TNF inhibitors and Heart Failure

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Chronic systemic inflammation yields a notable and proportional risk for myocardial infarction, coronary artery disease, heart failure and cardiovascular (CV) death. The role of tumor necrosis factor (TNF) in the pathogenesis of cardiovascular events and congestive heart failure (CHF) in rheumatoid arthritis (RA) has been well documented [1-4]. TNFα mediates anorexia, cardiac cachexia and endotoxic shock, and also induces left ventricular hypertrophy (LVH), LV dysfunction/remodeling/dilation and has negative inotropic effects on the myocardium. Many studies have shown increased circulating levels of TNF in heart failure, especially in those with New York Heart Association (NYHA) class III and IV disease, which correlates with the morbidity and mortality of CHF. Finally, transgenic mice that over express TNFα tend to die prematurely from dilated cardiomyopathy.

The vascular and myotonic effects of TNF have led to the hypothesis that TNF inhibition may benefit patients with CHF, improving both myocardial function and overall survival. Two large trials examined the use of etanercept and 1 trial studied infliximab in patients with NYHA class III and IV CHF (without any history of RA). Surprisingly, and paradoxically, these trials failed showing both a lack of CV benefit and poorer outcomes – especially for those treated with higher doses [5]. Etanercept has been tested in 2,048 CHF patients followed for less than two years and failed to show any improvement in survival, hospitalizations or NYHA class. Trials were suspended and no further use was planned. Infliximab was also tested in a 150 patient-controlled trial performed in patients with NYHA Class III/IV disease. An interim analysis at 24 weeks resulted in this trial being prematurely discontinued for a dose-related increase in hospitalizations and deaths [6,7]. Reasons for these failed results are thus far inexplicable.

Prescribing guidelines suggest that TNF inhibitors (TNFi) may cause worsening or new onset CHF and that clinicians should exercise caution when using TNFi in patients with CHF. Such patients should be monitored closely and the TNFi use suspended with the onset or worsening of CHF. In the early registration trials, the risk of new-onset CHF was 0.06%, 0.2% and 0.26% for etanercept, infliximab and adalimumab respectively [8]. In 2003, Kwon reported 47 RA cases with new onset or worsening CHF. When TNFi was given to patients with or without prior CHF, CHF rates were not higher in those receiving DMARDs [9]. Factors most predictive of new onset CHF included age, prior CHF, DAS activity, male sex and higher BMI. Effective reduction of inflammatory activity in RA with TNFα therapy was more likely to be beneficial than harmful with regard to the risk of heart failure – especially if there is no concomitant therapy with glucocorticoids or cyclooxygenase-2 inhibitors.

Using administrative claims from a large U.S. health care organization and studying individuals under the age of age 50, Curtis focused on 4,018 RA and Crohn’s disease (CD) patients and identified 9 new cases of CHF (0.2%). The relative risk of incident CHF among TNFi-treated RA and CD patients was elevated reported to the FDA; 38 with new-onset CHF and 9 with CHF worsening [10]. Half had no identifiable risk factors, and 10 patients were younger than 50 years of age when they developed new-onset heart failure. Although there have been several reports of new onset CHF in patients initiating TNFi therapy, this appears to be a rare event. Most have recommended the avoidance of TNFi in patients with NYHA Class III or IV heart disease.

Nevertheless, there is a growing body of literature supporting the cardiac safety or benefits of TNF targeted therapies in patients with RA. Recognizing that patients with CHF and cardiac disease are usually excluded from clinical trials, the early trials of etanercept, infliximab and adalimumab showed more de novo CHF events in those on placebo than the TNFi comparator [11]. Numerous studies and registries of RA patients have demonstrated a cardioprotective effect of TNF inhibition on myocardial infarction and new cardiac events [12]. Wolfe and Michaud studied 13,171 RA patients in the National Databank for Rheumatic Disease, noting more cases of CHF in RA (compared with osteoarthritis), however this was not higher in patients receiving TNFi [13]. A retrospective cohort study of 303 Veterans Administration RA patients failed to show a higher rate of CHF admissions or mortality amongst those treated with TNF blockers [14].Listing examined 4,248 RA patients on TNFi and DMARDs in the RABBIT registry over 3 years and found that CHF was 5 more times likely in those with CV disease compared to those without (2.2% vs. 0.4%). When TNFi was given to patients with or without prior CHF, CHF rates were not higher in those receiving DMARDs [15]. Factors most predictive of new onset CHF included age, prior CHF, DAS activity, male sex and higher BMI. Effective reduction of inflammatory activity in RA with TNF therapy was more likely to be beneficial than harmful with regard to the risk of heart failure – especially if there is no concomitant therapy with glucocorticoids or cyclooxygenase-2 inhibitors.

