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Effectiveness of Adjunctive High-Dose Infliximab Therapy to Improve Disability-Free Survival Among Patients With Severe Central Nervous System Tuberculosis: A Matched Retrospective Cohort Study

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Background. Few treatment options exist for patients with severe central nervous system (CNS) tuberculosis (TB) worsening due to inflammatory lesions, despite optimal antitubercular therapy (ATT) and steroids. Data regarding the efficacy and safety of infliximab in these patients are sparse.

Methods. We performed a matched retrospective cohort study based on Medical Research Council (MRC) grading system and modified Rankin Scale (mRS) scores comparing 2 groups of adults with CNS TB. Cohort A received at least 1 dose of infliximab after optimal ATT and steroids between March 2019 and July 2022. Cohort B received only ATT and steroids. Disability-free survival (mRS score $\leq$2) at 6 months was the primary outcome.

Results. Baseline MRC grades and mRS scores were similar between the cohorts. Median duration before initiation of infliximab therapy from start of ATT and steroids was 6 (IQR: 3.7–13) months and for neurological deficits was 4 (IQR: 2–6.2) months. Indications for infliximab were symptomatic tuberculomas (20/30; 66.7%), spinal cord involvement with paraparesis (8/30; 26.7%), and optochiasmatic arachnoiditis (3/30; 10%), worsening despite adequate ATT and steroids. Severe disability (5/30 [16.7%] and 21/60 [35%]) and all-cause mortality (2/30 [6.7%] and 13/60 [21.7%]) at 6 months were lower in cohort A versus cohort B, respectively. In the combined study population, only exposure to infliximab was positively associated (aRR: 6.2; 95% CI: 2.18–17.83; $P = .001$) with disability-free survival at 6 months. There were no clear infliximab-related side effects noted.

Conclusions. Infliximab may be an effective and safe adjunctive strategy among severely disabled patients with CNS TB not improving despite optimal ATT and steroids. Adequately powered phase 3 clinical trials are required to confirm these early findings.

Keywords. infliximab; TNF-α inhibitor; CNS tuberculosis; disability-free survival.

Central nervous system (CNS) tuberculosis (TB) disables or kills up to 50% of affected patients [1]. The pathogen *Mycobacterium tuberculosis,* together with the host immune response, synergistically contributes to these poor outcomes. Multiple attempts to intensify ATT have not improved disability-free survival [2, 3]. The use of steroids to address the exaggerated host immune response has significantly reduced mortality but not disability [4, 5]. No therapeutic agent has been studied specifically to reduce disability in severe CNS TB, except for aspirin [6]. Hence, the severity of early neurological deficits remains one of the best predictors of long-term outcomes [7].

Many patients continue to develop new deficits despite receiving optimal ATT and steroids [8]. Inflammatory lesions like large tuberculomas or adhesive arachnoiditis are often responsible for these deficits. Therapeutic options for these patients are poorly studied; steroids, thalidomide, and cyclophosphamide have been tried with variable degrees of success. In contrast, infliximab, a tumor necrosis factor alpha (TNF-α) inhibitor, has good CNS penetration and has shown potential benefits among these patients in scattered case reports [9, 10].

TNF-α, a proinflammatory cytokine, is important for the formation and maintenance of tuberculous granulomas [11]. Intuitively, TNF-α blockade is an attractive treatment strategy

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for addressing inflammatory granulomatous lesions causing clinical deficits. Infliximab, despite being a large molecule, enters the cerebrospinal fluid (CSF) well in the presence of neuroinflammation [12]. However, there are significant concerns regarding its potential to disseminate or worsen TB and other infections. Concerns regarding selective reporting of patients who improved with TNF-α inhibitors also exist. In this context, larger studies on consecutive patients receiving TNF-α inhibitors can inform the real-world efficacy and harm and may identify the specific group of patients in whom it can be studied in future clinical trials.

We studied the effectiveness of infliximab among patients with CNS TB by retrospectively comparing a cohort that received infliximab along with steroids and ATT (cohort A) with patients who did not receive infliximab (cohort B).

