Wound Healing and Anti-Rheumatic Agents

Susan M. Goodman\(^1\), Miguel Perez-As\(^2\) and Bruce N. Cronstein\(^2\)

\(^1\)Hospital for Special Surgery, Department of Medicine; \(^2\)New York University School of Medicine, Department of Medicine, Division of Translational Medicine

Patients with rheumatoid arthritis (RA) are often on multiple medications to control disease activity and these medications may have significant toxicities, including effects on wound healing. Deep surgical site infections are of particular concern when prostheses such as arthroplasties are implanted, given the morbidity, mortality, and expense associated with prosthetic joint infection. Wound healing complications, including prolonged drainage or superficial infection, are highly associated with deep surgical site infection, so medications which delay wound healing following elective surgery are particularly worrisome\(^{(2)}\). However, active RA also confers an increased risk for infection\(^{(2)}\) and slows post-operative mobilization, so perioperative management strategies must balance the risks. Because poor wound healing often leads to infection (e.g. up to 50% of diabetic foot ulcers will become infected\(^{(2)}\), and infection often contributes to delayed wound healing) it is often difficult to disentangle infection from poor wound healing in the postoperative period. This review will concentrate on the effects of anti-rheumatic therapy on wound healing, and identify those effects which are well documented versus those which are less well studied. This review will not address the effects of therapy on fracture healing.

Healthy wound healing proceeds through an inflammatory phase, followed by wound remodeling and finally re-epithelialization, normal stages of wound healing which are blunted by systemic corticosteroids in both patients and animal models\(^{(2,4,5)}\). Although the corticosteroid doses used in RA are usually low, even low dose corticosteroid therapy confers an increased infection risk, and duration of therapy, frequently prolonged in RA, also contributes to infection risk\(^{(2)}\). The increase in risk of infection associated with corticosteroid use has been demonstrated in multiple surgical contexts \(^{(7)}\). However, the clinical distinction between slowed wound healing and surgical site infection can be difficult and the clinical literature often makes little distinction between poor wound healing and wound infections. Moreover, the contribution of disease activity to infection risk in the post-operative period has not been studied.

Patients may be taking analgesic, anti-inflammatory, biologic or synthetic disease-modifying antirheumatic drugs (DMARDs) to manage their systemic disease-raising concerns with respect to wound healing problems\(^{(8)}\). With the exception of methotrexate, there are few prospective controlled studies addressing the effects of these medications on infection and wound healing in the perioperative period. Recommendations for medication management are frequently made based on retrospective series\(^{(9)}\) or large data base studies regarding the incidence of infection rates and risk factors\(^{(10,11)}\). Here, we provide a careful synthesis of the available data regarding wound healing risk.

Methotrexate is the most commonly used DMARD in RA, and its anti-inflammatory activity is likely due to multiple mechanisms with the best documented being increased extracellular adenosine levels\(^{(12)}\). Currently methotrexate is usually administered as the initial remittive agent and patients tend to remain on methotrexate longer than other DMARDs. The question of methotrexate safety during the perioperative period has been addressed in prospective studies which support the practice of continuing methotrexate during the perioperative period without an increase in infection or wound healing complications. In a prospective randomized controlled trial of 388 MTX treated RA patients undergoing orthopedic surgery, those who continued MTX had an infection and orthopedic complication rate of 2%, while those who discontinued MTX had an infection and orthopedic complication rate of 15%. These cases were additionally compared to 228 not on MTX at the time of surgery, who had an infection and surgical complication rate of 10.5%. Joint flares were also increased in the patients who were not taking perioperative methotrexate\(^{(13)}\). These findings were confirmed in two small prospective studies\(^{(14,15)}\).

Letter to the Editors

Dear DSQ,

I was told that there were reported anaphylactic reactions to Prolia injections recently. I spoke to our rep and medical liaison who could/would not answer two specific questions: 1. How many patients were reported with this reaction? 2. How many died?

- Joshua Stolow, M.D., San Antonio Arthritis Care Centers

In July 2013 the FDA issued a MedWatch update of denosumab’s (Prolia) labeling to include clinically significant hypersensitivity warnings, including anaphylaxis. No additional information was given on the FDA website. Two other sources (AdverseEvents.com and DrugCite.com) noted that as of 8/27/12 there were 4230 reports of serious adverse events ascribed to Prolia; the top three

see Letter to the Editors, page 8

Send letters to DSQ@rheumatology.org
In a retrospective review of 725 foot and ankle procedures in 104 patients with RA with an overall complication rate of 32%, there was no statistical association of wound or infectious complications with use of corticosteroids, methotrexate, or hydroxychloroquine[20]. Thus, the clinical data that address wound healing in patients with RA treated with methotrexate suggests no significant increase in healing complications although lack of a consistent clinical definition for differentiation of pathologic wound healing from infection hampers the interpretation of these studies. Taken together, current data suggests that methotrexate can be continued in the perioperative period to avoid flare, without impairing wound healing or increasing the infection risk.

