In Remembrance of Dr. Foster (1930 - 2018)

A native of El Paso, TX, Dr. Daniel W. Foster completed his undergraduate studies at Texas Western College (now UT El Paso) in 1951 and went on to medical school at UT Southwestern, graduating first in his class in 1955. He pursued a fellowship in Endocrinology at UT Southwestern from 1959-1960 and the National Institutes of Health from 1960-1962, after which he returned to UT Southwestern as a faculty member.

Dr. Foster’s distinguished career and service at UT Southwestern spanned over half a century. He excelled in clinical, academic and research fields, with career accomplishments including describing the malonyl-CoA regulatory system for fatty acid oxidation and ketogenesis, hosting a nationally televised medical program, and receiving numerous teaching awards. He served as Chair of Internal Medicine at UT Southwestern from 1987 to 2003. His achievements have been recognized nationally with memberships to the American Academy of Arts and Sciences, the American Association for the Advancement of Science, and the National Academy of Medicine.

Dr. Foster died at the age of 87 on January 18, 2018. A giant of medicine, he will be truly missed by the UT Southwestern community.

Image courtesy of the UT Southwestern Archives
# Table Of Contents

- Introduction .................................................................................................................. 3
- EKG Challenge ................................................................................................................. 4
- Dermatology Image Challenge ......................................................................................... 6
- Arts and Humanities in Medicine ..................................................................................... 9
- Allergy and Immunology ................................................................................................. 10
- Cardiology ....................................................................................................................... 12
- Endocrinology .................................................................................................................. 14
- Gastroenterology and Hepatology .................................................................................... 16
- General Internal Medicine and Primary Care ................................................................. 18
- Geriatrics .......................................................................................................................... 20
- Health Policy .................................................................................................................... 22
- Hematology and Oncology ............................................................................................... 24
- Infectious Diseases ........................................................................................................... 26
- Nephrology ....................................................................................................................... 28
- Palliative Care ................................................................................................................... 30
- Quality Improvement and High Value Care ..................................................................... 32
- Rheumatology ................................................................................................................... 34
Welcome and thank you for reading the fourth issue of UTSW Internal Medicine Journal Watch! UTSW IM Journal Watch is a bi-monthly publication produced and edited by the residents of the Internal Medicine Residency at UTSW with the assistance of faculty mentors. The purpose of the publication is to provide quick updates and commentary on recent publications in all the specialties in internal medicine, including general internal medicine, geriatrics, and quality improvement. It is our goal to provide everyone with opportunities to critically read and interpret recent medical literature to improve and advance the care for the patients we serve.

The editors welcome feedback about the publication as well as suggestions for recent articles to review in future editions. The editors can be reached at UTSWIMJournalWatch@gmail.com. In the meantime, you can follow us on twitter @UTSWIMJW and on our blog at http://www.utswimjournalwatch.wordpress.com/.

We thank the authors of the following reviews, as well as the faculty mentors, for dedicating their time to further our education. We hope you enjoy reading!

Timothy Brown, Christina Yek, Emily Bowen, Stephanie Chiao
UTSW IM Journal Watch Editors, 2017-2018
EKG Challenge

Dr. Allexa Hammond

CASE

A 21 year old male with no significant past medical history presented with complaints of diffuse myalgias after 5 days of heavy weightlifting at the gym. On presentation, the patient was afebrile and hemodynamically stable. Laboratory testing was notable for an extremely elevated creatinine kinase (CK) level of 19,000 U/L. The patient was diagnosed with rhabdomyolysis and started on aggressive intravenous fluids. A routine EKG was performed (Fig. 1).

Figure 1. Resting EKG.

WHAT IS THE LIKELY EXPLANATION FOR THESE EKG FINDINGS?
A. Limb lead reversal
B. Right ventricular hypertrophy
C. Dextrocardia
D. Lateral myocardial infarction

WHAT IS THE NEXT BEST STEP IN MANAGEMENT?
A. Obtain a transthoracic echocardiogram
B. Assume the EKG was incorrectly performed and obtain a repeat EKG
C. Obtain a troponin level, start ACS protocol
D. Perform an EKG stress test
**DISCUSSION**

Dextrocardia is a rare condition affecting 0.01% of live births. Although dextrocardia is often detected during childhood such as when occurring with concomitant congenital heart defects, situs inversus, or manifestations of Kartagener’s syndrome (primary ciliary dyskinesia leading to recurrent respiratory tract infections), asymptomatic cases may occur and remain undiagnosed until adolescence or early adulthood. In this case of dextrocardia diagnosed in an asymptomatic adult, one should consider obtaining a transthoracic echocardiogram to evaluate for additional cardiac malformations.

Dextrocardia may be apparent upon examination findings of predominant heart sounds on the right side of the chest or radiographic findings of a cardiac silhouette in the right hemithorax (Fig. 2). In certain cases the diagnosis is made on EKG or echocardiogram. A diagnosis of dextrocardia should be suspected when there are findings of a positive QRS complex in lead aVR, inversion of all complexes in lead I, absent R-wave progression in the precordial leads, and right axis deviation.\(^1\) Differentials to consider in the presence of a positive QRS complex in the aVR lead and right axis deviation include limb lead reversal (a relatively common mishap), which is differentiated from dextrocardia by normal R wave progression in the precordial leads.\(^2\) Another possibility is lateral myocardial infarction, although this is less likely in this scenario given the absence of known risk factors for premature coronary artery disease, as well as EKG findings of diffuse T-wave inversions in no clear distribution, lack of discrete ST elevation, and absence of Q waves. Finally, right axis deviation can be seen in a variety of different pathological conditions, such as right ventricular hypertrophy (where one should also observe a dominant R wave in the V1 precordial lead and a dominant S wave in V5-V6 precordial leads), left posterior fascicular block, pulmonary embolism, and lateral myocardial infarction.

![Figure 2. CXR demonstrating an abnormal cardiac silhouette with apex located in the right hemithorax.](image)

**REFERENCES**

CASE

A 29 year-old man presented to the Parkland ED with a pruritic rash. The rash had started over the patient’s arms and legs 5 days prior and had subsequently progressed to involve his palms, soles, and torso. The patient denied fevers, sore throat or arthralgias. Social history was notable for chronic alcohol abuse and unprotected intercourse with multiple male partners. He had recently been admitted for alcohol detoxification for which he had been medicated with lorazepam and chlordiazepoxide.

On presentation the patient was afebrile with normal vital signs. Examination of the skin revealed non-blanching, non-tender, pruritic erythematous papules and plaques with dusky centers distributed over the trunk and extremities, and coalescing two-ring target lesions on the palms and soles. Superficial erosions were seen on the tongue and buccal mucosa. Neurologic exam was unremarkable.

Initial laboratory testing showed a white cell count of 4.8x10^9/L (differential with mild lymphopenia, other cell lines normal), hemoglobin 11 g/dL, platelet count 343x10^9/L, and normal renal and hepatic function. HIV-1/2 Ag/Ab testing was positive, as was an RPR screen (titer 1:128). Punch biopsy of a skin lesion was performed with pathology showing vacuolar interface dermatitis with individual keratinocyte necrosis and superficial perivascular infiltrate of lymphocytes.

