Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome

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Objective: Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is a frequent complication of antiretroviral therapy in resource-limited countries. We aimed to assess whether a 4-week course of prednisone would reduce morbidity in patients with paradoxical TB-IRIS without excess adverse events.

Design: A randomized, double-blind, placebo-controlled trial of prednisone (1.5 mg/kg per day for 2 weeks then 0.75 mg/kg per day for 2 weeks). Patients with immediately life-threatening TB-IRIS manifestations were excluded.

Methods: The primary combined endpoint was days of hospitalization and outpatient therapeutic procedures, which were counted as one hospital day.

Results: One hundred and ten participants were enrolled (55 to each arm). The primary combined endpoint was more frequent in the placebo than the prednisone arm {median hospital days 3 [interquartile range (IQR) 0–9] and 0 (IQR 0–3), respectively; $P = 0.04$}. There were significantly greater improvements in symptoms, Karnofsky score, and quality of life (MOS-HIV) in the prednisone vs. the placebo arm at 2 and 4 weeks, but not at later time points. Chest radiographs improved significantly more in the prednisone arm at weeks 2 ($P = 0.002$) and 4 ($P = 0.02$). Infections on study medication occurred in more participants in prednisone than in placebo arm (27 vs. 17, respectively; $P = 0.05$), but there was no difference in severe infections (2 vs. 4, respectively; $P = 0.40$). Isolates from 10 participants were found to be resistant to rifampicin after enrolment.

Conclusion: Prednisone reduced the need for hospitalization and therapeutic procedures and hastened improvements in symptoms, performance, and quality of life. It is important to investigate for drug-resistant tuberculosis and other causes for deterioration before administering glucocorticoids.

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Introduction

The roll out of antiretroviral therapy (ART) in resource-limited countries has been associated with dramatic improvements in survival and quality of life. In these settings, a high proportion of patients commence ART while on treatment for active tuberculosis, resulting in a range of management challenges [1]. Paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) is increasingly recognized as an early complication of ART [2,3]. Paradoxical TB-IRIS is thought to result from restoration of tuberculosis-specific immune responses resulting in inflammation at disease sites of tuberculosis wherein antigen persists despite antitubercular treatment [4,5]. Typically, there is initial improvement on antitubercular therapy, then, after commencing ART, new, recurrent, or worsening tuberculosis symptoms, signs, or radiographic manifestations occur. Paradoxical TB-IRIS occurs in 8–43% patients starting ART while on antitubercular therapy [3,6–13]. Paradoxical TB-IRIS causes substantial morbidity, often resulting in hospitalization and/or the need for diagnostic and therapeutic procedures [13].

Glucocorticoids have been recommended for the treatment of paradoxical TB-IRIS [14,15], but there is little evidence for this recommendation, the largest study being a retrospective report of nine patients [7]. In tuberculous meningitis, glucocorticoids reduce mortality [16], in tuberculous pericarditis, reduce mortality and the need for repeat aspiration [17,18], and in pulmonary tuberculosis, cause modest clinical and radiographic improvement [19]. However, there is potential for harm when prescribing glucocorticoids in HIV-infected patients. Increased risk or progression of herpes zoster and Kaposi's sarcoma [20–22] have been reported. We have recently reported that a substantial proportion of patients presenting with suspected paradoxical TB-IRIS have undiagnosed drug-resistant *Mycobacterium tuberculosis* [23], another situation in which glucocorticoids may potentially cause harm.

We, therefore, conducted a randomized controlled trial of glucocorticoid therapy for patients with paradoxical TB-IRIS with the hypothesis that a 4-week course of prednisone would reduce morbidity without an excess of adverse events.

Methods

Study participants

Patients were recruited at GF Jooste Hospital, a secondary-level university-affiliated hospital in the Western Cape Province of South Africa serving communities with an antenatal HIV seroprevalence of up to 33% [24]. In 2006, the annual tuberculosis case notification rate in the province was 1031/100 000 [25]. Most patients initiate antitubercular treatment and ART in primary care clinics. We have previously described the ART and antitubercular therapy regimens used in these clinics [23]. In accordance with national guidelines, antitubercular drug susceptibility testing (DST) is not routinely performed for new tuberculosis cases, but in patients receiving re-treatment or not responding to antitubercular treatment. Clinicians at the primary care ART clinics were informed of the study and encouraged to refer all patients with suspected paradoxical TB-IRIS for assessment.

