ORIGINAL ARTICLE

Prednisolone and *Mycobacterium indicus pranii* in Tuberculous Pericarditis

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ABSTRACT

BACKGROUND

Tuberculous pericarditis is associated with high morbidity and mortality even if antituberculosis therapy is administered. We evaluated the effects of adjunctive glucocorticoid therapy and *Mycobacterium indicus pranii* immunotherapy in patients with tuberculous pericarditis.

METHODS

Using a 2-by-2 factorial design, we randomly assigned 1400 adults with definite or probable tuberculous pericarditis to either prednisolone or placebo for 6 weeks and to either *M. indicus pranii* or placebo, administered in five injections over the course of 3 months. Two thirds of the participants had concomitant human immunodeficiency virus (HIV) infection. The primary efficacy outcome was a composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis.

RESULTS

There was no significant difference in the primary outcome between patients who received prednisolone and those who received placebo (23.8% and 24.5%, respectively; hazard ratio, 0.95; 95% confidence interval [CI], 0.77 to 1.18; P=0.66) or between those who received *M. indicus pranii* immunotherapy and those who received placebo (25.0% and 24.3%, respectively; hazard ratio, 1.03; 95% CI, 0.82 to 1.29; P=0.81). Prednisolone therapy, as compared with placebo, was associated with significant reductions in the incidence of constrictive pericarditis (4.4% vs. 7.8%; hazard ratio, 0.56; 95% CI, 0.36 to 0.87; P=0.009) and hospitalization (20.7% vs. 25.2%; hazard ratio, 0.79; 95% CI, 0.63 to 0.99; P=0.04). Both prednisolone and *M. indicus pranii*, each as compared with placebo, were associated with a significant increase in the incidence of cancer (1.8% vs. 0.6%; hazard ratio, 3.27; 95% CI, 1.07 to 10.03; P=0.03, and 1.8% vs. 0.5%; hazard ratio, 3.69; 95% CI, 1.03 to 13.24; P=0.03, respectively), owing mainly to an increase in HIV-associated cancer.

CONCLUSIONS

In patients with tuberculous pericarditis, neither prednisolone nor *M. indicus pranii* had a significant effect on the composite of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. (Funded by the Canadian Institutes of Health Research and others; IMPI ClinicalTrials.gov number, NCT00810849.)

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Tuberculous pericarditis is a common cause of pericardial effusion, cardiac tamponade, and constrictive pericarditis in sub-Saharan Africa and parts of Asia.[1-3] Patients with tuberculous pericarditis often have concomitant human immunodeficiency virus (HIV) infection.[1] Despite antituberculosis therapy, pericardial drainage, or pericardiectomy, mortality and morbidity remain high.[4] Mortality is as high as 26% at 6 months but is even higher (approximately 40%) among persons with the acquired immunodeficiency syndrome.[5]

The use of glucocorticoid therapy in patients with tuberculous pericarditis to attenuate the inflammatory response may improve outcomes and decrease the risk of death by reducing cardiac tamponade and pericardial constriction,[6] but the clinical effectiveness of adjunctive glucocorticoids is unclear.[7-9] A meta-analysis of randomized, controlled trials of glucocorticoid therapy for tuberculous pericarditis showed a nonsignificant reduction in mortality,[7,8] but the numbers of events and patients included were very small. A meta-analysis of all trials of adjunctive glucocorticoid therapy for all forms of tuberculosis also suggested reduced mortality.[10]

However, glucocorticoids may increase the risk of cancer in HIV-infected patients,[11,12] and there is scant evidence of the effects of adjunctive glucocorticoid therapy for tuberculosis in this population.[10] These considerations have led to conflicting recommendations in international guidelines regarding the role of adjunctive glucocorticoid therapy in patients with tuberculous pericarditis.[9,13,14] We hypothesized that there would be an overall benefit of adjunctive prednisolone for these patients.