Figure 1. Erythematous papular rash with occasional atypical targetoid appearance over torso and upper extremities (A). Blanching, non-tender two-tone lesions symmetrically distributed over palms (B).

WHAT IS THE DIAGNOSIS?

A. Erythema multiforme
B. Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)
C. Secondary syphilis
D. Measles
E. Rash of acute Human Immunodeficiency Virus (HIV) infection


**Diagnosis**
Erythema multiforme

**Discussion**
When patients present with diffuse eruption, including lesions on the palms and soles, it is important to have a wide differential diagnosis. In this case, the diagnosis was confirmed with biopsy findings showing dermatitis, necrotic keratinocytes and lymphocytic infiltration diagnostic of erythema multiforme. Erythema multiforme (EM) is an immune-mediated condition that is associated with infection in up to 90% of cases. While herpes simplex virus is the most common infectious cause of EM, the condition can be caused by a multitude of infections. This patient had newly diagnosed HIV and syphilis, both of which might have contributed to the development of EM. The hallmark rash of EM involves round, erythematous papules that develop into target lesions with dusky centers or erosions surrounded by a pale, edematous rim circumscribed by an erythematous halo. Lesions tend to appear first in a symmetrical distribution over the extensor surfaces of the extremities and may progress centripetally to involve the trunk. Oral involvement with mucosal ulcers or erythema is seen in up to 70% of cases. Our patient displayed targetoid lesions that were atypical in the lack of a true “halo”, making diagnosis challenging, although similar atypical lesions have been described in patients with EM.

The working differential included drug reaction, secondary syphilis, acute viral exanthem, and erythema multiforme. DRESS is a severe exanthematous drug eruption with systemic manifestations. Our patient lacked the internal organ involvement (hepatic and renal dysfunction) and peripheral eosinophilia frequently seen in DRESS. Additionally, benzodiazepines are not commonly associated with drug reactions (more usual culprits include non-steroidal anti-inflammatory drugs, anticonvulsants, antibiotics and allopurinol). Measles is not the correct diagnosis here because of lack of characteristic symptoms and signs including fever, cough, coryza and conjunctivitis. The rash of measles is an erythematous maculopapular eruption that begins after the onset of fever, first on the face before spreading to involve trunk and extremities. Koplik’s spots are small white papules that may be seen on the buccal mucosa. Acute HIV infection can present as a flu-like syndrome with development of a maculopapular skin rash and mucosal ulceration 48 to 72 hours after onset of fever. While it is important to consider this in the differential, the lack of fever, sore throat and malaise, and the two-toned lesions with dusky centers would be uncharacteristic of this syndrome. Finally, secondary syphilis was a concern. It is important to remember that the “classic rash of secondary syphilis” does not exist! Syphilis is known as the great mimicker and can resemble a wide variety of conditions in presentation. The most common cutaneous findings in secondary syphilis involve ham-colored lesions on the palms and soles and a diffuse, maculopapular, slightly scaly eruption over the trunk and extremities. However, in certain cases the rash may also appear pustular, ulcerative, or involve mucus membranes with raised gray/ white lesions known as condyloma lata. Skin biopsy is characterized by a mononuclear infiltrate with vasculitis; samples may also be positive for Treponema pallidum on immunohistochemical staining or nucleic acid amplification techniques.
REFERENCES
Arts and Humanities in Medicine

From Boy to Oncologist
A poem by Dr. Arjun Gupta

You are a zodiac sign, you are a constellation. You are the Northern Tropic, you are but a crab.
You are a summer project in sixth grade. You sound so ubiquitous - are you really a deadly disease?
You are now a skeleton- the skull on a cigarette pack.
You are the reason grandfather is so sick.
You are the reason he puts tomato ketchup on ice-cream, unable to taste anything else.

You are the cause of much grief, four months before medical school starts.
How proud he would have been, seeing his grandson in a white coat.
I touch you for the first time, a cluster of lymph nodes in a cadaver we dissect.
You are now growth factors and viruses, mutations and alcohol.
You are chapter seven in Robbin’s pathology, marked with multiple post-its.
You become countless hours in the library, your swirling patterns terrifying even under the microscope.
You seem invincible on paper, but maybe you are too greedy?
We will attack you when you divide the most, when you reveal yourself.
You are sprayed with antimetabolites, and blasted with radiation; and sometimes cut away.
You showcase your reserve, you hide and you come back, always mocking.
You are dismaying and intimidating.

Internal Medicine residency begins- you become my first patient, then the fourth.
You attack a dear friend, then a friend’s mother.
They cough up blood, they lose their hair.
One lovely man says he can only taste ketchup after the chemotherapy; is that you saying hello, Grandpa?
You become a familiar foe, an almost every day encounter.
Several heroes emerge- their body taken, their dignity not.

Now I wait to start an oncology fellowship.
To come closer face to face.
Oh Cancer, we will fight.
You have affected too many.
Summary

In this study, investigators sought to identify potential biomarkers to aid in the diagnosis of various forms of chronic rhinosinusitis (CRS), including CRS without nasal polyps (CRSsNP), CRS with nasal polyps (CRSsNP), and aspirin-exacerbated respiratory disease (AERD). Nasal lavage fluid (NLF) samples were obtained from 33 patients with CRSsNP, 45 patients with CRSsNP, 31 patients with AERD, and 24 control patients. Samples were then evaluated for the presence of microparticles (MP), which are submicron-sized shed membrane vesicles from injured or activated cells. MPs for various cell types, including endothelial and epithelial cells, platelets, eosinophils, mast cells, and basophils, were detected in NLF samples using flow cytometry.

EndoMPs and ActEndoMPs (markers of endothelial cell injury and activation, respectively), were significantly increased in patients with CRSsNP, CRSsNP, and AERD compared to controls. Platelet MPs were significantly increased only in patients with AERD (3.5-fold, P<0.003). Eosinophil MPs were significantly increased in patients with all 3 conditions compared to controls, though mast cell MPs (MCMPs) were only significantly increased in AERD patients (4.3-fold, P<0.002). Significant differences in levels of ActEndoMPs, platelet MPs, epithelial MPs, mast cell MPs, and basophil MPs were noted in area-under-curve (AUC) analyses when comparing AERD to CRSsNP patients as well.

The study provides evidence for the release of MPs from activated immune and injured structural cells in the pathophysiology of CRS, and shows that nasal lavage fluid sampling in CRS patients to detect specific MPs and their quantitative levels can help clarify the specific diagnoses of CRS in an outpatient setting, particularly for distinguishing AERD versus CRSsNP.

Commentary

Chronic rhinosinusitis affects ~1-5% of the US population and costs our healthcare system nearly 3-5 billion dollars annually in office visits and treatment. The most severe form of CRS is AERD, in which patients have comorbid asthma, atopy, and/or aspirin sensitivity. Distinguishing these patients from patients with CRSsNP is important since morbidity is high in asthma exacerbations secondary to aspirin sensitivity, and the pathophysiology of the two phenotypes appears to be distinct. The gold standard for diagnosing AERD is an oral aspirin challenge, which can take many hours as symptoms are monitored while dosages are increased every few hours. The logistics of this test make it difficult to fully utilize in an outpatient setting, and the risk of a severe reaction occurring outside of the hospital or ER setting can be dangerous.

