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INSIDE

Have a Cow! And an Egg, Too!

ABSTRACT & COMMENTARY

Synopsis: *A high saturated-fat and no-starch diet resulted in modest weight loss without negative effects on serum lipid levels; weight loss can be continued for up to a year with such a diet.*

Source: Hays JH, et al. *Mayo Clin Proc*. 2003;78:1331-1336.

TWENTY-THREE PATIENTS WITH SIGNIFICANT CORONARY ARTERY disease (6 of whom were women), 15 women with polycystic ovarian syndrome (PCOS) and 8 women with "reactive hypoglycemia," were recruited for the study. The patients with cardiovascular disease were all being treated with statins (the doses of which were unchanged during this study) and had well-documented cardiovascular disease. Those with diabetes, documented cerebrovascular disease, or recent acute cardiac events were excluded. The patients with PCOS were referred by gynecologists because of desired pregnancy (8), hirsutism (4), and oligomenorrhea (3). The patients with reactive hypoglycemia were extremely obese (mean BMI 46.8 kg/m^2) and were defined by "repeated episodes of postprandial dysphoria relieved by food," without a requirement for documented hypoglycemia. The patients in the PCOS and reactive hypoglycemia groups were not taking statins.

The patients on the high saturated-fat and no-starch diet were advised to consume half of their calories as saturated fat, especially red meat and cheese. Eggs were unlimited, and there was no attempt to restrict cholesterol intake. Fresh fruit and nonstarchy vegetables were restricted, and starch was forbidden. Patients kept dietary logs. Weight, serum lipids, and chemistries were measured at baseline for all subjects and again after 6 weeks for the patients with cardiovascular disease, at 24 weeks for those with PCOS, and at 52 weeks for those with reactive hypoglycemia. Lipid fractions were determined by Nuclear Magnetic Resonance (NMR).

Patients were compliant with the meat consumption requirement, and estimated caloric intake fell. Patients in the cardiovascular group ate 2-4 eggs and 1½ pounds of red meat *per day*. In this group (with cardiovascular disease), mean body weight fell 10%, or 5.5 kg in weeks, with a resultant mean fall in BMI of 2.2 kg/m^2. Neck circumference decreased 0.4 inches. Insulin sensitivity

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EDITOR
Stephen A. Brunton, MD
Clinical Professor,
University of California Irvine

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Chief of Medicine, Charity, and University Hospitals, Associate Chairman of Medicine, Tulane Health Sciences Center

Allan J. Wilke, MD
Assistant Professor of Family Medicine, Medical College of Ohio, Toledo, OH

improved and fasting glucose levels fell. Mean triglycerides fell 58 mg/dL, mean very low-density lipoproteins (VLDL) fell 56 mg/dL, and mean VLDL particle size fell 9 nm. Total cholesterol, HDL cholesterol, and LDL cholesterol levels were unchanged, and HDL and LDL size increased. Mean plasma homocysteine levels increased but C reactive protein levels were unchanged. Ten patients in this group had been classified with metabolic syndrome prior to the study; after 6 weeks, 8 of these 10 patients were no longer in that category, but 1 patient who had not previously been classified as such developed the metabolic syndrome profile. Five of these patients had fasting ketonuria with elevated serum beta hydroxybutyrate levels.

The patients with PCOS lost a mean of 14% of body weight in 24 weeks, and patients with reactive hypoglycemia lost 19.9% of body weight in 52 weeks. No patient in these 2 groups had changes in lipid levels or positive urine ketones.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

In the accompanying editorial,[1] Gerald Gau, also of the Mayo Clinic, says ". . . I am concerned about the long-term cardiovascular risk shown in the published studies . . .We should continue to examine the risk-benefit profiles of the caloric-restricted more rational diets such as the Mediterranean diet." This is true, of course. But maybe we need to re-examine the notion, evident in the title of his editorial, that one size fits all when it comes to weight loss. The people in this study were experiencing significant medical complications of obesity and had likely experienced failure with a variety of diets, including "rational" ones. I think this type of patient is, unfortunately, all too familiar to most of us. Patients restrict fat grams, as instructed, but eat huge amounts of calories because they are never satisfied. Fat satisfies; carbohydrates don't. Ultimately, weight loss depends on reduction in calories. In the current study, patients ate fewer calories and, of course, lost weight. The breakthrough with this study was that they appeared to be able to consume very high-fat foods with actual improvement in serum lipid levels.

