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Infectious Disease [ALERT]

Incisive Commentary and Clinical Abstracts on Current Issues in Infectious Diseases

ABSTRACT & COMMENTARY

Xenotourism — Live Cell Therapy, Maybe Not So Therapeutic

By Stan Deresinski, MD, FACP, FIDSA

Dr. Deresinski is Clinical Profesor of Medicine, Stanford University.

Dr. Deresinski reports no financial relationships relevant to this field of study.

SYNOPSIS: Beware injection with sheep fetal cells.

SOURCE: Robyn MP, Newman AP, Amato M, et al. Q fever outbreak among travelers to Germany who received live cell therapy — United States and Canada, 2014. *MMWR Morb Mortal Wkly Rep* 2015;64:1071-1073.

In the autumn of 2014, the New York State Department of Health learned of five patients with a diagnosis of Q fever who had traveled to Germany as part of a larger group in May 2014. On May 30, they each received intramuscular injections of fetal sheep cells, becoming ill approximately one week later. In addition, a Canadian resident who had received an injection from the same physician on May 28 was found to have Q fever in July. All six patients had serological tests consistent with acute Q fever. Their *Coxiella burnetii* phase I IgG antibody titers ranged from1:512 to 1:2048, while their phase II IgG titers ranged from 1:4096 to 1:65,536. Phase I IgM titers were elevated in four patients, while phase II IgM titers were elevated in all six patients, ranging from 1:64 to 1:32,768. All patients were treated with doxycycline.

When notified, German authorities reported that, at the time, they were investigating an outbreak of Q fever in humans due to inhalation exposure to the very sheep flock that was the source of the fetal sheep cells administered to these six patients.

■ COMMENTARY

The diagnosis and management of Q fever is discussed in an excellent CDC monograph[1] that I

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highly recommend.

The two patients who consented to be interviewed indicated that they were among a group that had traveled to Germany for injections twice each year for the past 5 years. Live cell therapy, developed in Switzerland more than 75 years ago, is purported to have innumerable health benefits, including improvement in energy and erectile function, as well as reversal of multiple diseases and slowing of aging.[2] A wide array of cell types of varying animal origin have been used. One startling example of a live cell therapist is John R. Brinkley, commonly referred to as "the goat gland doctor," who reportedly implanted as many as 16,000 men with tissue from the testicles of young goats.[2]

A variety of adverse consequences have been reported, many of which, such as polyradiculitis, leukoencephalitis, Guillain-Barré syndrome, vasculitis, encephalopathy, and skin reactions, may be immunologic in nature, but clostridial infections have also occurred. Many countries, including some where the treatment is offered, have no relevant regulations of the practice of live cell therapy. As a form of xenotransplantation, it is allowed in Germany as a "drug" manufactured by physicians only for the use in their own patients. In the United States, its use in a clinical trial setting would require the filing of an Investigational New Drug Application. The FDA recommends that recipients enrolled in research studies remain under lifelong surveillance with periodic clinical and laboratory monitoring and that both they and their intimate contacts refrain from blood and tissue donation. No such monitoring or restrictions are placed on "xenotourists" in the United States. As a consequence, xenotourism poses a potential threat that goes beyond the personal. ■

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ABSTRACT & COMMENTARY

Cutaneous Leishmaniasis in Syrian Refugees

By Philip R. Fischer, MD, DTM&H

Dr. Fischer is Professor of Pediatrics, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, MN.

Dr. Fischer reports no financial relationships relevant to this field of study.

SYNOPSIS: Cutaneous leishmaniasis is spreading as refugees move from Syria through Turkey into Europe and throughout the world. Aware clinicians can consider diagnostic testing when facing unusual skin lesions in refugees.

SOURCE: Hayani K, Dandashli A, Weisshaar E. Cutaneous leishmaniasis in Syria: Clinical features, current status, and the effects of war. *Acta Derm Venereol* 2015;95:62-66.

Cutaneous leishmaniasis is transmitted in nearly 100 countries and is especially common in some developing countries, including Syria. Concerned about war-induced changes in the epidemiology of infections in Syria, the investigators reviewed Syrian experience with cutaneous leishmaniasis.

Oral tradition includes stories of a Syrian "one year sore" with unusual cutaneous lesions. This condition was documented in the Middle Ages. More recently (in 1756), a British physician referred to the illness as Aleppo boil and Aleppo evil — named for the north Syrian city where the authors worked. With widespread

insecticide use during the middle of the last century, cutaneous leishmaniasis became less common. The incidence, however, began to rise in recent decades when insecticide was not commonly used. The incidence has risen more than 10-fold during the past decade.

In Aleppo, *Leishmania tropica* accounts for most cutaneous leishmaniasis, and *L. major* is a more common cause in the suburbs of Damascus. Fat sand rats, gerbils, and dogs are the typical animal reservoirs, but human-to-human transmission occurs through phlebotomine sand flies without other animal involvement in some areas.

