Literature Highlight:
Tofacitinib versus Placebo in Rheumatoid Arthritis

Biologic agents are reserved as second-line therapy for patients who have failed treatment with methotrexate, the disease-modifying agent of choice for patients with rheumatoid arthritis (RA). A new disease-modifying agent, tofacitinib, is being investigated as an alternative option to biologic agents in patients with RA who have had an inadequate response to methotrexate. This 12-month, phase III, randomized, multicenter trial compared the safety and efficacy of tofacitinib to placebo.

A total of 717 patients with active RA were randomized to receive either tofacitinib 5 mg twice daily (n=204), tofacitinib 10 mg twice daily (n=201), adalimumab 40 mg every two weeks (n=204), or placebo (n=108). Placebo patients with no response at three months were randomized to receive either 5 mg or 10 mg of tofacitinib. All other placebo patients were switched to one of the tofacitinib groups at six months. All patients continued stable doses of methotrexate throughout the trial. Adalimumab was included in this trial to allow for a relative safety and efficacy comparison to tofacitinib, but a formal comparison was not conducted.

The three primary efficacy endpoints were the percentage of treatment responders at six months (defined as a 20% reduction in RA symptoms according to the American College of Rheumatology (ACR) criteria [ACR 20]), the mean change in physical function status at three months (measured with the Health Assessment Questionnaire-Disability Index [HAQ-DI]), and the number of patients with a Disease Activity Score (DAS28-4) <2.6 at six months (higher scores indicate greater disease activity). The secondary endpoints included the percentage of patients who had a 50% (ACR 50) or 70% (ACR 70) reduction in RA symptoms. The safety of tofacitinib was also compared to placebo.

Compared with 28.3% of the placebo group, 51.5%, 52.6%, and 47.2% of the 5 mg tofacitinib, 10 mg tofacitinib, and 40 mg adalimumab groups, respectively, were treatment responders at six months (p<0.001 for all comparisons). The active treatment groups also had greater improvements in the HAQ-DI scores at three months (p<0.001) and significantly more patients with DAS28-4 <2.6 at six months (p<0.05 for 5 mg tofacitinib and adalimumab groups; p<0.001 for 10 mg tofacitinib group). Both tofacitinib groups had significantly more patients with ACR 50 and ACR 70 responses compared to placebo (p≤0.05). Infection occurred in 18%, 17%, 16%, and 9% of the 5 mg and 10 mg tofacitinib, adalimumab, and placebo groups, respectively. The authors concluded that tofacitinib was superior in improving RA symptoms, disability, and disease activity compared to placebo. The study was potentially biased because of the heavy involvement of the manufacturer of tofacitinib (Pfizer) in designing and editing the study.

CONCLUSION: When compared to placebo, the number of tender and swollen joints and disease disability significantly improved in patients taking tofacitinib. Side effects were more common in the tofacitinib groups when compared to placebo. The most common adverse event was infection.


By Jordan Peck, Pharm.D. Candidate
Metformin and Breast Cancer

Increasing evidence has emerged of metformin decreasing the incidence of and possibly treating breast cancer. Insulin receptors may be overexpressed in breast cancer tissues, which may contribute to the development and progression of breast cancer. Metformin is thought to reduce the incidence of breast cancer by activating adenosine 5-monophosphate-activated protein kinase (AMPK). Activation of AMPK decreases blood glucose levels and improves insulin sensitivity. Two studies that evaluated metformin in preventing and treating breast cancer are presented here.1,2

A prospective cohort study assessed the incidence of breast cancer in postmenopausal women with type 2 diabetes using metformin.1 This was part of the Women’s Health Initiative (WHI) clinical trials. A total of 68,109 women were observed for an average of 11.8 years. Postmenopausal women with type 2 diabetes using metformin in preventing and treating breast cancer were diagnosed with diabetes, 3273 with breast cancer. A total of 11,290 women were taking medications other than metformin. The primary endpoint was the incidence of breast cancer in postmenopausal women. 3,302.

