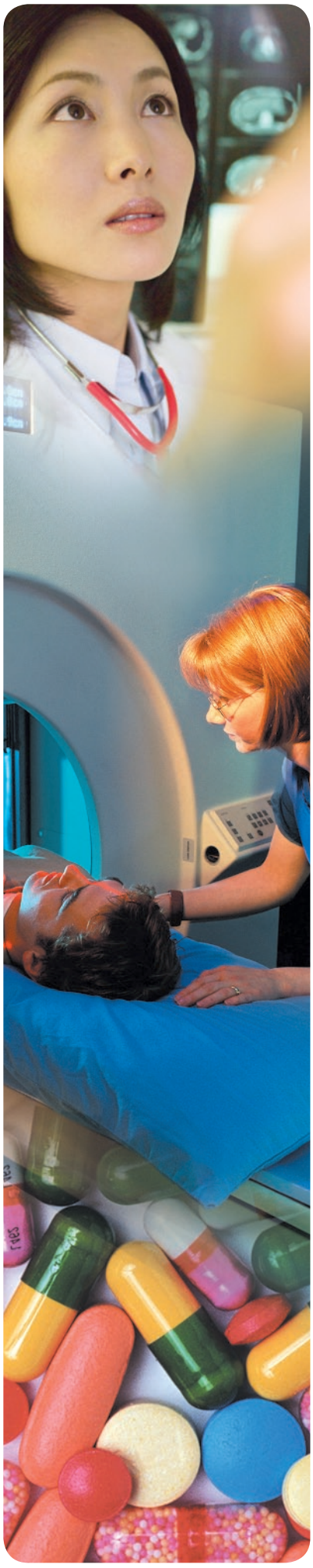

U.S. Food and Drug Administration
Protecting and Promoting Public Health

DRUG SAFETY NEWSLETTER

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IN THIS ISSUE

THE NEWSLETTER'S MISSION

This publication provides postmarketing information to healthcare professionals to enhance communication of new drug safety information, raise awareness of reported adverse events, and stimulate additional adverse event reporting. For more information, visit the FDA Drug Safety Newsletter Fact Sheet at *www.fda.gov/cder/dsn/factsheet.htm*.

REPORTING ADVERSE EVENTS

FDA encourages the reporting of all suspected adverse reactions to all drugs, all suspected drug interactions, and all suspected reactions resulting in death, life-threatening outcomes, hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, or congenital anomaly/birth defects.

Report serious adverse events to FDA's MedWatch reporting system by completing a form online at *www.fda.gov/medwatch/report.htm*, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

EDITOR'S NOTE

In our third issue, an article on pemetrexed (Alimta), an antimetabolic antineoplastic agent, summarizes postmarket cases of radiation recall, an inflammatory reaction that may occur years after radiation exposure. Pemetrexed is the first drug to be approved for the treatment of malignant pleural mesothelioma (MPM), a rare type of cancer usually associated with a history of asbestos exposure. It is also approved as a second-line therapy for the treatment of locally advanced or metastatic non–small cell lung cancer (NSCLC).

We also describe the occurrence of serious liver injury in patients treated with the monoclonal antibody, natalizumab (Tysabri). This drug is indicated for the treatment of relapsing multiple sclerosis and moderate-to-severe Crohn's disease. Tysabri is also associated with other serious adverse events, including, but not limited to, anaphylaxis, opportunistic infections, and progressive multifocal leukoencephalopathy (PML). Patients receiving Tysabri for multiple sclerosis and Crohn's disease must be enrolled in a special restricted distribution program designed to help ensure the safe use of this product.

In the third article, we revisit carbamazepine (Carbatrol, Equetro, Tegretol, and generics) and the research and data behind the findings of increased risk of rare serious skin reactions (Stevens-Johnson syndrome and toxic epidermal necrolysis) for patients of Asian ancestry. As a follow-up to the feature article in the second issue of the *Newsletter*, it describes the role of pharmacogenomics in making a therapeutic and safety-based decision.

Finally, this *Newsletter* presents a brief description of FDA's Adverse Event Reporting System (AERS). The several hundred thousand adverse event and medication error reports FDA receives every year from manufacturers, healthcare professionals, and the public are vital in identifying postmarket drug safety issues. The summary statistics of the AERS data and information about access to the public data files are available at *www.fda.gov/cder/aers/default.htm*.

We would like to thank all who report adverse events to FDA and for their contribution to improve product safety and protect the public health. We value your comments. Let us know what you think of the *Newsletter* by contacting us at *www.fda.gov/cder/comment.htm*.

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Senior Scientific Editor

POSTMARKETING REVIEWS

PEMETREXED (MARKETED AS ALIMTA)

Radiation Recall

A postmarket safety review of pemetrexed, an antimetabolic antineoplastic agent, identified an association of the drug with radiation recall. Pemetrexed is a multitargeted antifolate, antimetabolite that inhibits thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase, key folate dependent enzymes for the *de novo* biosynthesis of thymidine and purine nucleotides.

Radiation recall is an inflammatory reaction within a previously irradiated field, most often occurring with the administration of pharmacologic agents (see Box 1). Healthcare professionals should be aware of the possibility of radiation recall phenomena with pemetrexed use and report cases to FDA's MedWatch.

In February 2004, pemetrexed (in combination with cisplatin) was the first drug approved for the treatment of patients with unresectable malignant pleural mesothelioma (MPM). MPM is a rare type of cancer that is usually associated with previous asbestos exposure. In August 2004, pemetrexed was approved as a single–agent (used alone) for the treatment of patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) after prior chemotherapy.[1]

From the date of the original approval in February 2004 through September 2007, FDA has received 12 reports (domestic-8, foreign-4) of radiation recall associated with pemetrexed therapy. This article summarizes FDA's analysis of these 12 cases from FDA's AERS database.