In contrast to methotrexate there is relatively little information on the risks of continuation of other DMARDs and the biological agents in the perioperative period[8,19]. There are no randomized studies addressing perioperative complications in RA patients treated with other commonly used antirheumatic drugs, including hydroxychloroquine, leflunomide, azathioprine or sulfasalazine. Thus any and all recommendations on these agents are drawn from case series and retrospective studies. Although not studied in a surgical setting, hydroxychloroquine has an extremely favorable toxicity profile and consensus considers hydroxychloroquine to be safe to use in the perioperative period as it is not a potent immunosuppressant. Two small, uncontrolled series describe leflunomide patients undergoing orthopedic surgery with different results. While 41 leflunomide-treated RA patients undergoing orthopedic surgery in one study suffered no increase in post-operative infections[20], a second series of 32 leflunomide-treated patients reported an increase in wound healing complications[20]. As no standard definition has been applied, clinical differentiation of infection vs. wound healing hampers our analysis, as noted above. As the concomitant use of corticosteroid, leflunomide, and methotrexate has been reported to heighten infection risk[20], leflunomide is often withheld prior to surgery. When patients on leflunomide fall into a higher risk group due to other co-morbidities or medications, cholestyramine can be given 8 grams BID-TID for 5–11 days to accelerate drug elimination, with the higher dose regimen effecting a more complete washout. Although unstudied in this context, other immunosuppressant medications such as azathioprine and mycophenolate mofetil are frequently withheld prior to surgery as well.

The data assessing anti-TNF agents and wound healing are conflicting and comprise a mixture of large database studies and small retrospective and prospective studies in RA[8]. Similar to DMARDs other than methotrexate, we lack data on the perioperative safety of anti-TNF agents with regard to wound healing. Moreover, animal and experimental studies reveal conflicting effects of TNF-α on wound healing and only a few small studies address the use of TNF-α antagonists in patients with RA [reviewed in[19]]. In one small prospective study of foot and ankle surgery in patients with RA 31 patients were prospectively followed: 16 patients in the study were treated with TNF inhibitors, and had no increase in wound healing or infectious complications[20]. However, as noted above, delayed wound healing is associated with an increased risk of infection and clinical studies rarely differentiate between wound healing and surgical site infection. Unsurprisingly, given the paucity of high quality data, rheumatology associations from different countries offer different recommendations, largely basing the recommendations on the reduction of perioperative infection. The French Society of Rheumatology has issued some extremely conservative guidelines suggesting prolonged drug withdrawal for perioperative use of TNF-α antagonists, with resumption of therapy after complete wound healing assuming the absence of infection[20]. Similarly, the British Society of Rheumatology recommends that treatment with infliximab, etanercept, and adalimumab should be withheld 2 to 4 weeks prior to major surgical procedures and they recommend restarting treatment when wound healing is satisfactory and there are no signs of infection[20]. The American College of Rheumatology recommends withholding TNF-α antagonists for >1 week (one drug dosing cycle) before and after surgery until the wound has healed without signs of infection, a recommendation which provides a practical framework permitting vigilance in wound care without prolonged drug withdrawal which can increase the risk of disease flares. The differing recommendations reflect the lack of clear randomized control trial data on which to base recommendations and available data do not allow more definitive conclusions about the use of TNF-α antagonist perioperatively. This difficulty in developing accurate guidelines is further complicated by the different risks of infection and poor wound healing posed by different surgical procedures. As described above, there is significant clinical difficulty in separating poor wound healing from wound infections.

There is surprisingly little data on the effect of NSAIDs on wound healing in rheumatic diseases patients who have undergone surgery. A recent systematic review on this subject suggests that there is little effect of NSAIDs on healing of soft tissues after sports injury or surgery but that NSAIDs do interfere with bone healing and should be avoided[20].

In summary, with the exception of methotrexate, there is a lack of data regarding optimal practice for perioperative management of antirheumatic treatment in RA patients undergoing surgery. Existing data, however, indicates that methotrexate may be continued throughout the perioperative period for otherwise healthy individuals. For the other anti-rheumatic drugs, while continuing medication may hamper wound healing and predispose to infections, discontinuation may lead to disease flare, which increases the need for corticosteroids or other medications that may also increase the risk for inadequate wound healing and infection to regain disease control. Moreover, there is no consensus among the various rheumatic disease societies regarding optimal practice. Although there are clear effects of anti-rheumatic therapy on wound healing and clear infection risk, the role of RA inflammatory activity on wound healing, infection, and rehabilitation should also be considered. For surgeries such as the implantation of a prosthetic joint, where surgical site infection carries significant morbidity, current practice favors a conservative approach.

Methotrexate does not affect wound healing after joint surgery. But there is minimal information on the effect of DMARDs and biologics on post-op wound healing.

Table 1. Drug Effects on Wound Healing

<table>
<thead>
<tr>
<th>Anti-rheumatic Rx</th>
<th>Effect on Wound Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Effect</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>X</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>X</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>X</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>X</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>X</td>
</tr>
<tr>
<td>TNF inhibitors</td>
<td>X</td>
</tr>
</tbody>
</table>

References
TNF inhibitors and Severe Hepatic Injury

Marked elevations of liver function tests are rarely encountered in patients receiving TNF inhibitors. CORRONA analyzed 6861 rheumatoid arthritis patients and found that 6.9% had any elevation of LFTs but <1% had greater than 2 fold elevations of LFTs. In their cohort elevations were more likely with infliximab and less likely with etanercept.