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Do Tumor Necrosis Factor α Inhibitors Cause Weight Gain?

Weight gain associated with TNFα inhibitors (TNFi) was never noted in early development trials, but has since been reported and is a concern for a minority of patients. Do these class of biologics induce weight gain, and if so, via what mechanism? Scant data have been published evaluating this issue. This review will highlight the current available research and theory on TNFi and weight gain.

Cachexia in autoimmune diseases: Cachexia is defined as a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass [1]. The prominent feature of cachexia is weight loss in adults after correction for fluid retention. Anorexia, inflammation, insulin resistance, and increased muscle protein breakdown have been frequently associated with cachexia. In 2008, a consensus statement was made that cachexia is an entity distinct from starvation, age-related loss of muscle mass, primary depression, malabsorption, and hyperthyroidism. Cachexia is associated with increased morbidity and mortality in patients with AIDS, malignancy, and in...
**Heart Failure** continued from cover

(RR = 4.3 and 1.2, respectively), but this was not statistically significant for those exposed to TNFi [14]. Solomon also analyzed claims data from 4 U.S. health care programs, focusing on RA patients on methotrexate (MTX) who either started a TNFi or nonbiologic DMARD [15]. When comparing 11,587 TNFi- and 8,656 nbDMARD-treated RA patients, the risk of TNFi-related CHF was not increased (HR=0.85, 95% CI 0.63 to 1.14).

The biologic and pharmacologic plausibility of this potential association has not been well studied or explained. Circulating N-terminal pro-brain natriuretic peptide (NT-proBNP) may be a biomarker for CV event risk – as high levels are seen with ventricular dysfunction. NT-proBNP levels have been examined in 171 patients with active RA (no evidence of CHF) before and after 16 weeks of adalimumab [16]. Adalimumab significantly reduced NT-proBNP level by 18% and was not associated with any deterioration in cardiac function in these RA patients. Another study by Daini demonstrated that etanercept (but not DMARD therapy) significantly lowered LV mass, without changing BP or aortic pulse wave velocity [17]. These findings may explain the improved CV outcomes in RA where TNF contributes to LVH and CV events. The unexpected harm of TNFi therapy in CHF patients may relate to the compensatory effects of TNFα on the failing myocardium and the negative effect of TNF inhibition and LV mass diminution in high-risk CHF patients.

Can TNFi therapy be safely used in patients with heart failure? Clinical trials strongly suggest TNF inhibition would be unsafe in CHF patients, especially those with uncompensated or poorly controlled CHF or those with NYHA Class III or IV disease. While there are no prospective or controlled trials of TNFi in RA patients with NYHA class II-IV disease, observational studies with large numbers of RA patients receiving TNFi suggest little risk of new or worsening CHF. TNFi use in RA patients without heart failure or with well-compensated and treated CHF can be considered, provided the patient’s cardiac status is monitored clinically.

The Frequency and Risk of CHF in RA patients receiving TNF inhibitors*

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Population</th>
<th># Patients</th>
<th>Freq. of CHF in RA (CHF Freq. on DMARD)</th>
<th>TNF-Related risk of CHF* (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wolfe</td>
<td>2004</td>
<td>RA</td>
<td>13171</td>
<td>3.9%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Listing</td>
<td>2008</td>
<td>RA</td>
<td>4248</td>
<td>2.2% w/ CV hx 0.4% without CV hx</td>
<td>HR = 1.7 (0.7–4.1)</td>
</tr>
<tr>
<td>Curtis</td>
<td>2007</td>
<td>RA &lt; 50yrs</td>
<td>4018</td>
<td>0.2%</td>
<td>RR = 4.3 (NS)</td>
</tr>
<tr>
<td>Solomon</td>
<td>2012</td>
<td>RA</td>
<td>20243</td>
<td>4.2%</td>
<td>HR = 0.9 (0.6-1.1)</td>
</tr>
</tbody>
</table>