BOX 1

What is radiation recall?

Radiation recall is an inflammatory reaction limited to previously irradiated areas of the body that occurs following the subsequent administration of a drug. It appears initially as a rash similar to severe sunburn with redness, tenderness, swelling, and sores. Although this reaction most commonly involves the skin, it has also been reported in the oral mucosa, the larynx, esophagus, small intestine, lung, muscle tissue, and brain. Several chemotherapeutic agents have been associated with radiation recall including, but not limited to, doxorubicin, paclitaxel, docetaxel, etoposide, vinorelbine, vinblastine, gemcitabine, and capecitabine.[2] Two cases of pemetrexed-associated radiation recall have been reported in the medical literature.[3,4]

While the mechanism of radiation recall remains unclear, hypotheses to explain this reaction include vascular damage, epithelial stem cell inadequacy or sensitivity, and an idiosyncratic hypersensitivity reaction.

Several factors have been identified that increase the risk of radiation recall. These include the total dose of radiation therapy and the interval between radiation therapy and administration of the recall-triggering agent. Although no threshold dose of radiation leading to radiation recall has been determined, a recent review by Azria et al. reports occurrences of radiation recall following doses ranging from 10 to 81 gray (Gy).[2] This factor, however, may not be as important as a) the dose of radiation therapy and b) interval between radiation therapy and drug exposure (i.e., these factors may affect both the risk and rate of onset of recall).

The interval between the completion of radiation therapy and the administration of a possible promoting agent is also important in distinguishing radiation recall from either a radiosensitizing effect or interference with ongoing dermal repair after radiation damage. Typically, skin reactions brought on by drugs administered less than seven days following radiation therapy are considered radiosensitization rather than radiation recall.[5] After radiotherapy has been completed, a radiation recall reaction may develop months to years later when a drug is given. The radiation recall reaction can be more severe than an acute radiation reaction.

The toxicity criteria of radiation recall dermatitis (Grade 0-4) from the National Cancer Institute (NCI) can be found at *www.fda.gov/cder/cancer/toxicityframe.htm*. The treatment of a radiation recall reaction includes corticosteroids (topical, oral, or IV) or non-steroidal anti-inflammatory agents in conjunction with discontinuation of the drug.

REPORTED CASES OF RADIATION RECALL

The 12 cases of radiation recall involved patients ranging in age from 49 to 78 years (median age 62.5 years). Nine patients (9/12; 75%) were male. Ten patients received pemetrexed for the approved indications of malignant pleural mesothelioma (3) and non- small cell lung cancer (7). In the remaining two cases, pemetrexed was used for the treatment of an unspecified lung cancer. The median time-to-onset from first administration of pemetrexed to reaction was 6 days (range 1-35 days). All radiation recall events were temporally related to the initiation of pemetrexed. The time interval between the radiation course and the chemotherapy administration varied between 15 days to 27 years. Some patients received treatment with corticosteroids (7) and an antibiotic (2). Serious outcomes included hospitalization (5) and death (1). The reported death was caused by respiratory insufficiency which may or may not have been related to radiation recall. Eight cases reported positive dechallenge, and six cases reported positive rechallenge.

Two representative case reports implicating pemetrexed in the development of radiation recall are described in Box 2. These cases were selected based on specific attributes, including a close temporal relationship of the adverse event to the drug, the time interval between radiation with subsequent chemotherapy administration, and the seriousness of the events. The second case has been reported in the medical literature.[5]

In the first case, a serious reaction restricted to a previously irradiated region occurred shortly after beginning pemetrexed therapy. The radiation recall resulted in extensive skin damage and myonecrosis that ultimately required multiple prolongued hospitalizations for corrective surgeries.

The second case provides evidence of the temporal relationship of radiation recall and pemetrexed treatment with positive rechallenge. Both the initial and subsequent dermatologic events occurred three days following each pemetrexed dose despite premedication with prednisolone. This case is noteworthy given that both recall events occurred in an area that had been irradiated 27 years earlier.

Although some patients in this case series may have received previous chemotherapeutic agents labeled for this adverse event (i.e., gemcitabine, docetaxel, paclitaxel, vinorelbine, or etoposide), the temporal relationship of the event with the initiation of pemetrexed in all cases, and a definitive report of a positive dechallenge and rechallenge in one case, supports the association between pemetrexed and radiation recall. In some cases, the events were serious, required surgical intervention, and resulted in substantial long-term morbidity.

BOX 2

Case 1

A 50-year-old female smoker with a diagnosis of grade IV non-small-cell lung cancer received initial therapy that included radiation therapy plus six cycles of chemotherapy with carboplatin and paclitaxel weekly for 5 months. The patient did not report any aggravation to the radiated areas (left brachial plexus) related to this first course of chemotherapy.

Thirteen weeks later, following disease progression, the patient received the first cycle of pemetrexed. The patient received standard pemetrexed premedications with folic acid, vitamin B_{12}, and dexamethasone. Other medications included esomeprazole magnesium, paracetamol, gabapentin, and tizanidine hydrochloride, all for unknown indications. The patient had no known drug allergies.

On the day of the second pemetrexed infusion (25 days following the first infusion), the patient experienced severe, necrotic recall dermatitis on her left scapula (a previously irradiated area) during the infusion. The pemetrexed administration was discontinued. Skin biopsy was performed to exclude cutaneous metastases (results not reported). Despite topical therapy, the patient was hospitalized with fever, severe pain, and a purulent inflammatory reaction of the skin over her left scapula one month after discontinuation of pemetrexed. Despite negative microbiological cultures, a bacterial superinfection was suspected.

