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ABSTRACT & COMMENTARY

Procalcitonin to Guide Antibiotic Therapy for Acute Respiratory Infections

By David Fiore, MD

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

SYNOPSIS: The authors of this meta-analysis reviewed patient-level data on 6,708 patients from 26 randomized studies that examined procalcitonin-directed antibiotic therapy for acute respiratory tract infections. They found a 1% reduction in mortality and a 2.4-day reduction in antibiotic exposure for the procalcitonin-directed therapy groups. How procalcitonin can be incorporated into routine clinical practice, in what settings, and whether it is cost-effective are still unclear.

SOURCE: Schuetz P, Wirz Y, Sager R, et al. Effect of procalcitonin-guided antibiotic treatment on mortality in acute respiratory infections: A patient level meta-analysis. *Lancet Infect Dis* 2017 Oct 13. pii: S1473-3099(17)30592-3. doi: 10.1016/S1473-3099(17)30592-3. [Epub ahead of print].

Procalcitonin was first identified by Leonard J. Deftos and Bernard A. Roos in the 1970s. It is composed of 116 amino acids and is produced by parafollicular cells (C cells) of the thyroid and by the neuroendocrine cells of the lung and the intestine.[1] In the 1990s, investigators started examining the relationship of procalcitonin to bacterial infection.[2] In the 2000s, investigators began testing procalcitonin as a marker for bacterial infection and its use in clinical decision-making.[3,4] In 2017, the FDA approved the use of procalcitonin for guiding antibiotic therapy in acute respiratory infections. These authors, who reported funding from Thermo Fisher (makers of the procalcitonin lab test), published this review in October 2017 both as a meta-analysis in *Lancet Infectious Diseases* and as a Cochrane Review. They reviewed patient-level data for 6,708 patients from 26 trials in 12 countries. Two trials were outpatient-based and looked at upper respiritory infections (URIs) (n = 1,008), 11 were from EDs and medical wards (n = 3,253), and 13 were from ICUs (n = 2,447). Each study used its own protocol and algorithm to determine how procalcitonin should direct therapy. Compliance with the algorithms ranged from 44-100%. The baseline

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characteristics of the patients in the two groups were similar, with most patients recruited from the ED or ICU.

The primary endpoints were 30-day mortality and treatment failure (defined by each study). Schuetz et al reported a statistically significant reduction in mortality in the procalcitonin group, which demonstrated a mortality of 9%, compared to 10% in the control group, resulting in a number to test and treat to save one life of 100 and a relative risk reduction of 10%.

These results are slightly better if the outpatient (URI) studies are excluded; the absolute risk reduction of mortality increases to 1.4% (number needed to test and treat = 71, relative risk reduction of 13%).

The authors also reported a reduction of antibiotic duration of 2.4 days in the procalcitonin-guided treatment groups and a reduction in antibiotic-related side effects (16% vs. 12%).

■ COMMENTARY

Although these results are very promising and are consistent with prior studies and a 2012 Cochrane Review (conducted by some of the same authors),[5] there still are some important questions that must be answered before we can feel confident using procalcitonin to guide our clinical practice.

The first concern is that different cutoffs and algorithms were used to direct therapy. As clinicians, we will need to see prospective confirmation of previously developed algorithms using a preset cutoff before we can be confident in using procalcitonin in our own practices. Furthermore, the issue of variability between different methods of assessing procalcitonin must be addressed.
In addition to the technical issues mentioned above, the "human" factor in ordering procalcitonin may limit its cost-effectiveness and its utility.

If physicians start ordering procalcitonin on patients with a very low risk of bacterial infection (as we've seen with D-dimer for venous thromboembolism), the false-positive rate will overwhelm the true positive rate and the utility of the test.