In a 2003 FDA arthritis advisory committee meeting the FDA reported its review of 134 reports of liver failure seen with TNF inhibitors. While minor elevations of AST/ALT were seen in 29-42% of patients in the ATTRACT (RA) and ACCENT I (Crohn's) trials, extreme elevation (>5 fold elevations) was rare. The Medwatch AERS database revealed 134 reports of liver failure seen with TNF inhibitors. Analyses of the Medwatch database, continuous leflunomide treatment on the incidence of infectious complications after joint arthroplasty in patients with rheumatoid arthritis. The Journal of Rheumatology 20, 1129-1132. PMID:16731943

Table. Package Insert Data on >3 fold ALT Elevations with TNF inhibitors

<table>
<thead>
<tr>
<th>TNF inhibitor</th>
<th>RA, PaA, AS</th>
<th>Crohn's disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TNFi</td>
<td>PBO</td>
<td>TNFi</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>3.5%</td>
<td>1.5%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Infliximab</td>
<td>4-10%</td>
<td>0-3%</td>
<td>2%</td>
</tr>
<tr>
<td>Golimumab</td>
<td>2%</td>
<td>2%</td>
<td>ND</td>
</tr>
</tbody>
</table>

Abbreviations: TNFi - TNF inhibitor; PBO- Placebo; x ULN- times the upper limit of normal; ND- no data included.

References
**EULAR 2013 Safety Update**

**TNF inhibitor therapy lowers risk of type II diabetes.** A CORRONA study (Lillegaven OP0161) of 21,775 RA patients showed that TNF inhibitor therapy was associated with a 65% reduced risk of type II DM (HR 0.35).

**TB risk is even higher with TNFi + MTX.** In a pooled analysis of 86 clinical trials involving RA, PsA, psoriasis, IBD and AS patients treated with either adalimumab, infliximab or certolizumab, 0.2% developed incident TB. TNFi alone increased the odds ratio to 9.9, the combined use of TNFi and MTX increased the OR to 49.8 (Bruzese, et al #OP0070).

**Rheumatoid arthritis and Pregnancy outcomes.** RA patients were shown to have increased rates of miscarriage (Wallenius M, #SAT0532) and infertility, with the latter being associated with high disease activity, NSAID and prednisone use (Brouwer J, #FR1045).

**Tofacitinib and Severe Lymphopenia.** van Vollenhoven (THU0252) showed that lymphopenia with absolute lymphocyte counts <1500 ALC occurred in 35-39% of 3252 patients in Phase 3 trials in RA. ALC of 500-1500 was not associated with a risk of serious infections, although ALC <500 occurred in 0.2-0.3% of patients and all developed infection but only one-third had serious or opportunistic infections.

**Safety of Anti-osteoporosis Medications**

intake of calcium above 800-1200 mg. Daily supplements of 1000 mg in patients with dietary intake of 800-1000 mg have been associated with an increased risk of kidney stones and a 30-40% increased risk of cardiovascular events in some but not all studies. Vitamin D intake of >10,000 units daily may cause hypercalcemia and hypercalcuria. Serum concentration of 25-hydroxyvitamin D of more than 50 ng/mL has been associated with an increase overall in cancer-related mortality. The Institute of Medicine suggests that 4000 units daily is the upper limit of safety.

**Salmon Calcitonin:** Weak evidence linking therapy to cancer risk resulted in the drug being withdrawn from European market.

**Raloxifene:** Excess venous thrombotic events occurred in 0.7% of patients over 3 years, usually within first months of therapy and perhaps more commonly in women with previous thrombotic events. Discontinue therapy 72 hours before episodes of immobilization. There was no effect on overall incidence of cardiovascular disease, but increased risk of death following stroke was observed. Muscle cramps may also occur.

**Teriparatide:** Serum calcium increases transiently after dosing. Persistent hypercalcemia is infrequent. Muscle cramps may occur. Treatment of patients on glucocorticoids for up to 3 years was not associated with untoward effects. However, therapy is limited by regulation to 24 months in the United States (18 months in Europe). High dose, long term treatment induced osteosarcoma in rats. Although a few patients who received teriparatide may have developed osteosarcoma, the estimated incidence does not appear to exceed that expected in untreated older adults. Avoid use in adolescents, Paget’s disease or skeletal metastases or with history of radiation therapy to skeleton.

**Denosumab:** This subcutaneously injected anti-RANK ligand monoclonal antibody was associated with eczema (3% versus 1.2% with placebo) and cellulitis requiring hospitalization during the 3 year FREEDOM study. These skin disorders were not related to the injection site or to the timing of injection and did not increase in frequency with longer therapy. Hypocalcemia can occur, especially in patients with osteomalacia.

**Bisphosphonates:** In clinical trials, oral and intravenous bisphosphonates have been well tolerated. Upper GI intolerance, usually mild or moderate, is observed in daily practice, especially if the tablets are taken incorrectly. GI bleeding, esophageal ulceration or rupture, and inflammatory eye disease (uveitis, iritis) have been reported very rarely. Acute phase reaction occurs with IV or high dose oral dosing. Bone and muscle pain, not observed in the clinical trials, has been reported. Both the incidence and mechanism of this potential side effect is unknown. Hypocalcemia can occur, especially in patients with osteomalacia. Renal failure is reported in clinical practice with intravenous zoledronic acid which is contraindicated in patients with estimated GFR <35 cc/min. Atrial fibrillation associated with hospitalization but not temporally related to the annual dose occurred more frequently (1.3%) with intravenous zoledronic acid compared to placebo (0.5%) in the HORIZON Pivotal Fracture Trial. However, the incidence of atrial fibrillation, other arrhythmias or cardiac events and stroke was similar between treatment and control groups. After review of all bisphosphate studies, the FDA concluded that a causal link between bisphosphonate therapy and atrial fibrillation has not been established. Cases of esophageal cancer have been reported in patients who took oral bisphosphonates. No evidence of this association was observed in placebo-controlled clinical trials or in several observational cohorts. One of two analyses (but not the other) of the UK General Practice Research Database suggested an increased risk of esophageal cancer (3% vs 2.3% in controls), and especially with treatment for >5 years (relative risk 2.24, 1.47 to 3.43). The FDA has stated that evidence is insufficient to evaluate this association. In contrast, decreased mortality and risks of breast, prostate, colon and pancreatic cancer have been reported with bisphosphonates in observational and, for mortality, in randomized controlled trials.

