Drug-induced Muscle Disease

Christine Castro, DO, Mark Gourley, MD, National Institutes of Health, National Institutes of Arthritis, Musculoskeletal and Skin Diseases, Bethesda, Maryland USA

Background/Introduction
Agents that are implicated in drug-induced muscle disease include both medicinal and recreational drugs. While the list of drugs is long, we will focus on the most common medicinal offenders. It is important to recognize drug-induced disease because withdrawal of the offending agent is often curative.

Diagnosing drug-induced muscle disease
The manifestations of drug-induced muscle disease (aka, myopathies) are variable so that the actual incidence of disease is unknown. Signs and symptoms of drug-induced muscle disease can be seen anywhere from weeks to months after drug initiation. Be suspicious of new onset myalgias, elevated creatine kinase (CK), weakness, and myoglobinuria. Symptoms usually resolve within weeks to months after discontinuation of the offending agent. If the patient doesn’t improve as expected, a further search to better define the illness is necessary and may include imaging studies of the muscle, electromyography and/or muscle biopsy. A muscle biopsy can be extremely helpful to establish a diagnosis. The various forms of muscle injury can be classified by type of injury. Table 1 is helpful to elucidate the possible offending agent.1,2

Drugs associated with Drug-Induced Myopathies
The list of possible agents is long; here-in we report the better known associations with muscle diseases that practitioners should be aware.

1. Cardiovascular Disease
1.1 Lipid lowering agents
HMG-CoA reductase inhibitors, or statins, are the most widely known offenders in muscle disease. Fibric acid derivatives, niacin, and ezetimibe are also well-recognized culprits. In fact, combination lipid lowering therapy may be more myotoxic than monotherapy. The deleterious effects of these agents on muscle have been well studied. Symptoms of statin induced muscle disease can include myalgias, predominantly proximal muscle weakness, elevated CK greater than 10 times the upper limit of normal, rarely rhabdomyolysis, and muscle cramps and tendon pain. Certain statins convey a greater risk of muscle disease than others and are dose dependent. One study found the order of myotoxicity to be (highest to lowest): lovastatin, simvastatin, atorvastatin more than pravastatin and fluvastatin.3 Risk factors for developing statin-induced myopathy include: low body mass index, comorbid diseases (diabetes, hypothryoidism, renal and/or liver insufficiency), concomitant use of drugs that inhibits cytochrome P450 (fibrates, nicotinic acid, calcium channel blockers, cyclosporine, warfarin, and macrolide antibiotics, and others), excessive alcohol or grapefruit juice intake, surgery, major trauma, infections and vigorous exercise.4 Several mechanisms of statin-induced muscle disease have been proposed.1,14 These mechanisms include alterations in cellular membrane cholesterol that cause changes in ion channels, mitochondrial impairments, injury to calcium homeostasis and cell apoptosis. An association with the SLC01B1 gene has been reported.6 Recent studies suggest autoantibody against 3-Hydroxy-3-Methylglutaryl-Coenzyme A reductase may be involved in a subset of patients.7

2. Antiarrhythmics
Several reports have noted muscle disease caused by antiarrhythmic agents, such as procainamide, that can cause myalgias and weakness, often as part of a lupus-like syndrome.8,9 Amiodarone has been associated with cases of muscle cramping, distal and proximal muscle weakness, elevated CK, myopathic EMG, and muscle biopsies with autophagic vacuoles and myeloid inclusions.9 Other cardiovascular medications that can cause muscle disease include calcium-channel blockers, beta blockers, aminocaproic acid and warfarin.2

Biologic Safety with Resolved Hepatitis B infection

John J. Cush, Kathryn H. Dao

Two billion people have been infected with hepatitis B virus (HBV) and 350 million have chronic infection worldwide. In the United States nearly one million are infected and there are 50-100,000 new HBV infections each year. After acute HBV infection, many become inactive, some assume a chronic carrier state and some develop a "resolved HBV" phenotype. Resolved HBV is defined as an asymptomatic individual with normal hepatocellular enzymes, undetectable HBV DNA viral loads, who is HBsAg- and HbcAb+ (+/- HBsAb positivity). This differs from chronic HBV and inactive HBV who are both HBsAg+. Reactivation may occur in those with resolved HBV and may result in necroinflammatory disease and any of the above consequences of HBV that may include liver failure, cirrhosis, cancer and death.

