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INSIDE

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Update on Moxifloxacin (Avelox): New Indications

SPECIAL FEATURE (PART 1 OF 3-PART SERIES)

By Joanne Hsu, PharmD Candidate, Cindy Tat, PharmD Candidate, Jessica C. Song, MA, PharmD

Joanne Hsu and Cindy Tat are PharmD Candidates at the University of the Pacific, School of Pharmacy, and Jessica Song is Pharmacy Residency Coordinator at SCVMC

Joanne, Cindy, and Jessica report no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company related to this field of study.

Introduction

SINCE THE FDA APPROVAL OF MOXIFLOXACIN IN DECEMBER 1991 for the treatment of community-acquired pneumonia, sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated skin/skin structure infections, its indications for use has been expanded to include the treatment of complicated skin/skin structure infections[2] and complicated intra-abdominal infections.[3] A variety of factors must be taken into consideration when making decisions about which fluoroquinolones to include in the formulary. These factors include safety, clinical efficacy, spectrum of indications, and cost. In view of the fact that moxifloxacin's indications for use were expanded to include 2 new indications within the past 6 months, clinicians should be educated on these new developments. This article will: 1) review the clinical efficacy of moxifloxacin for the treatment of complicated intra-abdominal infections and 2) review the clinical efficacy of moxifloxacin for the treatment of complicated skin/skin structure infections.

Complicated Intra-Abdominal Infections

Complicated intra-abdominal infections are defined as infections that extend beyond the hollow viscus of origin into the peritoneal space, and are associated with abscess formation or peritonitis. Furthermore, resolution of these types of infections requires either oper-

ative or percutaneous intervention.[4] There is a wide variety of conditions associated with intra-abdominal infections, including perforated gastroduodenal ulcers, biliary tract infections, small bowel perforations, appendicitis, and diverticulitis.[5] The pathogens causing complicated intra-abdominal infections vary depending on whether the infection is community-acquired or health care associated. Empirical treatment will, thus, be dependent on the type of infection the patient presents with on hospital admission.

According to the 2003 Infectious Diseases Society of America (IDSA) Guidelines, empiric antimicrobial agents for community-acquired intra-abdominal infections should cover enteric gram-negative aerobic and facultative bacilli and beta-lactam-susceptible gram-positive cocci. Additionally, coverage for obligate anaerobic bacilli is needed for distal small-bowel and colon-derived infections and for more proximal perforations when obstruction is present. Narrower spectrum agents that are not commonly used for nosocomial infections are preferred over broader spectrum antimicrobials for mild-to-moderate community-acquired intra-abdominal infections. These agents include ampicillin/sulbactam, ticarcillin/clavulanate, ertapenem, (cefazolin or cefuroxime) plus metronidazole, or a fluoroquinolone (ciprofloxacin, levofloxacin, moxifloxacin, or gatifloxacin) plus metronidazole. High-severity infections (higher APACHE II scores, significant cardiovascular disease, poor nutritional status, immunosuppression) may benefit from antimicrobials, with a broader spectrum of activity against facultative and aerobic gram-negative pathogens. These agents include piperacillin/tazobactam, imipenem/cilastatin, meropenem, a third- or fourth-generation cephalosporin (cefotaxime, ceftriaxone, ceftizoxime, ceftazidime, or cefepime) plus metronidazole, ciprofloxacin plus metronidazole, or aztreonam plus metronidazole.[4]

Health care associated intra-abdominal infections occur as a result of complications of previous elective or emergent intra-abdominal operations, and are caused by more resistant pathogens, including *Pseudomonas aeruginosa*, Enterobacter spp, Proteus spp, methicillin-resistant *Staphylococcus aureus*, enterococci, and Candida spp. These infections often require complex multidrug regimens, where local nosocomial resistance patterns dictate empirical treatment. Once results of microbiology workup of infected fluid are obtained, antimicrobial therapy should be adjusted accordingly.[4]

Previously, moxifloxacin was only recommended as dual-therapy with metronidazole for the treatment of mild-to-moderate community-acquired intra-abdominal infections. Malongoni and colleagues conducted a prospective, randomized, double-blind, multicenter, Phase III study (n = 379) comparing the efficacy of moxifloxacin (400 mg once-daily sequential IV/PO) with that of piperacillin/tazobactam (3.375 mg IV 4 times daily), followed by amoxicillin/clavulanate (800 mg PO twice daily) for the treatment of complicated intra-abdominal infections in adult patients (total treatment duration of 5-14 days). The primary efficacy end point was based on clinical response rate at the test-of-cure visit (25-50 days after study entry). Baseline patient demographics and infection characteristics (85% community-acquired; complicated appendicitis, appendix abscess, gangrenous appendix, large or distal small bowel perforations, diverticulitis) were similar in both study groups. The 2 most common causative pathogens were *E. coli* and *B. fragilis*, with a majority of the patients having polymicrobial infections in both the moxifloxacin-treated group and the comparator group, 84% and 79.1% respectively.[6]

Of note, the study population was comprised mainly of relatively younger and otherwise healthy patients, as the average patient age was approximately 46 years, and an APACHE II score of 6.9 ± 4.2 was reported for the moxifloxacin-treated group, and a score of 5.9 ± 4.2 was observed in the comparator-treated group. Additionally, the study lacked infections caused by more resistant pathogens, such as *Pseudomonas aeruginosa*, MRSA, extended-spectrum β-lactamase-producing (ESBL) *Klebsiella pneumoniae*, and had a limited number of

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Questions & Comments

Leslie Hamlin,
Associate Managing Editor, at (404) 262-5416, or e-mail to leslie.hamlin@thomson.com between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

infections caused by *Enterococcus faecalis*, all of which may complicate the treatment of health care associated intra-abdominal infections.[6]