Preliminary evidence suggests that repeated doses of intradermal heat-killed *Mycobacterium indicus pranii* (formerly known as *Mycobacterium w*) immunotherapy may reduce inflammation associated with tuberculosis and increase the CD4+ T-cell count in persons infected with HIV.[15-17] *M. indicus pranii* is a nonpathogenic, saprophytic, rapidly growing atypical mycobacterium species that has shown clinical benefit when administered as a heat-killed intradermal formulation in patients with leprosy and that may have benefits in patients with pulmonary tuberculosis and HIV infection.[16,18-22] We hypothesized that intradermal *M. indicus pranii* could be effective in suppressing inflammation and its sequelae in patients with tuberculous pericarditis. In the Investigation of the Management of Pericarditis (IMPI) trial, we evaluated the efficacy and safety of adjunctive prednisolone and *M. indicus pranii* in patients in Africa who had tuberculous pericarditis.

METHODS

STUDY DESIGN, CONDUCT, AND OVERSIGHT

We used a 2-by-2 factorial design to independently evaluate prednisolone and intradermal *M. indicus pranii*, as compared with placebo, for the treatment of tuberculous pericarditis (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). A detailed description of the design of the trial has been published previously.[4,23-25] The study was approved by the appropriate national regulatory authorities and by the ethics committee at each participating site. All the participants provided written informed consent.

Cadila Pharmaceuticals donated the study drugs used in the trial and distributed them to the research sites but had no role in the design or conduct of the study, in the analysis of the data, or in the decision to submit the manuscript for publication. The Canadian Institutes of Health Research reviewed the protocol, and changes were made according to the comments of the reviewers; the South African Medical Research Council also reviewed the protocol, but no changes were recommended or made.

The study was coordinated by teams at the University of Cape Town, South Africa, and the Population Health Research Institute (PHRI) at Hamilton Health Sciences and McMaster University, Canada. The steering committee (see the Supplementary Appendix) designed the study, oversaw its conduct, wrote the manuscript, and made the decision to submit it for publication. An independent trial monitoring committee monitored the trial for safety and efficacy. Data were collected and analyzed at the PHRI. The first and last authors vouch for the accuracy of the data and the analyses and for the fidelity of this report to the trial protocol, which is available at NEJM.org.

ENROLLMENT CRITERIA

Details of the inclusion and exclusion criteria are provided in Table S1 in the Supplementary Ap-

pendix. Patients were eligible for inclusion in the trial if they were 18 years of age or older, had a pericardial effusion confirmed by echocardiography, had evidence of definite or probable tuberculous pericarditis (as defined in Tables S2 and S3 in the Supplementary Appendix), and had begun to receive antituberculosis treatment less than 1 week before enrollment. Patients were excluded if an alternative cause of pericardial disease could be identified, if they had used glucocorticoids within the previous month, if they had known hypersensitivity or allergy to the *M. indicus pranii* preparation, or if they were pregnant.

STUDY PROCEDURES

Eligible patients who had provided written informed consent were assigned to an active-treatment or placebo group for each of the two randomized comparisons. Randomization was performed with the use of a central computer-generated randomization list, with stratification according to center and with a random block size. For the comparison of prednisolone with placebo, participants were assigned to receive prednisolone or placebo for 6 weeks at a dose of 120 mg per day in the first week, 90 mg per day in the second week, 60 mg per day in the third week, 30 mg per day in the fourth week, 15 mg per day in the fifth week, and 5 mg per day in the sixth week. For the comparison of *M. indicus pranii* with placebo, participants were assigned to receive the *M. indicus pranii* preparation (CADI-Mw injection, Cadila Pharmaceuticals) or placebo in five doses — at the time of enrollment and at 2 weeks, 4 weeks, 6 weeks, and 3 months. The first dose was given as two injections of 0.1 ml (containing 0.5×10^9 organisms) in each deltoid region of the upper arm; the four subsequent doses were given as a single injection of 0.1 ml.

Trial participants received antimicrobial treatment for tuberculosis and antiretroviral treatment for HIV according to World Health Organization (WHO) guidelines; management during the course of the trial was revised as recommended treatment practices evolved.[13,26-28] No routine testing for drug resistance of either *M. tuberculosis* isolates or HIV isolates was performed before or during treatment.

