ORIGINAL ARTICLE

Adjunctive Dexamethasone in HIV-Associated Cryptococcal Meningitis

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ABSTRACT

BACKGROUND

Cryptococcal meningitis associated with human immunodeficiency virus (HIV) infection causes more than 600,000 deaths each year worldwide. Treatment has changed little in 20 years, and there are no imminent new anticryptococcal agents. The use of adjuvant glucocorticoids reduces mortality among patients with other forms of meningitis in some populations, but their use is untested in patients with cryptococcal meningitis.

METHODS

In this double-blind, randomized, placebo-controlled trial, we recruited adult patients with HIV-associated cryptococcal meningitis in Vietnam, Thailand, Indonesia, Laos, Uganda, and Malawi. All the patients received either dexamethasone or placebo for 6 weeks, along with combination antifungal therapy with amphotericin B and fluconazole.

RESULTS

The trial was stopped for safety reasons after the enrollment of 451 patients. Mortality was 47% in the dexamethasone group and 41% in the placebo group by 10 weeks (hazard ratio in the dexamethasone group, 1.11; 95% confidence interval [CI], 0.84 to 1.47; P=0.45) and 57% and 49%, respectively, by 6 months (hazard ratio, 1.18; 95% CI, 0.91 to 1.53; P=0.20). The percentage of patients with disability at 10 weeks was higher in the dexamethasone group than in the placebo group, with 13% versus 25% having a prespecified good outcome (odds ratio, 0.42; 95% CI, 0.25 to 0.69; P<0.001). Clinical adverse events were more common in the dexamethasone group than in the placebo group (667 vs. 494 events, P=0.01), with more patients in the dexamethasone group having grade 3 or 4 infection (48 vs. 25 patients, P=0.003), renal events (22 vs. 7, P=0.004), and cardiac events (8 vs. 0, P=0.004). Fungal clearance in cerebrospinal fluid was slower in the dexamethasone group. Results were consistent across Asian and African sites.

CONCLUSIONS

Dexamethasone did not reduce mortality among patients with HIV-associated cryptococcal meningitis and was associated with more adverse events and disability than was placebo. (Funded by the United Kingdom Department for International Development and others through the Joint Global Health Trials program; Current Controlled Trials number, ISRCTN59144167.)

CRYPTOCOCCAL MENINGITIS ASSOCIATED with human immunodeficiency virus (HIV) infection is estimated to cause more than 600,000 deaths each year, the vast majority in sub-Saharan Africa and in South and Southeast Asia.[1] Among patients receiving combination antifungal therapy with amphotericin B and either flucytosine or fluconazole, mortality remains more than 30% at 10 weeks, and survivors often have substantial disability.[2,3] There is a pressing need to improve outcomes. However, no new anticryptococcal agents are currently close to approval for clinical use, so innovative strategies are needed.

Adjunctive treatments, such as glucocorticoids, have shown some benefit in central nervous system (CNS) infections in certain settings. For example, dexamethasone reduced mortality from acute bacterial meningitis among adults in Europe and those with microbiologically confirmed disease in Vietnam.[4,5] Dexamethasone reduced mortality in a mixed cohort of HIV-infected and uninfected adults with tuberculous meningitis in Vietnam, but the study was not powered to show an effect in the subgroup of patients with HIV infection.[6] Cryptococcal meningitis shares pathophysiological features with tuberculous meningitis, including vasculitis, cerebral edema, and raised intracranial pressure,[7] all of which may be modified by glucocorticoids.

Glucocorticoids are inexpensive and readily available in regions in which the burden of cryptococcal meningitis is highest; low rates of adverse events have been observed among patients with CNS infections.[5,6,8] Retrospective data suggest that glucocorticoids may reduce the risk of blindness in HIV-uninfected patients with cryptococcal meningitis,[9] and studies in animals suggest that the use of such drugs does not reduce the sterilizing power of amphotericin or fluconazole and improves survival even in the absence of antifungal therapy.[10,11] Glucocorticoids are widely used in clinical practice for cryptococcal meningitis in high-burden settings, particularly in Asia, and international guidelines recommend their use in some circumstances.[12] However, data from controlled trials are lacking. We conducted a double-blind, randomized, placebo-controlled trial to determine whether adjunctive treatment with dexamethasone would improve survival among adults with HIV-associated cryptococcal meningitis.[13]

METHODS

STUDY DESIGN AND PARTICIPANTS

The full details regarding the enrollment procedures have been described previously[13] and are provided in the study protocol (available with the full text of this article at NEJM.org), with study-site information provided in Section 1 in the Supplementary Appendix, also available at NEJM.org. In brief, we recruited adult patients (≥18 years of age) in 13 hospitals in Indonesia, Laos, Thailand, Vietnam, Malawi, and Uganda. Eligible patients had HIV infection, a clinical syndrome consistent with cryptococcal meningitis, and microbiologic confirmation of disease, as indicated by one or more of the following test results: positive India ink staining of cerebrospinal fluid (CSF), culture of cryptococcus species from CSF or blood, or cryptococcal antigen detected in CSF on cryptococcal antigen lateral flow assay (IMMY). We excluded patients who were pregnant, had renal failure, had gastrointestinal bleeding, had received more than 7 days of anticryptococcal antifungal therapy, were already taking glucocorticoids, or required glucocorticoid therapy for coexisting conditions. Informed written consent was obtained from all patients or their representatives.

RANDOMIZATION, TREATMENT CONCEALMENT, AND BLINDING

Randomization in a 1:1 ratio was performed with variable block sizes of 4 and 6, with stratification according to site. The computer-generated randomization list was accessible only to the central study pharmacists in Vietnam, who used it to prepare blinded, sealed treatment packs containing dexamethasone or identical placebo, which were distributed to the sites. We used site-specific enrollment logs to assign patients to the next available sequential patient number and corresponding treatment pack.

LABORATORY INVESTIGATIONS

Lumbar punctures were performed on study days 1, 3, 7, and 14 and more frequently if clinically indicated; quantitative fungal counts[14] and CSF opening pressures were determined at every sampling. The laboratory investigation schedule is provided in Section 2 in the Supplementary Appendix.