At the test-of-cure visit, moxifloxacin IV/PO monotherapy was shown to be noninferior to standard therapy of IV piperacillin/tazobactam, followed by oral amoxicillin/clavulanate, as 79.8% of the moxifloxacin-treated patients and 78.2% of the comparator-treated patients achieved an overall clinical response (95% CI, -7.6 to 9.2). The clinical cure rates for patients with abscess were 76.3% for the moxifloxacin group and 77.6% for the comparator group. Patients with community-acquired infections achieved a clinical cure rate of 79.4% in the moxifloxacin group vs 82.5% in the comparator group. Overall bacterial eradication rates for the moxifloxacin and the comparator group were 77.9% and 77.4%, respectively. Time to recovery, duration of hospitalization, clinical response rates and improvement in APACHE scores at day 3-5, and microbiologic success rates were all comparable in both groups, with no statistically significant difference. Overall safety profile was also similar in the 2 groups, with the percentage of patients who prematurely discontinued the study due to an adverse event being 10.4% in the moxifloxacin group and 8.5% in the control group.[6]

From this study, moxifloxacin gained FDA approval for the treatment of complicated intra-abdominal infections, including polymicrobial infections, such as abscesses caused by Gram-positive pathogens (*Enterococcus faecalis*, *Streptococcus anginosus*, *Streptococcus constellatus*), Gram-negative pathogens (*Escherichia coli*, *Proteus mirabilis*), and anaerobic pathogens (*Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Clostridium perfringens*, Peptostreptococcus species).[7] Moxifloxacin is the only marketed fluoroquinolone antibiotic approved by the FDA as monotherapy to treat this indication.

Complicated Skin/Skin-Structure Infections

Complicated skin and skin-structure infections (cSSSI) are defined as infections involving deeper soft tissue, requiring significant surgical intervention, or occurring in compromised hosts. Complicated infections include secondary infections of diseased skin, as well as post-operative/traumatic wound infections, bite-related infections, venous stasis ulcers, pressure sores, diabetic foot infections, and perianal cellulitis with or without abscess.[8,9] The most common pathogens involved in skin infections are gram-positive cocci, *Staphylococcus aureus*, and streptococci. However, complicated infections often involve enteric gram-negative bacilli and anaerobic bacteria, especially for patients with underlying risk factors (diabetic, immunocompromised, vascular compromise). Common gram negative pathogens include *Escherichia coli*, Klebsiella spp., Enterobacter spp., and *Pseudomonas aeruginosa*.[8-10]

The 2005 Infectious Disease Society of America (IDSA) guidelines for the treatment of skin and soft-tissue infections (SSTI) recommend several antibiotics as effective therapy of various types of skin and skin-structure infections. Management of cSSSI involves empirical broad-spectrum antibiotic therapy to cover the likely polymicrobial etiology of the infection in conjunction with appropriate surgical interventions.[9] *Table 1* summarizes the IDSA recommendations for the treatment and management of the most commonly encountered cSSSIs, including cellulitis and diabetic foot infections. Cellulitis cases are typically caused by ?-hemolytic streptococci and rarely *Staphylococcus aureus*, unless underlying abscess or penetrating trauma is present.[11] Diabetic foot infections predominantly involve aerobic gram-positive cocci, specifically *Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA). Enterobacteriaceae, *Pseudomonas aeruginosa*, and obligate anaerobic pathogens may also be present in patients with chronic wounds, recent antibiotic therapy, or foot ischemia or gangrene.[12] Therapy should be based on clinical severity of the infection and targeted to cover the appropriate pathogens.[8,11,12]

Moxifloxacin was previously indicated for uncomplicated skin and skin-structure infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. Recently, moxifloxacin gained FDA-approval for the treatment of complicated skin and skin-structure infections involving methicillin-susceptible *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, or *Enterobacter clocae*.[7] It has been shown to have broad-spectrum in vitro activity against the common cSSSI pathogens, along with rapid bactericidal action and adequate tissue concentrations at skin and soft tissue infection sites.[13,14]

Giordano and colleagues conducted a prospective, randomized, multicenter, double-blind, active-control Phase IIIb trial, in which once daily moxifloxacin 400 mg intravenously (IV) followed by oral moxifloxacin was compared with piperacillin/tazobactam 3.375 g IV every 6 hours followed by oral amoxicillin-clavulanic acid suspension 800 mg twice daily for cSSSI. Adult patients (n = 617) were randomized to one of the 2 treatment regimens for 7-14 days, with at least 3 days consisting of intravenous therapy, of which 367 were eligible for inclusion in the efficacy-valid population (180 moxifloxacin,187 control) and 237 were determined to

be microbiologically-evaluable (119 moxifloxacin, 118 control). The most commonly reported cSSSIs in this trial included abscess, cellulitis, and diabetic foot infections. Surgical procedures were performed in 34% of piperacillin-tazobactam-treated patients and in 31% of moxifloxacin-treated patients. The primary end point was efficacy, which was defined by clinical response at the test-of-cure (TOC) visit 10-42 days post-therapy. Safety and tolerability were evaluated by monitoring adverse events, routine laboratory assessments, and physical examinations.[9]

Moxifloxacin was shown to have similar clinical cure rates at TOC compared to the control regimen of piperacillin/tazobactam, as 79% of the moxifloxacin group and 82% of the comparator group achieved a clinical response (95% CI -12.0%, 3.3%). The clinical cure rates were also comparable among different infection types between the treatment groups, with the exception of abscesses. Patients with abscess had a higher response rate in the control group (79% vs 93%, P = 0.04). Bacteriological eradication rates were also similar between treatment groups. The most frequently encountered pathogen, methicillin-sensitive *Staphylococcus aureus* (54% moxifloxacin, 50% control), showed comparable bacteriological eradication with moxifloxacin versus the control regimen (78% vs 80%; 95% CI -14.8%, 5.2%). As expected, both groups had lower eradication rates for MRSA (60% moxifloxacin, 71% control). Moxifloxacin also provided comparable bacteriological eradication of other common pathogens of cSSSI, including *Streptococcus pyogenes*, *Escherichia coli*, *Klebsiella pneumonia*, and *Enterobacter cloacae*. The safety and tolerability data showed no clinically significant difference between moxifloxacin and the comparator. The only drug-related adverse events that occurred in > 3% of patients were diarrhea (5% moxifloxacin, 8% control) and nausea (4% moxifloxacin, 2% control).[9]