Follow-up data were collected at the time of hospital discharge; at 2 weeks, 4 weeks, 6 weeks, 3 months, and 6 months; then every 6 months through 2 years; and every 12 months thereafter. Follow-up visits included assessments of study outcomes, adherence to treatment, and adverse events. Site monitoring throughout the study was performed through the project coordinating office according to a standard operating procedure (see the Site Monitoring and Quality Control Section in the Supplementary Appendix).

OUTCOMES

The primary efficacy outcome was a composite of death or the first occurrence of cardiac tamponade requiring pericardiocentesis or constrictive pericarditis. Secondary efficacy outcomes included the individual components of the primary outcome as well as hospitalization. Safety outcomes included opportunistic infections and cancer, as well as the effect of interventions on the CD4+ T-lymphocyte cell count (as a measure of immunosuppression) and the incidence of the immune reconstitution inflammatory syndrome (in HIV-infected patients). Detailed definitions of outcome events are provided in Tables S4 through S8 and the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

We based our sample-size calculation on the following assumptions: the event rate among patients receiving placebos for both interventions would be 35% at a mean follow-up of 2 years; half the patients in the control group for each intervention would receive another effective intervention, which would result in a 30% relative risk reduction in the event rate; the nonadherence rate would be 10%; and the rate of loss to follow-up would be 6%. On the basis of these assumptions, we estimated that with a sample of 1400 patients, the study would have 90% power to detect a 22.9% reduction in the hazard ratio, with the use of a log-rank test and a two-sided type I error rate of 5%.

Data were analyzed with the use of SAS software, version 9.1, according to an intention-to-treat approach (as described in the protocol and the prespecified statistical analysis plan). Time-to-event curves were constructed by means of product-limit estimation and were compared with the use of stratified log-rank tests. Cox proportional-hazards models stratified according to factorial treatment assignment were used to determine hazard ratios and 95% confidence intervals. We assessed interactions between the

two active treatments by including an interaction term in the model.

We also performed analyses for the primary outcome in subgroups defined according to HIV status, the strength of the evidence supporting the tuberculous pericarditis diagnosis (definite or probable diagnosis), exposure of HIV-infected persons to antiretroviral therapy (>6 months, ≤6 months, or no exposure), the CD4+ T-cell count threshold for treatment (≤200 per cubic millimeter vs. >200 per cubic millimeter and ≤350 per cubic millimeter vs. >350 per cubic millimeter), and pericardiocentesis status at baseline (performed vs. not performed), using the Cox proportional-hazards model, with an interaction term for treatment effects across the subgroups. For all analyses, P values of less than 0.05 were considered to indicate statistical significance.

The trial monitoring committee performed seven interim analyses of the primary outcome data; at the sixth interim analysis, the trial monitoring committee recommended that the *M. indicus pranii* randomization be discontinued for reasons of futility.

RESULTS

STUDY POPULATION

The trial was conducted from January 2009 through February 2014 at 19 hospitals in eight African countries (see the Supplementary Appendix). A total of 1400 patients were enrolled for

