INTERNAL MEDICINE ALERT

Providing Evidence-based Clinical Information for 35 Years

A twice-monthly update of developments in internal and family medicine

AHC Media Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com
www.cmecity.com

AHC Media

INSIDE

Financial Disclosure: *Internal Medicine Alert's* editor, Stephen Brunton, MD, serves on the advisory board for Abbott, Boehringer Ingelheim, Janssen, Novo Nordisk, Sanofi, Sunovion, and Teva; he serves on the speakers bureau of Boehringer Ingelheim, Kowa, Novo Nordisk, and Teva. Peer reviewer Gerald Roberts, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Does MRI Have Your Patient's Back?

ABSTRACT & COMMENTARY

By Rahul Gupta, MD, MPH, FACP

Clinical Assistant Professor, West Virginia University School of Medicine, Charleston, WV

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

Synopsis: *MRI scan was unable to discriminate between patients with favorable outcome and those with an unfavorable outcome when conducted at 1-year follow-up in patients who were treated for sciatica and disk herniation.*

Source: el Barzouhi A, et al. Magnetic resonance imaging in follow-up assessment of sciatica. *N Engl J Med* 2013;368:999-1007.

SCIATICA IS A COMMON PRESENTING CONDITION, AFFECTING AS MANY AS 40% of adults at some time in their lives. Although herniated disc tends to be a common etiology for this diagnosis, it resolves in most people in up to 8 weeks time. Clinicians commonly order diagnostic scans such as MRI in those cases where either the symptoms do not resolve in a timely manner or seem to have unusual or progressive presentation. With studies demonstrating that up to 76% of people who do not have symptoms will show signs of disk herniation on an MRI, it is difficult to associate MRI findings to clinical symptoms.[1] Therefore, it is fair to say that many people have herniated discs, often without any clinical symptoms. In fact, even after successful lumbar disc surgery, more than half of the asymptomatic patients may show persistent disc herniation on follow-up MRI. However, despite these existing data, the fact is that physicians often repeat MRI after treatment just to be sure that "everything is fine." While these MRIs can cost hundreds to thousands of dollars per scan, there is the issue of contrast-related adverse effects as well as anxiety related to findings of persistent herniation while asymptomatic.

In their study, el Barzouhi and colleagues conducted a multicenter, randomized trial comparing surgery and prolonged conservative care

VOLUME 35 • NUMBER 8 • APRIL 29, 2013 • PAGES 57-64

INTERNAL MEDICINE ALERT IS AVAILABLE ONLINE
www.internalmedicinealert.com

for sciatica and lumbar-disk herniation and included 267 patients with a history of 6-12 weeks of sciatica and disk herniation. The patients were randomly assigned to an early surgery strategy group (n = 131) or to a nonsurgical prolonged conservative care (n = 136) group. Fifteen in the surgery group recovered without surgery, and 54 in the nonsurgery group underwent surgery within the year. All patients underwent MRI at baseline and after 1 year. According to the researchers, the 1-year evaluation period was selected since postoperative fibrosis usually stabilizes by 6 months, with no further changes at 1 year. A 4-point scale to assess disk herniation on MRI was used, ranging from 1 for "definitely present" to 4 for "definitely absent." A favorable clinical outcome was defined as complete or nearly complete disappearance of symptoms at 1 year. The researchers found that 84% of the patients reported having a favorable outcome at 1 year. Disk herniation was visible in 35% of patients with a favorable outcome and in 33% with an unfavorable outcome (95% confidence interval [CI] for difference in proportion, -18.8 to 12.6; P = 0.70). Nerve root compression was present in 24% of those with a favorable outcome and in 26% of those with an unfavorable outcome. Of patients with disk herniation, 85% reported a favorable outcome compared with 83% with no disk herniation (P = 0.70). After adjustment for randomized treatment, the presence of disk herniation on MRI was not associated with a favorable outcome at 1 year (odds ratio, 0.82; 95% CI, 0.40-1.71; P = 0.60). In other words, having a MRI scan at 1 year after treatment had no discriminatory power to assess the difference between having a favorable outcome or not having a favorable outcome.

