Correspondence

Angiotensin-Receptor Blockers, Type 2 Diabetes, and Renoprotection

To the Editor: I am surprised that the target systolic blood pressures in three studies of the renoprotective effects of angiotensin-receptor blockers in patients with type 2 diabetes (Sept. 20 issue) exceeded the threshold of less than 130 mm Hg recommended in the sixth report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-VI). After treatment, the mean systolic blood pressure for all treatment groups in each study was 140 mm Hg or higher. What kind of example is this for practicing physicians who treat hypertensive patients with diabetes?

If one strictly adheres to the principle that one should not extrapolate from studies to populations that are not represented in those studies, then one cannot say with complete assurance that the findings of the three studies apply to patients with diabetes whose systolic blood pressure is lower than 130 mm Hg. It is possible, albeit unlikely, that various blood-pressure–lowering agents would affect renal function in hypertensive patients with diabetes differently when the JNC-VI blood-pressure goals were achieved.

ROBERT P. BLANKFIELD, M.D.
Berea Health Center
Berea, OH 44017
rblankmd@aol.com


To the Editor: The finding by Lewis et al., Brenner et al., and Parving et al. of a renoprotective effect independent of the blood-pressure–lowering effect of two angiotensin II–receptor antagonists, losartan and irbesartan, in patients with diabetic nephropathy is consistent with the results obtained in the Study to Evaluate Carotid Ultrasound Changes in Patients Treated with Ramipril and Vitamin E (SECURE), the Heart Outcomes Prevention Evaluation (HOPE) study, and the Micro-HOPE substudy with angiotensin-converting–enzyme (ACE) inhibitors in patients with cardiovascular disease (with or without diabetes).

The possibility that the generation of oxidative stress may play a part in the development of diabetic complications has been noted. We have recently demonstrated that subjects with diabetic nephropathy have a defective cellular antioxidant response to the oxidative stress generated by hyperglycemia, predisposing them to organ damage. Given this defect, inhibiting the generation of oxidative stress may be particularly advantageous in patients with diabetes who are prone to the development of nephropathy.

Angiotensin generates free radicals, ACE inhibitors, losartan, and irbesartan inhibit this activity, whereas classic antioxidants only scavenge lipid peroxides that have already been formed. Thus, it may be argued that the protective effect of losartan and irbesartan may result from their indirect antioxidant properties.

ANTONIO CERIELLO, M.D.
ENRICO MOTZ, M.D.
University of Udine
33100 Udine, Italy
antonio.ceriello@dpmsc.uniud.it


INSTRUCTIONS FOR LETTERS TO THE EDITOR

Letters to the Editor are considered for publication (subject to editing and abridgment) provided they do not contain material that has been submitted or published elsewhere. Please note the following: • Your letter must be typewritten and triple-spaced. • Its text, not including references, must not exceed 250 words if it is in reference to a recent Journal article, or 400 words in all other cases (please provide a word count). • It must have no more than five references and one figure or table. • It must not be signed by any more than three authors. • Letters referring to a recent Journal article must be received within four weeks of its publication. • Please include your full address, telephone number, fax number, and e-mail address. • You may send us your letter by standard mail, fax, or e-mail.

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To the Editor: Brenner et al. and Lewis et al. clearly demonstrate that angiotensin-receptor blockers have a small but significant inhibitory effect on the progression of renal failure in patients with diabetes. The principal danger of using these drugs in such patients — hyperkalemia — is scarcely mentioned.

It is well known that ACE inhibitors carry a risk of hyperkalemia. Ahuja et al. studied patients with renal failure who were given ACE inhibitors, not angiotensin-receptor blockers, but as Hostetter notes in an editorial in the same issue of the Journal, there is no reason to believe that angiotensin-receptor blockers are less likely than ACE inhibitors to cause hyperkalemia. Ahuja et al. found hyperkalemia in 43.5 percent of patients with renal failure who were taking ACE inhibitors and cite several references documenting fatal cases. The great danger of hyperkalemia is that it may go unrecognized. Few, if any, symptoms occur before cardiac arrest; autopsy shows nothing.