This study was the first to show that analyzing levels and types of MPs from NLF samples can provide a standardized, straightforward method to further learn the pathophysiology of CRS and clarify the diagnosis of various subtypes of CRS to
help guide management. Further analyses of MPs in a large cohort of challenge-confirmed AERD are still needed to confirm the usefulness of MPs as biomarkers. Regardless, the use of MP analysis in NLF samples may provide a new tool to study prevalence, progression, and remission in patients with these conditions.

**Figure:** Released MP types and levels in subjects with CRSwNP and subjects with AERD. Text on *right* indicates difference in CRSwNP compared to control. *Red asterisk* indicates those in which values are higher in AERD than in CRSwNP.
PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock (CULPRIT-SHOCK)


SUMMARY

This multicenter, randomized, open-label trial compared multivessel percutaneous coronary intervention (PCI) (n=341) to culprit-lesion-only-PCI (n=344) in the setting of myocardial infarction (MI) complicated by cardiogenic shock. To be eligible, patients had to have multivessel coronary artery disease (CAD) discovered on early PCI; shock symptoms including low blood pressure or pressor requirement, pulmonary edema, or other signs of end organ damage; and either an ST elevation (STEMI) or a non-ST elevation MI (NSTEMI). Patients were excluded mainly for urgent coronary artery bypass graft (CABG) indication, noncardiogenic shock, creatinine clearance < 30 ml/min, or life expectancy < 6 months. Of note, patients with chronic thrombotic occlusions (CTO) were not excluded from the study.

The primary outcome was defined as a composite of all-cause death or renal-replacement therapy (RRT) within 30 days of randomization. Secondary outcomes included death, RRT, recurrent MI, heart failure readmission, repeat revascularization, time to stabilization, use and duration of pressors, duration in ICU, the Simplified Acute Physiology Score II (SAPS-II), and use and duration of mechanical ventilation. Safety outcomes included bleeding (scaled according to the Bleeding Academic Research Consortium) and stroke.

The composite outcome at 30 days was significantly lower in the culprit-lesion-only PCI group (45.9% vs 55.4%, RR 0.83, 95% CI 0.71 to 0.96; p=0.01). Analyses of the per-protocol and as-treated populations were similarly significant. All-cause mortality was significantly lower in the culprit-lesion-only PCI group (43.3% vs 51.6%, RR 0.84, 95% CI 0.72 to 0.98; p=0.03). The lower rate of RRT in the culprit-lesion-only PCI group, however, was not significant (11.6% vs 16.4%, RR 0.71, 95% CI 0.49 to 1.03; p=0.07). Despite higher rates of revascularization in the culprit-only group, all other outcomes did not differ significantly between the groups. Crossover occurred in 12.5% of the culprit-lesion-only PCI group and in 9.4% of the multivessel PCI group, and staged revascularization occurred in 17.7% of the culprit-lesion-only group. Subgroup analyses assessing for interactions with sex, age, diabetes, hypertension, history of MI, type of MI (STEMI vs NSTEMI), territory of MI (anterior vs nonanterior), number of occluded vessels, and presence of chronic thrombotic occlusion (CTO) were all insignificant.

COMMENTARY

European guidelines recommend that multivessel PCI be considered for patients presenting with MI complicated by shock, suggesting that improved myocardial perfusion could theoretically assist with overall function. Additionally, multiple studies in hemodynamically stable MI patients have shown composite benefits with multivessel PCI but never a significant mortality benefit. On the other hand, multivessel PCI could theoretically induce further ischemia or lead to renal impairment from increased procedure contrast loads, amongst other potential complications. CULPRIT-SHOCK was designed to settle the debate over the ideal
PCI strategy for the subset of MI patients who present with shock, and the overall winner was culprit-lesion-only PCI.

In the study, the increased primary outcome of death or RRT in the multivessel PCI group—driven mostly by increased mortality—was attributed to increased procedure time and contrast load. A major limitation of the study was the high levels of crossover from culprit-lesion-only to multivessel PCI, occurring often in patients who had lack of hemodynamic improvement after intervention, plaque shifts, or newly detected possible culprit lesions after the initial PCI. Another obvious limitation was the lack of blinding, which could potentially have led to confounding management differences post-PCI. Additionally, as PCI to CTO in non-shock STEMI patients has failed to show benefit, the inclusion of CTO patients and mandatory PCI of CTO lesions in the multivessel PCI group possibly mitigated the potential measured benefit of multivessel PCI overall. Lastly, it is worth noting that all patients with indication for urgent CABG were excluded; additionally, subgroup analysis in diabetics showed an insignificant trend toward a benefit in multivessel PCI. One wonders if truly severe and complex CAD may still benefit from multivessel PCI in this setting. The likely result of this trial will be a standard practice of culprit-lesion-only PCI in shock, but a frequent decision to pursue non-culprit-lesion PCI when interventionalists are faced with similar scenarios that led to crossover in this study.
Opioid Receptor Activation Impairs Hypoglycemic Counterregulation in Humans


Summary

Hypoglycemia is a major risk factor for morbidity and mortality in patients on insulin therapy. Two risk factors for hypoglycemia include hypoglycemia-associated autonomic failure (HAAF), associated with a recent episode of hypoglycemia, and exercise-associated autonomic failure (EAAF), associated with vigorous exercise. In both of these conditions, counterregulatory responses to hypoglycemia are blunted. Endogenous opioid pathways have been speculated to play a role in these responses. Carey et al. tested this hypothesis using morphine administration.

Twelve healthy subjects without diabetes, recent hypoglycemia, family history of diabetes, or present medication usage were randomized to saline or morphine infusion in a crossover design with 5-week washout. Each study period took place across two days. On day one, either normal saline or morphine (0.1 µg/kg/min) were infused over 120 minutes, followed by a 120 minute break with snack, followed by the same infusion over 120 minutes. Day two consisted of insulin and glucose infusions titrating to blood glucose levels of 90, 80, 70, and 60 mg/dL with monitoring of laboratory and symptomatic responses.

The researchers found significantly lower epinephrine concentrations in the morphine versus control group at 70 and 60 mg/dL of blood glucose on day two. At a blood glucose of 60 mg/dL, the epinephrine level in the morphine group was 292.5 +/- 15.7 pg/mL compared to 419.4 +/- 20.4 pg/mL in the control group, which is a 30% reduction in the morphine group (p = 0.02). The morphine group also required higher glucose infusion rates to maintain blood glucose at 70 and 60 mg/dL (p < 0.01) and experienced significantly fewer hypoglycemic symptoms at 60 mg/dL (p = 0.03) compared to the control group. In a subsequent test of 6 additional participants subjected to episodes of hypoglycemia in the laboratory across two days, there was a 45% reduction in epinephrine concentrations during the hypoglycemic episode on day two compared to controls.