The clinical presentation varies with the parasite species involved and with the immune status of the patient, and the character of the skin lesions is quite variable. A reddish papule appears (presumably at the site of a sand fly bite), and nodules and ulcerations can develop. Lesions can appear to be poorly healing acne, unremitting lichenified eczema-like sores, papulo-vesicular spots, and ulcerating plaques. Within 12-18 months, the local infection usually resolves, but scars can be extensive and unsightly. Affected patients, even if the infection self-resolves, have higher anxiety and depression scores, lower body image satisfaction scores, and poor scores on quality-of-life testing.

The diagnosis is made by identifying Leishmania parasites in Geimsa-stained skin or, sometimes, by finding non-casseating granulomas in skin biopsies. Polymerase chain reaction (PCR) testing is not always available in endemic areas. Treatment depends on the extent of the disease. Topical treatment can be employed when there are three or fewer small lesions; intralesional injection of meglumine antimonate is effective. (NOTE: This treatment is not approved for use in the United States.) Larger, more numerous, and potentially more disfiguring lesions can be treated systemically with intramuscular meglumine antimonate or intravenous sodium stibogluconate for 2 to 3 weeks. In other areas with greater medication availability, meltifosine and liposomal amphotericin can be used.

■ COMMENTARY

Syria Struggles

A protest in March 2011 in southern Syria prompted a governmental reaction and widespread civil unrest. More than 200,000 people have died. The political situation has grown more complicated with the involvement of not just the government and rebels, but now also the Islamic State. Aleppo, formerly a thriving city of 2.5 million with 6000 doctors, is now said to be "a city in ruins."[1] Hundreds of health care professionals have died in the conflict, and it is said that 75% of health workers are part of the more than 4 million people leaving the country.[1] Interestingly, the two authors of this paper who were from Aleppo now have addresses in Germany and the United Arab Emirates. The crisis has provoked increases not only in cutaneous leishmaniasis, but also polio, measles, and tuberculosis.[1]

Spreading to Lebanon and Turkey

As Syrians leave their homeland, they sometimes carry their germs with them. There have been dramatic increases in the number of cases of cutaneous leishmaniasis in southeastern Turkey.[2] In Turkey, 69% of cutaneous leishmaniasis patients are Syrians living in tent cities. There, it is suggested that control efforts include improved housing, improved access to health care, and better vector control.[2] While Lebanon previously only recorded 0-6 cases of leishmaniasis each year, there are now more than 1000.[3]

Risks in Europe and Beyond

As is clear from recent news reports, Syrian refuges don't all stay in Turkey and Lebanon. There is a significant risk that cutaneous leishmaniasis will re-emerge in southern Europe where the natural vector of *L. tropica* already exists.[4,5] Not just refugees, but also travelers can be affected by leishmaniasis and potentially serve as sources of transmission where the relevant sand flies reside. Most travel-related leishmaniasis has come from South America in recent decades,[6] but that situation might change. While cutaneous leishmaniasis is more common in Brazil and Peru than in other countries of Latin America, most travel-associated leishmaniasis in the United States comes from Central America and Mexico.[6]

Clinical Suspicion Critical

Clinical suspicion of cutaneous leishmaniasis is the key to diagnosis. It is reported that infected Americans see six doctors and have multiple skin grafts prior to the correct diagnosis being considered.[6] Skin samples are the first choice for seeking confirmation of the parasitic cause of otherwise unexplained skin lesions, but tissue PCR is more sensitive and is particularly useful when skin sample/biopsy histology is unrevealing.[6] However, PCR can remain positive with lingering parasite antigens long after clinical cure; thus, PCR is not a good test to determine outcomes of treatment.[6,7] Treatment is as noted in the Syrian report. ■

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ABSTRACT & COMMENTARY

Dual Combination ART with Cabotegravir and Rilpivirine Is Effective for Maintaining HIV Virological Suppression

By Richard R. Watkins, MD, MS, FACP

Division of Infectious Diseases, Akron General Medical Center, Akron, OH; Associate Professor of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH

Dr. Watkins reports that he has received research support from Forest Laboratories.

SYNOPSIS: Results of the phase 2 LATTE study show that after 24 weeks of induction triple therapy, maintenance therapy with cabotegravir (a long-acting dolutegravir analogue) and rilpivirine led to virological suppression in 82% of patients, compared to 71% who received efavirenz plus two NRTIs.

SOURCE: Margolis DA, et al. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): A randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis* 2015;15:1145-1155.

Combination antiretroviral therapy (ART) with three drugs has been the standard of care for almost two decades. While the efficacy of triple therapy is well-established, there are increasing concerns about long-term toxicities of the drugs, particularly in patients with comorbid illnesses like renal and cardiovascular disease. Margolis and colleagues compared the ability to maintain viral suppression of a two-drug regimen including cabotegravir, a integrase inhibitor and structural analogue of dolutegravir, and rilpivirine with conventional three-drug efavirenz-based ART.