Table 1. Baseline Characteristics of the Patients and Diagnosis at 3 Months.*

Variable	Prednisolone (N=706)	Placebo (N=694)	*Mycobacterium indicus pranii* (N=625)	Placebo (N=625)
Age — yr	38.8±13.5	38.5±13.3	37.7±12.5	39.3±14.1
Weight — kg	59.6±12.3	59.2±12.1	58.6±12.2	59.6±12.0
Female sex — no. (%)	317 (44.9)	299 (43.1)	292 (46.7)	263 (42.1)
Size of pericardial effusion — no. (%)				
Small, <1 cm	51 (7.2)	56 (8.1)	58 (9.3)	40 (6.4)
Moderate, 1–2 cm	172 (24.4)	159 (22.9)	154 (24.6)	140 (22.4)
Large, >2 cm	462 (65.4)	460 (66.3)	391 (62.6)	428 (68.5)
Not measured	21 (3.0)	19 (2.7)	22 (3.5)	17 (2.7)
Pericardiocentesis — no. (%)				
Performed	428 (60.6)	419 (60.4)	372 (59.5)	381 (61.0)
Not performed	278 (39.4)	275 (39.6)	253 (40.5)	244 (39.0)
Diagnosis at 3 months — no. (%)				
Definite tuberculous pericarditis	116 (16.4)	122 (17.6)	100 (16.0)	105 (16.8)
Probable tuberculous pericarditis				
Tuberculosis proven elsewhere	73 (10.3)	63 (9.1)	67 (10.7)	53 (8.5)
Tuberculosis not proven elsewhere	506 (71.7)	506 (72.9)	450 (72.0)	462 (73.9)
Non-tuberculous cause	11 (1.6)	3 (0.4)	8 (1.3)	5 (0.8)
HIV status — no. (%)				
Positive	474 (67.1)	465 (67.0)	437 (69.9)	403 (64.5)
Negative	218 (30.9)	213 (30.7)	175 (28.0)	209 (33.4)
Unknown	14 (2.0)	16 (2.3)	13 (2.1)	13 (2.1)
Antituberculosis medication at randomization — no. (%)	541 (76.6)	531 (76.5)	460 (73.6)	462 (73.9)
Antiretroviral medication at randomization — no. (%)	99 (14.0)	104 (15.0)	88 (14.1)	84 (13.4)

* Plus–minus values are means ±SD. There were no significant differences among the study groups in any of the baseline characteristics listed here. HIV denotes human immunodeficiency virus.

the comparison of prednisolone with placebo; 706 were assigned to receive prednisolone and 694 to receive placebo. The median follow-up period was 636.5 days (interquartile range, 317.5 to 1085.5); at study end, the primary-outcome status was known for 1371 participants (97.9%) (Fig. S2 in the Supplementary Appendix).

A total of 1250 patients were enrolled for the comparison of *M. indicus pranii* with placebo, before this comparison was stopped early for futility (on February 14, 2013); 625 were assigned to receive *M. indicus pranii* and 625 to receive placebo. The median follow-up period was 720.5 days (interquartile range, 368.0 to 1095.0); at study end, the primary-outcome status was known for 1223 participants (97.8%) (Fig. S3 in the Supplementary Appendix).

The baseline characteristics were similar across the groups (Table 1, and Table S9 in the Supplementary Appendix). Approximately two thirds of the participants had a large pericardial effusion; pericardiocentesis was performed in 60.5%. The diagnosis of tuberculous pericarditis was considered to be definite in 17.1% of the patients (details are provided in Table S10 in the Supplementary Appendix). Two thirds of the participants were HIV-positive.

TREATMENT REGIMENS AND ADHERENCE

For the comparison of prednisolone with placebo, 88.5% of the patients in the prednisolone group and 88.7% of those in the placebo group adhered to the regimen for the full 6 weeks of the study treatment. A total of 44 patients (3.1%) received nonstudy glucocorticoids during the trial; this rate was similar in the prednisolone and placebo groups. For the comparison of *M. indicus pranii* with placebo, 75.9% of the patients in the *M. indicus pranii* group and 81.4% of those in the placebo group adhered to the regimen for the full 3 months of the study treatment.

Of the 1400 patients enrolled in the trial, 76.6% were receiving antituberculosis treatment at the time of randomization, and 14.5% were receiving antiretroviral treatment (Table S11 in the Supplementary Appendix). The rates of ongoing use of antituberculosis therapy and antiretroviral therapy during the trial are shown in Tables S12 and S13 in the Supplementary Appendix. The increasing use of antiretroviral therapy during the course of the trial reflects the adoption of revised WHO guidelines recommending early initiation

Table 2. Effects of Prednisolone and *Mycobacterium indicus pranii* Immunotherapy on Efficacy Outcomes.*

