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New England Journal of Medicine
Volume 357 Number 21 & 22 - 24 & 29 Nov, 2007
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The past decade has not been kind to observational studies of medications. The damage began in 1998 with the publication of the Heart and Estrogen–Progestin Replacement Study, a randomized controlled trial showing that hormone replacement increased the risk of cardiac events among postmenopausal women with heart disease. Like many physicians, I had been teaching the gospel that estrogen use prevented heart disease — an idea based on observational studies showing that postmenopausal women who regularly took estrogen were less likely to have heart disease than apparently similar women who did not take hormones. It now appeared that this had been . . .


To appreciate the power of the U.S. presidency — even when its current occupant’s approval rating is only 31% — one need look no further than the political brawl over the State Children’s Health Insurance Program (SCHIP). On October 3, 2007, President George W. Bush vetoed legislation that would have reauthorized SCHIP for 5 years, asserting that it was too expensive and would lead down a path to socialized medicine. On October 18, despite pleas by Democrats and some senior Republican legislators, the House failed to garner the necessary two-thirds vote to override Bush’s veto; the vote count was 273 . . .


Dengue is an important human viral disease transmitted by insects. Although nearly half the world’s population is at risk for infection and as many as 100 million cases occur annually,1 we have no antiviral drugs to treat it and no vaccines to prevent it. A closely related but much more lethal mosquito-borne virus, yellow fever, used to be one of the great scourges among humans. Although yellow fever is now largely controlled by vaccination, many regions are susceptible to a reemergence if the disease is introduced by travelers, and substantial recent problems with vaccine safety will no doubt change vaccination . . .


Comprehensive health care reform disappeared from the national agenda after the Clinton administration failed to enact universal coverage in 1993 and 1994. Instead, Congress adopted incremental measures that enjoyed bipartisan support, including the State Children’s Health Insurance Program (SCHIP) and the Health Insurance Portability and Accountability Act (HIPAA). The retreat from comprehensive reform reflected, in part, the calculus that ambitious plans were too controversial and too hazardous to their sponsors’ political health to attempt. But that political calculus is changing. Health care ranks as the top domestic issue in opinion polls, and talk of major reform is back in vogue . . .


The modern era of drug development began with the 1962 Kefauver-Harris Drug Amendments, which required that drugs be tested for efficacy as well as safety and gave the Food and Drug Administration (FDA) the authority to require sophisticated clinical trials before approving drugs. Today, we can be confident that an approved drug will be effective for its labeled uses. The same cannot be said of the drug’s safety. At the time of approval, a drug has typically been tested in several thousand patients, in studies powered to identify only relatively common adverse reactions. For example, a study that includes 3000 . . .


Inhibition of cholesteryl ester transfer protein (CETP) has been shown to have a substantial effect on plasma lipoprotein levels. We investigated whether torcetrapib, a potent CETP inhibitor, might reduce major cardiovascular events. The trial was terminated prematurely because of an increased risk of death and cardiac events in patients receiving torcetrapib. We conducted a randomized, double-blind study involving 15,067 patients at high cardiovascular risk. The patients received either
torcetrapib plus atorvastatin or atorvastatin alone. The primary outcome was the time to the first major cardiovascular event, which was defined as death from coronary heart disease, nonfatal myocardial infarction, stroke, or hospitalization for unstable angina. At 12 months in patients who received torcetrapib, there was an increase of 72.1% in high-density lipoprotein cholesterol and a decrease of 24.9% in low-density lipoprotein cholesterol, as compared with baseline (P<0.001 for both comparisons), in addition to an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone (P<0.001 for all comparisons). There was also an increased risk of cardiovascular events (hazard ratio, 1.25; 95% confidence interval [CI], 1.09 to 1.44; P=0.001) and death from any cause (hazard ratio, 1.58; 95% CI, 1.14 to 2.19; P=0.006). Post hoc analyses showed an increased risk of death in patients treated with torcetrapib whose reduction in potassium or increase in bicarbonate was greater than the median change. Torcetrapib therapy resulted in an increased risk of mortality and morbidity of unknown mechanism. Although there was evidence of an off-target effect of torcetrapib, we cannot rule out adverse effects related to CETP inhibition.