METHODS

Study Design and Participants

We conducted a matched retrospective cohort study based on Medical Research Council (MRC) grades and modified Rankin Scale (mRS) scores among patients with CNS TB in a large teaching hospital in South India. The hospital treats approximately 200 patients with CNS TB yearly at the Infectious Diseases, Internal Medicine, Neurology, and Physical Medicine and Rehabilitation departments. All patients included in the study received weight-based ATT and steroids, the current standard of care (SOC) in the management of CNS TB. Central nervous system TB in our cohort included patients with TB meningitis (TBM), tuberculomas, tuberculous vasculitis, spinal involvement, and optochiasmatic TB. Cohort A received infliximab in addition to SOC. Cohort B was treated with SOC alone. Several patients underwent neurosurgical procedures and received antiepileptic agents, physiotherapy, and occupational therapy as part of routine care.

Description of Study Cohorts

Cohort A

Our cohort A consisted of patients who received at least a single dose of infliximab (Infimab; biosimilar manufactured by Sun Pharmaceuticals), after optimal ATT and steroids, between March 2019 and July 2022.

At the inception of the study, after reviewing the available evidence, the physicians at the Department of Infectious Diseases identified the following subgroups as potential patients who were suitable candidates to receive infliximab in addition to the SOC. Patients with CNS TB with new-onset or persistent unimproved deficits despite weight-optimized ATT and steroids with (1) refractory symptomatic tuberculomas, (2) recurrent clinical worsening on steroid tapering, (3) optochiasmatic TB with visual deficits, and (4) recent-onset arachnoiditis with paraparesis were considered for infliximab therapy.

Prior to starting infliximab, consensus between at least 2 infectious disease physicians was required and there was a detailed discussion with patients regarding the risks and benefits of the intervention. Infliximab was used among patients with significant clinical deficits. Most of our patients presented with paradoxical worsening (PW) with high MRC grades and mRS scores. Hence, we opted to administer a higher dose of 10 mg/kg. Three 10-mg/kg doses of infliximab were administered intravenously to the patients at monthly intervals with close monitoring. However, infliximab doses were stopped early if there was a complete response or futility of response as decided by the clinical team. We performed baseline brain imaging in all patients to rule out other reversible causes of neurological deficits, such as hydrocephalus, before considering infliximab therapy.

Cohort B

We included twice the number of patients (n = 60; 1:2), who were matched for the MRC grades and mRS scores for TBM. They were treated with routine SOC (ATT and steroids) under the Departments of Infectious Diseases, Internal Medicine, Neurological Sciences, and Physical Medicine and Rehabilitation in the last 10 years.

Follow-up

Both of the cohorts had clinical records that documented follow-up details of at least 6 months after discharge from the hospital. The duration of follow-up for cohort A was from the time of the first dose of infliximab to 6 months later. In situations where physical follow-up was not available, telephone calls were made. All of the patients underwent CNS imaging at baseline and whenever indicated.

Data Collection

Demographic and clinical data of both groups were retrieved from the hospital's electronic clinical workstation on to a structured questionnaire. The data were collected for both cohorts using a predesigned questionnaire that included separate sections for demographics, diagnosis, clinical features, baseline imaging, treatment, and outcomes. The imaging findings of patients who received infliximab therapy were reviewed by 2 neuroradiologists independently.

Outcome Assessment

An independent team of 3 physicians, not involved in the care of patients in cohort A, from the Internal Medicine, Neurology, and Physical Medicine and Rehabilitation departments with at least 5 years' experience in treating patients with CNS TB evaluated the records and assigned treatment outcomes. Outcome assessment of cohort B was assigned by 2 infectious disease experts working in the field with more than 5 years of experience. The mRS scores of each patient in cohort B were rechecked according to the hospital charts and confirmed by telephone calls. The disability levels were assessed by using the mRS scoring [13].

Primary Outcome

A successful outcome, defined as disability-free survival (mRS score ≤ 2) at 6 months, was the primary outcome of the study. The secondary outcomes included severe disability and all-cause mortality in both the groups at 6 months. Severe disability was defined by an mRS score of 4 or 5 at the 6-month follow-up.

Statistical Analysis

The descriptive statistics of the baseline clinical parameters of the study population are presented as numbers and percentages and means and standard deviations (SDs) for categorical and continuous variables with normal distribution, respectively. Nonparametric data are presented as medians and interquartile ranges (IQRs) for continuous variables. We performed Mann-Whitney *U* tests to compare the medians. Bivariate analysis was performed using Pearson chi-square and Fisher's exact tests to assess the association between categorical variables. Independent-sample *t* tests were used to find the mean difference between 2 groups with continuous variables. Binary logistic regression was used to assess the magnitude of the association between the groups. Statistically significant factors were taken for the multivariate model. Sensitivity analysis was performed to account for the differences between the cohorts. The variance inflation factor (VIF) value was used to evaluate collinearity diagnostics. A mean VIF value of 1.61 indicated absence of multicollinearity. All tests were 2-sided at an $\alpha < .05$ level of significance. We did not perform multiple subgroup analysis. All analyses were performed using SPSS (version 23; IBM Corporation).