■ COMMENTARY

In most clinical settings, it is not uncommon for the busy clinician to end the patient interview with the words, "but let's go ahead and order some tests just to be sure." These "tests" often mean a battery of laboratory and imaging tests. Both the physician and the patient/family "feel" better. There is comfort on both sides that all that can be tested is being tested. This "just in case" scenario is probably repeated tens of thousands of times in clinical settings each day in the United States. However, over the past 2 decades or so, our ability to detect abnormalities by modern-day imaging techniques has grown at a more rapid rate than our ability to understand the relevance and clinical implications of such findings. As a result, often a deluge of further evaluations and interventions is conducted, leading to significant anxiety and suffering of the patient, in addition to unnecessary cost to the health care system. Findings by el Barzouhi and colleagues highlight this issue by demonstrating the absence of clinical correlation between symptoms and anatomical abnormalities visible on MRI done 1 year after treatment for symptomatic lumbar-disc herniation.

This study questions the value of MRI in clinical decision making for patients with persistent or recurrent sciatica after initial treatment. Interestingly, in a study conducted more than 20 years ago, Boden et al performed MRI on individuals who had never suffered from sciatica or low back pain and found a substantial abnormality in about one-third of the study subjects.[2] In the subgroup that was ≥ 60 years of age, 57% of the scans had abnormal findings, including herniated nucleus pulposus and spinal stenosis. Since then, we have learned that patients who receive an MRI are more likely to undergo surgery over the subsequent year than those undergoing plain radiography, and yet the outcomes at 1 year are equivalent.[3] Once again, good clinical history taking and physical examination can often alleviate the need for repeated MRI scans. Instead of treating the MRI, we cannot go wrong by refocusing on the patient, including explaining limitations of imaging tests such as MRI to our patients so that the results do not lead to further unnecessary testing or anxiety. ■

References

1. Boos N, et al. 1995 Volvo Award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying symptomatic disc herniations. *Spine* 1995;20:2613-2625.
2. Boden SD, et al. Abnormal magnetic-resonance scans of

Internal Medicine Alert, ISSN 0195-315X, is published monthly by AHC Media, a division of Thompson Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie Coplin.
MANAGING EDITOR: Neill L. Kimball.
SENIOR VICE PRESIDENT/GROUP PUBLISHER: Donald R. Johnston.

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Internal Medicine Alert***, P.O. Box 105109, Atlanta, GA 30348.

Back Issues: $21.

Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

AHC Media

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: neill.kimball@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $349
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.

Canada
Add 7% GST and $30 shipping.

Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of 45 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This enduring material activity, *Internal Medicine Alert*, has been reviewed and is acceptable for up to 24 Prescribed credit(s) by the American Academy of Family Physicians. AAFP certification begins January 15, 2013. Term of approval is for one year from this date with the option of yearly renewal. Each issue is approved for 1 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the internist/family physician. It is in effect for 36 months from the date of the publication.

Questions & Comments
Please call **Neill Kimball**, Managing Editor, at (404) 262-5404.

the lumbar spine in asymptomatic subjects. A prospective investigation. *J Bone Joint Surg Am* 1990;72:403-408.
3. Jarvik JG, et al. Rapid magnetic resonance imaging vs radiographs for patients with low back pain: A randomized controlled trial. *JAMA* 2003;289:2810-2818.

Doxycycline May Protect Against *Clostridium Difficile* Infection

ABSTRACT & COMMENTARY

By Betty Tran, MD, MS

Assistant Professor of Medicine, Pulmonary and Critical Care Medicine, Rush University Medical Center, Chicago

Dr. Tran reports no financial relationships relevant to this field of study. This article originally appeared in the January 2013 issue of Critical Care Alert.

Synopsis: *This retrospective study of hospitalized patients receiving ceftriaxone found that additional treatment with doxycycline compared to other antibiotics was associated with a lower risk of* Clostridium difficile *infection.*

Source: Doernberg SB, et al. Does doxycycline protect against development of *Clostridium difficile* infection? *Clin Infect Dis* 2012;55:615-620.

