

Review Article

ADJUNCTIVE CORTICOSTEROID THERAPY IN TUBERCULOSIS MANAGEMENT: A CRITICAL REAPPRAISALDr. Naveen Chhabra¹, Dr. Ramakant Dixit², Dr. M.L.Aseri³**Address for Correspondence**¹Resident Doctor, Deptt. of Pharmacology; J.L.N. Medical College, Ajmer, Raj. INDIA²Asstt. Professor, Deptt. of Respiratory Medicine, J.L.N. Medical College, Ajmer Raj. INDIA³Prof. & Head; Deptt. of Pharmacology; J.L.N. Medical College, Ajmer Raj. INDIAE mail: drchhabranaveen12@gmail.com**ABSTRACT**

Despite availability of effective chemotherapy for tuberculosis, significant morbidity and mortality due to this disease continue to occur. With global increase in tuberculosis following HIV pandemic, there are many unusual and more extra pulmonary tuberculosis with paradoxical reactions during anti tuberculosis therapy. An extensive, although largely forgotten literature addresses the utility of adjunctive corticosteroid therapy in the management of tuberculosis. This has been shown to improve outcome and decrease mortality in severe form of tuberculosis and strongly recommended by CDC in CNS and pericardial tuberculosis. Patients with extensive pulmonary disease with severe systemic and respiratory morbidity, improves faster of tuberculosis and management related complications at times also requires systemic steroid therapy provided there are sensitive organisms. However, one should closely observe such patients and should not forget drug interactions that may occur during treatment.

KEY WORDS: Corticosteroids, IRIS, Tuberculous meningitis, Pericardial TB, HIV Infection, Miliary TB, Adesonian Crisis

INTRODUCTION

The effectiveness of corticosteroids against M.Tuberculosis was studied earlier in animal models of Tuberculosis & it was found that in those animals who didn't receive any specific antituberculous therapy, the virulence of M. tuberculosis was enhanced markedly by Corticosteroid administration^(1,2).

When anti tuberculous agents were developed, results of various studies conducted repeatedly suggested that harmful effects of corticosteroid administration on M. tuberculosis infection were abrogated when effective antitubercular therapy (streptomycin or isoniazid) was co administered⁽³⁾ (reviewed⁽⁴⁾). Anecdotal experiences, by the 1950s, with humans parallels to the animal models suggested that corticosteroid therapy for patients with TB, without anti tuberculous therapy, was hazardous⁽⁴⁾, but co administration of corticosteroids with anti tuberculous drugs could improve outcomes⁽⁵⁻⁹⁾. The results of these studies motivated various clinicians & scientific bodies to carry out controlled studies investigating the utility of adjunctive corticosteroid therapy for clinical TB. Corticosteroids when used in conjunction with effective antituberculous therapy has been beneficial in miliary tuberculosis, tuberculous meningitis, tuberculous pericarditis. Corticosteroids improve the outcome in tuberculosis by suppressing the host mediated inflammation. Review of the literature reveals that the effects of steroids on tuberculosis in patients being treated with effective

antituberculous therapy are beneficial, but the benefits are variable. Adjunctive corticosteroid therapy may be life saving in patients with miliary tuberculosis, is little doubtful. The recent increase in tuberculosis is disturbing and not entirely related to the increase in AIDS. Although corticosteroid therapy has been one of the great therapeutic advances in the history of medicine, for decades it has been appreciated that steroid therapy given to patients with untreated or unrecognized tuberculosis results in overwhelming disease and death. Eleanor Roosevelt died of undiagnosed miliary tuberculosis while being treated with steroids for what was thought to be sarcoidosis. Therefore, clinician must closely observe patients and drug interactions that may occurs during treatment should be kept in mind.

When to use steroids in Tuberculosis:

Definite indications to use steroids are CNS Tuberculosis, Pericardial Tuberculosis & Adrenal insufficiency while Reasonable indications are IRIS/Paradoxical response, Far advanced Pulmonary TB with severe systemic & respiratory morbidity, Severe cutaneous hypersensitivity reactions to anti-TB drugs, Persistent fever even after 3-4 weeks of T/t, Bronchial obstruction, Miliary TB with toxemia and Other indications are BCG scar Keloid, Sick/elderly/extensive primary TB with large pleural effusion, TB in HIV Positive patients(?), laryngeal TB(?), Genitourinary TB(?), Tubercular pneumonia with

Acute Respiratory Failure, Tubercular sarcoidosis; lymph node TB.