However, it is important to realize that although moxifloxacin has significant coverage for the common cSSSI pathogens, it is not indicated for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa*. Skin infections caused by *Pseudomonas aeruginosa* are more often associated with nosocomially-acquired infections, and less commonly seen in the community. The presence of *Pseudomonas aeruginosa* in some diabetic foot infections is sometimes considered a contaminate or colonization, rather than a pathological infection. However, it can be the cause of wound infections following fresh water exposure, hot-tub folliculitis, or deep foot infections from a sports shoe puncture.[8]

There is a growing concern regarding MRSA skin infections, as these infections are occurring not only in hospitals, but also increasingly in the community in patients with no other risk factors.[8,15] If MRSA is a suspected pathogen of cSSSI, moxifloxacin is not indicated for MRSA and will not provide adequate coverage. Community isolates of MRSA have been shown to display susceptibility to tetracyclines (doxycycline, minocycline), clindamycin (no resistance to erythromycin), and trimethoprim-sulfamethoxazole.[11,16] Vancomycin, linezolid, and daptomycin should be reserved for use in the treatment of patients with MRSA skin infections that necessitate hospitalization, or if earlier eradication measures have failed.[11]

Other antibiotics (marketed in the United States) that show much potential for the management and treatment of cSSSI include ertapenem and tigecycline. Like moxifloxacin, ertapenem covers most of the common pathogens of cSSSI, including MSSA, streptococci, enterobacteriaceae, anaerobes, but not most Enterococcus or Pseudomonas species. The once-daily dosed ertapenem (1 g every 24h) was shown to be as safe and effective as piperacillin-tazobactam (3.375 g every 6h) in a randomized, double-blinded study consisting of 540 adults with cSSSI.[17] Recently, a once-daily dose ertapenem (1 g every 24h) was shown to be as safe and effective as piperacillin-tazobactam (3.375 g every 6h) in a randomized, double-blinded study consisting of 586 diabetic adults with moderate-to-severe foot infection (*S. aureus* (80% methicillin-sensitive) identified in ~40% of subjects).[18] Tigecycline is also indicated for cSSSI infections attributable to *Escherichia coli*, *Enterococcus faecalis* (vancomycin susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* group, *Streptococcus pyogenes*, and *Bacteroides fragilis*.[19] The advantage of tigecycline over moxifloxacin is its coverage against MRSA. However, as with ertapenem, tigecycline is only available as a parenteral product whereas moxifloxacin has both a parenteral and oral formulation.

Conclusion

At present, moxifloxacin is indicated for the treatment of community-acquired pneumonia, sinusitis, acute bacterial exacerbation of chronic bronchitis, complicated skin/skin structure infections, uncomplicated skin/skin structure infections, and complicated intra-abdominal infections. This drug is the only marketed fluoroquinolone approved by the FDA as monotherapy for the indication of complicated intra-abdominal infection. While moxifloxacin has been shown to be as effec-

Table 1

IDSA suggested empirical regimens for cellulitis (2005) and diabetic foot infections (2004)[11,12]

Infection Type	Recommended Antibiotic Agents	Mild (Oral for most)	Moderate (Oral or IV)	Severe (IV initially)
Cellulitis[a]	Dicloxacillin	X	X	
	Cephalexin	X	X	
	Clindamycin	X	X	
	Erythromycin	X	X	
	Nafcillin			X
	Cefaxolin			X
	Vancomycin			X
Diabetic Foot Infections[b]	Dicloxacillin	X		
	Clindamycin	X		
	Cephalexin	X		
	Trimethoprim-Sulfamethoxazole	X	X	
	Amoxicillin/clavulanate	X	X	
	Levofloxacin	X	X	
	Cefoxitin		X	
	Ceftriaxone		X	
	Ampicillin/sulbactam		X	
	Linezolid (± aztreonam)- for MRSA		X	
	Daptomycin (± aztreonam)- for MRSA		X	
	Ertapenem		X	
	Cefuroxime with or without metronidazole		X	
	Ticarcillin/clavulanate		X	
	Piperacillin/tazobactam		X	X
	Levofloxacin or ciprofloxacin with clindamycin		X	X
	Imipenem-cilastatin			X
	Vancomycin (for MRSA) and ceftazidime (with or without metronizadole			X

[a]IDSA guidelines recommend parenteral antibiotics for severely ill patients with cellulitis.

[b]IDSA clinical classification of diabetic foot infection: (1) mild—presences of ≥ 2 manifestations of inflammation, but any cellulitis/erythema extends ≥ 2 cm around ulcer, and infection limited to skin or superficial subcutaneous tissue; no other local complications or systemic illness; (2) moderate—infection as above in patient who is systemically well and metabolically stable but has ≥ 1 of the following: cellulitis extends ≥ 2 cm, lymphangitis streaking, spread beneath superficial fascia, deep-tissue abscess, gangrene, and involvement of muscle, tendon, joint, bone; (3) severe—infection with systemic toxicity or metabolic instability.

tive as piperacillin-tazobactam in the treatment of complicated intra-abdominal infection, it should be noted that this finding primarily applies to patients with community-acquired infections, where more resistant causative organisms, such as *Pseudomonas aeruginosa*, *Enterococcus faecalis*, and MRSA are unlikely pathogens. Similarly, moxifloxacin has been shown to provide comparable clinical cure rates to that of piperacillin-tazobactam for patients with complicated skin/skin structure infection, comprised of cellulitis, abscess, and diabetic foot infections. However, because of the growing concern of MRSA skin infections, it is important to realize that coverage against this pathogen will not be provided by monotherapy with moxifloxacin or any of the other fluoroquinolones. ■

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Diabetic Foot Infections: Culture Results from Bone Biopsy and Swab Specimens

ABSTRACT AND COMMENTARY

By Dean L. Winslow, MD, FACP

Chief, Division of AIDS Medicine, Santa Clara Valley Medical Center, Clinical Professor of Medicine, Stanford University School of Medicine

Dr. Winslow is a consultant for Bayer Diagnostics and Pfizer/Agouron, and is on the speaker's bureau for Pfizer/Agouron.

