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an online publication of the ACR Drug Safety Committee

FDA UPDATE: TNF inhibitors may increase risk of malignancy in children

In June 2008, the FDA issued an alert of 30 reported cases of cancer in children exposed to tumor necrosis factor inhibitors. The FDA has updated its analysis of TNF blockers and neoplasms in children, and concluded that there is an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescents (FDA Alert 8/4/09). This new safety information is now being added to the Boxed Warning for these products.

An FDA analysis (from 2001 – 2008) identified 48 cases of malignancies in children and adolescents exposed to TNF inhibitors: 32 U.S. and 16 non-U.S. cases. Of the 48 cases reviewed by FDA, indications for use included inflammatory bowel disease (n=25), juvenile arthritis (15) and spondyloarthropathy (4). Approximately half were lymphomas, including Hodgkin's (n=6) and non-Hodgkin's lymphoma (n=7). Ten patients had hepatosplenic T-cell lymphoma. Other malignancies reported include leukemia (6), and malignant melanoma (3). Rare childhood malignancies such as leiomyosarcoma, hepatic malignancies, neuroblastoma and renal cell carcinoma were also seen. Of the 48 malignancies, there were 11 deaths, with 9 deaths from hepatosplenic T-cell lymphoma and one from T-cell lymphoma. The remaining death resulted from sepsis after achieving remission from lymphoma.

The FDA analysis showed that U.S. reporting rates of malignancies seen with infliximab use were consistently

higher compared to expected background rates for lymphomas and all malignancies. Reporting rates for etanercept-related malignancies were also higher than background rates for lymphomas, but were similar to background rates for all malignancies (Table 1). The malignancy reporting rates for adalimumab and certolizumabpegol were not calculated because of their minimal use in pediatric patients thus far. Golimumab was not FDA approved at the time of the analysis and therefore was not included. The observed reporting rates offer very limited inference into the potential differences in malignancy risk among the TNF blockers because of uncertainties about actual patient exposure to treatment and the possibility of underreporting of malignancy cases.

Nearly 88% of these cancers were diagnosed between 2006 and 2008. Calculated event frequency was based on manufacturer-supplied estimates for exposure to infliximab (22,645 treatment years for ages 0-16 years from 2003 through 2007) and etanercept (26,800 treatment years for ages 0-17 years from 1998 through 2007). The observed drug-related cancer rates were compared to expected rates derived from the National Cancer Institutes SEER database (representing 14% of U.S. population) of >29,000 childhood and adolescent cancers diagnosed between 1975 and 2005.

The majority of the 48 patients (88%) were also using other immunosuppressive medications such as azathioprine

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IN THE NEWS

COLCHICINE (MARKETED AS COLCRYS) APPROVED BY FDA

Colchicine use in gout dates back to 1810 and was first FDA approved (in combination with a uricosuric) in 1939. In 2009, the FDA approved the first single-ingredient oral colchicine product, Colcris, for the treatment of Familial Mediterranean Fever and acute gout. Acute gout approval was based on a 184 patient, 24 hour placebo-controlled trial that showed low dose (1.8mg) and high dose (4.8mg) Colcris to be equally effective. However, the low dose had significantly fewer adverse events (diarrhea and nausea) compared with the high dose group. This product's approval falls under a new FDA initiative to replace marketed "grandfathered" products, like colchicine, with products

meeting modern standards for safety, effectiveness, quality and labeling. Until recently there was no FDA-approved prescribing information, dosage recommendations, or drug interaction warnings.

Colchicine metabolism and excretion is mediated by P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP 3A4). Drugs that are potent inhibitors of P-gp (cyclosporine, quinidine) and CYP3A4 (clarithromycin, erythromycin, ketoconazole, diltiazam, grapefruit juice) may raise colchicine levels and the risk of serious toxicity. The FDA recommends that prescribers avoid P-glycoprotein or a strong CYP3A4 inhibitors in patients who are taking colchicine, especially in the setting of renal or hepatic impairment. Overall, these studies have

helped establish prescribing guidelines to improve drug safety and limit drug-drug interactions. However, the safety of this product when used in combination with NSAIDs or corticosteroids and its use for chronic prophylaxis (gout or pseudogout) has not yet been studied.

MMWR OCTOBER 30, 2009 – OPIOID DEATHS INCREASING

Between 1999 and 2006, the number of overdose deaths involving prescription opioid painkillers increased, coinciding with a nearly fourfold increase in use of prescription opioids. Washington state reported a rate of 6.4 overdose deaths per 100,000 per year: 58.9% were male, 34.4% were between ages of 45-54 yrs, and 45.4% of deaths were among persons enrolled in

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Editors Introduction

We hope you enjoy this inaugural issue of the DSQ. Herein we provide reports of recent updates from the FDA, key literature references, safety news and capsule summaries of novel issues: Atrial fibrillation and bisphosphonates; TNF inhibitors inducing sarcoid or psoriasis; leflunomide lung disease; and narcotic prescribing guidelines. Send questions, comments or suggestions to DSQ@rheumatology.org.