The LATTE study was a phase 2 industry-sponsored, multicenter, randomized clinical trial that enrolled adults aged 18 years and older with HIV-1 RNA copies of at least 1000 per mL, a CD4 count of at least 200 per µL, were ART naïve, and had no major drug resistance mutations. In the initial induction phase of therapy, patients were randomized to receive oral cabotegravir (an integrase inhibitor) 10 mg once a day, 30 mg once a day, 60 mg once a day, or efavirenz 600 mg once a day with investigator-selected background NRTI (abacavir-lamivudine or tenofovir-emtricitabine). After 24 weeks, patients who received cabotegravir and had viral suppression (i.e., plasma HIV RNA levels < 50 per mL) had their NRTIs replaced with rilpivirine for an additional 72 weeks. Patients randomized to the efavirenz group continued NRTIs through the end of week 96. The primary endpoint of the study was the proportion of patients with HIV RNA copies < 50 per mL at week 48.

A total of 244 patients were randomized to the four treatment groups. For the primary endpoint, at 48 weeks 82% of patients in the cabotegravir group were virologically suppressed (95% confidence interval [CI]; 77-88) compared to 71% (95% CI; 60-82) in the efavirenz group. After 72 weeks of two-drug maintenance therapy, 76% of those given cabotegravir and rilpivirine and 63% continued on efavirenz plus dual NRTIs were virologically suppressed. Furthermore, there were more virological non-responders in the efavirenz group compared to the two-drug group (16% vs. 10%, respectively). After 24 weeks of maintenance therapy (week 48), the median increase in CD4 count from baseline was

219 cells per µL (141-343) in the two-drug group and 216 cells per µL (133-363) in the efavirenz group. Five patients had virologic failure: two in the cabotegravir 10 mg group, one in the 30 mg group, and two patients in the efavirenz group.

Two of the three patients in the cabotegravir-rilpivirine group were found to have the NNRTI resistance mutations K101K/E and E138E/A, while the third was lost to follow up. Headache was reported in 22% of patients in the cabotegravir groups, compared with 11% in the efavirenz group. There was no association between the dose of cabotegravir and headache incidence. Serious adverse events occurred in 10% of the cabotegravir-treated patients, none of which were determined to be related to the drug, while 6% occurred in the efavirenz group, including one suicide attempt.

■ COMMENTARY

This study provides evidence for a potential paradigm shift in the treatment of HIV. Until now, experts, including those who write the HIV treatment guidelines, have considered dual therapy inferior to triple therapy for viral suppression. The LATTE trial has shown that the two-drug regimen of cabotegravir and rilpivirine is at least as effective as efavirenz and dual NRTIs for maintaining viral suppression. Avoiding tenofovir disoproxil fumarate (TDF) would help mitigate bone loss and nephrotoxicity, while avoiding abacavir could reduce the risk of cardiovascular disease. Cabotegravir was well-tolerated in the trial, with side effects similar to efavirenz in incidence and severity. Interestingly, the company developing cabotegravir has used the LATTE study to prove the concept that dual therapy is effective so they can further develop cabotegravir as a long-acting intramuscular (IM) injection. As noted in an accompanying commentary, both cabotegravir and rilpivirine have long pharmacokinetic half-lives, and theoretically a single combination injection of both drugs could be a powerful addition to the ART arsenal.[1] Thus, the LATTE study may prove to be the seminal trial that ushered in the era of dual maintenance therapy, as well as laid the foundation for long-acting therapy.

As with all phase 2 trials, the LATTE study was not powered to make definitive conclusions about the performance of the experimental regimen. Therefore, additional trials (e.g., phase 3) are necessary before dual therapy for maintenance viral suppression can be advocated. Another limitation to the study design is that neither the patients nor the investigators were blinded as to whether the participants received efavirenz or cabotegravir, which may have affected the rate of patient retention and reporting of adverse events.

The LATTE-2 trial evaluating intramuscular cabotegravir and rilpivirine is currently underway. Long-acting IM injections might improve adherence and have the potential to be used for pre-exposure prophylaxis. However, sustained viral suppression, i.e., for years, must be the standard by which IM-ART is judged. Results from LATTE-2 are eagerly awaited. ■

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ABSTRACT & COMMENTARY

Acetaminophen for Fever in the ICU

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Clinical Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine.

Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Seven hundred ICU patients with fever and known or suspected infection were randomly assigned to receive acetaminophen 1 g IV or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. Early administration of acetaminophen did not affect number of ICU-free days.

SOURCE: Young P, et al. Acetaminophen for fever in critically ill patients with suspected infection. *N Engl J Med* 2015 Oct. 5; [Epub ahead of print].

Seven hundred adult intensive care unit (ICU) patients with fever (temperature ≥ 38°C) and known or suspected infection were randomized to receive either acetaminophen 1 g IV or placebo every 6 hours until ICU discharge, resolution of fever, cessation of antimicrobial therapy, or death. The

primary outcome was ICU-free days (days alive and free from need for ICU care) from randomization to day 28.