The pCR is defined as the absence of tumor in the removed tissue at the time of surgery and can be a strong predictor of long-term survival. Disease-free survival is decreased if tumor residuals are found in tissues. The study enrolled 68 patients with diabetes taking metformin, 87 patients with diabetes not taking metformin, and 2374 patients without diabetes. Neither the severity of diabetes nor the amount of chemotherapy received differed between groups. The primary endpoint was pCR rates. The pCR rates were significantly higher in the patients using metformin (24%, 95% CI 13%-34%) compared to the patients with diabetes not using metformin (8%, 95% CI 2.3%-14%) and the patients without diabetes (16%, 95% CI 15%-18%; p=0.02). There was a significant difference in pCR rates between the metformin patients and patients with diabetes not using metformin (p=0.007) and between the patients with diabetes not using metformin and patients without diabetes (p=0.04). Patients with diabetes and breast cancer who were receiving metformin and neoadjuvant chemotherapy had a higher pCR rate than patients with diabetes not taking metformin (24% vs. 8%, respectively; p=0.007). The authors concluded that metformin increased the effectiveness of neoadjuvant chemotherapy and increased pCR rates.

The lack of control for confounding factors such as body mass index, menopausal status, and age limit this study. There may have been unidentified confounders because it was a retrospective trial.2

A phase III, placebo-controlled, randomized, five-year clinical trial is currently underway to assess the effects of metformin on cancer response rates in early-stage breast cancer patients without diabetes.3

In conclusion, insulin is thought to be a key factor in breast cancer progression. Between the studies described, metformin was associated with a decrease in the incidence of breast cancer in women with diabetes and increased response rates in women with breast cancer receiving neoadjuvant chemotherapy. These findings support the hypothesis that metformin has a positive association with breast cancer and may reduce incidence and improve cancer therapy. More trials are needed in understanding the mechanism and determining the exact role of metformin in breast cancer.

By Carla Jacobson, Pharm.D. Candidate

REFERENCES:
Pertussis Vaccination and Treatment

Pertussis is an endemic disease in the United States.¹ There have been 28,703 reported cases of pertussis so far in 2012. In Montana, 432 cases have been reported in 2012.² The incidence of pertussis in Montana is 39.5/100,000 persons, higher than the national incidence of 7.36/100,000 persons.¹

Pertussis is most often caused by *Bordetella pertussis* and is commonly referred to as whooping cough, due to its presentation of a prolonged cough followed by an inspiratory whoop. Infection can result in breathing difficulty, vomiting, and disturbed sleep in adults and pneumonia, seizures, brain damage, or even death in infants. Severe disease is most common in young, unvaccinated infants, and pneumonia is the most common complication.³ Vaccination against pertussis is the best way to limit further outbreaks and prevent infection of this disease.¹

The two whooping cough vaccines available are the DTaP (Infanrix® and Daptacel®) and the Tdap (Adacel® and Boostrix®). Each is a three-disease vaccine for protection against tetanus, diphtheria, and pertussis.³⁴ Contraindications to pertussis vaccination include a history of encephalopathy with, or a severe allergic reaction to, any of the diphtheria/tetanus vaccines. Precautions of vaccination include a history of Guillian-Barré syndrome or an allergic reaction after the diphtheria/tetanus vaccine.⁴

The pertussis vaccines are given intramuscularly (0.5 mL), and either one can be given at the same time as other vaccines.³⁴ Infants and children should receive five separated doses of the DTaP vaccine (one at two, four, and six months; one between 15 and 18 months; and one between years four and six).⁵ Children who have not been vaccinated and who are in close contact with a pertussis-infected patient should receive the five-dose series with a minimum of four weeks between dose one, two, and three. There should be a minimum of six months between doses three and four.³ A fifth dose should be given according to recommendations above, only if the previous four vaccinations have been given. If a child is not fully vaccinated with DTaP at seven to ten years of age, they should receive a single dose of Tdap.⁵

Adolescents 11 through 18 years old should receive the Tdap vaccine at their next check-up. Adults 19 years and older should receive a one-time Tdap in place of their 10-year Td booster, given at any time. Unvaccinated pregnant women should receive a one-time Tdap during late second trimester (after 20 weeks gestation), the third trimester, or immediately postpartum.⁴⁵ Maternal antibodies produced after pregnancy vaccination protect both the mother and the newborn.⁵

Pharmacists in Montana who have a collaborative practice agreement with an authorized practitioner and who hold a current immunization and CPR certification are authorized to administer the pertussis vaccine to persons 18 years of age or older.⁶