Synopsis: *Seventy-six patients with diabetic foot osteomyelitis underwent surgical bone biopsy for culture had bone culture results compared to swab culture results. The results of bone and swab cultures were identical in only 17% of patients and bone bacteria were isolated from swab cultures only 30% of the time.*

Source: Senneville E, et al. Culture of Percutaneous Bone Biopsy Specimens for Diagnosis of Diabetic Foot Osteomyelitis: Concordance with Ulcer Swab Cultures. *Clin Infect Dis*. 2006;42:57-62.

THIS STUDY FROM A SINGLE DIABETIC FOOT CLINIC IN France involved a retrospective chart review of patients who underwent surgical percutaneous bone biopsy with culture for microbiologic diagnosis of osteomyelitis. Patients included for study were those who had not

received either local or systemic antibiotics for at least 4 weeks prior to cultures being obtained. Osteomyelitis was defined by a variety of reasonable criteria, which are detailed in the article. Swab specimens were obtained from foot ulcers after brief cleansing of the ulcer with sterile physiologic glucose solution applied with a sterile compress. Percutaneous bone biopsies were performed in the operating room using sterile technique with an 11-gauge biopsy needle inserted through a 5-10 mm skin incision made at least 20 mm from the periphery of the ulcer. When debridement was required, the biopsy was obtained prior to the foot being opened. Standard microbiological methods were employed to isolate and identify bacterial pathogens.

Eighty-one bone biopsy samples and 69 swab samples were obtained from 76 patients. A mean of approximately 1.5-1.6 bacterial species were isolated from both culture sources. Interestingly, staphylococci were isolated much more frequently from bone samples (52%) than from swab samples (38%), but the isolation rate for *Staphylococcus aureus* was fairly similar (26% bone vs 33% swab). Somewhat counterintuitively, the difference is largely explained by the fact that coagulase negative staphylococci were isolated much more often from bone than from wound swabs (26% vs 5%). Streptococci were isolated from only 12% of bone biopsy specimens and 20% of ulcers. Gram negative bacilli were obtained from 18% of bone and 26% of swab samples. Anaerobes were isolated from 5% of bone and 3% of swab specimens. When looking at the proportion of pathogens isolated from cultures of bone biopsy and/or swab samples obtained from the 69 patients who had cultures from both sources, the concordance was poor. The percent concordance for *S. aureus* was 43%, for Gram negative bacilli 29%, streptococci 26%, enterococci 7%, coagulase negative staphylococci 3%, and there was no concordance for corynebacteria and anaerobes.

COMMENTARY

This study serves as a good reminder of the historically poor reliability of superficial swab cultures in diagnosis of the etiologic agents causing diabetic foot infections in individual patients. Even the old saw I have been repeating for 30 years to fellows, residents, and students that, "only when one isolates *S. aureus* in pure culture from an ulcer can one assume that is the cause of the osteomyelitis," is proved false by this study. While surgical debridement is necessary in many cases, virtually all patients with osteomyelitis complicating diabetic foot infections will also require prolonged, often parenterally administered antibiotics. Because of the toxicities, expense, and potential inactivity of empirically chosen and excessively broad-spectrum antibiotics, it behooves us as infectious disease clinicians to push our medical and surgical colleagues to obtain bone biopsies for culture so we can properly treat these serious infections. ■

Napoleon, Typhus, and Trench Fever

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

Synopsis: *Retreating troops of Napoleon's army were devastated by two louse-borne diseases, typhus and trench fever.*

Source: Raoult D, et al. Evidence for Louse-Transmitted Diseases in Soldiers of Napoleon's Grand Army in Vilnius. *J Infect Dis*. 2006;193:112-120.

Raoult and colleagues examined material from a recently uncovered mass grave site dating to 1812 in Vilnius, Lithuania, and identified the presence of body lice (*Pediculus humanus*), 3 of 5 of which contained DNA of *Bartonella quintana*, the etiologic agent of trench fever. DNA of *B. quintana* was also identified by PCR and sequencing in the dental pulp of 7 of 35 soldiers, while DNA of *Rickettsia prowazekii*, the agent of epidemic louse-borne typhus, was identified in 3 of the 35.

COMMENTARY

In the autumn of 2001, construction workers in the Siaures Miestalis ("Northern Town") section of Vilnius uncovered a mass grave containing several thousand neatly stacked skeletons, most in a fetal position. While initial assumptions led to conjectures that these were victims of either the Nazis or of the Soviet Red Army, examination of medals, buttons, coins, and cloth found with the remains indicated that they were soldiers of the Grand Armée, members of 40 different regiments, who had died during Vilnius in that ghastly frigid winter of 1812, toward the end of the Little Ice Age.

The humiliating return of the Grand Armée to Vilnius in December 1812 was a pitiful contrast to the scene earlier that year when more than half a

million soldiers from multiple nations had gathered there to set off to invade and conquer Russia. The fact that fewer than 10% of that vast army escaped the Russian countryside to reach the capital of the Duchy of Lithuania was evidence that they were the conquered, rather than the conquerors. Unfortunately for them, the horror was not yet over—only approximately 3000 would ultimately reach home.

Napoleon himself did not tarry in Vilnius on his way back from Moscow, but returned directly to Paris. He was not alone in fleeing—Napoleon's brother-in-law, later the King of Naples who had been left in command, left Vilnius declaring, "I'm not going to be trapped in this piss-pot." He made a good choice. Vilnius became a charnel house for the rest—not as the result of combat, but as the result of cold, famine, and, importantly, typhus. Thus, it has been said that several "Generals" defeated Napoleon's army. These include "General Cold" and "General Famine", but perhaps most important of all was "General Typhus".

Rickettsia prowazekii causes epidemic louse-borne typhus, recrudescent typhus (Brill-Zinsser disease), and flying squirrel-associated typhus. It has previously been suggested, based on descriptive information, that louse-borne typhus may have killed as many as half of Napoleon's Grand Armée. The findings by Raoult and colleagues, that definitively identify *R. prowazekii*-associated mortality among members of the army who died in Vilnius during their retreat, is the first scientifically acceptable evidence in support of typhus as a cause of mortality among Napoleon's troops.

Bartonella quintana, which is also transmitted by body lice, is the cause of trench fever, an infection which was reported in 1915 among lice-infested soldiers in the trenches of the Western Front of World War I. It currently is predominantly identified in homeless individuals.