Although Hays and colleagues never state it outright, a "high saturated-fat and no-starch diet" is essentially the infamous Atkins diet. This study is one of a handful of papers comparing low- or no-carbohydrate diets with the low-fat diets, such as the NCEP (National Cholesterol Education Program) diet promulgated by the American Heart Association, American College of Cardiology, AMA, and others. Most have been short term and have had very poor compliance rates[2,3] but have tended to show that patients lose more weight on a high-fat than a low-fat diet. There is 1 study comparing the Atkins diet with low-fat diets for 1 year.[4] In this study, only the patients on the high-fat diet had lost significant weight at the end of the year, but a variety of serum lipid measures had worsened in these patients. On the other hand, those on low- or medium-fat diets did not lose a significant amount of weight but had improvement in some serum lipid measures. This is somewhat like choosing between the devil and the deep blue sea. What we still need to know is which is the greater risk factor: obesity or hyperlipidemia. Personally, I think that hyperlipidemia is overrated as a risk factor, especially when compared with obesity. I am impressed that the patients in this study had significant reductions in neck circumference, since neck size is a robust predictor of the likelihood of obstructive sleep apnea (more than 17 inches in a man or

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Please call **Robin Mason,** Managing Editor, at (404) 262-5517 (e-mail: robin.mason@ahcpub.com) or **Robert Kimball**, Assistant Managing Editor, at (404) 262-5413 (e-mail: robert.kimball@ahcpub.com) between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

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Editorial E-Mail: robert.kimball@ahcpub.com

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16 inches in a woman strongly predicts significant sleep-disordered breathing).[5]

Because of the concern about cardiac risk, many physicians now advocate a variant of a high-fat diet, the "South Beach Diet," which is perceived to be a less extreme version of the Atkins diet. Interestingly, while a Google search for "south beach diet" turned up more than 45,000 matching sites, a PubMed search turned up only 2 articles, one of which was a letter and one of which was irrelevant. In my consequently rather non-scientific reading about the 2 diets, the primary difference seems to be that the Atkins diet stresses avoidance of all carbohydrates, while the South Beach Diet sorts carbohydrates as "good" and "bad," based on their glycemic index.

The take-home message from this paper may be that some patients who are refractory to "rational" diets do finally lose weight by avoiding carbohydrates. This is the first paper to suggest that they may be able to do it without adversely affecting serum lipids.

The sad thing about all this is that Dr. Atkins died just as his work was finally being vindicated! ■

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Immunologic Therapies for Psoriasis

ABSTRACTS & COMMENTARY

Synopsis: *Two injectable biologic therapies, etanercept and efalizumab, have been shown to be highly effective in treating psoriasis. Etanercept has been used in rheumatoid arthritis since 1998, and efalizumab is a new agent in phase III trials. Psoriasis is a debilitating autoimmune illness, and these new therapies, while expensive, will be a welcome addition for patients suffering from a severe form of this disease.*

Sources: Lebwohl M, et al. *N Engl J Med*. 2003;349: 2004-2013; Leonardi CL, et al. *N Engl J Med*. 2003;349: 2014-2022.

Chronic plaque psoriasis affects 2% of the population, and these 2 studies argue that its disability is similar to other major illnesses such as diabetes, arthritis, depression, and cancer. Current therapies are limited by their toxicity and have low efficacy. Psoriasis is an incurable autoimmune disease that is mediated by T lymphocytes. The unique immunologic features of the skin, which protect it from infection, may be manipulated in treating psoriasis.

In the study by Lebwohl and associates using the T-cell modulator, efalizumab, 597 patients received weekly injections of 1 or 2 mg/kg of body weight of drug or placebo for 12 weeks. The response rate of at least 75% improvement was 22% of patients receiving 1 mg and 28% receiving 2 mg, compared with 5% receiving placebo. The responders were continued in therapy for 24 weeks with continued improvement that lasted in 30% of patients 12 weeks after discontinuation of therapy. Pictures of study patients in the article show the dramatic results, which became apparent in responders as soon as 4 weeks of therapy. Adverse side effects of the drug were mild, with headache being the most common. Efalizumab is made by Genetech, which funded the study.