TREATMENT

Patients received either dexamethasone or identical placebo for 6 weeks as follows: intravenous administration of 0.3 mg per kilogram of body weight per day during the first week and 0.2 mg per kilogram per day during the second week, followed by oral administration of 0.1 mg per kilogram per day during the third week, 3 mg per day during the fourth week, 2 mg per day during the fifth week, and 1 mg per day during the sixth week. Patients received antifungal therapy according to international guidelines for regions in which flucytosine is unavailable.[12] Induction therapy consisted of amphotericin B deoxycholate (Bharat Pharmaceuticals) at a dose of 1 mg per kilogram per day and fluconazole (Ranbaxy) at a dose of 800 mg per day for 2 weeks, followed by consolidation therapy (800 mg of fluconazole per day for 8 weeks) and then maintenance therapy (200 mg of fluconazole per day). The protocol initially recommended starting antiretroviral therapy 2 to 4 weeks after the initiation of antifungal treatment; this recommendation was updated to 5 weeks after the initiation of antifungal treatment after the publication of the results of the Cryptococcal Optimal ART (Antiretroviral Therapy) Timing (COAT) trial.[15] All the patients received daily pneumocystis prophylaxis with trimethoprim–sulfamethoxazole.

ASSESSMENT OF OUTCOMES

The primary outcome was survival until 10 weeks after randomization. Secondary outcomes were survival until 6 months; the level of disability at 10 weeks and 6 months, with the outcome classified as good, intermediate, poor, or death[6] (see Section 3 in the Supplementary Appendix); visual acuity at 10 weeks; the rate of decrease in cryptococcal counts in CSF; and the change in opening pressure during the first 2 weeks. We compared the incidence of new neurologic events, new acquired immunodeficiency syndrome (AIDS)–defining illness, the immune reconstitution inflammatory syndrome (IRIS), and any other grade 3 or 4 adverse event in the two study groups. Adverse events were assessed according to definitions in the protocol[13] and categorized according to the *Medical Dictionary for Regulatory Activities* system organ class.[16]

ETHICS AND STUDY OVERSIGHT

The study protocol was approved by the institutional review board and regulatory authority at each site and by the Oxford University tropical research ethics committee. An independent data and safety monitoring committee oversaw trial safety and analyzed unblinded data after every 50 deaths, according to its charter (Section 5 in the Supplementary Appendix). A trial steering committee consisting of three independent members, two study investigators, and an observer provided advice on the conduct of the trial. The funding bodies and drug manufacturers played no part in the study design, implementation, analysis, or manuscript preparation. All the authors made the decision to submit the manuscript for publication and vouch for the accuracy and completeness of the data and analyses presented.

STATISTICAL ANALYSIS

Assuming an overall 10-week mortality of at least 30%, we determined that we would need to enroll at least 880 patients for the trial to have 80% power to detect a hazard ratio of 0.70 in favor of dexamethasone for the primary outcome, at a two-sided 5% significance level.[13] All analyses were specified before unblinding, as detailed in the protocol[13] and the statistical analysis plan (Section 4 in the Supplementary Appendix). In brief, we used a Cox proportional-hazards model with stratification according to continent to analyze survival in the intention-to-treat population and prespecified subgroups. Since testing on the basis of weighted Schoenfeld residuals provided clear evidence of nonproportional hazards, we also formally compared 10-week and 6-month survival probabilities between the two groups on the basis of Kaplan–Meier estimation and Greenwood's formula to approximate variance. We used a logistic-regression model with the study group as the main covariate and with adjustment for continent to perform a between-group comparison of the probability of a good outcome with respect to disability status. Log_{10}-transformed longitudinal quantitative measurements of fungal counts were modeled by means of a linear mixed-effects model, which treated undetectable measurements as left-censored. Statistical analyses were performed with the use of R software, version 3.1.2.[17]

RESULTS

TRIAL SUSPENSION

Recruitment began in February 2013. In August 2014, the data and safety monitoring committee recommended that the trial be stopped, a decision that was based on clinical judgment that dexamethasone was causing harm across key outcomes, including fungal clearance, adverse events, and disability outcomes, rather than on the basis of a prespecified stopping boundary having been crossed with respect to the primary outcome. We immediately suspended recruitment, and the trial was formally stopped in September 2014. All the patients completed 6 months of follow-up as planned.

At the time of the suspension of the trial, we had screened 823 patients and enrolled 451, with 224 patients assigned to the dexamethasone group and 227 assigned to the placebo group (Fig. 1). During screening, 42 patients (including 41 in Asia) had already received more than 24 hours of glucocorticoid therapy and thus were not enrolled. In the intention-to-treat analysis, we excluded 1 patient in the placebo group who did not receive the assigned intervention because of a drug-administration error. We excluded 24 patients from the per-protocol analysis (Fig. 1). All the patients who were enrolled in the study received directly observed therapy for at least the first 2 weeks of treatment and while they were hospitalized. At discharge, all the patients received counseling and written instructions on the importance of completing dexamethasone therapy as prescribed. Outpatient assessments with medication review were performed weekly until 4 weeks and then at the completion of week 6 and week 10, unless more frequent review was indicated clinically. More than 99% of the planned dexamethasone doses were taken, according to this review.