The patient received intravenous antibiotic therapy, topical treatment with glucocorticoids, and treatment with fusidic acid. The patient's condition worsened over time. After two weeks of high dose antibiotic treatment, the patient's inflammation had improved, but the area of the recall dermatitis remained unchanged. The necrosis of muscle and skin required two subsequent hospitalizations for surgical debridement and skin grafting. At the time of this report, the patient had not recovered from the necrosis at the left scapula.

Case 2

A 75-year-old female was treated for stage IV primary adenocarcinoma of the lung with carboplatin and gemcitabine as first-line therapy followed by pemetrexed as second line therapy. The patient tolerated carboplatin and gemcitabine treatment poorly, experiencing severe anemia, nausea, and fatigue. Despite first-line therapy, her disease progressed and second-line therapy with pemetrexed 500 mg/m^2 was initiated. The patient received folic acid, vitamin B_{12}, and prednisolone, before, during, and after pemetrexed infusion. Her medical history included breast cancer treated by lumpectomy and adjuvant radiotherapy to the right breast 27 years prior to the lung cancer diagnosis.

Three days after the first pemetrexed infusion, the patient reported pain and induration of the right breast. Clinical examination revealed a redness of the right breast and the right upper hemithorax. The area of reaction matched the prior radiotherapy field.

Pathology findings from the skin biopsy were compatible with radiation recall dermatitis with perivascular and interstitial mononuclear infiltrate in the upper dermis and focal vacuolar changes in the basal epidermal layer. Prednisolone (1 mg/kg/daily) was initiated and, over the next 48 hours, improvement was noted. After two weeks, all the skin lesions had disappeared. A second dose of pemetrexed was administered. Prednisolone (40 mg twice daily) was continued in the interval between the first and second infusion of pemetrexed. Three days following the second infusion the patient had recurrent pain and reddening of the breast, although less intense than the previous episode (**positive rechallenge**). Pemetrexed was discontinued.

REFERERENCES

1. Pemetrexed disodium (Alimta) product labeling. *www.fda.gov/cder/foi/label/2007/021462s012lbl.pdf*
2. Azria D, Magne N, Zoulair A, et al. Radiation recall: A well recognized but neglected phenomenon. Cancer Treatment Rev. 2005;31(7):555-570.
3. Hureaux J, Le Guen Y, Tuchais C, et al. Radiation recall dermatitis with pemetrexed. Lung Cancer. 2005;50:255-258.
4. Barlési F, Tummino C, Tasei A-M, Astoul P. Unsuccessful rechallenge with pemetrexed after previous radiation recall dermatitis. Lung Cancer. 2006;54:423-425.
5. Camidge R, Price A. Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol. 2001;59:37-245

This information reflects FDA's current analysis of available data concerning this drug. Posting this information does not mean that FDA has concluded there is a causal relationship between the drug product and the emerging drug safety issue. Nor does it mean that FDA is advising healthcare professionals to discontinue prescribing the product. FDA is considering, but has not reached a conclusion about, whether this information warrants any regulatory action.

✓ REMINDER: HOW TO REPORT ADVERSE REACTIONS

Report serious adverse events to FDA's MedWatch reporting system by completing a form online at www.fda.gov/medwatch/report.htm, by faxing (1-800-FDA-0178), by mail using the postage-paid address form provided online (5600 Fishers Lane, Rockville, MD 20852-9787), or by telephone (1-800-FDA-1088).

NATALIZUMAB (MARKETED AS TYSABRI)

Serious liver injury

A safety review of natalizumab identified four cases of serious hepatic injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin. The *Warnings* and *Precautions* sections of the product labeling have been updated to reflect this new safety information. Healthcare professionals should be alerted to possible serious liver injury in patients receiving natalizumab, to discontinue natalizumab in patients with signs of significant liver injury such as jaundice, and report cases to FDA's MedWatch program.

Natalizumab was approved by the FDA in November 2004 for treatment of relapsing forms of multiple sclerosis (MS). This medication is aimed at delaying the accumulation of physical disability and reducing the frequency of clinical exacerbations of MS. In January 2008, natalizumab was approved for adult patients with moderate-to-severe Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional Crohn's disease therapies, including inhibitors of tumor necrosis factor-alpha. Currently, both patient populations using the drug must be enrolled in a special restricted distribution program called the TOUCH™ Prescribing Program.[†]