Outcome	Prednisolone (N=706)		Placebo (N=694)		Hazard Ratio (95% CI)	P Value	*Mycobacterium indicus pranii* (N=625)		Placebo (N=625)		Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*			*no. of patients (%)*	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*		
Primary composite outcome: death, cardiac tamponade, or constrictive pericarditis	168 (23.8)	14.3	170 (24.5)	14.8	0.95 (0.77–1.18)	0.66	156 (25.0)	13.97	152 (24.3)	13.4	1.03 (0.82–1.29)	0.81
Secondary outcomes												
Death from any cause	133 (18.8)	10.6	115 (16.6)	9.1	1.15 (0.90–1.48)	0.26	119 (19.0)	9.81	111 (17.8)	9.02	1.07 (0.83–1.39)	0.59
Cardiac tamponade	22 (3.1)	1.8	28 (4.0)	2.3	0.77 (0.44–1.35)	0.37	22 (3.5)	1.86	22 (3.5)	1.84	0.99 (0.55–1.79)	0.98
Constrictive pericarditis	31 (4.4)	2.58	54 (7.8)	4.56	0.56 (0.36–0.87)	0.009	36 (5.8)	3.15	37 (5.9)	3.15	0.97 (0.61–1.53)	0.89
Hospitalization	146 (20.7)	13.27	175 (25.2)	16.7	0.79 (0.63–0.99)	0.04	152 (24.3)	14.90	141 (22.6)	13.3	1.09 (0.87–1.37)	0.46

* Percentages were calculated with the use of the Kaplan–Meier method. Hazard ratios are for the active-treatment group as compared with the placebo group.

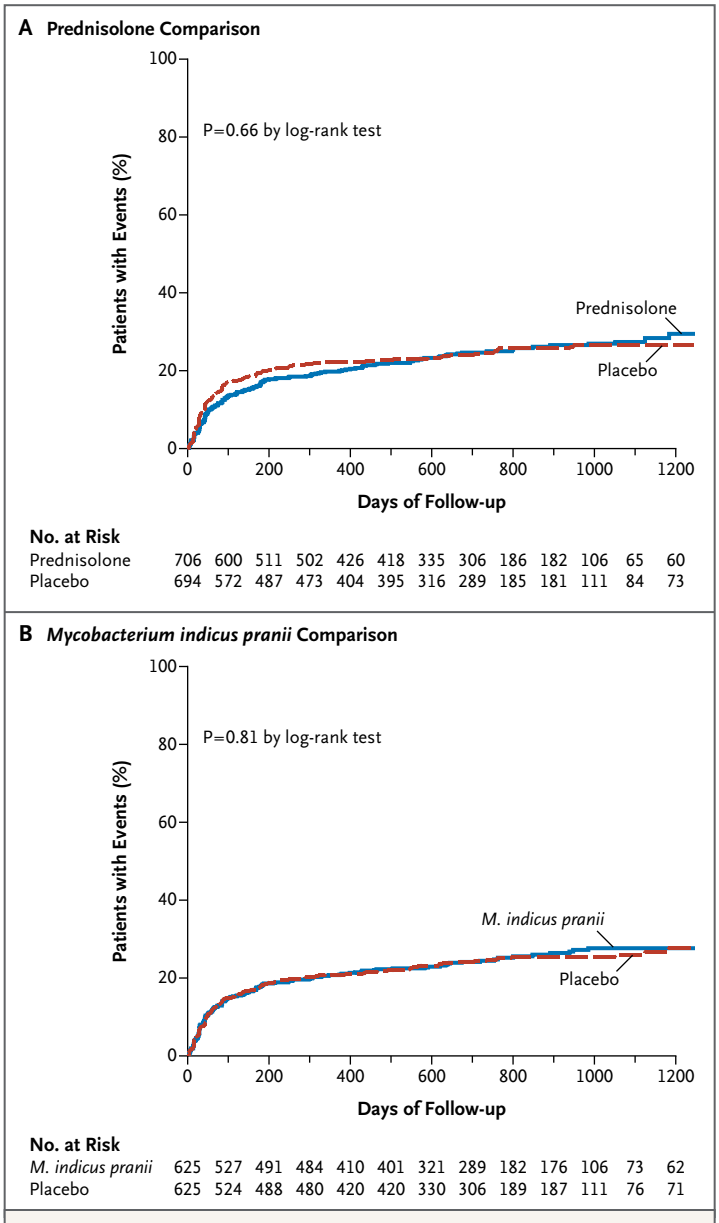


Figure 1. Kaplan–Meier Estimates of the Time to the Primary Efficacy Outcome, According to Treatment Group.