Doernberg and colleagues sought to determine whether receipt of doxycycline was associated with protection from development of *Clostridium difficile* infection (CDI) in hospitalized patients being treated with ceftriaxone, a known high-risk antibiotic for CDI. They retrospectively identified 2734 hospitalizations involving 2305 adult patients at San Francisco General Hospital who received ceftriaxone during their hospitalization. Of these, 1066 (39%) patients also received doxycycline; these patients tended to be older, were more likely to have pneumonia on admission, were less likely to be surgical patients, had higher Charlson Comorbidity Index scores, and received shorter courses of additional antibiotics. The duration of treatment with ceftriaxone, the number of hospital days before development of CDI, and total length of hospital stay, however, were similar between the group that received doxycycline and the group that did not. The primary outcome of interest was development of CDI within 30 days of receiving ceftriaxone.

During the 2005-2010 study period, the overall incidence of CDI was 5.60 per 10,000 patient-days, a rate that is lower than reported in other studies. The incidence of CDI in patients who received doxycycline was 1.67 per 10,000 patient-days compared to 8.11 per 10,000 patient-days in patients who did not receive doxycycline. For each day that a patient received doxycycline, there was a 27% lower risk of CDI compared to a patient who was not receiving doxycycline (95% confidence interval [CI], 0.56-0.96; $P = 0.03$). When the authors directly compared common therapies for community-acquired pneumonia (CAP), a 5-day course of ceftriaxone plus doxycycline was associated with an 85% lower rate of CDI (95% CI, 0.03-0.77) compared to a 5-day course of ceftriaxone plus a macrolide, and an 87% lower rate of CDI (95% CI, 0.03-0.62) compared to a 5-day course of ceftriaxone plus a fluoroquinolone. Because of the uncertainty of capturing all data on antibiotic exposure and CDI cases after discharge, a sensitivity analysis was performed using only hospital data up until discharge with similar results, according to the authors.

■ COMMENTARY

Given the increasing morbidity and mortality of CDI, especially among hospitalized patients, and the high prevalence with which inpatients receive at least one dose of antibiotics, this article poses a fascinating question and springboard for further clinical and laboratory investigations.

San Francisco General Hospital, the study site, presented a unique opportunity for investigators as doxycycline was the recommended first-line therapy for CAP in non-ICU inpatients. Current American Thoracic Society and Infectious Diseases Society of America guidelines, however, recommend doxycycline as an alternative to either a macrolide or a fluoroquinolone as part of a treatment regimen for CAP based only on level III evidence. Findings from this study suggest that further research is needed to revisit the use of doxycycline as a preferred antibiotic in CAP treatment. Doxycycline may reduce the burden of CDI in already vulnerable patient populations, but widespread recommendations for its use may be tempered by differences in clinical outcomes of CAP depending on the setting (outpatient vs inpatient vs ICU).

The mechanisms to explain the association between receiving doxycycline and having a lower risk of CDI also need to be explored. The authors posit a few possibilities, including doxycycline's in vitro activity against *C. difficile*, its attenuation of *C. difficile* toxin production, and its minimal effects on bowel flora due to maximal absorption in the upper gastrointestinal tract. These hypotheses sound plausible, although further data will be informative, especially to ensure that doxycycline use does not result in inadvertent but

unwanted outcomes such as the selection of rarer but more virulent strains of *C. difficile*.

Although further data are needed to support the findings reported, this study is encouraging and also highlights an approach to reducing the rate of CDI by using "lower-risk" antibiotics, a method that may prove to be a valuable weapon in the antibiotic stewardship arsenal. ■

'Off-target' Effects? The Role of Statins in Cancer Biology

ABSTRACT & COMMENTARY

By Robert L. Coleman, MD

Professor, University of Texas; M.D. Anderson Cancer Center, Houston

Dr. Coleman reports no financial relationships relevant to this field of study. This article originally appeared in the March 2013 issue of OB/GYN Clinical Alert.

