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INSIDE

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Hepatitis C: A Scourge of the Baby Boomers?

ABSTRACT & COMMENTARY

By Mary Elina Ferris, MD

Clinical Associate Professor, University of Southern California

Dr. Ferris reports no financial relationship to this field of study.

Synopsis: *Survey data suggest more than 4.1 million Americans have antibodies to Hepatitis C, and 3.2 million have chronic infection. Most were born between 1945-1964, with past injection drug use as the strongest risk factor.*

Source: Armstrong GL, et al. The Prevalence of Hepatitis C Virus Infection in the United States, 1999 through 2002. *Ann Int Med*. 2006;144:705-714.

THE NATIONAL CENTER FOR HEALTH STATISTICS CONDUCTS PERIodic surveys of nationally representative statistics on the health of the US population. The most recent series was begun in 1999 and is designed to run continuously; data are released every 2 years. This research analyzed data collected from 1999 through 2002 on 15,079 statistically chosen participants. After initial home interviews, 80% completed computer-administered medical histories and gave blood samples.

Anti-Hepatitis C antibodies (anti-HCV) were found in 1.6%, with 1.3% positive for HCV RNA, indicating chronic infection. Prevalence was higher in men and non-Hispanic black ethnicity. Age differences were apparent with 1% in age 20-29, a peak of 4.3% in those 40 to 49 years, then a decline to 0.9% in persons age 60 years and older. Participants who were born in the United States had a higher prevalence of anti-HCV than those who were not, and prevalence increased with decreasing family income and level of education.

Characteristics most often found in HCV RNA-positive participants 20-59 years old were elevated serum ALT levels (58.7%) and history of injection drug use (48.4%). Of all persons reporting an injection drug history, 83.3% had not used injection drugs for at least 1 year before the survey. For HCV RNA-positive persons 60 years

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of age and older, 21.1% had received a blood transfusion before 1992 or had an abnormal serum ALT level.

COMMENTARY

This interesting survey reveals some startling associations: the large number of chronic Hepatitis C virus (HCV) infections in the United States are limited to a specific age group, and seem to be associated with use of injection drugs and increased sexual contacts in the baby-boomer generation.

Past studies[1] have suggested that the incidence of HCV infection increased substantially in 1960-1970 and peaked in the 1980s. This new information confirms those observations and probes more deeply to explain this pattern. Although it did not include homeless or incarcerated persons, it was able to identify 2 risk factors (past injection drug use and elevated serum ALT) for ages 20-59 that would have led to finding 85% of chronic HCV infections. For age 60 and older, the major risk factor was receiving a blood transfusion before screening for HCV began in 1992.

Based on these extrapolations, the authors estimate that 85% of all chronic HCV infections in the United States could be found by screening persons of any age for injection drug history, high risk sexual practices, blood transfusions before 1992 and elevated serum ALT levels. ■

Reference

1. Armstrong GL, et al. The past incidence of hepatitis C virus infection: implications for the future burden of chronic liver disease in the United States. *Hepatology*. 2000;31:777-782.

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Risk of Death and AMI in Apparently Healthy Subjects with Ventricular Arrhythmias

ABSTRACT & COMMENTARY

By Harold L. Karpman, MD, FACC, FACP

Clinical Professor of Medicine, UCLA School of Medicine

Dr. Karpman reports no financial relationship to this field of study.

Synopsis: *apparently healthy, middle-aged and older subjects with frequent PVCs have a poor prognosis and should be considered to be high-risk subjects who require strict risk factor modification and primary prevention.*

Source: Sajadieh A, et al. Ventricular arrhythmias and risk of death and acute myocardial infarction in apparently healthy subjects of age >or=55 years. *Am J Cardiol*. 2006;97: 1351-1357.