* in the absence of preexisting CVD; *compared with non-TNFi treated group

References

5. Anker SD, Coats AJ. How to RECOVER from RENAISSANCE? The significance of the results of RECOVERY, RENAISEANCE, RENEWAL and ATTACH. Int J Cardiol 2002;86:123-30. PMID: 12419548

**Calcitonin Risk** continued from cover

The importance of this small, but consistent increase in the risk of cancer was compounded by the controversial efficacy of CS in the treatment of osteoporosis. Data supporting the efficacy of CS for osteoporosis treatment is scant, consisting of a small increase in lumbar spine bone density and fracture reduction shown in one randomized clinical trial of intranasal CS in patients with postmenopausal osteoporosis[16]. Other trials assessing fracture reduction with CS have failed to support a risk reduction.1

In animal carcinogenicity studies, calcitonin treatment was associated with development of benign pituitary neoplasms in rats, although definitive conclusions in humans are difficult to draw. Postmarketing data has not identified any potential signal for prostate cancer or other malignancies but this data is limited by bias of reporting, incomplete data, and difficulties proving causality. In summary, CS has a small, but plausible increase risk for cancer that should not be ignored. Currently we are awaiting the final decision by the FDA regarding the recommendations by this panel to withdraw the osteoporosis indication for all CS products. CS is also currently approved for use in Paget’s disease and hypercalcemia. These data should preclude CS use for the treatment of osteoporosis as there are safer and more effective alternatives available. 

References

Safety Signals: Spring 2013

Vitamin D and Calcium Supplementation to Prevent Fractures in Adults: U.S. Preventive Services Task Force Recommendation Statement. Moyer VA. Ann Intern Med. 26 February 2013. PMID: 23440163. The USPSTF concluded that the current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women, in men or postmenopausal women who are not institutionalized.

Response from the American Society for Bone and Mineral Research 2/26/13 on their website: http://www.asbmr.org. “The ASBMR continues to support the recommendations of the IOM (for high risk elderly, the recommended daily intake is 800 units of vitamin D and 1,200 milligrams of calcium. For healthy adults is 600 units of vitamin D3 and 1,000 milligrams of calcium) because they are based on a broader evaluation of the data rather than only fracture outcomes.”

Dietary and Supplemental Calcium Intake and Cardiovascular Disease Mortality: The National Institutes of Health-AARP Diet and Health Study. Xiao Q, et al. JAMA Intern Med. 2013 Feb 4-11. PMID: 23381719. In women, supplemental calcium intake was not associated with CVD death, heart disease or cerebrovascular disease death. In men, supplemental calcium intake was associated with an elevated risk of CVD death (RR 1000 mg/d vs 0 mg/d, 1.20; 95% CI, 1.05-1.36), more specifically with heart disease death (RR, 1.19; 95% CI, 1.03-1.37) but not significantly with cerebrovascular disease death (RR, 1.14; 95% CI, 0.81-1.61).

Low-dose aspirin use and recurrent gout attacks. Zhang Y, et al. Ann Rheum Dis. 2013 Jan 23. [Epub ahead of print]. PMID: 23345599. Online case-crossover study evaluating the use of cardioprotective doses of aspirin and the risk of gout attacks. Compared with no aspirin use, the adjusted OR of gout attacks increased by 81% (OR=1.81, 95% CI 1.30 to 2.51) for ≤325 mg/day of aspirin use on two consecutive days. Concomitant use of allopurinol nullified the detrimental effect of aspirin.

Effect of Corticosteroid Injection, Physiotherapy, or Both on Clinical Outcomes in Patients With Unilateral Lateral Epicondylalgia. Coombes BK, et al. JAMA. 2013 Feb 6;309(5):461-9. PMID: 23385272. Among patients with chronic unilateral lateral epicondylalgia, the use of corticosteroid injection vs placebo injection resulted in worse clinical outcomes after 1 year. Physiotherapy did not result in any significant differences.