Data on the time to the primary efficacy outcome of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis are shown for patients who received prednisolone or placebo (Panel A) and *Mycobacterium indicus pranii* or placebo (Panel B).

of antiretroviral treatment in HIV-positive patients with tuberculosis.[27,28]

PREDNISOLONE COMPARISON

The rate of the primary composite outcome (death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis) was 14.3 events per 100 patient-years of follow-up in the prednisolone group and 14.8 per 100 patient-years in the placebo group (hazard ratio with prednisolone, 0.95; 95% confidence interval [CI], 0.77 to 1.18; P=0.66) (Table 2 and Fig. 1A, and Fig. S4 in the Supplementary Appendix). There was also no significant difference between the two groups in the rate of death or the rate of cardiac tamponade requiring pericardiocentesis, when considered individually (Fig. S5 and S6 in the Supplementary Appendix). The main causes of death were pericarditis (23.8%), disseminated tuberculosis (18.6%), HIV infection (7.3%), and other cardiovascular causes (5.7%) (Table S14 in the Supplementary Appendix). The prednisolone group had a lower rate of constrictive pericarditis and fewer hospitalizations than the placebo group (Table 2, and Table S15 and Fig. S7 and S8 in the Supplementary Appendix).

The incidence of opportunistic infection was 6.89 cases per 100 patient-years in the prednisolone group, as compared with 5.91 per 100 patient-years in the placebo group (hazard ratio, 1.16; 95% CI, 0.84 to 1.61; P=0.36) (Fig. S9 in the Supplementary Appendix). The proportion of patients with candidiasis was higher in the prednisolone group than in the placebo group (7.7% vs. 5.2%, P=0.05) (Table 3, and Table S16 in the Supplementary Appendix).

Prednisolone, as compared with placebo, was associated with an increased incidence of cancer (1.05 vs. 0.32 cases per 100 person-years; hazard ratio, 3.27; 95% CI, 1.07 to 10.03; P=0.03) (Table 3, and Fig. S10 in the Supplementary Appendix). This increase was due to a higher incidence of HIV-related cancers in the prednisolone group than in the placebo group (0.73 vs. 0.08 per 100 person-years; hazard ratio, 9.04; 95% CI, 1.14 to 71.33; P=0.04). (Table 3). A list of the causes of cancer is provided in Table S17 in the Supplementary Appendix.

There were two cases of the immune reconstitution inflammatory syndrome in the prednisolone group and one in the placebo group. There was a similar increase in CD4+ T-cell counts in the two groups (Table S18 in the Supplementary Appendix).

M. INDICUS PRANII COMPARISON

The rates of the primary composite outcome and its components, as well as the rates of hospital-

ization and opportunistic infection, did not differ significantly between the *M. indicus pranii* group and the placebo group (Tables 2 and 3 and Fig. 1B, and Fig. S11 through S16 in the Supplementary Appendix). However, *M. indicus pranii* was associated with an increased incidence of cancer, as compared with placebo (0.92 vs. 0.24 cases per 100 person-years; hazard ratio, 3.69; 95% CI, 1.03 to 13.24; P=0.03) (Table 3, and Fig. S17 in the Supplementary Appendix), which was due mainly to an increase in HIV-associated cancer. There was one case of the immune reconstitution inflammatory syndrome in each group. There was a similar increase in CD4+ T-cell counts in the two groups.

Significantly more patients in the *M. indicus pranii* group than in the placebo group had injection-site reactions (41.4% vs. 2.9%, P<0.001) (Table S19 and Fig. S18 in the Supplementary Appendix). Although the majority of these reaction were characterized by minor symptoms and signs of inflammation (i.e., induration, redness, and pain), there was a significantly greater proportion of patients with abscess formation in the *M. indicus pranii* group than in the placebo group (15.0% vs. 1.0%, P<0.001).