Biologic use often mandates screening for hepatitis B and C virus infection. While the use of TNF inhibition has not been shown to exacerbate hepatitis C infection, numerous reports of hepatitis B virus (HBV) reactivation and fatalities have been described with rituximab (RTX) and TNF inhibitors (particularly infliximab). Vaughn’s cohort study of 816 patients receiving anti-TNF therapy showed that only 25% of patients were screened for hepatitis B.3

The risk of HBV reactivation with immunosuppressive use is greatest in HBsAg+ individuals.4-6 Numerous guidelines and product labels have proposed hepatitis screening prior to biologic use and that these agents should be avoided in HBsAg+ individuals. However, biologics (e.g., RTX, TNF inhibitors) may be used in HBsAg+ patients if the clinical need is sufficiently great, and then only if the

Letter to the Editors

Dear DSQ,
I closely read the article from November 2012 Drug Safety Quarterly on off-label prescribing of medications in general and specifically in rheumatology. I noticed that in Table 1 (page 2), entitled “Off-Label Drugs Used in Rheumatology and the Strength of Evidence” indicates there is strong evidence for use of hydroxychloroquine in juvenile idiopathic arthritis (JIA).

Actually in controlled studies there is strong evidence that hydroxychloroquine is not effective in the treatment of JIA.1,2 The ACR JIA treatment recommendation paper from 20113 stated explicitly that use of monotherapy hydroxychloroquine

see Letter page 3

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Send letters to DSQ@rheumatology.org.
II. Rheumatologic, immunosuppressive, and immunomodulatory agents

1. Corticosteroids

Corticosteroids can cause a steroid-induced myopathy. This is characterized by
insidious onset of proximal muscle weakness and normal CK. Myopathy usually
occurs with chronic use; however, rapid onset myositis can be seen with high doses
of steroids. Mechanisms have been proposed for steroid-induced muscle injury10
including alterations of protein synthesis and degradation, alterations in metabolism,
inhibition of myogenesis, electrolyte disturbances (hypokalemia), and decreased
sarcoplasmic excitation-contraction coupling. EMG in steroid induced myopathy can show deterioration
in motor potentials, but can also be normal. Muscle biopsy can be normal or show
nonspecific type 2 fiber atrophy.

2. Antimalarials

Hydroxychloroquine and chloroquine have been reported to cause a neuromuscular
toxicity that causes weakness, typically without increased CK.11 Reports of this
complication are rare and typically involve long-term use of the drug. Muscle biopsy
may be helpful in diagnosis by showing curvilinear bodies with or without myeloid
bodies on electron microscopy. EMG shows a myopathic pattern. The proposed
mechanisms of disease involve chloroquine’s ability to form drug-lipid complexes in
cellular membranes that can cause accumulation of autophagic vacuoles.

3. Leflunomide

Typically prescribed in rheumatoid arthritis, myopathy rarely results from its use.12
Symptoms include proximal muscle weakness associated with a CK elevation. EMG
can show a myopathic pattern. Muscle biopsy may be normal or reveal variations in
fiber size, fiber degeneration, and/or non-necrotic fibers surrounded by mononuclear
infiltrates.

4. Colchicine

Multiple neuromuscular effects including fatigue and weakness with elevated
CK levels have been reported with colchicine use.13,14 Long-term use of colchicine
can cause a vacuolar myopathy with accumulation of lysosomes and autophagic
vacuoles. Individuals with renal insufficiency or who are also taking nephrotoxic
drugs (cyclosporine) are more likely to have myopathy.

5. TNF-α inhibitors

A collection of cases have reported myopathy associated with TNF-α inhibitors.
These cases report myalgia, proximal muscle weakness, rashes of dermatomyositis
(heliotrope, V-sign), and the development of Jo-1 auto antibodies. Several
hypotheses may shed light on this mechanism.15 TNF-α inhibitor use can increase
interferon-α which has been shown to exacerbate dermatomyositis. Another
possibility is that TNF-α inhibition can interfere with apoptosis resulting in
development of autoantibodies.