Safety of osteoanabolic therapy: a decade of experience. Cipriani C, et al. J Bone Miner Res. 2012 Dec;27(12):2419-28. PMID:23165426. Teriparatide and PTH (1–84) have shown to be effective and safe in the treatment of osteoporosis. Thus far, there have been 3 reported cases of osteosarcoma in patients treated with teriparatide out of 1 million treated patients. This rate is consistent with the epidemiology of osteosarcoma in adults. Other potential safety concerns include GI symptoms, transient hypercalcemia, and hyperuricemia.


Incidence of atypical nontraumatic diaphyseal fractures of the femur. Dell RM, et al. J Bone Miner Res. 2012 Dec;27(12):2544-50. PMID: 22836783. In a retrospective study of over 1 million patients the incidence of atypical fractures of the femur increased with longer duration of bisphosphonate use (incidence rates for an atypical fracture were 1.78/100,000 pt-year (95% CI, 1.5-2.0) with exposure from 0.1 to 1.9 years, vs. 113.1/100,000 pt-year (95% CI, 69.3-156.8) with exposure from 8 to 9.9 years). These rates, were lower than the rate of femoral neck fractures.

Rituximab for remission induction and maintenance in refractory granulomatosis with polyangiitis (Wegener’s): ten-year experience at a single center. Cartin-Ceba R, et al. Arthritis Rheum. 2012 Nov;64(11):3770-8. PMID: 22730028. Observational study of 53 patients with refractory GPA, who had gotten at least two courses of Rituximab (RTX) for treatment of their disease. Overall RTX was well tolerated and safe. Infections (n=30) and infusion reactions (n=16) were the most common adverse events.

Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Weinblatt ME, et al. Rheumatology (Oxford). 2012 Dec;51(12):2204-14. PMID: 22627353. This randomized clinical trial of RA patients treated with certolizumab pegol (CZP) showed a rapid and consistent clinical response. Adverse and serious adverse events were comparable between CZP and placebo, without new safety signals.


FDA MEDWATCH: Spring 2013

FDA recommends lower doses of zolpidem. Due to new data showing that blood levels of zolpidem remain high enough to impair activities the next morning, the FDA issued a safety announcement for zolpidem products, including: Ambien, Ambien CR, Edluar, Zolpimist, and their generics. Risk is highest in patients taking extended-release forms of the drug and in women. The agency recommends that doses be lowered for women to 5 mg/day for immediate release products and to 6.25 mg/day for extended release products. The recommended dose for Intermezzo, approved for middle-of-the-night awakenings, did not change. The FDA issued a safety announcement for zolpidem products, including: Ambien, Ambien CR, Edluar, Zolpimist, and their generics. Risk is highest in patients taking extended-release forms of the drug and in women. The agency recommends that doses be lowered for women to 5 mg/day for immediate release products and to 6.25 mg/day for extended release products. The recommended dose for Intermezzo, approved for middle-of-the-night awakenings, did not change. The FDA

Codeine in Children Post-tonsillectomy/adenoectomy Poses Risk for Death. The FDA issued a new BOXED WARNING and CONTRAINDICATION for codeine for children post-tonsillectomy/adenoectomy. After reviewing reports of life-threatening respiratory depression and pediatrics deaths in children with obstructive sleep apnea who underwent these procedures, the FDA has found evidence that these children may have a genetic ability to rapidly metabolize the drug, converting the usual dose of codeine to fatal amounts of morphine in the body. However, given it is difficult to determine which children are ultra-rapid metabolizers of codeine, the warning and contraindications applies to all children undergoing tonsillectomy/adenoectomy.[Posted 2/20/13]

Drug Counterfeiters Exploit Anxious Patients During Influenza Outbreaks. During this flu season’s epidemic, the FDA warns of scammers who promote products with claims to prevent, treat, or cure the flu. These products may be found online and in retail stores, marketed as dietary supplements, conventional foods, drugs, nasal sprays and devices. Several warning letters have been sent to businesses marketing these fraudulent products. Mary Malarkey, director of the