BASELINE CHARACTERISTICS

The characteristics of the patients at baseline were well balanced between the two study groups (Table 1). The Asian and African patients differed significantly with respect to some characteristics, including the prevalence of intravenous drug use (18% vs. 0%, P<0.001), cranial-nerve palsies (19% vs. 6%, P<0.001), visual
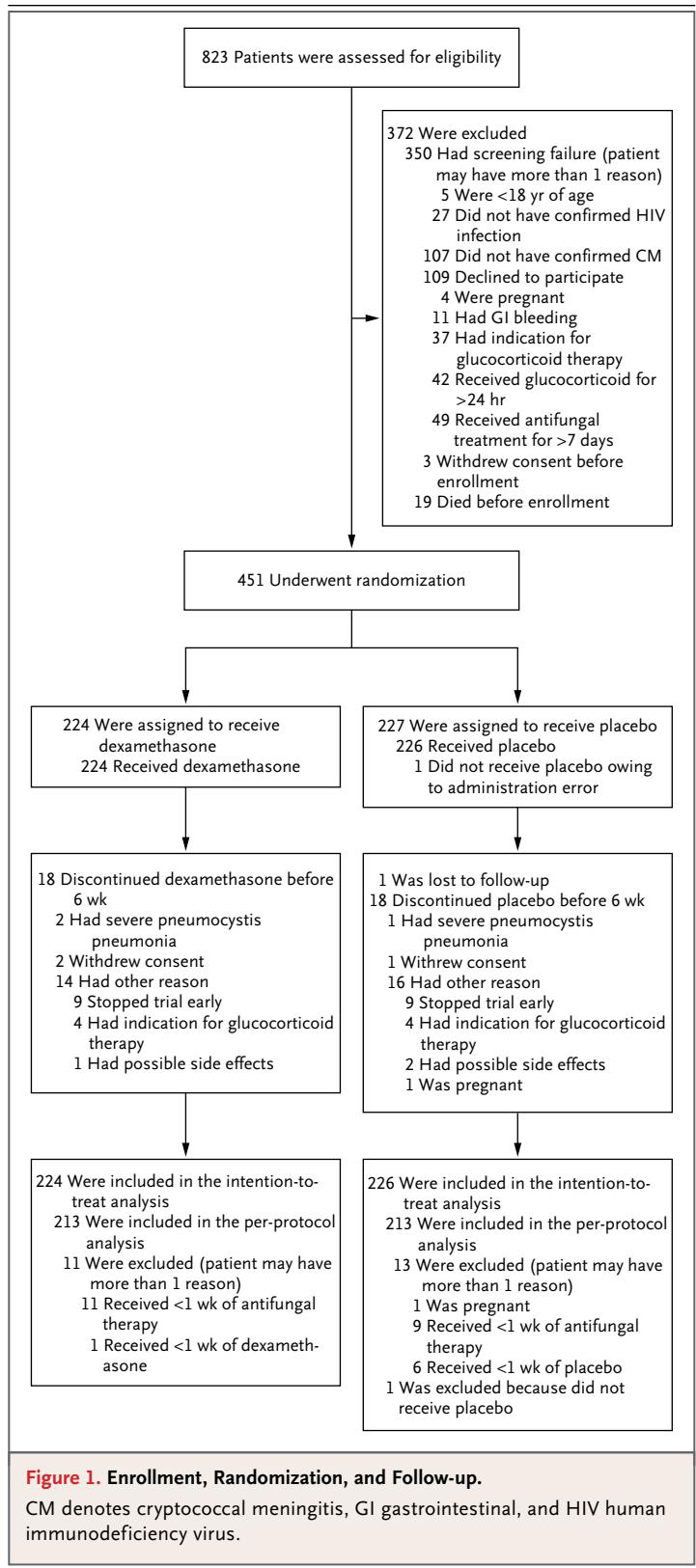

Figure 1. Enrollment, Randomization, and Follow-up.

CM denotes cryptococcal meningitis, GI gastrointestinal, and HIV human immunodeficiency virus.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Dexamethasone (N=224)	Placebo (N=226)	Residence in Africa (N=246)	Residence in Asia (N=204)	P Value for Comparison between Continents
Residence — no. (%)					
Africa	122 (54)	124 (55)	NA	NA	NA
Asia	102 (46)	102 (45)	NA	NA	NA
Male sex — no. (%)	147 (66)	132 (58)	144 (59)	135 (66)	0.10
Median age (IQR) — yr	35 (31–41)	35 (30–40)	35 (30–41)	35 (31–40)	0.81
History of intravenous drug use — no./total no. (%)	17/215 (8)	18/215 (8)	0	35/196 (18)	<0.001
Current antiretroviral-therapy status — no. (%)					<0.001
None	135 (60)	133 (59)	111 (45)	157 (77)	
≤3 mo duration	41 (18)	46 (20)	54 (22)	33 (16)	
>3 mo duration	48 (21)	47 (21)	81 (33)	14 (7)	
Median illness duration (IQR) — days	14 (7–21)	14 (7–28)	14 (7–30)	13 (7–21)	0.01
Symptoms — no./total no. (%)					
Headache	217/224 (97)	212/226 (94)	230/246 (93)	199/204 (98)	0.05
Fever	147/222 (66)	134/223 (60)	127/244 (52)	154/201 (77)	<0.001
Neck stiffness	106/222 (48)	103/219 (47)	90/244 (37)	119/197 (60)	<0.001
Seizures	35/223 (16)	43/225 (19)	33/245 (13)	45/203 (22)	0.02
Abnormal visual acuity	34/208 (16)	32/205 (16)	26/220 (12)	40/193 (21)	0.02
Papilledema	26/195 (13)	23/195 (12)	28/233 (12)	21/157 (13)	0.76
Score on Glasgow Coma Scale — no./total no. (%)†					0.21
≤10	5/223 (2)	9/226 (4)	10/246 (4)	4/203 (2)	
11–14	31/223 (14)	41/226 (18)	44/246 (18)	28/203 (14)	
15	187/223 (84)	176/226 (78)	192/246 (78)	171/203 (84)	
Cranial nerve palsy — no./total no. (%)					<0.001
None	199/221 (90)	185/215 (86)	222/237 (94)	162/199 (81)	
Cranial nerve VI	10/221 (5)	11/215 (5)	3/237 (1)	18/199 (9)	
Other cranial nerve	12/221 (5)	19/215 (9)	12/237 (5)	19/199 (10)	
Laboratory measures					
CSF opening pressure					
Median (IQR) — cm of CSF	22 (15–32)	24 (16–35)	21 (16–31)	25 (15–35)	0.28
>18 cm — no./total no. (%)	129/200 (64)	135/203 (67)	139/213 (65)	125/190 (66)	0.92
Median CSF white-cell count (IQR) — cells/mm³	20 (5–60)	19 (5–55)	15 (5–40)	30 (8–92)	<0.001
Median CSF glucose (IQR) — mmol/liter	2.27 (1.54–2.87)	2.34 (1.57–2.93)	2.43 (1.75–2.96)	2.11 (1.39–2.82)	0.01
Median blood glucose (IQR) — mmol/liter	5.70 (4.99–6.60)	5.60 (4.92–6.76)	5.50 (4.80–6.27)	6.05 (5.09–7.12)	<0.001
Median CSF:blood glucose ratio (IQR)	0.37 (0.24–0.48)	0.39 (0.27–0.50)	0.42 (0.27–0.52)	0.34 (0.24–0.44)	<0.001
Median CSF fungal count (IQR) — log₁₀ CFU/ml	4.25 (2.07–5.36)	4.37 (2.56–5.55)	3.83 (1.60–5.04)	4.80 (3.16–5.78)	<0.001
Median CD4+ count (IQR) — cells/mm³	18 (7–52)	20 (7–52)	26 (7–71)	16 (8–40)	0.04
Median creatinine (IQR) — mg/dl	0.72 (0.59–0.88)	0.73 (0.58–0.92)	0.70 (0.57–0.92)	0.74 (0.60–0.89)	0.41