VENTRICULAR PREMATURE BEATS AND EVEN TRANsient complex ventricular arrhythmias are not uncommon findings in patients without apparent heart disease. The clinical relevance of these arrhythmias in otherwise healthy subjects has been extremely difficult to accurately assess because of the lack of appropriate epidemiologic studies utilizing properly acquired electrocardiographic (EKG) monitoring information. The data derived from most large studies of ventricular arrhythmias in healthy subjects have been inadequate to determine prognostic significance because these studies

have been based solely on short-term EKG monitoring which has proven to be incapable of determining PVC frequency and usually has also not been able to provide sufficient data to properly evaluate complex arrhythmias.[1-5]

Sajadieh and associates studied the prevalence and prognostic significance of different ventricular arrhythmias in 678 men and women aged 55 to 75 years without a prior history of heart disease or stroke.[6] The study was part of the Copenhagen Holter study which was designed to determine the value of a 48-hour Holter recording in risk assessment in middle-aged and elderly men and women without apparent heart disease. All patients were followed for up to 5 years. Frequent PVCs (> 30 per hour) proved to be a significant predictor of increased all-cause mortality, acute myocardial infarction and/or cardiovascular death. Runs of > 4 PVCs or > 2 episodes of paired PVCs were also associated with a poor prognosis but only in the presence of frequent PVCs. The detection of a single PVC on standard EKG screening was a significant predictor of frequent PVCs and therefore an important independent predictor of cardiovascular events. They concluded that apparently healthy, middle-aged and older subjects with frequent PVCs have a poor prognosis and should be considered to be high-risk subjects who require strict risk factor modification and primary prevention.

COMMENTARY

The Copenhagen Holter study evaluated 48-hour Holter recordings in risk assessment in middle-aged and elderly men and women with no apparent heart disease.[7-8] All men age 55 years and older and all men and women aged 60-75 in 2 geographic areas of Copenhagen were studied. The 8% of subjects with an increased frequency of PVCs (ie, > 30 per hour) were found to have an over 2½ times greater risk for death or AMI and this increased risk was noted to occur especially in men but also in all subjects with a Framingham risk score greater than average. Increased ventricular activity was found in 9% of all men and, it is important to note that 25% of all events (ie, all cause mortality, AMI, and/or cardiovascular death) occurred in this select group. The findings of the study confirmed Lown and Wolf's early observations regarding the significance of PVCs occuring at a frequency of > 30 per hour.[9]

For the practicing cardiologist, the results of this study suggests that the accidental detection of increased ventricular ectopic activity (eg, > 1 PVC on a resting EKG, a run of PVCs or couplets) in middle-aged or elderly patients with no apparent heart disease and/or symptoms should be followed up with a 24-48 hour Holter recording especially in those individuals who have an elevated Framingham risk score. If PVCs are found to be present with a frequency of > 30 PVCs per hour, a careful and complete diagnostic workup for structural and ischemic heart disease should be performed in all of these patients according to current national and international guidelines.[10-12] Finally, it should be noted that anti-arrhythmic therapy has not been demonstrated to be of clinical benefit in PVC suppression and, given the negative results of previous anti-arrhythmic studies,[10-12] anti-arrhythmic therapy is usually not recommended except in carefully select groups of patients. ■

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Low-dose Aspirin and Endoscopic Gastric and Duodenal Ulcer Rates in Users of NSAIDs or COX-2 inhibitors

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

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Dr. Robinson serves as a consultant for TAP, Pfizer, Janssen, Eisai, J&J-Merck, and Procter & Gamble, is on the speaker's bureau of Janssen, Eli Lilly, Solvay, TAP, and Aventis, and does research for Forest Labs, Wyeth-Ayerst, AstraZeneca, and Centocor.

