risk With Liquid Vitamin D" in pdf format is available on FDA's website for download:

http://www.fda.gov/downloads/ForConsumers/ConsumerUpdates/UCM215586.pdf

Market Withdrawal of Mylotarg (gemtuzumab ozogamicin)

A recent clinical trial result urges Pfizer to prepare for voluntary withdrawal of U.S. New Drug Application (NDA) and for discontinuation of commercial availability of Mylotarg (gemtuzumab ozogamicin) for relapsed acute myeloid leukemia.

Mylotarg (gemtuzumab ozogamicin) is indicated for patients with CD33+ acute myeloid leukemia (AML) in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy. It was approved in May 2000 under the FDA's accelerated approval program.

The decision to voluntarily withdraw the NDA is based on data from SWOG Study S0106 which failed to confirm clinical benefit. This study was stopped early based on interim results from the study showing no evidence of improved efficacy for patients treated with Mylotarg in addition to chemotherapy for previously untreated AML. Additionally, the fatal induction toxicity rate was significantly higher in the daunorubicin and cytosine arabinoside (cytarabine) + Mylotarg arm (16/283=5.7% vs. 4/281=1.4%, P=0.01) SWOG Update, April 15, 2010,https://www.swogstat.org/ROS/ROSBooks/Spring%202010/Leukemia.pdf)

After discussions with the FDA, Pfizer will be discontinuing commercial availability of Mylotarg and will be voluntarily withdrawing the NDA for Mylotarg in the United States effective October 15, 2010. Mylotarg will not be commercially available to new patients. Patients who are currently receiving the drug may complete their therapy following consultation with their health care professional. Health care professionals should inform all patients receiving Mylotarg of the product's potential safety risks. Any future use of Mylotarg in the United States will require submission of an investigational new drug application to the FDA.

Daptomycin linked to eosinophilic pneumonia

The U.S. Food and Drug Administration (FDA) is informing patients and healthcare professionals about the potential for developing eosinophilic pneumonia during treatment with daptomycin (Cubicin), an intravenous cyclic lipopeptide antibiotic licensed for the treatment of complicated skin and skin structure infections caused by susceptible aerobic gram-positive organisms, and Staphylococcus aureus bacteremia including right-sided infective endocarditis caused by MSSA or MRSA.

FDA identified 6 cases of eosinophilic pneumonia reported to FDA's Adverse Event Reporting System (AERS) between 2004 and 2010 that were most likely associated with daptomycin. One additional case of eosinophilic pneumonia most likely associated with daptomycin was identified in the medical literature.

For FDA's review, a likely case of eosinophilic pneumonia associated with daptomycin was defined as one meeting all of the following criteria: concurrent exposure, fever, dyspnea, new infiltrates on chest x-ray or computed tomography scan, bronchoalveolar lavage with > 25% eosinophils, and clinical improvement following withdrawal. Of the 7 cases identified using the above definition:

- Daptomycin was prescribed for non-FDA approved indications, including osteomyelitis (n=4), prosthetic hip infection (n=1), enterococcal endocarditis (n=1), and aortic valve endocarditis (n=1).
- Eosinophilic pneumonia developed 2-4 weeks after treatment initiation.
- The ages of patients ranged from 60 to 87 years. All 7 cases reported improvement or resolution of symptoms after daptomycin was discontinued. 5 of them were also treated with systemic corticosteroids. 2 cases reported recurrence of eosinophilic pneumonia after daptomycin was restarted.

FDA also identified 36 possible cases (that did not meet the full criteria for a likely case) of eosinophilic pneumonia associated with daptomycin use. FDA believes that these cases provide additional support for an association between use of daptomycin and development of eosinophilic pneumonia. Thus, FDA requested that Cubist, the manufacturer of the product, revise the Warnings and Precautions and Adverse Reactions, Post-Marketing Experience sections of the Cubicin product label to further inform healthcare professionals of this association.

Videos on drug administration methods available on the internet

Methods of applying eye drops and using emulsifying ointment as soap have been demonstrated by Mr So Yiu Wah, President of SHPHK. The videos are available on the "3P" homepage (http://www.3phk.com/) and the SHPHK Facebook page (http://www.facebook.com/shphk?ref=ts) as well. The following is a list of preliminary topics to be videotaped for patient education:-

1. Metered Dose Inhaler and Volumatic
2. Turbuhaler
3. Spinhaler
4. Nasal Spray
5. Eye Drop and Ointment
6. Rectal Suppository
7. Enema
8. Pessary
9. Ear Drops

If you have any suggestion on new topics for videotaping, please do not hesitate to contact Mr So Yiu Wah (email address: ywso@shphk.org.hk) to provide your ideas.

DERC website revamp

DERC is planning to revamp the website (http://www.derchk.org/) by adding new drug monographs and updating drug information. It is decided that each article or monograph will be reviewed by an editorial board of the DERC before they are posted on the website. If you are interested in joining the editorial board, please kindly contact Mr So Yiu Wah, President of SHPHK at ywso@shphk.org.hk. Your participation in assisting the provision of drug information to the public will be much appreciated.

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