* There were no significant between-group differences at baseline (all P>0.10) according to Fisher's exact test for categorical data or the Wilcoxon rank-sum test for continuous data. To convert the values for glucose to milligrams per deciliter, divide by 0.05551. To convert the values for creatinine to micromoles per liter, multiply by 88.4. CFU denotes colony-forming units, CSF cerebrospinal fluid, IQR interquartile range, and NA not applicable.

† Scores on the Glasgow Coma Scale range from 3 (deep coma) to 15 (normal consciousness).

impairment (21% vs. 12%, P=0.02), the median CSF fungal load (4.80 vs. 3.83 $\log_{10}$ colony-forming units per milliliter, P<0.001), and the median CD4+ count (16 vs. 26 cells per cubic millimeter, P=0.04). At baseline, Asian patients were less likely than African patients to have received previous antiretroviral therapy (23% vs. 55%, P<0.001).

PRIMARY OUTCOME

The key study outcomes are summarized in Table 2. Kaplan–Meier curves for survival up to 6 months for the whole study population and according to continent are shown in Figure 2. By 10 weeks (the cutoff time for the primary outcome), 106 of 224 patients (47%) in the dexamethasone group and 93 of 226 (41%) in the placebo group had died. The intention-to-treat analysis showed no significant between-group difference in survival at 10 weeks (hazard ratio for death in the dexamethasone group, 1.11; 95% confidence interval [CI], 0.84 to 1.47; P=0.45). However, tests for nonproportional hazards were highly significant, which suggested that the effect of dexamethasone changed over time. Therefore, we performed an exploratory analysis to determine hazard ratios at three discrete periods after randomization. The hazard ratios for death were 0.77 (95% CI, 0.54 to 1.09; P=0.14) for days 1 to 22, 1.94 (95% CI, 0.97 to 3.88; P=0.06) for days 23 through 43, and 2.50 (95% CI, 1.23 to 5.05; P=0.01) for days 44 to 71 (Section 6 in the Supplementary Appendix).

MORTALITY BY 6 MONTHS

By 6 months, 128 of 224 patients in the dexamethasone group, as compared with 109 of 226 patients in the placebo group, had died; the associated Kaplan–Meier mortality estimates were 57% and 49%, respectively. The prespecified Cox regression time-to-event analysis of mortality did not show a significant between-group difference (hazard ratio, 1.18; 95% CI, 0.91 to 1.53; P=0.20). However, a formal comparison of the risk of death at 6 months showed a trend toward harm in the dexamethasone group, with an absolute increase in risk of 9 percentage points (95% CI, −1 to 18; P=0.07) in the intention-to-treat population and of 11 percentage points (95% CI, 1 to 20; P=0.03) in the per-protocol population.

DISABILITY

Dexamethasone was associated with a significantly higher risk of death or disability than was placebo at both 10 weeks and 6 months, with odds ratios for a good outcome of 0.42 (95% CI, 0.25 to 0.69; P<0.001) at 10 weeks and 0.49 (95% CI, 0.31 to 0.77; P=0.002) at 6 months. Results were consistent across continents (Table 2). The prespecified analyses of visual impairment among 234 survivors at 10 weeks indicated that normal visual acuity was less common among those receiving dexamethasone than among those receiving placebo (88% [94 of 107 patients] vs. 96% [122 of 127 patients]; odds ratio, 0.30; 95% CI, 0.09 to 0.84; P=0.02). However, an exploratory analysis that excluded the 37 survivors who had visual abnormalities at baseline showed no significant between-group difference (odds ratio, 0.51; 95% CI, 0.10 to 2.20; P=0.37).

EARLY FUNGICIDAL ACTIVITY

Dexamethasone was associated with significantly slower rates of decline in the number of cryptococcal colony-forming units in CSF than was placebo during the first 2 weeks of treatment (Fig. 3). The rate of decline per day was −0.21 $\log_{10}$ colony-forming units per milliliter (95% CI, −0.24 to −0.19) in the dexamethasone group versus −0.31 $\log_{10}$ colony-forming units per milliliter (95% CI, −0.34 to −0.28) in the placebo group (P<0.001) (Table 2). The numbers of patients with relapse were similar in the two groups (5 in the dexamethasone group and 7 in the placebo group). A detailed definition of relapse is provided in Section 7 in the Supplementary Appendix.

CLINICAL ADVERSE EVENTS

By 6 months, there were 667 clinical adverse events in the dexamethasone group and 494 in the placebo group (P=0.01). A summary of adverse events is provided in Table 3, and a detailed listing is provided in Section 8 in the Supplementary Appendix.

