Immunotherapy for Tuberculous Pericarditis

Richard E. Chaisson, M.D., and Wendy S. Post, M.D.

Pericardial tuberculosis is an important clinical problem in resource-limited countries, particularly in those with concomitant epidemics of human immunodeficiency virus (HIV) infection. Tuberculosis involving closed anatomical spaces such as the pericardium or meninges can cause devastating inflammatory injury, and management with antimicrobial therapy alone may not prevent complications. Host-directed therapies that attenuate destructive inflammatory responses may prevent serious sequelae. Current American and World Health Organization guidelines strongly recommend treatment with glucocorticoids in addition to antituberculosis drugs in patients with tuberculous pericarditis, but expert European guidelines are more muted, reflecting the uncertainty of the evidence.1-3

Mayosi and colleagues now report in the Journal the results of the Investigation of the Management of Pericarditis (IMPI) trial, a multicenter, factorial-design trial that tested two host-directed therapies in patients in Africa who had presumed tuberculous pericarditis.4 Participants were randomly assigned to receive a course of high-dose prednisolone tapered over the course of 6 weeks or placebo and were further randomly assigned to receive five injections of heat-killed Mycobacterium indicus pranii, a rapidly growing nontuberculous mycobacterium species with putative therapeutic effects, or placebo. The study enrolled 1400 patients; approximately two thirds of the patients had HIV infection, about three quarters had New York Heart Association class II or III symptoms, and approximately 90% had moderate or large pericardial effusions. Patients were followed for a median of more than 600 days, and the rates of adherence and follow-up were high. Glucocorticoid therapy had no significant effect on the primary composite efficacy outcome of death, cardiac tamponade requiring pericardiocentesis, or development of constrictive pericarditis — a finding that will surprise many. Glucocorticoid therapy, as compared with placebo, was associated with significantly reduced incidences of the secondary outcomes of constrictive pericarditis (4.4% vs. 7.8%, P=0.009) and hospitalizations (20.7% vs. 25.2%, P=0.04). Patients receiving M. indicus pranii injections had no significant benefit with respect to any of the outcomes. Glucocorticoid therapy was associated with higher rates of infections, mostly candida, and both interventions were associated with a significantly increased risk of cancer, primarily Kaposi’s sarcoma. Patients who received both glucocorticoids and M. indicus pranii had a notably higher risk of cancer.

There are several possible reasons that this large trial failed to confirm earlier, smaller trials of glucocorticoids that showed a benefit with respect to both death and cardiac tamponade.5,6 First, more than 70% of the participants had a diagnosis of possible tuberculous pericarditis, without microbiologic evidence of tuberculosis in the pericardium or elsewhere. Although reasonable diagnostic criteria were used, patients with other causes of pericarditis could have diluted the results, though outcomes were similar in the subgroup of patients with confirmed tuberculous pericarditis. The composite outcome included death, which is irrefutable, but the need for pericardiocentesis and the diagnosis of constrictive pericarditis are often subjective. Almost 20% of the patients died, however, with approximately one quarter of those deaths attributed to pericarditis, and glucocorticoid therapy did not alter this outcome. Older studies of glucocorticoid therapy were conducted before the HIV epidemic had reached southern Africa,5 and
the pathogenesis of tuberculous pericarditis may be different in patients with HIV infection than in those who are not HIV-infected. HIV-related tuberculosis tends to be disseminated, involving multiple organs, but induces considerably less inflammatory response than non–HIV-related tuberculosis. Antiinflammatory therapies may at best have only modest effects in patients with HIV-related tuberculosis. The benefit of glucocorticoid therapy in subgroup analyses was greatest in participants who were not infected with HIV.

The overall reduction in the development of constrictive pericarditis and in hospitalizations with prednisolone treatment is clinically meaningful, and further subgroup analyses to determine which patients benefited most will be informative. For example, since constriction due to fibrinous exudate or calcification of the pericardium is often a later manifestation of disease, the timing of glucocorticoid administration relative to the initial diagnosis might influence the outcome.

The lack of benefit from *M. indicus pranii* therapy is not surprising, since the scientific rationale for this therapy in patients with tuberculous pericarditis is underwhelming, and the hypothesis that stimulating antituberculosis immunity might reduce inflammatory responses in the pericardial space is not compelling. *M. indicus pranii* therapy increased the risk of cancer, however, particularly among patients who were also receiving glucocorticoids. The strong signal that combining immunostimulatory and immunosuppressive therapies increases the risk of cancer should give pause to proponents of therapeutic (as opposed to preventive) vaccines.

How should the IMPI trial results affect clinical practice? The results of this large, pragmatic trial clearly suggest that routine use of adjunctive glucocorticoids for all patients with tuberculous pericarditis should not be endorsed. But the prevention of constrictive pericarditis and the reduction in rates of hospitalization are important goals in treating patients. Selective use of glucocorticoids in patients who are at the highest risk for inflammatory complications would be appropriate. Such patients might include those with large effusions, those with high levels of inflammatory cells or markers in pericardial fluid, or those with early signs of constriction, and additional formal subgroup analyses are awaited. Patients with HIV infection are at the greater risk for cancer, so the use of glucocorticoids should be curtailed in this population unless the risk of constrictive pericarditis is high.

Finally, the poor outcomes in the IMPI trial (18% mortality) underscore the importance of preventing tuberculosis in sub-Saharan Africa, where HIV fuels the highest global rates of the disease. Early diagnosis of HIV infection, early initiation of antiretroviral therapy, and provision of preventive therapy for tuberculosis are highly effective strategies that can reduce the risks of tuberculosis by up to 90%. Increasing delivery of these interventions to populations that are at the greatest risk remains a top priority for improving global health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Johns Hopkins University School of Medicine, Baltimore.

This article was published on September 2, 2014, at NEJM.org.