Ethics Statement

The study was approved by the Institutional Review Board (IRB) and Ethics Committee of the Christian Medical College, Vellore (IRB no. 14728). Individual consent to participate was waived by the IRB since this was a retrospective collection and data were recorded and analyzed anonymously.

RESULTS

Cohort A included 30 patients who received infliximab in addition to SOC. The mean age in this cohort was 31.1 (SD: 8.7) years. Twenty-two patients (22/30; 73.3%) had microbiologically confirmed TB. Most patients (27/30; 90%) had disseminated TB.

All patients in cohort A had baseline magnetic resonance imaging of the brain: tuberculomas (25/30; 83.3%) followed by basal meningitis (21/30; 70%), infarct (11/30; 36.7%), and hydrocephalus (11/30; 36.7%) were the common findings. The median duration from start of ATT and steroids to consideration of treatment with infliximab was 6 (IQR: 3.7–13) months. The median duration of neurological deficits before initiation of infliximab therapy was 4 (IQR: 2–6.2) months. Twenty-six (26/30; 86.7%) patients had focal neurological deficits (Table 1). Nineteen out of 30 patients (63.3%) showed PW. Among the 10 patients with mycobacterial culture-confirmed disease, 1 patient had multidrug-resistant TB, 1 patient had poly-resistant TB, while 2 patients had isoniazid-resistant TB (Supplementary Table 1).

At baseline, most patients in cohort A were severely disabled. A total of 26 of 30 (86.6%) patients had severe disability with mRS scores of 4 and 5. The indications for infliximab in cohort A were symptomatic multiple or large tuberculomas (20/30; 66.7%), spinal cord involvement with paraparesis (8/30; 26.7%), and vision-threatening optochiasmatic arachnoiditis (3/30; 10%). The duration of follow-up ranged from 6 to 40 months (median: 13 mo). Nineteen of our patients received 3 doses of infliximab, 7 received 2 doses, and 4 received only 1 dose. The details of patients in cohort A are described in Supplementary Tables 1 and 2. Brain and spinal images documenting treatment responses are shown in Figures 1 and 2.

We identified 60 patients in cohort B with CNS TB, with the majority (51/60; 84.9%) fulfilling definite and probable Lancet consensus criteria for TBM diagnosis. All patients received weight-optimized ATT and steroids. The median duration of ATT and steroids received was 12 (IQR: 7.3–18) months. The median duration of neurological deficits for this group was 2 (IQR: 1–5) months. Focal neurological deficits (50/60; 83.3%), basal meningitis (49/60; 81.7%), infarcts (31/60; 51.7%), and hydrocephalus (32/60; 53.3%) were comparable in both of the groups. A total of 27 of 60 (45%) patients had tuberculomas and 35% (21/60) had paradoxical worsening. Six people with human immunodeficiency virus (HIV), 4 with multidrug-resistant TB, and 1 each with isoniazid and ethambutol monoresistance were also present in cohort B. More data regarding CSF studies and radiological improvement are in shown in Supplementary Table 3.

All of the 25 patients (83.3%) who improved on infliximab had marked neurological improvement after the first dose. We also evaluated specific factors associated with improved outcomes in the infliximab group. There were no immediate infusion-related adverse events in the infliximab group. One patient developed multi-dermatomal herpes zoster 3 weeks post–infliximab therapy. Radiological improvement was noted in 19 of 26 patients (73.1%) receiving infliximab, 5 of 26 patients (19.2%) showed stable disease and 2 of 26 patients (7.6%) had worsening imaging findings. Four did not undergo follow-up imaging.