Baseline characteristics of the patients were similar between the groups. Common coexisting conditions included cancer (20-21%), chronic pulmonary disease (12-14%), diabetes (25-26%), and ischemic heart disease (15%). Virtually all patients met criteria for "sepsis," 50-53% required vasopressors, and 57-60% required mechanical ventilation.

There was no difference between the acetaminophen and placebo groups in the primary outcome (23 ICU-free days in acetaminophen group vs. 22 days in the placebo group), nor in the secondary endpoints (hospital-free days, days free from mechanical ventilation, days free from inotropes/vasopressors, renal replacement therapy, or days free from ICU support). Similarly, there was no difference between the groups in death by day 28 (13.9 vs. 13.7%), and death by day 90 (15.9 vs. 16.6%) in the acetaminophen and placebo groups, respectively. Hospital length of stay among non-survivors was significantly longer (13.9 days vs. 7.7 days), as was ICU length of stay in non-survivors (10.4 days vs. 4.0 days) in acetaminophen-treated patients compared to placebo-treated patients. There was no difference between the groups in either hospital length of stay or ICU length of stay in survivors.

There were no discernible differences in adverse events between acetaminophen- and placebo-treated patients. Slightly more than 8% of acetaminophen-treated patients and 9.9% of placebo-treated patients experienced liver dysfunction leading to study drug discontinuation.

■ COMMENTARY

This is an interesting study, conducted in New Zealand, which demonstrates no discernible benefit from routine administration of acetaminophen in critically ill febrile patients with known or suspected sepsis. The use of acetaminophen in this setting also did not appear to result in any obvious harm. The observation that ICU and hospital lengths of stay were longer in acetaminophen-treated patients who eventually died is intriguing. This result is consistent with an earlier study, which showed that physical cooling to normothermia delayed death in mechanically ventilated patients with septic shock.[1] Similarly, an older retrospective cohort study in ICU patients showed that acetaminophen-treated patients had a significantly longer time to death than did those who did not receive acetaminophen.[2] This effect of acetaminophen delaying death without affecting mortality at day 28 or day 90 is intriguing and potentially generates many different hypotheses as to why this phenomenon is observed. ■

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Oritavancin: Formulary Considerations

By Samit Patel, PharmD

Dr. Patel is a Pharmacist at Stanford Health Care.

Dr. Patel reports no financial relationships in this field of study.

Oritavancin is a lipoglycopeptide bactericidal antibiotic for intravenous administration with activity against Gram-positive organisms, including methicillin-resistant *Staphylococcus aureus*. It exerts activity by disrupting bacterial cell membrane integrity through inhibition of transglycosylation and transpeptidation steps of cell wall biosynthesis.
GENERIC NAME: Oritavancin
TRADE NAME (U.S.): Orbactiv
U.S FDA APPROVAL DATE: August 6, 2014

SIMILAR APPROVED DRUGS

Dalbavancin and telavancin, like oritavancin, are semisynthetic lipoglycopeptides. All three are related to the glycopeptide antibiotic, vancomycin.

U.S FDA-APPROVED INDICATION

Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Enterococcus faecalis* (vancomycin-

susceptible isolates only).

PHARMACOKINETICS

Pharmacokinetc parameters following a single 1200 mg intravenous dose of oritavancin:

PK parameters	
C_{max}	138 mcg/mL
AUC 0-24	1110 mcg*h/mL
AUC 0-inf	2800 mcg*h/mL
$t_{½}$ (alpha)	2.29 h
$t_{½}$ (beta)	13.4 h
$t_{½}$ (gamma)	245 h
Vss	87.6 L
CLT	0.445 L/hr

Oritavancin exhibits linear pharmacokinetics at a dose up to 1200 mg.

DISTRIBUTION

Approximately 85% of oritavancin is bound to human plasma proteins. Oritavancin is extensively distributed into the tissues (total volume of distribution, 87.6 L). After a single 800 mg dose, exposures of oritavancin in skin blister fluid were approximately 20% of those in plasma concentration.

METABOLISM

Oritavancin is not metabolized by the liver.

EXCRETION

Oritavancin is slowly excreted unchanged in feces and urine with less than 1% and 5% of the dose recovered in feces and urine, respectively, after 2 weeks. Oritavancin has a long terminal elimination phase with a half-life of 245 hours.

RENAL IMPAIRMENT

No dosage adjustment of oritavancin is needed in patients with mild (CrCL 50-79 mL/min) to moderate (CrCL 30-49 mL/min) renal impairment. Oritavancin has not been evaluated in severe renal impairment. Oritavancin is not removed from blood by hemodialysis.

HEPATIC IMPAIRMENT

No dosage adjustment of oritavancin is needed in patients with mild or moderate (Child-Pugh Class B) hepatic impairment. Oritavancin has not been evaluated in severe hepatic impairment.