Angiotensin-receptor blockers are safe in patients with early renal failure, but when renal failure becomes severe, they are dangerous. Perhaps this is why neither losartan nor irbesartan reduced mortality, even though they both slowed the progression of renal failure.

MACKENZIE WALSER, M.D.
Johns Hopkins University
Baltimore, MD 21205-2185


The authors reply:

To the Editor: It is not clear that the strategy for patients with diabetes and hypertension proposed in the JNC-VI recommendations (published in 1997) are either practical or safe for patients with advanced nephropathy, many of whom also have autonomic neuropathy and orthostatic hypotension. We elected to not alter the blood-pressure goals in our study, which began in 1996. The mean systolic blood pressure achieved in our patients was 141 mm Hg — 18 mm Hg lower than the mean level at entry. The mean diastolic pressure achieved in our patients was 78 mm Hg (the JNC-VI recommendation is 85 mm Hg), and the mean arterial pressure was 99 mm Hg (the JNC-VI recommendation is 100 mm Hg). Despite substantial efforts, our investigators were unable to achieve in many patients the goals recommended by JNC-VI for systolic blood pressure. Orthostatic hypotension was reported in 9.8 percent of our patients during the study, with no significant differences among the groups. We are currently conducting analyses to determine the possible risks and benefits associated with the levels of blood pressure achieved in our study.

With regard to Dr. Walser’s comment, the slowing of the progression of renal disease was significant and should not be misleadingly described as a “small effect.” In the light of that significant benefit, it is valid to look at the potential risks. Hyperkalemia, defined as a confirmed measurement of serum potassium of at least 6.0 mmol per liter, occurred in 9 patients in the placebo group (1.6 percent), 2 in the amlodipine group (0.4 percent), and 26 in the irbesartan group (4.5 percent). Analysis of the clinical course of these 37 patients by our clinical-outcomes committee revealed no unexplained sudden deaths. As noted in the article, hyperkalemia requiring discontinuation of the study medication (because of failure to lower the serum potassium concentration from 6.0 mmol per liter or higher to 5.5 mmol per liter or lower) was an uncommon event, occurring in 11 patients in the irbesartan group (1.9 percent), 3 in the amlodipine group (0.5 percent), and 2 in the placebo group (0.4 percent).

The numbers of adjudicated unexplained sudden deaths were similar in all groups: there were 30 such deaths in the placebo group (5.3 percent), 29 in the irbesartan group (5.0 percent), and 23 in the amlodipine group (4.1 percent). There is no evidence that an increased risk of hyperkalemia in the irbesartan group explains these results. Physicians should be aware that patients with progressive renal disease must be carefully monitored for hyperkalemia.

We thank Drs. Ceriello and Motz for suggesting yet another potential beneficial mechanism that might explain the renoprotective activity that we have documented.

EDMUND J. LEWIS, M.D.
Rush-Presbyterian–St. Luke’s Medical Center
Chicago, IL 60612
cally given that a mean blood pressure of 144/82 mm Hg was obtained in a group with tight blood-pressure control in the United Kingdom Prospective Diabetes Study, which enrolled patients without advanced renal impairment.

We agree with Drs. Ceriello and Motz that oxidative stress may be an important factor contributing to the progression of diabetic renal disease. Losartan has been shown to have an antioxidant effect, which may indeed lead to renal protection. Many other hemodynamic and nonhemodynamic effects of losartan could also account for the observed benefits. Unfortunately, clinical trials are not designed to address specific mechanisms.

We monitored serum potassium concentrations closely during the study for the reasons noted by Dr. Walser. To our knowledge, no patient died because of hyperkalemia, and the rates of death due to cardiac arrhythmias were similar in the losartan group and the placebo group. Although hyperkalemia was reported slightly more frequently in the losartan group and the placebo group, although hyperkalemia associated with losartan use is infrequent and manageable.

