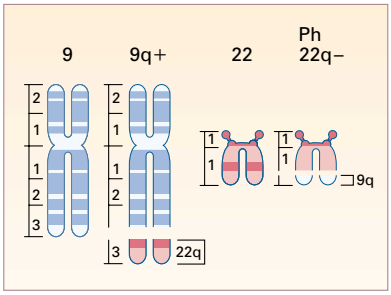
This Week in the Journal

February 28, 2002

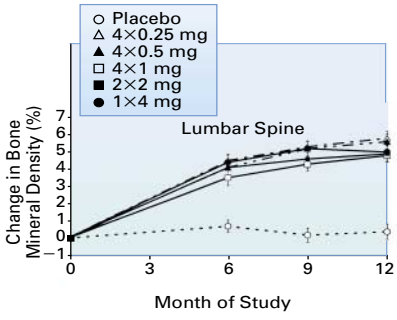


Hematologic and Cytogenetic Responses to Imatinib Mesylate in Chronic Myelogenous Leukemia

The t(9;22) translocation that forms the Philadelphia chromosome of chronic myelogenous leukemia (CML) also forms a fusion gene, *BCR-ABL*. The new gene encodes an abnormal tyrosine kinase, which causes the leukemia. Imatinib mesylate inhibits the function of the BCR-ABL protein and can induce remission of CML. This large trial found that imatinib induced cytogenetic and hematologic responses in most patients in whom standard therapy with interferon alfa had failed.

This study provides further encouraging evidence that imatinib, a well-tolerated oral agent, is effective against CML. However, since the cytogenetic response was not evaluated by the highly sensitive polymerase chain reaction, it is likely that most patients who responded have residual disease and will require continuous therapy with the drug.

see page 645



Intravenous Zoledronic Acid in Postmenopausal Women with Low Bone Mineral Density

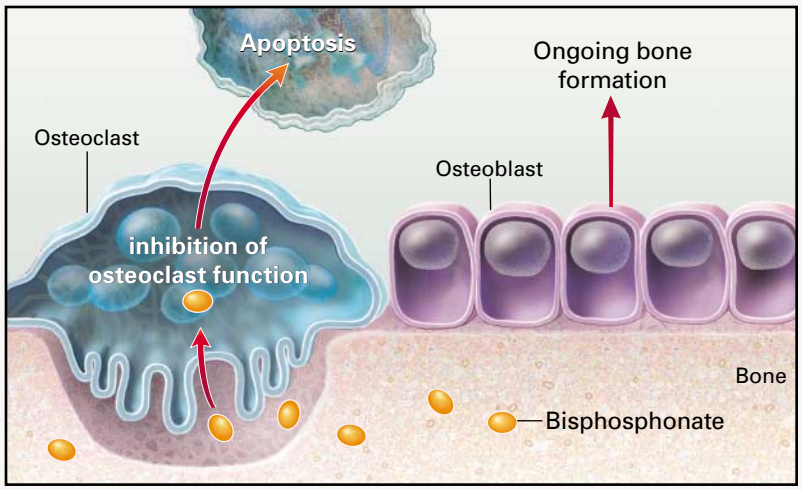
Bisphosphonates ameliorate osteoporosis, yet gastrointestinal side effects have limited patients' adherence to oral regimens. Intermittent intravenous therapy is effective, but the optimal interval between doses is unknown. This study examined five intravenous regimens of the potent bisphosphonate zoledronic acid (a total of 1 to 4 mg in one to four doses over the course of one year) and compared them with placebo in postmenopausal women with low bone mineral density.

Lumbar-spine bone mineral density increased similarly in all five zoledronic acid groups. Zoledronic acid infusions at intervals of up to one year produce effects on bone turnover and bone density similar to those achieved with daily oral bisphosphonates. An annual infusion of zoledronic acid might be effective as therapy for postmenopausal osteoporosis.

see page 653

PERSPECTIVE

Bisphosphonates and Osteoporosis



Proposed Mechanism of Action of Bisphosphonates.