ONJ is primarily observed in patients receiving high dose intravenous therapy for cancer-related bone diseases. The incidence in patients treated for osteoporosis is very low with estimates ranging from 1:4000 to 1:250,000. A causal link between oral bisphosphonates and ONJ has not been established, and minimal evidence exists suggesting a relationship between the risk and duration of therapy. Fractures of the femoral shaft with “atypical” features suggesting a brittle bone-type fracture are observed with long-term therapy (average duration 7 years). Two studies suggest that risk increases with long-term therapy, the risk being 2, 20 and about 100 per 100,000 patients after 2, 5 and 8-10 years, respectively. Atypical fracture risk appears to decrease within 1-2 years after stopping therapy. Interruption of treatment for 1-3 years is recommended for patients at modest fracture risk after 3-5 years of treatment. Patients still at high risk of fracture after that interval of treatment benefit from continued therapy. In my opinion, most patients may be candidates for a “drug holiday” after 10 years of therapy.

**Strontium ranelate:** This drug is widely available except in North America and was associated with a modest increase in venous thrombotic events in clinical trials. Rare but very serious skin disorders have been observed in postmarketing surveillance. Recent evidence links strontium ranelate therapy with increased cardiovascular risk, leading European regulatory authorities to limit the use of this agent.

Continued on page 8
**FDA MEDWATCH: Fall 2013**

**Fluoroquinolones and Risk for Permanent Nerve Damage.** The FDA required drug labels of all oral and intravenous fluoroquinolone antibiotics updated to reflect the serious side effects of peripheral neuropathy. The warnings came after review of data from the FDA Adverse Event Reporting System (AERS). The onset of neuropathy is rapid, occurring within days of starting the fluoroquinolone and can occur at any time during treatment with the drug and can last months to years after discontinuation, in some cases, the condition can be permanent. About 23.1 million unique patients received an oral fluoroquinolone from retail pharmacies in 2011. (posted 8/15/13)

**Acetaminophen Associated with Risk for Serious Skin Reactions.** Through the FAERS database and medical literature, new information suggest that Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGED) have been associated with acetaminophen. These reactions are rare but can be fatal, occurring with first-time use or at any time the drug is taken. Healthcare workers should be aware of this rare risk associated with acetaminophen. Given the new information, the FDA will require that a new warning be added to labels of OTC acetaminophen drug products as well as prescription drug products containing acetaminophen. (Posted 8/2/13)

**Ketacozole (Nizoral) tablets and Risk for Adrenal Insufficiency, Fatal Liver Injury.** The FDA warns that oral ketacozole should not be a first line treatment for any fungal infection and has taken several actions to limit the drug’s use, including a revised boxed warning stating the drug is contraindicated in patients with liver disease and included new recommendations for monitoring liver function. In addition, adrenal function should be monitored in patients who are at risk for adrenal insufficiency (major surgery, intensive care, prolonged steroid use, etc). Topical formulations have not been associated with the above adverse effects. (Posted 7/26/13)

**Olmesartan Medoxomil and Sprue-like Enteropathy.** The FDA found clear evidence that olmesartan, an angiotensin II receptor blocker (ARB) blood pressure medicine marketed as Benicar, Azor, and Tribenzor can cause sprue-like symptoms including, severe, chronic diarrhea and weight loss. 23 cases were identified in the FAERS database; patients presented with late-onset diarrhea, significant weight loss, and in some cases have intestinal villous atrophy on biopsy. Symptoms develop months to years after starting olmesartan, some required hospitalization. All patients improved after discontinuation of the drug, and in 10 cases, a positive re-challenge was seen. In 2012, the Mayo Clinic published a case series of 22 patients with similar findings whose clinical symptoms improved after discontinuation of olmesartan; 18 patients had follow-up intestinal biopsies which showed clinical recovery. Another case series was reported in May 2013, patients had negative serologies for celiac disease but were found to have villous atrophy associated with olmesartan use. The signal of sprue-like enteropathy was further investigated for ARB class effects by the Mini-Sentinel and CMS Medicare database; olmesartan had a higher rate of association with celiac disease than other ARBs. Mechanism for olmesartan-associated sprue-like enteropathy is unknown but delayed symptom latency and findings of collagenous colitis along with high association with HLA-DQ2/8 suggest a localized delayed hypersensitivity or cell-mediated immune response to the drug. TGF-B inhibition by ARB is being explored as a possible mechanism; as TGF-B is considered an important mediator of gut homeostasis. (Posted 7/3/13)

**Sulfasalazine (SSZ) and Neural Tube Defects –** The FDA is reviewing reports of babies with neural tube defects born to mothers who take SSZ during pregnancy, though the role of this drug in these defects is not established, it is speculated that oral sulfasalazine can inhibit the absorption and metabolism of folic acid. A national survey evaluated the outcome of pregnancies associated with inflammatory bowel disease (IBD). In a group of 186 women treated with sulfasalazine, the incidence of fetal morbidity and mortality was comparable to untreated IBD pregnancies and pregnancies in the general population. A study of 1,455 pregnancies associated with exposure to sulfonamides indicated that this group of drugs, including sulfasalazine, did not appear to be associated with fetal malformation. No clinical studies have evaluated the effect of sulfasalazine on the growth development of children whose mothers received the drug during pregnancy. SSZ remains a pregnancy category B. (posted July 2013)

