INOSINE PRANOBEX — IS A SINGLE POSITIVE TRIAL ENOUGH?

Recognition of the myriad immunologic defects associated with human immunodeficiency virus (HIV) infection has stimulated the development of novel approaches to its treatment. To date, the most effective treatments have been antiviral agents directed against HIV itself, such as zidovudine (formerly AZT, or azidothymidine). However, active efforts continue in the search for agents to restore or improve the defensive immune systems of persons infected with HIV. Although the distinction between immunomodulatory and antiretroviral therapy is not always clear, the possibility of a combined approach is conceptually exciting. The clinical testing of potential immunomodulators increases the complexity of drug development by raising questions about the role of any agent as single-drug therapy and by highlighting uncertainty about what markers of disease are most appropriate for assessing the potential efficacy of agents in either class.

When they are monitored during the early clinical testing of antiretroviral agents, changes in laboratory markers of HIV infection (such as CD4+ cell counts and serum p24-antigen concentrations) may contribute to the understanding of a drug’s activity and help identify the most promising doses. Later in drug development, especially in randomized trials designed to demonstrate efficacy, changes in laboratory markers can provide important evidence of drug activity and support for clinical endpoints suggesting benefit. No relevant markers that specifically reflect in vivo activity of immunomodulators have yet been identified, although it seems likely that notable benefit in terms of slowing the progression of disease will be reflected in a parallel delay in the decline of CD4+ cell counts, an immunologic measure that closely tracks the development of opportunistic infections in patients infected with HIV.

Inosine pranobex is postulated to be an immunomodulator and has been investigated for the treatment
of various cancers, subacute sclerosing panencephalitis, herpesvirus infection, and other viral infections. Substantial evidence of efficacy has not been provided to the Food and Drug Administration to support approval of the marketing of this drug for any of these indications in the United States. Despite a large body of data reporting the potentiation of various T-cell, neutrophil, and mononuclear-cell functions in cell culture and laboratory rodents, the mechanism or mechanisms of action of this drug remain speculative.1 There is little if any evidence of direct activity against HIV, and the drug does not appear to interact with zidovudine in vitro.2 Early reports suggested that inosine pranobex in a total daily dose of 3 to 4 g may improve natural-killer-cell activity3 and mitogen-induced lymphocyte transformation4 in some persons with HIV infection. A consistent effect on CD4+ cell counts has not been shown.

In this issue of the Journal, Pedersen et al. report the results of a randomized, placebo-controlled trial of inosine pranobex conducted in a heterogeneous group of 866 people with HIV infection in Sweden and Denmark.5 The chief finding of this study is that significantly fewer subjects who received inosine pranobex (3 g per day) than who received placebo had progression to the acquired immunodeficiency syndrome6 (AIDS) during the 24-week study period (2 vs. 17). Although the finding is interesting and provocative, the conclusion that inosine pranobex delays progression to AIDS in people with HIV infection must be viewed with considerable caution.

Several issues in the design and analysis of this study warrant attention. First, no difference was detected between the inosine pranobex and placebo groups in progression of disease according to the modified Walter Reed Staging Classification, the primary end point designated before the study began. The substitution of the classification system of the Centers for Disease Control (CDC) after the study had ended was well reasoned but resulted in a post hoc claim of efficacy that must therefore be viewed with some skepticism. Second, no significant differences in the decrease in peripheral-blood CD4+ cell counts, level of p24 antigenemia, progression to symptomatic disease (CDC Group IV) other than AIDS, or progression from symptomatic HIV disease to AIDS were noted between treatment groups over the 24-week study period. Although it is possible that inosine pranobex may delay progression to AIDS but may not affect other clinical manifestations or laboratory markers of disease progression, the lack of additional evidence of the drug’s activity is disconcerting in the light of current knowledge about the pathogenesis and natural history of HIV infection.

The fact that 33 randomized subjects were excluded from the analysis of efficacy should also be noted, since such exclusions were not prospectively specified by the study design. In addition, because the inosine moiety of inosine pranobex is metabolized to uric acid, this indicator of ingestion of the drug may have biased the clinical assessment of symptomatic patients, despite the authors’ statement that the blinding of the investigators was unaffected. The preservation of blinding is particularly important in trials that use progression to opportunistic infections as a primary end point, since the decision to initiate an evaluation for their presence can be quite subjective, as can the use of CDC-suggested guidelines for the presumptive diagnosis of diseases indicative of AIDS.6 Finally, the relatively short study period and the absence of follow-up after 24 weeks limit any assessment of the prolonged effectiveness of inosine pranobex — an important issue in view of the broad range of people with HIV infection for whom the authors imply that the drug may be useful.

