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Therapeutic reviews

Anti-tubercular therapy for intraocular tuberculosis: A systematic review and meta-analysis

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ABSTRACT

Intraocular tuberculosis remains a diagnostic and management conundrum for both ophthalmologists and pulmonologists. We analyze the efficacy and safety of anti-tubercular therapy (ATT) in patients with intraocular tuberculosis and factors associated with favorable outcome. Twenty-eight studies are included in this review, with a total of 1,917 patients. Nonrecurrence of inflammation was observed in pooled estimate of 84% of ATT-treated patients (95% CI 79–89). There was minimal difference in the outcome between patients treated with ATT alone (85% successful outcome; 95% CI 25–100) and those with concomitant systemic corticosteroid (82%; 95% CI 73–90). The use of ATT may be of benefit to patients with suspected intraocular tuberculosis; however, this conclusion is limited by the lack of control group analysis and standardized recruitment and treatment protocols.

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We propose further prospective studies to better establish the efficacy of ATT and ascertain the factors associated with favorable treatment outcomes.

1. Background

Tuberculosis (TB), a chronic systemic infectious disease caused by *Mycobacterium tuberculosis* (MTB), is a global disease with a significant health burden and an estimated 1 in 3 persons affected worldwide.[A] Pulmonary and extrapulmonary manifestations are widely recognized clinical phenotypes of the disease. There has been an increase in the prevalence of extrapulmonary TB because of both better reporting and improvement in diagnostic tools. Extrapulmonary manifestations can involve skin, eye,[35] cardiovascular,[62] gastrointestinal,[65] genitourinary,[45] and central nervous system.[61] Extrapulmonary TB may occur either in isolation or concurrently with pulmonary disease.[27] Extrapulmonary manifestations are more common in immunosuppressed patients such as those coinfected with human immunodeficiency virus (HIV).[29]

Intraocular manifestations are the most common and frequent presentation of all the known forms of ocular TB. Intraocular TB accounts for 6.9%–10.5% of uveitis cases[40,53,75] without a known active systemic disease, and 1.4%–6.8% of patients with active pulmonary disease have concurrent ocular TB.[10,22,47] There are two possible pathophysiological mechanisms:

1) Active mycobacterial infection—hematogenous spread and direct invasion of MTB into local ocular tissues, such as in choroidal granuloma.[35]
2) Immunological response (not associated with local replication of the infectious agent)—delayed hypersensitivity reaction to MTB situated elsewhere in the body, such as in serpiginous choroiditis.[11]

Local intraocular lesions are often characterized by granulomatous inflammation. The diagnosis and management of intraocular TB remains a challenge as a result of the wide spectrum of clinical signs, lack of associated systemic signs, absence of an agreed diagnostic criteria, and limitations of currently available diagnostic tests and tools.[4,18] Delayed diagnosis and treatment may lead to permanent structural damage that can affect long-term functional visual outcome. Therefore, prompt diagnosis and treatment of intraocular TB is critical in improving visual outcomes.[50]

Ocular investigations described and currently used include histopathological examination of the biopsied tissue, smears and cultures of the tissue fluid, and the polymerase chain reaction. Cultures are usually not practical because of the difficulty in obtaining a large volume of ocular fluid and poor diagnostic yield.[12] Systemic investigations include tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) such as QuantiFERON-TB Gold and T-Spot TB. TST has a low positive predictive value and a high false negative rate[39,49] in the absence of systemic disease, whereas IGRA, although more specific than TST, has a high false positive rate and a higher rate of reversion.[58,76] Approximately half of patients with intraocular TB have a normal chest X ray.[16]

There is a lack of agreed management guidelines among ophthalmologists in part because of the previously mentioned difficulties in establishing the diagnosis of intraocular TB.[48] Similarly, there is no agreed consensus between ophthalmologists and other physicians with regard to the role of antitubercular therapy (ATT) and duration of treatment in cases of isolated intraocular TB (Fig. 1). As such, ophthalmologists play a pivotal role in diagnosing and managing patients with intraocular TB who do not present with any systemic manifestations of TB. Isolated intraocular TB may be characterized by negative chest radiograph, negative workup for other available investigations, but a positive TST and a rapid response to ATT.[52] In such settings, ophthalmologists need to have a strong suspicion that TB is confined purely to the eye and promptly institute appropriate treatment for these patients in conjunction with a physician knowledgeable about infectious disease.

The Center for Disease Control and Prevention recommends[B] a 4-drug ATT regimen of isoniazid, rifampicin, ethambutol, and pyrazinamide for patients with active pulmonary or extrapulmonary TB. The role and duration of additional systemic corticosteroids remains controversial. In addition, the interaction between steroids and some of the ATT drugs adds to the difficulties faced in management of this disorder. There are some unmet medical needs within current practice patterns (Fig. 1) and a recent upsurge in incidence of TB. Moreover, the emergence of drug-resistant TB[79] has added to challenges already present.

Tabbara proposed guidelines for the diagnosis of intraocular TB in 2007.[66] This includes a combination of clinical ocular findings, ocular and systemic investigations, and exclusion of other systemic conditions that can mimic TB and therapeutic response to ATT. Based on these and their own results, Gupta and colleagues proposed classifying intraocular TB into confirmed, probable, and possible intraocular TB; however, this model needs validation by future studies.[31]

The primary objective of this systematic review was to evaluate the role of ATT in patients with presumed intraocular TB and treatment outcomes (recurrence/relapse/progression of intraocular inflammation or worsening of visual acuity).[1,2] A secondary objective was to analyze the demographic, clinical, laboratory, and therapeutic factors that may influence the clinical outcome in patients with intraocular TB who have been treated with ATT.

2. Methods

2.1. Study selection

Selection of articles was conducted according to predetermined selection criteria by author Ae Ra Kee, who