Synopsis: *Low-dose aspirin plus celecoxib led to ulcers in 19% of recipients vs 27% ulcers in patients receiving naproxen and low-dose aspirin. The group receiving low-dose aspirin plus placebo had 8% ulcer development.*

Source: Goldstein, JL, et al. The impact of low-dose aspirin on endoscopic gastric and duodenal ulcer rates in users of a non-selective non-steroidal anti-inflammatory drug or a cyclooxygenase-2-selective inhibitor. *Aliment Pharmacol Ther*. 2006;23:1489-1498

ASPIRIN HAS WELL-DOCUMENTED ANTI-THROMBOTIC effects and is extensively used in cardiovascular prophylaxis. However, 11% gastric and/or duodenal ulcer prevalence has been reported with low dose aspirin administration in the past, presumably due to aspirin's unfavorable impact on cyclooxygenase-1 (COX-1) in the gastric mucosa. Non-selective non-steroidal anti-inflammatory drugs (NSAIDs) are known to cause gastric and duodenal mucosal damage, and it is believed that aspirin worsens the propensity of non-selective NSAIDs to cause mucosal damage. COX-2 selective NSAIDs are thought to cause significantly fewer ulcers than COX-1 NSAIDs, but controversy continues regarding the risks associated with co-administration of COX-2 selective NSAIDs plus low-dose aspirin. The present 39-center study was done in 50-75 year old *H. pylori*-negative volunteers with normal baseline endoscopy. 450 subjects were ultimately evaluable. Of the evaluable group, 92 received 325 mg aspirin (ASA) plus placebo, 176 received naproxen 500 mg b.i.d. and ASA, and 182 evaluable subjects received celecoxib 200 mg daily plus ASA. Repeat endoscopy was performed after one week of the assigned therapy. Relative risk of gastric ulceration was highest with naproxen and aspirin at 3.3 (CI, 1.5-7.3) and numerically lower with celecoxib and aspirin at 2.7 (CI, 1.2-6.4). However, this difference was not statistically significant ($P = 0.269$). Duodenal ulcers, far less common in both groups, occurred in more naproxen plus ASA recipients than in the celecoxib plus ASA group (RR = 0.40; 95% CI, 0.17-0.94). Naproxen plus ASA was more likely to cause duodenal ulcers than ASA alone (RR 9.9; 95% CI, 1.2-83.9; $P = 0.006$). There was a numerical trend in the same direction for celecoxib plus ASA vs ASA alone (4.4% duodenal ulcers vs 1.1% duodenal ulcers, NS). Overall, celecoxib and ASA led to 18.7% combined gastric and duodenal ulcers vs 27.3% for naproxen and ASA vs 7.6% for ASA alone. Data for erosions of the mucosal paralleled the ulcer findings with even higher numbers for each of the respective groups.

Unlike some previous studies that suggested that ASA might totally negate the safety benefit of COX-2 administration, this study definitively demonstrates some improved safety (at least, in terms of endoscopic findings) with COX-2 plus ASA vs nonselective NSAID plus ASA. Nevertheless, as the authors point out, endoscopic differences may or may not directly translate to improved clinical safety.

COMMENTARY

It seems to this reviewer that the take-home message from this study should be that danger lurks in administration of aspirin alone—and even more danger is associated with the combination of ASA and either selective or nonselective NSAIDs. High-risk patients (eg, those with severe co-morbidities) should probably avoid ASA and/or NSAIDs under most circumstances. The question that has been raised but not answered as yet is the potential for protection that might be afforded by co-administration of prostaglandins and/or proton pump inhibitors along with aspirin and COX-2 selective NSAIDS in some patients. Presumably such a study will ultimately be performed. In the meantime, many physicians will opt for such complex co-therapy in the hope that the known serious dangers of ASA and NSAIDs can be ameliorated. ■

The Pressure of Air Travel: Headaches on the Plane

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

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Weill Medical College, Cornell University

Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: *Barotrauma to the paranasal sinuses may cause sudden and severe headache during airplane travel.*

Source: Berilgen MS, Mungen B. Headache Associated with Airplane Travel: Report of Six Cases. *Cephalalgia.* 2006:26: 707-711.