From November 2004 (the date of original approval) to

BOX 3

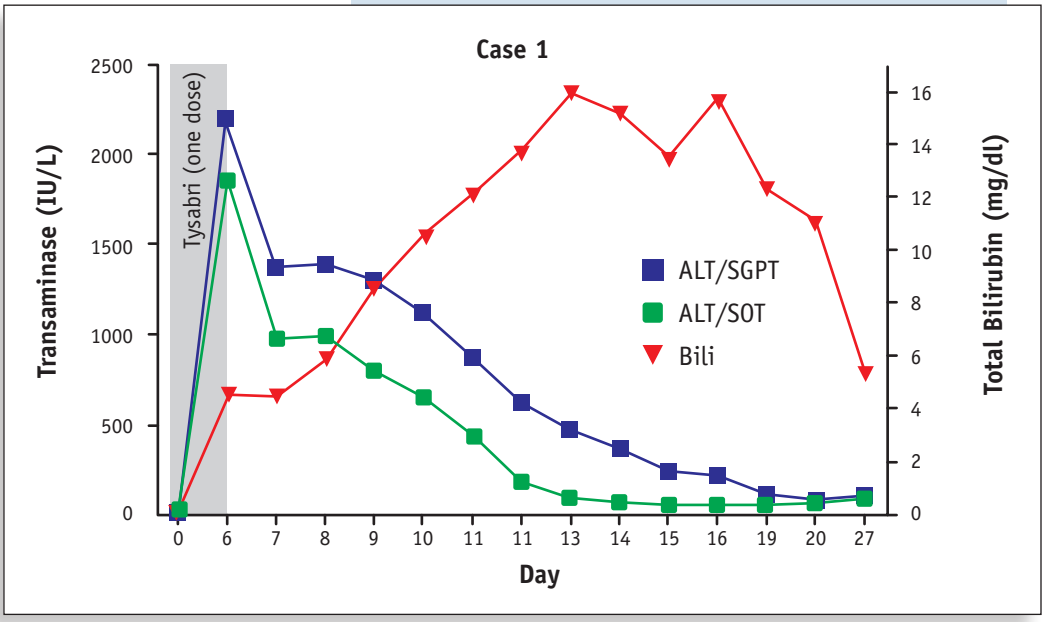
Case 1

A 26-year-old female with a history of multiple sclerosis (MS) received natalizumab 300 mg IV. Six days after the first dose of natalizumab, the patient was hospitalized with nausea, weakness, constipation, and tachycardia. Baseline serum ALT, AST, and bilirubin levels prior to natalizumab treatment were normal. Admission laboratory results were significant for an elevated serum ALT of 2,212 IU/L, AST of 1,863 IU/L, and total bilirubin of 4.6 mg/dl. Total bilirubin peaked at 16.1 mg/dl during hospitalization. The time course of the elevations in liver enzymes and total bilirubin are illustrated in Figure 1.

Viral screening was negative for hepatitis A, B, C, HIV, CMV, EBV, HSV, parvovirus, and toxoplasmosis. Liver biopsy findings concluded that significant increases in serum ALT and AST with appearance of hepatitis and confluent hepatic necrosis were highly suggestive of drug-induced liver injury. Natalizumab was permanently discontinued. The patient was treated with IV steroids and mycophenolate and fully recovered. Her concomitant medications included an oral contraceptive, acetaminophen, calcium, potassium, baclofen, and alprazolam. There was no history of excessive alcohol intake, recreational drug use or recent transfusion of blood products.

Figure 1.

▼ This figure illustrates the patient's serum AST, ALT, and bilirubin values during the course of illness. The shaded area of the figure indicates when natalizumab treatment was started.



[†] TOUCH™ - Tysabri Outreach Unified Commitment to Health is a risk management plan designed to limit the distribution of the drug to registered infusion centers and improve the monitoring and reporting of serious opportunistic infections.

September 2007, 28 cases of liver dysfunction were identified. Twenty-four of the 28 cases were mild abnormalities of serum liver transaminases or were potentially due to another etiology. The remaining four cases described clinically significant serious liver injury, including markedly elevated serum hepatic enzymes (AST and ALT at least three times the upper limit of normal) and total bilirubin (at least three times the upper limit of normal) with two of these cases reporting coagulopathy (increased INR [international normalized ratio]).

The four cases (domestic-3, foreign-1) occurred in three females and one male aged 26, 33, 43, and 59 years old, respectively. All cases received natalizumab at recommended doses for multiple sclerosis. The median time-to-onset for the adverse event following administration of a natalizumab dose was eight days (the range was 6-18 days). Signs of liver injury, including markedly elevated serum hepatic enzymes and total bilirubin, occurred as early as six days after the first dose of natalizumab. All cases had significant increases in hepatic enzymes (peak AST and ALT levels were 1,863 IU/L and 2,212 IU/L, respectively; peak total bilirubin in one case was 16.1 mg/dl). Three cases provided relevant clinical details including liver biopsies. All four patients tested negative for Hepatitis A, B, and C. Two of the four patients were hospitalized. There were no deaths and none of the patients required a liver transplant. One patient had a positive rechallenge with development of jaundice and significant elevation of liver enzymes after resuming natalizumab.

The four cases in this series had no other clear alternative etiologies for the serious liver injury. Two patients used a potential hepatotoxin, acetaminophen; however, follow-up information revealed minimal usage. A third patient who had completely recovered from hepatotoxic-

