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## Assessing Skin Cancer Risk in Patients with RA and Psoriatic Arthritis

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Rheumatoid arthritis and psoriasis patients are at increased risk for non-melanoma skin cancers (NMSC), and TNF antagonists may increase the risk further. This association has resulted in recent changes to product labeling, indicating an increased risk of skin cancer and the need for detailed skin examinations in patients receiving TNF inhibitors. Specifically, these regulatory guidelines suggest that patients receiving chronic immunosuppressive therapies or psoriasis patients with a history of PUVA should be examined for presence of NMSC before and during treatment with TNF inhibitor. This review will address the issue of skin cancer screening and risk in patients receiving TNF inhibitor.

Cancer is highly prevalent in society, with an estimated one-third of the population having a lifetime risk of neoplasia. Skin cancer is most prevalent with an estimated lifetime risk of 20%. Nonmelanoma skin cancers includes basal cell carcinoma, invasive squamous cell carcinoma, and in situ SCC.

A recent metaanalysis of 74 clinical trials and 15,418 individuals treated with TNF inhibitors failed to show a significant increase in cancer in those treated with TNF inhibitors compared to the DMARD therapy (0.84% vs. 0.64%).<sup>(1)</sup> However, a higher relative rate of NMSC (RR=2.02, 95%CI 1.11-3.95) was observed for those receiving TNF inhibitors. Another metaanalysis of patients with plaque psoriasis and psoriatic arthritis identified 20 studies and 6810 patients treated with TNF inhibitors and yielded a higher odds ratio for NMSC (OR=1.33, 95% CI 0.58-3.04).<sup>(2)</sup> In these studies, the incidence of melanoma was too low to draw any conclusions; however, observational databases have shown higher rates of NMSC and melanoma with TNF inhibitor use.<sup>(3,4)</sup> Wolfe and Michaud reported higher rates of NMSC (OR 1.5, 95% CI 1.2-1.8) and melanoma (OR 2.3, 95% CI 0.9-5.4) among 13,001 RA patients followed in a longitudinal database.<sup>(3)</sup> Dixon et al has examined a British RA biologics and DMARD registry and found that among the 293 patients with a prior malignancy, TNF inhibitor

use was associated with a higher rate of melanoma recurrence (3/17 or 18%), compared to no recurrence in those treated with DMARDs (0/10).<sup>(4)</sup>

It should be noted that many, but not all, trials have shown higher rates of NMSC and melanoma in active RA patients treated with MTX or DMARDs only.<sup>(5)</sup> A recent study in Alberta, Canada concluded that between 1988 and 2007 the incidence of NMSC remained stable, but that risk is highest in the elderly<sup>(6)</sup> and is rare under age 40 years. As these lesions are often found in clothed areas, the authors recommend complete skin examinations after 40 years of age.

These data indicate a higher risk of NMSC in patients with RA and psoriatic disease and the product label for three of the five available TNF inhibitors has been changed to reflect this warning. The following entries are from current package inserts:

**REMICADE:** "Psoriasis patients should be monitored for nonmelanomatous skin cancers (NMSC), particularly those patients who have had prolonged phototherapy treatment. In the maintenance portion of clinical trials with Remicade, NMSCs were more common in patients with previous phototherapy".

**ENBREL:** "Melanoma and NMSC have been reported in patients treated with TNF blockers, including Enbrel. Periodic skin examinations should be considered for all patients at increased risk for skin cancer".

**HUMIRA:** "Non-melanoma skin cancer (NMSC) has been reported during clinical trials for HUMIRA-treated patients. All patients should be examined for the presence of NMSC prior to and during treatment".

For the practitioner, these changes imparts a pharmacovigilance and public health challenge and gives rise to several questions worthy of discussion:

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## In the News

### Revised Recommendations for Chloroquine and Hydroxychloroquine Retinopathy

The American Academy of Ophthalmology recently published revised guidelines for screening for chloroquine and hydroxychloroquine retinopathy. Risk for toxicity increases toward 1% after 5-7 years of exposure (cumulative dose 1000 g of HCO). Current AAO guidelines recommend a baseline examination to serve as a reference point and to evaluate for maculopathy; annual screening should then begin after 5 years of use (or sooner if there are unusual risk factors). Newer screening tests uses multifocal electroretinogram (mfERG), spectral domain optical coherence tomography (SD-OCT), and fundus autofluorescence (FAF). The AAO recommends screening with one of these procedures where available. The Amsler grid testing is no longer recommended. Fundal examinations are advised for documentation, but the bull's eye maculopathy is a late change; hence the goal of screening is to recognize toxicity at an earlier stage. (Ophthalmology. 2011 Feb;118(2):415-22. PMID: 21292109)

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## Assessing Skin Cancer Risk continued from cover

### 1. Who should assume the responsibility for “periodic skin examinations” associated with TNF inhibitor use – rheumatologists, dermatologists, primary care physicians or patients?