Steroids for treating tubercular meningitis

Tuberculous meningitis (TBM) is an inflammation of the meninges covering the brain and spinal cord caused by infection with mycobacteria, most usually *Mycobacterium tuberculosis*. The condition usually presents with headache, fever, and convulsions and is diagnosed clinically, with confirmation by microscopy and culture of cerebrospinal fluid.

HIV-infected patients are at higher risk of TB, and this has increased the incidence of TBM in these populations. TBM was the most common cause of meningitis, accounting for more than 25% of cases. Without drug treatment patients with TBM die. Monotherapy with streptomycin, an early TB drug, reduced the case fatality rate to 63%. TB drugs (isoniazid, rifampicin, and pyrazinamide) used in combination are associated with better survival, but the mortality remains substantial. Recent reports estimate fatality rates varying from 20% to 32%, with permanent neurological deficits in 5% to 40% of the survivors.

Corticosteroids improve outcome as these

- (1) Decrease inflammation, especially in the subarachnoid space.
- (2) Reduce cerebral and spinal cord oedema.
- (3) Reduce inflammation of small blood vessels and therefore reduce damage from blood flow slowing to the underlying brain tissue.

Corticosteroid therapy based upon urgent warning signs:

Patients who are progressing from one stage to the next at or before the introduction of chemotherapy,

especially if associated with any of the conditions listed below.

- a. Patients with an acute "encephalitis" presentation, especially if the CSF opening pressure is > 400 mmH₂O or if there is clinical or CT evidence of cerebral edema.
- b. Exacerbation of clinical signs (eg, fever, change in mentation) after beginning antituberculous chemotherapy.
- c. Spinal block or incipient block (CSF protein >500 mg/dL and rising)
- d. Head CT evidence of marked basilar enhancement (portends an increased risk for infarction of the basal ganglia) or moderate or advancing hydrocephalus
- e. Patients with intracerebral tuberculoma, where edema is out of proportion to the mass effect and there are any clinical neurologic signs

Steroid in Pericardial TB

In early stages of Pericardial TB corticosteroid therapy decreases fluid accumulation, ↓ need for procedure and even in late stage improve symptomatic & hemodynamic recovery. In a study⁽¹¹⁾ results were: active effusive TB Pericarditis the mortality rate was 3% vs. 14% & reduced need for repeated pericardiocentesis (7 of 76 vs. 17 of 74) & in inactive constrictive TB pericarditis mortality reduced and need for subsequent pericardiectomy (9% vs 23%). Above 143 with constrictive TB and 240 with effusive TB pericarditis, re evaluated at 10 yrs; steroid receiver conferred a significant survival advantage

Recommended dosage regimens of Corticosteroids in Tubercular Meningitis⁽¹⁰⁾

Stage 1	Total duration of treatment – 6 weeks
Glassgow Coma scale score <15; no focal neurological deficit	Inj. Dexamethasone .3 mg/kg i.v. day 1-7; .2 mg/kg day 8-14; .1 mg/kg 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 day 36-42
Stage 2 & 3;	Total duration of treatment – 8 weeks
Stage 2- Glassgow Coma scale score- 11-14; or focal neurological deficit present	Inj. Dexamethasone .4 mg/kg i.v. day 1-7; .3 mg/kg day 8-14; .2 mg/kg day 15- 21; .1 mg/kg day 22-28 followed by tab. Dexamethasone 4 mg/day orally days 29-35
Stage 3- Glassgow Coma scale Score - < 11	3 mg/day orally days 36-42 2 mg/day orally days 43-49 1 mg/day orally day 50-56

Steroids for Pulmonary TB

After Systemic review of 11 randomized comparative clinical trials⁽¹²⁾ conducted from 1958-1999 which included 1814 steroid treated patient analyzed with moderate to severe disease with regimens : prednisolone, prednisolone &/or ACTH along with ATT; Outcome evaluation in these trials was based on clinical, radiographic, microbiological and overall survival ;the results in these trials were ,clinical outcome were :more rapid in time of defervence, more earlier significant weight gain ,rapid normalization of ESR & S. albumin ,more reduction in hospital stay; Radiological outcome were: 9 of 11 studies showed earlier resolution of pulmonary infiltrates more rapid ↓ & closer of cavities in 6 of 11 studies & bacteriological outcome were : no statistically significance in rapidity of sputum conversion one showed delay while 3 showed +ve effect on sputum conversion.

The summary of 11 controlled trials of steroids use in PTB is⁽¹³⁾: Clinical condition improved more rapidly (effect more pronounced in severely ill), absence of long term beneficial effect (on mortality and chronic restrictive disease), faster radiological response (rates of cavities does not affected), minority of patients may have mild 'rebound' phenomenon if steroids discontinued too abruptly ;Steroids administration in the face of inadequate ATT appears harmful to patients.