In past centuries, infectious disease was the leading cause of mortality among soldiers at war. Napoleon's Grand Armée, assembled for the invasion of Russia, was no exception. While cold, famine, and Russian troops took their toll, the human body louse and 2 of its associated human pathogens may have provided the death knell.

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Putting on Hold Orders to "Hold the Blood Cultures"

ABSTRACT & COMMENTARY

By Stan Deresinski, MD

Synopsis: *Extensive processing and prolonged incubation of blood cultures in patients with fever of unknown origin or of endocarditis were not effective in the detection of etiologic pathogens.*

Source: Baron EJ, Scott JD, Tompkins LS. Prolonged Incubation and Extensive Subculturing Do Not Increase Recovery Clinically Significant Microorganisms from Standard Automated Blood Cultures. *Clin Infect Dis*. 2005;41:1677-1680.

Beginning in 1995, a remarkably extensive blood culture protocol was established at Stanford University Hospital for use in patients with fever of unknown origin or suspected endocarditis. This included the use of an average of almost 90 mL of blood from patients obtained by several venipunctures. Blood inoculated into Bactec bottles was incubated for 21 days, but was also subcultured after 3 and 10 days onto a variety of enrichment media, including buffered charcoal yeast agar, chocolate and rabbit agars, Sabouraud dextrose agar, and Lowenstein-Jensen agar, each with prolonged incubation. Aliquots from anaerobic bottles were subcultured to hemin-supplemented Brucella blood agar and anaerobically incubated. Acridine orange stains were performed on media at days 3 and 10. For patients with suspected endocarditis, blood treated by lysis-centrifugation was inoculated onto the same media mentioned above and incubated for 6 days to 6 weeks, depending upon the target organism and medium.

Blood from 215 patients was managed this way over a 3-year period, during which approximately 42,000 blood cultures were treated in the standard manner with 5 days of incubation on the Bactec 9240 instrument. During that time, 24 HACEK organisms were recovered from the standard 5-day-incubation cultures, and 98% of all positive blood cultures were recovered by the 4th day of incubation.

Only 15 isolates from the 215 patients that were recovered with the special protocol would not have been detected by the standard method, and 12 of these were apparent contaminant. Of the remaining 3, 2 were *Mycobacterium avium* complex (MAC) isolates from a patient with AIDS with samples obtained months apart, and one was a Legionella species.

COMMENTARY

I don't know how many times I've heard the term "HACEK" and the phrase "hold the blood cultures" mentioned in the same breath. This is true despite the fact that it has seemed obvious for some time that, with the use of modern microbiologic techniques, prolongation of incubation does not improve the yield of this group of relatively fastidious organisms (*Haemophilus aphrophilus*, *Haemophilus paraphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominem*, *Eikenella corrodens*, and *Kingella kingae*). In addition to the results discussed here, this conclusion has also recently been confirmed in a report in which HACEK organisms were recovered from < 0.005% of more than 59,000 blood cultures.[1] In addition, none of 407 blood cultures with extended incubation yielded any bacteria after 5 days. A recommendation against prolonged incubation has been incorporated into the most recently published guidelines of the American Society for Microbiology, which have recently been outlined in *Infectious Disease Alert*.[2,3]

The experience of Baron and colleagues takes this finding much further by demonstrating that an amazingly complex blood culture protocol, using multiple methods and media, together with prolonged incubation, failed to provide significant benefit in a group of patients with fever of unknown origin or suspected endocarditis. The only clinically relevant organisms exclusively recovered with the extended multifaceted protocol were MAC isolates from an AIDS patient and Legionella from another patient.

Baron et al counsel against a blanket approach to the use of special methods and prolonged incubation in the diagnosis of, eg, endocarditis. They instead provide a series of recommendations for the detection of agents of septicemia or endocarditis not recovered by routine blood cultures. These apply to a variety of suspected agents, including filamentous fungi, Legionella, Bartonella, and others. In addition, Stanford now requires a mandatory Infectious Disease consultation when special approaches are needed for the detection of suspected pathogens. ■

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Abacavir/Tenofovir- and Didanosine/Tenofovir-Containing Antiretroviral Regimens

ABSTRACTS AND COMMENTARY

By Dean L. Winslow, MD

Synopsis: *The ESS30009 study included antiretroviral-naïve patients randomized to either tenofovir (TDF)/abacavir (ABC)/lamivudine (3TC) or efavirenz (EFV)/abacavir/lamivudine. Patients in the TDF/ABC/3TC arm had a significantly higher risk of nonresponse or virologic failure as well as development of K65R and M184V substitutions in RT. The TEDDI trial consisted treatment-naïve patients given TDF/didanosine (ddI)/EFV. A high rate of virologic failure/nonresponse was seen along with the frequent development of K65R, L74V, and typical nnRTI substitutions.*

Sources: Gallant JE, et al. Early Virologic Nonresponse to Tenofovir, Abacavir, and Lamivudine in HIV-Infected Antiretroviral-Naïve Subjects. *J Infect Dis*. 2005;192:1921-1930; Van Lunzen J, et al. High Rate of Virologic Failure During Once Daily Therapy with Tenofovir + Didanosine 250 mg + Efavirenz in Antiretroviral Naïve Patients: Results of the TEDDI Trial. Program and Abstracts of the 3rd IAS Conference on HIV Pathogenesis and Treatment; 2005; Abstract # TuP p0306.

THE FIRST ARTICLE REPORTS THE RESULTS OF AN industry-sponsored clinical trial comparing TDF/ABC/3TC vs EFV/ABC/3TC in treatment-naïve patients. Three hundred forty patients were randomized. Baseline characteristics, including CD4 count and HIV RNA level were similar between the arms. In an unplanned interim analysis performed in patients who had received at least 8 weeks of therapy, only 5 patients (5.4%) in the EFV experienced virologic nonresponse, whereas 50 patients (49%) in the TDF group failed to respond. In patients on the TDF/ABC/3TC arm failing therapy, K65R with or without M184V was commonly seen.