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To the Editor: To the Editor: Herndon et al. (Oct. 25 issue) report that propranolol attenuates hypermetabolism and reverses muscle-protein catabolism in patients with severe burns. However, these conclusions must be critically examined, because the findings may be attributable to overfeeding. Patients in both groups received approximately 2000 kcal per day (57 and 70 kcal per kilogram of body weight in the control and propranolol groups, respectively). Both groups had a positive energy balance, with measured energy expenditures of 1670 and 1321 kcal per day, respectively, at two weeks, but the propranolol group had a daily caloric balance that was greater than that in the control group by approximately 210 kcal.

Increased carbohydrate intake improves nitrogen balance and skeletal-muscle balance. Beta-blockade, by reducing energy expenditure, would lead to a more positive energy balance and a more positive nitrogen balance if energy intake is maintained. The high energy expenditure in the control group is partly due to overfeeding through increases in lipogenesis and stimulation of catecholamine secretion by carbohydrates.

The respiratory quotient at two weeks in the patients in the study by Herndon et al. was 0.9, indicating the absence of a steady state. Overfeeding with carbohydrates requires a nonoxidative pathway. Net lipogenesis produces a respiratory quotient above 1.0. Because the respiratory quotient in the current study was below 1.0, excess carbohydrate was used for glycogen repletion without consequence to the respiratory quotient, but with a limited capacity for glycogen storage. Since the carbohydrate balance was greater in the propranolol group than in the control group, so was the rate of glycogen repletion, measured as lean tissue by dual-energy x-ray absorptiometry and whole-body potassium scanning. As a result, values for lean tissue would be higher in the propranolol group than in the control group, without necessarily indicating increases in protein.

We question whether the results reported by Herndon et al. have implications for a wide variety of patients, such as adults with trauma or patients undergoing general surgery, since hypercaloric feeding to this degree is no longer practiced.

HANS-HENRIK PARVING, M.D.
Steno Diabetes Center
2820 Gentofte, Denmark

FOR THE IRBESARTAN IN PATIENTS WITH TYPE 2 DIABETES AND MICROALBUMINURIA STUDY INVESTIGATORS

Beta-Blockade and Severe Burns

To the Editor: Herndon et al. (Oct. 25 issue) report that propranolol attenuates hypermetabolism and reverses muscle-protein catabolism in patients with severe burns. However, these conclusions must be critically examined, because the findings may be attributable to overfeeding. Patients in both groups received approximately 2000 kcal per day (57 and 70 kcal per kilogram of body weight in the control and propranolol groups, respectively). Both groups had a positive energy balance, with measured energy expenditures of 1670 and 1321 kcal per day, respectively, at two weeks, but the propranolol group had a daily caloric balance that was greater than that in the control group by approximately 210 kcal.

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We question whether the results reported by Herndon et al. have implications for a wide variety of patients, such as adults with trauma or patients undergoing general surgery, since hypercaloric feeding to this degree is no longer practiced.

JUSTIN A. MAYKEL, M.D.
SASSAN PAZIRANDEH, M.D.
BRUCE R. BISTRIAN, M.D., PH.D.
Harvard Medical School
Boston, MA 02115
bbistria@caregroup.harvard.edu


The authors reply:

To the Editor: Dr. Maykel and his group suggest that the results we demonstrated with propranolol treatment were due to carbohydrate overfeeding, resulting in a net gain of lean mass through accrual of muscle glycogen, not muscle protein. We recognize the limitations of the methods used to measure lean mass in critically ill patients (dual-energy x-ray absorptiometry and total-body potassium counting), and we acknowledge that if muscle glycogen concentrations increase, the resulting increase in intracellular water could be mistakenly interpreted as an increase in protein (lean muscle) mass.

In this study, feeding was based on a formula devised to maintain total body weight during hospitalization. Patients in the control group actually received 1918±346 kcal per day, and those in the propranolol group received 1996±215 kcal per day (P=0.83). However, propranolol treatment did reduce energy expenditure. It is conceivable that carbohydrate calories not used for energy expenditure might have been stored as muscle glycogen, but we emphasize that in addition to changes in lean mass measured by dual-energy x-ray absorptiometry and total-body potassium counting, increased net synthesis of muscle protein was measured in association with propranolol treatment by stable-isotope kinetic techniques performed independently. Thus, three independent methods yielded data that suggest that there was accrual of lean mass and protein in the severely burned children given propranolol.