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FDA’s Office of Compliance and Biologics Quality stated, “The unproven products give consumers a false sense of security.” Be wary of websites that sell generic Tamiflu or Relenza. Currently there are no FDA-approved generics available for these drugs on the U.S. market. The FDA encourages consumers to buy prescription drugs only through an online pharmacy that requires a valid prescription from a doctor or other authorized health care provider and is licensed by the state board of pharmacy (or equivalent state agency) where the patient is located. (posted 2/15/13)

New Drug Labeling Changes Approved by the FDA in Jan 2013

Augmentin - Drug interaction with oral anti-coagulants, may raise the PT/INR.
Bentyl (dicyclomine) - A warning posted that psychosis and delirium have been reported in elderly patients and in those with mental illness; symptoms typically resolve within 24 hours after discontinuation of drug.
Ciprofloxin - Warnings have been updated to reflect CNS system effects-psychotic reactions can occur after the first dose of drug; use with caution in epileptic patients can lower seizure threshold.
Norvasc (amlodipine) - Drug interaction with cyclosporine, in a prospective study of renal transplant patients, the cyclosporine trough level increased by 40% when patients were treated with amlodipine.

Opana ER (oxymorphone) - Patient should be counseled that the inactive ingredients of Opana ER can be eliminated as a soft mass in the stool that may resemble the original tablet; reassure patients that active ingredients have been absorbed.
Prozac (fluoxetine HCl) - The drug is contraindicated in patients treated with MAOIs, linezolid, IV methylene blue due to risk for serotonin syndrome. Infants exposed to SSRIs in pregnancy may be at increased risk for persistent pulmonary hypertension of the newborn.
Stelara (ustekinumab) - Postmarketing reports of rapid appearance of multiple cutaneous squamous cell CA in patients at risk for skin CA prompted a warning that all patients who are receiving Stelara should be monitored for non-melanoma skin CA.

IN THE NEWS—Spring 2013

Prescription Opioids are the top cause of drug overdose deaths. The CDC recently released data from the National Center for Health Statistics confirming the predominant role that prescription opioids play in overdose deaths. The report also highlighted the frequent involvement of drugs typically prescribed for mental health conditions such as benzodiazepines, antidepressants, and antipsychotics. People with mental health disorders are at increased risk for polypharmacy. Jones CM, Mack KA, Paulozzi LJ. Pharmaceutical overdose deaths, United States, 2010. JAMA 2013;309:657-9. PMID: 23423407.

Editor’s note: Screening, identifying, and monitoring patients who are at risk for prescription drug abuse has been challenging to physicians, but new tools such as state prescription drug monitoring programs can help clinicians identify these patients. These programs allow prescribers full access to a patient’s history of all controlled substances filled within a specified time period: listing date, name, and quantity of all controlled prescriptions along with the names of prescribers and the pharmacies where the Rx’s were dispensed. Currently, 37 states have a prescription drug monitoring program accessible to practitioners. The Harold Rogers Prescription Drug Monitoring Program (HRPDMP), through federal funds administered by the U.S. Department of Justice, Office of Justice Programs, and Bureau of Justice Assistance, is working with states and pharmaceutical societies to implement the Prescription Drug Monitoring Information Exchange (PMIX) which will permit data sharing among states with drug monitoring programs. To find out if your state participates in this program and how to access the program, visit www.deadiversion.usdoj.gov/fag/ox_monitort.htm4

Reclassifying hydrocodone. The FDA Advisory panel recommended in a 19-to-10 vote that hydrocodone be reclassified as a Schedule II narcotic, placing it in the same category as OxyContin and fentanyl. Should the agency approve the change, patients would be dispensed fewer pills at a time and refills would be restricted. In addition, pharmacies would need to follow stricter procedures for handling and storing the drug. The FDA acknowledges the difficulty in combating hydrocodone abuse, while keeping the drugs available for patients who legitimately need them. Douglas Throckmorton, the agency’s deputy director for regulatory programs, said, “There is an unquestioned epidemic of opioid abuse, overdose and death in this country, an epidemic we need to address as a society.” (Associated Press, 1/25/13)