Cohort A showed a higher likelihood of a successful outcome at 6 months compared with cohort B (Relative risk, RR: 2.3; 95% confidence interval [CI]: 1.28–4.36). Additionally, severe

Table 1. Baseline Characteristics of Patients With Tuberculous Meningitis in Cohort A and Cohort B

Variable	Total (N = 90)	Cohort A (n = 30)	Cohort B (n = 60)	*P*
Age (mean ± SD), y	34.48 ± 11.8	31.10 ± 8.7	36.17 ± 12.8	.056
Sex, male, n (%)	54 (60)	15 (50)	39 (65)	.171
HIV-positive status, n (%)	7 (7.8)	1 (3.3)	6 (10)	.417
Microbiologically confirmed TB,[a] n (%)	53 (58.9)	22 (73.3)	31 (51.7)	.049
Lancet criteria (n = 84),[b] n (%)				
Definite	20 (22.2)	10 (33.3)	10 (16.6)	.209
Probable	55 (61.1)	14 (46.7)	41 (68.3)	
Possible	9 (10)	4 (13.3)	5 (8.3)	
Resistance,[c] n (%)	10 (11.1)	4 (13.3)	6 (10)	.726
Disseminated TB, n (%)	75 (83.3)	27 (90)	48 (80)	.369
TBM brain alone	66 (73.3)	19 (63.3)	47 (78.3)	.129
TBM brain + spinal cord	22 (24.4)	11 (36.7)	11 (18.3)	.056
Focal neurological deficits, n (%)	76 (84.4)	26 (86.7)	50 (83.3)	.767
Hemiparesis	32 (35.6)	8 (26.7)	24 (40)	.213
Paraparesis	21 (23.3)	9 (30)	12 (20)	.290
Visual impairment	19 (21.1)	8 (26.7)	11 (18.3)	.361
Arachnoiditis	21 (23.3)	7 (23.3)	14 (23.3)	1.000
Brain meningitis on imaging, n (%)	70 (77.8)	21 (70)	49 (81.7)	.209
Brain tuberculoma on imaging, n (%)	52 (57.8)	25 (83.3)	27 (45)	.001
Abnormal chest X-ray, n (%)	55 (61.1)	19 (63.1)	36 (60)	.760
Suboptimal dosing of ATT, n (%)	32 (35.6)	11 (36.7)	21 (35)	.876
Cumulative steroid dose (dexamethasone equivalents), median (IQR) (n = 86), mg	721.5 (387.7–1227.5)	717 (407.5–1244.1)	771.7 (383.5–1179)	.964
Paradoxical worsening,[d] n (%)	40 (44.4)	19 (63.3)	21 (35)	.011
MRC grades, n (%)				
Grade 1	10 (11.1)	3 (10)	7 (11.7)	.958
Grade 2	66 (73.3)	22 (73.3)	44 (73.3)	
Grade 3	14 (15.6)	5 (16.7)	9 (15)	
mRS scores at presentation, n (%)				
mRS grade 1–2	10 (11.1)	1 (3.3)	9 (15)	.155
mRS grade 3 to 5	80 (88.9)	29 (96.7)	51 (85)	

Abbreviations: ATT, antitubercular therapy; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; IQR, interquartile range; MRC, Medical Research Council; mRS, modified Rankin Scale; SD, standard deviation; TB, tuberculosis; TBM, tuberculosis meningitis.

[a] Microbiologically confirmed TB comprises either Xpert MTB/RIF Ultra (Cepheid, Sunnyvale, USA) or culture-positive patients.

[b] Six patients did not have CSF samples.

[c] Resistance comprises 5 multidrug-resistant TB, 1 polyresistant TB, 3 isoniazid-resistant, and 1 ethambutol-resistant.

[d] Cohort A showed paradoxical worsening (PW) in the form of the appearance of new or worsening tuberculomas (15), new infarcts (10), hydrocephalus (7), optochiasmatic arachnoiditis (2), or spine involvement (5). Cohort B developed PW in the form of the appearance of new infarcts (9), new tuberculomas or increased size of persisting tuberculomas (7), hydrocephalus (7), worsening basal meningitis (2), seizures (1), optochiasmatic involvement (3), and cognitive decline (2).

disability (mRS score: 4 and 5) at 6 months was observed in 5 of 30 patients (16.7%) in cohort A compared with 21 of 60 patients (35%) in cohort B. Cohort A showed a trend towards reduced mortality compared with cohort B (2/30 [6.7%] and 13/60 [21.7%], respectively). Two patients in cohort A and 13 patients in cohort B died. Both deaths in cohort A occurred at a mean of 4.5 (SD: 0.7) months after the last dose of infliximab while receiving ATT (Table 2).

