Corticosteroid Effects on Sputum Culture in Pulmonary Tuberculosis: A Meta-Regression Analysis

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Background. There is increasing interest in the potential role of adjunctive anti-inflammatory therapy to accelerate tuberculosis (TB) treatment. Sputum culture conversion is an important biomarker predictor of durable TB cure.

Methods. This study used meta-regression analysis to examine the relationship between corticosteroid dose and sputum culture conversion, using published data from controlled clinical trials including 1806 corticosteroid-treated TB patients.

Results. Linear models with 2 or 3 variables, including corticosteroid dose and the proportion of culture positive control subjects, predicted therapeutic benefit of corticosteroids at 1 and 2 months. The 3-variable model predicted that 134 mg of prednisolone per day, given together with standard 4-drug TB chemotherapy, would reduce the proportion of positive culture at 2 months from 15% to 2%. The estimate accounts for a 50% reduction in steroid exposure due to rifampin. A proportion of 2% of subjects with positive cultures at 2 months has been proposed as a target for new 4-month TB regimens.

Conclusions. These positive findings must be tempered by recognition that the metabolic and cardiovascular risks of corticosteroids administered at this dose for this duration are unlikely to be acceptable when examined from a patient-level benefit-risk perspective. In future research studies to shorten TB treatment, biologic anti-inflammatory therapies with similar therapeutic effects but superior safety profiles should be considered.

Keywords. corticosteroids; sputum culture conversion; tuberculosis.

The clinical and radiographic manifestations of pulmonary tuberculosis are often slow to resolve despite fully effective antimicrobial chemotherapy. In the 1960s, the recognition that lung damage in tuberculosis (TB) is mainly due to a prolonged host inflammatory response led to a series of controlled clinical trials of adjunctive corticosteroids administered during the early phase of TB chemotherapy. These study results (eloquently reviewed by Dooley et al in 1997 [1]) indicated that, for the most part, steroids hastened resolution of constitutional and radiographic findings, although steroid treatment did not affect long-term outcomes. A recent formal meta-analysis by Critchley et al [2] concurred, finding a trend toward a survival advantage favoring steroids in pulmonary TB that fell short of statistical significance.

The microbiologic response to treatment in pulmonary TB is similarly delayed. It has been proposed that this response may be accelerated by adjunctive anti-inflammatory treatment, which could potentially facilitate drug penetration into lung lesions and thereby increase effectiveness [3]. The concentric rings of tightly apposed epithelioid cells that are characteristic of human TB granulomas exclude oxygen and nutrients as well as TB drugs [4]. Mycobacterial survival under these harsh circumstances is facilitated by a dormancy response that limits bacterial cell wall synthesis, cell division, and dependence on aerobic respiration, and favors

drug tolerance [5, 6]. Reactivation of experimental latent TB infection is preceded by increasing oxygen levels in previously hypoxic lesions [7]. The resulting changes in bacillary metabolism may restore the bactericidal activity of administered drugs, adding a second level of benefit beyond that of improved drug penetration.

Four cellular mechanisms have been described through which corticosteroids exert their diverse immunologic effects [8]. Each is dependent on concentration and dose. Steroid inhibition of proinflammatory cytokines is thought to occur mainly via a binding to the cytosolic glucocorticoid receptor, which then interferes with transcription factors such as nuclear factor--κB. In whole blood cultures of healthy volunteers, methylprednisolone concentrations of 0.1, 1, and 50 μg/mL decrease *Mycobacterium tuberculosis*-induced tumor necrosis factor (TNF) production by 40%, 84%, and 98%, respectively [9]. To place these effects in context, peak concentrations of methylprednisolone in plasma of healthy volunteers reach only 0.2 μg/mL 2 h after a 20 mg oral dose [10]. In a pilot study in TB patients on standard 4-drug therapy reported in 2005, orally administered prednisolone produced dose-dependent inhibition of *M tuberculosis*-induced TNF production, with doses of 2.75 mg/kg per day required to reduce TNF production by more than half [11]. No prior or subsequent TB trials have tested corticosteroids at this high a dose, nor have any retrospective meta-analyses to date examined the clinical or microbiologic steroid dose-response relationship in TB.

Therefore, the present meta-regression analysis was conducted to determine the effect of adjunctive corticosteroids on *M tuberculosis* sputum culture conversion, in relation to the administered steroid dose. The analysis focused on culture status after 2 months of treatment, given the role of this marker as an indicator of sterilizing activity [12], and as a predictor of relapse risk [13, 14].