Parents not overly concerned that their children are on pain meds. The University of Michigan Mott Children’s Hospital National Poll on Children’s Health reported their findings that among 1300 parents with children age 5-17 years old, only 35% and 19% were very concerned about misuse of narcotic pain medicines by children in their community and in their families, respectively. Black parents (38%) and Hispanic parents (26%) were more likely than white parents (13%) to be very concerned about the misuse of narcotic pain medicines in their own families, even though use of the medicines has been shown to be 3 times higher among white teens than other races. “Recent estimates are that 1 in 4 high school seniors have ever used a narcotic pain medicine. However, parents may downplay the risks of narcotic pain medicine because they are prescribed by a doctor,” Sarah Clark, associate director of the Child Health Evaluation and Research Unit at the University of Michigan. (HealthDay 1/23/13)

Changes in generic drug appearance may make patients less likely to take their drug. Generic drugs are required by the FDA to contain the same active ingredients in the same strength and to be metabolized and effective as their name brand counterpart. But because of patent laws, these generics are required to look different. Multiple manufacturers of the same generic medicine will make pills that have different shapes, sizes, and color; this result in a possibility that each time a patient goes into the pharmacy to fill their drug, they will receive a different appearing drug. A recently published study in the JAMA Internal Medicine highlighted the problem of how variations in pill appearance may increase the risk for patient non-adherence. In the study, pill color discordance can carry non-adherence risk with an OR 1.53 (95% CI 1.07-2.18); trend for non-adherence also increases with pill shape changes OR 1.47 (95% CI 0.85-2.54). Kesselheim AS, Misono AS, Shrank WH, Greene JA, Doherty M, Avorn J, et al. Variations in pill appearance of antiepileptic drugs and the risk of nonadherence. JAMA Intern Med 2013;173:202-8. PMID: 23277164.

Editor’s note: To avoid confusion with whether or not patients are on the right medicine, physicians and patients can check to see if the right generic drug was dispensed by going to a pill identifier website: www.drugs.com/pill_identification.html

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Reducing Medication Problems in Seniors. The Centers for Medicare & Medicaid Services (CMS) implemented a patient-centered, community-based drug safety project in Brick, NJ in spring of 2009 to reduce potential medication-related problems in seniors. The project, which is still ongoing, has been able to reduce 33% of potentially inappropriate medications and prevent 12% of drug-drug interaction. The key points that came from the study noted that patients should be able to answer 3 questions when a new drug is prescribed:

1. What is the purpose of the medication?
2. What are the instructions for taking the medication?
3. What adverse effects should they be aware of?  (source: Healthcare Quality Strategies, www.hqsi.org)

Steroid injections worsen Tennis Elbow in the Long run. In an Australian study published in JAMA, researchers reported that patients who received placebo injections or physical therapy were more likely to recover after a year and have less recurrence than those given steroid injections (96 vs. 83%, RR 0.86 (99%CI 0.75-0.99) for lateral epicondylitis. Coombs BK, Bisset L, Brooks P, Khan A, Vicenzino B. Effect of corticosteroid injection, physiotherapy, or both on clinical outcomes in patients with unilateral lateral epicondyliaga: a randomized controlled trial. JAMA 2013;309:461-9. PMID: 23385272

Calcium supplements linked to death from heart disease in men. High intakes of calcium supplements may correlate with an increased risk of death for men but not for women according to the NIH-AARP Diet and Health study published in JAMA Internal Medicine. In this prospective study of 388,229 men and women with a mean follow-up of 12 years, men who took 1,000 mg or more of calcium supplements had a 20% higher risk of dying from cardiovascular disease compared to those who did not (RR 1.20, 95% CI 1.05-1.36). This risk was not seen in women (RR 1.06, 95% CI 0.96-1.18), and there was no link and women with a mean follow-up of 12 years, men who took 1,000 mg or more of calcium supplements had a 20% higher risk of dying from cardiovascular disease compared to those who did not (RR 1.20, 95% CI 1.05-1.36). This risk was not seen in women (RR 1.06, 95% CI 0.96-1.18), and there was no link