THIS SUMMER, MOST HEADACHES CAUSED BY AIRPLANE travel will be due to long security lines and delayed take-offs. But once the plane is in the air, more than just cramped seats and lack of food may cause headaches. Berilgen and colleagues describe 6 men in their 30s and 40s who suffer from intermittent but recurrent, severe, short lasting, unilateral, periocular headaches thought to be related to sinus barotrauma, caused by changes in cabin pressure. The most severe pain lasted from 15-20 minutes. Five of the men described the headaches as occurring during landing, especially at seaside airports. Only one man had an occasional headache of the same description while a plane was gaining altitude. Most of the men did not have any accompanying symptoms, and only half had any other headache type. None suffered from cluster-like headaches. Three of the men had a long smoking history. No abnormalities were found on a thorough evaluation of the men, including brain and sinus imaging, performed soon after a headache.

COMMENTARY

Subclinical congestion and inflammation in the ethmoid sinus and middle turbinate mucosa, with a vacuum effect triggering ethmoid nerve branches of the trigeminal nerve and nociceptors on the anterior ethmoid artery, is a possible explanation for the attacks. The name barotrauma-related headache was suggested to identify the mechanism of these brief but severe, travel-related headaches. Prevention of these headaches may be possible with the use of a potent nasal and sinus decongestant (oxymetazoline) prior to boarding the airplane and just before the approach to landing. ■

Many Factors are Responsible for Treatment Outcome in Acute Exacerbations of Chronic Bronchitis

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

Professor, University of Texas Health Science Center, Houston; St. Luke's Episcopal Hospital, Houston

Dr. Varon reports no financial relationship to this field of study.

Synopsis: *The number of previous acute exacerbations of chronic bronchitis (AECBs) and the baseline FEV_1 level are potent prognostic factors of the short and long-term outcomes of AECB.*

Source: Wilson R, et al. Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. *Thorax*. 2006;61:337-342.

THIS MULTICENTER STUDY WAS AIMED AT EVALUATING the short- and long-term outcome of patients with AECB treated with antibiotics. The study was designed as a prospective, randomized, double-blinded trial and was part of the MOSAIC study. Outpatients aged 45 years and older with documented chronic bronchitis were eligible for inclusion during an AECB-free period if they had a smoking history of at least 20 packs years, 2 or more documented AECBs in the previous year, and a forced vital capacity in one second (FEV_1) of < 85% of predicted at the enrollment visit. Patients were then randomized to received either moxifloxacin (400 mg daily for 5 days) or one of the following comparators: amoxicillin (500 mg three times daily for 7 days), clarithromycin (500 mg twice daily for 7 days), or cefuroxime-axetil (250 mg twice daily for 7 days). Clinical response was evaluated 7-10 days at the end of the treatment. Factors with potential impact on the clinical outcomes studied included: age (> 65 or < 65 years), body mass index (< 30 kg/m^2 or > 30 kg/m^2), gender, co-morbidities, number of AECBs in the previous years (severity of chronic bronchitis), concomitant medications and FEV_1.

Over the study period, 730 patients were studied. The mean age was 63.2 ± 9.8 years. 43.2% had and FEV_1 < 50% and 27.7% had ≥ 4 exacerbations the previous year. Moxifloxacin was independently associated with a higher cure rate than the comparator drugs while co-morbidities, FEV_1, < 50% predicted, and ≥ 4 AECBs in the previous year had a detrimental effect in the outcome.

Once adjustments were made, in univariate analysis, the factors that had a statistically significant impact on the occurrence of the composite event were ≥ 4 AECBs in the previous year, age > 65 years, FEV_1 < 50% predicted and acute bronchodilator use. The effect noted for moxifloxacin was primarily linked to benefits in the subgroup of patients aged > 65 years.

COMMENTARY

AECBs are commonly seen in primary care practices worldwide. This study is interesting because it reaffirms that the severity of airflow obstruction, coexistent comorbidities (such as cardiac disease) and the frequency of exacerbations are risk factors for poorer short term outcomes in AECB.