Steroids in Pleural TB

Corticosteroids in pleural TB reduces the fibrotic sequale .In a study results were⁽¹⁴⁾: early resolution of clinical symptoms & signs i.e. fever, chest pain, dyspnea, no difference in dev. of residual pleural thickening or adhesions on follow-up, residual functions were similar at completion on treatment, evidence regarding use of steroids in TB pleural effusion not clear. Steroids in Pleural TB are reserved for patients with large effusions, dyspnoea &/or disabling chest pain and elder patients. Benefits are more palliative & temporary & systemic steroids are superior to local steroids

Steroids in HIV-TB Disease

Non randomized trials in Zambia used in pericardial effusion, pleural effusion or cutaneous

drug eruptions, there was⁽¹⁵⁾ Significant decrease in generalized lymph-adenopathy & cough at 2 months but Undesirable increase in H zoster (13%) & Kaposi sarcoma(6%) & there was no difference in survival at 1 yr.

Data do not support use of steroids in reducing morbidity & mortality due to TB directly or influencing survival due to slowing of HIV progression.

Steroids in Miliary TB

Study from China⁽¹⁶⁾ in 1981 suggest non significant trend toward better outcome in steroid group than for controls (death: 2 of 27 Vs 5 of 28). Available data suggest a lack of effect of steroids on acute miliary TB & Severely ill patients needs.

Adesonian crisis during ATT

Some patients of post-primary TB may have true addison disease (1% to 58%)⁽¹⁷⁾ ;'stress' of infection & use of 'rifampicin' may cause adrenal failure^{(18) (19) (20)}.

Steroids in endobronchial obstruction or peribronchial lymphnodal compression^{(21) (22)}

Streoids causes reduction in bronchial compression; favorable response in radiographic & bronchoscopic appearance. Use depends upon degree, site & nature of obstruction

Steroids in lymph node TB⁽²³⁾

One third nodes involved in tubercular peripheral lymphadenopathy 'flare' with an exacerbation of pain & swelling after starting ATT ,Intra lesional/Intra lymph nodal depot steroid therapy may beneficial in Hilar/mediastinal lymphadenopathy with pressure symptoms .

Steroids in laryngeal TB

Laryngeal TB usually respond to voice rest & ATT.Short course prednisolone may be used in severe pain.there are lack of datas to support their use, but a number of scientific bodies recommend their use.

Steroids in ATT induced fever⁽²⁴⁾

Drug fever not uncommon with use of antituberculosis therapy, Fever is usually due to INH or rifampicin. Patients usually present with elevated temperature accompanied by increase serum transaminase levels, relative bradycardia; Eosinophilia is uncommon. Serial ESR

measurement important. ATT induced fever promptly response to prednisolone.

Steroids in cutaneous hypersensitivity reactions to anti-TB drugs

Anti-TB drugs can cause SJ syndrome & TEN, Severe reactions may require systemic steroids.

Steroids in peritoneal and intestinal TB

In patients of peritoneal & intestinal TB fever usually resolves within 1 week of ATT & > 90% patients have improvement in ascites within wks of initiating Treatment. Steroids for first 2 to 3 months of T/t may reduce late adhesive complications. Most clinicians avoid using this, since its efficacy has not been well established & there is risk of TB dissemination. There are insufficient data/studies to recommend their use.

Steroids in Genitourinary TB Steroids in Genitourinary TB decreases inflammation & stricture formation

But use is not universally advocated.

IRIS (Immune Reconstitution Inflammatory Syndrome):

IRIS is pathological Inflammatory response and paradoxical clinical deterioration as a result of HAART related immune recovery or reconstitution in HIV infected persons; also referred to as Immune Restoration Disease or Immune Recovery Syndrome. 40% of cases reported through 2002 occurred in the context of mycobacterial infections and HIV .Also seen in the context of CMV, Cryptococcal Disease.