Synopsis: *Statin use among cancer patients with diverse malignancies is associated with reduced cancer-related mortality. The mechanism is plausible since statins inhibit cholesterol synthesis, which reduces the pool of compounds necessary in cellular proliferation and maintenance of critical cellular functions, such as membrane integrity, signaling, protein synthesis, and cell cycle progression. Prospective clinical trials are warranted.*

Source: Nielsen SF, et al. Statin use and reduced cancer-related mortality. *N Engl J Med* 2012;367:1792-1802.

Cholesterol-reducing statin agents have been associated preclinically with cancer cell growth inhibition and metastases prevention. Given the ubiquitous use of statins in the general population for reduction in cardiovascular risk, the authors evaluated statin use in cancer patients for effects on cancer-specific mortality. They assessed mortality among patients from the entire Danish population who had received a diagnosis of cancer between 1995 and 2007, accompanied by a minimum follow-up of 2 years. Among patients 40 years of age or older, 18,721 had used statins regularly before the cancer diagnosis and 277,204 had never used statins. Multivariable-adjusted hazard ratios for statin users, as compared with patients who had never used statins, were 0.85 (95% confidence interval [CI], 0.83-0.87) for death from any cause and 0.85 (95% CI, 0.82-0.87) for death from cancer. Adjusted hazard ratios for death from any cause according to the defined daily statin dose (the assumed average maintenance dose per day) were 0.82 (95% CI, 0.81-0.85) for a "low" dose (0.01-0.75 defined daily dose per day), 0.87 (95% CI, 0.83-0.89) for "average" dose (0.76-1.50 defined daily dose per day), and 0.87 (95% CI, 0.81-0.91) for "high" dose (> 1.50 defined daily dose per day); the corresponding hazard ratios for death from cancer were 0.83 (95% CI, 0.81-0.86), 0.87 (95% CI, 0.83-0.91), and 0.87 (95% CI, 0.81-0.92), respectively. The reduced cancer-related mortality among statin users as compared with those who had never used statins was observed for each of 13 cancer types. A nested case-control study matched statin cancer patients to three non-statin using cancer patients to control for changes in staging and cancer treatment. The effects were similar to the larger general population analysis. The authors concluded that statin use in patients with cancer is associated with reduced cancer-related mortality. Further study of mechanism and effect in prospective studies is warranted.

■ COMMENTARY

This is a provocative report of statin use. To summarize, statin use was associated with reduced cancer-specific mortality across 13 different malignancies. The data were derived from a unique resource, the enviable National Registry of Patients, which has nearly unbelievable quality control within the Danish health care system. Lending credibility to the study's conclusions are the 98% capture of index cancers associated with nearly 100% complete follow-up and prescriptive practices over a 13-year period among the entire Danish population. Also, to confront changes in the cancer classifications, staging, and treatment over the study period, a nested 1:3 matched case-control study was also conducted. In that analysis, statin users with cancer were matched to three non-statin users with cancer controlling for cancer type, gender, age at diagnosis, and year of diagnosis. The consistency of effect in "all-cause" death and "cancer-specific" death in the two analyses provide legitimacy to the hypothesis that statin use in patients developing cancer may provide up to a 15% reduction in the cumulative risk of these events. This is bolstered by a credible link to the mechanism of action of the statins, which is to perturb cholesterol synthesis. As is recognized, cholesterol is a fundamental structural component of mammalian cell membranes and structures. It is also critical to many cellular processes that govern proliferation, and in cancer cells, processes that are involved in tumor growth, invasion, and metastases.[1,2] In particular, the mevalonate pathway (cholesterol synthesis pathway) is up-regulated in P53

mutated cancers, where cholesterol metabolites serve as important signaling substrates promoting the malignant phenotype.[3] Statin use in preclinical experiments has been shown to inhibit cellular growth and metastases. There is also evidence that statins can block the P-glycoprotein pump, which serves as a mechanism of resistance to some chemotherapeutics.[4]

Since the sample is so large and homogeneous, the clinical impact may be trivial in some cancers and not easily extrapolated to other ethnic groups. In addition, the combination of statins (which are metabolized via intestinal and hepatic cytochrome P450 oxygenases) with chemotherapy needs to be carefully considered, as they may compete for metabolic clearance. Further, there are gaps in the analysis, such as the consideration of important cofactors (tobacco use, balance of screening/early detection practices, cholesterol levels) and the observed lack of a dose effect, which may suggest a minimal dose could be just as important to mortality reduction but with fewer side effects. Nevertheless, the results are thought-provoking and support more definitive clinical investigation into the role of statins in cancer therapy and their effect on long-term survival. ■