Lenalidomide is a structural analogue of thalidomide with similar but more potent biologic activity. This phase 3, placebo-controlled trial investigated the efficacy of lenalidomide plus dexamethasone in the treatment of relapsed or refractory multiple myeloma. Of 351 patients who had received at least one previous antimyeloma therapy, 176 were randomly assigned to receive 25 mg of oral lenalidomide and 175 to receive placebo on days 1 to 21 of a 28-day cycle. In addition, all patients received 40 mg of oral dexamethasone on days 1 to 2, 9 to 12, and 17 to 20 for the first four cycles and subsequently, after the fourth cycle, only on days 1 to 4. Patients continued in the study until the occurrence of disease progression or unacceptable toxic effects. The primary end point was time to progression. The time to progression was significantly longer in the patients who received lenalidomide plus dexamethasone (lenalidomide group) than in those who received placebo plus dexamethasone (placebo group) (median, 11.3 months vs. 4.7 months; P<0.001). A complete or partial response occurred in 106 patients in the lenalidomide group (60.2%) and in 42 patients in the placebo group (24.0%, P<0.001), with a complete response in 15.9% and 3.4% of patients, respectively (P<0.001). Overall survival was significantly improved in the lenalidomide group (hazard ratio for death, 0.66; P=0.03). Grade 3 or 4 adverse events that occurred in more than 10% of patients in the lenalidomide group were neutropenia (29.5%, vs. 2.3% in the placebo group), thrombocytopenia (11.4% vs. 5.7%), and venous thromboembolism (11.4% vs. 4.6%). Lenalidomide plus dexamethasone is more effective than high-dose dexamethasone alone in relapsed or refractory multiple myeloma.


Eltrombopag is a new, orally active thrombopoietin-receptor agonist that stimulates thrombopoiesis. We evaluated its ability to increase platelet counts and facilitate treatment for hepatitis C virus (HCV) infection in patients with thrombocytopenia associated with HCV-related cirrhosis. Seventy-four patients with HCV-related cirrhosis and platelet counts of 20,000 to less than 70,000 per cubic millimeter were randomly assigned to receive eltrombopag (30, 50, or 75 mg daily) or placebo daily for 4 weeks. The primary end point was a platelet count of 100,000 per cubic millimeter or more at week 4. Peginterferon and ribavirin could then be initiated, with continuation of eltrombopag or placebo for 12 additional weeks. At week 4, platelet counts were increased to 100,000 per cubic millimeter or more in a dose-dependent manner among patients for whom these data were available: in 0 of the 17 patients receiving placebo, in 9 of 12 (75%) receiving 30 mg of eltrombopag, in 15 of 19 (79%) receiving 50 mg of eltrombopag, and in 20 of 21 (95%) receiving 75 mg of eltrombopag (P<0.001). Antiviral therapy was initiated in 49 patients (in 4 of 18 patients receiving placebo, 10 of 14 receiving 30 mg of eltrombopag, 14 of 19 receiving 50 mg of eltrombopag, and 21 of 23 receiving 75 mg of eltrombopag) while the administration of eltrombopag or placebo was continued. Twelve weeks of antiviral therapy, with concurrent
receipt of eltrombopag or placebo, were completed by 36%, 53%, and 65% of patients receiving 30 mg, 50 mg, and 75 mg of eltrombopag, respectively, and by 6% of patients in the placebo group. The most common adverse event during the initial 4 weeks was headache; thereafter, the adverse events were those expected with interferon-based therapy. Eltrombopag therapy increases platelet counts in patients with thrombocytopenia due to HCV-related cirrhosis, thereby permitting the initiation of antiviral therapy.