Commentary

Many patients with diabetes mellitus (DM) are treated with insulin, and patients with type I DM have been shown to have fewer diabetic complications with tighter glycemic control. However, hypoglycemia is a cause of death in 6-10% of patients with type I DM and is the cause of 100,000 ED visits and 30,000 hospital admissions annually in the United States. Better understanding of the blunting of counterregulatory response pathways to hypoglycemia in HAAF and EAAF may help to lower morbidity and mortality.

Recent animal models have shown a relationship between endogenous opioids and a blunted hypoglycemic response. Additionally, acute naloxone administration has been shown to prevent the development of HAAF in humans in experimental hypoglycemia, although short courses of naltrexone have not shown similar effects. This study was undertaken to better understand the physiologic role of opioid receptor activation in HAAF.

The authors found a decrease in epinephrine release during hypoglycemia after morphine administration. However, the hypoglycemic epinephrine response
was less blunted after one day of morphine administration than after one day of hypoglycemia (30% decrease versus 45% decrease compared to controls). Additionally, a number of other counterregulatory hormones were unaffected by morphine administration. This implies that endogenous opioids play a significant role in the HAAF/EAAF pathways, but other factors are also likely at work.

Based on these findings, it is also important to consider the role prescription opioids may have in hypoglycemia-induced morbidity and mortality. Many diabetic patients managed with insulin also suffer from chronic pain managed with opioid therapy. Assuming an average-sized man, the infusions used in this trial would represent around a 2 mg total dose of morphine, lower than the daily dose of many chronic pain regimens. Given growing national concern about opioid use, the blunted hypoglycemia response represents another pathway by which opioids may harm patients.

**Figure**: Plasma epinephrine concentration during day two hypoglycemia: day one saline infusion group (triangles) versus day one morphine infusion group (squares).
Analysis of Fusobacterium Persistence and Antibiotic Response in Colorectal Cancer


Summary

Fusobacterium nucleatum is a common constituent of the intestinal microenvironment and has recently been identified in gene sequencing studies of colorectal cancer samples but has unclear clinical significance. Here, Bullman and colleagues studied colorectal cancer patient tissue samples and found that Fusobacterium and other bacteria were present not only in the primary tumors but also in distant metastases in 9 of 11 patients. The bacteria in the metastatic tumors were nearly identical in sequence and species as the primary tumor, suggesting that the bacteria traveled with primary tumor cells, likely within endosomal compartments. In a separate cohort of primary colorectal cancers (n = 77 patients, 45% Fusobacterium-positive), however, the authors found no association between Fusobacterium and subsequent clinical recurrence. Finally, patient-derived xenografts were established in mice from primary Fusobacterium-positive colorectal cancer cells. Antibiotic treatment of mice with metronidazole (active against Fusobacterium) but not erythromycin (inactive against Fusobacterium) decreased tumor growth, suggesting a causal role for the bacteria in tumor growth and maintenance.

Commentary

This study adds to the complex understanding of the tumor microenvironment and role of the normal intestinal microenvironment on tumorigenesis. It raises the possibility that Fusobacterium necrophorum interacts with tumor cells to play an important role in the initiation and progression of colorectal cancers. Recent clinical observations have associated increased tumor levels of Fusobacterium with less T-cell infiltration, advanced disease stage and poorer patient survival. A separate study linked fusobacterial lipopolysaccharide to activation of a key growth signaling pathway in cancer cells. But this raises more questions: does antibiotic treatment change the microbiota and alter the risk of colon tumor initiation? Will there be a role for narrow-spectrum antibiotics in the treatment or prevention of colorectal cancer? Several limitations of the study were that it did not replicate an earlier report that Fusobacterium load predicted clinical outcomes like recurrence after resection. Moreover, if bacteria promoted clonal selection of the tumor it is unclear why bacteria were 10-100x lower in distant metastases compared with primary tumors. Nevertheless, Bullman et al have put forth a biologically plausible argument that the intestinal microbiota regulates immune function and cell growth outside of the gut—and raise hopes that the causal relationship identified in mice will be replicated in the clinical studies.
Figure: Potential interactions and mechanisms of tumor potentiation between *F. nucleatum* and host cells. From Yang et al.1

REFERENCES


**Association of Cardiovascular Risk With Inhaled Long-Acting Bronchodilators in Patients With Chronic Obstructive Pulmonary Disease: A Nested Case-Control Study**


**Summary**

This nested case-control study aimed to evaluate the risk of cardiovascular events occurring after initiation of long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) in patients with chronic obstructive pulmonary disease (COPD).

The study included 284,220 patients obtained from the Taiwan National Health Insurance Research Database from 2007 to 2011. Cohort entry date was marked as date of first COPD clinic visit or date of discharge from a hospital for COPD. Cases were identified at earliest cardiovascular disease (CVD) outcome, defined as an inpatient or ED visit with primary diagnosis of coronary heart disease, cardiac arrhythmia, heart failure or ischemic stroke. Exposure was measured via LABA and LAMA prescription records in the 12 months leading up to the event date for cases and controls. Exclusion criteria included LABA or LAMA use within 12 months prior to cohort entry, patients who initiated any cardiovascular medications within 30 days prior to event date, and patients with a diagnosis of chest pain or dyspnea within 30 days prior to event date.

The results of the study show that new LABA use was associated with a 1.50-fold increased risk of CVD events (95% CI, 1.35-1.67; \( p < 0.001 \)) and new LAMA use was associated with 1.52-fold increased risk of CVD events (95% CI, 1.28-1.80; \( p < 0.001 \)) within 30 days of initiation.

**Commentary**

Almost 16 million adults in the United States have been diagnosed with COPD, making it one of the country’s leading causes of hospital and clinic visits. The staple therapies for COPD include LABAs and LAMAs, which are often considered to be relatively safe with very mild side-effect profiles. Previous investigations of the association between LABAs/LAMAs and cardiovascular disease have proven inconclusive, with many studies suggesting a link and many more suggesting no association at all. This study continues the query into the association between COPD therapies and cardiovascular events, suggesting a temporal relationship between initiation of therapy and cardiovascular events with statistical significance within 30 days of onset of medication use.

A major strength of this study includes the thorough investigation of the timing of LABA and LAMA usage as it pertains to CVD events. Additionally, because of the design and breadth of the study, the results are generalizable across many of the common comorbidities of COPD. However, there are a few limitations that are important to discuss. Although the study included almost 300,000 patients, they were all of Taiwanese descent, which limits the generalizability of the findings across the spectrum of ethnicity. Baseline CVD status of individual patients could be considered a confounding variable (as this is difficult to assess); however, the authors do not consider this to be substantial because prior medical history, cardiac
events, current medical problems and current CVD medications were balanced among the studied groups. Furthermore, LABA- and LAMA-associated CVD risk was statistically significant even among patients without prior CVD history. There is still a large amount of investigation that needs to be done to fully elucidate the link between COPD therapies and cardiovascular events; in the meantime, it is reasonable to monitor patients starting new COPD medications for cardiovascular symptoms.