In my estimation, the bottom line still is somewhat mixed. It seems that ordering and carefully using a procalcitonin level as part of your clinical reasoning likely is useful, especially in those patients about whom you are unsure as to whether they have a bacterial infection. But widespread use should wait until we see more studies that are not funded by the makers of the test and should use consistent cutoff levels and algorithms. ■

REFERENCES

1. Deftos LJ, Roos BA, Parthemore JG. Calcium and skeletal metabolism. *West J Med* 1975;123:447-458.
2. Dandona P, Nix D, Wilson MF, et al. Procalcitonin increase after endotoxin injection in normal subjects. *J Clin Endocrinol Metab* 1994;79:1605-1608.
3. Daubin C, Parienti JJ, Fradin S, et al. Procalcitonin levels and bacterial aetiology among COPD patients admitted to the ICU with severe pneumonia: A prospective cohort study. *BMC Infect Dis* 2009;9:157.
4. Guven H, Altintop L, Baydin A, et al. Diagnostic value of procalcitonin levels as an early indicator of sepsis. *Am J Emerg Med* 2002;20:202-206.
5. Schuetz P, Müller B, Christ-Crain M, et al. Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. *Cochrane Database Syst Rev* 2012 Sep 12;(9):CD007498. doi: 10.1002/14651858.CD007498.pub2.

STROKE ALERT

Migraine With Aura, Stroke Risk, and Biomarkers

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Roche.

SYNOPSIS: A longitudinal cohort study of twins found no increased stroke risk related to migraine overall, but there was a modestly increased risk for stroke related to migraine with aura. Familial factors and vascular biomarkers associated with migraine with aura may explain its correlation with vascular disease.

SOURCES: Lantz M, et al. Migraine and risk of stroke: A national population-based twin study. *Brain* 2017;140:2653-2662.

Tietjen GE, et al. Migraine and vascular disease biomarkers: A population-based case-control study. *Cephalalgia* 2017; Jan 1:333102417698936. doi: 10.1177/0333102417698936 [Epub ahead of print].

A population-based cohort study used data from the Swedish Twin Registry to follow twins without cerebrovascular disease to evaluate migraine as a risk factor for eventual stroke. Twins who were born in the years 1935 to 1958 answered a headache questionnaire during the 1998 to 2002 time period; twins born between 1959 and 1985 answered a headache questionnaire during the 2005 to 2006 time period. Migraine with and without aura and probable migraine were defined according to the International Classification of Headache Disorders criteria. Cerebral ischemia and intracerebral hemorrhage diagnoses were obtained from national patient and cause of death registries. Twins were followed longitudinally, by linkage of national registers, from the date of interview until the date of first stroke, death, or until the study ended late in 2014. In total, 8,635 twins had any migraine/probable migraine headache (3,553 with migraine with aura and 5,082 with non-aura migraine/probable migraine headache) and 44,769 twins had no migraine headache history. Hypertension, peripheral arterial disease, and obesity were more common in non-migraineurs, with atrial fibrillation being less common. During the mean follow-up time of 12 years, there were 1,297 incident (1,073 ischemic and 276 hemorrhagic) strokes, with a mean age at the end of follow-up of 57 years. The data were analyzed using a Cox proportional hazards model, with results finding that any migraine/probable migraine headache and non-aura migraine/probable migraine headache were not associated with an increased risk for stroke. Migraine with aura was associated with a barely significant 27% increased risk for stroke in the initial analysis; but, there were no significant associations between migraine and specific stroke type. The age- and gender-adjusted hazard ratio (HR) for stroke related to migraine with aura was 1.27 (95% confidence interval [CI], 1.00-1.62; $P = 0.05$) and 1.07 (95% CI, 0.91-1.26; $P = 0.39$) related to any migraine/probable migraine headache. The estimated HR for stroke was non-significantly higher in twins younger than 50 years of age and in females. The 2,142 twin pairs discordant for migraine with aura showed an HR for stroke of 1.09 (95% CI, 0.81-1.46), which attenuated the association compared to the primary analysis. Genetic markers for stroke may contribute to this migraine with aura and stroke association.

The association of migraine and vascular disease biomarkers was evaluated in 300 women and 117 men (mean age 48 years) in the CAMERA 1 (Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis) substudy of the Dutch general population-based Genetic Epidemiology of Migraine. There were 155 migraineurs with aura, 128 migraineurs without aura, and 134 controls with no severe headaches. The vascular disease biomarkers compared between groups were: fibrinogen, Factor II, D-dimer, high-sensitivity C-reactive protein (hs-CRP), and von Willebrand factor antigen. Stroke-associated clinical phenotypes, including migraine with aura, female sex, and long duration and high attack frequency of aura and of headache, also were evaluated. Fibrinogen and hs-CRP were elevated in migraineurs compared to headache-free controls. Migraine was associated with an increased likelihood of elevated Factor II and hs-CRP. Fibrinogen and Factor II were associated with migraine with aura in women, but not in men. The vascular biomarker hs-CRP was correlated with both increased years and numbers of migraine aura attacks. An increased number of attacks was a significant predictor of elevated von Willebrand factor antigen, D-dimer, and fibrinogen.