Patients with systolic heart failure have generally been excluded from statin trials. Acute coronary events are uncommon in this population, and statins have theoretical risks in these patients. A total of 5011 patients at least 60 years of age with New York Heart Association class II, III, or IV ischemic, systolic heart failure were randomly assigned to receive 10 mg of rosvuastatin or placebo per day. The primary composite outcome was death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Secondary outcomes included death from any cause, any coronary event, death from cardiovascular causes, and the number of hospitalizations. As compared with the placebo group, patients in the rosvuastatin group had decreased levels of low-density lipoprotein cholesterol (difference between groups, 45.0%; P<0.001) and of high-sensitivity C-reactive protein (difference between groups, 37.1%; P<0.001). During a median follow-up of 32.8 months, the primary outcome occurred in 692 patients in the rosvuastatin group and 732 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.83 to 1.02; P=0.12), and 728 patients and 759 patients, respectively, died (hazard ratio, 0.95; 95% CI, 0.86 to 1.05; P=0.31). There were no significant differences between the two groups in the coronary outcome or death from cardiovascular causes. In a prespecified secondary analysis, there were fewer hospitalizations for cardiovascular causes in the rosvuastatin group (2193) than in the placebo group (2564) (P<0.001). No excessive episodes of muscle-related or other adverse events occurred in the rosvuastatin group. Rosuvastatin did not reduce the primary outcome or the number of deaths from any cause in older patients with systolic heart failure, although the drug did reduce the number of cardiovascular hospitalizations. The drug did not cause safety problems.


The effects of lung transplantation on the survival and quality of life in children with cystic fibrosis are uncertain. We used data from the U.S. Cystic Fibrosis Foundation Patient Registry and from the Organ Procurement and Transplantation Network to identify children with cystic fibrosis who were on the waiting list for lung transplantation during the period from 1992 through 2002. We performed proportional-hazards survival modeling, using multiple clinically relevant covariates that were available before the children were on the waiting list and the interactions of these covariates with lung transplantation as a time-dependent covariate. The data were insufficient in quality and quantity for a retrospective quality-of-life analysis. A total of 248 of the 514 children on the waiting list underwent lung transplantation in the United States during the period from 1992 through 2002. Proportional-hazards modeling identified four variables besides transplantation that were associated with changes in survival. Burkholderia cepacia infection increased waiting-list survival but decreased post-transplantation survival, whereas older age did not affect waiting-list survival but decreased post-transplantation survival. Staphylococcus aureus infection increased waiting-list survival but decreased post-transplantation survival. Using age, diabetes status, and S. aureus infection status as covariates, we estimated the effect of transplantation on survival for each patient group, expressed as a hazard factor of less than 1 for a benefit and more than 1 for a risk of harm. Five patients had a significant estimated benefit, 315 patients had a significant risk of harm, 76 patients had an insignificant benefit, and 118 patients had an insignificant risk of harm associated with lung transplantation. Our analyses estimated clearly improved survival for only 5 of 514 patients on the waiting list for lung transplantation. Prolongation of life by means of lung transplantation should not
be expected in children with cystic fibrosis. A prospective, randomized trial is needed to clarify whether and when patients derive a survival and quality-of-life benefit from lung transplantation.