A total of 87 patients in each group had a new AIDS-defining illness. However, the rate of the combined outcome of a new AIDS-defining illness or death by 6 months was higher in the dexamethasone group than in the placebo group (hazard ratio, 1.26; 95% CI, 1.00 to 1.58; P=0.05). Adverse events that were categorized as infections or infestations occurred in 48 patients

Table 2. Primary and Key Secondary Outcomes.*

Outcome and Analysis Population	Dexamethasone (N = 224)	Placebo (N = 226)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Death by week 10: primary outcome — no./total no. (%)†				
Intention-to-treat population	106/224 (47)	93/226 (41)	1.11 (0.84–1.47)	0.45‡
Per-protocol population	103/213 (49)	87/213 (41)	1.16 (0.87–1.54)	0.31§
African patients	63/122 (52)	51/124 (42)	1.26 (0.87–1.82)	0.23¶
Asian patients	43/102 (42)	42/102 (41)	0.95 (0.62–1.45)	0.80‖
Score on Glasgow Coma Scale				
<15	23/36 (64)	33/50 (66)	0.86 (0.51–1.48)	0.60
15	82/187 (44)	60/176 (34)	1.29 (0.93–1.80)	0.13
Antiretroviral therapy status at baseline				
None	68/135 (50)	57/133 (43)	1.15 (0.81–1.63)	0.45
Duration ≤3 mo	21/41 (51)	16/46 (35)	1.49 (0.77–2.87)	0.23
Duration >3 mo	17/48 (36)	20/47 (43)	0.77 (0.40–1.47)	0.43
Quantitative fungal count				
≤10^5 CFU/ml	63/141 (45)	47/131 (36)	1.24 (0.85–1.81)	0.26
>10^5 CFU/ml	35/63 (56)	42/81 (53)	0.99 (0.63–1.56)	0.98
CSF opening pressure >18 cm	64/129 (50)	57/135 (43)	1.14 (0.80–1.63)	0.47
CSF white-cell count <5 cells/mm³	11/25 (44)	12/17 (71)	0.53 (0.23–1.21)	0.13
Death by 6 mo — no./total no. (%)†				
Intention-to-treat population	128/224 (57)	109/226 (49)	1.18 (0.91–1.53)	0.20‡
Per-protocol population	125/213 (59)	103/213 (48)	1.23 (0.95–1.60)	0.12§
African patients	75/122 (62)	62/124 (51)	1.28 (0.91–1.79)	0.16¶
Asian patients	53/102 (52)	47/102 (46)	1.06 (0.72–1.58)	0.76‖
Disability at 10 wk in intention-to-treat population — no./total no. (%)				
Good outcome**	28/222 (13)	55/220 (25)	0.42 (0.25–0.69)	<0.001
Intermediate outcome	53/222 (24)	46/220 (21)		
Severe disability	35/222 (16)	26/220 (12)		
Death	106/222 (48)	93/220 (42)		
Disability at 6 mo in intention-to-treat population — no./total no. (%)				
Good outcome††	40/223 (18)	68/223 (30)	0.49 (0.31–0.77)	0.002
Intermediate outcome	40/223 (18)	34/223 (15)		
Severe disability	15/223 (7)	12/223 (5)		
Death	128/223 (57)	109/223 (49)		
			Difference in Estimated Change (95% CI)	
Estimated decrease in CSF fungal count during first 14 days (95% CI) — $\log_{10}$ CFU/ml per day				
Intention-to-treat population	−0.21 (−0.24 to −0.19)	−0.31 (−0.34 to −0.28)	0.09 (0.06 to 0.13)	<0.001
African patients	−0.20 (−0.24 to −0.17)	−0.28 (−0.32 to −0.24)	0.07 (0.03 to 0.12)	0.002
Asian patients	−0.22 (−0.26 to −0.19)	−0.35 (−0.39 to −0.30)	0.12 (0.07 to 0.18)	<0.001

Table 2. (Continued.)

Outcome and Analysis Population	Dexamethasone (N = 224)	Placebo (N = 226)	Hazard Ratio or Odds Ratio (95% CI)	P Value
Absolute decrease in CSF opening pressure during first 14 days (95% CI) — cm of CSF				
Intention-to-treat population	–9.2 (–11.9 to –6.5)	–3.2 (–5.8 to –0.5)	–6.1 (–9.4 to –2.7)	<0.001
African patients	–10.7 (–14.3 to –7.0)	–5.5 (–9.0 to –2.1)	–5.1 (–9.4 to –0.8)	0.02
Asian patients	–7.7 (–11.7 to –3.8)	0.1 (–4.1 to 4.2)	–7.8 (–12.9 to –2.6)	0.003

* Hazard ratios were calculated for death, and odds ratios for disability. CI denotes confidence interval.
† Risks were estimated by means of the Kaplan–Meier method, so percentages may not calculate mathematically.
‡ According to the test for proportional hazards, P<0.001 by 10 weeks and P=0.001 by 6 months. The estimated absolute difference in the risk of death was 6.01 percentage points (95% CI, –3.19 to 15.20; P=0.20) at 10 weeks and 8.68 percentage points (95% CI, –0.54 to 17.90; P=0.07) at 6 months.
§ According to the test for proportional hazards, P<0.001 by 10 weeks and by 6 months. The estimated absolute difference in the risk of death was 7.61 percentage points (95% CI, –1.82 to 17.05; P=0.11) at 10 weeks and 10.50 percentage points (95% CI, 1.07 to 19.94; P=0.03) at 6 months.
¶ According to the test for proportional hazards, P=0.03 by 10 weeks and P=0.08 by 6 months. The estimated absolute difference in the risk of death was 10.23 percentage points (95% CI, –2.25 to 22.71; P=0.11) at 10 weeks and 11.13 percentage points (95% CI, –1.27 to 23.52; P=0.08) at 6 months.
‖ According to the test for proportional hazards, P=0.01 by 10 weeks and P=0.004 by 6 months. The estimated absolute difference in the risk of death was 0.98 percentage points (95% CI, –12.55 to 14.51; P=0.89) at 10 weeks and 5.80 percentage points (95% CI, –7.91 to 19.51; P=0.41) at 6 months.
** At 10 weeks, the odds ratios for a good outcome were 0.43 (95% CI, 0.18 to 0.97; P=0.04) for African patients and 0.41 (95% CI, 0.21 to 0.77; P=0.005) for Asian patients.
†† At 6 months, the odds ratios for a good outcome were 0.63 (95% CI, 0.32 to 1.19; P=0.15) for African patients and 0.40 (95% CI, 0.21 to 0.73; P=0.003) for Asian patients.