**Immunoglobulin (IVIG, subcutaneous IG, intramuscular IG) -** new boxed warnings were added after more data indicated risk for thrombosis with immunoglobulin products. Retrospective data analysis of a large health-claims database and post-marketing events noted thrombosis regardless of route of administration. Risk factors for thrombosis included: advanced age, prolonged immobilization, hypercoagulable conditions, h/o venous/arterial thrombosis, use of estrogen, indwelling vascular catheters, but can occur without these risk factors. Adequate hydration is advised before administration (Posted June 2013)

**Trimethoprim-Sulfamethoxazole (TMX-SMX, Bactrim)-** The FDA published new warnings that severe and symptomatic hyponatremia can occur, particularly when using this drug for the treatment of Pneumocystis jiroveci pneumonia (PJP) pneumonia. In addition, the label will also reflect a warning of increased congenital malformations, particularly neural tube defects and cardiovascular malformation, urinary tract defects, oral clefts, and club foot. Patients should be advised of potential hazards during pregnancy. Pregnancy labeling: category D. (Posted July 2013)

**Editor’s note:** Several studies have looked at hyponatremia and hyperkalemia associated with TMP-SMX use and found that the drug can affect the distal renal tubules affecting electrolyte balance. This effect has been described in granulomatosis with polyangiitis (GPA) patients prophylactically given TMP-SMX for PJP prophylaxis. Patients with renal dysfunction and those who receive higher doses of the drug have greater risk for hyponatremia/hyperkalemia and should be regularly monitored for electrolyte disturbances. PMID: 12924488

**Lupron (leuprolide) -** new warnings were added after the FDA reviewed post-marketing reports of convulsion in patients receiving leuprolide. Those at highest risk include patients with history of seizures, epilepsy, cerebrovascular disorders, CNS anomalies or tumors, and patients taking concomitant bupropion/SSRI. (Posted July 2013)

**Nifedipine (Procardia) -** label changes reflect that nifedipine is transferred through breast milk and should be avoided in breast feeding women. The drug remains a Pregnancy category C. (Posted July 2013)

**Doxycycline -** post-marketing reports of pseudotumor cerebri had been noted by the FDA. (Posted July 2013)

**Aldactone (spironolactone) -** warnings and precautions added to the labeling that concomitant administration of Aldactone with the following drugs may lead to severe hyperkalemia: NSAIDs, heparin, ACE inhibitors, ARB, aldosterone blockers. Hyperkalemia metabolic acidosis has been reported in patients who receive aldactone concurrently with cholestyramine. (Posted June 2013)
IN THE NEWS: Fall 2013

Electronic Health Record (EHR) Identifies Drug Safety Issues Before National Alerts Are Issued. Not all safety issues with new drugs are identified before they are marketed due to small study sizes, heterogeneity of study populations, and short duration of follow-up. Stanford University recently published their success in a computer algorithm to allow doctors to differentiate between drug adverse events (AE) from another illness. The algorithm was tested on a database of patient and physician AE reports from the FDA and confirmed with the EHR records of patients at Stanford. One example analysis examined arrhythmias and deaths due to drug interactions between SSRIs and thiazides and showed that patients on the combination are more likely to experience prolonged QT intervals compared to those on other combinations. With the new tool, 1300 AE from more than 59,000 pairs of drugs were identified. Similar research from Vanderbilt University reviewed lab results from patients receiving a particular medication compared to those who did not. Results confirmed previously reported adverse drug reactions and allowed for detection of new ones; their tool showed high correlation with 77% precision and 61% recall. In addition, internet search patterns by patients have also been used as means to flag drug interactions. Researchers from Microsoft, Stanford, and Columbia University examined logs of patient queries entered into Google, Microsoft, and Yahoo search engines looking for side effects. They found strong signals for combination paroxetine with pravastatin which later, the pair was reported to cause hyperglycemia. (FierceEMR 2013)

Opioid Knowledge Lacking in Healthcare Providers. The Pennsylvania Patient Safety Authority published a study looking at medication errors related to knowledge deficits regarding opioids in prescribers. Serious AE related to opioid errors ranged from allergic reactions, failure to control pain, oversedation, respiratory depression, seizures and death. Morphine, hydromorphone, meperidine, and fentanyl are drugs highly associated with patient harm. To decrease these errors, an opioid knowledge assessment tool was developed for prescribers, pharmacists, and nurses. The questions covered differences between opioid naive vs. tolerant patients, indications for long-acting opioids, comparative dosing between opioids, patient specific conditions requiring lower starting doses, impact of concomitant medications used in combination with opioids, and opioid monitoring. The assessment tool was administered to 2000 practitioners; results indicated that lowest scoring questions involved predictors of respiratory depression, defining the opioid tolerant patients and drug interactions that can potentiate the effects of opioids. The study findings suggest a greater need for education about opioids among healthcare providers. The assessment tool can be found at: http://www.patientsafetyauthority.org/EducationalTools/PatientSafetyTools/opioids/Documents/assessment.pdf (Pa Patient Saf Advis 2013)