■ COMMENTARY

Epidemiological studies have shown that migraine with aura is associated with an increased risk of cerebral and cardiac ischemia. However, an increased

cerebrovascular risk has not been shown for individuals with migraine without aura, the predominant migraine subtype. The reason for this consistently demonstrated increase in vascular risk associated with migraine with aura is not clear, with theories including cortical spreading depression, endothelial dysfunction, hypercoagulability, arterial dissection, and embolization through a patent foramen ovale. The Swedish twin study lends credence to a genetic theory linking migraine with aura and ischemic stroke; however, the relatively weak twin correlation indicates a multifactorial association. Given that migraine in general, as well as the specific migraine type, has a very strong familial correlation, a twin association could be expected, even if the migraine type was discordant between twin pairs. Elevated vascular biomarkers were associated with migraine, particularly migraine with aura, as well as with increased years of aura and number of aura attacks. Other studies, including the CAMERA study, have linked increased frequency and duration of migraine auras with neuroimaging findings that have the appearance of white matter ischemic disease.

Elevated vascular biomarkers should be investigated to determine which markers, if any, can be used to stratify risk of vascular events in patients with migraine with aura. All patients at risk of vascular disease should be counseled on the management of the more well-established vascular risk factors. However, migraine with aura in combination with some estrogen-containing contraceptives appears to increase the risk of cerebral ischemia. The ability to counsel women with migraine with aura about contraceptive choices potentially could be enhanced by using biomarker screening to determine the degree of vascular risk. ■

ABSTRACT & COMMENTARY

Cardiac Stenting No Better Than Aggressive Medical Management for Stable Angina and Single Vessel Disease

By David Fiore, MD

Professor of Family Medicine, University of Nevada, Reno

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

SYNOPSIS: Investigators conducted the first blinded, randomized trial comparing percutaneous coronary intervention with medical management.

SOURCE: Al-Lamee R, Thompson D, Dehbi HM, et al. Percutaneous coronary intervention in stable angina (ORBITA): A double-blind,randomised controlled trial. *Lancet* 2017 Nov 1. pii: S0140-6736(17)32714-9. doi: 10.1016/S0140-6736(17)32714-9. [Epub ahead of print].

Percutaneous coronary intervention (PCI) was born in Switzerland in 1977 with the first percutaneous transluminal coronary angioplasty (PCTA), which today is performed worldwide.[1] Although it is well known that PCI does not improve mortality or prevent myocardial infarctions, it is considered by many to be the optimal treatment for control of angina. The American College of Cardiology, the American Heart Association, and the European Society of Cardiology give PCI a 1A recommendation for symptom control in patients with "unacceptable angina" despite guideline-directed medical therapy.[2,3] The lack of effect of PCI on mortality or morbidity was reinforced by the COURAGE trial (2007), an open-label (unblinded) comparison of PCI and optimal medical therapy, which demonstrated no differences in death or myocardial infarction at three years (although there was a short-term benefit to PCI).[4] Despite the evidence and recommendations to only perform PCI in cases in which optimal medical management is unsuccessful in controlling symptoms or is inappropriate or undesired by the patient, it is still performed in more than 500,000 patients each year. In fact, less than half the patients undergoing PCI were found to have optimal medical therapy.[4] In its 40-year history, there has never been a blinded, randomized trial comparing PCI with medical management. Al-Lamee et al corrected that oversight.

The ORBITA investigators randomized 200 patients with angina and at least one severe coronary artery stenosis in a single vessel to either sham PCI or actual PCI. All patients received intensive optimal medical management and were followed for six weeks. Blinding was excellent, with no placebo patients correctly identifying their assignment. The primary outcome was change in exercise time on a treadmill. Secondary endpoints included a change in peak oxygen uptake,

a change in exercise time to 1 mm ST-segment depression, angina severity, physical limitations, angina stability and angina frequency, Duke treadmill score, and a change in dobutamine stress echocardiographic (DSE) wall motion score index. The authors powered the study to detect a 30-second difference in exercise time based on previous studies, which showed that single antianginal medical therapy provides 48-55 seconds of exercise time.[5] ORBITA failed to show a benefit of PCI over optimal medical therapy at six weeks.