METHODS

Trials were initially identified through review of the papers cited by Dooley et al [1] and Critchley et al [2]. Additional studies were identified by examination of the citations of each of the primary publications discussed in these reviews and by a search of PubMed using the terms TB, clinical trial, corticosteroids, and the names of various specific steroid agents. The search was limited to English language articles. Trials were included in the present analysis if the patients studied were adults with pulmonary TB confirmed by sputum smear and culture, the trial design included corticosteroid and control arms to which patients were randomly assigned, and sputum culture results at 1, 2, or 3 months using solid culture medium were reported. Duplicate and preliminary reports were removed. A summary of the content curation process is shown in Figure 1.

Subject demographic characteristics were extracted from the reports. The TB regimens were scored from 0 to 2 according to inclusion of rifampin and pyrazinamide (RZ score). The steroid dose for each day of treatment was calculated according to the reported dosing schedule. Subjects whose corticosteroid doses had been reduced to zero were retained in the analysis as steroid-treated at 0 mg/day. Doses were adjusted according to steroid potency, with prednisolone and prednisone (PN) assigned a relative potency of 1.0 and methylprednisolone assigned a relative potency of 1.25. Adrenocorticotropic hormone (ACTH), the subject of a few studies, was assigned a relative potency of 0.2 mg/IU, because it seemed to have substantially reduced anti-inflammatory effect compared with prednisolone [1, 15]. A sensitivity analysis tested other ACTH potencies. For studies in which prednisolone was administered concurrently with rifampin, doses were adjusted by a factor of 0.5, reflecting reduced exposure and effect due to accelerated clearance [16–18]. The
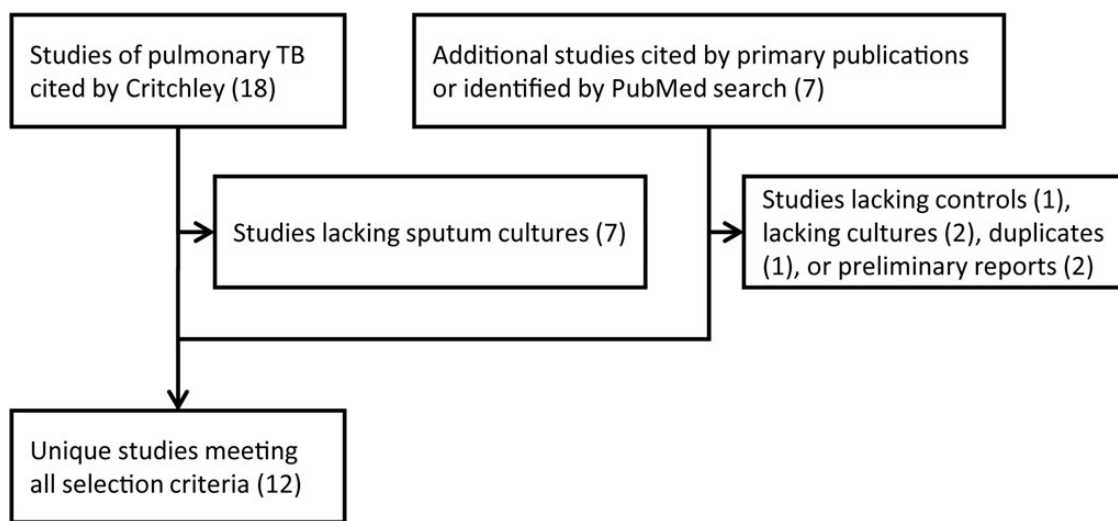

Figure 1. Curation of manuscripts for this analysis.

average adjusted steroid dose at each culture time point was calculated as the mean of the preceding 4 weeks. A sensitivity analysis was performed to examine the effect of other averaging intervals.

The proportions of subjects with positive cultures were logit-transformed. Logit transformation of proportions stretches values to plus or minus infinity as they approach 0% or 100%, thus avoiding predictions that exceed these limits. The dependent variable in regression analysis was defined as the difference between the logit-transformed proportions of culture-positive subjects in steroid and control arms (treatment effect), with negative values indicating a therapeutic benefit attributable to corticosteroids (ie, a smaller proportion positive). A correlation matrix examined the univariate relationship of candidate explanatory variables to the dependent variable and to each other. The matrix was prepared by the Pearson product method, weighted according to the inverse of within-study variance. Three studies included 2 steroid arms that shared a common control arm. Weights for these trials were reduced by half.