Consecutive patients were screened using standardized case definitions for paradoxical TB-IRIS [23]. We limited enrolment to four TB-IRIS manifestations to reduce clinical heterogeneity and allow longitudinal radiographic comparison. Only patients with new or recurrent tuberculosis symptoms and at least one of the following TB-IRIS manifestations were enrolled: infiltrate on chest radiograph, enlarging lymph node(s), serous effusion, or cold abscess. Each participant underwent full clinical evaluation and chest radiography. Further investigations were conducted to exclude alternative reasons for clinical deterioration, according to presentation.

Exclusion criteria were age less than 18 years, known rifampicin-resistant tuberculosis, previous glucocorticoid therapy during this tuberculosis episode, prior ART exposure, pregnancy, uncontrolled diabetes mellitus, Kaposi's sarcoma, and immediately life-threatening TB-IRIS [defined as respiratory failure with arterial pO_2 <8 kPa, altered level of consciousness, new focal neurological sign(s), or compression of a vital structure].

The study was approved by the University of Cape Town Research Ethics Committee (337/2004). Written informed consent was provided by all participants. The trial was registered on 17 August 2005 with the International Standard Randomised Controlled Trial Number Register (ISRCTN 21322548). The trial was conducted in accordance with the Helsinki Declaration.

Laboratory investigations

One or more clinical specimens (e.g., sputum, lymph node aspirate) were sent for tuberculosis microscopy, culture, and drug susceptibility testing. Specimens were also sent for rapid rifampicin resistance determination using a mycobacteriophage reporter system (FASTPlaque) [26]. Repeat samples were sent if deterioration occurred during follow-up.

Baseline investigations included electrolytes, urea and creatinine, random glucose, full blood count, liver function tests, calcium and albumin, random cortisol, C-reactive protein (CRP), $CD4^+$ lymphocyte count (CD4 cell count), and hepatitis B surface antigen. Arterial blood gas determination was performed in patients with

respiratory distress. Routine follow-up investigations included CRP and glucose at each visit. CD4 cell count was repeated at week 4.

Treatment

Study medication consisted of prednisone tablets (5 mg) or matching placebo. Prior to the study, a randomization sequence assigning participants in a 1 : 1 ratio was generated using Excel by the study statistician and given to an independent pharmacist. Study medication was packaged according to sequence by the independent pharmacist off-site. The study medication was then transferred to the GF Jooste Hospital pharmacy. The hospital pharmacists, study clinicians, and participants remained blind to sequence and randomization throughout the trial. Participants were enrolled by the study clinicians and consecutive participants received the next study medication container from number 1 to 110. Participants received study medication 1.5 mg/kg per day for 2 weeks followed by 0.75 mg/kg per day for 2 weeks. The initial high dose of prednisone (1.5 mg/kg per day) was chosen because rifampicin induces prednisone metabolism [27]. Follow-up was at weeks 1, 2, 4, 8, and 12 with a full clinical assessment at each visit.

If significant clinical deterioration occurred after 2 weeks of follow-up, the study protocol allowed participants to be switched to open-label prednisone. If life-threatening deterioration occurred before 2 weeks, participants could be switched earlier. Unblinding, after switch to open-label prednisone, was considered only if this information influenced clinical management. Participants with significant relapse of TB-IRIS symptoms after completing 4 weeks of study medication could also receive open-label prednisone. Initiation of open-label prednisone required agreement between at least two senior clinical investigators. Participants were re-investigated at deterioration for alternative diagnoses.

Most patients with respiratory presentations were prescribed broad-spectrum antibiotics prior to enrolment. If such patients experienced symptom resolution on antibiotics, the diagnosis of TB-IRIS was reconsidered and the patient was not enrolled. Nonsteroidal anti-inflammatory drugs were not prescribed.

Assessment of outcome

The primary endpoint was cumulative days of hospital admission during the 12-week study period, combined with outpatient therapeutic procedures (including aspiration of lymph nodes, cold abscesses, and serous effusions) that were assigned a value of one hospital day. Procedures performed prior to or at enrolment were not included.

There were several secondary outcome measures. At each study visit, participants were asked about the TB-IRIS symptoms they had presented with and the study clinician enquired about any new TB-IRIS symptoms. The study clinician, blinded to treatment allocation, graded TB-IRIS symptom response at week 2 and 4 visits in relation to the symptoms described at study entry. Symptom response was graded in one of three categories: deteriorated, no change, or improved/resolved. All patients who developed new TB-IRIS symptoms were graded as 'deteriorated'. Participants who switched to open-label prednisone within 2 weeks or between 2 and 4 weeks had their symptoms scored at the time of switching for their 2-week and 4-week scores, respectively. Symptoms of participants who switched to open-label prednisone at or before week 2 were not scored at week 4. The Medical Outcomes Study-HIV (MOS-HIV) Health Survey [28] and Karnofsky performance score were performed at each visit. Participants were assessed for glucocorticoid adverse drug reactions and new infections.