**Figure**: Duration-response curves for adjusted odds ratios (95% CIs) of cardiovascular risk as a function of duration of new LABA (A) and new LAMA therapy (B). Solid line indicates adjusted odds ratio, dashed line indicates 95% CI.

**References**

Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis


SUMMARY

The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk) trial was a phase 3, double-blinded, randomized trial powered to evaluate the superiority of romosozumab versus alendronate for fracture prevention in postmenopausal women with osteoporosis. 4,093 patients were randomized to receive either a monthly injection of romosozumab or weekly oral alendronate for 12 months. All patients then received another 12 months of weekly alendronate. All patients underwent baseline DEXA studies, which were repeated every 12 months. Measures of bone-turnover (such as \(\beta\)-CTX, a bone-resorption marker, and P1NP, a bone formation marker) were also obtained from a subgroup of patients at baseline and at the conclusion of the study. The primary endpoints of the study included the cumulative incidence of new vertebral fracture at 24 months and the cumulative incidence of non-vertebral and symptomatic vertebral fractures. Secondary endpoints included bone mineral density at the lumbar spine, hip and femoral neck at 12 and 24 months.

Results were analyzed using an intention-to-treat approach. Patients in the romosozumab group suffered fewer fractures than the alendronate only group, with a 48% lower relative risk of new vertebral fractures (6.2% vs 11.9%, RR 0.52, 95% CI 0.40-0.66; \(p\)<0.001). There were also fewer new non-vertebral and hip fractures in the romosozumab group. Increased efficacy of romosozumab compared to alendronate alone was also inferred based on greater improvement in DEXA scores, increased levels of P1NP and decreased levels of \(\beta\)-CTX. However, there were also a greater number of adjudicated cardiovascular adverse events observed in the first 12 months in the romosozumab group than in the alendronate group (2.5% vs 1.9%, OR 1.31, 95% CI 0.85-2.00). In particular, there were more cardiac ischemic events in the romosozumab group (0.8% vs 0.3%, OR 2.65, 95% CI 1.03-6.77).

Ultimately, the authors conclude that romosozumab followed by alendronate is more efficacious than alendronate alone in reducing fracture risk in post-menopausal women affected by osteoporosis. The greater number of serious cardiovascular adverse events identified in the romosozumab group was unable to be explored further given the study design and small total number of events.

COMMENTARY

Osteoporosis is common in post-menopausal women, and if left untreated, can result in devastating consequences that increase morbidity, such as fractures. Although bisphosphonates are considered the first line of treatment, concerns regarding compliance and fear of side effects, such as osteonecrosis of the jaw and atypical fractures, are often reasons why both patients and providers may hesitate when discussing treatment options.\(^1\) Romosozumab, a monoclonal antibody against sclerostin, has been shown to reduce the risk of osteoporotic fractures by increasing bone formation and decreasing bone resorption. Even more striking, the ARCH trial
provides evidence that romosozumab is more efficacious than bisphosphonates, which are currently considered the gold standard for the treatment of osteoporosis.

Although these findings have the potential to change the clinical approach to osteoporosis, one should also take notice of the potential downfalls associated with this novel agent. The increased number of adverse cardiovascular events associated with romosozumab compared to alendronate in the ARCH trial is concerning and warrants further investigation. Multiple hypotheses have been offered as possible explanations. For example, alendronate has been shown to have a cardio-protective benefit with long-term use, which may have contributed to the decreased incidence of adverse cardiovascular events reported in this group. In addition, sclerostin, through unclear mechanisms, has been speculated to play a role as a negative regulator of vascular calcification, particularly in the aorta where this molecule is widely expressed. By inhibiting sclerostin, one may expect to observe a greater incidence of cardiac ischemic events as witnessed in the romosozumab group. Further still, questions as to the study population itself have arisen, as ARCH’s sister trial, the FRAME study, yielded no significant differences in adverse cardiovascular events between those taking romosozumab versus placebo. Regardless of the cause, this observation has ultimately swayed the Food and Drug Administration to delay approval of the medication until further data is available to ensure its safety. Thus, although there is true promise in regards to the efficacy of romosozumab, it remains to be determined at what cost. More research is needed to investigate the potential adverse outcomes associated with its use and which populations may have the most benefit (and likewise, the least benefit) from use of this otherwise highly promising therapy.

REFERENCES
Health Literacy Impact on National Healthcare Utilization and Expenditure


SUMMARY

Health literacy is associated with healthcare utilization and expenditure, and is an essential aspect of patient care. It is defined as “the degree to which an individual has the capacity to obtain, communicate, process and understand basic health information and services to make appropriate health decisions”. Health literacy presents a challenge in the delivery of effective healthcare and quality outcomes. The National Assessment of Adult Literacy (NAAL) from 2003 found that only 12% of U.S. adults had a proficient health literacy level (HLL), while 75% had an intermediate or basic HLL and 14% had a below basic HLL. In 2011, U.S. healthcare costs reached 2.7 trillion dollars, which is about $8680 per person, and poor health literacy is thought to play a significant role in healthcare costs.

This study used multivariate regression analysis to evaluate the effect of health literacy on the utilization and cost of healthcare. Data was analyzed from the MEPS (Medical Expenditure Panel Survey Household Component), which surveys U.S. families and individuals regarding the use of medical services, medications, and medical expenditures. The health literacy variable was derived using a validated, predictive model based on patient demographic and socioeconomic factors from U.S. census data, incorporating community level predictors of health literacy. The model provided a health literacy score (HLS) which is a continuous variable on a 0 to 500 point scale (mean = 245 and standard deviation (SD) = 55), with a higher score reflecting higher health literacy. Then, two categories of HLL were created: below basic or basic HLL (HLS <226) and above basic HLL (HLS ≥ 226).

A total of 22,599 samples representing approximately 503,000,000 U.S. adults from 2005-2008 were analyzed. The mean HLS was 247.5 with a SD of ±28.3, and 22.4% of the cohort had basic or below basic health literacy. Individuals with a below basic or basic HLL had statistically significantly more healthcare utilization in all categories compared to individuals with above basic HLL: 5.8 vs 4.5 annual physician visits, 4.1 vs 2.7 annual non-physician provider visits, and 0.2 vs 0.1 annual emergency room (ER) visits (p < 0.05). The annual healthcare expenditures were also statistically significantly higher in the below basic or basic HLL group compared to the above basic HLL group: $1862 vs $1027 in annual prescription drugs and $1121 vs $871 in total annual healthcare visits (p < 0.05). These trends remained statistically significant after adjusting for health insurance.

COMMENTARY

These findings may be explained by many factors. Two specific reasons may be a greater prominence of preventative services and self-management in those with higher HLL. Furthermore, increased expenditures in those with lower HLL may result from decreased understanding of disease and improper medication use. As providers in inpatient and outpatient settings, we have the opportunity to mitigate these disparities. In our outpatient clinics, taking time to explain disease processes at the level of understanding of each patient is essential. Providing our patients with
warning signs that warrant ER visits and encouraging close follow up with primary care providers may decrease unnecessary ER visits. Furthermore, explaining proper use of medications can improve administration, which could decrease the need for additional medications to be purchased. Tools such as the AHRQ Health Literacy Universal Precautions Toolkit can help us to understand and address the unique health literacy needs of each patient we encounter. (The toolkit is available at https://www.ahrq.gov/professionals/quality-patient-safety/quality-resources/tools/literacy-toolkit/index.html).