In reply to the contention that muscle glycogen increased with propranolol treatment: We have now measured muscle glycogen concentrations in samples obtained from patients in both groups at their second isotopic study. We found no significant difference in muscle glycogen concentrations between patients in the control group and those in the propranolol group (mean ±SE, 16.9±2.1 and 15.8±1.6 mg of glucose per gram of muscle, respectively), further supporting our stated conclusions.

Perhaps the feeding regimen described in our article should be practiced more commonly in other populations. In fact, we have found that burned patients who obtain fewer calories than would be provided in this regimen lose weight, and weight loss in burned patients has been associated with poor outcomes. Although we and others have shown no direct benefit in terms of protein kinetics with high caloric feedings in critically ill patients, we have demonstrated that body mass is preserved, albeit with an overall gain in fat mass. Abundant calories in conjunction with anabolic agents such as propranolol appear to increase muscle protein accrual in critically ill patients so that strength and the ability to rehabilitate are improved.

STEVEN E. WOLF, M.D.
ROBERT R. WOLFE, PH.D.
DAVID N. HERNDON, M.D.

University of Texas Medical Branch
Galveston, TX 77550
swolf@utmb.edu

Shipped and Locally Transplanted Renal Allografts

To the Editor: Mange et al. (Oct. 25 issue) report on the survival of shipped and locally transplanted cadaveric renal allografts. On the basis of their findings, the authors conclude that national shipment of such allografts “increases the risk of failure of HLA mismatched grafts during the first year after transplantation.” However, the allocation scheme used for shipping the organs is not apparent. Only 31.4 percent of shipped organs had no HLA mismatches at HLA-A, B, and DR loci. Why were the rest of the kidneys shipped? We assume that they were shipped because HLA matching outside the region was better than that of the local center. But comparisons at various levels of mismatching were not performed. Were other factors taken into account before deciding where to offer organs? If factors such as age, sex, race, or level of panel-reactive antibodies were considered for the allocation, then the analysis of survival need not be adjusted for these factors. An unadjusted analysis does show better survival for the shipped organs than for those transplanted locally. This finding merely confirms that the existing allocation system is effective for longer graft survival.

The policy of giving preference to recipients with no mismatches has been supported by large studies on both sides of the Atlantic. In the United Kingdom, the national kidney- allocation scheme requires the shipment of not only kidneys with no mismatches but also kidneys with a complete match for HLA DR and at least one match for HLA A and B (termed “favorable matches”). Whether shipped kidneys that are favorably matched will have a survival advantage over locally transplanted organs that are less well matched but that have a shorter duration of cold ischemia remains a moot question.

S. SUDHINDRAN, M.S., F.R.C.S.
ANNA TAYLOR, M.B., CH.B.
Addenbrooke’s Hospital
Cambridge CB2 2QQ, United Kingdom
sudhindran@ntworld.com

The authors reply:

To the Editor: The allocation of cadaveric renal allografts in the United States is a complex process that is the result of national and regional policies. Thus, the receipt of an organ in the United States, whether it has been shipped or transplanted locally, does not represent a single allocation scheme. Current allocation policies can be found at the Web site for the United Network for Organ Sharing (http://www.unos.org).

There is interorganizational variation in the factors considered for the acceptance of an organ shipped to an organ-procurement organization. Data that are provided to an organ-procurement organization include but are not limited to the donor's age, race, and sex. Such factors confound the relation between organ shipment and allograft survival. A multivariate analysis was the strategy our group chose to account for these and other factors that confounded the association between organ shipment and allograft survival. A policy that requires the allocation of organs on the basis of the number of HLA mismatches or on any other factor does not guarantee that the intended recipient will be the actual recipient, because illness or immunologic incompatibility may preclude transplantation. The recipients of organs that are well matched at HLA loci may benefit from such a policy, but as a consequence of such strategies, secondary recipients, who usually receive organs with one or more HLA mismatches and with an extended duration of ischemia, may be at a disadvantage. Since there will probably continue to be a shortage of organs and shipments of organs, the challenge remains to devise an allocation strategy that ensures an equitable distribution and that provides for the longest possible allograft survival for all recipients.