6. Other agents

Cyclosporine and tacrolimus, often in the presence of other drugs – particularly statins
and colchicine, have been shown to cause muscle cramping, myalgias, proximal
muscle weakness, and rarely rhabdomyolysis.16 D-penicillamine is noted to rarely
cause inflammatory myopathy.17 Azathioprine is reported to cause rhabdomyolysis.3
Antisynthetase syndrome has been reported with use of interferon-α.18 Interferon-β
has been implicated in the development or exacerbation of dermatomyositis.3

III. Infectious Disease Agents

1. Antivirals and antiretrovirals

The most common offending agent in this class is zidovudine (AZT)19 causing
myalgias, elevated CK, and severe weakness. Other antiretrovirals have also been
implicated. EMG findings show myopathic findings. Biopsy shows ragged red
fibers, necrosis, and nemaline rods. Proposed mechanisms include oxidative stress,
inhibition of mitochondrial function, L-carnitine depletion, and apoptosis.

2. Antifungals

The triazoles and imidazoles are commonly used antifungal agents and have been
reported to cause generalized weakness and elevated CK levels.1 Rifampin is
described to be associated with proximal myopathy with normal EMG findings and
CK levels.

IV. Oncologic agents and small molecules

Established oncologic agents and the newer small molecules are reported to cause
myalgias and proximal weakness20-23. Reported drugs include: imatinib mesylate24,25,
sorafenib26, 5-azacytidine, cyclophosphamide plus mitoxantrone, cytarabine, all-
trans retinoic acids26 and solumetinib27.

V. Gastrointestinal Drugs

Proton pump inhibitors and histamine blockers rarely cause myalgias, weakness,
elevations in CK weakness, and/or the rashes of dermatomyositis. Symptoms can
be worse with concomitant use of statins, clarithromycin, or methotrexate.22,23

VI. Psychiatric and neurologic drugs

This class of agents is rarely associated with muscle disease. The drugs implicated in
muscle disease include phenytoin, valproic acid, levodopa, antipsychotics (clozapine,
risperdone, haloperidol), lithium tricyclics, and MAO inhibitors.3

Treatment

Withdrawing the offending agent is the primary treatment for DIM. The best data
available for drug withdrawal outcomes are statin studies. Typically, myalgias and
weakness abate within a few months. Some patients may take up to a year for full
recovery. If a recovery is not seen and the patient has myositis, therapy should
be targeted for an inflammatory myopathy. Rechallenge to a different statin class
has been successfully employed but should be done under close observation.

References


continued next page
**ACR 2012 Safety Update**

**Biologics and TNF inhibitors reduce mortality.** Lacaille (#1642) reported a 10 yr analysis of 4312 patients treated with biologics (TNFi, RTX, ABA, ANK) versus those who have received ≥3 nonbiologic DMARDs and found a reduction in all cause mortality, with a hazard ratio of 0.25 (95% CI, 0.18–0.36).

**Lymphoma risk in RA.** Hellgren (#1229) studied 10,367 RA patients and matched (5:1) controls from the Swedish Registry (1987–2011), and found more lymphoma in the RA than controls (RR = 1.7; 95% CI 1.2–2.4). Lymphoma risk appears to increase after 5 yrs of disease. Another abstract from the British Biologics Register (#1593) showed that the risk of lymphoma was the same when comparing TNF inhibitors to nonbiologic DMARDs (HR 1.13; 95% CI 0.55–2.31).

**Restarting biologic with active TB treatment.** The BIOBADASER registry (#1641) from Spain reported on 52 cases who developed active TB requiring biologic withdrawal; 27 of whom resumed biologics. Biologics were restarted either during (1/3) or upon completion (2/3) of TB treatment and no differences were seen as far as TB recurrences (with 46–56 months of follow-up). Hence it appears TNF may be restarted after 2 months without a recurrence risk.

**Infection Risk with Orthopaedic Surgery and when to stop TNF inhibitors.** Scherrer, et al (#1669) presented data from 50,359 orthopedic surgeries in 37,137 patients over 8 yrs. Patients with inflammatory arthritis had more perioperative infections, as did patients on TNF inhibitors (OR 2.6; 95%CI 1.1–6.2; P=0.027). Perioperative infections increased 10 fold when surgery was done within one dosing interval of the TNFi (OR 10, 95%CI 1.17-86.3; p=0.035). Thus, the risk can be reduced if surgery is performed after skipping a dose.