CLINICAL TRIALS/EVIDENCE SUMMARY

Both the SOLO I and SOLO II trials were identically designed Phase 3 randomized, double-blind, multicenter non-inferiority clinical trials. Patients with ABSSSI thought or proven to be caused by a gram-positive pathogen were randomized 1:1 to receive a single dose of oritavancin 1200 mg on day 1 followed by twice daily infusions of placebo or vancomycin IV 1 gram or 15 mg/kg every 12 hours for 7-10 days. After day 1, the vancomycin dose could be adjusted based on renal function, clinical status, or vancomycin tough plasma concentrations. The primary endpoint in each trial was early clinical response at 48-72 hours: a composite endpoint of cessation of spread or reduction in size of baseline lesion, absence of fever, and no rescue antibiotic medication. In the SOLO I, this endpoint was achieved in 82.3% of oritavancin and 78.9% of vancomycin recipients. In the SOLO II, this endpoint was achieved in 80.1% of oritavancin and 82.9% of vancomycin recipients. Secondary endpoints for lesion size reduction ≥ 20% at early clinical response and investigator-assessed sustained clinical response at post-therapy were evaluated at day 14-24 (7-14 days after the end of therapy). Sustained clinical response was defined as complete or nearly complete resolution of baseline signs or symptoms related to the primary ABSSSI site (erythema, induration/edema, purulent drainage, fluctuance, pain, tenderness, local increase in heat/warmth) such that no further treatment with antibiotics was needed.

Table 1. Clinical Trials/Evidence Summary

	Oritavancin	Vancomycin	Absolute Difference (95% CI)
Primary Endpoint: Early clinical response at 48-72 hours			
SOLO I	391/475 (82.3%)	378/479 (78.9%)	3.4 (-1.6 - 8.4)
SOLO II	403/503 (80.1%)	416/502 (82.9%)	-2.8 (-7.5 - 2)
Secondary Endpoint: ≥ 20% reduction in lesion area at early clinical response (at 48-72 hours from baseline)			
SOLO I	413/475 (86.9%)	397/479 (82.9%)	4.1 (-0.5 - 8.6)
SOLO II	432/503 (85.9%)	383/479 (80%)	0.6 (-3.7 - 5)
Secondary Endpoint: Sustained clinical response (7-14 days after the end of therapy)			
SOLO I	379/475 (79.6%)	383/479 (80%)	0.4 (-5.5 - 4.7)
SOLO II	416/503 (82.7%)	404/502 (80.5%)	2.2 (-2.6 - 7)

Table 2. Comparative Cost

Agent		AWP Cost per Unit ($)	Cost per Day ($)	Cost per Week ($)
Vancomycin	1 gram vial	4.41	8.82	61.74
	1 gram pre-mixed bag	27.64	55.28	386.96
Ceftaroline	600 mg vial	75.81	151.62	1,061.34
Tedizolid	200 mg vial	282.00	282.00	1,974.00
	200 mg tablet	354.00	354.00	2,478.00
Linezolid	600 mg tablet	162.68	325.36	2,277.52
	600 mg pre-mixed bag	167.35	334.70	2,342.90
Daptomycin	500 mg vial	425.66	425.66	2,979.62
Dalbavancin	500 mg vial	1,490.00	–	2,980.00
Oritavancin	1200 mg vial	1,160.00	–	–

ADVERSE EFFECTS

Serious adverse reactions were reported in 57/976 (5.8%) patients treated with oritavancin and 58/983 (5.9%) treated with vancomycin (comparator). The most commonly reported serious adverse reaction was cellulitis in both treatment groups: 11/976 (1.1%) in oritavancin and 12/983 (1.2%) in the vancomycin arms, respectively.

Oritavancin was discontinued due to adverse reactions in 36/976 (3.7%) of patients; the most common reported reactions leading to discontinuation were cellulitis (4/976, 0.4%) and osteomyelitis (3/976, 0.3%).

The most commonly reported adverse reactions (≥ 5%): headache, nausea. Adverse reactions reported in 1.5-5% included: diarrhea, vomiting, dizziness, infusion site phlebitis, abscess (limb and subcutaneous), ALT and AST elevation, tachycardia, infusion site reaction.

The following adverse reactions were reported in oritavancin-treated patients at a rate of less than 1.5%:
Blood and lymphatic system disorders: anemia, eosinophilia
Administration: infusion site erythema, extravasation, induration, pruritis, rash, edema peripheral
Immune system disorders: hypersensitivity
Infections and infestations: osteomyelitis
Investigations: total bilirubin increased, hyperuricemia
Metabolism and nutrition disorders: hypoglycemia
Musculoskeletal and connective tissue disorders: tenosynovitis, myalgia
Respiratory, thoracic, and mediastinal disorders: bronchospasm, wheezing
Skin and subcutaneous tissue disorders: urticaria, angioedema, erythema multiforme, pruritis, leucocytoclastic vasculitis, rash

CONTRAINDICATIONS/WARNINGS/ PRECAUTIONS

Oritavancin can interfere with coagulation tests by binding and preventing action of the phospholipid reagents, which activate coagulation in commonly used laboratory coagulation tests. This causes activated partial thromboplastin time (aPTT) test results to remain falsely elevated for approximately 48 hours and the PT and INR for 24 hours. Unfractionated heparin is contraindicated for 48 hours after oritavancin administration.