PREDNISOLONE AND *M. INDICUS PRANII* INTERACTION AND SUBGROUP ANALYSES

There was no significant interaction between the effects of *M. indicus pranii* and those of prednisolone on the primary efficacy and safety outcomes (P>0.30 for all interactions), except for injection-site reactions (P=0.004) (Fig. S4 and S11 in the Supplementary Appendix). However, 9 of the 13 cases of cancer in the prednisolone group occurred in patients who also received *M. indicus pranii* (Fig. 2). Although a clinical interaction of the two interventions on cancer cannot be ruled out, the number of cases is small.

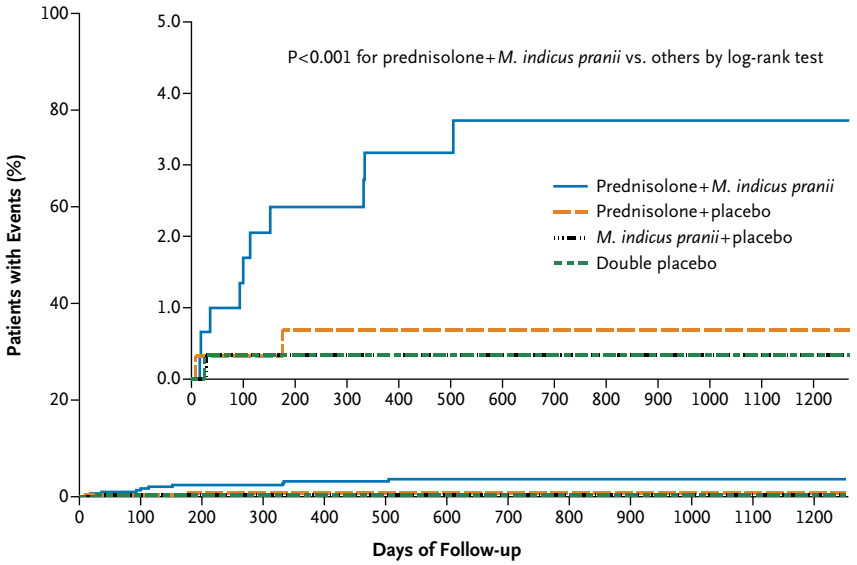
The effects of prednisolone and *M. indicus pranii* immunotherapy on the primary composite efficacy outcome were similar across prespecified subgroups (Fig. S19 and S20 in the Supplementary Appendix).

DISCUSSION

In this trial, adjunctive prednisolone therapy and *M. indicus pranii* immunotherapy were compared with placebo in patients with definite or probable tuberculous pericarditis. Neither therapy had

Table 3. Effects of Prednisolone and *Mycobacterium indicus pranii* immunotherapy on Safety Outcomes.

Outcome	Prednisolone (N=706)		*Mycobacterium indicus pranii* (N=625)			Placebo (N=694)			Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/100 person-yr*	*no. of patients (%)*	*no. of events/100 person-yr*	P Value	*no. of patients (%)*	*no. of events/100 person-yr*	P Value		
Opportunistic infection	78 (11.0)	6.89	75 (12.0)	6.86	0.36	61 (9.8)	5.45	0.20	1.25 (0.89–1.75)	0.20
Candida infection	54 (7.6)	4.68	47 (7.5)	4.17	0.05	37 (5.9)	3.20	0.26	1.28 (0.83–1.96)	0.26
Cancer	13 (1.8)	1.05	11 (1.8)	0.92	0.03	3 (0.5)	0.24	0.03	3.69 (1.03–13.24)	0.03
HIV-related cancer	9 (1.3)	0.73	7 (1.1)	0.58	0.04	2 (0.3)	0.16	0.09	3.53 (0.73–17.01)	0.09
Immune reconstitution disease	2 (0.3)	0.16	1 (0.2)	0.08	0.56	1 (0.2)	0.08	>0.99	1.00 (0.06–16.02)	>0.99



No. at Risk													
Prednisolone+*M. indicus pranii*	316	280	260	259	219	215	173	152	96	93	55	34	31
Prednisolone+placebo	315	284	266	262	227	222	181	171	104	103	62	37	35
M. indicus pranii+placebo	309	284	268	258	218	214	171	156	103	100	66	48	39
Double placebo	310	277	263	259	225	220	179	163	101	100	62	49	46

Figure 2. Time to Cancer Occurrence.