In unadjusted analysis, the infliximab-receiving cohort was more likely to experience disability-free survival than the patients in cohort B (RR: 2.0; 95% CI: 1.26–3.17) as shown in Supplementary Figure 1. Patients with presence of focal neurological deficits, higher MRC grades of 2 and 3, and higher baseline mRS scores of 3 or more were less likely to have disability-free survival. On adjusting these covariates in a multivariate analysis model, receiving infliximab (adjusted RR [aRR]: 6.2; 95% CI: 2.18–17.83; *P* = .001) was the only exposure factor that was positively associated with disability-free survival, while the presence of focal neurological deficits was negatively associated (aRR: .2; 95% CI: .05–.89; *P* = .035) with disability-free survival (Table 3). Sensitivity analysis among the microbiological confirmed patients also showed a similar trend (RR: 1.4; 95% CI: .78–2.52).

DISCUSSION

In a carefully selected group of patients with CNS TB, who continue to worsen despite optimal ATT and steroids, adjunctive infliximab therapy may be a safe and effective agent to improve disability-free survival. Most of our patients were severely

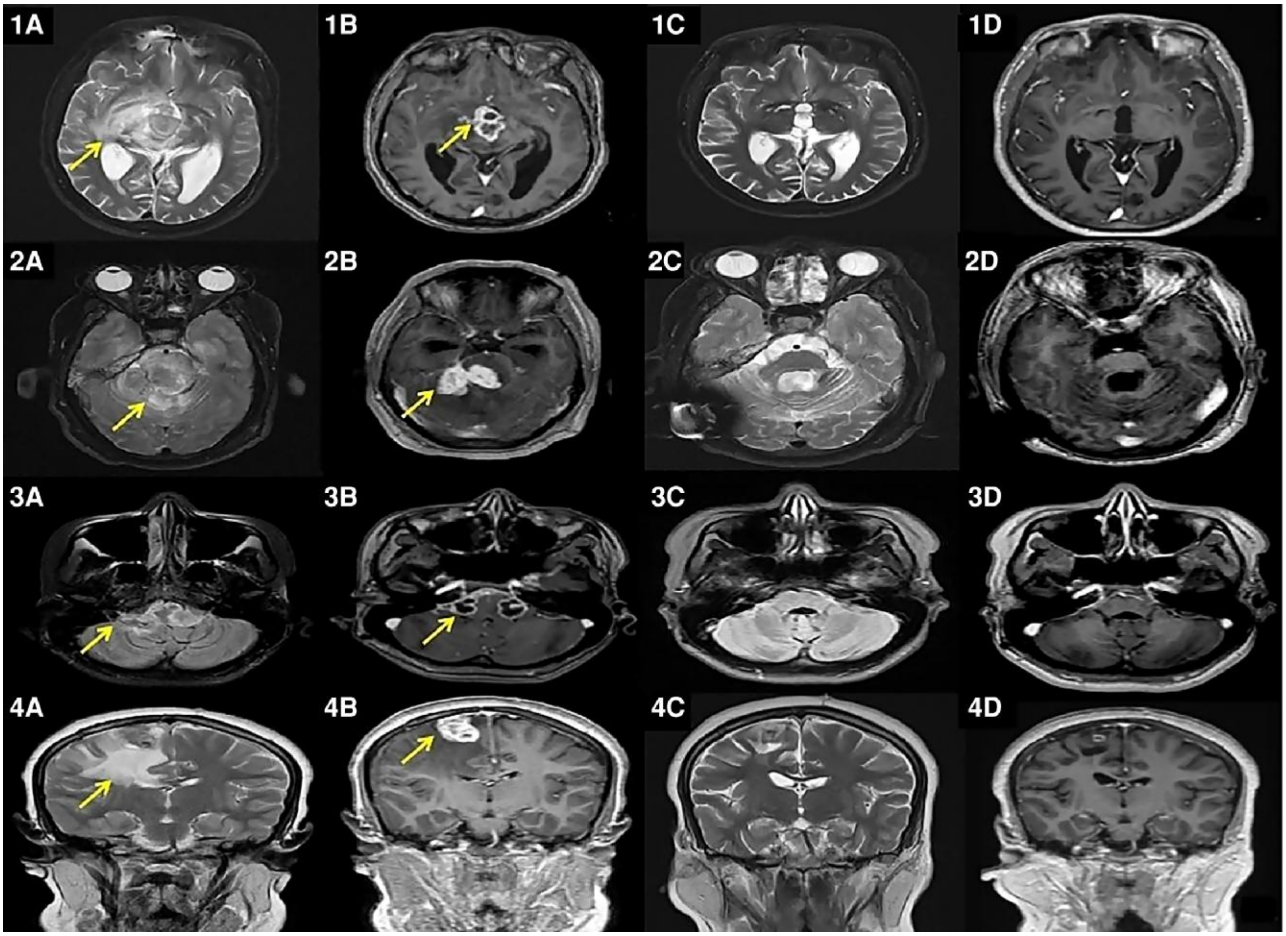

Figure 1. Baseline and post-infliximab MRI brain findings of 4 patients. Patient 1: T2-weighted axial scan (1*A*) shows a hypointense right capsulo-ganglionic and interpeduncular–suprasellar lesion with marked perilesional edema, and T1-weighted postcontrast axial scan (1*B*) shows a corresponding lesion that is a conglomerate ring. Post-infliximab T2-weighted axial scan (1*C*) after 12 months indicates marked resolution of the lesion and the perilesional edema, and post-infliximab T1-weighted postcontrast axial scan (1*D*) shows the resolution of the previous conglomerate ring enhancing lesion. Patient 2: T2-weighted axial scan (2*A*) reveals T2 hypointense middle cerebellar peduncle and pontine lesions with moderate to severe perilesional edema, and T1-weighted postcontrast axial scan (2*B*) indicates a corresponding conglomerate ring enhancing lesion. After 17 months, post-infliximab T2-weighted axial scan (2*C*) demonstrates marked resolution of the lesion and the perilesional edema with volume loss, and post-infliximab T1-weighted postcontrast axial scan (2*D*) shows resolution of the previous conglomerate ring enhancing lesion. Patient 3: FLAIR axial scan (3*A*) shows hyperintense bilateral middle cerebellar peduncle and ventral pontine parenchyma, and T1-weighted postcontrast axial scan (3*B*) shows corresponding bilateral ring enhancing lesions in the middle cerebellar peduncles with leptomeningeal enhancement along the ventral surface of the pons. After 10 months post-infliximab therapy, a FLAIR axial scan (3*C*) demonstrates marked resolution of the lesion and the perilesional edema, and post-infliximab T1-weighted postcontrast scan (3*D*) shows resolution of the previous ring enhancing lesions. Patient 4: T2-weighted coronal scan (4*A*) shows hypointense right frontal lesion with marked perilesional edema, and T1-weighted postcontrast coronal scan (4*B*) indicates thick, irregular enhancement with central, irregular nonenhancing areas. After 13 months post-infliximab therapy, T2-weighted coronal scan (4*C*) shows significant resolution of the lesion and the perilesional edema, and the post-infliximab T1 postcontrast scan (4*D*) shows the small residual ring enhancing lesion. Abbreviations: FLAIR, fluid attenuated inversion recovery; MRI, magnetic resonance imaging.