It is important to recognize that there is no clear consensus or accepted guidelines for skin cancer screening in general. The 2009 US Preventative Service task force concluded that the current evidence is insufficient to assess the balance of benefits and harms of screening by primary care physicians or patients’ skin self-examination.<sup>(7)</sup>

The responsibility of screening low risk patients can generally be carried out by PCPs, or a health care worker or specialist trained in skin examination. High risk patients or patients who have a lesion suspicious for skin cancer could be referred to a dermatologist for further assessment.

It is important that rheumatologists integrate skin cancer education in the counseling of patients when initiating TNF antagonists (e.g., photoprotection, minimizing exposure during peak hours of UV exposure 11:00 AM – 4:00 PM, avoidance of tanning beds, and skin self-examination). Patients should be educated about the importance of self-examination and referred to relevant educational sources (<http://www.aad.org/skin-conditions/skin-cancer-detection>).

### 2. How often should periodic skin examinations be performed?

In general, skin self-examinations can be done on an annual basis. In high risk patients, more frequent examinations may be warranted. For example, patients with solid organ transplant are at relatively greater increased risk of developing NMSC and melanoma skin cancer (in the order of 65 fold for squamous cell carcinoma, basal cell carcinoma 10-fold, and melanoma 3-fold). In this at risk population, current recommendations for skin cancer surveillance are complete skin examination every 12 months in patients without a history of skin cancer. In patients with a history of a single skin or multiple skin cancers, however, this interval may be reduced to three to six months, depending on the situation.<sup>(8,9)</sup>

### 3. Is there a population you would avoid the use TNFi because the risk of NMSC or melanoma would be unacceptable to patient or physician?

There are currently no specific risk factors for non-melanoma skin cancer that would preclude the use of TNF antagonists in patients with psoriasis and psoriatic arthritis. Patients with multiple non-melanoma skin cancers or having extensive exposure to phototherapy should be considered at particularly high risk and should be monitored more frequently, as noted above. In such patients, the decision to initiate therapy should be made on a case-by-case basis, assessing and discussing risks/benefits and allowing the patient to make an informed treatment choice. In the authors experience, patients with metastatic non-melanoma skin cancer (invariably squamous cell cancer, as basal cell cancer rarely metastasizes) generally do not receive TNF antagonists.

### 4. Should the patient’s biologic be discontinued if they develop NMSC or melanoma?

In the randomized controlled trials involving the use of TNF antagonists and anti-P40 antagonists, there has not been any exclusion of patients with prior history of non-melanoma skin cancer from initiating therapy. In certain situations, we have excluded patients with multiple non-melanoma skin cancers given the relatively high risk, although there is no consensus on the need to do so. If a patient had a melanoma at baseline, these patients were generally excluded from clinical studies.

### 5. Would you use a TNF inhibitor in a patient with a remote history of melanoma or a family history of melanoma?

In our clinical studies, we did not specifically exclude patients from receiving TNF antagonists who have a family history of melanoma or risk factors for melanoma (e.g., light skin pigmentation, number of melanocytic nevi, ease of developing sunburn, family history of melanoma in two first degree relatives, prior history of melanoma, presence and number of dysplastic nevi, freckling, history of blistering sunburns before the age of 14).<sup>(10)</sup>

Patients with history of melanoma were excluded in clinical studies. The decision to use TNF antagonists in a patient with melanoma should be addressed on a case-by-case basis, carefully addressing risk/benefit and letting the patient make an informed choice. It is the practice of the authors to exclude patients with a history of invasive melanoma or metastatic melanoma from use of biologic therapies in general. The use of biologic therapies in a patient with a low risk melanoma (remote history and melanoma in situ) can be considered on a case-by-case basis. This decision is based on a thorough risk/benefit analysis discussion with the patient, although there are no current guidelines on the use of these agents in such patients. **DSQ**

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## FDA MedWatch

**PPI may lower magnesium levels; FDA recommends monitoring.** Healthcare professionals were issued a notification that proton pump inhibitors (PPI) may cause low serum magnesium if taken for prolonged periods. Serious adverse events as muscle spasms, tetany, arrhythmias, and seizures may occur. Hypomagnesemia typically improves with magnesium supplementation; however, in one quarter of cases that were reviewed, supplementation alone did not improve the magnesium levels, and the PPI had to be discontinued. The FDA recommends that magnesium levels be obtained prior to initiation of PPI treatment and periodically in patients who are expected to be on these drugs for extended periods, and also in patients who are on medications that may cause hypomagnesemia (e.g, diuretics, digoxin). (March 2011)