In the study by Leonardi and colleagues, using etanercept, 672 patients were randomized to 3 dosages of the drug and placebo. Etanercept is a tissue necrosis factor (TNF) antagonist. TNF is involved in T-cell signaling, and its inhibition is helpful in a wide variety of inflammatory, autoimmune diseases. The response rate of at least 75% improvement over 12 weeks was achieved by just 14% of patients receiving 25 mg once weekly, but 34% of patients receiving 25 mg twice weekly, and 49% of patients receiving 50 mg twice weekly. The placebo response rate was 4% of patients. Nintey percent of patients receiving the medium- and high-dose therapy had at least a 50% improvement in lesions. The drug responders showed continued improvement for the 24-week treatment period. Adverse events and infections were mild.

■ **COMMENT BY JOSEPH E. SCHERGER, MD, MPH**

The results of these studies are impressive and most likely represent a breakthrough in the treatment of psoriasis. It is unfortunate that less than 50% of patients have the 75% improvement of their disease. This therapy is expensive and should be reserved mainly for patients disabled by their disease, or have widespread lesions. In an accompanying editorial, Kupper further describes the immunologic targets in psoriasis, and predicts that biologic therapies for this disease and others will increase in number.[1] He also states that genetic testing is likely to predict which patients will respond to biologic therapies. ■

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Dr. Scherger is Clinical Professor, University of California, San Diego.

Advances in Neuropathic Pain: Diagnosis, Mechanisms, and Treatment Recommendations

ABSTRACT & COMMENTARY

Synopsis: *A consensus panel updates recent understanding about the causes and treatment in common neuropathic pain problems.*

Source: Dworkin RH, et al. *Arch Neurol*. 2003;289:295-305.

Neuropathic pain results from lesions of the peripheral or central nervous system most often seen as a consequence of long-standing diabetes mellitus, but it is also observed in many other conditions. The presence of both negative (eg, numbness) and positive (eg, paresthesias) sensory neurologic symptoms are common presenting complaints. Nerve conduction velocity and electromyography may be normal despite profound abnormalities in small myelinated and unmyelinated nerves. Inflammatory and myofascial pain mechanisms may combine with neuropathic processes making differential diagnosis difficult. Advances in understanding the underlying pathophysiology demonstrate that a variety of peripheral and central processes may be present in any one patient.

Randomized, controlled trials have shown efficacy in neuropathic pain with gabapentin, lidocaine patch 5%, opioids, tramadol, and tricyclic antidepressants. The underlying pathophysiology suggests that treatment approaches involving one drug or a combination of drugs is justified in any pain syndrome involving nerve injury even without clinical trial results.

COMMENT BY BILL McCARBERG, MD, FABPM

Neuropathy is common and difficult to treat. Diagnosis is often the result of a characteristic history confirmed by physical examination and laboratory findings. Neuropathic pain mechanisms may significantly contribute to the discomfort felt in many common chronic pain problems including chronic low back and neck pain. Treatment is often difficult and requires several drugs with different mechanisms of action. Although 5 drugs or drug categories have demonstrated efficacy in randomized trials, only gabapentin, lidocaine patch 5%, and carbamazepine have FDA approval for treatment in specific neuropathic problems. Head-to-head trials are lacking to guide therapy of one drug class compared to another or a combination of drug categories. Polypharmacy is the rule in difficult cases. Special consideration should be given to tricyclic antidepressants and opioids due to increased risk of use—especially in selected populations. ■

Dr. McCarberg is Director of the Chronic Pain Management Program; Coordinator of Pain Services, Kaiser Permanente, San Diego, Calif.

A Prospective Study of Anticoagulation Intensities in Patients With APA Syndrome

ABSTRACTS & COMMENTARY

Synopsis: *The study found that high-intensity warfarin therapy was not necessary for the prevention of recurrent thrombosis in the APA syndrome.*

Sources: Crowther MA, et al. *N Eng J Med*. 2003;349:1133-1138; Lockshin MD, Erkan D. Editorial. *N Eng J Med*. 2003;349:1177-1179.