**Low IgG after Rituximab and Serious Infectious Event (SIE) risk.** van Vollenhoven (#1694) studied the effects of rituximab (RTX) on IgG and IgM levels in 3194 RA patients in the RTX clinical trials. Patients receiving between 9-17 RTX courses were followed for up to 9.5 yrs. In those who developed low IgG (3.5%) or IgM levels (22.4%), there was no difference in SIE event rates before and after low IgM levels (22.4%), there was no difference in SIE event rates before and after low IgG or IgM levels. However, when compared those who never had low IgG levels, SIE rates were increased in the low IgG group (9.3 vs 3.7 per 100 pt-yrs). It appears patients developing low IgG levels had an inherently higher risk of SIE that was unrelated to IgG depletion.

**Pregnancy and TNF inhibitors.** Several abstracts addressed pregnancy and therapy. Pregnancies conceived while on certolizumab (n=137, abstract #1643) or adalimumab (n=88, abstract #2466) revealed no significant increase in miscarriage, pre-term births or birth defects (3-5%). Analysis of 147 pregnancies from the CORRONA registry (#380) showed RA and PsA women planning to become pregnant had low activity before pregnancy. While most decreased overall drug use, a high percentage (54%) were on TNFi (54%) before pregnancy and half (27%) stayed on TNFi (27%) during pregnancy. Disease activity before pregnancy predicted activity during pregnancy. Those with high activity before pregnancy were 57% likely to stay in high activity during pregnancy.

**Lymphoma risk in RA**

<table>
<thead>
<tr>
<th>Type of myopathy</th>
<th>Histologic features</th>
<th>Drugs implicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Necrotizing</td>
<td>Scattered necrotic fibers with macrophage invasion, lack of widespread MHC-I upregulation, lack of lymphocytic infiltrates</td>
<td>Statins, fibrates, alcohol</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Lymphocytic infiltration with CD8+ T cell invasion of non-necrotic, MHC-I expressing cells</td>
<td>Statins, d-penicillamine, interferon-alpha, procainamide</td>
</tr>
<tr>
<td>Type II muscle fiber atrophy</td>
<td>Atrophy of type II muscle fibers</td>
<td>Long-term steroid use</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>“ragged red” or “ragged blue” fibers, COX negative fibers, increased lipid accumulation</td>
<td>Nucleoside analogues (zidovudine)</td>
</tr>
<tr>
<td>Lysosomal storage</td>
<td>Storage of myeloid structures within lysosomes as autophagic vacuoles</td>
<td>Chloroquine, hydroxychloroquine, amiodarone</td>
</tr>
<tr>
<td>Antimicrotubule</td>
<td>Inhibition of polymerization of microtubules resulting in cytoskeletal derangement; swollen lysosomes; autophagic vacuoles</td>
<td>Colchicine</td>
</tr>
<tr>
<td>Myofibrillar</td>
<td>Disruption of the Z disc; myofilament breakdown; accumulation of myofibrillar proteins</td>
<td>Emetin, IPECAC</td>
</tr>
<tr>
<td>Fascitis</td>
<td>Inflammation and thickening of the myofascia</td>
<td>L-tryptophan</td>
</tr>
</tbody>
</table>

**Letter continued from cover**

is inappropriate for JIA, with evidence level A in polyarthritis and C in oligoarthritis. There is still insufficient evidence whether hydroxychloroquine has a role as part of combination therapy. Therefore I suggest that the Table be corrected to move JIA to the weak/no evidence for use column for hydroxychloroquine to reflect our current knowledge.