Figure: Mean number of visits per person (left) and annual mean healthcare expenditure per person (right) by health literacy level.

REFERENCES
SUMMARY

Women with metastatic breast cancer develop bone metastases in 65-75% of cases. These bone metastases cause pain, and increase likelihood of pathologic fracture, spinal cord compression and hypercalcemia; treatment of these conditions comes with significant cost. To prevent complications from bone metastases (termed “skeletal related events” or SREs), both zoledronic acid (ZA) and denosumab are commonly prescribed.

This study used models to assess cost-effectiveness of monthly ZA, every three months ZA, or monthly denosumab. The modeling was based off multiple previous studies that demonstrated non-inferiority of ZA every three months as compared to monthly ZA in patients with skeletal metastases (including breast cancer). ZA overall reduces SREs up to 40%. Denosumab is more effective than ZA, as it delays the onset of first and subsequent SREs. Based on this background knowledge, this study was designed to determine whether denosumab is cost-effective compared to monthly or every 3 month ZA, a generic medication.

The investigators designed a Markov model with a hypothetical cohort of 10,000 women in each treatment arm for SRE prevention. A Markov model is used in predictive modeling and assumes that a patient is always in one of a finite number of discrete health states, and events are transitions between states. The different SRE states analyzed in this model were a pathologic bone fracture, radiation to bone, surgery to bone, and spinal cord compression. The model was set to analyze a two-year time course. Costs included the medication itself, administration cost, and treatments of fractures, radiation, surgeries, etc.

Every three months ZA was the least expensive and had slightly fewer SREs than monthly ZA, so was the dominant option. Quality-adjusted life-years were assessed and were similar across the three treatment groups. On assessing various probabilities of SRE events on denosumab of 50%, 70%, and 90% lower than on ZA, denosumab was still not cost effective. When comparing monthly ZA to denosumab in these scenarios, the mean incremental costs per mean SRE avoided for denosumab ranged from $137,905 to $283,109. When assumptions were changed to increased SRE probabilities of 50% or 100% with ZA over denosumab, mean costs became more comparable. The mean incremental costs per SRE avoided for denosumab now ranged from $6,072 to $41,432. However, this relied on an assumption that SREs with ZA were much greater than denosumab, which is not currently the case. Based on current studies, denosumab has 23% fewer SREs than monthly ZA, which makes the analysis most like when SRE probabilities of denosumab were assumed to be 75% of those of ZA every 3 months, and in this model the cost of denosumab per SRE avoided was over $200,000.
COMMENTARY

Overall, every three month ZA was found to be superior in cost effectiveness to both monthly ZA and monthly denosumab. The study is important because it is the first study of cost-effectiveness for these drugs that was not sponsored by a drug company. The study is limited by being a predictive model based on SRE probabilities rather than actual cost data from a cohort. Second, the model only assessed a two-year time course, and as treatment generally extends longer than this, long term cost-effectiveness could be different; however the authors feel that the cost difference is so substantial that the general results would not vary much. Costs of side effects of the medications (osteonecrosis of the jaw or atypical femoral fractures) were not included, as the rates of these complications are similar between monthly ZA and monthly denosumab. The authors conclude that despite improved outcomes with monthly denosumab, for the highest value care, ZA every three months is a viable alternative.
Optimisation of Empirical Antimicrobial Therapy in Patients With Haematological Malignancies and Febrile Neutropenia (How Long Study): An Open-label, Randomised, Controlled Phase 4 Trial


SUMMARY

This open-label, randomized controlled trial sought to determine whether stopping empiric antibiotic therapy (EAT) in patients with neutropenic fever without waiting for neutrophil recovery could optimize duration of therapy when compared to a traditional approach of continuing EAT until resolution of neutropenia. Investigators enrolled 157 patients presenting with neutropenic fever and followed them for up to 28 days or until death. Patients were randomized to receive EAT until the following criteria were met for 72 hours, regardless of neutrophil count: apyrexia, resolution of all signs and symptoms of infection, and normal vital signs (experimental group), or to receive EAT that was discontinued only when similar criteria were met and absolute neutrophil count (ANC) was >0.5x10⁹ cells/L (control group).

The primary outcome was duration of antibiotic therapy. Number of antibiotic free days in the intention-to-treat population was 15.1 in the experimental group and 13.6 in the control group, with an absolute difference of -2.4 (95% CI -4.6 to -0.3; p=0.026). In per-protocol analysis, number of antibiotic free days was 16.9 in the experimental group versus 13.0 in the control group, with an absolute difference of -3.8 (95% CI -6.1 to -1.6, p= 0.001).

All-cause mortality was 1.3% in experimental group and 3.8% in control group (p=0.62); only one death (of a patient in the control group) was due to infection. Adverse events occurred in 341 patients in the experimental group as compared to 295 patients in the control group (p=0.057), although fewer severe adverse events occurred in the experimental group (n=18) as compared to the control group (n=38). There was at least one episode of recurrent fever in 11 patients in the experimental group and 14 patients in the control group; where infection was found to be the cause of recurrent fever, none of the infections were noted to be severe nor the cause of the patient’s death. Finally, duration of fever was not statistically different between groups (mean of 5.7 days in experimental group vs mean of 6.3 days in control group).

COMMENTARY

For patients presenting with neutropenic fever, current IDSA guidelines recommend starting empiric antibiotic therapy with an anti-pseudomonal beta lactam agent until a patient clinically defervesces and ANC is > 0.5x10⁹ cells/L and rising. This is based on the idea that the return of adequate effector cells is necessary to protect the patient from infection without antibiotics being needed to contain an occult infection.¹ This has led to antibiotics being used for longer durations than in most documented serious infections, with a mean duration of antibiotics of 12 to 16 days in two contemporary studies.²,³ This practice contrasts with the European Conference of Infections in Leukemia guidelines from 2011 which
recommend discontinuation of empiric antibiotic therapy in those who are hemodynamically stable from presentation and afebrile for 72h or more, regardless of neutrophil count.\textsuperscript{4} These long durations of antibiotic therapy may expose patients to unnecessary risk from these therapies and increase the risk of multi-drug resistant organisms.

This study shows no difference in mortality when antibiotics were discontinued in patients who present with neutropenic fever, were clinically stable, and afebrile, despite continued neutropenia. The observation that recurrent fever and number of infections was similar in both groups is important, as these are concerns brought up when discontinuing antibiotic therapy in neutropenic patients. However, the study was powered based on the primary endpoint of antibiotic-free days so it may have been underpowered to demonstrate a difference in all-cause mortality, even though no such trend was detected. The open-label nature of the study and the lack of standardization of the empiric anti-bacterial and anti-fungal therapy could also have introduced bias or confounding. However, these results are promising enough from an antibiotic stewardship view to warrant further studies of this strategy and other potential strategies to safely reduce exposure duration and risks of antibiotics in this high-risk population.