The antiphospholipid antibody (APA) syndrome comprises a wide range of clinical features, including thromboembolism, fetal loss, thrombocytopenia, livido reticularis, cardiac valve vegetations, a multiple sclerosis-like condition, and progressive cognitive dysfunction—all associated with the persistence of moderate-to-high levels of IgG or IgM anticardiolipin antibodies or the lupus anticoagulant.

The varied clinical presentation of APA syndrome has led to various types of treatment. In pregnant women with a history of recurrent fetal loss, low doses of unfractionated heparin have been effective in preventing fetal loss[1] and thrombosis.[2] In patients with the rare catastrophic APA syndrome of progressive multisystemic vascular occlusions plasmapheresis,[3] intravenous immune globulin or both have been recommended. A

Table

APA Syndrome Patients at Baseline

Characteristic	Target	INR
	2.0 - 3.0	3.1 - 4.0
Number	58	56
Age years, mean range	4121-81	4320-80
Women no. (%)	41 (71)	27 (48)*
Venous thrombosis no. (%)	45 (78)	42 (75)
SLE no. (%)	6 (10)	8 (14)
Aspirin use at baseline and throughout study	6 (10)	8 (14)

*P = .01

Adapted from: Crowther M, et al. *N Engl J Med*. 2003;349: 1113-1138.

retrospective study[4] concluded that anticoagulant therapy at an international normalized ration (INR) of 3.0 or higher afforded better protection against recurrent thrombosis than less-intensive anticoagulation.

Crowther and associates reported the results of a prospective, randomized, controlled study of the use of 2 intensities of warfarin anticoagulation for prevention of thrombosis in patients with the APA syndrome who had previous thrombosis (*see Table*).

A total of 114 patients with moderate or high titers of anticardiolipin antibodies (n = 44), the lupus anticoagulant alone (n = 49), or both (n = 21) were treated with either moderate- or high-intensity warfarin anticoagulation. The follow-up period was 2.7 years.

In both treatment groups, the rate of recurrent thrombosis was low: 2 of 58 patients (3.4%) assigned to receive moderate-intensity warfarin and 6 of 56 patients (10.7%) assigned to receive high-intensity warfarin. Therefore, the lower dose of warfarin was as effective as the higher dose. Adverse effects were similar among patients in the 2 groups.

As pointed out by Lockshin and Erkan in their editorial, adherence to protocol was imperfect. In the moderate-intensity group, the INR was above the target range 11% of the time, within range 71% of the time, and below it 19% of the time. In the high-intensity group, INR was above the range 17% of the time, within the range only 40% of the time, and below it 43% of the time. In 5 of 8 patients with recurrent thrombosis during the follow-up period, INR was lower than 2.0. Therefore, at the time of recurrent thrombosis, INR was out of range or subtherapeutic in 4 of the patients in the high-intensity warfarin group. In addition, patients with arterial thrombosis, which in general is harder to treat than venous thrombosis, accounted for only one-fifth of the patients studied, although their outcomes were similar to those with venous thrombosis.

COMMENT BY JOHN J. CARONNA, MD

The treatment of the APA syndrome has been empirical because of both the lack of well-designed prospective studies and the heterogeneity of the clinical syndromes. This heterogeneity derives in part from the fact that there are 2 APA syndromes: the primary APA syndrome not associated with another illness and the secondary APA syndrome associated with systemic lupus erythematosus or other rheumatic disease.

In addition, even the term "antiphospholipid antibody" is inaccurate. As Lockshin and Erkan point out, the most important autoantigens in the syndrome are not negatively charged phospholipids as originally thought. The principal autoantigen is ß2-glycoprotein I (apolipoprotein H) that binds cardiolipin and other phospholipids. The phospholipid that is bound by the glycoprotein probably induces a conformational charge in the protein, thereby causing it to expose an antigenic epitope.

The study of Crowther et al found that high-intensity warfarin therapy was not necessary for the prevention of recurrent thrombosis in the APA syndrome. It can be argued, however, that the rate of recurrent thrombosis might have been lower if the INR in patients assigned to high-intensity anticoagulation had been in the target range during a greater portion of the study period. Nevertheless, the rate of recurrent thrombosis in the moderate-intensity group was so low that it is unlikely that strict maintenance of an INR > 3 would have improved outcome.