Multiple linear regression analysis was performed to identify multivariate models that best predicted steroid effect. Candidate variables included adjusted steroid dose, the proportion of culture-positive control subjects, RZ score, study year, and baseline subject characteristics. The analysis was performed with the same weighting as for univariate analysis, using the linear regression module of XLSTAT (www.xlstat.com). Models were limited to 2 or 3 explanatory variables due to the relatively small number of studies in the dataset. Models were selected according to the adjusted R^2 statistic. The prediction function of XLSTAT's regression module was used to predict steroid effect based on the designated model, a range of PN doses from 1 to 320 mg/day, the expected proportion of culture positives among control subjects based on results of standard therapy, and the RZ score of the expected regimen. Confidence intervals (5%–95%) were calculated. The analysis was performed separately for data at each month. Predicted proportions were back-transformed onto a linear scale for visualization.

RESULTS

The process of content curation for this analysis is shown in Figure 1. Seven of the 18 studies of pulmonary TB included in the Critchley et al [2] analysis were excluded due to lack of sputum culture data [19–25]. A review of the citations of the primary publications and search of PubMed identified 1 additional publication meeting eligibility criteria [26]. The corticosteroid regimens studied in these 12 publications and the baseline characteristics of study participants are described in Table 1. The studies are very diverse, having been conducted on 4 continents over 5 decades. Only 1 study, that of Mayanja-Kizza et al [11], included human immunodeficiency virus (HIV)-1-infected TB patients. The objective of that trial was to determine whether, by reducing inflammatory cytokines, corticosteroids could reduce HIV-1 expression and thereby delay acquired immune deficiency syndrome progression in TB patients with early stage HIV disease. The mean CD4 T-cell count in the trial was 357 cells/μL. Most patients in the trial had cavitary disease typical of HIV-uninfected TB cases (Table 1). All were sputum acid-fast bacilli smear and culture positive on entry.

Figure 2 summarizes the corticosteroid treatments in the trials, according to numbers of patients, adjusted steroid dose, and study day. Dosing was highest initially, and it was often reduced to an intermediate level after 1–2 weeks. Nearly 400 subjects started at an equivalent dose of >60 mg of prednisolone per day, but none received this dose for more than 5 weeks. Doses often were tapered to zero during the final 2 weeks.

Several studies described rebound phenomenon the month after steroid discontinuation. These phenomena included loss of apparent steroid benefit with regard to erythrocyte sedimentation rate [15, 27], chest radiography [15, 27–29], and sputum culture [11, 29]. These observations suggest that the inflammatory stimulus in pulmonary TB resolves slowly and that the anti-inflammatory effects of oral corticosteroids are relatively short-lived. Based on this finding, the initial analysis of the relationship between steroid dose and sputum culture positivity was conducted using the mean steroid dose during the 4 weeks preceding the culture time point. A sensitivity analysis subsequently examined the effect of other averaging intervals on the regression model.

The correlation matrix of candidate predictors of corticosteroid effect at month 2 is shown in Table 2. This univariate analysis revealed no significant predictors of steroid effect on sputum culture. However, several baseline and study characteristics were closely interrelated, including study year, subject age, the proportion of white subjects, the inclusion of rifampin and/or pyrazinamide in the TB regimen, and the proportion of control subjects culture positive at 2 months. These likely all reflect a single underlying factor: the initiation of studies of rifampin and pyrazinamide in Africa and India starting in the 1970s. The relationship between RZ score and the proportion of subjects culture positive at 2 months in this dataset is likely a biological one; the other relationships likely reflect differences in patient populations as trials shifted from the United States and Europe to Africa and Asia.

Multiple regression analysis was performed to identify linear models with 2 or 3 explanatory variables that could predict corticosteroid effects at month 2. The resulting models are described in Table 3. There was agreement among all the measures of model accuracy as to the selection process. Steroid dose and the proportion of control subjects culture positive at month 2 comprise the most accurate 2-variable model. In the best 3-variable model, these are joined by the RZ score. The adjusted R^2 of this model is 0.71, indicating that these variables