**Unapproved cold remedies to be removed.** FDA announced its intention to remove about 500 unapproved prescription cough/cold/allergy drugs. These drugs have not been evaluated by the FDA for safety, effectiveness, and quality. Many providers may be unaware of the unapproved status of the drugs and have unknowingly prescribed them. Some brands listed include: ACCUHIST DM, ALLERX D, ALLERGX DOSEPACKS, DALLERGY, DYNATUSS-EX, and ENTEX LA ER. For a complete list of the drugs, go to FDA website: <http://acr.tw/qVY6b8>. (March 2011)

**Topamax (topiramate) and cleft palate.** FDA is warning the public of risk for cleft lip/palate in infants born to mothers treated with topiramate during pregnancy. The drug has been classified as a Category D in pregnancy based on these new data. (March 2011)

**Hepatosplenic T cell lymphoma and TNF inhibitors.** The FDA has added hepatosplenic T cell lymphoma as a potential adverse event associated with TNF inhibitors (adalimumab, infliximab, etanercept, certolizumab, golimumab), 6-mercaptopurine or azathioprine use. This association has primarily been reported in children or adolescents with treated for inflammatory bowel disease with infliximab or adalimumab, usually in combination with either azathioprine or mercaptopurine. FDA has now documented 43 distinct cases of HSTCL in patients treated with TNF blockers as combination therapy or monotherapy. While most are IBD patients there are several patients with psoriasis or rheumatoid arthritis and HSTCL. HSTCL is a very rare, and usually fatal, condition that may manifest abdominal pain, hepatosplenomegaly, night sweats, persistent fever, weight loss and cytopenias without lymphadenopathy. (April 2011)

**Tysabri (natalizumab) and PML** - the FDA has issued a safety update on

*continued next page*

**FDA MedWatch** continued from page 2

Tysabri, which had been approved for treating relapsing multiple sclerosis and moderate to severely active Crohn's disease. 102 cases of progressive multifocal leukoencephalopathy have been reported among 82,732 patients treated with Tysabri worldwide through February 28, 2011. The new information address rates of PML according to number of infusion, wherein the risk of developing PML is greater in patients who have received more than 24 infusions (or 2 years of therapy). (April 2011)

Number of Tysabri infusions	PML Incidence per 1000 patients
up to 24	0.3
25-36	1.5
37-48	0.9

**NSAID interactions with anti-hypertensives.** FDA has added a precaution about the use of NSAIDs with antihypertensive agents in the elderly, volume-depleted (including those on diuretic therapy) and those with compromised renal function. The co-administration of NSAIDs, including selective COX-2 inhibitors with angiotensin II receptor antagonists (including valsartan, olmesartan) or ACE inhibitors (e.g., captopril), may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving valsartan and NSAID therapy. The antihypertensive effect of angiotensin II receptor antagonists may be attenuated by NSAIDs. (May 2011)

**Zocor (simvastatin) myopathy warnings.** New restrictions, contraindications and dose limitations are recommended by the FDA to reduce risk for muscle injury. Simvastatin 80 mg/day should not be started in new patients, including patients already on lower dosages of the drug as it may increase the risk for myopathy. The risk appears to be highest in the first year of treatment and is often associated with interactions with certain medicines (e.g., clarithromycin, erythromycin, gemfibrozil, cyclosporine, diltiazem). (June 2011)

**Confusion with Risperdal (risperidone) and Requip (ropinirole).** The FDA is alerting the public to medication errors where patients inadvertently were given the wrong drug, and in some cases, required hospitalization. Factors contributing to the confusion include: similarities to both brand and generic names, illegible handwriting on prescriptions, similarities of container labels and carton packaging, and overlapping product characteristics (e.g., drug strength, dosage forms and dosing intervals). The FDA is requesting the manufacturers of these products to use "tall man" lettering on labels as "risperiDONE" and "rOPINIrole" and to change carton packaging to provide better visual differentiation. (June 2011)