**Philip J Hashkes, MD, MSc**

Head, Pediatric Rheumatology Unit
Shaare Zedek Medical Center
Jerusalem, Israel

<table>
<thead>
<tr>
<th>Drug Shortage</th>
<th>Reason for shortage</th>
<th>Estimated Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir Caps and Tabs</td>
<td>Apotex halted manufacturing due to FDA audit, Ranbaxy reported raw materials shortage</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 HCI inj 0.25% (10, 20, 30, 50 mL)</td>
<td>Demand exceeded supply</td>
<td>Revised: Dec 2012</td>
</tr>
<tr>
<td>Cyanocobalamin Inj 1000 mcg/mL, 1 mL</td>
<td>Manufacturing delays, increased demand</td>
<td>Unknown</td>
</tr>
<tr>
<td>Dexamethasone 4mg/mL (1, 5, 30 mL)</td>
<td>American Regent voluntarily recalled this product due to particulate matter found in vials</td>
<td>Revised: Dec 2012</td>
</tr>
<tr>
<td>Diphenhydramine HCI Inj</td>
<td>Manufacturing delays, demand exceeded supply</td>
<td>Revised: Dec 2012</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>Furosemide Inj</td>
<td>Increased demand and manufacturing delays</td>
<td>Revised: Dec 2012</td>
</tr>
<tr>
<td>Hydrocortisone 100mg/2ml, 250mg/2ml, 500mg, 1000mg</td>
<td></td>
<td>2013</td>
</tr>
<tr>
<td>Ketorolac Inj</td>
<td>Supply issues and delayed release (note that 100 mg tabs are still available)</td>
<td>Revised to 2013</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>Oct 2012</td>
</tr>
<tr>
<td>Lidocaine 0.5%, 1%, 1.5%, 2%</td>
<td>Raw material shortage</td>
<td>Revised: Dec 2012</td>
</tr>
<tr>
<td>Mesna Inj</td>
<td>Hospira and APP reported manufacturing delays and increasing demands</td>
<td>Product released as it becomes available.</td>
</tr>
<tr>
<td>Methotrexate inj 25 mg/mL (2,4,8,10,40 mL vials) AND tablets 2.5 mg</td>
<td>Teva has manufacturing delays, Ben Venue suspended manufacturing/distribution temporarily due to maintenance and requalification of equipment.</td>
<td>MTX Inj - Unknown MTX tabs – Jan 2013</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 intrathecal use</td>
<td>Note: Depo-Medrol is available</td>
</tr>
<tr>
<td>Morphine sulfate inj</td>
<td>Watson noted supply constraints, Teval discontinued product</td>
<td>Dec 2012</td>
</tr>
<tr>
<td>Nitroglycerin 2% ointment</td>
<td>Unknown</td>
<td>Revised: Unknown</td>
</tr>
<tr>
<td>Ondansetron Inj 2mg/mL</td>
<td>Manufacturing delays, increased demand</td>
<td>Dec 2012</td>
</tr>
<tr>
<td>Pantoprazole Tabs (20,40 mg)</td>
<td>Increased demand</td>
<td>Dec 2012</td>
</tr>
<tr>
<td>Prednisone 1, 5, 10, 20 mg tab</td>
<td>Raw materials shortage</td>
<td>Dec 2012-Jan 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>Revised: 2013</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>March 2013</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resolved Shortages</th>
<th>Date of Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boniva 3 mL prefilled syringe</td>
<td>Nov 2012</td>
</tr>
<tr>
<td>Diclofenac gel (Voltaren gel) 1%</td>
<td>April 2012</td>
</tr>
<tr>
<td>Lansoprazole OTC</td>
<td>May 2012</td>
</tr>
<tr>
<td>Leflunomide 10, 20 mg</td>
<td>Aug 2012</td>
</tr>
<tr>
<td>Methylprednisolone tabs (4,8,16,32 mg)</td>
<td>Jan 2012</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Resolved Shortages</th>
<th>Date of Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate Sodium Tab (180, 360)</td>
<td>Mar 2012</td>
</tr>
<tr>
<td>Mofetil oral suspension</td>
<td></td>
</tr>
<tr>
<td>Trazodone 50,100,150 mg</td>
<td>July 2012</td>
</tr>
<tr>
<td>Warfarin Sodium (1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg)</td>
<td>Dec 2012</td>
</tr>
<tr>
<td>Zoster Vaccine</td>
<td>Jan 2012</td>
</tr>
</tbody>
</table>

Drugs with Increasing Involvement in Emergency Department (ED) Visits for Drug Misuse or Abuse: 2004 to 2010