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A recent ABC news story has focused concern on a potential risk of "atypical subtrochanteric (low energy) fractures" associated with bisphosphonate use. The FDA has stated that they have previously studied this issue and found no association. However, the FDA and other groups are currently analyzing this issue further as there are numerous reports describing these events (see Safety Signals, pg 3 and the citation from Lenart et al). The DSQ will continue to follow and report on this issue.

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and methotrexate, which currently have warnings of increased risk of lymphoma in their prescribing information. While there may be other contributory factors, the role of TNF blockers in the development of malignancies in children and adolescents could not be excluded. FDA concludes there is an increased risk of malignancy with TNF blockers in children. However, due to the relatively rare occurrence of these cancers, the limited number of pediatric patients treated with TNF blockers, and the possible role of other immunosuppressive therapies used concomitantly with TNF blockers,

FDA is unable at this time to fully characterize the strength of the association between using TNF blockers and developing a malignancy.

Additional data on this issue may come from manufacturer sponsored long-term, observational, post-marketing studies. At the 2009 ACR Annual Scientific Meeting, Bernatsky and colleagues reported no increase in cancers from two North American longitudinal JIA registries (1,168 patients and 16,396 patient-years) between 1974 and 2006. This suggests that the risk of malignancy may not be significantly increased in JIA patients. **DSQ**

Table 1. Cancer reporting rates amongst children receiving TNF inhibitors

	MALIGNANCIES †	OBSERVED RATE/100,000 PY	EXPECTED RATE/100,000 PY ‡
OVERALL MALIGNANCIES			
INFLIXIMAB	15	66	16.8
LYMPHOMAS (EXCLUDING HEPATOSPLENIC T CELL LYMPHOMA)			
INFLIXIMAB	10 (5)	44 (22)	2.4
ETANERCEPT	3	11	2.4

†from the FDA Adverse Event Reporting System (1999-2007)

‡SEER Cancer Statistics Review 1975-2005, Table XXIX-1, ages 0 – 19 years; PY: Patient-years exposure

NOTABLE CITATIONS ON DRUG SAFETY

IS THERE A RISK OF ATRIAL FIBRILLATION WITH BISPHOSPHONATES?

This potential association was found in the HORIZON study with zoledronate and has been the subject of several recent population-based case-control studies and meta-analyses. The first, from N. Denmark, analyzed the frequency of alendronate use in 13,586 patients with atrial fibrillation or atrial flutter and 68,054 population controls. With comparable use of bisphosphonates (3.2% and 2.9%), the adjusted relative risk of AF with bisphosphonate use compared with non-use was 0.95 (95% confidence interval 0.84 to 1.07), suggesting no increased association between the drug and adverse event (BMJ. 2008;336:813-6. PMID: 18334527). In contrast, another population-based study from Washington state compared 719 women with incident AF (2001-2004) with 966 control subjects without AF. They found more AF patients had ever used alendronate (6.5%) vs. controls (4.1%) (p=0.03) and hence a higher risk of incident AF was seen (odds ratio, 1.86; 95% confidence interval, 1.09-3.15) (Arch Intern Med 2008;168:826-31 PMID: 18443257). Lastly, the United Kingdom General Practice Research Database was used to assess the risk of atrial fibrillation and flutter in

women exposed to the oral bisphosphonates, alendronate acid and risedronate sodium (PLoS One;4:e4720 PMID: 19266096). The adjusted incidence rate ratio for AF with oral bisphosphonate use was 1.07 (95% CI 0.94-1.21). However, in post-hoc analyses, an increased risk of incident AF was detected during the first few months of alendronic acid therapy. A meta-analysis of existing data by Loke et al, stated that "heterogeneity of the existing evidence, as well as paucity of information on some of the agents, precludes any definitive conclusions on the exact nature of the risk" (Drug Saf 2009;32:219-28 PMID: 19338379). Another meta-analysis of 12 trials and 266,761 patients by Kim et al concluded that bisphosphonate exposure was not associated with an increased risk of AF (Arthritis Res Ther 2010, 12:R30 PMID: 20170505).

