Review Article

Role of Corticosteroids in the Treatment of Tuberculosis: An Evidence-based Update

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Abstract

Corticosteroids are often used as an adjunct in the treatment of various forms of tuberculosis (TB) and for the prevention of complications, such as constrictive pericarditis, hydrocephalus, focal neurological deficits, pleural adhesions, and intestinal strictures. Notwithstanding, they have been proven in clinical trials to improve the following outcomes only death or disability in human immunodeficiency virus (HIV)-seronegative patients with tubercular meningitis and tubercular pericarditis. Despite a lack of specific evidence for efficacy in HIV co-infected patients with tubercular meningitis or pericarditis, corticosteroids are generally recommended in them as well. Corticosteroids significantly decrease the risk of pleural thickening in patients with tubercular pleural effusion; the clinical significance of this finding, however, is unclear. Recently, it has been demonstrated that use of corticosteroids improves the morbidity in HIV co-infected patients with paradoxical TB immune reconstitution inflammatory syndrome (IRIS). However, evidence favouring the use of corticosteroids in other clinical situations is sparse or lacking. Likewise, the biological mechanisms underlying their beneficial effect in TB meningitis and pericarditis remain poorly understood.

Key words: Glucocorticoids; HIV infection; Immune reconstitution inflammatory syndrome; Treatment outcome; Tuberculosis

Introduction

Corticosteroids (specifically glucocorticoids) have been used as an adjunct in the treatment of various forms of tuberculosis (TB) for about six decades now. While considerable scepticism exists regarding their efficacy, corticosteroids are often over-prescribed in actual practice hoping to prevent the sequelae of TB, such as intestinal and constrictive pericarditis. Ever since the authoritative review on this topic by Dooley et al[1] was published, several large randomised controlled trials (RCTs) have been conducted, and at least three Cochrane systematic reviews have been performed. In the present article, we present an overview of these developments and also address the gaps in current evidence. The landmark British Medical Research Council trial of streptomycin for the treatment of pulmonary TB was published in the year 1948[2]. Incidentally, in the same year Philip Hench and colleagues[3] discovered the anti -inflammatory properties of cortisone. The worldwide popularity brought about by the award of Nobel prize to this discovery[4] perhaps inspired the early attempts to use corticosteroids for the treatment of TB despite a lack of empirical evidence . Rather, data from animal experiments actually suggested that the use of corticosteroids might worsen the disease[5]. This

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prompted the American Thoracic Society (then known as the American Trudeau Society) to caution against using corticosteroids in TB[6]. Soon, reports of reactivation and dissemination of TB in humans following corticosteroid use started appearing in the literature[7,8]. Undaunted by these setbacks , some investigators[9] demonstrated that clinical outcomes in certain forms of extrapulmonary TB (particularly meningitis) could potentially be improved by the concurrent use of antimycobacterial agents (streptomycin with para amino salicylic acid) and corticosteroids. Many of the early clinical studies also focused on the use of corticosteroids in pulmonary TB. However, the advent of combination chemotherapy dramatically improved the outcomes in pulmonary TB to such an extent that corticosteroids were almost abandoned as an adjunct in pulmonary TB. On the other hand, common occurrence of adverse outcomes such as death, neurological disability, and fibrotic sequelae such as pleural fibrosis loculations, constrictive pericarditis, and strictures of hollow viscera such as the intestine and ureter despite effective antimycobacterial treatment has kept alive the quest for adjunctive treatments in extrapulmonaryTB.