Osteoporosis affects millions of postmenopausal women in the United States alone. For white women who reach 50 years of age, the lifetime risk of vertebral fracture is about one in three, and that for hip fracture is one in six. One tenth to one fifth of the women who have a hip fracture die within a year after it occurs, and one quarter must move permanently to a nursing home.

Although potentially devastating, osteoporotic fractures can be prevented. Adequate calcium intake (at least 1200 mg daily for postmenopausal women) and vitamin D intake (400 to 800 IU daily) and regular weight-bearing exercise protect against bone loss, as do avoidance of smoking and excessive alcohol consumption. Furthermore, medications can increase bone density and, more important, reduce the risk of fracture in women with established osteoporosis; they may also benefit women with less severe bone loss.

Nonetheless, only a small fraction of women who might benefit from medication for the prevention or treatment of osteoporosis are receiving such therapy. What are the obstacles? One is establishing the diagnosis. Because osteoporosis is clinically silent until a fracture occurs, bone densitometry is needed to identify women who may benefit from treatment. Most women with risk factors for osteoporosis have never been screened. Another obstacle is lack of compliance with therapy. A woman has to accept the inconvenience and potential side effects of taking medication in the absence of symptoms of disease.

Of the therapies approved for the prevention or treatment of postmenopausal osteoporosis in the United States (which include hormone-replacement therapy, the selective estrogen-receptor modulator raloxifene, calcitonin, and the oral bisphosphonates alendronate and risedronate), the bisphosphonates are the only medications that have been shown in large randomized trials to reduce the risk of hip fracture. Bisphosphonates act on osteoclasts and may act on osteoblasts to inhibit bone resorption, although the specific mechanisms by which they prevent fractures remain uncertain.

Bisphosphonates have low oral bioavailability and can cause esophageal inflammation or, rarely, ulceration. Thus, when taking alendronate or risedronate, the patient must be upright, have an empty stomach, drink a full glass of water, and remain sitting or standing and eat nothing for 30 minutes. Giving a higher dose of an oral bisphosphonate weekly, instead of a daily dose, is a way to improve compliance. Pamidronate, an intravenous bisphosphonate approved for the treatment of hypercalcemia of malignancy, has also been used to treat postmenopausal osteoporosis, but data on this off-label use of the drug are limited, and infusion can take several hours.

Zoledronic acid is a very potent intravenous bisphosphonate that takes minutes to administer and is also approved for the treatment of hypercalcemia of malignancy. In this issue of the *Journal* (see pages 653-661), Reid et al. report the results of a one-year randomized, placebo-controlled trial of zoledronic acid in postmenopausal women with low bone mineral density. As compared with placebo, zoledronic acid given every three months, every six months, or as a single dose increased bone density at the spine and hip and suppressed markers of bone turnover. All treatment regimens had similar effects, which were also similar to those reported with the oral bisphosphonates in current use. Side effects, including myalgias and nausea, were generally mild. Most striking was the fact that one year after the administration of a single 4-mg dose, markers of bone turnover remained suppressed. This finding suggests that administering the drug even less frequently might also be effective.

The suggestion that an intravenous dose of zoledronic acid once a year or even less often might effectively treat postmenopausal osteoporosis is encouraging. However, before this treatment can be recommended for routine use, studies are clearly needed to determine whether the risk of fractures is actually reduced and to determine whether long-term use of this medication is safe.

CAREN G. SOLOMON, M.D., M.P.H.

"The association between the hydrolytic activity of antibodies against factor VIII . . . is plausible."

Proteolytic Antibodies against Factor VIII in Patients with Hemophilia A

Patients with severe hemophilia A in whom inhibitors of factor VIII developed during replacement treatment were found to have IgG antibodies with the ability to hydrolyze factor VIII. Such antibodies were found in more than half the patients with an inhibitor against factor VIII.