Pedersen et al. do not discuss the fact that other controlled trials of inosine pranobex in patients with HIV infection have yielded less positive results. Progression to AIDS did not occur in either the treated or control group in a study of 61 homosexual men with persistent generalized lymphadenopathy who were randomly assigned to receive placebo or inosine pranobex (1 or 3 g per day) for 28 days and then followed for up to one year.7 In a randomized but unblinded three-month study of 553 subjects in Italy, the proportions of asymptomatic subjects in whom either generalized adenopathy or symptomatic manifestations of HIV infection developed were similar in the treated (inosine pranobex, 4 g per day) and untreated groups. In no subject had AIDS developed by the end of the study.8 Of most concern is a report by the pharmaceutical sponsor in November 1988 that a multicenter trial conducted in the United States and the United Kingdom, involving 696 men with HIV infection but without AIDS who had CD4+ cell counts of 200 to 400 per cubic millimeter at entry, showed no benefit from 4 g of inosine pranobex per day for six months, as compared with placebo.8,9 Because the results of that study have not been published, they cannot be adequately compared with those of Pedersen et al. at this time.

Since the first subject entered the Pedersen study in 1986, considerable progress has been made in the treatment of HIV infection and its related complications. Primary prophylaxis against Pneumocystis carinii pneumonia is now routinely recommended for patients with CD4+ cell counts of less than 200 per cubic millimeter or levels less than 20 percent of the total lymphocyte count.10 The indications for zidovudine were recently expanded to encompass all persons with HIV infection, including children over three months of age, with laboratory evidence of significant immunosuppression (CD4+ cell counts of less than 500 per cubic millimeter in adults), regardless of symptoms. These therapeutic advances do not negate a potential role for immunomodulators in the treatment of HIV infection. Rather, as a variety of effective treatments become available to patients earlier in the course of their infection, the role of any
single-drug therapy must be reappraised. A controlled clinical study of inosine pranobex treatment in combination with pneumocystis prophylaxis and anti-retroviral therapy should be undertaken in an attempt to confirm, in the current therapeutic milieu, the provocative results reported in this issue of the Journal.

The lack of corroborating evidence of efficacy based on other clinical or laboratory markers of disease progression, combined with the absence of a basic understanding of the pharmacology and mechanism of action of inosine pranobex, makes a confirmatory study mandatory before claims of efficacy can be accepted by the scientific and medical community or by regulatory agencies such as the FDA. From our perspective, a carefully designed and conducted study to confirm the encouraging but isolated findings of an earlier controlled clinical trial of a new therapy for AIDS should be accorded a high priority. The only way to determine reliably whether inosine pranobex fulfills the promise reported here is to conduct such a trial. Otherwise, the drug will remain in scientific and regulatory limbo — an unacceptable status for any agent at this stage of development in the AIDS epidemic.

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REFERENCES


IS RATIONING INEVITABLE?

A compelling picture of the growing confrontation between physicians in private practice and third-party payers is provided by the correspondence in this issue on Dr. Gerald Grumet’s recent essay, “Health Care Rationing through Inconvenience.” The problem underlying the discontent is cost. The payers — government, business, and the health insurance companies — are at the end of their economic rope. Unable to support the continued escalation of medical costs, they are determined to use whatever means they can to control expenditures. Two consequences, vividly described by Grumet, are a growing morass of regulations and bureaucracy and an increasing surveillance of physicians’ decisions — particularly those involving the use of hospitals.

It is hardly surprising, therefore, that many practitioners now view the third-party payers as adversaries, who not only interfere with the way they practice but burden them with excessive paperwork. Recently, a number of obstetricians in Massachusetts, increasingly frustrated with these conditions, elected to withdraw from their contracts with Blue Shield and were charged by the state with violating antitrust law, thus further darkening the mood of the profession.

Few observers expect present cost-containment efforts to be successful. Conventional wisdom holds that unrestrained consumer demand coupled with the relentless development of increasingly sophisticated new technology will keep driving costs up until some major new approach is adopted. The most likely next step, many now believe, will be some form of systematic rationing.

Limited access to medical care has always been with us. Over five years ago Fuchs pointed out in the Journal that patients’ income and the geographic location of physicians and facilities have historically restricted the availability of medical services to many Americans. And Grumet has also reminded us that reimbursement regulations imposed by third-party payers (a part of what is euphemistically called “managed care”) can similarly result in a kind of rationing. But what is now being contemplated is something quite different: the deliberate and systematic denial of certain types of services, even when they are known to be beneficial, because they are deemed too expensive. This kind of rationing is different from global governmental budgetary restraints on facilities and personnel, such as occurs in centrally planned health economies like those of Great Britain or Sweden. Instead, it would be achieved through decisions not to pay doctors and hospitals for the delivery of particular services to particular groups of patients under defined circumstances.

Two Sounding Board articles in this issue of the Journal deal with this kind of rationing. One is by Daniel Callahan, director of the Hastings Center for Bioethics, who has recently written two thoughtful books about the role of medical care in our society. In the present essay, he criticizes what he calls our national addiction to new medical technology and our expectations of unlimited medical progress. He argues that to afford decent health care for all, as well as the other social goods with which our medical care budget

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