Studies to date have shown an association between the presence of patent foramen ovale and cryptogenic stroke in patients younger than 55 years of age. This association has not been established in patients 55 years of age or older. We prospectively examined 503 consecutive patients who had had a stroke, and we compared the 227 patients with cryptogenic stroke and the 276 control patients with stroke of known cause. We examined the prevalences of patent foramen ovale and of patent foramen ovale with concomitant atrial septal aneurysm in all patients, using transesophageal echocardiography. We also compared data for the 131 younger patients (<55 years of age) and those years of age. The prevalence of patent foramen ovale was significantly greater among patients with cryptogenic stroke than among those with stroke of known cause, for both younger patients (43.9% vs. 14.3%; odds ratio, 4.70; 95% confidence interval [CI], 1.89 to 11.68; P<0.001) and older patients (28.3% vs. 11.9%; odds ratio, 2.92; 95% CI, 1.70 to 5.01; P<0.001). Even stronger was the association between the presence of patent foramen ovale and concomitant atrial septal aneurysm and cryptogenic stroke, as compared with stroke of known cause, among both younger patients (13.4% vs. 2.0%; odds ratio, 7.36; 95% CI, 1.01 to 53.60; P=0.049) and older patients (15.2% vs. 4.4%; odds ratio, 3.88; 95% CI, 1.78 to 8.46; P<0.001). Multivariate analysis adjusted for age, plaque thickness, and presence or absence of coronary artery disease and hypertension showed that the presence of patent foramen ovale was independently associated with cryptogenic stroke in both the younger group (odds ratio, 3.70; 95% CI, 1.42 to 9.65; P=0.008) and the older group (odds ratio, 3.00; 95% CI, 1.73 to 5.23; P<0.001). There is an association between the presence of patent foramen ovale and cryptogenic stroke in both older patients and younger patients. These data suggest that paradoxical embolism is a cause of stroke in both age groups.


Lenalidomide, an oral immunomodulatory drug that is similar to thalidomide but has a different safety profile, has clinical activity in relapsed or refractory multiple myeloma.

Methods Patients in the United States and Canada who had received at least one previous therapy for multiple myeloma but who required additional treatment were randomly assigned to receive either 25 mg of lenalidomide or placebo on days 1 to 21 of a 28-day cycle. Both groups also received 40 mg of oral dexamethasone on days 1 to 4, 9 to 12, and 17 to 20 for the first four cycles. After the fourth cycle, 40 mg of dexamethasone was administered only on days 1 to 4. Safety, clinical response, time to progression, and overall survival were assessed. We assigned 177 patients to the lenalidomide group and 176 to the placebo group. Complete, near-complete, or partial responses occurred in 108 patients (61.0%) in the lenalidomide group and in 35 patients (19.9%) in the placebo group (P<0.001); complete responses occurred in 14.1% and 0.6%, respectively (P<0.001). The median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the placebo group (P<0.001). Median overall survival times in the two groups were 29.6 months and 20.2 months, respectively (P<0.001). Grade 3 or 4 adverse events were reported in 85.3% of the lenalidomide group and in 73.1% of the placebo group; these events resulted in study discontinuation in 19.8% and 10.2%, respectively. Grade 3 or 4 neutropenia and venous thromboembolism were more common in the lenalidomide group than in the placebo group (41.2% vs. 4.6% and 14.7% vs. 3.4%, respectively; P=0.001 for both comparisons). Lenalidomide plus dexamethasone is superior to placebo plus dexamethasone in patients with relapsed or refractory multiple myeloma.
REVIEW ARTICLE


The advent of computed tomography (CT) has revolutionized diagnostic radiology. Since the inception of CT in the 1970s, its use has increased rapidly. It is estimated that more than 62 million CT scans per year are currently obtained in the United States, including at least 4 million for children. By its nature, CT involves larger radiation doses than the more common, conventional x-ray imaging procedures (Table 1). We briefly review the nature of CT scanning and its main clinical applications, both in symptomatic patients and, in a more recent development, in the screening of asymptomatic patients. We focus . . .


The modern history of sarcoidosis, an enigmatic multisystem disease, goes back to 1899, when the pioneering Norwegian dermatologist Caesar Boeck coined the term to describe skin nodules characterized by compact, sharply defined foci of “epithelioid cells with large pale nuclei and also a few giant cells.” Thinking this resembled sarcoma, he called the condition “multiple benign sarcoid of the skin.” Since sarcoidosis was last reviewed in the Journal 10 years ago, more than 5000 articles related to this condition have been published. This review summarizes recent advances and addresses pitfalls in the diagnosis and treatment of sarcoidosis.

