The Future of Warfarin Dosing: What is in the Pipeline?

Pharmacogenetic testing has been researched to find genetic variability among individuals who require warfarin therapy and to possibly reduce the occurrence of adverse events; indeed, the FDA recently approved a labeling change for Coumadin and issued a statement that “lower initiation doses should be considered for patients with certain genetic variations in the CYP2C9 and VKORCI enzymes.” The latter enzymes are the primary agents in the metabolism of warfarin; researches have found 37 different alleles for the CYP2C9 gene with CYP2C9*1 representing the wild (normal metabolizer) type.

Patients who are homozygous for a variant allele generally require less warfarin. The most common variants are CYP2C9*2 and CYP2C9*3, with the latter producing the slowest metabolism of warfarin. The variant alleles have been found to be most common in European-American and African-American populations. While studies demonstrate that pharmacogenetic testing helps to guide dosing and improve safety, it remains to be seen whether such testing proves to be cost effective.


CASE REPORT

A 76 year old male was transferred to MU for management of pneumonia and rhabdomyolysis. He gave a history of cough, green sputum, fever, chills and malaise for the past several weeks; these symptoms did not improve after a 14 day course of Augmentin. He developed increasing weakness, anorexia and an inability to stand up and was taken to his local ER for evaluation. His chronic mild dyspnea had begun to increase and he gave a vague history of weight loss; he denied hemoptysis. Evaluation in the ER revealed WBC 32.3 with 88 segs, Hgb 10.4, BUN 35, Cr 2.6 and CK 1706. A CT of the head was negative but a CXR showed a RUL infiltrate. He was transferred to MU for further evaluation and management.

The patient reported a history of pulmonary fibrosis (diagnosed in 1989), chronic kidney disease secondary to ANCA+ vasculitis (since 2003), peripheral neuropathy and myelodysplastic syndrome. Medications included Prednisone 5mg qd and Cytoxan every 14 weeks. He lives and works on a farm where he raises pigs and grows corn, beans and wheat. Pets include a dog and three cats. He quit tobacco use 20 years ago and stopped using alcohol several years ago; he denied any past use of illicit drugs. He was in the Navy during the Korean war. Though he was a hunter, he has not done so for 6 years and has not travelled over the past six months; he denied recent tick bites. He also denied a past +PPD, history of TB or exposure to TB.

Initial exam revealed a weak, lethargic, elderly male who was otherwise in no acute distress. T was 38.2 and BP was 132/92. No rash or jaundice was noted. HEENT was unremarkable except for poor dentition. Neck revealed no adenopathy or JVD. Chest was reported to be clear and cardiovascular exam was normal; there was no peripheral edema. Abdominal exam was normal with no organomegaly or tenderness.
Admission labs were remarkable for pH 7.30, pCO2 43, pO2 94, saturation 96% (5L), WBC 21.8, Hgb 9.8, HCT 28.7, MCV 93.2, MCH 31.9, Platelets 274, serum K 6.2, BUN 46, Cr 3.0, Alb 2.7, AST 88 and CK 1952 with a CK-MB of 8.0. A CXR revealed a RUL opacity with evidence of cavitation, focal bilateral atelectasis and possible small bilateral pleural effusions.

The patient was admitted to the ICU and placed in respiratory isolation. After appropriate cultures were obtained, he was started on IV Vancomycin, Ertapenem and Azithromycin. Within 24 hours, three sputums were reported negative for AFB and he was moved to the general medical floor with plans for a CT of the chest and possible bronchoscopy. Soon thereafter, one of the sputum samples was reported to be positive for AFB and he was placed back in isolation; the CT of the Chest demonstrated two thick-walled cavities in the RUL, multiple nodular opacities in the right lung and LUL and changes consistent with underlying emphysema. The radiologic differential included mycobacterial infection, malignancy, septic emboli, Wegener’s granulomatosis and fungal infection in emphysematous blebs.

A presumptive diagnosis of active TB was made (especially in light of his moderate immunosuppression), an ID consultation was placed and the patient was started on four-drug therapy (INH, Rifampin, Ethambutol and Pyrazinamide); Vancomycin was discontinued but the Ertapenem and Azithromycin were temporarily continued (the latter having anti-mycobacterial activity). Sputum was sent for culture and PCR testing; the latter proved to be negative for TB 5 days later. Pending culture results, the four-drug therapy was continued.

During his early hospital course, the patient continued to spike high fevers, complained of anorexia and was too weak to cooperate with physical therapy. He developed diarrhea which was negative for C diff X3; stool cultures were also negative and no WBCs were present. On the 16th hospital day, the sputum culture was reported to be positive for Mycobacterium avium complex (MAC) and he was switched to a three drug regimen of Clarithromycin, Ethambutol and Rifampin. Modest improvement in the patient’s condition occurred over the next week and he was discharged from the hospital with plans for followup by ID. He will be continued on the triple drug regimen until his sputums are negative for 12 months.

Discussion: Non-tuberculous Mycobacteria are ubiquitous in the environment but are not transmitted between humans. Their most common clinical presentation in immunocompetent hosts is chronic pulmonary disease; in such cases, MAC is the most common pathogen. Women with pre-existing lung disease generally develop nodular densities and bronchiectasis. Men with underlying COPD usually get a cavitary lesion which, as in our case, often mimics TB. Diagnosis must include classic CXR/CT findings, at least 3 sputum samples positive for AFB and the exclusion of malignancy and TB. The infection generally develops with the insidious onset of cough, fever, sputum production, weight loss, weakness, hemoptysis and weight loss.

Macrolide-resistant MAC carries a poor prognosis and this infection should never be treated with a macrolide alone; indeed, macrolide resistance often develops under such conditions or if co-therapy is inadequate. Surgical resection is considered if the infection is isolated, if uncontrolled hemoptysis develops or if the drugs cannot be tolerated. Triple therapy with clarithromycin (or azithromycin), ethambutol and rifampin is recommended; in severe cases, streptomycin or amikacin are suggested.

References:
Clinical Infectious Diseases, Edited by David Schlossberg, Cambridge University Press, 2008