Although there has been a buzz in the news, it is not quite the death knell for PCI for stable angina that some have touted (an editorial accompanying the trial was titled, "Last nail in the coffin for PCI in stable angina?"). The first brake on the enthusiasm for burying PCI for stable angina is that some patients may prefer an acute intervention with real, but rare complications to taking triple medical therapy indefinitely. A second concern, which is more related to this particular study, is that the exercise improvement times in both groups were much less than the anticipated improvements (11.8 seconds in the placebo group vs. 28.4 seconds in the PCI group). In addition, the PCI group exhibited more than twice the improvement over the placebo group. While the difference was not statistically significant in this study, if this was born out in a larger study, the conclusion would be quite different.

■ COMMENTARY

The investigators of this trial deserve to be lauded for performing the first known placebo-controlled trial of PCI. That alone should be enough to add this trial to the pantheon of ground-breaking medical studies. Hopefully, this will be followed by more placebo-controlled trials for all types of procedures, not just PCI. In the meantime, this trial clearly demonstrates that the decision to go to PCI for stable angina is not a "slam dunk" and that shared decision-making with your patient would be the most appropriate approach. ■

REFERENCES

1. Brown DL, Redberg RF. Last nail in the coffin for PCI in stable angina? *Lancet* 2017 Nov 1. pii: S0140-6736(17)32757-5. doi: 10.1016/S0140-6736(17)32757-5. [Epub ahead of print].
2. Fihn SD, Gardin JM, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2012;60:e44-e164.
3. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: The task force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J* 2013;34:2949-3003.
4. Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007;356:1503-1516.
5. Chaitman BR, Skettino SL, Parker JO, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. *J Am Coll Cardiol* 2004;43:1375-1382.

PHARMACOLOGY UPDATE

Abemaciclib Tablets (Verzenio)

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

Dr. Elliott is Assistant Clinical Professor of Medicine, University of California, San Francisco.
Dr. Chan is Associate Clinical Professor, School of Pharmacy, University of California, San Francisco.

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

The FDA has approved a new targeted, oral treatment option for patients with breast cancer who are not responding to or who have not progressed following endocrine treatment. Abemaciclib is the third cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor (after palbociclib and ribociclib). Theses kinases are involved in cell cycle transition and cell division. Abemaciclib was designated as breakthrough therapy and given a priority review. Abemaciclib is marketed as Verzenio.

INDICATIONS

Abemaciclib is indicated in combination with fulvestrant for the treatment of women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer with disease progression following endocrine therapy.[1] It is also indicated as monotherapy for the treatment of adults with HR+, HER2-, advanced, or metastatic breast cancer with disease progression following endocrine therapy and prior chemotherapy in the metastatic setting.

DOSAGE

The recommended dose is 150 mg twice daily with fulvestrant or 200 mg twice daily as monotherapy.[1] Dosage interruption and/or modification is based on severity of adverse events such as hematologic

conditions, diarrhea, hepatotoxicity, and other toxicities.[1] Abemaciclib is available as 50 mg, 100 mg, 150 mg, and 200 mg tablets.

POTENTIAL ADVANTAGES

Abemaciclib differs chemically compared to previous CDK4/6 inhibitors and is much more selective for CDK4 than CDK6.[2,3] Cytopenia is less likely, thus allowing for continuous therapy compared to 21 days on and seven days off for palbociclib and ribociclib. It is the first CDK4/6 inhibitor approved for monotherapy.