The drug is contraindicated in patients with known hypersensitivity to oritavancin. In the Phase 3 clinical trials, the median onset of hypersensitivity reactions was 1.2 days, and the median duration of these reactions was 2.4 days. No data are available on cross-reactivity between oritavancin and other glycopeptides, including vancomycin.

Co-administration with warfarin may result in higher exposure of warfarin, which may increase the risk of bleeding.

Infusion-related reactions include pruritus, urticarial, or flushing.

USE IN SPECIAL POPULATIONS

Pregnancy Category C
There is no well-controlled study with oritavancin in pregnant women.

Oritavancin is excreted into the breast milk of rats. It is unknown whether oritavancin is excreted in human milk.

Clinical studies of oritavancin did not include sufficient number of subjects aged 65 and older to determine whether they respond differently than younger subjects.

DRUG INTERACTIONS

A drug-drug interaction study showed that oritavancin is a weak inducer of CYP3A4 (a decrease of 18% in the mean AUC of midazolam) and CYP2D6 (decrease of 31% in the ratio of dextromethorphan to dextrorphan concentrations in the urine after administration of dextromethorphan). Oritavancin was also a weak inhibitor of CYP2C19 and a weak inhibitor of CYP2C9 (with an increase of 31% in the mean AUC of warfarin).

DOSE AND ADMINISTRATION

The recommended dosing for oritavancin is a single intravenous dose of 1200 mg infused over 3 hours in patients 18 years and older.

CONCLUSION

Oritavancin is FDA approved for adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible gram-positive microorganisms. The SOLO I and SOLO II trails demonstrated non-inferiority of a single dose administration of oritavancin compared to 7-10 days of vancomycin for the treatment of ABSSSI. The acquisition cost of oritavancin is higher than other broad-spectrum Gram-positive agents; however, its prolonged half-life may offer advantages in the emergency department or outpatient setting. ■

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ABSTRACT & COMMENTARY

Anti-parasitic Therapy of Chronic Chagas' Cardiomyopathy

By Dean L. Winslow, MD, FACP, FIDSA

Dr. Winslow is Clinical Professor of Medicine, Division of General Medical Disciplines, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine.

Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Two thousand eight hundred fifty-four patients with Chagas' cardiomyopathy were randomized to benznidazole or placebo, were treated for up to 80 days, and were followed for a mean of 5.4 years. Trypanocidal treatment with benznidazole reduced serum parasite detection but did not reduce clinical cardiac deterioration.

SOURCE: Morillo CA, et al. Randomized trial of benznidazole for chronic Chagas' cardiomyopathy. *N Engl J Med* 2015;373:1295-1306.

A prospective, multicenter, randomized trial was conducted involving 2854 patients with chronic Chagas' cardiomyopathy in which patients received either benznidazole or placebo for up to 80 days and were followed for a mean of 5.4 years. The primary outcome was time-to-event of any component of the composite outcome of death, resuscitated cardiac arrest, sustained ventricular tachycardia, insertion of pacemaker or implantable cardioverter-defibrillator, cardiac transplantation, new heart failure, stroke, or other thromboembolic event.

The primary outcome occurred in 27.5% of the benznidazole group and in 29.1% of the placebo recipients. Baseline polymerase chain reaction (PCR) assay was performed on blood from 1896 patients, and 61% were positive for *Trypanosoma cruzi*. Sixty-six percent of the benznidazole-treated patients and 34% of the placebo-treated patients converted to negative by this PCR assay at the end of treatment. However, only 47% and 33% of benznidazole and placebo-treated patients, respectively, remained PCR-negative at 5 years or more.

Geographic variation in treatment response was seen with odds ratio (OR) of PCR conversion in Brazil of 3.03 at 2 years and 1.87 after 5 years. In Columbia and El Salvador, the OR was 1.33 at 2 years and 0.96 at 5 years. In Argentina and Bolivia, the odds ratio was 2.63 at 2 years and 2.79 at 5 years or more. PCR conversion did not correspond to effects on clinical outcomes.

Serious adverse events leading to drug interruption

or discontinuation were more common in benznidazole recipients comparet to placebo recipients, with 6.7% of benznidazole vs. 1.1% of placebo recipients requiring permanent treatment discontinuation. Common adverse events included skin rash, gastrointestinal symptoms, and peripheral neuropathy.