European Medicines Agency (EMA) Recommended Precautions with Diclofenac. The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) concluded that diclofenac, particularly in high doses (e.g. 150 mg/day) and in longterm treatment, has similar cardiovascular risk as selective COX-2 inhibitors after reviewing data generated by independent academic research, including one called The Safety of Non-Steroidal Anti-Inflammatory Drugs (SOS), set up and funded by the European Commission’s 7th Framework Programme in 2012. The agency recommended precautions to minimize the risk for arterial thrombotic events: a) patients who have serious underlying cardiovascular diseases, such as heart failure, heart disease, circulatory problems, previous heart attack or stroke, should not use diclofenac b) patients with certain cardiovascular risk factors (e.g. hypertension, hyperlipidemia, diabetes or smoking) should only use diclofenac after careful consideration. Healthcare professionals were advised to periodically re-assess the need for patients to continue taking the medicine. PRAC concluded that the benefits of diclofenac still outweigh the risks. (European Medicines Agency June 2013)

Fostamatinib Drug Development Halted. Astra-Zeneca announced it would not pursue regulatory approval for the Syk-kinase inhibitor fostamatinib. Although early trials showed promise, subsequent randomized clinical trials failed to show competitive improvements in ACR20 response rates for patients participating in the OSKIRA-2 (DMARD incomplete responders) and the OSKIRA-3 (TNF inhibitor partial responder) trials. The toxicity profile was consistent across several studies with diarrhea, hypertension, headache and URI as the most common events reported. Astra Zeneca will return drug rights to Rigol Pharmaceuticals (who originally developed the compound) for further consideration. (NASDAQ.com June 2013).

Tofacitinib Application Denied by EMA. In April Pfizer announced that its application for regulatory approval of Xelijanz (tofacitinib) was negatively viewed by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP). CHMP noted concerns regarding safety (serious infections, GI perforations, lipid elevations, certain malignancies) and the consistency of reductions in disease activity and structural damage – especially for the 5 mg dose proposed. The EMA re-examined this decision and on July 25, 2013 confirmed the refusal of the marketing authorization of tofacitinib, stating its major concerns were over safety issues. (European Medicines Agency July 26, 2013)

FDA Allows Updates of Generic Drug Warnings. Two years ago the Supreme Court ruled that inadequate labeling of a generic drug was not just cause for a lawsuit against the maker. Branded drugs are liable if the product’s safety label is inadequate. Given the regulatory gap, the watchdog group, Public Citizen had lobbied for making generic and brand-name producers equally responsible for updating safety labeling. Under current rules, brand-name makers can update safety labels without FDA approval, while generics are restricted from this activity unless certain criteria are met, such as when ordered by the FDA or if the brand name equivalent has already made similar changes. However, 434 generic drugs have no comparable brand-name product, and 80% of prescriptions filled in the U.S. were for generic drugs according to Public Citizen. The FDA announced in July 2013 that generic drug manufacturers now have permission and responsibility to change safety labels when new potential risks are uncovered. (USA Today July 2013)

Drug Safety Information for Pregnant Consumers Hard to Find. Women often use the Internet to find answers related to medication safety during their pregnancy, but a new study conducted by the Centers for Disease Control and Prevention (CDC) examining 25 pregnancy related websites found discrepancies in lists that were supposedly safe. Twenty-two products called safe by one site were deemed risky by another. In addition, there was lack of evidence to support the safety claims for 40% of drugs. The CDC noted that medication use has increased 60% in the last 3 decades during the 1st trimester, a time when developing fetal organs have the greatest vulnerability for birth defects. The CDC is initiating a “Treating for Two” program to improve pregnancy drug safety information; the FDA will also revamp prescription drug labels with updated information on pregnancy and will tighten control on drugs that pose pregnancy risks. Several barriers to accurate information exist. Drug manufacturers shy from studying pregnant women, hence, safety data can take years to accumulate; in addition, 1 in 33 babies will have some type of birth abnormalities regardless of medication use. Unfortunately, Clinicians and patients will have to balance risk to the mother for not taking the medication vs. risk to the fetus off of medications given the limited available data. (Associated Press Mar 2013)

Sleep Aids Will Have to Demonstrate Safety with Next Day Driving. The FDA had taken interest in how safely sleep aids will allow people to wake up. The effects of common sleep aids can last into the next day, and of concern is how safely people can drive the next morning. The FDA recently rejected an application by Merck for the new sleep drug, suvorexant, because...
IN THE NEWS: Fall 2013 continued from previous page

tests showed that some people had trouble driving the next day. In May 2013
the agency warned patients taking common allergy drugs like Benadryl not to
drive, and in January, the FDA posted warnings that zolpidem dose should be
reduced by half in women. They are now taking a closer look at all sleep aids
on the market and will ask manufacturers to conduct extensive driving tests
for new sleep drugs and any drug that can cause drowsiness. Sixty million
prescriptions for sleep aids were distributed last year, almost 5% of daytime
drivers tested positive for prescription or over the counter drugs that can

Quick Drug Approvals Do Not Impact Safety. In a new research study
published in Canadian Health Policy, data about the number of drug safety
warnings issued by regulators in Canada and U.S. were compared to number of
discontinuation of new drugs related to safety concerns. In the analysis, 454 new
drugs were approved in Canada and U.S. over a 20 year period (1992-2011); new
drug approval times were faster in the U.S. but were not linked to an increased in
issuance of regulatory safety warnings or withdrawal of drug. In addition, rates
of discontinuation were lower for expedited approval drugs than for standard
products, opposite of what would be expected if faster approvals led to more
dangerous drugs approved. The study strongly suggests that changes in the
regulatory behavior of drug approval agencies offer a better explanation for
the increased number of serious warnings than from expedited drug approval.
(Drug Discovery and Development 8/15/13)

Safety Signals: September 2013

Trends in the use of aspirin and nonsteroidal anti-inflammatory drugs in the
general U.S. population. Zhou Y, et al. Pharmacoepidemiol Drug Saf. 2013 May 30. [Epub ahead of print] PMID: 23723142. National Health Interview Survey (NHIS) showed an increase in regular use to 43 million US adults (19.0%) and NSAIDs to more than 29 million adults (12.1%), representing a 57% and 41% increase use (respectively) from 2005 to 2010.