(21%) in the dexamethasone group and in 25 (11%) in the placebo group (P=0.003). Patients in the dexamethasone group had more adverse events than those in the placebo group with respect to gastrointestinal disorders (29 [13%] vs. 16 [7%], P=0.04), renal or urinary disorders (22 [10%] vs. 7 [3%], P=0.004), and cardiac disorders (8 [4%] vs. 0, P=0.004). Gastrointestinal bleeding was uncommon, and rates were similar in the two groups. There were 19 cases of acute renal failure in the dexamethasone group and 7 in the placebo group; in the dexamethasone group, 15 of the 19 cases (79%) occurred during an infectious episode. The rates of paradoxical IRIS (i.e., clinical deterioration that occurs after the initiation of antiretroviral therapy despite a microbiologic response to antifungal therapy) at 10 weeks and 6 months were similar in the two study groups. The median time from study entry until the initiation of antiretroviral therapy was 46 days in the dexamethasone group and 42 days in the placebo group.

LABORATORY ADVERSE EVENTS

By 6 months, there were 1023 grade 3 or 4 laboratory adverse events in the dexamethasone group and 835 in the placebo group (P=0.02) (Table 3). Hyperglycemia, hypercreatinemia, hyperkalemia, and hyponatremia all occurred significantly more frequently among patients receiving dexamethasone than among those receiving placebo.

CSF OPENING PRESSURE

Dexamethasone was associated with a larger reduction in CSF opening pressure during the first 2 weeks than was placebo. The estimated change was –9.2 cm of CSF (95% CI, –11.9 to –6.5) in the dexamethasone group and –3.2 cm of CSF (95% CI, –5.8 to –0.5) in the placebo group (P<0.001) (Table 2).

SUBGROUP ANALYSES

Prespecified subgroup analyses showed no significant between-group differences in 10-week mortality in any of the subgroups — those defined according to continent, country, sex, baseline score on the Glasgow Coma Scale, antiretroviral-therapy status, age, fungal burden, CD4+ count, baseline CSF opening pressure, and CSF white-cell count. No evidence of heterogeneity of effect was seen (Section 9 in the Supplementary Appendix).
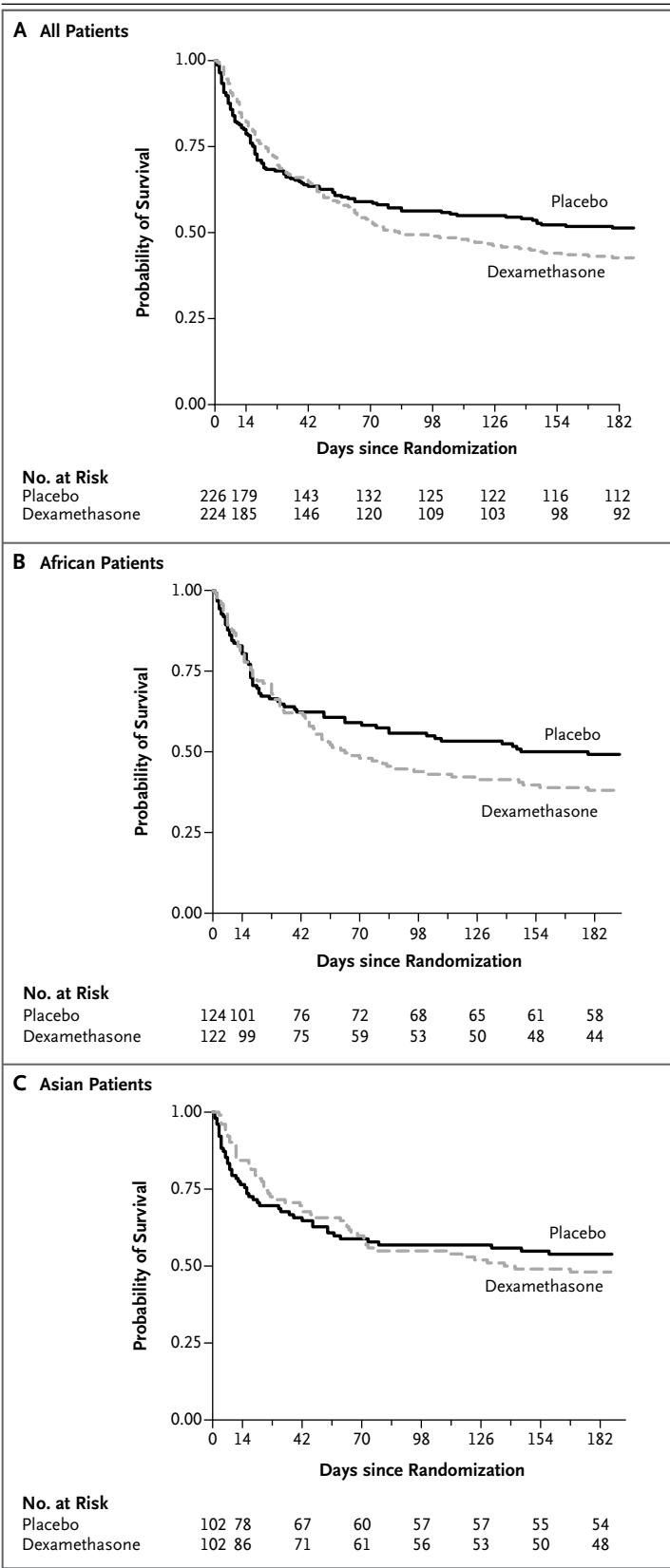
A All Patients

No. at Risk
Placebo   226 179   143   132   125   122   116   112
Dexamethasone   224 185   146   120   109   103   98   92

B African Patients

No. at Risk
Placebo   124 101   76   72   68   65   61   58
Dexamethasone   122 99   75   59   53   50   48   44

C Asian Patients

No. at Risk
Placebo   102 78   67   60   57   57   55   54
Dexamethasone   102 86   71   61   56   53   50   48

Figure 2. Survival among All Patients and According to Continent.