Corticosteroids in tubercular meningitis

Tubercular meningitis (TBM) is uniformly fatal if not treated. An earlier Cochrane systematic review[10] concluded that corticosteroids significantly improved the mortality among children with TBM while the effect on mortality in adults was inconclusive .Recently, Thwaites and colleagues[11] had carried out the largest-ever RCT of corticosteroids in adolescents and adults with TBM in Vietnam. Following the publication of this trial, Prasad and Singh[12] updated their Cochrane systematic review on the efficacy of corticosteroids in TBM.[12] The combined mortality in the control arms (anti-tuberculosis treatment [ATT] only) of the seven RCTs included in this systematic review was 40%; the overall disability-free survival was only 48 percent. Thus, in patients with TBM, risk of death and residual disability still remains very high despite the use of combination chemotherapy regimens that otherwise have more than 95% efficacy in new sputum smear-positive pulmonary TB cases. The poor outcomes are often attributed to the development of complications, such as hydrocephalus, arachnoiditis, and vasculitic infarcts, as a result of unbridled inflammation. Corticosteroids have been found to significantly decrease the risk of death by 22 % (relative risk reduction) and improve the disability-free survival by about 22 % in TBM12 (Figure). Treating about 13 patients with corticosteroids in addition to ATT could prevent one additional death in TBM[12]. Contrary to conventional knowledge, Prasad and Singh[12] found that corticosteroids confer a survival benefit irrespective of the severity of TBM. On the other hand, evidence to use of corticosteroids in human immunodeficiency virus (HIV) co-infected patients with TBM is scanty. Only one RCT 11 had included patients with HIV -associated TBM. In this study, subgroup analysis failed to demonstrate a statistically significant benefit of corticosteroids in HIV -associated TBM. Central nervous system TB may at times present as focal space-occupying lesions of the brain parenchyma or the spinal cord (tuberculoma) with or without evidence of meningitis. Anecdotal reports suggest that corticosteroids might hasten symptomatic improvement when tuberculoma results in mass effect or refractory seizures[13]. However, efficacy of corticosteroids in this clinical setting has not been formally evaluated in clinical trials. Paradoxically, tuberculoma may develop in patients being treated for TBM despite the use of adjunctive corticosteroids.

Corticosteroids in tubercular pericarditis

As with TBM, patients with tubercular pericarditis often develop complications such as cardiac tamponade and constrictive pericarditis necessitating therapeutic interventions. In addition, tubercular pericarditis is associated with a considerable mortality of about 15%, and only about two-third of patients (66%) survive without disability at two years[14,15]. Four RCTs have evaluated the role of corticosteroids in TB pericarditis; one of them was exclusively for HIV co-infected patients[16]. A meta-analysis of these trials found that corticosteroids decreased the risk of all-cause mortality by 35% (relative risk reduction) in HIV-seronegative patients with tubercular pericarditis.[17] However, this reduction failed to achieve statistical significance. Likewise, corticosteroids did not significantly reduce the need for pericardiectomy (Figure). Nonetheless, corticosteroids resulted in a modest 45% improvement in disability-free survival at two years with considerable heterogeneity among the trials[17]. Strang et al[18] reported in a long-term follow-up of the Transkei trial participants that the apparent clinical benefit of corticosteroids was maintained even 10 years

after treatment. Although it may not be a valid interpretation, it seems that the clinical benefit of corticosteroids, if any, is attenuated in patients with established constrictive pericarditis as compared to those with effusive tubercular pericarditis[17]. The only trial of corticosteroids in HIV co-infected patients with tubercular pericarditis found a 50% relative reduction in all-cause mortality; however, this improvement was not statistically significant[18].

Corticosteroids in tubercular pleural effusion

Most tubercular pleural effusions resolve spontaneously even without specific ATT[19]. However, the resolution is often incomplete leaving behind loculated collections and considerable pleural thickening. It is believed that corticosteroids might reduce these fibrotic sequelae and hasten the resolution of pleural effusion as well as clinical symptoms. In a Cochrane systematic review, Engel et al[20] found that corticosteroid use had no appreciable effect on the resolution of pleural effusion at eight weeks and development of pleural adhesions. However , two small trials[21,22] found that corticosteroids significantly decreased the duration of clinical symptoms by about 4.3 days .Unexpectedly, Engel et al[20] found that corticosteroids significantly reduced the risk of pleural thickening by about 31% (Figure). It is worth noting that two of the four trials that assessed pleural thickening had also compared the pulmonary functions by forced vital capacity at the end of treatment between the corticosteroid and control arms[23,24]. Discordant with the effect on pleural thickening , no significant improvement in pulmonary functions was found. Thus, the clinical significance of the reduction in pleural thickening by corticosteroids is questionable. Only one trial[25] was conducted in HIV co-infected patients with TB pleural effusion. In this trial, use of corticosteroids was associated with faster clinical as well as radiological improvement. However, it was also associated with a significantly increased risk of Kaposi's sarcoma and a non-significant but higher risk of recurrent TB.