disabled at baseline, requiring help in executing activities of daily living. Infliximab potentially improved every third patient compared with conventional therapy. However, several caveats need to be borne in mind before the potential of this therapy is widely recommended.

First, the infliximab group had more patients with inflammatory lesions such as large tuberculomas compressing vital structures and adhesive, hyperplastic arachnoiditis. Mechanistically, these lesions are aggregates of granulomas, the pathological hallmark of TB. Granulomas are conglomerates of macrophages along with other cell types, coalescing to form multinucleated giant cells. TNF-α is a critical cytokine for the structure of the tubercular granuloma [14]. Both in vivo and in vitro data support the role of TNF blockade to disrupt and disintegrate granulomas [15, 16]. Hence, infliximab and similar agents are most beneficial among patients with solid enhancing lesions as against lesions like infarcts. Often, such lesions develop while receiving appropriate therapy, producing devastating clinical effects, such as tuberculomas producing neurological deficits or seizures, optochiasmatic arachnoiditis causing blindness, and spinal arachnoiditis resulting in paraparesis. Early consideration of TNF blockade in these patients may improve disability.

Figure 2. Baseline and post-infliximab MRI spine findings of 2 patients. Patient 1: T2-weighted sagittal scan (1*A*) shows expansile, heterogeneously hyperintense distal thoracic cord and conus, and T1-weighted postcontrast scan (1*B*) shows moderate heterogeneous enhancement in the intradural and subpial regions with small nonenhancing areas within. After 9 months post-infliximab therapy, T2-weighted sagittal scan (1*C*) shows residual lower thoracic cord conus hyperintensity and T1-weighted postcontrast scan (1*D*) demonstrates that the previously seen enhancing lesion has resolved. Patient 2: T2-weighted sagittal scan (2*A*) shows conglomerate extramedullary, intradural, T2-weighted hypointense lesions along the dorsal aspect of the thoracic cord extending from the C7 to T10 level with edema of the cord extending from the C6 level up to the conus, and T1-weighted postcontrast scan (2*B*) shows extensive linear and peripheral enhancement of the lesions in the intradural, subpial regions. After 9 months post-infliximab, T2-weighted sagittal scan (2*C*) shows lesions appearing more hypointense on T2 with a mild reduction in size. No change in the extent of the lesions and cord hyperintensity is seen; also, the T1-weighted postcontrast scan (2*D*) shows a reduction in the degree of postcontrast enhancement. Abbreviation: MRI, magnetic resonance imaging.