References

1. Agarwal B, et al. Mechanism of lovastatin-induced apoptosis in intestinal epithelial cells. *Carcinogenesis* 2002;23:521-528.
2. Gruenbacher G, et al. IL-2 costimulation enables statin-mediated activation of human NK cells, preferentially through a mechanism involving CD56+ dendritic cells. *Cancer Res* 2010;70:9611-9620.
3. Freed-Pastor WA, et al. Mutant p53 disrupts mammary tissue architecture via the mevalonate pathway. *Cell* 2012;148:244-258.
4. Follet J, et al. The association of statins and taxanes: An efficient combination trigger of cancer cell apoptosis. *Br J Cancer* 2012;106:685-692.

Pharmacology Update

Canagliflozin Tablets (Invokana™)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

THE FIRST IN A NEW CLASS OF DRUGS HAS BEEN APPROVED by the FDA for the treatment of diabetes mellitus. This new class of drugs decreases the renal threshold for glucose excretion by inhibiting the sodium-glucose cotransporter 2 (SGLT2), thus increasing renal clearance of glucose. Canagliflozin is licensed from Mitsubishi Tanabe Pharma Corporation and marketed by Janssen Pharmaceuticals as Invokana.

Indications

Canagliflozin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1]

Dosage

The recommended dose is 100 mg once daily taken before the first meal of the day.[1] The dose may be increased to 300 mg once daily if tolerated in patients with an eGFR of 60 mL/min/1.73 m^2 or greater. The dose should not exceed 100 mg daily in patients with an eGFR between 45 and 60 mL/min/1.73 m^2. Canagliflozin is available as 100 mg and 300 mg tablets.

Potential Advantages

Canagliflozin provides an effective and new mechanism of action for reducing plasma glucose.

Potential Disadvantages

Canagliflozin has an adverse reaction profile that differs from currently marketed antidiabetic agents. By promoting glucose excretion, it acts as an osmotic diuretic.[1] Adverse reactions include reduction in intravascular volume and hypotension. Other adverse events include increased SCr, decrease in eGFR, hyperkalemia, increases in LDL-C, serum magnesium, serum phosphate, and genital mycotic infections.

Comments

Canagliflozin lowers plasma glucose primarily by inhibiting SGLT2. Renal glucose threshold can be lowered to 70-90 mg/dL from a norm of 240 mg/dL. It also transiently inhibits intestinal SGLT1, which results in delaying intestinal glucose absorption.[1,2] Canagliflozin was evaluated as monotherapy and in combination with insulin, metformin, sulfonylurea, metformin and sulfonylurea, and metformin and pioglitazone. It was also compared directly to sitagliptin and glimepiride. Subjects had type 2 diabetes inadequately controlled with diet and exercise or baseline therapy. The primary efficacy endpoint was change (difference from placebo or com-