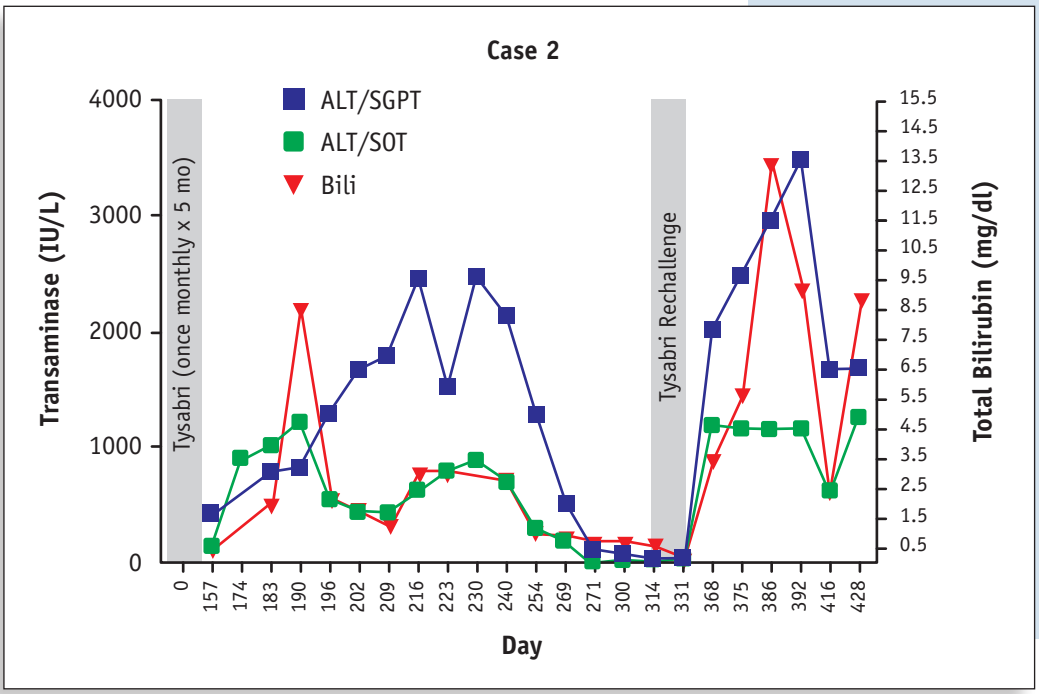
BOX 4

Case 2

A 43-year-old male with MS received natalizumab 300 mg IV once a month. Eight days after the 5th dose of natalizumab, the patient presented with fatigue, fever, back pain, and "kidney stone". Admission laboratory serum hepatic enzymes were elevated (ALT of 410 IU/L, AST of 134 IU/L) with an INR of 1.7 and a total bilirubin of 0.4 mg/dl. The serum bilirubin gradually increased and peaked at 3 mg/dl. The liver biopsy showed acute lobular hepatitis with portal hepatitis and mild pericellular fibrosis. The biopsy results could not distinguish between drug reaction and autoimmune hepatitis. Viral screening was negative for hepatitis A, B, and C.

Natalizumab was discontinued and the patient received prednisone therapy. The patient was considered for liver transplant, but ultimately recovered. Concomitant medications included spirulina[T], multivitamin, and prednisone. This case reported no concomitant acetaminophen, non-steroidal anti-inflammatory drug, or alcohol use.

Six months later, after his serum hepatic enzymes and bilirubin had normalized, the patient was resumed on natalizumab treatment. Following the second dose of natalizumab, the patient once again presented with fatigue, jaundice, brown urine, significant elevation of serum liver enzymes and bilirubin (**positive rechallenge**). The serum ALT, AST, and bilirubin peaked at 3494 IU/L, 1259 IU/L and 13.4 mg/dl, respectively. The second liver biopsy confirmed drug-induced hepatitis. Natalizumab was discontinued and he received tapering doses of prednisone. At the time of the report, he was still improving.



[T] Spirulina: common names: spirulina, dihe, Techuitlatl, blue-green algae: It is a cyanobacterium valued as a food or nutritional supplement for its high protein.

Figure 2.
This figure illustrates the patient's serum AST, ALT, and bilirubin levels during the course of illness. The shaded areas of the figure depict the first course of natalizumab and the natalizumab rechallenge.

ity due to interferon beta-1a (Rebif) experienced liver re-injury after the first dose of Tysabri.

Two representative cases illustrating the temporal relationship between natalizumab use and serious liver injury are summarized in Box 3 and 4. In one case, liver injury was observed after the first dose of natalizumab (see Figure 1). In the other case, the patient received multiple doses of the drug (see Figure 2).

The cases, of which the two described above are representative, describe a temporal relationship between serious liver injury and the use of natalizumab with detailed clinical descriptions, relevant laboratory data, biopsy confirmation of drug-induced liver injury, positive dechallenge, and/or a positive rechallenge. These cases support an association between natalizumab use and serious liver injury. The mechanism of natalizumab-induced liver injury remains to be elucidated. The combination of elevated serum transaminase and bilirubin levels without evidence of obstruction is an important indicator of the potential for a medication to cause severe liver injury that may lead to death or the need for a liver transplant in some patients.[1-4] FDA will continue to monitor AERS for reports of serious liver injury in association with natalizumab.

FDA encourages physicians to:

- inform their patients that natalizumab (Tysabri) may cause liver injury
- instruct patients to read the Medication Guide to learn about the symptoms of liver damage
- discontinue natalizumab (Tysabri) in patients with jaundice or other evidence of significant liver injury (e.g., laboratory evidence)
- report cases of serious liver injury to FDA's MedWatch program

RELEVANT WEBSITES

www.fda.gov/medwatch/safety/2008/safety08.htm#Tysabri
www.fda.gov/medwatch/safety/2008/Tysabri_dhcp_letter.pdf

REFERENCES

1. Natalizumab (Tysabri) product labeling *www.fda.gov/cder/foi/label/2008/125104s033lbl.pdf*
2. Zimmerman HJ. Drug-induced liver disease. Clin Liver Dis. 2000;4:73-96.
3. Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. Hepatology. 2005;42:481-489.
4. Li B, Wang Z, Fang JJ, et al. Evaluation of prognostic markers in severe drug-induced liver disease. World J Gastroenterol. 2007;13(4):628-32.

CARBAMAZEPINE (MARKETED AS CARBATROL, EQUETRO, TEGRETOL AND GENERICS)

Stevens-Johnson syndrome, toxic epidermal necrolysis, and HLA-B*1502

A safety review of carbamazepine (CBZ) identified an increased risk for Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Asian individuals who carry the HLA-B*1502 allele. The potential risk for SJS and/or TEN in individuals carrying the HLA-B*1502 allele has now been described in a *Boxed Warning*, and in the *Warning and Precautions*, *Laboratory Tests* and *Geriatric Use* sections of the CBZ product labeling.