■ COMMENTARY

Chagas' disease is the third most common parasitic disease in the world (after malaria and schistosomiasis).[1] Unfortunately, in humans, acute infection with Chagas' usually presents as a nonspecific, self-limited febrile illness, which in about one-third of patients results in progressive non-ischemic cardiomyopathy (after a latent period of two or more decades). While acute infection (if recognized) can be cured with trypanocidal drugs, the utility and effectiveness of anti-parasitic therapy in patients with established cardiac disease has been uncertain.

The results of this trial are disappointing in that while some anti-parasitic effect (as assessed by PCR) was seen with benznidazole, this did not translate into any significant clinical benefit. The potential reasons for this lack of clinical efficacy could include factors such as: It may be that treatment is "too little, too late" for benznidazole to reverse established myocardial damage; Perhaps more prolonged courses of treatment would be more effective; Antigen persistence in the myocardium may result in an ongoing immune response, which is not affected by antiparasitic therapy.

In any case, it is imperative that earlier diagnosis of *T. cruzi* infection be made so that treatment of early acute disease (which is potentially curable) can be done. Awareness and earlier recognition of Chagas' disease is of increasing importance to North American physicians since endemic transmission of Chagas' is now clearly occurring in Texas. ■

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Infectious Disease [ALERT]

Updates

By Carol A. Kemper, MD, FACP

Meningitis Diagnostics on Fire!

Source: FDA News Release. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm466360.htm.

I read this press release with delight, especially in light of a current clinical dilemma. A 23-year-old, previously health young woman was admitted just last week with acute meningitis, with 1 day of headache, nausea and vomiting, blurred vision, altered mental status, and meningismus. She had returned from a trip to Scotland with her mother two days earlier; that same evening, she had done some heavy partying at the bar with girlfriends for her birthday. Her mother thought her initial symptoms were from a hangover until she clearly worsened and was brought to the emergency department (ED). Her cerebrospinal fluid (CSF) was remarkable for a white cell count of 12,400, a protein of 763, and a glucose of 3. She began receiving empiric antimicrobials with IV vancomycin and ceftriaxone within 50 minutes of presentation to the ED, and a lumbar tap was performed. Her blood and CSF cultures remained negative, and imaging was unremarkable. Parenterally administered ampicillin 2 g Q4 hours was added to her regimen. After 5 days of steady clinical improvement and diminishing peripheral white blood count (24K → 16K), ampicillin was discontinued. Within 48 hours, her condition worsened, with increasing headache, nausea, dizziness, and increased white blood cells (WBC) to 24.9 cells/mm^3. Repeat blood cultures, urinalysis, and radiographic studies were unremarkable. Now what?

The U.S. Food and Drug Administration gave de novo clearance on October 8 for the first CSF diagnostic "meningitis panel," designed to simultaneously detect multiple nucleic acid targets for multiple pathogens causing central nervous system (CNS) infection. The BioFire FilmArray Meningitis/Encephalitis (ME) Panel (bioMerieux, Marcy-l'Etoile, France) is designed to rapidly (within 60 minutes) detect 14 different viral, bacterial, and yeast pathogens. After injection of hydration solution and the CSF sample into a packet, the instrument extracts and purifies nucleic acid in the sample, and then performs a nested multiplex PCR. The organism is identified by examination of the generated end-point melting curve, and the

Table. Target Organisms

Bacteria
- *Escherichia coli* K1
- *Haemophilus influenzae*
- *Listeria monocytogenes*
- *Neisseria meningitidis*
- *Streptococcus agalactiae*
- *Streptococcus pneumoniae*

Viruses
- Cytomegalovirus
- Enterovirus
- Herpes simplex virus 1
- Herpes simplex virus 2
- Human herpesvirus 6
- Human parechovirus
- Varicella zoster virus