<table>
<thead>
<tr>
<th>Drug</th>
<th>ED Visits, 2004</th>
<th>ED Visits, 2010</th>
<th>Percent Change, 2004 to 2010*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmaceuticals</td>
<td>626,472</td>
<td>1,345,645</td>
<td>115%</td>
</tr>
<tr>
<td>Anti-anxiety and Insomnia Drugs</td>
<td>210,711</td>
<td>472,769</td>
<td>124%</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>170,471</td>
<td>408,021</td>
<td>139%</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>41,930</td>
<td>69,149</td>
<td>65%</td>
</tr>
<tr>
<td>CNS Stimulants (e.g., ADHD Drugs)</td>
<td>10,656</td>
<td>31,507</td>
<td>196%</td>
</tr>
<tr>
<td>Muscle Relaxants</td>
<td>29,014</td>
<td>58,783</td>
<td>103%</td>
</tr>
<tr>
<td>Pain Relievers</td>
<td>282,275</td>
<td>659,969</td>
<td>134%</td>
</tr>
<tr>
<td>Narcotic Pain Relievers</td>
<td>166,338</td>
<td>425,247</td>
<td>156%</td>
</tr>
<tr>
<td>Hydrocodone Products</td>
<td>46,536</td>
<td>115,739</td>
<td>149%</td>
</tr>
<tr>
<td>Oxycodone Products</td>
<td>51,418</td>
<td>182,748</td>
<td>255%</td>
</tr>
</tbody>
</table>

* Percent change is measured as difference in the estimated number of visits between 2004 and 2010. Reported changes are significant at the .05 level. "NC" signifies no significant change.

Source: 2010 SAMHSA Drug Abuse Warning Network (DAWN)
Long-term safety profile of belimumab plus standard therapy in patients with systemic lupus erythematosus. Mierli JT, et al. Arthritis Rheum. 2012;64:3364-73 (PMID: 22674457). 364 patients in a 1 yr trial of belimumab and 286 continued in the long-term continuation study. With 4 years of belimumab follow-up(1,165 cumulative patient-years), the most common adverse events included arthralgia, upper respiratory infection, headaches, fatigue, and nausea. Serious infection reactions were very rare. Serious infection ranged from 5.9 to 3.4/100 patient-years.

Long-term safety of Rituximab in rheumatoid arthritis: 9.5-year follow-up of the global clinical trial programme with a focus on adverse events of interest in RA patients. van Vollenhoven RF, et al. Ann Rheum Dis. 2012 Nov 7. [Epub ahead of print] (PMID: 23136242). Review of 3194 patients (11962 patient-years) receiving up to 17 rituximab courses over 9.5 years reveals no new safety signals. No increase in cancer. Serious infections occurred at a rate of 3.94/100 patient-years of exposure. Low IgM (22.4%) and IgG (3.5%) levels were seen in few. For those with low Ig levels, infection rates were not different comparing SIE rates before or after low Ig levels. However, those with low IgG levels had significantly more SIE when compared to those who never had low Ig levels.

Abuse of carisoprodol (Soma) Increasing. Carisoprodol, marketed as a muscle relaxant, centrally acts on the CNS when metabolized to meprobamate. Abuse of carisoprodol (Soma) has been noted to be related to the age of the patient. Abuse of carisoprodol may be due to a potential pharmacodynamic interaction between COX-2 selective inhibitors and Soma.

Bisphosphonates reduced the risk of acute myocardial infarction: a 2-year follow-up study. Kang JH, et al. Osteoporos Int. 2012 Nov 14. [Epub ahead of print] (PMID: 23152093). This 2 yr study compared outcomes in 1,548 bisphosphonate treated and 4,644 untreated subjects with a history of vertebral or hip fractures. Bisphosphonates were associated with significantly fewer acute MI with a hazard ratio of 0.36 (95 % CI=0.14-0.84, p=0.020). The reason for this benefit is unclear.