Corticosteroids in other forms of extrapulmonary TB

Credible evidence from clinical trials for the use of corticosteroids in other infrequent forms of TB, such as genitourinary TB and laryngeal TB, is sparse. Scanty evidence does exist on the use of adjunctive corticosteroids in peritoneal TB, miliary TB, and mediastinal TB lymphadenitis.1 However, they are all inconclusive in nature. A small RCT[26] of 47 patients with peritoneal TB from India found a non-significant reduction in the development of late fibrotic complications (symptomatic intestinal obstruction). Likewise, another trial[27] of corticosteroids in 55 patients with miliary TB found a statistically non-significant reduction in mortality. Acute respiratory distress syndrome (ARDS) occasionally complicates the clinical course of pulmonary and miliary forms of TB[28]. Most patients with TB-related ARDS succumb to the illness. Corticosteroids might be used in such settings as a desperate measure despite a lack of specific evidence, which is unlikely to be ever generated.

For obvious reasons, clinically manifest adrenal insufficiency as a result of TB is an absolute indication for corticosteroids . On the other hand, corticosteroid replacement may not be necessary for subclinical adrenal insufficiency which is common among patients with pulmonary as well as extrapulmonary TB. Adrenal function recovers in most of these patients with ATT alone[29]. However, it is worth exploring whether correcting the subclinical adrenal insufficiency, if present, could improve the short-term mortality in critically-ill patients with TB.

Corticosteroids in Pulmonary TB

Several RCTs have been conducted in the past to evaluate the effect of corticosteroids in pulmonary TB. Smego and Ahmed[30] in a systematic review on this topic identified 11 such trials. However, we did not come across any new published trial after this systematic review. Although many trials found significantly faster clinical and radiological improvement in patients treated with adjunctive corticosteroids, it is important to note that only two of these 11 trials had used rifampicin-based regimens. Of the two trials that used rifampicin-based regimens, one was a fairly larger one with 530 sputum smear-positive patients conducted at the Tuberculosis Research Centre, Chennai[31]. Interestingly, in this trial corticosteroids had no significant effect on radiological and bacteriological responses. Thus, the role of corticosteroids in pulmonary TB when used alongside modern-day rifampicin-based regimens is questionable. Notwithstanding, these trials do bring out a fact that bacteriological response will not be adversely affected by concurrent use of corticosteroids and effective ATT; only one of the 11 trials found delayed sputum

conversion with corticosteroids[30]. However, it needs to be cautioned that this finding might not hold true for patients with drug-resistant TB[32].

Anecdotal reports suggest that corticosteroids might be beneficial in patients with endobronchial TB. However, in one trial 32 of 34 patients with endobronchial TB, corticosteroids had no appreciable effect on bronchoscopic healing rate, radiological findings, and pulmonary functions.

Corticosteroids in HIV-related TB

Evidence from clinical trials on the use of corticosteroids in specific forms of HIV related extrapulmonary TB has been dealt with earlier. Immune reconstitution inflammatory syndrome (IRIS) reactions occur commonly in HIV co-infected patients with TB. While most instances of IRIS reactions are self -limited and respond to nonsteroidal anti inflammatory drugs, corticosteroids may be used to treat severe TB-IRIS reactions and those unresponsive to non -steroidal anti - inflammatory drugs[33]. In a recently concluded RCT [34] of 1 0 9 HIV co -infected patients with paradoxical TB-IRIS, corticosteroids modestly improved the composite outcome of duration of hospital stay and outpatient therapeutic procedures (counted as one additional day of hospitalisation). Further, corticosteroids also improved secondary outcomes, such as symptom score, performance status, quality of life, radiological severity, and C-reactive protein level. However, this trial was not powered to detect a difference in mortality between the two groups.