KEVIN C. MANGE, M.D., M.S.C.E.
Center for Clinical Epidemiology and Biostatistics
at the University of Pennsylvania
Philadelphia, PA 19104
kmange@ccce.med.upenn.edu

ROY D. BLOOM, M.D.
University of Pennsylvania Health System
Philadelphia, PA 19104


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**Essential Tremor**

To the Editor: In his article on essential tremor (Sept. 20 issue), Louis does not mention alcohol. Ethanol in small doses usually stops the tremor, and this finding may be useful in diagnosis. Some people may use ethanol to hide their tremor; they risk alcohol dependence as a result.

Primidone is noted to be an effective agent, but as Louis points out, nausea and vomiting are common when treatment with this drug is initiated and may lead to its discontinuation. It should be noted that there is tachyphylaxis with respect to these effects. Use of a very low starting dose (25 mg daily) with gradual increases in the dose over a month or so can improve tolerability and compliance with this medication.

STANLEY VAN DEN NOORT, M.D.
University of California at Irvine
Irvine, CA 92697
svandenn@uci.edu

Dr. Louis replies:

To the Editor: I thank Dr. van den Noort for noting the use of ethanol in the treatment of essential tremor. Growdon et al.1 documented a 46 to 83 percent decrease in the amplitude of tremor, measured by accelerometry, in five patients with essential tremor 10 to 15 minutes after the oral ingestion of ethanol. In another study, the intravenous infusion of ethanol, but not placebo, significantly reduced the amplitude of tremor in 15 patients with essential tremor.2 With the use of positron-emission tomography, it has been found that ethanol ingestion leads to the suppression of tremor and to bilateral decreases in cerebellar blood flow.3 One third of patients with essential tremor report that the tremor responds to ethanol, although many are reluctant to use ethanol for a variety of reasons. First, older patients may be taking medications that are contraindications to the concurrent use of ethanol. Second, although some patients report that a glass of wine during an evening social event will reduce the amplitude of their tremor, they are reluctant to consume ethanol during daytime hours, particularly while working, because of its cognitive and soporific effects. Third, there is concern about ethanol dependence and the social stigma of its use.

Lower doses of primidone have been reported anecdotally to result in less nausea and vomiting than higher doses. However, the tolerability of various starting doses needs to be studied in a double-blind manner.

I want to note that in the third paragraph of my article, the term “akinetic tremor” should have been “a kinetic tremor.”

ELAN D. LOUIS, M.D.
College of Physicians and Surgeons of Columbia University
New York, NY 10032
cdl2@columbia.edu

To the Editor: The review of Tourette’s syndrome by Jankovic (Oct. 18 issue) contains a Venn diagram (Fig. 1 of the article) that may be misleading. The figure suggests that Tourette’s syndrome lies at the intersection of tics, attention-deficit–hyperactivity disorder, obsessive–compulsive disorder, and other behavioral disorders. Although these disorders often coexist with Tourette’s syndrome and even with each other, they are not necessary for the diagnosis of Tourette’s syndrome. The presence of tics alone, not caused by other conditions, is sufficient for the diagnosis.1

JOSEPH DeVEAUGH-GEISS, M.D.
Duke University Medical Center
Durham, NC 27705


To the Editor: To the Editor: Two additional diseases to consider in the differential diagnosis of Tourette’s syndrome are allergic rhinoconjunctivitis and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Failure to discriminate allergic rhinoconjunctivitis from Tourette’s syndrome or PANDAS can lead to misdiagnosis and inappropriate treatment.1,2

ANITA GEWURZ, M.D.
Rush Medical College
Chicago, IL 60612-3828
agewurz@rush.edu


Dr. Jankovic replies:

To the Editor: I agree with Dr. DeVegaugh-Geiss that motor and phonic tics without coexisting disorders are sufficient for a diagnosis of Tourette’s syndrome. On the basis of the personal evaluation of well over 1000 patients with Tourette’s syndrome, however, I believe that Tourette’s syndrome consisting of tics alone occurs in only a minority of the patients who present to our Movement Disorders Clinic — admittedly, a biased sample of patients. According to a survey of 3500 patients with a diagnosis of Tourette’s syndrome, only 12 percent had tics alone as the manifestation of the disorder.1 Thus, the Venn diagram was designed to draw attention to the frequent association of other disorders with tics and to highlight the importance of focusing on the whole person, rather than one particular symptom, such as tics.