Inhibitors of factor VIII create major problems in the treatment of hemophilia because they nullify the therapeutic effect of replacement therapy. The cost of treating patients with inhibitors is enormous. The hydrolytic mechanism described in this article could lead to new approaches to the care of patients with hemophilia who have antibodies that neutralize factor VIII.

see page 662 (editorial, page 702)

Eosinophilic Meningitis after Travel to the Carribbean

In the weeks after a group of 23 young adults returned from a trip to Jamaica, eosinophilic meningitis developed in 12. Symptoms included headache, neck pain, visual disturbances, and hyperesthesias. Nine of the travelers required hospitalization. A case–control study showed that consumption of a Caesar salad at one dinner was strongly associated with the development of aseptic meningitis.

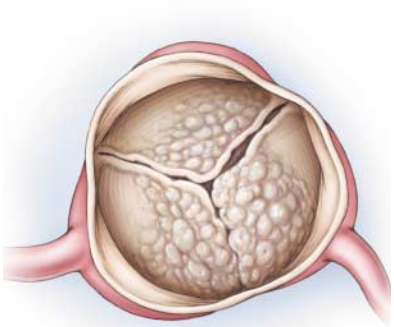
Although the parasitic infection was not confirmed directly, the clinical manifestations plus the serologic data offer strong evidence that the nematode (roundworm) Angiostrongylus cantonensis *was the etiologic agent of this outbreak. This parasitic infection has rarely been documented in the Western Hemisphere.*

see page 668

Images in Clinical Medicine: **Syphilitic Aortitis**

Examination of a 74-year-old man with a one-year history of mild, stable angina revealed a murmur consistent with the presence of aortic regurgitation.

see page 676

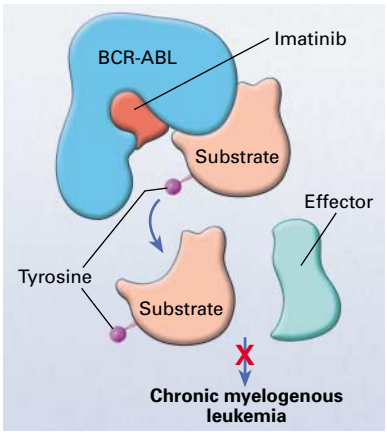


Clinical Practice: **Aortic Stenosis**

A 60-year-old man is evaluated for a heart murmur. He jogs regularly and has no cardiac symptoms. Examination reveals a delayed carotid upstroke and a grade 3/6 late-peaking systolic ejection murmur. Echocardiography shows normal systolic function and a heavily calcified aortic valve, with a peak Doppler transvalvular gradient of 64 mm Hg and a calculated valve area of 0.7 cm^2.

This article discusses the management of aortic stenosis, which can be a challenging problem even for experienced clinicians.

see page 677



Drug Therapy: **Targeted Treatment of Malignant Disorders with Imatinib Mesylate**

This review discusses the development and uses of imatinib mesylate, a protein tyrosine kinase inhibitor useful in the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors that was recently approved by the Food and Drug Administration. Imatinib targets platelet-derived growth factor receptor, inhibits the fusion product of the Philadelphia chromosome, and targets c-kit, a protein tyrosine kinase. The drug may also be effective in the treatment of other tumors that express platelet-derived growth factor receptor or c-kit.

Imatinib mesylate is an anticancer drug with increased capacity to target defined pathways of neoplastic development.

see page 683

"Johns Hopkins has now committed itself 'to do the best job we can and to be responsive.'"

Health Policy Report: **Protecting Research Subjects — The Crisis at Johns Hopkins**

In June 2001, Ellen Roche, a healthy young technician at the Johns Hopkins Asthma and Allergy Center, died during an asthma study. The tragedy prompted several intensive investigations of research oversight at Johns Hopkins and led to the temporary suspension of all federally funded research projects at the institution. In this Health Policy Report, Steinbrook provides a detailed discussion of the outcome of the investigations, the response from Johns Hopkins, and the wider lessons for all involved in clinical investigation.

see page 716