Antibiotic treatment and prophylaxis will eradicate pertussis in infected persons (symptomatic or asymptomatic). Treatment can decrease the severity and duration of symptoms if given early in the course of illness and will reduce the risk of transmission.⁷ Common antibacterial treatments include azithromycin and clarithromycin. Trimethoprim-sulfamethoxazole can be used for patients who have a contraindication to primary treatment or if resistance is suspected.⁷ The recommended dose and duration for each age group is shown in Table 1.⁸ Untreated patients will spontaneously clear pertussis within three to four weeks from the onset of cough but can remain culture-positive for greater than six weeks.⁷ Chemoprophylaxis is recommended for close contacts and for all household members of a pertussis-infected patient.³

*Bordetella pertussis* is a bacterial infection that has become an endemic disease in the United States. The best way to prevent illness and limit outbreaks is by getting vaccinated. Two vaccines are available (DTaP and Tdap), and vaccination should be done according to the age recommendations. Antibiotic treatment is available to help decrease the severity and duration of illness, as well as reduce transmission.⁸

**By Amanda Schneider, Pharm.D. Candidate**

**REFERENCES:**


Table 1: Antibiotic Treatment of Pertussis⁸

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Age Group</th>
<th>Dose</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>azithromycin</td>
<td>&lt; 6 months</td>
<td>10 mg/kg</td>
<td>one dose/day x 5 days</td>
</tr>
<tr>
<td></td>
<td>&gt;6 months</td>
<td>10 mg/kg, then 5 mg/kg</td>
<td>1st dose day 1, 2nd dose day 2 to 5</td>
</tr>
<tr>
<td></td>
<td>adults</td>
<td>500 mg, then 250 mg</td>
<td>1st dose day 1, 2nd dose day 2 to 5</td>
</tr>
<tr>
<td>clarithromycin</td>
<td>&gt;1 month</td>
<td>7.5 mg/kg</td>
<td>two doses/day x 7 days</td>
</tr>
<tr>
<td></td>
<td>adults</td>
<td>500 mg</td>
<td>two doses/day x 7 days</td>
</tr>
<tr>
<td>*trimethoprim/sulfamethoxazole</td>
<td>&gt;2 months</td>
<td>8 mg/kg/40 mg/kg</td>
<td>two doses/day x 14 days</td>
</tr>
<tr>
<td></td>
<td>adults</td>
<td>320 mg/1600 mg</td>
<td>two doses/day x 14 days</td>
</tr>
</tbody>
</table>

*alternative treatment

(continued on page 4)
Outbreak of Mycobacterium chelonae Infection

*Mycobacterium chelonae* is a rapid growing, atypical tubercular type of mycobacterium usually found in water, soil, and dust.1–4 Since 2003, cases have emerged throughout the United States linking local infection with *M. chelonae* to contaminated ink used in tattooing.1,2 Many isolates are known to be resistant to a variety of antimicrobial therapies.1–5 Clarithromycin remains the therapy of choice for the treatment of *M. chelonae*.5 There was a recent outbreak of *M. chelonae* in 19 people who received tattoos.1 Seventeen of the 19 recently infected patients were biopsied, from which 14 cultures of *M. chelonae* were isolated. Two patients received antimicrobial susceptibility testing. *M. chelonae* was susceptible to clarithromycin, doxycycline, and linezolid; had intermediate susceptibility to ciprofloxacin; and was resistant to cefoxitin in the first patient. In the second patient, *M. chelonae* was susceptible to clarithromycin and doxycycline, had intermediate susceptibility to linezolid, and was resistant to ciprofloxacin and cefoxitin. Patients were treated with appropriate antimicrobial therapy and recovered.1

A separate case report described a 32-year-old male who developed skin lesions across a tattoo he had received three weeks prior. *M. chelonae* grew from a skin biopsy obtained from his tattoo site. Testing revealed susceptibility to clarithromycin; intermediate susceptibility to moxifloxacin, tobramycin, and azithromycin; and resistance to other agents, including minocycline, rifampicin, cotrimoxazole, imipenem, ciprofloxacin, cefoxitin, and amikacin. Due to the high rate of resistance, dual therapy was started with clarithromycin 500 mg twice daily and moxifloxacin 400 mg once daily. The patient improved with no signs of recurrent infection.2