Although the present study leaves many questions unanswered, such as the role of aspirin alone or in combination with warfarin in preventing thrombosis in the APA syndrome, the results appear to be valid and generalizable to the care of patients. ■

Dr. Caronna is Vice Chairman, Department of Neurology, Cornell University Medical Center; Professor of Clinical Neurology, New York Hospital, New York, NY.

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Gastric Fundic Gland Polyps

ABSTRACT & COMMENTARY

Synopsis: *A majority of gastric fundic polyps are benign. Their presence in unscreened individuals older than 50 might warrant colonoscopy.*

Source: Burt RW. *Gastroenterology*. 2003;125:1462-1469.

GASTRIC FUNDIC GLAND POLYPS CAN BE VISUALLY horrifying when seen on endoscopy, and they are now quite commonly present in patients taking chronic acid suppressive therapy with proton pump inhibitors (PPIs). Despite their appearance, their significance in the setting of profound acid suppression is entirely trivial. However, in the absence of PPI therapy, they can be evidence of potentially life-threatening familial adenomatous polyposis (FAP).

Sporadic fundic gland polyps comprise 50% of all gastric polyps, and they may be seen in up to 2% of upper GI endoscopies (EGDs). They seem particularly common in middle-aged women, but they are also identified in men and even in pediatric patients (0.3%). More ominously, fundic gland polyps are present in 12.5-84% of patients with familial adenomatous polyposis. On histology, these polyps have irregular cystically dilated fundic glands, lined by flattened parietal cells and chief cells. These polyps have been considered to be benign hamartomas. Oddly enough, fundic gland polyps seem to have an inverse relationship with *Helicobacter pylori*. Fundic polyps present in FAP, a disease associated with mutational inactivation of the adenomatous polyp coli gene, can develop dysplasia and very rare gastric cancer (0.6%). Far more serious than rare gastric cancer, the real concern about fundic gland polyps in FAP is their association with multiple colonic polyposes and a very high risk of colon cancer.

With a mean of 32.5 months of PPI therapy, fundic polyposis has been seen in 7.3% of patients. This scenario of acid suppression will undoubtedly represent the great majority of fundic gland polyposis seen in clinical practice and such polyps require absolutely no follow-up. However, it has been suggested in this paper that the presence of fundic gland polyps probably should lead to colonoscopy—since several syndromes that lead to such polyps (FAP, Cowden's syndrome, and Peutz-Jeghers Syndrome) all could be associated with colonic polyposis and high colon cancer risk. Familial colon polyposis involves multiple colon polyps, often innumerable. If several polyps are found in the colon of a patient with multiple fundic gland polyps, attenuated FAP could be the diagnosis (to be confirmed with genetic testing, also involving appropriate family screening if the genetic test is positive).

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

This paper deals with an important issue. Many primary care physicians perform endoscopy. Due to the very wide use of PPIs, they are certain to see fundic gland polyps. Anyone who performs endoscopy or who cares for patients who undergo upper GI endoscopic evaluation needs to be aware of the issues surrounding fundic gland polyposis. A reasonable management protocol should exist for patients with this finding. Although Bert makes a cogent argument for screening colonoscopy in all such patients, I am not convinced. It seems to me that huge numbers of patients will have fundic gland polyps from PPI treatment, and the overall risk of colon cancer may be quite low. Of course, there is the alternative argument that everyone older than 50 should undergo screening colonoscopy. Therefore, a compromise position could be that fundic gland polyps in an unscreened person older than age 50 could warrant colonoscopy. Perhaps the presence of extremely numerous and large fundic gland polyps might raise more concern than a few apparently sporadic polyps, and some evidence-based findings suggest the appropriateness of this approach. In general, there is no reason to biopsy or excise obvious fundic gland polyps unless there is some other abnormality consistent with malignant degeneration. ■

Pharmacology Update

Tadalafil Tablets (Cialis)

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

THE FDA HAS APPROVED TADALAFIL, THE THIRD phosphodiesterase type 5 inhibitor (PDE5) for the treatment of erectile dysfunction. The approval of tadalafil occurred just 3 months after the approval of vardenafil (Levitra), which, along with sildenafil (Viagra) represent the 2 previously approved drugs for this indication. Tadalafil has a duration of action of up to 36 hours (hence the nickname the "weekend drug") and will be marketed by Lilly as "Cialis."