Table 1. Studies and Regimens Included in This Analysis*

Author	Year	Baseline Subject Characteristics					R, Z	Steroid-Treated Subjects (N)	TB Regimen	Steroid Regimen
		Age (yrs)	Male (%)	White (%)	Cavitary Disease (%)	Far Advanced Disease (%)				
Weinstein and Koler [35]	1959	43.9	53%	83%	75%	65%	0	51	HP	PN 20 mg x10d, 15 mg x10d, 10 mg x40d, 5 mg x4d, 2.5 mg x4d
Horne [27]	1960	32.0	61%	–	66%	71%	0	87	HPS	PN 20 mg daily plus ACTH 30U for 2d every 2 weeks, both for 3 months
Bell et al [36]	1960	–	–	0%	100%	–	0	44	HPS	PN 20 mg days 8–63, tapered to zero over subsequent 14 days
Angel et al [37]	1961	36.7	61%	43%	77%	79%	0	41	HPS	ACTH 60U x4d, 50U x4d, 40U x21d, 30U x42d
British TB Association [15]	1961	34.2	64%	–	97%	51%	0	95	HPS	ACTH 60U x4d, 40U x4d, 30U x10wks, 20U x7d, 10U x7d
		35.3	66%	–	99%	52%	0	107	HPS	PN 50 mg x4d, 37.5 mg x4d, 30 mg x10wks, followed by single daily doses of 20 mg, 15 mg, 10 mg, 5 mg, 0 mg, 0 mg, 0 mg, plus ACTH 20U daily for the last 7 days of PN treatment, followed by 7 days of ACTH 10U daily
Poppius and Jalas [26]	1961	39.0	60%	–	80%	76%	0	13	HPS	PN 15 mg x10 wk, 10 mg x1 wk, 5 mg x1 wk, plus ACTH 30U for 2d every 2wk
Marcus et al [38]	1963	30.5	51%	53%	73%	12%	0	100	HPS	PN 40 mg x5d, 37.5 mg x5d, 35 mg x5d, 32.5 mg x5d, 30 mg x5d, 27.5 mg x5d, 25 mg x5d, 22.5 mg x5d, 20 mg x29d, 17.5 mg x5d, 15 mg x5d, 12.5 mg x5d, 10 mg x5d, 7.5 mg x5d, 5 mg x5d, 2.5 mg x5d
McLean [28]	1963	42.6	59%	19%	93%	89%	0	12	HP	MP 48 mg x14d, 24 mg x4d, 12 mg x3d, 6 mg x4d, 3 mg x3d
Johnson et al [29]	1965	44.9	100%	73%	–	72%	0	52	HP	MP 16 mg x70d, 12 mg x4d, 8 mg x4d, 4 mg x4d
Halleck [39]	1965	40.3	63%	66%	71%	52%	0.5	426	SZ, HP	PN 20 mg x3d, 15 mg x4d, 10 mg x21d, 5 mg x4d, 2.5 mg x3d
		40.0	65%	70%	71%	51%	0.5	425	SZ, HP	PN 20 mg x3d, 15 mg x4d, 10 mg x49d, 5 mg x4d, 2.5 mg x3d
Tripathy et al [33]	1983	33.3	75%	0%	95%	25%	2	131	SHRZ	PN daily except Sunday: 60 mg x1 wk, 20 mg x5 wk, 10 mg x1 wk, 5 mg x1wk
		33.3	75%	0%	95%	25%	1	129	SHZ	PN daily except Sunday: 60 mg x1 wk, 20 mg x5 wk, 10 mg x1 wk, 5 mg x1wk
Mayanja-Kizza et al [11]	2005	31.0	65%	0%	82%	70%	2	93	HRZE	PN 2.75 mg/kg x28d, 60 mg x7d, 20 mg x7d, 10 mg x7d, 5 mg x7d

Abbreviations: ACTH, adrenocorticotropic hormone; E, ethambutol; H, isoniazid; MP, methylprednisolone; P, para-aminosalicylic acid; PN, prednisolone or prednisone; R, rifampin; S, streptomycin; TB, tuberculosis; Z, pyrazinamide.