SARCOIDOSIS INDUCED BY TNF INHIBITION

The potency of TNF inhibition has led to its experimental and untested use in novel and sometimes difficult to treat conditions, including sarcoidosis. While there are mixed reports regarding the efficacy of TNF blockade in patients with sarcoidosis, it is surprising to note several

case reports describing the onset of sarcoid in patients taking a TNF blocker for usual indications. In France, researchers estimated the frequency of TNF inhibitor-induced sarcoid to be 1/2800 exposed (Rheumatology 2009;48:883-6 PMID: 19423648). They described 10 patients with sarcoid-like granulomatosis on anti-TNF treatment (5 etanercept; 5 monoclonal antibodies; 4 treated for RA and 6 for SpA). Most cases had pulmonary or cutaneous presentations and the median delay from drug initiation to granulomatosis diagnosis was 18 (range 1-51) months. All resolved with drug discontinuation usually within 6 (range 1-12) months. In Italy two more patients were described who presented with low-grade fever, chest pain, and dyspnea and the diagnosis was established by noncaseating granulomas on transbronchial biopsy (Semin Arthritis Rheum. 2010;39:313-9 PMID: 19147181). Their review article describes 13 additional cases from the literature.

NEW ONSET PSORIASIS WITH TNF INHIBITORS

Numerous descriptive reports have suggested that TNF inhibitors may rarely cause new onset psoriasis. Fouache et al analyzed 296 patients with spondylarthropathy [198 AS, 21 SpA with

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IBD and 77 psoriatic arthritis] treated with 287, 290 and 62 patient-years of infliximab, etanercept and adalimumab therapy, respectively. They found five psoriasis (three infliximab; one each etanercept or adalimumab), 3 acute anterior uveitis (all etanercept) and four IBD (three etanercept, one infliximab) (Rheumatology 2009;48:761-4 PMID: 19395543). A study from The British Society for Rheumatology Biologics Register examined 9826 anti-TNF-treated and 2880 DMARD-treated RA patients and found 15 incident psoriasis cases in the TNF-treated group but none in the controls with a crude incidence rate of 1.04 (95% CI 0.67 to 1.54) per 1000 person years (Ann Rheum Dis. 2009;68:209-15 PMID: 18385277). A recent FDA alert (8/4/09) disclosed 69 cases of new onset psoriasis (identified from their Adverse Event Reporting system), including pustular (17) and palmoplantar (15) cases, in patients using TNF blockers for treatment of autoimmune and rheumatic conditions other than psoriasis and psoriatic arthritis (FDA Alert 8/4/09). Of the 69 cases, there were 2 pediatric cases of new onset psoriasis. The development of psoriasis during treatment with TNF blockers occurred with varying duration from weeks to years after drug initiation. Twelve of the psoriasis

cases resulted in hospitalization, which was the most severe outcome reported. The majority of patients experienced improvements of their psoriasis following discontinuation of the TNF blocker. None of the cases reported pre-existing psoriasis prior to the initiation of TNF blocker therapy. FDA concluded there is a possible association between the development of psoriasis and use of these drugs. Therefore, FDA is requiring an update to the Adverse Events comment section of the prescribing information.

(Editors' note: there are no current guidelines on how to respond when new-onset psoriasis occurs while on TNF inhibitors. Many advocate continuation unless widespread, palmoplantar or pustular skin disease is present.)

HEPATITIS B REACTIVATION IN CD20+ LYMPHOMA PATIENTS TREATED WITH RITUXIMAB

Yeo et al has reported on 104 patients with CD20(+) diffuse, large B-cell, non-Hodgkin lymphoma who were treated with CHOP, with or without rituximab (R-CHOP). Resolved hepatitis B infection (negative HBsAg; positive HB core Ab) was found in 46 patients. HBV reactivation was not seen in the 25 CHOP only patients. However, five (24%) of the 21 rituximab treated (R-CHOP)

patients experienced HBV reactivation (J Clin Oncol 2009; 27:605-11 PMID: 19075267).

LEFLUNOMIDE INTERSTITIAL LUNG DISEASE?

Several recent reports suggest leflunomide-related lung disease in patients with RA. This issue is often confounded by interstitial lung disease and chronic lung disease related to either RA or prior therapies (MTX, penicillamine, etc). Nonetheless, several series have suggested an association of LEF with ILD. Chikura et al reported on their 32 RA patients with LEF-ILD; all of whom had a prior history of MTX pneumonitis, RA-ILD or both (Rheumatology 2009;48: 1069-72. PMID: 19321513); 82% occurred within the first 20 weeks of LEF therapy and 19% died. Mortality was associated with pre-existing ILD, MTX pneumonitis and ground glass changes on high-resolution CT imaging. In contrast, a population-based, nested case controlled study found 74 cases of ILD from 62734 RA patients and showed an increased risk in LEF patients (RR=1.9), but no increase when those with prior MTX pneumonitis or ILD were excluded (Arthritis Rheum. 2006;54:1435-9 PMID: 16645972). At this time there is no clear association between LEF and ILD. **DSQ**