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 Caps and Tabs</td>
<td>Apotex halted manufacturing due to FDA audit, Ranbaxy reported raw materials shortage</td>
<td>March 2013</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>Updated: March 2013</td>
</tr>
<tr>
<td>Cytocobalamin 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>Updated: March 2013</td>
</tr>
<tr>
<td>Diphenhydramine HCl inj</td>
<td>Manufacturing delays, demand exceeded supply</td>
<td>Unknown</td>
</tr>
<tr>
<td>Doxycycline (50, 75, 100, 150 mg)</td>
<td>Raw material shortage</td>
<td>March 2013</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: March 2013</td>
</tr>
<tr>
<td>Heparin inj</td>
<td>FDA issued import bans against Chinese mfg due to inadequate manufacturing practices</td>
<td>Unknown</td>
</tr>
<tr>
<td>Hepatitis A virus vaccine</td>
<td>Merck awaiting regulatory approval for manufacturing change</td>
<td>March 2013</td>
</tr>
<tr>
<td>Hydrocortisone 100 mg/2mL, 250 mg/2mL, 500 mg, 1000 mg</td>
<td>Increased demand</td>
<td>2013</td>
</tr>
<tr>
<td>Indomethacin inj (lyophilized powder)</td>
<td>Nationwide backorder due to manufacturing issues</td>
<td>Unknown</td>
</tr>
<tr>
<td>Isoniazid tab (100, 300 mg)</td>
<td>Unknown</td>
<td>March 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>Labetalol Tabs (100, 200, 300 mg) and Inj</td>
<td>Increase demand</td>
<td>Feb-March 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>Unknown</td>
</tr>
<tr>
<td>Lidocaine (with and without Epi) 0.5%, 1%, 1.5%, 2%</td>
<td>Raw material shortage</td>
<td>Revised: March 2013</td>
</tr>
<tr>
<td>Meperidine Injx</td>
<td>Increase demand</td>
<td>2nd quarter 2013</td>
</tr>
<tr>
<td>Mesna Inj</td>
<td>Manufacturing delays and increase demands</td>
<td>Unknown</td>
</tr>
<tr>
<td>Methotrexate Inj 25 mg/mL (2,4,8,10,40 mL vials) AND tablets 2.5 mg</td>
<td>Manufacturing delays</td>
<td>MTX Inj - Unknown MTX tabs – April 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>Product released as it becomes available</td>
</tr>
<tr>
<td>Morphine sulfate inj</td>
<td>Watson noted supply constraints, Teval discontinued product</td>
<td>Revised: Unknown</td>
</tr>
<tr>
<td>Nitroglycerin 2% ointment</td>
<td>Unknown</td>
<td>Revised: March 2013</td>
</tr>
<tr>
<td>Ondansetron Inj 2mg/mL</td>
<td>Manufacturing delays, increased demand</td>
<td>Revised: April 2013</td>
</tr>
<tr>
<td>Pantoprazole Tabs (20,40 mg)</td>
<td>Increased demand</td>
<td>Revised: March 2013</td>
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<tr>
<td>Prednisone 1, 5, 10, 20 mg tab</td>
<td>Raw materials shortage</td>
<td>Revised: March 2013</td>
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<tr>
<td>Promethazine Inj 25 mg/mL, 50 mg/mL</td>
<td>Increase demand, temporary suspension of mfg by Bedford</td>
<td>Revised: March 2013</td>
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<tr>
<td>Tetracycline caps 250 mg, 500 mg</td>
<td>Manufacturing delays, increased demand</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tuberculin PPD, intradermal inj</td>
<td>Increase demand, low supply</td>
<td>March 2013</td>
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autoimmune diseases, such as rheumatoid arthritis (RA), spondyloarthopathies (SpA), and psoriatic arthritis (PsA). Elevated levels of circulating cytokines have also been implicated in these diseases, most notably tumor necrosis factor α (TNFα), also known as cachectin. TNFα acts directly on skeletal muscles to induce proteolysis while inhibiting the response to anabolic stimuli—resulting in myofibrillar atrophy and perpetuating physical inactivity and weakness/atrophy. Additionally, patients with long-standing, untreated autoimmune diseases have altered body composition, with decreased lean body mass along with unchanged autoimmune diseases, such as rheumatoid arthritis (RA), spondyloarthropathies (SpA), and psoriatic arthritis (PsA). The use of TNFα has significantly slowed joint damage and has improved functionality in patients with moderate-to-severe autoimmune diseases. In addition, there have been reports of weight gain in patients using biologics and anti-cachectic effects in animal models, sparking recent investigation as to whether the use of biologic treatments could reverse the cachexia seen in chronic inflammatory diseases and result in weight gain.