*M. chelonae* is highly resistant to cefoxitin, with a minimum inhibitory concentration (MIC) >128 mg/mL. Imipenem is considered the parenteral agent of choice based on *in vitro* studies. Many oral agents are also ineffective in treating *M. chelonae* infection.3,4 In one study, 83%, 95%, 79%, 93%, and 15% of *M. chelonae* isolates were found to be resistant to ciprofloxacin (MIC breakpoint <2.0 mg/mL), ofloxacin (MIC breakpoint <4.0 mg/mL), doxycycline (MIC breakpoint >4.0 mg/mL), sulfamethoxazole (MIC breakpoint >32 mg/mL), and erythromycin (MIC breakpoint >4 mg/mL), respectively.5 Susceptibility to clarithromycin is excellent, with most isolates of *M. chelonae* having an MIC ≤0.25 to 1.0 mg/mL.3 Antimicrobial handbooks also list clarithromycin as a first-line treatment for *M. chelonae*, with recommended doses of 500 mg by mouth twice daily for six months. For serious disseminated infections, other medications such as moxifloxacin or levofloxacin should be added to clarithromycin.5

While most isolates of *M. chelonae* are found in water, soil, and dust, there have been several outbreaks linking it to tattooing. *M. chelonae* is resistant to many treatment options. Clarithromycin remains the best treatment option and is recommended as first-line treatment. However, susceptibility testing should be done to pick the best available option for each individual when treating this atypical form of mycobacterium.

By Jordan Peck, Pharm.D. Candidate

**REFERENCES:**


**Pertussis (from page 3)**

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2. DRUGDDEX® System [Internet database]. Greenwood Village, Colo: Thomson Reuters (Healthcare) Inc. Updated periodically.

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Literature Highlight:
Biolimus-Eluting Stents vs. Bare-Metal Stents in Patients with Acute Myocardial Infarction

Previous studies have shown a lower risk of revascularization with the use of drug-eluting stents when compared to bare-metal stents. However, very-late stent thrombosis was more common in the drug-eluting stents. The newer-generation biolimus-eluting stent (BES) contains a biodegradable polymer, which makes it more comparable to a bare-metal stent (BMS) after degradation has occurred. The BES was shown to have a lower rate of major adverse cardiac events when compared to BMS in this prospective, multi-center, randomized, single (assessor)-blinded, controlled superiority trial. The study compared the two stents after one year of placement in patients with an ST-segment elevation myocardial infarction (STEMI).

All patients also received acetylsalicylic acid (>250 mg) and either prasugrel 60 mg, with a 10 mg/day maintenance dose, or clopidogrel 600 mg, followed by 75 mg twice daily for seven days, with a 75 mg/day maintenance dose. The primary outcome was major adverse cardiac events (cardiac death, target vessel-related reinfarction, and ischemia-driven target-lesion revascularization). Secondary outcomes were cardiac death, any reinfarction or revascularization, stent thrombosis, and all-cause mortality. Patients were evaluated at 1 and 12 months.

Major cardiac events occurred in 4.3% of patients receiving BES and in 8.7% of patients receiving BMS (HR 0.49; 95% CI 0.30-0.80; p=0.004). BES was associated with a 4.4% absolute reduction and a 51% relative reduction in the risk of major adverse cardiac events. The combined occurrence of death, any reinfarction, and any revascularization occurred more frequently in patients with BMS (12.2%) compared to patients with BES (8.4%; HR 0.68; 95% CI 0.47-0.98; p=0.04). Among patients using BES, stent thrombosis occurred in two patients and restenosis occurred in one patient.

In patients using BMS, stent thrombosis occurred in 10 patients, restenosis occurred in four patients, and spontaneous MI occurred in one patient. No differences were seen in all-cause and cardiac mortality between the two groups. BES had a lower risk of major cardiac events compared to BMS.

The authors concluded that fewer major adverse cardiac events occurred in STEMI patients using a BES with a biodegradable polymer compared to patients using a BMS. The variable use of prasugrel and clopidogrel limits the study, and additional studies should be done with consistent use of antiplatelet therapy. Further studies are needed to evaluate the efficacy of BES and BMS beyond one year of placement.

CONCLUSION: In patients with STEMI undergoing percutaneous coronary intervention, biolimus-eluting stents with a biodegradable polymer were associated with a lower rate of major adverse cardiac events at one year compared to bare metal stents.


By Amanda Schneider, Pharm.D. Candidate