Two radiologists, blinded to study allocation, compared chest radiographs at weeks 2 and 4 with baseline (week 0). They utilized a three-point scale (deteriorated, no change, or improved/resolved). If there was a disagreement, they met to agree on a final consensus score. Ultrasound scans (measuring lymph node diameter or pericardial effusion width) were also scored at the same time points using a three-point scale: more than 25% increase, less than 25% increase or decrease, and more than 25% decrease in size.

Statistical analysis

Defervescence in paradoxical TB-IRIS is reported to occur in 50% by 2 weeks [6]. We based our sample size calculation on the assumption that spontaneous resolution of paradoxical TB-IRIS at 2 weeks would occur in 50% of the participants who received placebo. We estimated resolution in 80% of the participants on prednisone by 2 weeks. A sample size of 90 would be required to detect these rates of resolution for an α of 0.05 and β of 0.2. Therefore, we planned recruitment of 100 patients, assuming a 10% drop-out rate. Sample size was subsequently increased to 110, as we found that approximately 10% of our participants had unsuspected rifampicin-resistant tuberculosis [23].

A data and safety monitoring board (DSMB) of three clinical researchers and an independent statistician reviewed the study results after 50 participants had completed the study follow-up. They advised continuing based on predetermined stopping rules.

The analysis of the primary endpoint included all participants, according to the intention-to-treat principle. Analysis of the primary combined endpoint was performed using the Wilcoxon rank-sum test. Other comparisons between the two groups were made using Wilcoxon rank-sum, chi-squared, and Fisher's exact tests, as appropriate. Quantile regression was performed to adjust the primary endpoint for baseline differences between the two groups in duration from start of

antitubercular therapy to initiation of ART and random cortisol level. Kaplan–Meier methods were used to construct time-to-event curves for the two groups and the Gehan–Breslow–Wilcoxon test was used for comparison. Reported *P* values are two-sided.

Results

Two hundred and eighty-seven patients were screened and 110 were enrolled (55 to prednisone, 55 to placebo). Progress of participants through the trial is shown in Fig. 1. There were six protocol deviations (Supplementary Table 4, http://links.lww.com/QAD/A85).

Seventy (64%) were women and the median age was 31.6 years (range 19–56). Median CD4 cell count prior to ART was 53 cells/μl and at enrolment was 116 cells/μl. Table 1 shows baseline characteristics comparing the two arms. Median duration from antitubercular therapy to ART initiation was significantly longer in the prednisone arm. Random cortisol was significantly lower in the prednisone arm, but no participant had a value below reference range. Otherwise the arms were evenly matched. Forty-four participants received antibiotics prior to enrolment.

Initial tuberculosis diagnosis was made by culture of *M. tuberculosis* in 46 (42%), a positive smear for acid-fast bacilli in 26 (24%), and was empiric based on clinical and radiographic findings in 38 (35%). Fourteen of the 38 participants with an initial empiric tuberculosis diagnosis had microbiologic confirmation at some stage during the study (seven culture positive and seven smear positive).

Outcomes are shown in Table 2 and Fig. 2. The median cumulative number of hospital days (with outpatient therapeutic procedures counted as one additional day) was 0 [interquartile range (IQR) 0–3] in the prednisone arm and 3 (IQR 0–9) in the placebo arm ($P = 0.04$). In a multivariate regression model controlling for baseline differences between the two arms, this difference remained significant ($P = 0.009$).