Second, our results support the excellent responses noted in case reports available in the literature. All of the 16 patients reported so far showed significant improvement on infliximab therapy [9, 10, 17–22]. The mean improvement in mRS score was 2.7 as compared to 2.1 in our cohort. Also, 88.2% of patients among the reported literature showed improvement after the first dose at 2.8 (SD: 2.5) weeks versus the 83.3% of our group at 1 month. Radiological improvement in the available literature occurred after 8.8 (SD: 8.3) weeks as compared to 12 (SD: 5.0) weeks in our cohort [9, 10, 17–22]. Clinical improvement after the first dose, rather than radiological changes, predicted overall outcome and response to future doses. The median duration of follow-up available from the literature was 10 (IQR: 6–17.5) months in comparison to 13 (IQR: 10–21.2) months in our cohort. There have so far been no side effects reported from the use of infliximab. Our patient with multi-dermatomal herpes zoster had advanced HIV infection (CD4 count: 52 µL/mL) and was simultaneously receiving high-dose steroids as well.

Table 2. Treatment Outcomes for Cohort A and Cohort B at 6 Months

Variable	Total (N = 90)	Cohort A (n = 30)	Cohort B (n = 60)	RR (95% CI)	*P*
Successful outcome, post-therapy, mRS ≤2	38 (42.2)	19 (63.3)	19 (31.7)	2.3 (1.28–4.36)	.004
Unsuccessful outcome, post-therapy mRS 3–6	52 (57.8)	11 (36.7)	41 (68.3)		
Severe disability, post-therapy mRS scores 4 and 5	26 (28.9)	5 (16.7)	21 (35)	.4 (.21–1.14)	0.070
Mortality[a]	15 (16.7)	2 (6.7)	13 (21.7)	.3 (.09–1.34)	.081

Data are presented as n (%) unless otherwise indicated.

Abbreviations: CI, confidence interval; mRS, modified Rankin Scale; RR, Relative risk; TBM, tuberculosis meningitis.

[a] In cohort A, 1 patient died due to probable aspiration pneumonia and another had sudden death in sleep. In cohort B, of the 13 deaths, 11 patients died due to TBM disease progression. The other 2 died of unrelated causes, 1 due to acute *Escherichia coli* pyelonephritis with bacteremia and another because of enterococcal bacteremia.

Table 3. Multivariate Logistic Regression for Predictors of Treatment Outcome at 6 Months

				Univariate Analysis		Multivariate Analysis	
Variable	Total (N = 90)	Successful Outcome (n = 38)	Unsuccessful Outcome (n = 52)	RR (95% CI)	*P*	Adjusted RR (95% CI)	*P*
Age (mean ± SD), y	34.48 ± 11.8	33.4 ± 9.4	35.2 ± 13.4	1.0 (.97–1.05)	.491	…	
HIV-positive status, n (%)	7 (7.8)	3 (7.9)	4 (7.9)	1.0 (.41–2.47)	1.000	…	
Microbiologically confirmed TB, n (%)	53 (58.9)	24 (63.2)	29 (55.8)	1.1 (.72–1.98)	.482	…	
Presence of focal neurological deficit, n (%)	76 (84.4)	28 (73.7)	48 (92.3)	.5 (.33–.80)	.020	.2 (.05–.89)	.035
MRC grades 2 and 3, n (%)	80 (88.9)	30 (78.9)	50 (96.2)	.4 (.30–.71)	.016	1.0 (.08–12.92)	.955
MRC grade 1, n (%)	10 (11.1)	8 (21.1)	2 (3.8)				
Baseline mRS 3–5, n (%)	80 (88.9)	30 (78.9)	50 (96.2)	.4 (.30–.71)	.016	.09 (.007–1.12)	.062
Baseline mRS ≤2, n (%)	10 (11.1)	8 (21.1)	2 (3.8)				
Received infliximab, n (%)	30 (33.3)	19 (50)	11 (21.1)	2.0 (1.26–3.17)	.004	6.2 (2.18–17.83)	.001
Did not receive infliximab, n (%)	60 (66.7)	19 (50)	41 (78.8)				

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MRC, Medical Research Council; mRS, modified Rankin Scale; RR, Relative risk; SD, standard deviation; TB, tuberculosis.