JOSEPH JANKOVIC, M.D.
Baylor College of Medicine
Houston, TX 77030
joseph@bcm.tmc.edu


AIDS — Past and Future

To the Editor: Reviews of the accomplishments in the fight against the human immunodeficiency virus (HIV) such as those in the June 7 issue1,2 cannot help but sound self-congratulatory when there are more than 30 million people with untreated AIDS — a total equivalent to the combined populations of Australia, Sweden, and Denmark. Memories of the patients with AIDS we have seen but cannot treat in Thailand are indelibly imprinted, like the images of Dr. Gottlieb’s patients.3 We, too, are astounded by their courage. However, unlike the patients that Dr. Gottlieb cared for 20 years ago, ours are not brave because they realize how little we know about what is wrong with them. They are courageous because they realize that we know a great deal about what is wrong with them and how to treat their disease but cannot do so. Soon the number of untreated victims of AIDS who have died since effective drugs became available will exceed the 25 million people who died from the Black Death in Europe more than 600 years ago.1

Dr. DeVegaugh-Geiss refers to the criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV),2 which include a requirement that the tics “cause marked distress or significant impairment in social, occupational, or other important areas of functioning.” Because of this vague language, milder cases of Tourette’s syndrome would be difficult to classify, and the criteria do not take into account the frequently associated behavioral disorders that may be more distressing than the tics. Because of these and other matters of concern (e.g., the onset of tics is defined in DSM-IV as occurring before 18 years of age, rather than 21 years of age), the criteria will be modified in subsequent editions. Until then, I and others who engage in research on Tourette’s syndrome prefer to use the classification developed by the Tourette Syndrome Classification Study Group.3

Dr. Gewurz comments on allergic rhinoconjunctivitis and PANDAS. Because of the controversy about their relationship to Tourette’s syndrome, I did not specifically mention PANDAS, but in the section on immunology I brieﬂy discussed the overlap between poststreptococcal syndromes and Tourette’s syndrome. I recognize that this topic requires further discussion, but because of space limitations I only brieﬂy summarized the evidence for and against immunologic and other causes of tics.4

JOSEPH JANKOVIC, M.D.
Baylor College of Medicine
Houston, TX 77030
joseph@bcm.tmc.edu


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JOSEPH JANKOVIC, M.D.
Baylor College of Medicine
Houston, TX 77030
joseph@bcm.tmc.edu

“Living with AIDS” is the politically correct euphemism. Dying with potentially manageable HIV infection is the horrible reality. Can there be a more shameful medical emergency than 30 million patients urgently requiring life-prolonging therapy and not getting it? Not only should existing antiretroviral drugs be provided, but massive efforts to explore all other potential therapeutic options should begin immediately.

GEORGE WATT, M.D.
Armed Forces Research Institute of Medical Science
Bangkok 10400, Thailand
wartgh@thai.amedd.army.mil

THIERRY BURNOUF, Ph.D.
Human Plasma Product Services
59800 Lille, France

Combined Aortic Surgery and Implantation of a Left Ventricular Assist Device

To the Editor: There is no clearly established strategy for the treatment of a patient with cardiomyopathy and a symptomatic aneurysm of the thoracic aorta. We report the successful use of an approach combining aortic surgery and the implantation of a left ventricular assist device.

Chest pain developed in a 36-year-old heart-transplant candidate with Marfan's syndrome, terminal heart failure, and chronic type B aortic dissection. He had a history of multiple aortic and cardiac surgical procedures, including prosthetic replacement of the ascending aorta, partial replacement of the aortic arch, and aortic- and mitral-valve replacement. He had had recurrent episodes of cardiac decompensation because of cardiomyopathy. The left ventricular ejection fraction was only 15 percent, and the left ventricular end-diastolic diameter was 87 mm, indicating the need for the implantation of a left ventricular assist device.