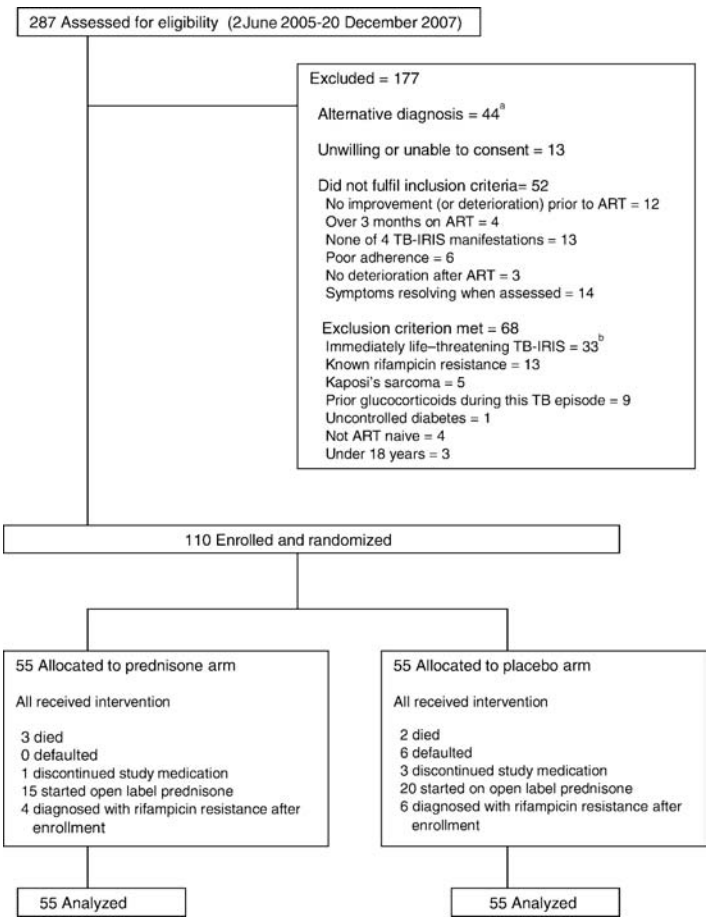

Fig. 1. Progress of participants through the trial. [a]Common alternative diagnoses were drug reaction (nine), bacterial infection (eight), cryptococcosis (four), diarrhoeal illness (four), and heart failure (four). [b]Among these 33 patients, the most frequent immediately life-threatening manifestation was neurological tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) ($n = 25$).

Table 1. Participant characteristics at enrolment.

	Placebo arm ($N=55$)	Prednisone arm ($N=55$)	P value for comparison
Age	31.6 (19–56.9)	31.5 (19.1–46)	0.82
Female sex	32 (58%)	38 (69%)	0.23
Previous tuberculosis	10 (18%)	15 (27%)	0.26
CD4 cell count prior to ART (cells/μl)	48 (20–92)	56 (30–103)	0.15
WHO stage 4 at ART initiation	33 (60%)	29 (53%)	0.44
Duration antitubercular therapy to ART in days	43.5 (23.8–76)	66 (35–84)	0.02
Duration ART to TB-IRIS in days	10 (7–19)	14 (7–21)	0.21
Duration TB-IRIS to enrolment in days	14 (8–23.5)	12.5 (7–21)	0.24
TB-IRIS manifestations			
New/recurrent lymphadenopathy	28 (51%)	19 (35%)	0.10
New/recurrent cold abscess	1 (2%)	1 (2%)	1.0
New/worsening pulmonary infiltrate	16 (29%)	19 (35%)	0.54
New/worsening serous effusion	9 (16%)	9 (16%)	1.0
Recurrent symptoms and consistent radiography, but without baseline radiography available for comparison	14 (25%)	15 (27%)	0.83
CD4 cell count at enrolment (cells/μl) ($n=97$)	109 (55–190)	138 (78–243)	0.07
Random glucose (mmol/l, 4.1–11.1) ($n=108$)	5.3 (4.8–5.7)	5.1 (4.8–6)	0.79
Haemoglobin (g/dl, male 13–17, female: 12–15) ($n=107$)	9.2 (7.8–10.1)	9.1 (8.1–10.3)	0.79
Albumin (g/l, 35–52) ($n=108$)	23 (19.5–26.5)	23 (20–26)	0.62
C-reactive protein (mg/l, 0–10) ($n=108$)	106 (79–172)	104 (50–150)	0.18
Random cortisol (nmol/l, 138–690) ($n=97$)	559.5 (405.8–774)	471 (350–614)	0.03
Hepatitis B surface antigen positive ($n=94$)	3/42 (7%)	3/52 (6%)	0.79
Weight (kg)	52.2 (46.6–58.8)	51.6 (48.1–56.5)	0.69
Hospitalized at enrolment	19 (35%)	14 (25%)	0.30
Antibiotics prior to enrolment	19 (35%)	25 (45%)	0.24
Karnofsky performance score ($n=107$)	70 (30–80)	70 (30–80)	0.96
MOS-HIV Health Survey ($n=106$)			
Physical health summary score	37.9 (32.8–44.9)	36.3 (33.4–43.1)	0.97
Mental health summary score	49.8 (39.1–56.9)	49.7 (44.5–56)	0.75

Values shown are medians (interquartile range) or numbers (%). Reference ranges for laboratory tests are shown in brackets. ART, antiretroviral therapy; MOS, Medical Outcomes Study; TB-IRIS, tuberculosis-associated immune reconstitution inflammatory syndrome.