IRIS: Proposed Diagnostic criteria (French et al 2004)

- Major Criteria
 1. Atypical presentation of OI or tumours in pts on HAART
 2. Exaggerated Inflammatory response
- Fever, painful lesions
 1. Atypical Inflammatory Response In affected tissues
- Granulomas,Suppuration,Necrosis
 1. Progression of organ dysfunction or enlargement of pre existing lesions after definite clinical improvement with specific OI therapy and exclusion of toxicity prior to starting HAART

- Tuberculomas, Worsening Kaposi's, New onset CMV retinitis or CMV uveitis,
 1. Reduction in Plasma HIV RNA by > 1 log 10 copies /ml
- Minor Criteria
 1. Increase in CD4 count
 2. Increase in specific immune response to the pathogen
 3. Spontaneous resolution of disease without specific therapy with continued anti retroviral therapy

IRIS in TB and HIV Co- infected patients were reported initially around 1998. Paradoxical reactions have been seen in TB prior to HIV thus IRIS phenomena in co infected pts may have been under reported. 29 - 36 % co infected patients on TB treatment and HAART develop clinically apparent IRIS.

IRIS is more frequent in HIV +ve than HIV -ve patients: 36% (12/33)⁽²⁵⁾ ; 32% (6/19)⁽²⁶⁾; 6% (6/82)⁽²⁷⁾ ;30.2% (26/86)⁽²⁸⁾ IRIS is associated with restoration of TST reactivity.

IRIS - HIV and TB reported cases in the literature:

Patients usually present with c/o: Fever, Worsening Lymphadenopathy, Increasing respiratory distress, Deterioration of parenchymal lung disease, new effusions, ascites, abscesses, Hypercalcaemia, Acute respiratory failure.

Management of TB-IRIS:

- a. Ensure correct diagnosis
- b. Steroids
 1. 40mg of prednisolone 2 weeks
 2. Reducing course over next 2-4 weeks
 3. Prolonged courses may be required depending on clinical response
- c. Beware secondary infections
- d. Adjunctive therapy
 1. Thalidomide
 2. Pentoxifylline
 3. Monteleukast in refractory cases
 4. NSAIDS
 5. Surgery to drain abscesses
 6. Supportive care

INTRALESIONAL STEROIDS IN TB :⁽²⁹⁾

The bronchoscopic injection of corticosteroids has also been successfully applied to patients with

endobronchial tuberculous lesions. Endobronchial tuberculosis (EBTB) can lead to significant tracheobronchial stenosis. Multimodality therapy is the standard in this patient population and involves multidrug anti-mycobacterial therapy, systemic corticosteroids, surgical resection, aerosolized anti-microbial agents, and dilatational techniques.

Steroids in BCG scar keloid (Intralesional injection of triamcinolone⁽³⁰⁾ :

Local corticosteroid therapy of BCG-related keloid reactions may also be useful.

Is there any risk of using steroids along with anti-TB drugs?

Yes, there is risk of dissemination of disease more commonly in drug resistant organism; inadequate anti TB therapy (dose/combination/poor absorption) & premature cessation of anti-TB drugs.

Glucocorticoid equivalencies, potencies, and half-life

Glucocorticoid	Equivalent potency dose(mg)*	Anti-inflammatory potency*	Sodium-retaining potency	T1/2 plasma (min)
Short-acting				
Cortisone	25	0.8	2	30
Hydrocortisone	20	1	2	80-118
Intermediate-acting				
Prednisone	5	4	1	60
Prednisolone	5	4	1	115-212
Triamcinolone	4	5	0	200+
Methylprednisolone	4	5	0	78-188
Long-acting				
Dexamethasone	0.75	20-30	0	110-210
Betamethasone	0.6-0.75	20-30	0	300+

Is there any chance of drug interaction during ATT & steroid therapy?

Yes; with rifampicin regimen dose of steroid needs to be increased as rifampicin induces metabolism of steroids by inducing enzymes.

Steroid should be avoided in

- Mild to moderate cavitory disease without toxemia
- Old fibrocavitory disease

- Mild to moderate pleural effusion with minimal symptoms
- Patients with resistance to one or more anti-TB drugs
- Patients having poor compliance with anti-TB drug therapy

CONCLUSIONS

There are sufficient data to recommend adjunctive use of corticosteroids therapy in tubercular meningitis, acute phase of tubercular pericarditis, for advanced pulmonary TB with severe systemic & respiratory morbidity & tubercular pleurisy with severe symptoms; Suggestive data to recommend it in intrathoracic lymphadenopathy with mass effect & Inadequate data to recommend this approach in peritoneal, miliary, laryngeal, endobronchial, HIV infection & lymph node TB etc. Adjunctive use of corticosteroids do not appear to diminish the efficacy of 'adequate' anti tuberculosis therapy. There are significant short term benefits in most forms of TB & long term benefits in TBM & effusive pericarditis.

- Dose & Duration are important usual dose: 40-60 mg/d pred. tapered over 4-8 wks (in pericardial TB-60 mg/d tapered over 6-12 wks)

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