Shown are Kaplan–Meier survival estimates for all patients (Panel A) and for those in Africa (Panel B) and Asia (Panel C) during the 6 months of follow-up. By 10 weeks (the cutoff for the primary outcome), 106 of 224 patients (47%) in the dexamethasone group and 93 of 226 (41%) in the placebo group had died. At 6 months, the estimated risks of death were 57% and 49%, respectively.
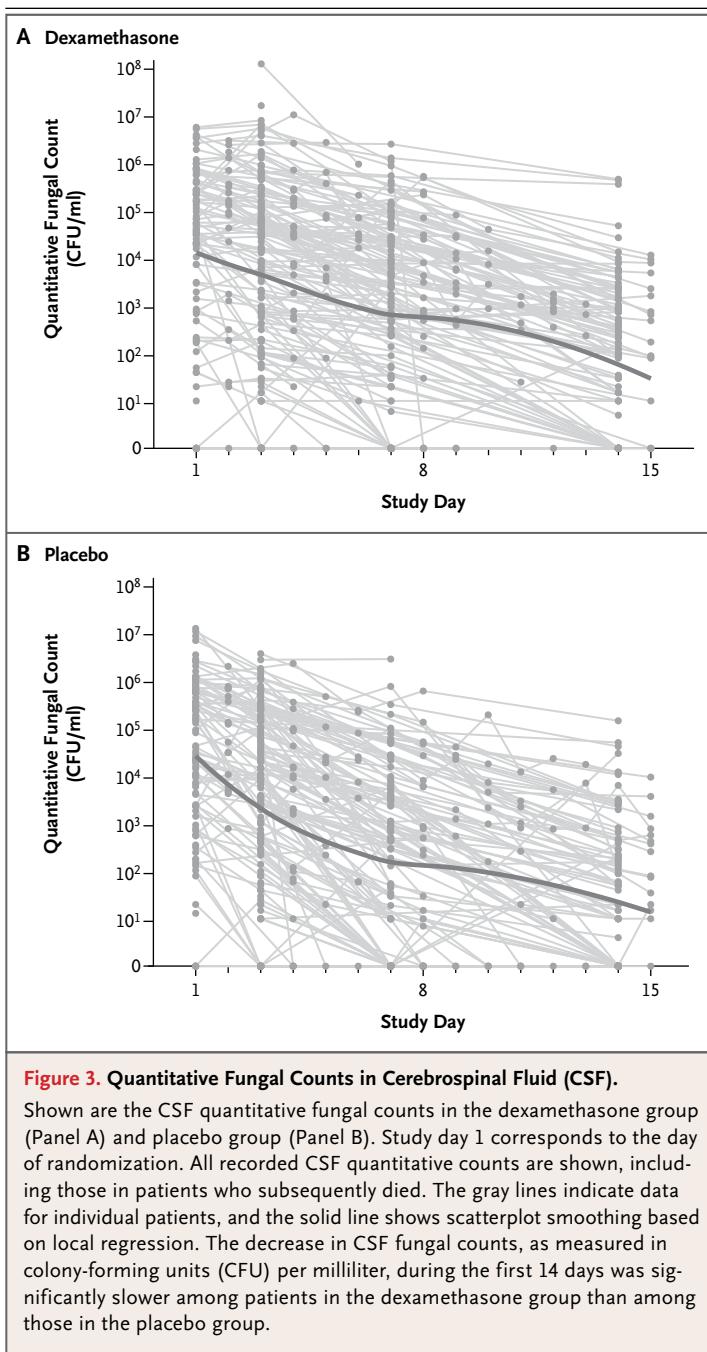
DISCUSSION

We set out to test whether adjunctive treatment with dexamethasone, initiated at the time of diagnosis, would be beneficial for all patients with HIV-associated cryptococcal meningitis. We found compelling evidence that at the dose and regimen used in the study such use was harmful, with significantly increased rates of disability and excess severe adverse events, including infectious episodes and renal, gastrointestinal, and cardiac disorders. The study was stopped early because of consistent evidence of harm across several outcomes. Consequently, the study did not have the statistical power to show an effect of dexamethasone on the primary outcome of mortality at 10 weeks. However, consistent with the evidence of harm, the hazard ratios for survival at 10 weeks and 6 months did not favor dexamethasone, and a formal between-group comparison of the risk of death at 6 months was suggestive of harm ($P=0.07$) and reached significance in the per-protocol analysis ($P=0.03$). Therefore, it is highly unlikely that dexamethasone benefits survival in such patients. The consistency of findings across Asian and African populations and all prespecified subgroups strengthens this conclusion.

We had hypothesized that dexamethasone would improve outcomes by reducing intracranial pressure and inflammatory complications and by decreasing the incidence of IRIS. The CSF opening pressure decreased more rapidly in patients receiving dexamethasone, but no survival benefit was seen, even among patients with increased pressures at baseline. Tests for proportional hazards suggested that the effect of dexamethasone may be time-dependent, and our exploratory analysis suggested that dexamethasone may have benefit during the first 3 weeks

of treatment — a possible reflection of modulation of pressure. A shorter duration of dexamethasone might have resulted in a different outcome. However, overall, the effects of dexamethasone are negative.

IRIS is a difficult management problem in cryptococcal meningitis. Current guidelines suggest that the use of glucocorticoids may be beneficial.[12,18] Almost 20% of the patients had initiated antiretroviral therapy in the 3 months before study entry. It is likely that these patients had occult cryptococcal infection that was revealed and worsened by immune reconstitution induced by antiretroviral therapy (so-called unmasking IRIS).[19] Even in this subgroup, we found no suggestion of benefit with dexamethasone therapy. Paradoxical IRIS occurred in 13 patients, and the study did not have the power to detect any effect of dexamethasone on this outcome. However, prespecified subgroup analyses for factors that have been associated with an increased risk of paradoxical IRIS (low CD4+ count, low CSF cellularity, and high CSF fungal burden[18,20]) did not identify a beneficial effect of dexamethasone.