GI-REASONS: a novel 6-month, prospective, randomized, open-label, blinded endpoint (PROBE) trial. Cryer B, et al. Am J Gastroenterol. 2013;108:392-400. PMID: 23399552. Prospective, open-label trial of 8,067 adults requiring NSAIDs for OA demonstrated fewer clinically significant upper and/or lower GI events in patients taking celecoxib (1.3%) versus nonselective-NSAIDS (2.4%) (P = 0.0003).

Vascular and upper gastrointestinal effects of non-steroidal anti-
inflammatory drugs: meta-analyses of individual participant data from randomised trials. Luntz 2013 May 29. [Epub ahead of print] PMID: 23726390. Metaanalyses of 754 clinical trials and 363,809 patients demonstrated that all NSAIDs increased the risk of upper gastrointestinal complications and heart failure. Compared to placebo, of 1000 patients treated with a coxib or diclofenac (but not naproxen) for one year, three more had major cardiovascular events (including one fatal). Vascular death was increased significantly by coxibs and diclofenac, but not by ibuprofen or naproxen.

Nonsteroidal anti-inflammatory drugs and risk of cardiovascular
disease in patients with rheumatoid arthritis: a nationwide cohort study. Lindhardt J, et al. Ann Rheum Dis. 2013 Jun 8 [Epub]. PMID: 23746810. Cardiovascular events were lower in RA patients receiving NSAIDs (compared with non-RA on NSAIDS) in a Danish national registry of 17320 RA patients and 89280 matched controls. However, higher CV event rates were seen with rofecoxib and diclofenac.

Statin toxicity from macrolide antibiotic coprescription: a population-

The risk of gastrointestinal perforations in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the BSRBR-RA. Závada J, et al. Ann Rheum Dis. [Epub ahead of print]. PMID: 23644671. Gastrointestinal perforations (GIP) were not increased in TNF inhibitor treated RA (n=11881) patients in the British Society for Rheumatology Biologics Register. However, steroids were shown to be a major risk factor for lower GIP (HR 8.0, 95% CI 2.6 to 24.1).

Use of glucosamine and chondroitin supplements and risk of colorectal
cancer. Kantor ED, et al. Cancer Causes Control, 2013; 24:1137-46. PMID: 23529472. Using surveys on supplement use in 75,137 Washington state residents aged 50-76 yrs, the use of glucosamine + chondroitin on 4+ days/week for >3 years was associated with a trend towards a lower risk of colorectal cancer (HR: 0.59, 95% CI 0.30-1.01). The use of glucosamine alone was not protective.

Is cancer associated with polymyalgia rheumatica? A cohort study in the General Practice Research Database. Muller S, et al. Ann Rheum Dis 2013. [Epub] PMID: 23842460. The incident risk of cancer was shown to be increased in PMR patients treated with corticosteroids only in the first 6 months after diagnosis; with an adjusted HR of 1.69 (95% CI 1.18 to 2.42).

Nonsteroidal anti-inflammatory drugs in late pregnancy and persistent


Primary care attitudes to methotrexate monitoring. Byng-Maddick R, et al. Qual Primary Care 2012;20:443-7. PMID: 23540824. In a UK survey of general practitioners about MTX use, 36/81 practices responded and showed that MTX use occurred in 1/743 practice patients. All GPs wrote MTX prescriptions, but only 77.4% monitored MTX levels. Roughly half were aware of local and national guidelines and one-third claimed to not need further education on MTX use.

Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAFety Assessment of Biologic ThErapy (SABER) Study. Baddley JW, et al. Ann Rheum Dis. 2013 Jul 13. [Epub ahead of print] PMID: 23852763. Using several administrative claims databases and 33,324 new TNFI users - 80 non-viral opportunistic infections were found with pneumocystosis (n=16) as the most common. Overall non-viral OI were slightly increased by corticosteroids and new TNFI use, especially infliximab.

Improvement in safety monitoring of biologic response modifiers after the implementation of clinical care guidelines by a specialty. Hanson RL, J Manage Care Pharm 2013;19:49-57. PMID: 23863700. As standardized guidelines for the monitoring of BRMs have not been established, the University of Illinois developed multidisciplinary Clinical Care Guidelines for BRMs, which included prebiologic TB test, HBsAg, LFTs, CBC, vaccination review and update, cancer screening, transfusion guidelines and one-third claimed to not need further education on MTX use.