\textbf{References}


Association of Emergency-Only vs Standard Hemodialysis With Mortality and Health Care Use Among Undocumented Immigrants With End-stage Renal Disease


SUMMARY

This retrospective cohort study compared mortality and health care use among undocumented immigrants with end-stage renal disease (ESRD) receiving emergency-only hemodialysis (HD) versus those receiving standard three-times-weekly HD in 3 US county hospitals. A total of 211 eligible patients were included (125 men; mean age 46.5 years), of whom 169 received emergency-only HD and 42 received standard HD.

The primary outcome studied was mortality. Patients who received emergency-only HD had a close to 5-fold greater risk of 3-year mortality (HR 4.96, 95% CI 0.93 to 26.45; p=0.06 in adjusted analysis), and a 14-fold greater risk of 5-year mortality (HR 14.13, 95% CI 1.24 to 161; p=0.03 in adjusted analysis), as compared to those receiving standard HD. When compared with nation-wide data from the United States Renal Data System, undocumented immigrants receiving emergency-only HD had higher 5-year age-adjusted standardized mortality ratios (2.26, 95% CI 1.6 to 3.1), whereas those receiving standard HD had lower mortality ratios (0.84, 95% CI 0.23 to 2.16), as compared to their US citizen counterparts (receiving standard HD).

Secondary outcomes studied were health care use (acute care days and ambulatory visits) and rates of bacteremia in the two groups. The number of acute care days was almost 10-fold greater for patients receiving emergency-only HD than those receiving standard HD (rate ratio 9.81, 95% CI 6.27 to 15.35; p<0.001). Conversely, patients who received emergency-only HD had 3-fold fewer days of ambulatory visits (rate ratio 0.31, 95% CI 0.21 to 0.46; p<0.001) as compared to those receiving standard HD. There were no statistically significant differences in the expected number of bacteremia episodes between groups during 5 years of follow-up.

COMMENTARY

This study found that patients with access to emergency-only HD have higher mortality, more acute care days, and fewer ambulatory visits as compared to those with access to standard HD.

Limitations of the study include the small sample size and inclusion of just 3 study centers, which may limit generalizability of results to the greater population. Also, it is important to note the lack of randomization. Analysis of the baseline characteristics of patients showed that patients in the emergency-only HD group were both more ill (lower albumin and hemoglobin levels, higher Charlson comorbidity index scores) and were less likely to receive outpatient care at initiation of HD than patients in the standard HD group although these factors were subsequently adjusted for in outcomes analyses. Finally, any inter-center differences in standards and delivery of care may have confounded results: the patients receiving standard HD all received care at San Francisco General Hospital (San Francisco, CA), while those receiving emergency-only HD group received care...
at Denver Health (Denver, CO) and Harris Health (Houston, TX). However, the authors noted that the HD facilities in Denver and Houston actually had lower standardized mortality ratios than those in San Francisco based on data from a national ESRD quality measures database; suggesting that neither quality of care nor practice differences accounted for the results of the study.

Uncompensated outpatient dialysis care has been shown to be more cost effective than the cost of hospitalization associated with acute emergent dialysis.¹ This study shows that there may additionally be significant mortality benefits in standard HD over emergent HD. As physicians in Texas, our practice is limited by state law, which covers only emergency HD for undocumented immigrants with ESRD. However, we still have an ethical obligation to treat undocumented immigrants to the best of our ability. Even in the absence of federal or state policy changes, we should work with social workers, charitable organizations, and other stakeholders to explore all possible options for dialysis funding for our patients.

REFERENCES
Impact of Prognostic Discussions on the Patient-Physician Relationship: Prospective Cohort Study


SUMMARY

In advanced cancer, clinicians often emphasize treatment choices without enough discussion about end of life planning and prognostic awareness, often out of fear this will negatively impact the doctor-patient relationship. In this prospective cohort study, 265 adults with advanced cancer (Stage IV non-hematologic or stage III with prediction of death within 12 months) who visited 38 oncologists from community and hospital-based cancer centers in New York and California were enrolled. The oncologists’ discussion of prognosis was assessed by trained coders from audio-recorded visits using the Prognostic and Treatment Choices scale (PTCC). The coders assessed domains including cancer prognosis, curability, the likelihood of effective treatment and the transition from active to palliative treatment using a point-based scale. Patients rated the strength of the patient-physician relationship using two scales, The Human Connection (THC) and the Perceived Efficacy in Patient-Physician Interactions (PEPPI), at baseline, 2 to 7 days, and 3 months after the discussion.

Discussion of prognosis by the oncologist was not associated with a decline in either patient measure. A one-unit increase in PTCC was associated with improvement in THC at 2 to 7 days (parameter estimate 0.10, 95% CI -0.02 to 0.23) after the visit but this was not statistically significant (p=0.09). There was also an improvement at 3 months (parameter estimate 0.18, 95% CI 0.02 to 0.35) which was statistically significant (p=0.029). A one-unit increase in PTCC was not associated with improvement in PEPPI at either time interval. Standardized effect sizes (SES) associated with an increase of two standard deviations in PTCC at each time interval indicated small beneficial effects (SES 0.14 [95% CI -0.02 to 0.29] at 2 to 7 days; SES 0.24 [95% CI 0.02 to 0.45] at 3 months).

COMMENTARY

Western medicine has transitioned from a paternalistic model to one of shared decision making, by which there is a bidirectional exchange with collaboration between patient and provider. However, patients are still too often making decisions with inaccurate perception of prognosis. For example, in a study of 1193 patients with metastatic lung and colorectal cancer, 69% with lung cancer and 81% with colorectal cancer did not report understanding that chemotherapy was not likely to cure their cancer. Clinicians are often reluctant to discuss prognostic information out of concern this may negatively impact the therapeutic alliance. However, prognosis is an integral part of health decisions, as those with an accurate understanding of prognosis make different decisions compared to patients who are less informed. This impacts patient choices regarding aggressive care, which can affect the quality of the last years of life. This study illustrates that open prognostic discussion was not associated with a decline in the strength of the doctor-patient relationship and may strengthen the therapeutic alliance.

An important observation is that although an increase in the PTCC score was associated with a statistically significant improvement in the rating of the doctor-
patient relationship, this only applied to the THC scale at 3 months. This may not be clinically significant given the very small absolute value of change in scoring scales. A major limitation is that the measure of doctor-patient relationship may not be an appropriate metric to assess for the impact of conversations regarding prognosis. It may be more appropriate to ask patients and caregivers later in their disease trajectory whether these early prognostic conversations helped them prepare for the end of life. Lastly, while the PTCC scoring system evaluated domains of end of life and prognosis that were addressed, it provides limited information on the quality or depth of these conversations. This study could thus be strengthened in both the method used to assess prognostic discussion as well as overall outcomes measured.

REFERENCES
Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers: Insights Derived From the FOURIER Trial.