The second paper (presented at last summer's IAS Conference in Brazil) reported the results of European pilot study of TDF/ddI/EFV in 39 treatment-naïve patients. Virologic failure (or initial nonresponse) occurred in 11 (28%) of patients. NRTI substitutions

observed in failing patients included K65R and L74V. nnRTI substitutions included 101E, 103N, 188C, and 190S/E. This study was terminated early by European regulatory authorities.

COMMENTARY

The cornerstone of antiretroviral (ARV) therapy, since 1996, has consisted of regimens containing 2 nucleoside analog reverse transcriptase inhibitors (NRTIs) plus either a protease inhibitor (PI) or an non-nucleoside RT inhibitor (nnRTI). However, due to the increased potency of newer NRTIs and toxicities associated with nnRTIs and PIs (especially metabolic side effects with the latter), there has been interest in triple-nucleoside combination therapy. Unfortunately, despite the intrinsic potency of ABC, 3TC, and TDF individually (and in the double combinations of ABC/3TC and TDF/3TC or TDF/FTC), the rate of virologic failure and development of resistance-associated substitutions was surprisingly high with the triple nucleoside combination. Similarly, the double combination of ABC/TDF appears to be much less potent in vivo than either ABC/3TC or TDF/3TC or TDF/FTC, but does select for resistant variants.

The explanation for the poor performance of these regimens is unclear, and may be multifactorial. In vitro studies do not show antagonism between these agents in cell culture. Pharmacokinetic studies do not show any interaction of these drugs, which is reflected in plasma levels. Even in vitro studies of PBMCs to date have not shown conclusively any significant reductions of intracellular levels of nucleoside triphosphates when various combinations of these nucleosides are incubated with PBMCs in vitro. PMPA (the active moiety of TDF) inhibits purine nucleoside phosphorylase (PNP) and may cause accumulation of naturally-occurring dNTP's, favoring incorporation of the natural dNTPs over the other purine analog NRTIs,[1] but data suggesting alteration of nucleotide pools in vivo to the magnitude necessary to produce virologic nonresponse are equivocal. However, this inhibition of PNP by TDF is a likely explanation for the enhanced toxicity and CD4 cell decline seen with TDF combined with ddI in vivo. Another explanation of the high failure rate seen with these regimens includes the possibility that nucleosides and nucleoside analogues are not uniformly distributed or phosphorylated in different CD4+ cell populations.[2] Similarly, recent data suggest that distribution and metabolism of nucleoside analogue agents may vary considerably between PBMCs and lymph node mononuclear cells, due to differential expression of multidrug resistance (MDR) proteins in various compartments which affect efflux of nucleoside analogs.[3] Lastly, a low genetic barrier to resistance to TDF/ABC/3TC has been postulated since K65R alone may be sufficient to confer resistance to all 3 drugs in this regimen. However, only about half of patients genotyped at the time of virologic failure in the ESS30009 trial had K65R at the time of virologic failure.

While TDF plus either 3TC or FTC clearly provides a potent NRTI backbone for either a PI or nRTI-containing regimen, it is clear that TDF cannot be blindly combined with other agents, despite evidence of genotypic or phenotypic susceptibility test results. In any case, it is my personal opinion that regimens combining either TDF with either ddI or ABC should generally be avoided. The California Collaborative Treatment Group (CCTG) 584 study, which is performing detailed studies of intracellular pharmacokinetics of TDF and ABC (including assessment of PNP and MDR proteins), is currently enrolling patients and may shed light on what are complex drug interaction issues. ■

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In Future Issues:

Update on Moxifloxacin (Avelox): Potential Interactions with Warfarin and Cardiac Rhythm Safety

UPDATES

By Carol A. Kemper, MD, FACP

Deal Struck for Lower Cost HIV Treatment

New York Times, January 12, 2006, page A11.

THE CLINTON FOUNDATION announced the successful conclusion of negotiations with several pharmaceutical companies to provide lower cost HIV testing and treatment to poorer countries. Four companies—3 from India and 1 from South Africa— have agreed to provide nevirapine and abacavir (at $USD 240 and $447 per patient per year, respectively), provided that certain conditions are met on an ongoing basis. These include the receipt of large, advance orders for drug, with regular payments, and a dependable supply of materials. Cipla, an Indian pharmaceutical company, indicated the cost of nevirapine would increase by 11% if orders were lower than expected.

Demand should sadly not be a problem. Four companies from the United States, China, and India also agreed to provide lower cost HIV testing, ranging from $.49 to $.65 (down from about one dollar). It is estimated that 90% of those infected with HIV around the world—about 36 million people—are unaware of their infection. Low cost tests for detection are the first step to providing treatment for those who need it. ■

Risk of Fetal Death Increased with HAART

Suy A, et al. Increased Risk of Pre-Eclampsia and Fetal Death in HIV-Infected Pregnant Women Receiving Highly Active Antiretroviral Therapy. *AIDS*. 2006;20:59-66.

EARLIER REPORTS SUGGESTED THAT lactic acidosis and premature delivery are more common in HIV-positive pregnant women receiving antiretroviral therapy. These authors have found an increased risk for pre-eclampsia and fetal death in pregnant HIV-positive women receiving HAART. While rates per 1000 deliveries remained stable in HIV-negative women between the period of 1985-2000 to 2001-2003, rates per 1000 deliveries in HIV-positive women increased from 0 to 109.8 for pre-eclampsia, and from 7.7 to 61 for fetal death for the same time periods. Additional risk factors for both groups included multiple gestations, multiparity, and tobacco use.

Interestingly, in HIV-positive women, the use of HAART before pregnancy was also associated with a significantly higher risk of pre-eclampsia and fetal death. While the risk of HAART therapy administered prior to (adjusted OR 5.6, 95% CI, 1.8-18.1) versus during (adjusted OR 4.9, 95% CI 2.4-10.1) pregnancy appeared similar, it was not clear from this analysis to what degree the effect of cumulative therapy was on those risks. Whether it is possible to identify women at greater risk, such as those with lipodystrophy, is not known. HIV-positive women who are pregnant or desirous of pregnancy should be counseled regarding this additional threat. ■

Viread—The New Safe Sex Pill

Los Angeles Times, January 3, 2006.