Biological mechanisms underlying the clinical benefit of corticosteroids

While it is simple and logical to conceive that corticosteroids improve the clinical outcomes in TB by suppressing the host mediated inflammation, direct evidence for such an effect in humans has proved elusive. An earlier RCT[35] in children with TBM had found that corticosteroids resulted in faster recovery of cerebrospinal fluid (CSF) glucose levels and faster resolution of elevated CSF protein, while it had no effect on CSF pleocytosis. Very recently, Simmons et al36 found that the clinical benefit of corticosteroids in the Vietnam TBM trial was not accompanied by a measurable suppression of immune responses both in the peripheral blood as well as the CSF. Serial magnetic resonance imaging of the brain was also performed in a subset of patients in this study[36]. It was found that use of corticosteroids possibly reduced the risk of developing hydrocephalus and vasculitic infarcts; however, these findings were not statistically significant due to inadequate sample size[37]. Matrix metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) are purported to play an important role in the disruption of the blood-brain barrier in TBM. Corticosteroids significantly reduce the CSF levels of MMP - 9 in patients with TBM[38]. Corticosteroids also inhibit Mycobacterium tuberculosis-induced production of VEGF in vitro[39]. However, clinical significance of these laboratory findings is unclear. Thus, while credible evidence exists to support the beneficial effects of corticosteroids in TB, specifically TBM, the exact mechanisms of such benefit remain poorly understood[40]. Thwaites et al 11 have put forward an interesting hypothesis to explain the clinical benefit of corticosteroids in TBM . They observed that treatment-limiting adverse events that necessitated a change in ATT were less common in the corticosteroid arm, and such changes in ATT were independently associated with death on multivariable analysis[11]. Based on these findings ,they proposed that "dexamethasone may improve outcomes by reducing the frequency of adverse events that necessitate a change in the antituberculosis-drug dose or regimen - severe clinical hepatitis , in particular.[11] This hypothesis needs verification in future studies.

EVIDENCE-BASED RECOMMENDATIONS

From the foregoing discussion, it emerges that the only clinical indication for which corticosteroids have been demonstrated to be beneficial beyond reasonable doubt is TBM, especially in HIV-seronegative patients. Thus, corticosteroids are recommended in all HIV-seronegative patients with TBM irrespective of age and clinical stage (Table). While specific evidence for efficacy among HIV co-infected patients is lacking, it is reasonable to use corticosteroids to treat HIV co-infected patients with TBM as well[41].

Table.1 Recommended dosage regimens of corticosteroids in extrapulmonary TB.[41,42] (Adapted from Thwaites et al[11]) *=Stage 1, Glasgow coma scale (GCS) score 15 and no focal neurological deficits;
Stage 2, GCS score 11-14 or focal neurological deficits present;
Stage 3, GCS score less than 11
†=Administered as three divided doses in the Transkei trials;14,15 i.v.=intravenous.

Corticosteroids seem to have a potential benefit in

ClinicalCondition	Regimen
Tubercular meningitis Total duration 6 weeks (Stage 1)	*Inj. Dexamethasone 0.3 mg/kg i.v. Day 1-7; 0.2mg/kg i.v. Day 8-14; 0.1 mg/kg i.v.Day 15-21 Followed by Tab. Dexamethasone 3 mg/day orally Days 22-28; 2 mg/day orally Days 29-35; 1 mg/day orally Days 36-42
Tubercular meningitisTotal duration 8 weeks (Stages 2 and 3)*	Inj. Dexamethasone 0.4 mg/kg i.v. Day 1-7; 0.3 mg/kg i.v. Day 8-14; 0.2 mg/kg i.v. Day 15-21; 0.1 mg/kg i.v. Day 22-28 Followed by Tab. Dexamethasone 4 mg/day orally Days 29-35; 3 mg/day orally Day 36-42; 2 mg/day orally Day 43-49; 1 mg/day orally Day 50-56
Tubercular pericardial effusion Total duration 11 weeks	Tab. Prednisolone 60 mg/day† orally Day 1-28; 30 mg/day† orally Day 29-56; 15 mg/day† orally Day 57-70; 5 mg/day orally Day 71-77

patients with tubercular pericarditis. However, more robust evidence is required. Meanwhile, it is prudent to use corticosteroids in patients with tubercular pericarditis (both effusive and constrictive) irrespective of the HIV serostatus[42] (Table). However, these recommendations are likely to change with the availability of more clinical evidence in the future. On the other hand, although it has been found that corticosteroids reduced the risk of pleural thickening, clinical significance of this benefit is unclear. Hence, the use of corticosteroids is not recommended in tubercular pleural effusion.

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