Indications

Tadalafil is indicated for the treatment of erectile dysfunction.[1]

Dosage

The recommended dose is 10 mg taken prior to sexual activity. The dose range is 5 mg to 20 mg depending on effectiveness and side effects. It may be taken without regard to meals. In patients with moderate renal dysfunction, the dose should not exceed 5-mg once daily and 10-mg every 48 hours. In patients with mild or moderate hepatic dysfunction, the dose should not exceed 10-mg once daily. In patients taking concomitant drugs that are potent CYP3A4 inhibitors (eg, ritonavir, ketoconazole), the dose of taladafil should not exceed 10 mg every 72 hours.[1]

Tadalafil is available as 5-mg, 10-mg, and 20-mg tablets.

Potential Advantages

Tadalafil has a mean elimination half-life of 17.5 hours compared to 4-5 hours for sildenafil and vardenafil.[1-3] A single 10-mg or 20-mg dose has been reported to improve the likelihood of successful intercourse up to 36 hours.[1,4]

Potential Disadvantages

Similar to other PDE5 inhibitors, tadalafil is metabolized by CYP3A4. Potent inhibitors of this isoform are expected to increase the level of these drugs and 3A4 inducers (eg, rifampin) may decrease drug levels. Side effects are also similar among PDE5 inhibitors. The most common are headache (11-15% vs 5% for placebo) and dyspepsia (4-10% vs 1%).[1,5]

Comments

Similar to other PDE5 inhibitors, tadalafil improves erectile function in men with erectile dysfunction. Tadalafil has demonstrated efficacy in 2 US studies (n = 402) and 5 studies outside the United States (n = 1112) in men with general erectile dysfunction.[1] Efficacy was assessed primarily by the Erectile Function domain score of the International Index of Erectile Function and 2 questions on penetration and successful intercourse. Specifically efficacy has also been demonstrated in patients with diabetes mellitus and in patients following radical prostatectomy.[1,6] In contrast to sildenafil and vardenafil, tadalafil has shown efficacy up to 36 hours. In a randomized, placebo-controlled study (n = 348), after a 20-mg dose of tadalafil, 59.2% of intercourse attempts were successful 33-39 hours after dosing compared to 28.3% in the placebo group.[1,4] In a second study (n = 483), the percent successful intercourse at 36 hours post-dose were 33%, 56%, and 67% for placebo, 10 mg, and 20 mg dose, respectively.[1] Successful erection (1 in 4 attempts) within 30 minutes was more likely to be achieved with the 20-mg dose compared to the 10-mg or placebo, 52%, 38%, and 35%, respectively. Similar to other PDE5 inhibitors, tadalafil is well tolerated but has potential drug interactions including potent inhibitors of CYP3A4 isoform, nitrates, and alpha-blockers (except tamsulosin). A small decrease in blood pressure (eg, 4-6 mm Hg systolic and 1-4 mm Hg diastolic) may occur when tadalafil is used with other antihypertensive drugs such as diuretics, ACE inhibitors, or beta blockers.[1] As with other PDE5 inhibitors the wholesale cost for all the strengths are priced the same. Tadalafil and sildenafil are priced at $8.10 per tablet and vardenafil is priced at $6.93 per tablet.

Clinical Implications

Tadalafil offers another option to sildenafil and vardenafil with a longer duration of action that may be attractive. No comparative studies among PDE5 inhibitors have been published. ■

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CME Questions

30. Which statement best describes the response of immunologic therapies (efalizumab and etanercept) in psoriasis?

a. The majority of patients have a 75% improvement in their disease.
b. These therapies target B-cell lymphocyte function as a means of preventing the inflammatory response.
c. These therapies are given by injection and those patients who respond have a continued improvement over time.
d. These therapies have serious side effects and require intensive monitoring during treatment.