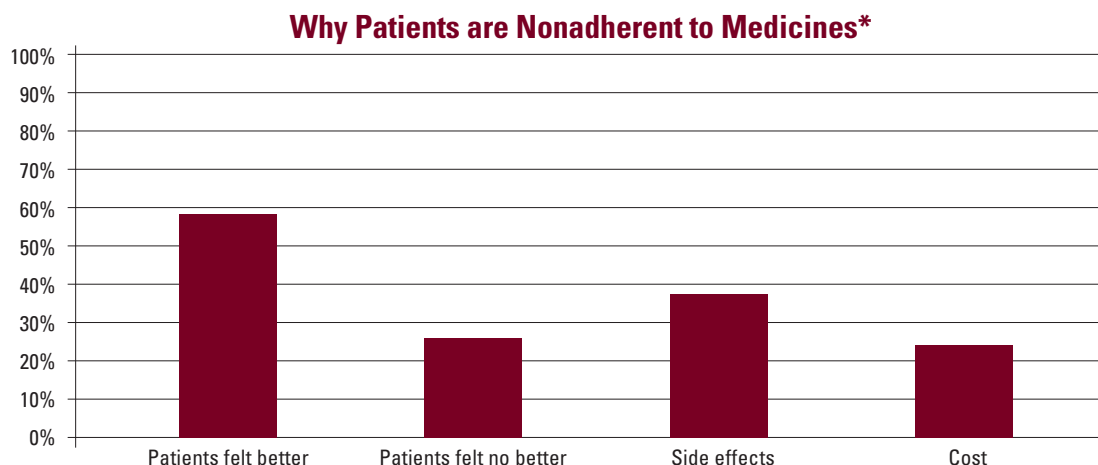
**Actos (pioglitazone) and bladder cancer.** Based on reviewed of a planned 5 years interim analysis of an ongoing 10 year epidemiological study, the FDA issued a new warning that use of Actos for greater than 1 year may be associated with an increased risk for bladder cancer. Healthcare professionals are urged not to use pioglitazone in patients with active bladder cancer and prior history of bladder cancer. (June 2011)

**Chantix (varenicline) and CV events.** The FDA cautions that the smoking cessation drug, Chantix, may be associated with a small, increased risk for certain cardiovascular adverse events in patients with cardiovascular disease. A randomized clinical trial of 700 smokers with CAD treated with Chantix vs. placebo noted improved efficacy for smoking cessation with Chantix, but myocardial infarctions, peripheral vascular disease, and need for coronary revascularization were reported more frequently in patients on Chantix compared to PCB. (June 2011)

**Bisphosphonates and esophageal cancer.** Esophagitis and other esophageal events have been reported with oral bisphosphonate use, particularly in patients who fail to follow specific directions for use. The FDA has notified healthcare professionals about its ongoing review of clinical studies to evaluate whether use of oral bisphosphonate drugs is associated with an increased risk of cancer of the esophagus. There has been no change in product labeling to date. [DSQ](#)

**In the News** continued from cover

**Poor Adherence to Medications can result in up to \$290 billion in medical expenses per year**



\*Cutler D, Everett W. N Engl J Med 2010; 362:1553

**Helping patients simplify complex prescription regimens.**

Wolf and colleagues from Northwestern University Feinberg School of Medicine conducted structured interviews with 464 adult patients followed in academic and local health centers. Participants were given a hypothetical, 7-drug medication regimen and asked to demonstrate how and when they would take all of the medications in a 24-hour period. Ideally, the medications would be taken in four sessions during the 24-hour period. On average, participants identified six times in 24 hours when they would take the seven drugs. Fully 29% of participants said they would take the medication doses seven or more times per day. Two drugs had the same instructions but 31% administered these differently. Drug dosing frequency was linked to low literacy and educational levels. Patients varied widely in their ability to dose medications efficiently. This study highlights prevalent patient confusion surrounding medication use and the need to educate patients on simplified and effective dosing regimens. (Arch Intern Med. 2011 Feb 28;171:300-5. PMID: 21357804) [DSQ](#)

## Drug Shortages\*

Updated	Drug	Reason	Est. Time for Resupply
6/17/11	Cyclophosphamide Inj (Baxter) 500, 1000, 2000 mg vials	Manufacturing delays	On allocation
7/6/11	Trazodone tablet 50, 100, 150 and 300 mg	On back order	August 2011
7/19/11	Dexamethasone Injectable 4 mg/mL and 10 mg/mL	Drug recalled due to presence of particulate matter. Increased demand has drug on backorder	Manufacturers will release as it becomes available (probably August 2011)
6/7/11	Gold Sodium Thiomalate Inj 50 mg/mL, 10 mL vials	Raw material shortages	Unknown
7/14/11	Methotrexate Inj 25 mg/mL 2, 4, 10, and 40 mL vials	Preservative free MTX recalled by 1 manufacturer and discontinued by another	Mid-late June 2011
7/18/11	Zostavax (shingles) vaccine	Shipping delays and raw material production	Shipments approx. 3 months after order
6/2/11	Mycophenolate oral suspension	Backorder	unknown
6/24/11	Leflunomide Tablets 10, 20 mg	Unavailability of raw materials and increase demand	Possibly mid-July

\* reported by the American Society of Health-System Pharmacists ([www.ashp.org/drugshortages](http://www.ashp.org/drugshortages))

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## SAFETY SIGNALS: REFERENCES & REVIEWS

Compiled by Kathryn H. Dao, MD and John J. Cush, MD from the Baylor Research Institute, Dallas TX

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