It is not clear why dexamethasone was harmful. We chose an administration schedule that is routinely used among similarly immunosuppressed patients with HIV infection and tuberculous meningitis in Vietnam. Among patients with tuberculous meningitis, this administration schedule is associated with a lower risk of adverse events than that among patients receiving placebo.[6,21,22] In our study, the dexamethasone group had slower rates of decline in cryptococcus counts in CSF than the placebo group, and a slower rate of decline has been associated with worse outcomes.[23] Increased levels of proinflammatory cytokines at baseline have been associated with faster clearance of CSF cryptococcus and improved survival. It might be expected that cytokine levels would be attenuated by dexamethasone.[24-26] However, in the dexamethasone trial involving patients with tuberculous meningitis, no effect on cytokine levels was seen.[27] In our study, the increased risk of other acute infections in the dexamethasone group may have contributed to the harm that was observed. Most cases of acute renal failure in this group were associated with severe infections and were probably a consequence of sepsis rather than the use of dexamethasone.

Figure 3. Quantitative Fungal Counts in Cerebrospinal Fluid (CSF).

Shown are the CSF quantitative fungal counts in the dexamethasone group (Panel A) and placebo group (Panel B). Study day 1 corresponds to the day of randomization. All recorded CSF quantitative counts are shown, including those in patients who subsequently died. The gray lines indicate data for individual patients, and the solid line shows scatterplot smoothing based on local regression. The decrease in CSF fungal counts, as measured in colony-forming units (CFU) per milliliter, during the first 14 days was significantly slower among patients in the dexamethasone group than among those in the placebo group.

In conclusion, we tested an adjunctive immune-modulating treatment for cryptococcal meningitis because of a lack of new antifungal agents and the poor performance of those currently available. This pragmatic trial was designed to determine whether treatment with adjuvant glucocorticoids, started at the point of diagnosis, would improve survival among patients with

Table 3. Adverse Events by 6 Months.*

Event	Dexamethasone (N = 224)	Placebo (N = 226)	P Value
	no. of patients (%)		
Clinical adverse events			
At least one event†	193 (86)	191 (85)	0.69
New neurologic event	61 (27)	59 (26)	0.83
New AIDS-defining illness	87 (39)	87 (38)	1.00
Immune reconstitution inflammatory syndrome	7 (3)	6 (3)	0.79
Metabolism or nutrition disorder	78 (35)	85 (38)	0.56
Blood or lymphatic system disorder	96 (43)	83 (37)	0.21
Infection or infestation	48 (21)	25 (11)	0.003
Gastrointestinal disorder	29 (13)	16 (7)	0.04
Renal or urinary disorder	22 (10)	7 (3)	0.004
Respiratory, thoracic, or mediastinal disorder	9 (4)	14 (6)	0.39
Hepatobiliary disorder	10 (4)	3 (1)	0.05
Vascular disorder	9 (4)	4 (2)	0.17
Skin or subcutaneous-tissue disorder	6 (3)	3 (1)	0.34
Cardiac disorder	8 (4)	0	0.004
Endocrine disorder	3 (1)	3 (1)	1.00
Psychiatric disorder	3 (1)	1 (<1)	0.37
Immune system disorder	1 (<1)	1 (<1)	1.00
Injury, poisoning, or procedural complication	2 (1)	1 (<1)	0.62
Reproductive system or breast disorder	1 (<1)	0	0.50
Pregnancy, puerperium, or perinatal condition	0	1 (<1)	1.00
Systemic disorder	0	1 (<1)	1.00
Grade 3 or 4 laboratory adverse events			
Any event‡	202 (90)	192 (85)	0.12
Anemia	120 (54)	112 (50)	0.40
Leukocytopenia	36 (16)	41 (18)	0.62
Neutropenia	42 (19)	59 (26)	0.07
Thrombocytopenia	33 (15)	25 (11)	0.26
Elevated alanine aminotransferase	10 (4)	3 (1)	0.05
Elevated aspartate aminotransferase	14 (6)	11 (5)	0.54
Hyperglycemia	32 (14)	6 (3)	<0.001
Hypoglycemia	5 (2)	6 (3)	1.00
Hypercreatinemia	79 (35)	50 (22)	0.002
Hyperkalemia	52 (23)	19 (8)	<0.001
Hypokalemia	108 (48)	132 (58)	0.04
Hypernatremia	2 (1)	7 (3)	0.18
Hyponatremia	114 (51)	75 (33)	<0.001

* Listed are the numbers of patients who had at least one adverse event of the respective type. All comparisons are based on Fisher's exact test, except for comparisons of the total number of adverse events, for which the Wilcoxon rank-sum test was used to compare the number of events per patient. AIDS denotes acquired immunodeficiency syndrome.
† The total number of clinical events was 667 in the dexamethasone group and 494 in the placebo group (P=0.01).
‡ The total number of grade 3 or 4 laboratory events was 1023 in the dexamethasone group and 835 in the placebo group (P=0.02).

HIV-associated cryptococcal meningitis. We found that it did not. However, even though we have shown that a universal approach to the use of dexamethasone in patients with HIV-associated cryptococcal meningitis is harmful, there may still be a role for glucocorticoids in such patients. Current guidelines recommend the use of glucocorticoids among patients who have cryptococcomas with mass effect, the acute respiratory distress syndrome, or IRIS. These events were infrequent in our study. Therefore, our study did not have the power to test these particular indications, and generating high-quality evidence to test these indications will be difficult. It should be noted that 11% of all the patients who were excluded from the study did not participate because they had received glucocorticoids for CNS disease. Here, we have shown that such use is not justified. With no effective adjunctive therapy yet identified, improving access to the most effective antifungal treatments, including flucytosine, must remain a global priority.[2,3,28,29]

APPENDIX

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