Vol. 4 (3)
Fall 2013

drug safety quarterly

a n o n l i n e p u b l i c a t i o n o f t h e A C R D r u g S a f e t y C o m m i t t e e

7
**Letter to the Editors** continued from page 1

were back pain, extremity pain and arthralgia. There were 12 reports of anaphylaxis found - but not adjudicated, and outcomes and relatedness are unknown. In response to these issues Amgen cited that anaphylaxis occurred rarely, between 0.01-0.1% of people who received the drug, with no deaths as of Nov 2012. As these are voluntary postmarketing reports, the incidence and prevalence of severe allergic reaction is unclear. Healthcare professionals and patients are encouraged by the FDA to report adverse events or side effects related to this and other drugs to the FDA’s MedWatch Safety Information and Adverse Event Reporting Program: www.fda.gov/MedWatch/report.htm

---DSQ Editors DSQ

**Safety of Anti-Osteoporosis Medications** continued from page 4

Intolerance and rare serious side effects occur in patients receiving osteoporosis drugs. However, in patients at high risk for fracture, the risk to benefit ratio for most therapies is very favorable, especially during the first 3-5 years of treatment.

**References**


2. Evista® Prescribing Information. 2012.


9. Green, J. et al., Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort. BMJ. 2010 Sep 1;341:c4444. PMID: 20821362


**Update on Drug Shortages**

<table>
<thead>
<tr>
<th>Drug Shortage</th>
<th>Reason for shortage</th>
<th>Estimated Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir IV</td>
<td>Manufacturing delays (note that oral acyclovir caps and tabs are now available)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Aspirin Tablets (Buffered) 325 mg</td>
<td>Novartis voluntarily recalled and suspended manufacturing of multiple drugs at the Lincoln facility; 2 other manufacturers discontinued the product</td>
<td>Unknown</td>
</tr>
<tr>
<td>Bupivacaine HCl inj 0.25% (10, 20, 30, 50 mL)</td>
<td>Demand exceeded supply</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Cortisone Acetate Tabs</td>
<td>Manufacturing delays- note conversion to prednisone is 5:1 (e.g, 25 mg cortisol is 5 mg prednisone)</td>
<td>Oct 2013</td>
</tr>
<tr>
<td>Cyanocobalamin Inj 1000 mcg/mL, 1 mL</td>
<td>Manufacturing delays, increase demand</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dexamethasone 4mg/mL, 1.5, 30 mL</td>
<td>American Regent: voluntary recall due to particulate matter found in vials</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Doxycycline (50, 75, 100, 150 mg)</td>
<td>Raw material shortage</td>
<td>Unknown</td>
</tr>
<tr>
<td>Epinephrine Inj 1 mg/mL, 1, 10, 30 mL</td>
<td>Manufacturing delays, increased demand</td>
<td>Unknown</td>
</tr>
<tr>
<td>Furomethione Inj</td>
<td>Increased demand and manufacturing delays</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Heparin Inj</td>
<td>FDA issued import bans against Chinese mfg due to inadequate manufacturing</td>
<td>Unknown</td>
</tr>
<tr>
<td>practices</td>
<td>Aug 2013</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Hydrocortisone 100 mg/2mL, 250 mg/2mL, 500 mg, 1000 mg</td>
<td>Increased demand</td>
<td>2014</td>
</tr>
<tr>
<td>Indomethacin Inj (lyophilized powder)</td>
<td>Nationwide backorder due to manufacturing issues</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Isoniazid tab (100, 300 mg)</td>
<td>Unknown</td>
<td>Sept 2013</td>
</tr>
<tr>
<td>Ketorolac Inj</td>
<td>Increase demand</td>
<td>Unknown</td>
</tr>
<tr>
<td>Leucovorin Calcium Inj 50, 100, 200, 350 mg</td>
<td>Manufacturing delays, increased demand. Note that leucovorin tablets are not affected</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lidocaine (with and without Epi) 0.5%, 1%, 1.5%, 2%</td>
<td>Raw material shortage</td>
<td>2014</td>
</tr>
<tr>
<td>Mercaptopurine 50 mg</td>
<td>Increase demand</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Continued on next page
Update on Drug Shortages  continued from previous page

<table>
<thead>
<tr>
<th>Drug Shortage</th>
<th>Reason for shortage</th>
<th>Estimated Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesna Inj</td>
<td>Manufacturing delays and increased demands</td>
<td>Unknown</td>
</tr>
<tr>
<td>Methylprednisolone Inj 40 mg, 80 mg (1, 5, 10 mL vials)</td>
<td>NECC closed manufacturing site due to fungal meningitis outbreak related to MTX Inj - Unknown MTX tabs – June 2013</td>
<td></td>
</tr>
<tr>
<td>intrathecal use</td>
<td>Product released as it</td>
<td>Revised: Unknown</td>
</tr>
<tr>
<td>becomes available</td>
<td>Watson noted supply constraints, Teval discontinued product</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Morphine sulfate inj</td>
<td>Watson noted supply constraints, Teval discontinued product</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Nitroglycerin 2% ointment</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Ondansetron Inj 2mg/mL</td>
<td>Manufacturing delays, increased demand</td>
<td>Oct 2013</td>
</tr>
<tr>
<td>Pantoprazole Tabs (20,40 mg)</td>
<td>Increased demand</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Prednisone 1, 5, 10, 20 mg tab</td>
<td>Raw materials shortage</td>
<td>Aug 2013</td>
</tr>
<tr>
<td>Promethazine Inj 25 mg/mL, 50 mg/mL</td>
<td>Increase demand, temporary suspension of mfg by Bedford</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tetracycline caps 250 mg, 500 mg</td>
<td>Manufacturing delays, increase demand</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tuberculin PPD, intradermal inj</td>
<td>Increase demand, low supply</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

Resolved Drug Shortages

- Acyclovir Tabs/Caps
- Diphenhydramin Inj
- Ibandronate sodium Inj (Boniva IV)
- Meperidine Inj
- Rifampin and Isoniazid Combination Tab (300/150)