parator) in HbA1c from baseline to the end of the study. Co-secondary endpoints included proportion achieving HbA1c < 7%, changes in fasting blood sugar, systolic blood pressure, body weight, and lipid profile. As monotherapy (n = 584), canagliflozin showed -0.91% (95% confidence interval [CI], -1.09, -0.73) change in HbA1c with the 100 mg and -1.16% (95% CI, -1.34, -0.99) for the 300 mg compared to placebo from baseline of approximately 8% to week 26.[1,3] Percent achieving HbA1c goal of < 7% was 45% and 62% for the two doses compared to 21% for placebo. There was significant change in fasting plasma glucose, -36 m/dL and -43 mg/dL, respectively, for the two doses and 2-hour postprandial glucose (-48 mg/dL, and -64 mg/dL, respectively). There was also a 2.2% and 3.3% difference in weight loss between the two doses of canagliflozin compared to placebo. Substantial reduction in HbA1c was observed by week 12.[3] In patients with HbA1c > 10%, changes in HbA1c were -2.13% and -2.56%, respectively.[3] There was a modest decrease in systolic blood pressure, increase in HDL-C, and modest increase in LDL-C. For subjects inadequately controlled on metformin (up to 2000 mg/day; n = 1284), the addition of canagliflozin resulted in changes of -0.62% to -0.77% in HbA1c, respectively, from baseline to week 26.[1] Similar changes (range -0.62% to -0.83%) were seen when canagliflozin was added to insulin, a sulfonylurea, metformin + sulfonylurea, and metformin + pioglitazone.[1] In two separate 52-week studies, canagliflozin 300 mg/day added to metformin showed a greater lowering of HbA1c than glimepiride (6 mg to 8 mg) + metformin and was also more efficacious when added to metformin + sulfonylurea than sitagliptan (100 mg) + metformin, and sulfonylurea. Most common adverse events (vs placebo) were female genital mycotic infections (10-11% vs 3.2%) and increase in serum magnesium (8-9% vs -0.6%). The risk for hypoglycemia is significant if a sulfonylurea is part of the regimen.

Clinical Implications

Canagliflozin is the first in the class of SGLT2 inhibitors. This action lowers the threshold for glucose excretion so plasma glucose is lowered by promoting glucose excretion and osmotic diuresis. The long-term effect of polyuria and pollakiuria remains to be determined. The drug is effective in lowering HbA1c with the magnitude of reduction as monotherapy similar or less than reported with metformin monotherapy.[4] According to American Diabetes Association's multidisciplinary Professional Practice Committee, metformin is still the first-line oral therapy for type 2 diabetics.[5] There are currently no comparative studies as monotherapy. The long-term safety and efficacy remain to be determined. The wholesale cost for a 30-day supply of canagliflozin (100 mg or 300 mg) is $263. ■

References

1. Invokana Prescribing Information. Titusville, NJ: Janssen Pharmaceuticals, Inc.; March 2013.
2. Polidori D, et al. Canagliflozin lowers postprandial glucose and insulin by delaying intestinal glucose absorption in addition to increasing urinary glucose excretion: Results of a randomized, placebo-controlled study. *Diabetes Care* 2013; Feb. 14. [Epub ahead of print.]
3. Stenlof K, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013;15:372-382.
4. Glucophage Prescribing Information. Princeton, NJ: Bristol-Myers Squibb Company; January 2009.
5. American Diabetes Association. Standards of medical care in diabetes — 2012. *Diabetes* Care 2012;35 (Suppl 1):S11-S63.

CME Questions

1. **In the study by el Barzouhi et al, having a MRI scan at 1 year after treatment had how much discriminatory power to assess the difference between having a favorable outcome or not having a favorable outcome?**
   a. No
   b. Minimal
   c. Moderate
   d. Significant

2. **Compared to other antibiotics, the use of doxycycline in conjunction with ceftriaxone resulted in a:**
   a. higher rate of community-acquired pneumonia treatment failure.
   b. higher rate of nosocomial infections.
   c. lower rate of *Clostridium difficile* diarrhea.
   d. lower rate of medical non-adherence.
   e. higher rate of antibiotic-associated diarrhea.

3. **What was the reason for the nested case-control study on statin use and cancer-related mortality?**
   a. To evaluate other agents that could affect cancer outcome
   b. To control for tobacco use
   c. To increase the sample size
   d. To account for changes in treatment practices
   e. To look at different endpoints that may be more relevant to prescriptive practices

CME Objectives

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

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter! ■

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is an advisor for Endo, Kowa, Pricara, and Takeda.

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. Does omalizumab make a difference to the real-life treatment of asthma exacerbations?: Results from a large cohort of patients with severe uncontrolled asthma. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: A 5-year open-label follow-up study. *Lancet* 2013;381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. Risk of recurrent *Helicobacter pylori* infection 1 year after initial eradication therapy in 7 Latin American communities. *JAMA* 2013; 309:578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included nonadherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

In Future Issues:

Response of Chronic Cough to Acid-Suppressive Therapy in Patients with Gastroesophageal Reflux Disease