*Regimens were scored 1 point each for inclusion of rifampin or pyrazinamide.
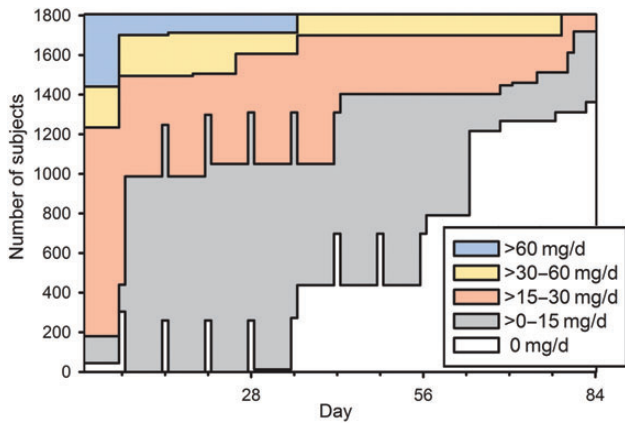
Figure 2. Number of corticosteroid treated subjects according to dose and treatment day. Doses are adjusted for potency (prednisolone = 1) and for coadministration of rifampin (x0.5), ie, rifampin is assumed absent.

examined the influence of the dose-averaging interval (which was initially set to 28 days). Shortening the interval had no effect on model accuracy, as adjusted R^2 values >0.7 were maintained at all intervals from 28 to 7 days. Lengthening the interval gradually reduced model accuracy, reaching an adjusted R^2 value of 0.55 at an interval of 56 days. The 28 day averaging interval was therefore kept unchanged. Likewise, changes in the potency of ACTH (assumed initially to be 0.2 mg of PN per IU) up to 0.5 or down to 0.05 had no effect on model accuracy, as the adjusted R^2 was maintained at 0.69. The ACTH potency factor was also kept without change. These findings indicate that the model's assumptions had little influence on the overall results.

The 3-variable model was then used to predict the effect on 2-month sputum culture positivity of prednisolone doses ranging from 1 to 320 mg/day, administered together with a modern rifampin and pyrazinamide-containing regimen. Steroid doses were increased by a factor of 2 to account for reduced exposure due to rifampin. Results are shown in Figure 3. The horizontal dotted line indicates the expected proportion culture positive in control subjects treated with standard 4-drug therapy. The solid curve indicates the predicted proportion of steroid-treated subjects with positive cultures; the dashed curves indicate 5%–95% confidence intervals. A dose of 43 mg/day is predicted to be sufficient to exclude zero steroid effect. A dose of 134 mg/day is predicted to reduce the culture-positive rate at 2 months from 0.15 to 0.02, the proposed target for new 4-month duration TB regimens [14].

Models were also developed to predict steroid effects on culture status at 1 month. The 3-variable model was similar

account for ~70% of the variation observed among studies. The statistical significance (P) of the dose and control-positive proportion terms are both <0.01, whereas that of the RZ term is at the threshold of significance (.058). The signs of all 3 parameters are negative, indicating that higher steroid doses, higher proportions of culture-positive control subjects, and full inclusion of rifampin and pyrazinamide all increase the therapeutic effect of corticosteroids.

Two sensitivity analyses were performed to assess the potential impact of assumptions on the model. The first analysis

Table 2. Correlation Matrix of Candidate Predictors of Corticosteroid Effect at Month 2*

Variables	Control positive	Dose	Year	Age	Male	White	Cavitary	Far Advanced	RZ
Steroid effect	−0.476	−0.064	0.026	−0.344	0.313	−0.166	−0.083	−0.21	−0.056
	0.195	0.870	0.946	0.364	0.413	0.669	0.831	0.588	0.885
Control- positive proportion		−0.471	−0.599	**0.951**	−0.215	**0.722**	−0.482	0.515	−0.649
		0.201	0.088	**< 0.0001**	0.579	**0.028**	0.189	0.156	0.058
Dose			0.179	−0.610	−0.294	−0.216	0.182	−0.504	0.189
			0.645	0.081	0.442	0.577	0.639	0.167	0.627
Year				−0.644	0.522	**−0.837**	0.625	−0.018	**0.949**
				0.061	0.150	**0.005**	0.072	0.963	**<0.0001**
Age					−0.128	**0.770**	−0.543	0.501	−0.648
					0.743	**0.015**	0.131	0.170	0.059
Male						−0.53	0.535	−0.081	0.509
						0.142	0.138	0.835	0.162
White							**−0.896**	0.166	**−0.872**
							0.001	0.670	**0.002**
Cavitary								−0.213	**0.738**
								0.582	**0.023**
Far advanced									−0.065
									0.867

Abbreviations: R, rifampin; Z, pyrazinamide.

*The upper value in each cell is the correlation coefficient (R); the lower value, P. Statistically significant relationships (P < .05) are indicated in bold.