31. Fundic gland polyposis can be seen in which of the following settings?

a. Chronic PPI therapy
b. Active *Helicobacter pylori* infection
c. Peutz-Jeghers syndrome
d. Familial adenomatous polyposis
e. In middle-aged women and in fewer men and children
f. All of the above except b

Answers: 30 (c); 31 (f)

By Louis Kuritzky, MD

Sulfonamide Antibiotics and Sulfonamide Nonantibiotics

SULFONAMIDE ANTIBIOTICS (SULF-a) are the drugs most commonly associated with both the dread consequences of Stevens-Johnson syndrome and agranulocystosis. More commonly, clinicians see modest allergic dermatitis in SULF-a allergic patients. The allergen responsible for inducing allergic reactions is common both to SULF-a and nonantibiotic sulfonamides, such as thiazide diuretics (SULF-na).

Strom and colleagues used the General Practice Research Database from the United Kingdom, to scrutinize the relationship between SULF-a allergic reactions and subsequent SULF-na allergic reactions. Because Strom et al entertained the possibility that reactions to SUFL-na reflect a patient with an allergic diathesis, rather than specific intolerance to sulfonamides, they also examined adverse experiences in persons who had been prescribed a nonsulfonamide antibiotic, penicillin.

Approximately 10% of persons receiving SULF-na after an adverse SULF-a experience developed an allergic reaction (compared with a background incidence of 1.6% allergic reactions to a SULF-na in persons without a prior allergic sulfonamide reaction). Surprisingly, the likelihood of an adverse reaction to penicillin after an experience of SULF-a allergy was actually greater than that of an adverse reaction to SULF-na! These data support the concept that it may be allergic diathesis, rather than sulfonamide crossreactivity, which is responsible for the substantial degree of dermatologic intolerance manifestations to SULF-na among persons with demonstrated SULF-a allergy. ■

Strom BL, et al. N Engl J Med. 2003; 349:1628-1635.

Autoantibodies Before Onset of SLE

THE DIAGNOSIS OF SYSTEMIC LUPUS erythematosus (SLE) is based, in part, upon laboratory findings, including measurement of autoantibodies (AAB) such as antinuclear antibody (ANA), anti-double-stranded DNA (aDS-DNA). Indeed, such AAB are contributors to the pathology of SLE. The timing of presentation of SLE AAB is not yet clearly established, since clinicians seek AAB status usually at the time of clinical presentation and are rewarded almost universally with positive AAB findings in persons with SLE diagnosis confirmation.

Among 130 patients with SLE, one or more AAB was present a mean of 3.3 years prior to diagnosis (range up to 9.4 years earlier). The most commonly detected AAB was ANA (78% at 1:120 or greater dilution), and the least common was antiphospholipid antibody (18%). Matched controls were positive 3.8% of the time.

The appearance of SLE AAB years prior to symptomatic presentation is established by these data to be commonplace and occurs in a predictable pattern much of the time. It appears that the number of different AAB increases over time until clinical presentation, after which the number remains constant, as if there is some self-limited aspect to AAB development. ■

Arbuckle MR, et al. N Engl J Med. 2003;349:1526-1533.

Prevention of VTE with Ximelagatran

TYPICALLY, AFTER A FIRST EPISODE of DVT, prophylaxis will be advised for 3-6 months, although recent data show no diminution of benefit when warfarin prophylaxis for recurrent DVT is continued for as long as 24 months. The rationale for 3-6 months of DVT prophylaxis is based upon a risk-benefit analysis that includes expense, adverse effects (primarily bleeding), and need for repeated long-term monitoring on the downside of the equation.

Ximelagatran (XIM) is an orally administered direct thrombin inhibitor that has already demonstrated efficacy equal or superior to well-titrated warfarin prophylaxis in settings of DVT or atrial fibrillation. The remarkable difference between XIM and warfarin is that consistent anticoagulation responsivity seen with XIM results in no need for coagulation monitoring; that is, once patients are started on the twice-daily drug, no further INR testing or other coagulation monitoring is required.

In this trial, persons who had successfully completed 6 months of warfarin (n = 1223) were randomized to either placebo or XIM twice daily for an additional 18 months. Confirmed symptomatic venous thromboembolism was seen in 12/612 XIM patients vs 71/611 placebo recipients. There was no significant difference in all-cause mortality or bleeding between XIM and placebo. XIM may be available as an oral anticoagulant in the very near future. ■

Schulman S, et al. N Engl J Med. 2003;349:1713-1721.

In Future Issues: Another Myth DeBUNKED