Summary

Innovative new medications such as monoclonal antibodies have the power to profoundly impact patients’ lives. However, due to their skyrocketing price, physicians need a framework to judge whether a certain patient will receive a benefit that is worthy of the costs. One such class of medications, proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), have been shown to significantly reduce LDL levels. The FOURIER trial recently compared major adverse cardiovascular events and LDL levels in patients receiving statins with evolocumab versus patients only on statins. This trial showed a significant reduction in LDL levels and lower rates of nonfatal MI, stroke, and revascularization without a significant change in mortality between the two groups. However, despite this benefit, the cost of evolocumab ($14,300 per year) has limited its clinical use.

In this study, the authors analyzed the cost effectiveness of evolocumab using a Markov model, which is a statistical tool used in probabilistic forecasting, applied to a hypothetical cohort of 1000 patients similar to the FOURIER population. The authors used the risk reductions in cardiovascular events observed in the FOURIER trial and projected the cardiovascular risks beyond the study length using the Framingham risk functions. The model does not account for a mortality benefit, per the FOURIER trial.

Cost effectiveness is analyzed using the quality-adjusted-life-year (QALY), where a QALY of 1 indicates one year of perfect health. The incremental cost-effectiveness ratio (ICER) is then used to summarize the cost-effectiveness of a health care intervention. The ICER is calculated by taking the difference in cost between two possible interventions and dividing by their effect. Typical cut-off values for societally acceptable prices are $50,000 to $100,000 per QALY. The study investigators also calculate the return on investment from the perspective of a private insurance company, which essentially compares the health savings from reduced events and gains from additional years of premiums paid to the cost of the medication.

In 1000 hypothetical patients resembling the FOURIER trial population, adding evolocumab to statins yielded an ICER of $337,729 per QALY. From the perspective of an insurer, for every dollar spent on evolocumab, the insurer would lose $1.86, representing a negative return on investment. This suggests that evolocumab is priced almost three times higher than the accepted societal cost-effectiveness threshold of $100,000 per QALY. Thus, a 62% price reduction to an annual cost of $5,459 would be required to reduce the ICER to this threshold.

Commentary

This cost-effectiveness analysis of evolocumab joins two other recently published analyses that delve into the same question. Kazi et al reported an ICER of $450,000 per QALY, while Fonarow et al estimated between $286,600 per QALY and $413,000 per QALY. This highlights the challenge in modeling cost-
effectiveness; the assumptions made by the models heavily influence the results. In this study by Arrieta et al, adding coronary revascularization as a cardiovascular event to the model reduced the ICER to $257,119 per QALY. These values are all dependent on the data from one trial, and further studies with longer follow-up time to assess mortality end points will be required to more accurately estimate the cost-effectiveness of PCSK9 inhibitors.

Effective therapies that are not cost-effective exacerbate healthcare inequalities, as the therapies are only available to patients who can afford them. All of the currently published models show that a reduction in annual drug costs is required to bring the cost-effectiveness of PCSK9i therapy into societally acceptable ranges. The current pricing of PCSK9 inhibitors coupled with the available data do not support widespread use until there are more impactful clinical outcomes associated with therapy, such as a mortality benefit, or a reduction in cost.

**Figure:** Estimation of different pricing on the cost-effectiveness of PCSK9 inhibitors

The current annual price of $14,300 has almost a 0% chance of being cost effective, while a price of $2,500 has almost a 90% chance of being cost effective at $100,000/QALY.

**References**

Effect of Methotrexate Discontinuation on Efficacy of Seasonal Influenza Vaccination in Patients With Rheumatoid Arthritis: A Randomised Clinical Trial


Summary

Each fall and winter, rheumatologists across the country encourage patients to get their annual influenza vaccination, however, current research has shown that patients on immunosuppressive agents like methotrexate (MTX) have an unsatisfactory response to influenza vaccination. This article describes a single center, randomized, single-blinded, parallel-group study evaluating influenza vaccination response with temporary discontinuation of methotrexate in patients with rheumatoid arthritis (RA). Inclusion criteria were 18 years of age, diagnosis of RA and methotrexate use for at least 6 weeks prior to start of the study. Most patients were female and had similar disease activity and treatment regimens at baseline including MTX and steroid use. Notable exclusion criteria included acute infection, previous anaphylactic reaction to eggs or vaccine components, pregnant or lactating women, other recent vaccine administration or concurrent rheumatic disease except Sjogren’s.

The study included 277 patients randomized to four groups: 1) continue MTX at current dose, 2) hold MTX for 4 weeks prior to vaccination, 3) hold MTX for 2 weeks prior to vaccination and 2 weeks afterwards and 4) hold MTX for 4 weeks after vaccination. Patients had a pre-vaccination antibody titer drawn prior to vaccination and serum was re-evaluated 4 weeks after vaccine administration to assess for satisfactory response. Patients were also seen in clinic 16 weeks after vaccination to assess RA disease activity. The primary endpoint (in the per-protocol population) was a satisfactory vaccine response which was defined as ≥4-fold increase in antibody titer (tested H1N1, H3N3, or B-Yamagata) 4 weeks after vaccine administration. At each visit, a patient's disease activity was measured with the 28-joint disease activity score (DAS-28) – an increase by >1.2 was considered an RA flare.

Patients in group 3 (holding MTX 2 weeks prior and 2 weeks post vaccination) had the best response to all components of the vaccination compared to group 1 (p=0.044). When looking at individual components of the vaccine, groups 3 and 4 had higher H3N2 antibody response (p=<0.001 and p=0.043, respectively) and B-Yamagata antibody response (p=0.48 and p=<0.01, respectively) compared to group 1. The response to antibody titer for H1N1 was greater in groups 3 and 4 but not statistically significant compared to groups 1 and 2. Of note, group 2 was similar to group 1 with every vaccine variable evaluated. Furthermore, in patients who lacked seroprotection at baseline, each group achieved a satisfactory response to the H3N3 antibody; however, groups 3 and 4 became seroprotected against H1N1 and B-Yamagata antibodies more frequently than groups 1 and 2. With regards to RA disease activity, flares were seen more commonly in groups 2 and 3 (34.1% and 38.8%, respectively) compared to groups 1 and 4 (24.1% and 21.2%, respectively), but these results were not statistically significant.
COMMENTARY

This study highlights a potential benefit to temporarily discontinuing methotrexate in patients with RA prior to influenza vaccine administration. However, there are several study limitations: (1) this was a single-center study in Korea where all patients were of Korean ancestry, (2) low recruitment led the study to be underpowered, and (3) only patients with stable RA and low disease activity were included. Moreover, the study did not address if a higher antibody titer is associated with decreased incidence of contracting influenza among patients with RA. However, a previous study has shown a correlation between titers and vaccine-induced protection. Given the higher incidence of RA flares in the groups with best vaccination response, future studies with larger and more generalizable populations are needed to assess the risk/benefit ratio of stopping MTX at time of vaccination. Overall, this study is suggestive that there may be some benefit to temporary discontinuation of MTX for improved humoral vaccine response to influenza vaccination in patients with RA on a stable dose of MTX.

**Figure**: Fold change in antibody titers before and after vaccination among the groups in all patients (A) or only in patients with baseline antibody titer <1:40 (B).