Table 3. Two and Three Variable Linear Regression Models of Steroid Effects on Sputum Culture Positivity*

A. Model Accuracy

No. variables	MSE	R²	Adj R²	Mallow Cp	Akaike AIC	Schwarz SBC	Amemiya PC
2	3.503	0.561	0.557	927	544	556	0.443
3	2.301	0.712	0.710	607	364	380	0.292

B. Model Parameters

Source	Value	SE	t	Pr > |t|	Lower bound (90%)	Upper bound (90%)
2 variable model						
Intercept	0.154	0.585	0.263	0.798	-0.906	1.214
Ctrl pos prop	-0.344	0.126	-2.723	0.021	-0.573	-0.115
Dose	-0.038	0.014	-2.738	0.021	-0.063	-0.013
3 variable model						
Intercept	0.212	0.500	0.425	0.681	-0.704	1.128
Ctrl pos prop	-0.552	0.144	-3.832	0.004	-0.816	-0.288
Dose	-0.041	0.012	-3.465	0.007	-0.063	-0.020
RZ score	-0.437	0.201	-2.176	0.058	-0.805	-0.069

*Abbreviations: AIC, Akaike's Information Criterion; Ctrl, control; MSE, mean square error; PC, Prediction Criterion; pos, positive; prop, proportion; R, R statistic; SE, standard error; t, t statistic; RZ, rifampin/pyrazinamide. The dependent variable is the difference between steroid-treated patients and controls in logit-transformed proportions of culture- positive subjects after 2 months of TB treatment. The explanatory variables are the logit-transformed proportion of culture-positive control subjects, corticosteroid dose, and RZ status of theTB regimen. The inclusion of RZ status as a 3rd variable improved the accuracy of the model according to all criteria examined.

to that at 2 months, with an adjusted R^2 of 0.63 and a significance value of the steroid term at $P = .002$. The most accurate 2-variable model at 1 month included steroid dose and RZ

Figure 3. Model predictions for corticosteroid effects on sputum culture positivity at 2 months. The horizontal dotted line indicates the expected proportion of culture-positive control subjects treated with standard 4-drug therapy. Prednisolone (PN) doses, shown on the horizontal axis, assume concurrent rifampin. The solid black line indicates the predicted proportion of steroid-treated subjects whose cultures are positive. The dashed curves indicate 5%–95% confidence intervals. A dose of 43 mg is predicted to be sufficient to exclude zero effect. A dose of 134 mg/day is predicted to reduce the culture-positive rate at 2 months from 0.15 to 0.02, the proposed target for new 4-month duration TB regimens [14].

status; its adjusted R^2 was 0.55. Both models produced curves that were similar to those at 2 months. Sputum culture status at 1 month has no known prognostic significance, however.

Corticosteroid dose was not identified as a significant predictor of effect at 3 months. This result appears to reflect the relatively small numbers of steroid-treated subjects and the low steroid doses to which they were exposed.
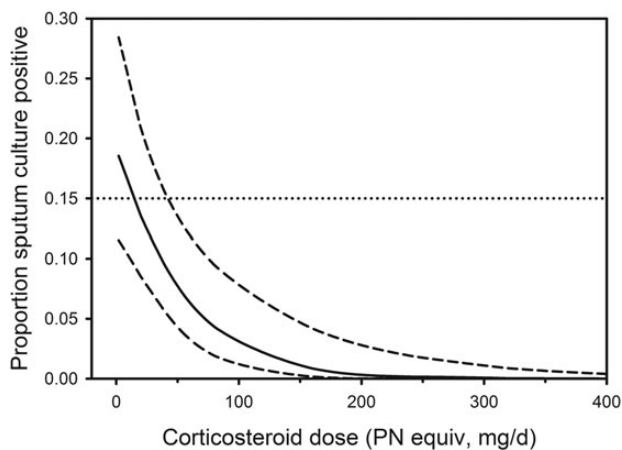
DISCUSSION

Sputum culture conversion is an important biomarker predictor of TB cure. Modern short-course TB regimens containing rifampin and pyrazinamide reduce the proportion of patients whose sputum cultures remain positive after 2 months of treatment [12]. Two meta-regression analyses found sputum culture positivity at 2 or 3 months to be directly associated with relapse risk when regimens of equal duration were compared [13, 30]. A third study found that the relapse risk of a new TB regimen could be predicted by its month 2 culture-positive rate and its duration [14]. That study proposed a month 2 positivity rate of 1%–2% as a target for new 4-month TB regimens, because this would result in <10% chance of a relapse rate >10% in a future phase 3 trial. Two recent phase 3 trials of novel 4-month fluoroquinolone-containing regimens failed to meet this criterion; they also failed to meet their primary endpoints of relapse risk [31, 32].