**TNFα inhibitors and weight changes:** There have been several studies comparing changes in weight in those patients treated with methotrexate (MTX) and TNFα for the treatment of psoriasis (Ps), PsA, SpA, and RA. Saraceno et al. reported that about half of psoriasis patients treated with etanercept, adalimumab, or infliximab gained a significant amount of weight by week 48. In the etanercept and adalimumab group, an average of 2.5 kg was gained (p < 0.01) and with infliximab, a 1.5 kg weight gain was noted (p < 0.0001). There was no significant weight or BMI changes in those treated with MTX. Additionally BMI was, on average, increased by 0.74 points in those treated with etanercept at the end of 48 weeks (p < 0.006), with similar statistically significant increases seen with infliximab and adalimumab. It is unclear in this study whether the weight changes were due to fat or fat-free mass, or possibly from lifestyle changes incorporated after symptoms improved with treatment. Another study by Renzo et al. measured body composition by Dual-X absortiometry in twenty patients treated with infliximab and etanercept for PsA. They reported 60% of patients gained about 2 kg in 24 weeks, p < 0.001. There was an 8.9% increase in fat mass and a 2.9% increase in lean mass. Similar results were seen in Briot et al., who looked at 106 patients treated with etanercept or infliximab for SpA at 1 and 2 years. Most of the weight gain was due to increased fat mass deposition over lean mass (mean gain of 1.4 kg vs. 0.8 kg, p < 0.0001) within a year. However, it was unclear whether this body composition change was due to TNFi therapy or by improvement of functionality in patients after systemic inflammation decreased. Metzios et al. explored this further by measuring resting energy expenditure (REE) and protein intake immediately after initiating TNFi. They report that in 20 RA patients, there were non-significant changes in fat-free mass or in REE in 2 to 24 weeks after starting TNFi. Through food diaries, the authors noted these patients increased protein intake and decreased carbohydrate intake, which could explain the persistently elevated REE due to anabolic stimuli in this study. Though these studies indicate increased fat mass deposition after initiating therapy, several reports suggest the reversal of insulin resistance, improved beta cell function, and euglycemia in patients with severe RA treated with TNFi therapy. Stagakis et al. reported that in thirty patients, serum insulin was decreased by 21.7 μU/mL (p < 0.001) and fasting blood glucose was decreased by 19.7 mg/dL (p = 0.016) twelve weeks after initiating infliximab, adalimumab, or etanercept therapy. It had previously been suggested that TNFα induces insulin resistance by phosphorylation of the Ser312 residue of the insulin receptor substrate (IRS)-1 and thus, down regulating the insulin response cascade. The authors further tested this hypothesis by analyzing peripheral blood mononuclear cells from 7 RA patients with high disease activity before and after 12 weeks of TNFi therapy. In all but 1 of these patients, a significant reduction in phosphorylated Ser312 was demonstrated by western blot analysis, suggesting that TNFi therapy may improve insulin resistance in patients with active RA by reversing defects in the phosphorylation/activation status of the insulin signaling pathway.

**Summary:** Initiation of TNFi in patients with moderate-to-severe inflammatory disease may be associated with weight gain. However, this treatment may normalize body composition, reverse the changes of the metabolic syndrome, and slow the progression of cardiovascular disease by decreasing inflammation. Physical activity and lifestyle modifications should be encouraged once functionality is improved to reduce the long-term effects of weight gain. Further studies are needed to clarify the role of TNFi in weight gain.

**References**


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