A number of studies in the past decade have shown similar results in patients with AECB.[1-3] Ball and coworkers have demonstrated that a past history of frequent exacerbations makes a future exacerbation more likely.[4] This is perhaps because the index exacerbation is not completely resolved and these patients tend to have persistent bacterial infection. Aggressive antibiotic treatment is therefore justified in patients meeting criteria. It is interesting to note that among the agents studied, moxifloxacin had a beneficial effect on the short and long-term outcome, despite presence of other negative prognostic factors. ■

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Pharmacology Update

Zoster Vaccine Live (Oka/Merck)

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

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

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

THE FDA HAS LICENSED A NEW VACCINE TO REDUCE the risk of shingles in the people 60 years of age and older. The vaccine is a live, attenuated, Oka/Merck strain of varicella zoster virus (VZV). It is marketed by Merck and Co., Inc. as Zostavax®.

Indications

VZV vaccine is indicated for prevention of herpes zoster (shingles) in individuals 60 years of age and older.[1]

Dosage

VZV vaccine is administered as a single subcutaneous injection. The vaccine should be administered immediately after reconstitution.

Potential Advantages

VZV vaccine reduces the burden of illness, the incidence of herpes zoster, and reduces the incidence of postherpetic neuralgia.[1,2]

Potential Disadvantages

Common adverse events include injection site reactions (erythema, pain, tenderness, swelling, pruritus). There is a theoretical risk of transmitting the vaccine virus to varicella-susceptible individuals. The vaccine reduces the herpes-associated events but does not prevent them. Protection has been demonstrated through 4 years; the duration of protection is not known.[1]

Comments

The efficacy of the vaccine was demonstrated in a trial of over 38,000 adults 60 years of age or older.[1,2] The median follow up time was 3.1 years (range, 31 days to 4.9 years) Zoster cases were confirmed primarily by polymerase chain reaction (93%). A single dose of the vaccine reduced the incidence of shingles by 51% (95% CI, 44%-58%). Efficacy appears to lessen with older age. Incidence of postherpetic neuralgia was reduced by 66.5% (95% CI,

47.5-79.2%). Burden of illness, based on a herpes-zoster severity-of-illness score, was reduced by 61% (95% CI, 51.1%-69.1%). In subjects who developed herpes zoster post-vaccination, subsequent postherpetic neuralgia was reduced by 39% (95% CI, 7- 59%). The duration of pain and discomfort was slightly shorter with vaccine recipients, 21 days vs 24 days. The vaccine appears to be well tolerated with injections site reactions being the most common.

Clinical Implications

Shingles is caused by the same virus that causes chicken pox and is due to reactivation of latent varicella-zoster virus within the sensory ganglia.[3] The incidence and severity increases with age. Post herpetic neuralgia is the most frequent complication of herpes zoster and similarly the frequency and severity increase with age. The VZV vaccine appears to be effective in reducing the incidence of shingles and post herpetic neuralgia. ■

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CME Questions

3. In apparently healthy patients older than age 55:

a. a single PVC on standard EKG screening is a significant predictor of frequent PVCs and an independent predictor of cardiovascular events.
b. increased frequency of PVCs (i.e. even >30 per hour) is of no clinical significance and should not be treated.
c. a 24-hour Holter recording is not indicated if only a single PVC is accidentally detected on a routine examination.
d. PVCs are detected in most of these patients.

4. Which of the following age groups is most at risk for chronic Hepatitis C infection in the United States in 2006?

a. Children
b. Teenagers
c. Age 20 to 40
d. Age 40 and older
e) All of the above

5. The risk of damage to the gastric and duodenal mucosa is greatest with which combination of therapeutic agents:

a. ASA alone.
b. ASA plus naproxen 500mg b.i.d.
c. ASA plus celecoxib 200mg once daily.
d. ASA plus naproxen 500mg b.i.d. plus misoprostol t.i.d.
e. ASA plus naproxen 500 mg b.i.d. plus omeprazole 40 mg b.i.d. a.c.

Answers: 3 (a); 4 (d); 5 (b)

CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances; and
- to describe cost-effective treatment regimens.

Clinical Briefs

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

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Air Travel and DVT Risk: Is Hypobaric Hypoxia the Culprit?