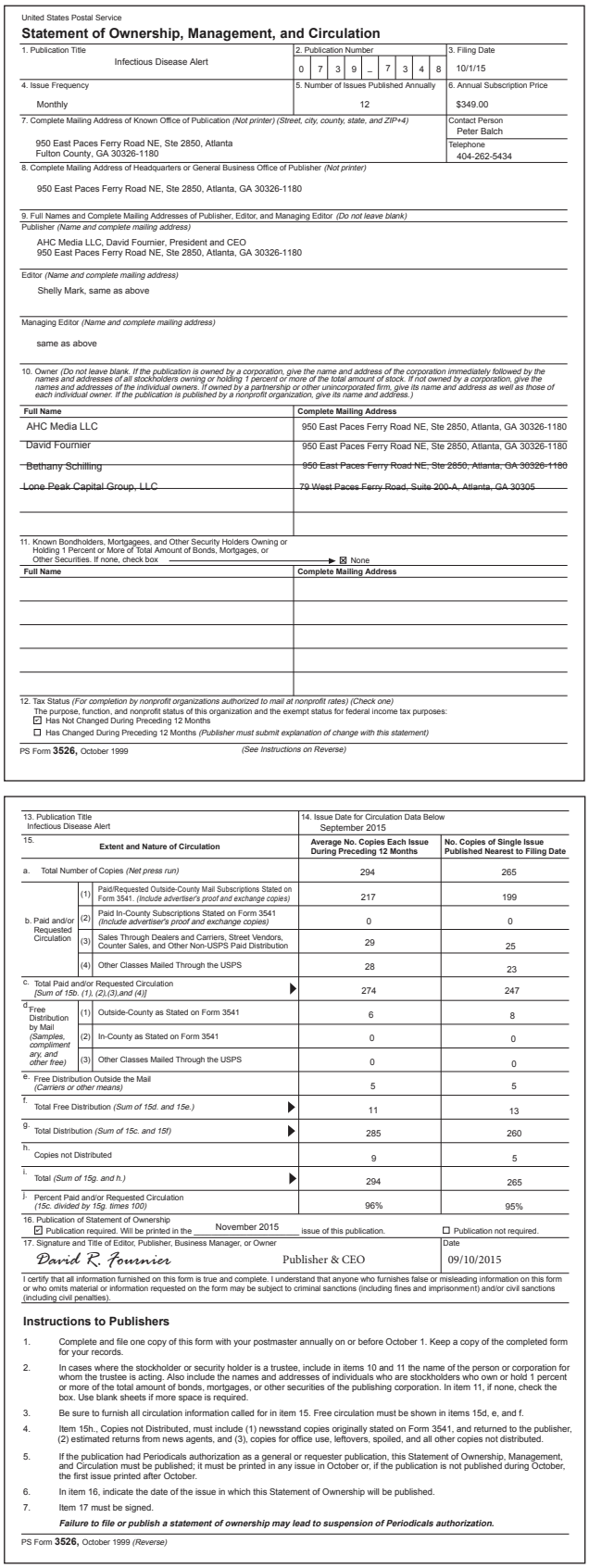
Fungus
- *Cryptococcus neoformans/gattii*

instrument automatically generates a report.

The assay was validated in a prospective study of CSF samples taken from 1560 patients with suspected meningitis/encephalitis, and the results were compared with those of standard methods, including cultures. Also evaluated were 150 test CSF samples from patients with recognized bacterial meningitis based on positive culture results, as well as 425 CSF samples "spiked" with microorganisms at varying concentrations. There was a high degree of agreement between the results of the FilmArray ME Panel and the conventional methods.

The test requires only 200 microliters of CSF. Despite its anticipated utility, the panel may generate some false-negative and false-positive results, and, similar to current PCR tests on CSF, may be overly sensitive, detecting low-grade up-regulation of HSV and VSV in CSF specimens of uncertain significance. In addition, the assay does not detect some organisms of interest, especially in immunocompromised hosts, such as EBV and JCV. Despite these limitations, this assay is bound to improve our ability to more rapidly detect bacterial and viral CNS pathogens, allowing for appropriate isolation, targeted therapy, and improvement in predicting outcome. The FDA cautions that conventional test methods and cultures should still be performed in conjunction with this assay.

The assay is manufactured by a small company in Salt Lake City, UT, called BioFire Diagnostics, which merged with bioMerieux in January 2014. The BioFire website states that they began their search for better diagnostic tests "in a corner of an Idaho potato equipment facility." In addition to the CNS panel, they are working on a blood panel, a gastrointestinal panel, and a comprehensive respiratory panel for the detection of 20 viral and bacterial targets. ■



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CME QUESTIONS

1. Which of the following statements is true regarding cutaneous leishmaniasis?

A. It is a benign, self-limited infection without long-term consequences.

B. It is spreading with refugees from Syria.

C. It cannot be transmitted in Europe due to the absence of relevant sand fly vectors.

D. It is readily treated with oral fluconazole.

2. Which of the following is correct regarding oritavancin?

A. It is 99% bound to serum proteins.

B. Its elimination half-life ($T_{1/2}$ gamma) is longer than a week.

C. It has broad activity in vitro against Gram-negative pathogens.

D. It is only available for oral administration.

3. Which of the following is correct regarding the treatment of patients with chronic cardiomyopathy due to Chagas' disease with benznidazole relative to placebo administration?

A. It was associated with a greater likelihood of a negative blood PCR test for *Trypanosoma cruzi*.

B. It was associated with reversal of cardiomyopathy.

C. The efficacy results were the same in all geographic areas that were studied.

D. The incidence of adverse events did not differ between benznidazole and placebo recipients.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss the diagnosis of infectious diseases;
- explain current data regarding the use of new antibiotics for commonly diagnosed diseases and new uses for traditional drugs;
- discuss the latest information regarding risks, benefits, and cost-effectiveness of new and traditional diagnostic tests; and
- discuss new information regarding how infectious diseases are transmitted and how such information can lead to the development of new therapies.

[IN FUTURE ISSUES]

Formulary Considerations: Ceftazidime-avibactam