Two rare, related, and potentially life-threatening adverse dermatological events associated with the use of the anticonvulsant drug CBZ (marketed as Carbatrol, Equetro, Tegretol, and generics) are SJS and TEN. Both SJS and TEN have similar pathophysiologies and symptoms (e.g., erythema, with varying degrees of blisters, skin erosions and detachment) and affect both skin and mucosal membranes. Differential diagnosis of SJS and/or TEN is based on the degree of skin surface area detachment (SJS affects 10% or less of skin surface area; SJS/TEN affects 10-30% of skin surface area; TEN affects 30% or greater skin surface area with high morbidity and mortality). For this article, these diagnoses are referred to as SJS/TEN.

Traditionally, the likelihood of developing CBZ-associated SJS/TEN has been considered low.[1,2] Recent reports, however, indicate that certain populations may be at increased risk for developing these conditions.[3-8] For instance, these reactions are estimated to occur in 1 to 6 per 10,000 new users of CBZ in countries with mainly Caucasian populations. The risk in some Asian countries is estimated to be about 10 times higher.

Recent findings highlighting an apparent increased risk of CBZ-associated SJS/TEN in a population with relatively homogeneous ethnicity provided FDA an opportunity to examine the pharmacogenomic risk for the development of these conditions. Specifically, Hung et al. compared the genotype of 60 Han Chinese patients in Taiwan who

had developed CBZ-associated SJS/TEN to 144 patients of a similar ethnic background who were taking CBZ, but had no signs or symptoms of SJS/TEN.[7] A strong association between the human leukocyte antigen (HLA) allele, HLA-B*1502, and CBZ-associated SJS/TEN was noted. Specifically, 98.3% of patients (59/60) with CBZ-associated SJS/TEN were positive for the HLA-B*1502. Of the 144 patients taking CBZ, but negative for SJS/TEN, only 4.2% (6/144) tested positive for HLA-B*1502.

In a similar study conducted in Europe, Lonjou et al. genotyped 12 patients who had developed CBZ-associated SJS/TEN. Although only four patients were positive for the HLA-B*1502, all four of these patients were Asian. None of the Caucasian patients with CBZ-associated SJS/TEN tested positive for HLA-B*1502. Together, these data suggest an association between HLA-B*1502 and CBZ-associated SJS/TEN, and that this allele may be a marker to predict CBZ-associated SJS/TEN in patients with Asian ancestry.

Based in large part on these scientific findings, FDA also assessed the risk to Asian patients of developing CBZ-associated SJS/TEN by evaluating the available data on HLA-B*1502, race and ethnicity, and existing postmarket reports of CBZ-associated SJS/TEN. Evaluating outside sources of postmarket data was necessary given that there is not direct inquiry on the MedWatch reporting form for a patient's race and ethnicity and, as a result, most spontaneous reports to FDA's Adverse Event Reporting System (AERS) do not provide this information.

According to the allele frequency database provided by *www.allelefrequencies.net*, a higher frequency of the HLA-B*1502 phenotype can be inferred to occur in certain Asian populations. Han Chinese, Filipino (Ivatan), Indonesians, Malaysians, Taiwanese (Minnan), Thai and certain Asian Indians (Khandesh Pawra) appear to be at significant risk for carrying this allele. There appears to be a lower incidence in the frequency of this allele, however, in Japanese individuals. Data provided to FDA by the World Health Organization Uppsala Monitoring Center (WHO-UMC), as well as by sponsors of CBZ products, also indicate a larger number of CBZ-associated SJS/TEN cases in certain Asian countries (as compared to countries with predominantly Caucasian populations). For instance, international sales data for CBZ provided by WHO-UMC demonstrate that, of the countries sampled, Asian countries (e.g., Malaysia and Thailand) have the highest number of SJS/TEN reports per 1 million grams of CBZ sold.

Although there are limitations inherent in the interpretation of postmarket adverse event data (e.g., estimated population exposure, uncertainty in the number of actual cases occurring, lack of details about individual cases), these data, combined with reported frequencies of HLA-B*1502 by race and ethnicity and the aforementioned scientific papers, were considered consistent enough to conclude that those positive for HLA-B*1502 are at a substantially increased risk for developing a dangerous and potentially fatal drug reaction.

In the United States, approximately 4-5% of individuals residing in this country (~12 million people) have identified themselves as Asian.[9] It is estimated that approximately 10% of Asian Americans, if tested, will be positive for HLA-B*1502. This predicted large prevalence of the HLA-B*1502 phenotype in the Asian-American population equates to a greater risk for developing CBZ-associated SJS/TEN over individuals not of Asian descent.

Based on the accumulation of data provided by the scientific literature and other available sources, the potential risk for SJS/TEN in individuals carrying the HLA-B*1502 allele has now been described in a *Boxed Warning*, and in the *Warning and Precautions*, *Laboratory Tests and Geriatric Use* sections of the CBZ product labeling. Included in this information are recommendations for HLA-B*1502 screening in patients of Asian ancestry. This new pharmacogenomic information may allow healthcare professionals to better identify and screen those at risk for developing CBZ-associated SJS/TEN. FDA distributed information on CBZ safety issues, including risks for SJS/TEN and HLA-B*1502, can be found at *www.fda.gov/cder/drug/infopage/carbamazepine/default.htm*.

BOX 5

HLA-B*1502 and how it may relate to CBZ-associated SJS/TEN.