Shown are Kaplan–Meier estimates of the time to cancer occurrence for all four comparisons in the 2-by-2 factorial trial. The inset shows the same data on an enlarged y axis.

a significant effect on the primary composite outcome of death, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. With respect to the secondary outcomes, adjunctive prednisolone therapy reduced the incidence of constrictive pericarditis and the incidence of hospitalizations. However, both interventions increased the incidence of cancer among trial participants.

Previous trials of adjunctive glucocorticoid therapy in patients with tuberculous pericarditis had relatively small samples (28 to 240 patients) and included few HIV-infected patients, and there was poor reporting of adverse events.[10,29-34] Our trial included 1400 patients, a substantial number of whom (940 patients) had HIV infection. To our knowledge, *M. indicus pranii* immunotherapy has not been studied previously in this population.

For the prednisolone comparison, we used an initiation dose of 120 mg per day, which is known to have a therapeutic effect when administered in combination with rifampin, an enzyme inducer that increases the metabolism of glucocorticoids.[35] Adherence to prednisolone therapy was high. The significant reduction in pericardial constriction with prednisolone indicates that the doses used were sufficient to achieve a substantial antiinflammatory effect. The reduction in the incidence of constrictive pericarditis translated to fewer hospitalizations in the prednisolone-treated group. This finding is important because pericardiectomy, the definitive treatment for chronic pericardial constriction, is associated with high perioperative mortality and morbidity, and cardiac surgery is not widely available in Africa.[2,36]

The marked increase in HIV-related cancer with prednisolone therapy is consistent with the results of two previous studies of HIV-associated tuberculosis, in which cases of Kaposi's sarcoma occurred only in the prednisolone-treated groups.[11,12] However, the association of *M. indicus pranii* immunotherapy with cancer that we observed in our study has not been reported previously. It is possible that adjunctive glucocorticoids and *M. indicus pranii* act synergistically to increase the risk of cancer in immunosup-

pressed patients. The available data on the interaction between adjunctive glucocorticoid therapy and *M. indicus pranii* immunotherapy are sparse.[23]

Our study has a few limitations. First, a definite diagnosis of tuberculosis either in the pericardium or elsewhere in the body was made in only one quarter of the patients. Thus, one potential interpretation of the trial result is that the interventions were not effective because relatively few of the trial participants actually had tuberculous pericarditis. However, the results were consistent between patients with definite tuberculosis and those with probable tuberculosis. Furthermore, the diagnosis of extrapulmonary tuberculosis is challenging, and only a minority of cases of extrapulmonary tuberculosis are treated on the basis of a definite diagnosis.[37] Second, a small proportion of patients (less than 2%) had a diagnosis other than tuberculosis. However, although the estimation of the sample size needed for this study was based on the clinical case definition of tuberculous pericarditis,[4] we expected that a small proportion of cases (up to 10%) would have an alternative cause of pericarditis.[23] Third, the trial was powered for a rate of nonadherence of 10% in the active-treatment groups. Although this rate was almost achieved in the prednisolone group (nonadherence rate of 11%), the nonadherence rate was higher in the *M. indicus pranii* group (21%), owing mainly to injection-site side effects. This relatively high nonadherence rate may have diminished the power of the study with respect to the analysis of the primary outcome in the *M. indicus pranii* group. Finally, because prednisolone is immunosuppressive and *M. indicus pranii* is immunostimulatory, there may be an interaction between them that could result in each one either reducing or increasing the effects of the other one.[23]

In conclusion, adjunctive therapy with prednisolone for 6 weeks and with *M. indicus pranii* for 3 months did not have a significant effect on the combined outcome of death from all causes, cardiac tamponade requiring pericardiocentesis, or constrictive pericarditis. Both therapies were also associated with an increased risk of HIV-associated cancer. However, the use of adjunctive glucocorticoids reduced the incidences of pericardial constriction and hospitalization. The beneficial effects of prednisolone with respect to pericardial constriction and hospitalization were similar in HIV-positive and HIV-negative patients.

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APPENDIX

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