The symptom score showed more rapid improvement in the prednisone arm at 2 weeks ($P=0.001$) and 4 weeks ($P=0.03$) (Fig. 2a). The chest radiograph score demonstrated greater improvement in the prednisone arm at 2 and 4 weeks (Fig. 2b). The ultrasound score ($n=29$) demonstrated no significant difference at either time point (data not shown). There were significantly greater improvements in MOS-HIV physical and mental health summary scores, Karnofsky performance score, and CRP at weeks 2 and 4 in the prednisone arm, but not at later time points.

Five participants switched to open-label prednisone during the period of study medication (first 4 weeks) in the prednisone arm and 18 in the placebo arm ($P=0.002$) (Fig. 3). Three such participants had study allocation unblinded. There was concern of hepatitis B flare in one, oesophagitis due to herpes virus (not confirmed) in another, and pancreatitis in a third. All three had been allocated placebo. Ten participants in the prednisone arm and two in the placebo arm were started on open-label prednisone after completing the 4 weeks of study medication ($P=0.01$) due to ongoing deterioration or, more frequently, relapse after having improved on study medication. Participants who initiated open-label prednisone were weaned according to response. Median duration of open-label prednisone was 84 days (IQR 60–126).

Eight participants in the prednisone arm and three in the placebo arm had events that could potentially be attributed to a glucocorticoid adverse drug reaction while on study medication ($P=0.11$). Infections while on study medication occurred in 27 participants in the prednisone arm and 17 in the placebo arm ($P=0.05$). The majority of these infections were mild, mainly oral and vaginal candidiasis, and uncomplicated herpes simplex (Supplementary Table 1, http://links.lww.com/QAD/A82). Severe infections, defined as invasive bacterial infections or new World Health Organisation stage 4 conditions, occurred in two participants in the prednisone arm and four in the placebo arm during the 12-week study period ($P=0.40$). These severe infections were a *Klebsiella* wound infection complicated by fatal sepsis syndrome, oesophageal candidiasis, pneumocystis pneumonia, and cryptococcal meningitis in the placebo arm. The participant who developed oesophageal candidiasis was on open-label prednisone when this occurred. In the prednisone arm, the severe infections were fatal pneumonia and cytomegalovirus retinitis.

There were three deaths in the prednisone arm and two in the placebo arm ($P=0.65$). Causes of death are shown in Supplementary Table 2 (http://links.lww.com/QAD/A83). Six participants defaulted follow-up for more than 7 days (all in the placebo arm; $P=0.01$). Five subsequently returned to care.

Table 2. Primary and secondary outcomes[a].

	Placebo arm ($N=55$)	Prednisone arm ($N=55$)	P value for comparison
Cumulative days hospitalized and outpatient therapeutic procedures	3 (0–9)	0 (0–3)	0.04
Number of participants hospitalized	25 (45%)	17 (31%)	0.12
Cumulative number of days hospitalized	463	282	–
Median number of days hospitalized (all participants)	0 (0–8)	0 (0–3)	0.07
Median number of days hospitalized (among 42 participants who were hospitalized)	12 (5–30)	4 (3–29)	0.26
Number of participants who had outpatient therapeutic procedure performed	12 (22%)	12 (22%)	1.0
Cumulative number of outpatient therapeutic procedures[b]	28	24	–
Karnofsky performance score			
Week 2 ($n=92$)	70 (50–90)	90 (80–90)	<0.001
Week 4 ($n=86$)	80 (60–90)	90 (80–100)	<0.001
Week 8 ($n=91$)	90 (75–100)	90 (90–100)	0.33
Week 12 ($n=89$)	90 (90–100)	100 (90–100)	0.16
MOS-HIV Health Survey			
Physical health summary score			
Week 2 ($n=98$)	44.5 (36.7–52.4)	51.5 (44.5–54.5)	0.01
Week 4 ($n=94$)	48.3 (39.7–55)	51.2 (46.6–56.8)	0.04
Week 8 ($n=96$)	52.9 (44.2–55.5)	53.3 (42.9–56)	0.97
Week 12 ($n=88$)	52.4 (48.1–56.1)	52.4 (48.9–55.5)	0.93
Mental health summary score			
Week 2 ($n=98$)	57.4 (48.8–60)	59.9 (54.2–62.1)	0.02
Week 4 ($n=94$)	55.5 (50.3–60)	58.5 (55.6–62.2)	0.01
Week 8 ($n=96$)	60.6 (55.8–62.6)	60.6 (54.4–62.7)	0.79
Week 12 ($n=88$)	61.7 (58.6–63)	60.7 (58.6–63.7)	0.68
CRP (mg/l)			
Week 2 ($n=101$)	96.5 (53.8–122.5)	35 (13.8–60.3)	<0.001
Week 4 ($n=94$)	63 (40.5–117.5)	34 (16.3–57)	0.001
Week 8 ($n=95$)	42 (20–83.5)	39 (13–84.3)	0.49
Week 12 ($n=97$)	36 (17–80)	25 (9–60.5)	0.12
Week 4 CD4 cell count (cells/μl) ($n=75$)	145 (61–224)	154 (78–248)	0.51
Glucocorticoid adverse drug reaction[c] while on study medication	3 (5%)	8 (15%)	0.11
Infections while on study medication	17 (31%)	27 (49%)	0.05
Death	2 (4%)	3 (5%)	0.65