IMAGE IN CLINICAL MEDICINE


A 29-year-old homeless man was admitted to the hospital after being stabbed in the chest. A hemothorax was diagnosed, and a chest tube was placed. One day after admission, he had a generalized tonic–clonic seizure. He was afebrile and had no meningeal signs but had left hemiparesis and hyperreflexia. On questioning, he reported having had increased weakness on the left side during the preceding year. Magnetic resonance imaging of the head with the administration of gadolinium showed a ring-enhancing mass in the right parietal lobe (Panels A and B, arrows). This was interpreted as a central nervous system neoplasm, and . . .


An 85-year-old woman was admitted with progressive dyspnea and chest pain that had started suddenly 2 days earlier. Physical examination revealed formerly undiagnosed atrial fibrillation with a normal heart rate and normal blood pressure. Examination of the lungs did not show any pathological findings. Pulmonary embolism was diagnosed on spiral computed tomography (Panel A, sagittal reconstruction), which showed intraluminal filling defects (arrows) and total occlusions of the upper and lower segmental arteries by clots (arrowheads). Duplex ultrasonography revealed an underlying deep-vein thrombosis of the right superficial femoral vein. Transthoracic echocardiography showed typical signs of moderate right heart strain. Anticoagulation therapy . . .


A previously healthy 18-year-old woman presented with a 5-month history of pain in the left upper quadrant of the abdomen, abdominal distention, postprandial emesis, and weight loss of 18 kg. Physical examination revealed a firm, tender, epigastric mass but was otherwise unremarkable. Computed tomography showed a large gastric mass extending from the fundus to the antrum (Panel A, arrow), with no indication of obstruction of the gastric outlet. Esophagogastroduodenoscopy revealed a large bezoar occluding nearly the entire stomach, without extension into the duodenum (Panel B). On questioning, the patient stated that she had had a habit of eating her hair . . .


A 39-year-old woman with ß-thalassemia major had required a transfusion of approximately 1 unit of red blood cells per month since she was 1 year old. Because of iron overload, chelation therapy was started when she was 6 years old. She presented with pain, swelling, and decreased joint mobility in both ankles. Laboratory evaluation was notable for a hemoglobin level of 8.3 g per deciliter, a mean corpuscular volume of 81.3 µm3, and a red-cell distribution width of 26.7%. Her older brother had also had ß-thalassemia major and died of heart failure at 31 years of age. Anteroposterior (Panel . . .
Dr. Jeffrey O. Greenberg (Medicine): A 31-year-old woman was admitted to this hospital because of facial swelling, fever, and hypotension. The patient had relapsing and remitting multiple sclerosis, associated with severe fatigue. Three weeks before admission, her neurologist prescribed modafinil to treat the fatigue. One week later, periorbital erythema, a clear conjunctival discharge, and a raised erythematous and pruritic rash developed on her face and scalp. She discontinued modafinil and used over-the-counter diphenhydramine, but the rash did not improve. Three days later, she went to the emergency room of a hospital near her home for evaluation. Cyproheptadine was prescribed, but . . .


Four weeks after he received a heart transplant, a 47-year-old man was admitted to this hospital because of ventricular dysfunction detected on echocardiography. The patient had been well until 19 months earlier, when congestive heart failure developed, followed by several syncopal episodes. Echocardiography performed at another hospital revealed a speckled pattern of reflectance of the ventricular myocardium, and pathological examination of a biopsy specimen of a fat pad obtained at that hospital was positive for the presence of amyloid. Examination of a bone marrow biopsy specimen revealed 10% plasma cells, and free lambda light chains were present in the serum.

CLINICAL PRACTICE


This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author’s clinical recommendations. A 71-year-old man, whose wife died 6 months previously, presents with foot pain from diabetic neuropathy, poor sleep, lack of energy, and increasing frustration about his inability to “keep his diabetes under control.” On examination, he also notes lack of interest in usual activities, decreased appetite, a weight loss of 4.5 kg (10 lb) over the past 3 months, and intermittent thoughts . . .