Infliximab is expensive, and it is important to identify the subgroup of patients who benefit from its use. This also avoids excess immunosuppression in patients who are unlikely to improve. Patients with symptomatic large inflammatory lesions with a shorter duration of neurological deficit (<3 mo) may respond better with infliximab. An absence of improvement with the first dose can identify patients who may not need subsequent doses. The responses with spinal pathologies were poorer in comparison to those with brain lesions [13].

Several other therapies to inhibit TNF-α in CNS TB exist in the literature. Thalidomide is a weak TNF blocker with dose-dependent immunomodulatory benefit [23]. A randomized trial in tubercular meningitis evaluating a high dose (24 mg/kg/d for 1 mo) of thalidomide was stopped early due to side effects and increased mortality [24]. Subsequently, lower doses of thalidomide (5 mg/kg/d) resulted in clinical benefit among children with tuberculomas and optochiasmatic arachnoiditis [25]. Another phase I study evaluating the efficacy and safety of etanercept in HIV-associated, sputum-positive pulmonary TB reported improved general status of patients, hastened radiological clearance, and accelerated CD4 recovery in relation to historical controls [26]. Adalimumab has also been shown to be beneficial in patients with CNS TB. However, the relative efficacy of these agents in comparison to other immunomodulatory strategies has not been well studied so far.

How best can we further study the efficacy of infliximab and other similar agents? No randomized controlled trials (RCTs) have even evaluated the role of steroids in the management of tuberculomas, for instance. Paradoxical worsening may happen months into treatment and can complicate recruitment [27]. The neurological lesions and the clinical deficits that may respond to these therapies are also heterogeneous. These agents are best studied in adaptive trial designs recruiting patients with clinical deficits that are new or not improving despite ATT and steroids. The possibility of dissemination or reactivation of TB elsewhere following infliximab is also an important consideration when these trials are designed [28]. Antitubercular therapy should be continued at least for 6 months (like in our study) to prevent active TB post–TNF blockade. A follow-up period of 2 years is needed to study TB reactivation [29] when interventional studies are planned. These interventions could be built within large RCTs evaluating various antimycobacterial regimens, subsequently randomizing patients who develop inflammatory worsening, to reduce morbidity and mortality [30].

While the study reports the potential benefit with aggressive TNF blockade among patients with CNS TB, several limitations need to be borne in mind when interpreting the results. First, the study was retrospective in design, with a relatively smaller number of patients. Second, the cohorts were matched only for functional status. The CNS TB lesions and incidence of PW were dissimilar between the cohorts. Hence, cohort B serves more as a background to interpret the impact of infliximab among patients in cohort A rather than rigorously matched controls. Third, our institution is a quaternary referral center and a considerable number of patients presented with late and advanced disease, precluding earlier infliximab administration. As with any intervention, outcomes may have been better if patients received infliximab early. We used a relatively higher dose of infliximab. More data on outcomes with lower doses (eg, 5 mg/kg) may reduce the cost of this intervention. Finally, as many of these patients had large lesions in the brain, relatively few patients could undergo lumbar puncture safely. This resulted in a lack of CSF data in many patients. Despite these significant limitations, this study provides early data to consider infliximab for further study in a future clinical trial.

In summary, infliximab may be a useful and safe adjunctive strategy among significantly disabled patients with CNS TB, despite adequate ATT and steroids.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. A. M. and S. S. K. D. conceptualized the study. P. G., S. S. K. D., K. G., and N. C. T. curated the data. P. M. and A. J. provided the radiological assessment of the patient images. P. G. and P. S. wrote and approved the statistical analysis plan. P. G. performed the formal analysis. A. M., P. G., and S. S. K. D. wrote the original draft of the manuscript. A. M., P. G., S. S. K. D., P. M., A. J., K. G., N. C. T., R. N. B., L. R. I., E. D., M. M. G., R. K., O. C. A., H. A. V., A. S., P. T. A., E. J., J. S. M., P. S., and G. M. V. reviewed, edited, and approved the manuscript.

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Data sharing. The data underlying this article will be shared on reasonable request to the corresponding author.

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