Values shown are medians (IQR) or numbers (%). ART, antiretroviral therapy; CRP, C-reactive protein; IQR, interquartile range; MOS, Medical Outcomes Study.
[a]Symptom and radiographic scores are not shown here, but are shown in Fig. 2.
[b]Outpatient therapeutic procedures performed during the 12 week study period are shown in Supplementary Table 3, http://links.lww.com/QAD/A84.
[c]Defined as clinical events that could potentially be attributed to glucocorticoid adverse drug reaction: blood pressure higher than 140/90 mmHg, glucose higher than 11.1 mmol/l, oedema, hypomania, Cushingoid features, acne or gastritis symptoms.

Drug resistance

Ten cases of rifampicin-resistant tuberculosis were diagnosed after study enrolment. In eight, it was diagnosed after completion of study medication. Three received open-label prednisone. In the placebo arm, there were six cases [five multidrug resistant (MDR) and one rifampicin monoresistant] and in the prednisone arm four (two MDR, one rifampicin monoresistant, and one rifampicin resistant on FASTPlaque assay, but other drug susceptibility testing could not be done due to contamination) ($P=0.50$). INH-monoresistant tuberculosis was present in one participant in the placebo arm (diagnosed at tuberculosis diagnosis) and one in the prednisone arm (diagnosed at TB-IRIS presentation).

Discussion

We found that a 4-week course of prednisone reduced the primary combined endpoint of days hospitalized and outpatient therapeutic procedures in patients presenting with paradoxical TB-IRIS. Mortality was not chosen as a primary outcome, as death due to paradoxical TB-IRIS is infrequent in reported series [3,12,13,29]. Furthermore, exclusion of patients with immediately life-threatening manifestations reduced the likelihood that we would demonstrate a significant difference. Additional benefits of prednisone were seen across a range of secondary outcome measures including symptom and Karnofsky performance scores, quality-of-life assessments, radiographic response, and reduction in CRP. The greatest effects were seen at the 2-week visit. Thereafter, the effect size and significance diminished, likely due to the combined effect of cross-overs from placebo to open-label prednisone for symptom deterioration and the self-limiting nature of most cases of paradoxical TB-IRIS in placebo group.

Switching to open-label prednisone while on study medication occurred significantly more frequently in the