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- Safety of contraceptive method use among women with systemic lupus erythematosus: a systematic review. Culwell KR, Curtis KM, del Carmen Cravioto M. Obstet Gynecol. 2009 Aug;114(2 Pt 1):341-53. PMID: 19622996

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Medicaid. Age adjusted rate of death was 30.8 per 100,000 in Medicaid enrolled population compared to 4.0 per 100,000 in non-Medicaid population (RR 5.7). The majority of deaths were associated with methadone overdose (64%) compared to 22.9% with oxycodone, and 13.9% with hydrocodone. A recent report from the U.S. Centers for Disease Control and Prevention and the National Center for Health Statistics (JAMA 2010; 303(6):495-7) also notes that opioid deaths "continues to soar". Poisoning deaths involving methadone rose 7-fold from 790 in 1999 to 5420 in 2006. These findings highlight the prominence of methadone in prescription opioid-related overdose. Notable is that methadone's use as a pain reliever has increased more than twelvefold in the U.S., presumably because of its low cost. (PMID: 19875978)

MMWR DECEMBER 11, 2009 - UPDATE ON SAFETY OF H1N1 FLU VACCINATIONS

From October 5 (introduction) to November 20, a total of 46.2 million doses of H1N1 vaccine and 98.9 million doses of seasonal flu vaccines were distributed in the U.S and surrounding territories. A slightly higher rate of serious adverse events was seen in patients who received H1N1 compared to seasonal flu vaccines (4.4/million vs. 2.9/million, respectively). However, there was no substantial difference between H1N1 and seasonal influenza vaccines in deaths or the types of SAE reported. As of November 24, there were 13 deaths, 12 cases of Guillain-Barré syndrome (four confirmed)

and 19 cases of anaphylaxis (13 confirmed) after receipt of the H1N1 vaccines. Nonserious adverse events were categorized as non-GBS neurologic/muscular conditions, influenza or pneumonia-like illness, pregnancy complications, respiratory, allergic, gastrointestinal, cardiovascular, and psychiatric conditions. The data indicate no increase above background rates for monitored health events among recipients of H1N1 vaccines. (PMID: 20010511)

CDC H1N1 Stats (Updated Estimates from April – December 12, 2009)

- Cases 55 million [95% CI 39-80 million]
- Hospitalizations 246,000 [CI 173,000-362,000]
- Deaths 11,160 [CI 7880-16,460]

NEW OPIOID PRESCRIBING GUIDELINES FROM THE APS

The American Pain Society and the American Academy of Pain Medicine has published a comprehensive clinical practice guideline to assist clinicians in prescribing potent opioid pain medications for patients with chronic non-cancer pain. (Chou R et al. J Pain 2009;10:113–30 PMID: 19187889) A key recommendation urges clinicians to continuously assess patients on chronic opioid therapy by monitoring pain intensity, level of functioning and adherence to prescribed treatments. Periodic drug screens should be ordered for patients at risk for aberrant drug behavior. Other recommendations in the APS/AAPM clinical practice guideline include:

- Methadone: Use of methadone for pain management has increased dramatically but few trials have evaluated its benefits and harms for treatment of chronic non-cancer pain. Methadone, therefore, should be started at low doses and titrated slowly. Because of its long half-life and variable pharmacokinetics, the panel recommends methadone not be used to treat breakthrough pain or as an as-needed medication.
- Abusers: Chronic opioid therapy must be discontinued in patients known to be diverting their medication or in those engaging in serious aberrant behaviors.
- Breakthrough Pain: As-needed opioids can be prescribed based on initial and ongoing analysis of therapeutic benefit versus risk.
- High Doses: Patients who need high doses of opioids (200 mg daily of morphine or equivalent) should be evaluated for adverse events on an ongoing basis. Clinicians should consider rotating pain medications when patients experience intolerable side effects or inadequate benefit despite appropriate dose increases.
- Driving and Work Safety: Patients should be educated about the greater risk for impairment when starting chronic opioid therapy and counseled not to drive or engage in potentially dangerous work if impaired.
- Pregnancy: Clinicians should counsel women about risks in pregnancy and encourage minimal or no use of chronic opioid therapy unless potential benefits outweigh risks. **DSQ**

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DSQ
Drug Safety Quarterly

Winter 2010

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Dr. Cush: clinical Investigator for Genentech, Pfizer, UCB, Celgene, Abbott, CORRONA; Consultant to Centocor, UCB, Wyeth, Amgen, Roche, BMS.

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This issue has been reviewed by members of the ACR Drug Safety Committee and Communications and Marketing Committee.

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