Safety of nonsteroidal antiinflammatory drugs and/or paracetamol in people receiving methotrexate for inflammatory arthritis: a Cochrane systematic review. Colebatch AN, et al. Rheumatol Suppl. 2012 Sep;90:62-73 (PMID: 22942332). While there is a potential pharmacodynamic interaction between methotrexate and NSAIDs – the combination is commonly used. A Cochrane metaanalysis reviews 17 studies and concludes there is no significant added toxicity when NSAIDs or acetaminophen are used with methotrexate.

Incidence, secular trends, and outcomes of prosthetic joint infection: a population-based study, Olmsted county, Minnesota, 1969-2007. Tsarsas G, et al. Infect Control Hosp Epidemiol. 2012;33:1207-12 (PMID: 23143557). In a 38 yr span, 75 prosthetic infections (PJI) (in 70 patients) were noted among 7,375 hip and knee replacements. The cumulative incidence of PJI was 0.5%, 0.8%, and 1.4% after 1, 5, and 10 years after arthroplasty, suggesting risk is related to the age of the implant. The incidence risk and outcomes did not change over 4 decades. 

Legislation introduced to bolster federal oversight of compounded drugs. Since the outbreak of fungal meningitis linked to steroid injections produced by the Massachusetts-based New England Compounding Center, new legislation was introduced requiring compounding companies to register with the FDA which would allow the agency to set minimum production standards and to impose new labeling restrictions on compounded drugs. The bill is known as the SAFE Compounding Act, introduced by Democratic representative Rosa DeLauro (CT) and Nita Lowey (NY). The FDA has asked Congress to allow itself to set national standards for large drug compounding operations. Officials will meet on December 19, 2012 to discuss a new regularly structure.
**Hepatitis B** continued from page 1

patient receives prophylaxis. Antiviral prophylaxis, with lamivudine (or like antiviral agent), should be started before and maintained throughout the course of biologic therapy.

Patients with resolved hepatitis (HBsAg-, HBeAb+) may safely receive immunosuppressives and biologic therapies. A literature review by Lee et al identified 468 patients with resolved (occult) HBV who also received TNF inhibitors for RA, psoriatic arthritis and spondyloarthropathy. With up to 60 months of observation, only 1.7% (8 patients) demonstrated reactivation with elevation of viral DNA. Results from 222 patients are represented in the attached table. Many of these patients were also receiving prednisone, methotrexate or other DMARDs. Hence the reactivation risk is low (<2%) when using TNF inhibitors in patients with resolved HBV. Similarly, there are few studies from Southeast Asia (where HBV is highly prevalent) showing that conventional DMARD use in resolved HBV may also yield a 2-3% reactivation rate.13 There are fewer reports of the safety of RTX in rheumatic disease patients with resolved HBV. There are several case reports of HBV reactivation in RA patients treated with RTX, however most reports of RTX use with resolved HBV comes from patients with lymphoma, where the results are less encouraging. Overall it appears that reactivation may occur in 5-10% of resolved HBV patients treated with RTX.12

Rheumatic disease patients who have resolved HBV and may receive biologic or immunosuppressive therapy should be monitored periodically for symptoms, hepatic enzymes and viral DNA quantitation. Consultation with a hepatologist for problematic patients should be considered.

<table>
<thead>
<tr>
<th>Reactivation risk in Resolved HBV (HBsAg-, HBeAb+) Patients Treated with TNF inhibitors</th>
<th>Author (year)</th>
<th>Indication</th>
<th>TNFi treated</th>
<th>Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charpin (2009)</td>
<td>RA, SpA</td>
<td>21</td>
<td>0/21</td>
<td></td>
</tr>
<tr>
<td>Chung (2009)</td>
<td>RA, AS, PsA</td>
<td>8</td>
<td>1/8 *</td>
<td></td>
</tr>
<tr>
<td>Vassilopoulous (2010)</td>
<td>Rheumatic disease</td>
<td>19</td>
<td>1/19</td>
<td></td>
</tr>
<tr>
<td>Caporali (2010)</td>
<td>RA, AS, PsA</td>
<td>67</td>
<td>0/67</td>
<td></td>
</tr>
<tr>
<td>Cassano (2011)</td>
<td>Psoriasis, PsA</td>
<td>62</td>
<td>0/62</td>
<td></td>
</tr>
<tr>
<td>Tamori (2011)</td>
<td>RA</td>
<td>45</td>
<td>1/45</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>3/222</strong> (1.35%)</td>
<td></td>
</tr>
</tbody>
</table>