The association between CBZ-associated SJS/TEN and the human leukocyte antigen HLA-B*1502 provides strong evidence that these severe drug-induced conditions are immunologically mediated. HLA-B*1502 is one allele in the gene that encodes proteins for the major histocompatability complex (MHC) Class I molecules. The MHC Class I molecules are used by cells to present pathogens that reside in the cytoplasm to CD8 T-cells. One hypothesis for why CBZ use results in SJS/TEN is that CBZ (or its metabolites) is recognized by and becomes attached to the MHC molecule encoded by HLA-B*1502. Once the MHC molecule presents this drug (or metabolite) on the cell's surface, T-Cells recognize the cell as foreign and destroy it in an attempt to eliminate the "pathogen" from the body.

RELEVANT WEBSITES:

www.allelefrequencies.net
www.census.gov/main/www/cen2000.html
www.fda.gov/cder/foi/label/2007/020712s029lbl.pdf
(Carbatrol label)
www.fda.gov/cder/foi/label/2007/016608s098lbl.pdf
(Tegretol label)
www.fda.gov/cder/foi/label/2006/021710s003lbl.pdf
(Equetro label)
www.fda.gov/cder/drug/infopage/carbamazepine/default.htm

REFERENCES:

1. Mockenhaupt M, Messenheimer J, Tennis P, Schlingmann J. Risk of Stevens-Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptics. Neurology. 2005;64(7):1134-8.

2. Tennis P, Stern RS. Risk of serious cutaneous disorders after initiation of use of phenytoin, carbamazepine, or sodium valproate: a record linkage study. Neurology. 1997;49(2):542-6.
3. Chung WH, Hung SI, Hong HS, et al. Medical genetics: a marker for Stevens-Johnson syndrome. Nature. 2004;428(6982):486.
4. Lonjou C, Thomas L, Borot N, et al. A marker for Stevens-Johnson syndrome … : ethnicity matters. Pharmacogenomics J. 2006;6(4):265-8.
5. Lonjou C, Borot N, Sekula P, et al. A European study of HLA-B in Stevens-Johnson syndrome and toxic epidermal necrolysis related to five high-risk drugs. Pharmacogenet Genomics. 2008;18(2):99-107.
6. Man CB, Kwan P, Baum L, et al. Association between HLA-B*1502 allele and antiepileptic drug-induced cutaneous reactions in Han Chinese. Epilepsia. 2007;48(5):1015-8.
7. Hung SI, Chung WH, Jee SH, et al. Genetic susceptibility to carbamazepine-induced cutaneous adverse drug reactions. Pharmacogenet Genomics. 2006;16(4):297-306.
8. Yang CW, Hung SI, Juo CG, et al. HLA-B*1502-bound peptides: implications for the pathogenesis of carbamazepine-induced Stevens-Johnson syndrome. J Allergy Clin Immunol. 2007;120(4):870-7.
9. Online data for the Year 2000 United States Census [Internet]. United States Census Bureau. [cited 2008 Apr 2]. Available from: *www.census.gov/main/www/cen2000.html*

FDA'S ADVERSE EVENT REPORTING SYSTEM

Many of the articles in the Drug Safety Newsletter are drawn from reviews of case series identified in FDA's Adverse Event Reporting System (AERS). AERS is a database that serves as the repository for voluntary postmarket case reports. Review and analysis of these cases are used by the FDA to monitor drug safety and identify potential safety concerns. FDA frequently uses these case series as the basis for taking further regulatory action to improve drug safety, such as updating a drug's labeling information, requiring a risk evaluation and mitigation strategy, communicating new safety information to the public, or removing a drug from the market.

The FDA receives adverse event reports from manufacturers as required by regulation. Manufacturers receive these reports from health care professionals and consumers. There is no requirement for professionals or consumers to report an adverse event to a manufacturer or to send reports directly to FDA's MedWatch program. All of these reports become part of the AERS database. Reporters of adverse events do not have to be certain that a drug caused the reaction in order to submit a report; they must just suspect that there is an association.

There are well-recognized limitations inherent to a system that depends on voluntary reports including underreporting and incomplete information on a case report. There are also challenges in assessing the relationship between a drug and an adverse event. For example, other causes of the adverse event could include the underlying disease being treated, another concurrent medical condition, or some other product being taken concomitantly. Finally, there is uncertainty around estimating how many people have been exposed to a given drug product. As a result, the safety signals generated by reviewing case reports in the AERS database often require further evaluation in the form of epidemiological studies or clinical trials.

Please visit: *www.fda.gov/cder/aers/default.htm* for further information on AERS and access to AERS Summary Statistics and Data files.

DRUG SAFETY COMMUNICATIONS

Drug Safety Communications posted by FDA from January 1, 2008 to April 30, 2008 (advisories are available at www.fda.gov/cder/drug/DrugSafety/DrugIndex.htm)

Date	Product(s)	Safety Issue and Web Address
April 25, 2008	Heparin sodium injection	Update on heparin and heparin-containing medical products and new information about a contaminant, oversulfated chondroitin sulfate, in the heparin. *www.fda.gov/cdrh/safety/heparin-healthcare-update.html*
April 10, 2008	Mycophenolate mofetil (CellCept) and Mycophenolate acid (Myfortic)[1]	Ongoing safety review to evaluate the potential risk of progressive multifocal leukoencephalopathy (PML). *www.fda.gov/cder/drug/early_comm/mycophenolate.htm*