POTENTIAL DISADVANTAGES

Most frequent (> 30%) adverse reactions reported were diarrhea (86%), neutropenia (46%), nausea (45%), infections (43%), elevation of liver enzymes (37-41%), and abdominal pain (35%). Venous thromboembolic events were reported in 5% of patients, and there is potential for embryo-fetal toxicity. Fatigue and gastrointestinal toxicity is more common with abemaciclib compared to other CDK4/6 inhibitors.[5] Strong CYP3A4 inhibitors may increase the toxicity of abemacicib.[1]

COMMENTS

The approval of abemaciclib was based on two clinical trials. One was a single-arm, open-label study, and the other a randomized, double-blind study with fulvestrant, an estrogen receptor antagonist.[1,4,5] The first study enrolled women with HR+ and HER2- metastatic breast cancer who had progressed on or after prior endocrine therapy, had received a taxane, and had received one or two chemotherapy regimens in the metastatic setting. Subjects (n= 132) were given abemaciclib (200 mg) every 12 hours until disease progression or unacceptable toxicity. Dose reduction and delay were allowed based on study protocol. The primary endpoint was investigator-assessed objective response rate (ORR). ORR was 19.7%, with a median duration of response of 8.6 months. This compares favorably to a historical response of 15% for chemotherapy.[4]

The authors of the second study examined subjects with HR+ and HER2- metastatic breast cancer who demonstrated disease progression following endocrine therapy who had not received chemotherapy in the metastatic setting.[1,5] Subjects were randomized to abemaciclib (150 mg every 12 hours) + fulvestrant (500 mg intramuscularly on days 1 and 15 of cycle 1 and on day 1 of every 28-day cycle thereafter) or placebo + fulvestrant. Results were assessed based on 446 subjects on abemaciclib and 223 on placebo. Efficacy endpoints were progression-free survival (PFS) and objective tumor response rate (OTR) in subjects with measurable disease. PFS was 16.4 months for abemaciclib vs. 9.3 months for placebo (hazard ratio, 0.55; 95% confidence interval, 0.45-0.68). OTR based on 318 subjects on abemaciclib and 164 on placebo was 48% vs. 21%. In another Phase III study, abemaciclib was evaluated as initial therapy and has been reported to improve PFS and OTR compared to placebo when added to anastrozole or letrozole (aromatase inhibitors).[6]

CLINICAL IMPLICATIONS

More than 70% of patients with metastatic breast cancer are HR+ and treated with endocrine therapy.[7] Over time, endocrine resistance can develop. Deregulation of CDK4/6 appears to play a role in breast cancer tumorigenesis and development of endocrine resistance.[2] Current Cancer Comprehensive Network guidelines list palbociclib and ribociclib with an aromatase inhibitor as category 1 treatment for HR+ and HER2- postmenopausal patients with recurrent or stage IV disease and no prior endocrine therapy within one year (initial therapy).[8] Abemaciclib plus fulvestrant is listed as an option for progression on prior endocrine therapy. There are no data to support trying another CDK4/6 regimen if there is disease progression.[8] Abemaciclib monotherapy is indicated after progression on prior endocrine therapy and prior chemotherapy in the metastatic setting. Currently, it has not been approved for initial therapy. ■

REFERENCES

1. Verzenio Prescribing Information. Eli Lilly and Company. September 2017.
2. Bilgin B, Sendur MAN, Şener Dede D, et al. A current and comprehensive review of cyclin-dependent kinase inhibitors for the treatment of metastatic breast cancer. *Curr Med Res Opin* 2017;33:1559-1569.
3. Spring LM, Zangardi ML, Moy B, Bardia A. Clinical management of potential toxicities and drug interactions related to cyclin-dependent kinase 4/6 inhibitors in breast cancer: Practical considerations and recommendations. *Oncologist* 2017;22:1039-1048.
4. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a Phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. *Clin Cancer Res* 2017;23:5218-5224.
5. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol* 2017;35:2875-2884.
6. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;35:3638-3646.
7. U.S. Food and Drug Administration. FDA approves new treatment for certain advanced or metastatic breast cancers, Sept. 28, 2017. Available at: http://bit.ly/2xJsFS7. Accessed Dec. 5, 2017.
8. National Comprehensive Cancer Network. NCCN Guidelines. Available at: http://bit.ly/2BKvQJa. Accessed Dec. 5, 2017.

Clinical Briefs

By Louis Kuritzky, MD

Cardiorespiratory Fitness and Mortality

SOURCE: Ehrman JK, Brawner CA, Al-Mallah MH, et al. Cardiorespiratory fitness change and mortality risk among black and white Patients: Henry Ford Exercise Testing (FIT) Project. *Am J Med* 2017;130:1177-1183.