Because of the development of acute progression (maximal diameter, 80 mm) of the chronic dissecting aneurysm involving the distal part of the aortic arch and the entire descending thoracic aorta, increased chest pain, and the risk of aortic rupture, the patient required urgent surgery to treat both aortic and myocardial problems. In view of recurrent episodes of myocardial decompensation and myocardial insufficiency, it was presumed that he could not survive isolated aortic surgery, and the implantation of the assist device alone would have left him with a risk of aortic rupture. Therefore, we decided to implant a left ventricular assist device during the aortic procedure.

Both procedures were performed through a left anterolateral thoracotomy, with cardiopulmonary bypass with femorofemoral cannulation. The distal part of the aortic arch and complete descending thoracic aorta were replaced with a Dacron graft (diameter, 24 mm) with the use of deep hypothermia, regional circulatory arrest, and regional perfusion. The left ventricle was then supported with a paracorporeal assist device. An 80-ml pump was connected to the left ventricular apex and to the descending aortic graft with the use of standard inflow and outflow cannulas (Fig. 1). The procedure was completed uneventfully, and the patient recovered well. He has now been waiting for an appropriate donor heart for almost five months.

Although urgent, lifesaving surgery was needed because of the imminent risk of aortic rupture, terminal cardiac insufficiency precluded the use of an open surgical procedure. Treatment with a less invasive endovascular stent-graft was not possible because of the extensive aortic disease. Combining surgery for both cardiac and aortic abnormalities proved successful in this case of an otherwise inoperable condition.

MIRALEM PASIC, M.D., Ph.D.
MANFRED HUMMEL, M.D.
ROLAND HETZER, M.D., Ph.D.
Deutsches Herzzentrum Berlin
D-13353 Berlin, Germany
pasic@dhzb.de

Adverse Events after Imatinib Mesylate Therapy

To the Editor: Chronic myelomonocytic leukemia and myelofibrosis with myeloid metaplasia are hematopoietic stem-cell disorders for which there is no effective drug therapy. Imatinib mesylate (Gleevec, Novartis, Basel, Switzerland), formerly known as STI571, is an orally bioavailable derivative of 2-phenylaminopyrimidine that stabilizes an inactive conformation of BCR-ABL and related kinases.1 One of these kinases is the platelet-derived growth factor receptor.2 Because the pathogenesis of both chronic myelomonocytic leukemia and myelofibrosis with myeloid metaplasia may involve signal transduction mediated by platelet-derived growth factor, we initiated two independent pilot studies of imatinib mesylate in these two disorders. We report 3 cases of splenic rupture: 2 occurred among 3 patients with chronic myelomonocytic leukemia, and 1 occurred among 23 patients with myelofibrosis with myeloid metaplasia who were enrolled in phase 2 trials that had been approved by the institutional review boards of participating institutions.

Patient 1, a 61-year-old woman with chronic myelomonocytic leukemia, was treated with 600 mg of imatinib mesylate per day for 12 days before the agent was discontinued because of gastrointestinal symptoms and abnormal results on liver-function tests. Before treatment, the patient’s spleen had been palpated 5 cm below the left costal margin and blood studies revealed a leukocyte count of 34.1×10⁹ per liter and a platelet count of 392×10⁹ per liter. Five days after treatment was discontinued, computed tomography (CT) performed to evaluate pain in the left upper quadrant demonstrated a splenic rupture (Fig. 1A). Splenectomy was performed, and histopathological analysis confirmed the occurrence of splenic rupture with extramedullary hematopoeisis and without evidence of leukemic transformation.

In Patient 2, a 71-year-old woman with chronic myelomonocytic leukemia, treatment with 600 mg of imatinib mesylate per day was stopped after eight days because of the appearance of constitutional symptoms. Before treatment, her spleen had not been palpable and she had had a leukocyte count of 16.8×10⁹ per liter and a platelet count of 50×10⁹ per liter. Treatment was resumed at a lower dose (300 mg per day) after the symptoms resolved. Treatment was again stopped one month later because of increasing splenomegaly and constitutional symptoms. Continued deterioration in the patient’s condition during the next month led to a CT scan, which demonstrated splenomegaly with a contained splenic rupture (Fig. 1B).