THIS ARTICLE CONFIRMS WHAT HIV clinicians—at least on the West Coast—have been facing for more than a year. Over the past few months, I have seen 5 newly diagnosed gay men, two with acute primary HIV infection, and two with positive syphilis titers; all 5 acquired their infection during weekend "clubbing" in San Francisco. All 5 reported "weekend" methamphetamine use, and they all believed they had good control of their drug use. Over the new few months, it became clearer that all of them used more frequently, and at least for 2 of them, their meth use had spun out of control. Two lost their jobs.

Meet the new face of HIV. New infections in gay and bisexual men having sex with men (MSM) increased 8% last year, and syphilis rates have increased 29%. San Francisco County reported 17 cases of syphilis diagnosed in 2003; last year the rate was expected to top 1700 cases.

Blame it on the new "cocktail." MSM are increasingly downing combinations of viread, viagra, ecstasy, and methamphetamines—the former in the hope of preventing HIV transmission, and the latter 2 to "heighten" the sexual experience. My gay friends tell me the clubs are filled on weekends with MSM; coupling occurs dozens of times in one night; bowls of condoms are readily available but ignored by half. Surveys performed at recent gay pride events found that 7% of gay men had taken an antiretroviral agent before engaging in risky sexual behavior. Other data that we collected from major urban areas on the West Coast found that about 40% of sexually active MSM engaged in unprotected oral or anal sex with at least one partner in the previous 3 months, and 25% had failed to disclose their HIV status.

Viread is a perfect drug for use—abuse—in these circumstances because it is remarkably well tolerated and has a long half-life (12-14.4 hrs). Viread is currently recommended, in combination with other agents, such as emtriva and efavirenz, for post-exposure prophylaxis (PEP) for percutaneous exposure, where antiretroviral therapy is increasingly believed to provide some protection against high risk needlesticks. And, preliminary data from 2 CDC studies suggest that viread may reduce sexual transmission of HIV when taken preventatively.

The gay community has extended this research to real world practice, thinking that if it can reduce transmission for one high risk exposure, why not multiple? If post-exposure prophylaxis provides som protection, why not *pre-exposure* exposure? Even if viread is successful in reducing the risk of sexual transmission to a similar degree as that estimated for a 4-week regimen of PEP for percutaneous exposure, back of the envelope calculations suggest, with a minimum of 100 exposures per year, this practice will result in a rate of annual infection somewhere between 1 to 10%. Early on, the gay community could not be held accountable for the spread of HIV, and over the years many health care providers have sought ways to better communicate the risks to their patients and modulate risky behavior. Sadly, these MSM know exactly what they are doing. ■

Hepatitis in a Traveler Receiving Atovaquone/Proguanil

Grieshaber M, et al. Acute Hepatitis and Atovaquone/Proguanil. *J Travel Med*. 2005;12:289-290.

THIS BRIEF REPORT DESCRIBES THE occurrence of acute hepatitis possibly related to the administration of atovaquone/proguanil (AP) for malaria prophylaxis. A 31-year previously healthy man took AP for 25 days while traveling in Southern Africa. About 2 weeks after his return, he developed flu-like symptoms, with anorexia and jaundice. Serologies for hepatitis viruses A, B, C, E, EBV, cytomegalovirus, schistosoma, and rickettsia; smears for malaria; and studies for autoimmune hepatitis were all negative. AP was discontinued, and within 6 to 8 weeks, the liver function tests normalized. The authors tentatively diagnosed a drug related hepatitis. Elevations in liver function studies have been reported during treatment of active malaria with AP. While the reported incidence of elevations in alkaline phosphatase and transaminases during AP treatment of active malaria varies, they may occur in up to 2-4% of cases. And, elevations in transaminases greater than 5 times the upper limit of normal occur in 4-6% of patients being treated with atovaquone for pneumocystosis, although only 2% of cases resulted in dose-limiting toxicity. While clinical hepatitis and jaundice during AP malaria prophylaxis has not been previously reported, a drug-induced hepatitis seems plausible in this case. ■

Bovine TB threatens Minnesota

Pro-MED-mail post, December 10, 2005; www.promedmail.org

MY HOME STATE OF MINNESOTA joins three other states that have lost their TB-free status for cattle, including Michigan, Texas and New Mexico. Last winter, the United States Department of Agriculture announced the discovery of bovine TB in a cow in Roseau County, near the Canadian border. Forty-two herds of cattle were quarantined, 4 of which were found to be infected (6 are still being tested) leading to the destruction of more than 4000 cattle in 2 counties. Ranchers in Minnesota will now be required to pay for mandatory testing of all cattle shipped outstate to feedlots, for slaughter, or for breeding.

Blame it on the insidious spread of TB among the white tailed deer populations in the Northwest. *Mycobacterium tuberculosis* vs *bovine* can infect a wide range of warm-blooded vertebrates, where it is generally transmitted through nose-to-nose contact or oral/nasal secretions. The United States TB eradication program has been widely successful in eradicating bovine TB in the United States, except in a few states where isolated animals have come in contact with infected wildlife. Michigan has been especially hard hit, with an estimated 150 million dollar loss in cattle sales last year. The problem has become so severe, that adjacent Indiana has considered fencing in its northern border to keep the deer population from migrating south.

Most TB in cattle is found in the lungs and in lymph nodes, and can readily be spotted at slaughter. There is little risk of contagion, or threat to humans caring for the animals, although disease can be transmitted through ingestion of unpasteurized mild products and undercooked meat or, rarely, close contact with nasal secretions. ■

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Letrozole for Postmenopausal Women with Breast Cancer

Letrozole (Femara) is a potent aromatase inhibitor that is used to treat women with metastatic breast cancer and, in a neoadjuvant role, for women who have failed tamoxifen. Aromatase inhibitors exert their effect by blocking the conversion of androgens to estrogens and reducing estrogen levels in tissue and plasma. Recently, letrozole was compared with tamoxifen for adjuvant therapy in postmenopausal women with steroid-hormone-receptor-positive breast cancer.