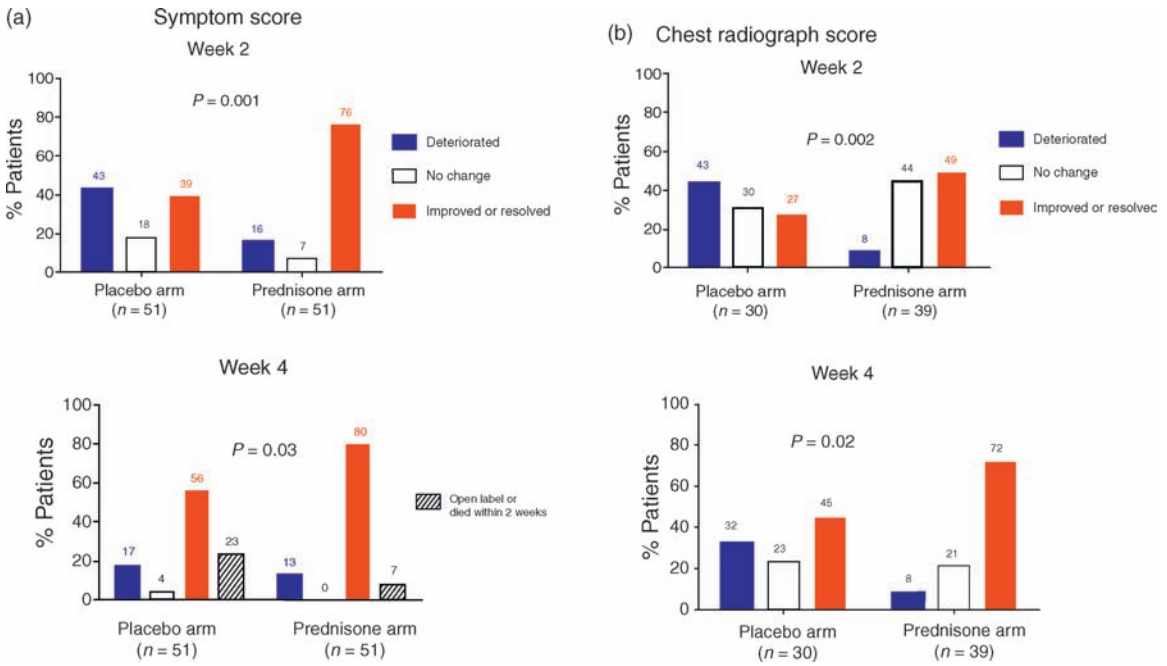

Fig. 2. Symptom and chest radiograph scores. (a) Symptom score at weeks 2 and 4. The distribution of symptom scores in percentage at weeks 2 and 4 in three categories (deteriorated, no change, improved/resolved) is shown. Participants who switched to open-label prednisone at or before week 2 were not scored at week 4 (they are shown in a separate category together with those who died within 2 weeks on the week 4 graph). There were significant differences between the two arms at week 2 ($P = 0.001$) and week 4 ($P = 0.03$). (b) Chest radiograph scores at weeks 2 and 4. Participants who had a pulmonary infiltrate on chest radiograph at baseline (week 0) had a chest radiograph score assigned at weeks 2 and 4 by two radiologists. Scores were allocated in three categories (deteriorated, no change, improved/resolved) in comparison with the week 0 chest radiograph. The distribution of scores in percentage is shown. There were significant differences between the two arms at week 2 ($P = 0.002$) and week 4 ($P = 0.02$).

placebo arm. This is further evidence of the benefit of prednisone. The fact that 10 participants in the prednisone arm needed to restart prednisone after 4 weeks suggests that this course was too short for a subset. Some participants were treated with open-label prednisone for several months. Paradoxical TB-IRIS is a heterogeneous condition with variable natural history and the glucocorticoid regime should in clinical practice be tailored to severity and response.

Prednisone was well tolerated. There was no excess of glucocorticoid adverse drug reactions while on study medication in the prednisone arm. More infections occurred in the prednisone arm while on study drug. The majority of these were mild infections and there was no difference in the incidence of severe infections by study arm.

When considering glucocorticoid therapy for paradoxical TB-IRIS, it is crucial to exclude alternative diagnoses, especially new infections or drug-resistant tuberculosis [23], because glucocorticoids may cause harm if the diagnosis of paradoxical TB-IRIS is incorrect. Most patients who had a respiratory presentation were treated with a broad-spectrum antibiotic prior to enrolment, as a bacterial chest infection is an important differential diagnosis in this context. An alternative diagnosis was made in 44 of the paradoxical TB-IRIS suspects screened, and rifampicin-resistant tuberculosis was diagnosed in a further 10 participants after enrolment, even though we excluded patients with known rifampicin-resistant tuberculosis and patients who had not symptomatically improved prior to ART. There is currently no diagnostic test for paradoxical TB-IRIS. In resource-limited settings, where most cases of paradoxical TB-IRIS occur, it is difficult to exclude alternative diagnoses and drug-resistant tuberculosis. Some caution, therefore, has to be exercised when prescribing glucocorticoids in resource-limited settings. In any setting, it is prudent to avoid or defer glucocorticoids until the diagnosis of paradoxical TB-IRIS is firmly established and reassess the diagnosis of paradoxical TB-IRIS should a patient further deteriorate while being treated with glucocorticoids.