*reactivation after 3rd infusion of infliximab (5mg/kg)

**References**


**FDA MedWatch – Winter 2012**

**Hydrocodone bitartrate and acetaminophen 10/500 tabs recalled.** Qualitest issued a voluntary nationwide recall of 101 lots of Hydrocodone bitartrate and acetaminophen 10/500 tabs after discovering that some tabs exceed weight requirements, containing more acetaminophen or hydrocodone than intended. The affected lots were distributed between Feb 20, 2012 and Nov 19, 2012. Consumers are warned not to exceed 6 tabs/day of this product and should take into account and OTC or prescription meds that may contain acetaminophen. No injuries have been reported to date. (Posted 12/6/12)

**Odanetron (Zofran) 32 mg Single IV Dose Removed.** Due to risk for QT syndrome and torsades de Pointe, Odanetron 32 mg single dose vials will be removed from the market early 2013. The FDA continues to recommend the intravenous regimen of 0.15 mg/kg q4hours for 3 doses (no single dose to exceed 16 mg) to prevent chemo-induced nausea and vomiting. (Posted 12/4/12)

**Atorvastatin Calcium Tablets (10, 20, 40 mg) may contain glass.** Ranbaxy voluntarily recalled these tablets as they may contain small glass particles resembling fine grain of sand (<1 mm). The expiry date of the recalled tablets is Aug 31, 2014. (Posted 11/9/12)

**Risk for bleeding with Pradaxa not increased compared to warfarin.** Following a large number of post-marketing reports of bleeding among Pradaxa users, the FDA, through its Mini-Sentinel project, evaluated the risk for GI bleeding and intracranial hemorrhage associated with new users of Pradaxa compared to new users of warfarin. Bleeding rates were not increased with Pradaxa consistent with the results from patients with lymphoma, where the results are less encouraging. Overall it appears that reactivation may occur in 5-10% of resolved HBV patients treated with RTX.12

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**Thrombotic thrombocytopenic purpura (TTP) related to Opana ER abuse.** Accidental ingestion of OTC eye drops and nasal sprays resulted in serious adverse events. The public was warned that accidental ingestion by children of OTC eye drops and nasal decongestant sprays can result in serious harm. These products contain active ingredients tetrahydrozoline, oxymetazoline or naphazoline which have vasoconstrictive effects. Reports of coma, CNS and respiratory depression, and cardiac arrest/miasin resulted from ingestion of as little as 1-2 mL in children <5 years old. These OTC bottles are not child resistant. (Posted 10/25/12)

**Pramipexole (Mirapex) and risk for heart failure.** Results of recent studies suggest a risk for heart failure with use of Mirapex, a drug commonly prescribed for the treatment of Parkinson’s and restless leg syndrome. After 2 epidemiologic studies suggested an increase in new onset heart failure, the FDA performed a pooled analysis of randomized clinical trials and found that the incidence of newly diagnosed heart failure heart failure was higher in patients taking Mirapex compared to placebo, but the difference was not statistically significant. The FDA is working with the manufacturer to clarify this risk and will update the public when more information is available. (Posted 9/19/12)

**Milnacipran (Savella) and Breast Milk.** Label was updated to indicate milnacipran is found in breast milk of lactating women treated with Savella. In a study of 8 lactating women who were at least 12 weeks postpartum, the maximum estimated fetal dose was 5% of the maternal dose. Hence caution should be exercised in nursing women. (October 2012)

**Fexubostat (Uloric) and hepatic effects.** There have been postmarketing reports of fatal and non-fatal hepatic failure, jaundice and serious hepatic enzyme elevations in patients taking fexubostat, although there is insufficient information to establish the probable cause. Marked elevations (>3 times the upper limit) are seen in less than 3% of patients on fexubostat or allopurinol. Laboratory monitoring is required and drug cessation for elevations >3 xULN is recommended (November 2012)

**Leflunomide (Arava) and skin adverse events.** Cutaneous lupus erythematosus, pustular psoriasis or worsening psoriasis were added to the potential adverse event listing in the label (November 2012).