A total of 8010 women were randomized to 5 years of letrozole (4003) or tamoxifen (4007). After a median follow-up of 25.8 months, there were 351 events (local or distant recurrence) in the letrozole group and 428 events in the tamoxifen group, with 5-year disease-free survival estimates of 84% and 81.4%, respectively. Adverse effects of the drugs were different with tamoxifen, resulting in a higher rate of thromboembolism, endometrial cancer, and vaginal bleeding, while letrozole was associated with a higher incidence of skeletal and cardiac events and hypercholesterolemia.

The authors suggest that in women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease (Thurlimann B, et al. A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer. *N Engl J Med*. 2005;353:2747-2757). In an accompanying editorial Sandra Swain, MD, from the National Cancer Institute, states that "all the evidence points to aromatase inhibitors as critically important for improving the outcome among postmenopausal women with breast cancer who have positive or negative lymph nodes and who are at a substantial risk for recurrent disease." (Swain SM, et al. Aromatase Inhibitors—A Triumph of Translational Oncology. *N Engl J Med*. 2005;353:2807-2809). Based on this study, the FDA has recently approved letrozole for adjuvant treatment (immediately after surgery) in postmenopausal women with hormone sense of breast cancer.

Do Antidepressants Increase Risk of Suicide?

An article in the January issue of the *American Journal of Psychiatry* asks "Is the FDA Warning About Antidepressants Wrong?" Researchers from Group Health Cooperative in the Pacific Northwest used population-based data to evaluate the risk of suicide death and serious suicide attempt in relation to the initiation of antidepressant treatment.

Computerized health plan records for over 65,000 patients with over 82,000 episodes of antidepressant treatment between 1992 and 2003 were reviewed. In the 6 months after initiation of antidepressant treatment, the risk of suicide was found be no higher than at any other time during treatment. The risk of suicide attempt was highest in the month before starting treatment, and declined progressively after starting medication. When newer drugs were compared to older drugs, an increase in suicidality was

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

only seen with the older drugs.

The authors conclude that the risk of suicide during acute-phase antidepressant treatment is approximately 1 in 3000 treatment episodes, and the risk of serious suicide attempt is approximately one in 1000. Available data do not indicate significant increase in risk of suicide or serious suicide attempt after starting treatment with newer antidepressant drugs (Simon GE, et al. Suicide Risk During Antidepressant Treatment. *Am J Psychiatry*. 2006;163:41-47, available free at ajp.psychiatryonline.org). The study calls into question the March 2004 FDA public health advisory regarding worsening depression and suicidality in pediatric and adult patients being treated with 10 newer antidepressants (bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, escitalopram, and venlafaxine).

Can Viagra Improve Heart Function?

Concern still lingers regarding the safety of erectile dysfunction drugs in patients with heart failure. A new study from Australia suggests that sildenafil (Viagra) actually improves heart function in patients with systolic dysfunction. In a randomized, placebo-controlled, double-blind, 2-way crossover study, 20 patients with controlled left ventricular failure and ejection fractions < 35% received sildenafil 50 mg or matching placebo. Cardiac output was determined by Doppler echocardiography, aortic pressure waveform, and aortic and femoral arterial stiffness was also evaluated. With a peak effect at 60 minutes after administration, sildenafil resulted in an increase in cardiac index of 0.37 L/min, decrease in total systemic resistance, decreased aortic and lower limb pulse-wave velocity, and decreased wave reflection (all significant at $P < .0001$). The authors conclude that sildenafil improved cardiac performance by decreasing LV load, resulting in increased cardiac output and increase in exercise capacity in heart failure patients (Hirata K, et al. Effect of Sildenafil on Cardiac Performance in Patients with Heart Failure. *Am J Cardiol*. 2005;96:1436-1440).

Can Tamoxifen Increase Your Height?

Tamoxifen may increase height potential in short pubertal periods, according to new study in the journal *Pediatrics*. The study was a retrospective chart review of 7 boys with a mean age of 15 who took tamoxifen 10-20 mg twice a day for a mean of 26 months. Six of the boys were also receiving growth hormone. Tamoxifen significantly decreased the rate of skeletal maturation and improved predicted adult height without negative effects on sexual maturation. Skeletal maturation was determined by review of bone radiographs by independent endocrinologists. The authors state that "additional evaluation of this therapy is now required to determine if the increase in predicted adult height results in a clinically significant increase in final adult height." (Kreher NC, et al. The Use of Tamoxifen to Improve Height Potential in Short Pubertal Boys. *Pediatrics*. 2005;116:1513-1515).

A Dramatic Increase of Clostridium difficile

Clostridium difficile is increasing in frequency and severity in both hospital and community settings. Widespread use of acid suppressing proton pump inhibitors (PPIs) and H2 receptor agonists (H2RAs) may be a contributing factor, according to new study. Two population-based, case-control studies from England reviewed all 1672 cases of *C. difficile* reported between 1994 and 2004, while a second study looked at cases defined as community acquired. All cases were matched 10 controls. The incidence of *C. difficile* increased dramatically between 1994 and 2004. The adjusted rate ratio of *C. difficile* associated disease with current use of PPIs was 2.9 (95% CI, 2.4-3.4) and, with H2RAs, the rate ratio was 2.0 (95% CI, 1.6-2.7). The authors conclude that the use of acid-suppressive therapy is associated with an increase risk of community-acquired *C. difficile*. Parenthetically, they also found an increased risk associated with use of nonsteroidal anti-inflammatory drugs (*JAMA*. 2005;294:2943-3048).

FDA Actions

The FDA has approved Bristol-Myers Squibb's abatacept (Orencia) for the treatment of rheumatoid arthritis. The drug, which is produced by recombinant DNA technology, is a T cell costimulation modulator. It is approved for patients with moderately-to-severely active rheumatoid arthritis who had an inadequate response to one or more DMARDs, including TNF antagonists. It may be used as monotherapy or with other non-TNF inhibitor DMARD. Abatacept is administered as a 30-minute IV infusion at 0, 2, and 4 weeks, then every 4 weeks thereafter.

The FDA and GlaxoSmithKline have issued a "Dear Doctor" letter regarding rare reports of macular edema in patients receiving rosiglitazone (Avandia). The majority of the cases involved concurrent peripheral edema and, in the majority of cases, macular edema improved with discontinuation of the drug. Macular edema presents as blurred or distorted vision, decrease color sensitivity, and decreased dark adaptation. ■