A major challenge in management and research of paradoxical TB-IRIS is that there is no confirmatory diagnostic test. We [23] have previously reported that CRP is almost universally elevated in paradoxical TB-IRIS and that its levels are higher in paradoxical TB-IRIS suspects who are subsequently diagnosed with rifampicin-resistant TB. However, CRP is unlikely to have diagnostic utility, as most of the differential diagnoses for

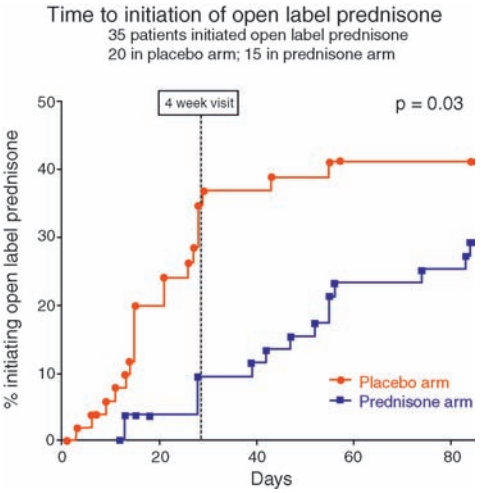

Fig. 3. Thirty-five participants were started on open-label prednisone (20 in the placebo arm and 15 in the prednisone arm). This Kaplan–Meier graph demonstrates the differences in the time that open-label prednisone was started between the two arms. In the first four weeks, while participants were receiving study medication, 18 in the placebo arm (33%) compared with five in the prednisone arm (9%) were switched to open-label prednisone ($P = 0.002$) because of significant symptom deterioration. After 4 weeks, two in the placebo arm (4%) compared with 10 in the prednisone arm (18%) were started on open-label prednisone ($P = 0.01$) mainly because of relapse of tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) symptoms.

paradoxical TB-IRIS also cause elevations of CRP. Interferon-gamma release assays (IGRAs) have been proposed as possible diagnostic tools. Certain studies [4,30] have demonstrated that IGRAs, with purified protein derivative as the antigen stimulus, differentiate paradoxical TB-IRIS cases from controls. Our own study [5] suggested that IGRAs do not sufficiently differentiate cases from controls to be considered as a diagnostic test. Other approaches being explored are the identification of a characteristic cytokine profile or gene expression signature for paradoxical TB-IRIS. In the interim, diagnosis relies upon the use of clinical case definitions [2].

The development of Kaposi's sarcoma in HIV-infected patients treated with glucocorticoids has been reported [20,21]. Kaposi's sarcoma was an exclusion criterion in our study and no cases occurred in our study, possibly due to the protective effect of ART. We recommend avoidance of glucocorticoids in patients with Kaposi's sarcoma, as life-threatening exacerbation may occur [22].

Our study has several limitations. It was conducted at a single site with a relatively small sample size that did not permit subgroup analyses. Radiography from the time of initial tuberculosis diagnosis and ART initiation was unavailable in some participants. In these participants, the diagnosis of paradoxical TB-IRIS was made on the basis of recurrent tuberculosis symptoms and the presence of compatible radiographic tuberculosis manifestations (pulmonary infiltrates, visceral lymphadenopathy, or serous effusions), but we did not know for certain whether the radiographic manifestations were worsening. Furthermore, it is possible that certain of the subjective measures of improvement (symptom score, quality-of-life assessment, and Karnofsky performance score) may have been influenced by the euphoric effect associated with high-dose glucocorticoids. Although the treatment allocation was randomized, two characteristics were found not to be evenly matched between the two arms (random cortisol and duration of antitubercular therapy to ART). These variables could thus potentially have confounded study findings, but no such effect could be found on the primary endpoint when these two variables were included in a multivariate regression model. An additional limitation was that the tuberculosis diagnosis was confirmed by culture in only 48% of participants. This reflects the practice in a programmatic setting in South Africa where culture is limited and not routinely performed in new tuberculosis cases.

In conclusion, a 4-week course of prednisone reduced days hospitalized and outpatient therapeutic procedures and resulted in more rapid improvements in symptoms, radiography, markers of inflammation, performance, and quality of life. An important caveat is that clinicians should be certain of the diagnosis of paradoxical TB-IRIS and investigate for antitubercular drug resistance when considering glucocorticoid therapy. Knowing that there is effective symptomatic therapy for paradoxical TB-IRIS may make clinicians less reluctant to start ART early in patients with tuberculosis and advanced immunosuppression [31].

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Authors' contributions: G.M., G.M., and R.J.W. designed and co-ordinated the study. G.M., D.J.P., K.R., M.X.R., and T.O. were involved in patient recruitment and follow-up and collected clinical outcomes data. Data management and analysis were performed by C.M. and G.M. G.M. wrote the manuscript, which was reviewed by all authors critically.

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