Some degree of caution is warranted if a model developed from studies of TB chemotherapy is now to be applied to

adjunctive immunotherapy. However, in the 2 studies included in the present analysis in which relapses were reported, steroid effects on relapse were consistent with those on 2-month culture status. In the study by Johnson et al [29], conducted in patients of the Veterans Administration Hospitals in Wisconsin, corticosteroids reduced the 2-month positive rate from 60% to 44% and reduced the rate of culture-confirmed relapses from 14% to 2%. Corticosteroids had no effect on either culture conversion or relapse in the study reported by Tripathy et al [33]. Both observations support the generalizability of the 2% target to treatment-shortening trials of TB adjunctive immunotherapy.

The key finding of the present study is that, although corticosteroids indeed accelerate sputum culture conversion, doses of at least 134 mg of prednisolone per day for at least 2 months will be required to have an effect consistent with that thought to be required for new 4-month TB regimens. Clinical experience with corticosteroids at this high a dose in TB is limited to a single trial reported by Mayanja-Kizza et al [11] in which 187 patients were randomly assigned to receive 2.75 mg/kg prednisolone per day or placebo for the first 4 weeks of standard rifampin-containing treatment [11]. The steroid dose was tapered to zero over the subsequent 4 weeks. This treatment schedule produced a striking reduction in the proportion of culture-positive patients at 1 month (38% vs 63%; $P < .001$), but it had no effect at 2 months (14% vs 15%), nor did it significantly affect relapse risk (8.6% vs 11.7%). The lack of effect on later endpoints may be attributable to the short duration of steroid treatment (1 month). The study is particularly informative for its reporting of adverse events, which, unlike earlier trials of adjunctive steroids, were monitored according to International Conference on Harmonization standards and graded according to severity using standardized toxicity tables. Hyperglycemia, hypertension, and fluid retention all occurred significantly more frequently in the 93 steroid-treated subjects (P ranging from .039 to <.001). Corticosteroid risks are well understood to include these types of adverse events. Twelve excess adverse events of moderate, severe, or life-threatening severity occurred in these categories in steroid-treated subjects. The 1 life-threatening event—hypertensive encephalopathy—indeed proved fatal.

It is unlikely that the schedules of corticosteroid treatment considered in the present analysis—with similar daily doses given for longer periods—will demonstrate a superior safety profile to that reported by Mayanja-Kizza et al [11]. This outcome presents a challenge to researchers hoping to use adjunctive anti-inflammatory drugs to develop shorter TB regimens. The main benefit of these new regimens—reduced clinical workload—will accrue to TB control programs and to society as a whole, whereas their risks will be borne entirely by individual patients. The regulatory approval process for new drugs presently focuses exclusively on the benefit-risk balance for individual patients. This balance is unlikely to be favorable for high-dose adjunctive corticosteroids in TB. Corticosteroid treatment of other chronic inflammatory conditions has largely been abandoned in favor of specific biologic agents, due to similar benefit-risk considerations. Specific biologic therapies, such as TNF antagonists, may be reconsidered in TB as our understanding evolves regarding the role of chronic granulomatous inflammation as an impediment to TB cure [3, 34].

Limitations of this analysis must be acknowledged. The relative paucity of data from patients treated at high steroid doses for prolonged intervals limits the certainty of predictions. Human and microbial populations may change over time, potentially affecting the validity of predictions based on historical data. The data from which the model was developed came from patients with first episodes of sputum smear-positive pulmonary TB in patients with fully drug-susceptible disease. It is well recognized that corticosteroids have deleterious effects in TB when antimicrobial therapy is inadequate due to drug resistance [33]. Newer culture methods using liquid medium show greater sensitivity for detection of *M tuberculosis* in sputum, particularly in patients who have started treatment. Additional data using liquid culture will be required to model these responses. Finally, these findings do not preclude beneficial effects on other outcomes at lower corticosteroid doses.

In summary, this study found that adjunctive corticosteroids accelerate sputum culture conversion in pulmonary TB, but that the doses required are unlikely to support a favorable benefit-risk balance for individual TB patients. Future studies should examine the medical risks, programmatic costs, and societal benefits of adjunctive biologic antigranuloma therapies in TB.

Note

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