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Date	Product(s)	Safety Issue and Web Address
March 27, 2008	Becaplermin (Regranex)[1]	Ongoing safety review of possible increased risk of cancer in patients with diabetes mellitus based upon a health insurance database study. *www.fda.gov/cder/drug/early_comm/becaplermin.htm*
March 27, 2008	Ziagen (Abacavir) and Videx (Didanosine)[1]	Ongoing safety review of potential risk of myocardial infarction based upon a large observational study to evaluate the short and long-term adverse effects of treatment with anti-HIV drugs. *www.fda.gov/cder/drug/early_comm/abacavir.htm*
March 27, 2008	Montelukast (Singulair)[1]	Ongoing safety review of reports of behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide. *www.fda.gov/cder/drug/early_comm/montelukast.htm*
March 21, 2008	Darunavir etalolate (Prezista)	Highlighting new labeled warnings about potential risk of hepatotoxicity. *www.fda.gov/cder/drug/infopage/darunavir/default.htm*
March 18, 2008	Tiotropium bromide inhalation powder (Spiriva HandiHaler)	Ongoing safety review to evaluate the potential risk of stroke based upon the pooled analysis from 29 placebo controlled studies. *www.fda.gov/cder/drug/early_comm/tiotropium.htm*
March 11, 2008	Long-Acting Hydrocodone-containing cough product (Tussionex Pennkinetic Extended-Release Suspension)	Reports of serious adverse events, including death due to respiratory depression, associated with overdose and misuse of the product in all age groups, especially in children under 6 years of age for whom the product is not recommended. *www.fda.gov/cder/drug/advisory/hydrocodone.htm*
March 5, 2008	Long-Acting Beta Agonists (LABAs) [salmeterol xinafoate (Serevent Diskus), fluticasone propionate; salmeterol xinafoate (Advair Diskus, Advair HFA), formoterol fumarate (Foradil Aerolizer, Perforomist) butenoside; formoterol fumarate dehydrate (Symbicort), aformotrol tartrate (Brovana)]	Update highlighting an ongoing benefit/risk assessment of LABAs in children with asthma. *www.fda.gov/cder/drug/infopage/LABA/default.htm*
February 29, 2008	Tiotropium bromide inhalation powder (Spiriva HandiHaler) and formoterol fumarate inhalation powder (Foradil Aerolizer)	Highlighting the correct use of Spiriva and Foradil capsules after receiving reports of patients swallowing the capsules rather than placing the capsules in the inhalation devices. *www.fda.gov/cder/drug/advisory/tiopropium_formoterol.htm*
February 11, 2008 (updated February 28, 2008 and April 25, 2008)	Heparin sodium injection	Reports of serious allergic reactions and severe hypotension following the administration of Baxter's multi-dose vials of heparin sodium injection and temporary suspension of the marketing of the product. *www.fda.gov/cder/drug/advisory/heparin.htm*
February 8, 2008	Botulinum toxin Type A (Botox and Botox Cosmetic) and Botulinum toxin Type B (Myobloc)[1]	Ongoing safety review of reports of systemic adverse reactions including respiratory compromise and death, occurring mostly in children treated for cerebral palsy-associated limb spasticity. *www.fda.gov/cder/drug/early_comm/botulinium_toxins.htm*
February 1, 2008	Varenicline (Chantix)	Update highlighting new labeled warnings and precautions about the potential risk of neuropsychiatric symptoms. *www.fda.gov/cder/drug/advisory/varenicline.htm*

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Date	Product(s)	Safety Issue and Web Address
January 31, 2008	Antiepileptic drugs [carbamazepine (Carbatrol, Equetro, Tegretol, Tegretol XR), felbamate (Felbatol), gabapentin (Neurontin), lamotrigine (Lamictal), levetiracetam (Keppra), oxcarbazepine (Trileptal), pregabalin (Lyrica), tiagabine (Gabitril), topiramate (Topamax), valproate (Depakote, (Depakote ER, Depakene, Depacon), zonisamide (Zonegran)]	Increased risk of suicidal behavior or ideation in patients who received antiepileptic drugs compared to the placebo group in randomized clinical studies of eleven drugs. *www.fda.gov/cder/drug/InfoSheets/HCP/antiepilepticsHCP.htm*
January 25, 2008	Ezetimibe/Simvastatin (Vytorin), Ezetimibe (Zetia)[1]	Ongoing data review evaluating the overall cardiovascular benefits of ezetimibe with simvastatin combination therapy. Preliminary findings suggest no benefit of combined ezetimibe and simvastatin over simvastation alone. *www.fda.gov/cder/drug/early_comm/ezetimibe_simvastatin.htm*
January 17, 2008	Nonprescription cough and cold drug products	Update of safety review findings that over-the-counter (OTC) cough and cold medicines should not be used to treat infants and children less than 2 years of age because of serious and potentially life-threatening adverse events. *www.fda.gov/cder/drug/advisory/cough_cold_2008.htm*
January 16, 2008	Edetate disodium (Endrate and generics)	Reports of death in children and adults who were mistakenly given Edetate Disodium instead of Edetate Calcium Disodium (Calcium Disodium Versenate) during intravenous chelation therapy. *www.fda.gov/cder/drug/advisory/edetate_disodium.htm*
January 7, 2008	Bisphosphonates [alendronate (Fosamax, Fosamax Plus D), etidronate (Didronel), ibandronate (Boniva), pamidronate (Aredia), risedronate (Actonel, Actonel W/Calcium), Tiludronate (Skelid), and zoledronic acid (Reclast, Zometa)]	Reports of severe and incapacitating musculoskeletal pain in patients taking bisphosphonates. *www.fda.gov/cder/drug/infopage/bisphosphonates/default.htm*
January 3, 2008	Erythropoiesis Stimulating Agents (ESAs) [darbepoetin alfa (Aranesp), epoetin alfa (Epogen), epoetin alfa (Procrit)][1]	Increased risk of death and tumor progression in patients with cancer who received ESAs for treatment of chemotherapy-induced anemia. *www.fda.gov/cder/drug/early_comm/ESA.htm*

FOOTNOTES:

1. Early Communication about Ongoing Safety Review.

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