Patient 3, a 51-year-old woman with myelofibrosis with myeloid metaplasia and massive splenomegaly, received 400 mg of imatinib mesylate per day for 20 days. The daily dose was then decreased to 200 mg because of lower-extremity edema, and treatment was discontinued 15 days thereafter because of drug-induced thrombocytosis. Spontaneous splenic rupture necessitating splenectomy occurred 50 days later.

One review of splenic rupture in hematologic cancers found that 136 such cases have been reported since 1861.3 Our findings suggest but do not prove a causal relation in these disease states. Communication with Novartis disclosed that there have been 3 reported cases of splenic rupture among the more than 10,000 patients with chronic myelogenous leukemia who have been treated with imatinib mesylate.

MICHELLE A. ELLIOTT, M.D.
RUBEN A. MESA, M.D.
AYALEW TEFERRI, M.D.
Mayo Clinic
Rochester, MN 55905
elliott.michelle@mayo.edu

To the Editor: Imatinib mesylate has recently been licensed for the treatment of selected patients with chronic myelogenous leukemia (CML).1 We report a case of bone marrow necrosis secondary to imatinib mesylate therapy in a patient with accelerated-phase CML.

A 73-year-old man was given a diagnosis of high-risk chronic-phase CML in September 1999. He was treated with hydroxyurea and then interferon, and his blood counts became normal. In March 2001, bone marrow examination and cytogenetic analysis demonstrated progression to accelerated-phase CML. Treatment with imatinib mesylate was commenced at a dose of 600 mg per day. After three weeks of treatment, high fevers and rigors developed. The following week, the patient reported having severe pain in the lower back and legs. He became wheelchair-bound over a period of a few days. At this time he had a white-cell count of $4.4 \times 10^9$ per liter, a hemoglobin level of 92 g per liter, and a platelet count of $395 \times 10^9$ per liter. Biochemical analysis demonstrated an alkaline phosphatase level of 398 U per liter. Examination of bone marrow aspirate and biopsy specimens obtained with a trephine revealed extensive bone marrow necrosis and osteonecrosis, with no evidence of transformation to blast crisis.

Bone marrow necrosis is defined pathologically by the loss of the normal bone marrow architecture; the degeneration of bone marrow cells results in indistinct cellular margins and pyknotic nuclei on an amorphous eosinophilic background. Bone marrow necrosis results from cellular hypoxia that is due to ischemia of the bone microcirculation as a consequence of inflammatory damage or mechanical obstruction. This may, in turn, be due to the release of prothrombotic toxins, cytokines, and vasoactive substances from damaged cells, particularly tumor necrosis factor α.2 The most prominent symptoms of bone marrow necrosis are bone pain and fever, usually with anemia and thrombocytopenia. The white-cell count usually declines, but it can increase or remain unchanged.

In retrospective reviews of unselected biopsy specimens of bone marrow, the incidence of bone marrow necrosis ranges from 0.15 percent to 0.32 percent.3 The majority of cases are caused by cancer, two thirds of which are hematologic cancers and one third of which are solid tumors. CML is the cause in 5 percent of cases, and bone marrow necrosis has been reported in 12 patients with CML.4 In these patients there was a strong association between bone marrow necrosis and blast transformation. Bone marrow necrosis has also been associated with the use of interferon alfa.5 Our patient had no evidence of disease progression that could account for the bone marrow necrosis. This case suggests that imatinib mesylate, perhaps by accelerating the rate of apoptosis and release of prothrombotic cellular material, may lead to bone marrow necrosis.

Catherine Burton, M.B., B.Chir., M.R.C.P.
Anthony Azzi, M.B., B.S.
Ian Kerridge, F.R.A.C.P., F.R.C.P.A.
Newcastle Mater Hospital
Newcastle, NSW 2298, Australia
cathyburton@hotmail.com


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