In both men and women in the United States, levels of cardiorespiratory fitness are inversely related to mortality. An encouraging epidemiologic study of women (the Nurses' Health Study, n = 72,488) found that even brisk walking for about 30 minutes daily was associated with near maximal cardiovascular (CV) health benefits. Additionally, even sedentary women who became physically active later in life enjoyed CV risk reduction.

But does race make a difference? African-Americans demonstrate higher CV event rates and mortality than Caucasians, which has been linked to disparities in hypertension, access to care, and other causes. However, for similar levels of fitness, are outcomes different between ethnicities? Investigators performed a retrospective analysis of data from a nine-year follow-up of patients (n = 13,345) who had undergone exercise treadmill testing at Henry Ford Hospital in Detroit on at least two occasions.

Approximately 75% of the population was Caucasian and 25% African-American. An analysis of fitness level in relation to mortality showed no meaningful difference between groups: For both ethnicities, each one metabolic equivalent increment of cardiorespiratory fitness was associated with a 13-16% reduction in mortality. ■

Searching for Answers on Knee Osteoarthritis

SOURCE: Bartels EM, Henrotin Y, Bliddal H, et al. Relationship between weight loss in obese knee osteoarthritis patients and serum biomarkers of cartilage breakdown: secondary analyses of a randomised trial. *Osteoarthritis Cartilage* 2017;25:1641-1646.

It is well-recognized that overweight and obesity are associated with osteoarthritis. Lest one becomes overly simplistic and assigns degenerative joint changes solely to the extra stress of excess weight, one should recognize that osteoarthritis of the hands also is associated with obesity, although it would be difficult to conjure any additional joint-loading burden.

At the same time, data consistently show that for knee osteoarthritis, weight loss is associated with symptomatic and functional improvement. The mechanism of this is incompletely understood, since weight loss has not been shown to affect the progressive degradation of cartilage typical of osteoarthritis.

Bartels et al studied biomarkers of collagen breakdown in persons with knee osteoarthritis who lost weight, wondering whether these potentially more sensitive indicators would corroborate that the symptomatic improvements seen with weight loss were actually reflecting less cartilage degradation that was too subtle to be identified radiographically. At the conclusion of the trial, changes in biomarkers were not found to be associated with symptomatic improvements. ■

Considering Systemic Treatment for Atopic Dermatitis

SOURCE: Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol* 2017;77:623-633.

Most patients with atopic dermatitis can control their disease with topical agents, including corticosteroids, calcineurin inhibitors (e.g., pimecrolimus, tacrolimus), local hygienic measures (e.g., moisturizers), and, most recently, a topical phosphodiesterase-4 inhibitor (crisaborole). A recent panel of eczema experts convened to provide advice about when clinicians should consider systemic treatment.

Their first recommendation was to optimize topical treatments. Patients refractory to topicals should be assessed for the presence of contact allergy (e.g., patch testing), as well as for the presence of viral, bacterial, or yeast cutaneous disease. Prior to the institution of systemic therapy, a trial of phototherapy should be considered.

If none of these interventions are sufficient, there are five different systemic therapies to consider: azathioprine, cyclosporine, dupilumab, methotrexate, and mycophenolate. At this stage of disease, most patients will be best served by referral to a dermatologic specialist. ■

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CME QUESTIONS

1. **Based on the study by Schuetz et al, which of the following statements is true about procalcitonin-directed therapy in acute respiratory infections?**
   a. Procalcitonin-directed therapy in the outpatient setting saves lives.
   b. Procalcitonin-directed therapy saves money.
   c. Procalcitonin-directed therapy can help determine which antibiotic to use.
   d. Procalcitonin-directed therapy reduces mortality and shortens the duration of antibiotic treatment.

2. **Which vascular biomarker was correlated with both increased years and numbers of migraine aura attacks?**
   a. Erythrocyte sedimentation rate
   b. Factor II
   c. hs-CRP
   d. Homocysteine

3. **The ORBITA study demonstrated which of the following?**
   a. Percutaneous coronary intervention (PCI) prevented more myocardial infarctions than medical management.
   b. PCI reduced symptoms compared to medical management.
   c. PCI and medical management were statistically equivalent in improving exercise times.
   d. Medical management was superior to PCI in improving exercise times.

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.

[IN FUTURE ISSUES]

Newer Guidelines for Influenza Testing This Season

Travelers Unaware of the Need for Pre-travel Vaccinations