That air travel is associated with increased risk of deep venous thrombosis (DVT) is well established. Recent data have suggested that very long flights (> 5 hours) are disproportionately associated with risk. We (*Internal Medicine Alert, May 29, 2006*) previously reviewed data that compared subjects sitting and watching movies for similar time periods as matched subjects taking a plane flight, and noted that there is something about air travel that activates coagulation factors differently than simply sitting in a chair.

Pressurization in airplane cabins produces a mean arterial oxygen saturation of about 93% in healthy persons (mean), but lower levels in older individuals and persons with cardiopulmonary disorders. Such relative hypoxemia has been shown in vitro to induce procoagulant activity as well as inhibit fibrinolysis; in vivo studies amongst healthy volunteers corroborate this.

Toff et al studied healthy volunteers (n = 73) in a single-blind fashion by comparing hemostatic markers after an 8-hour period of seated exposure in a hypobaric chamber. Persons with known thrombophilic disorders were excluded. Analyses included measurement of platelet aggregability, coagulation activation, fibrinolysis, platelet activation, and endothelial activation.

There was no demonstrable difference in measured markers of mean prothrombotic activity in these healthy volunteers. At least in healthy individuals, hypobaric hypoxemia does not appear to affect DVT risk in a meaningful fashion. ■

Toff WD, et al. JAMA. 2006;295: 2251-2261. Erratum in: JAMA. 2006; 296:46.

GERD: Size Matters

Obesity is a recognized risk factor for gastroesophageal reflux disease (GERD). In addition to the clinical observation that obese individuals suffer GERD more often, trial data have corroborated that BMI and GERD have a linear association. However, studies of the relationship between BMI and GERD have generally been restricted to overweight or obese individuals, rather than including all subjects. Hence, whether weight gain in non-overweight individuals increases their risk for GERD has not been previously reported.

Subjects for this report (n = 10,545) included participants in the Nurses Health Study. In response to a questionnaire about frequency and severity of GERD symptoms, there was a direct relationship between increasing weight and frequent GERD symptoms. When compared to women with a BMI of 20-22.4, there was a direct relationship between BMI and GERD: the relative odds ratio for frequent symptoms was 33% less for persons with a BMI < 20, 38% more for BMI 22.5-24.9, and there was a greater than 100% increase for persons with BMI 25.0-27.4 (all of these BMI measurements are below the threshold for overweight/obese). Weight change (an increase in weight, that is) was also associated with increased risk for GERD, even when persons simply increased their weight from one normal weight category to another.

Increased body weight, even in non-obese individuals, is associated with GERD. Weight reduction has been shown to improve these symptoms. ■

Jacobson et al. N Engl J Med. 2006;354:2340-2348

Does aTNFa for RA Increase Infections and Malignancies?

Anti-TNF antibody (aTNFa) therapy offers significant benefit to sufferers of rheumatoid arthritis (RA). TNF is involved in critical functions related both to infectious disease and tumor suppression. For instance, CD8 lymphoctye tumor killing is mediated by TNF. Hence, the risk that either infectious or malignant diseases might be more prevalent in persons who have been treated with aTNFa is plausible. Individual trials using aTNFa have not demonstrated a 'signal' of greater risk for infections or cancer, but because both are somewhat uncommon, they might be easily missed.

Bongartz et al pooled data from aTNFa trials which lasted at least 12 weeks, providing data on 3,493 patients. Serious infections were defined as those which required antimicrobial treatment and/or hospitalization. Ultimately, this pooled data set indicated that the odds ratio for malignancy was increased greater than 3-fold, and risk for serious infection was doubled. For malignancies, there was a dose-dependent effect: higher aTNFa doses produced increased risk. In their closing commentary, the authors suggest that because of the difficulty in identifying rare events during clinical trials submitted for FDA drug registration, planning meta-analysis ahead of time to include future ongoing trials might recognize signals of serious disease earlier. ■

Bongartz T, et al. JAMA. 2006;295:2275-2285. Erratum in: JAMA. 2006;295:2482.

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