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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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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 coinfecting 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 TB⁷⁹ 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 classified all titles and abstracts into 3 categories (exclude, unsure, include). This was further reviewed independently by a second author (Julio J Gonzalez-Lopez). If any discrepancies were identified, a third author (Rupesh Agrawal) was consulted, and any differences were resolved. Where full texts were not available, the authors were contacted. Relevant data of included studies were extracted from each article.

2.2. Data collection and risk of bias assessment

The data were collected using predetermined forms stating study details, sample population demographics, clinical features (laterality, phenotypes, relevant history, and investigation

results), diagnosis, intervention, treatment outcome, as well as factors influencing outcome (demographics, investigation findings, intervention). The key findings from each study were summarized in Tables 1–4. Risk of bias was assessed by an experienced systematic reviewer (Aws Al-Hity) using the Newcastle-Ottawa Quality Assessment Scale (Table 5) and reviewed by a second author (Julio J Gonzalez-Lopez). Any differing opinions were discussed and resolved by consensus.

2.3. Data synthesis and analysis

In this review, we evaluate the effect of ATT on ocular outcome of the patients. Outcome measures varied among the different studies and included recurrence of inflammation, visual acuity, and progression of lesion. In this study “successful outcome” was defined as no recurrence of inflammation, improved visual acuity, or no anatomical progression of lesion. The results are reported as percent of patients who achieved “successful outcome” after receiving ATT. Any other confounding factors as previously reported affecting treatment were also analyzed using the methodology set out in the Cochrane Collaboration Handbook [<http://handbook.cochrane.org/>].

Meta-analysis was performed on the proportion of patients with successful outcomes in patients treated with ATT, and separately in control groups. Random-effect meta-analysis was done using the DerSimonian-Laird model in Stata/SE. Software version 12 for Windows (Stata Corp., College Station, TX, USA) was used for statistical analysis.

3. Results

A total of 1,411 articles were identified through PubMed database, and 37 met our selection criteria (Fig. 2). Only 28 studies met all inclusion criteria after full-text review and are included in our analysis.^{2,3,5–9,17,23,24,26,32,33,36,37,42,46,54,55,57,59,60,63,64,70,72,74,77} Most of these (27/28) were retrospective studies; only one was a prospective study. Nine studies analyzed treatment outcome comparing ATT versus steroids or immunosuppressants alone in cases of intraocular TB (Table 1).

3.1. Demographics

There were a total of 1,917 patients, with the sample size of each study ranging from 10 to 343 (Table 1). The mean or median age of patients ranged from 21.7 to 66 years. Most studies reported higher male preponderance (57%, 16/28) with cumulative mean of 56.0% men affected. There was a bias toward the Asian ethnic population as most of the studies (46.4%, 13/28) were from Asia.

3.2. Clinical phenotypes and investigations suggestive of intraocular TB

Bilateral presentation was more common (mean 57.7%; bilateral: unilateral 1.36:1) among the reported studies. Symptoms consistent with intraocular TB were more common in eyes with bilateral presentation, 80% (16/20), than unilateral disease (Table 2). Further information was extrapolated and classified as suggested by Gupta and colleagues,³⁵ namely anterior uveitis, intermediate uveitis, posterior uveitis, panuveitis, retinitis and retinal

vasculitis, neuroretinitis, and optic neuropathy (Table 6). There was no reported case of endophthalmitis or panophthalmitis.

A total of 5 studies reported relevant history of previous TB (range 4.8%–11.1%)^{45, 50, 62, 73, 76}, 7 studies on contact history of TB (range 12.1%–70.6%)^{26,46,51,59,63,64,74} and 12 studies on presence of systemic TB (highest reported rate being 89.4% by Vos and colleagues⁷⁴). TST, QuantiFERON-TB Gold, and chest X ray were the more common adopted modalities of investigations with 10, 7, and 15 studies (of 28) using the aforementioned tests, respectively. Only 9 studies used both TST/QuantiFERON-TB Gold and chest X ray. Positive chest X ray, which may suggest possible concurrent or previous systemic TB, was reported in 4.4% to 100.0% of the cases.

3.3. Diagnostic criteria of intraocular TB

Most studies reported a diagnosis of intraocular TB based on clinical signs, systemic investigations, and exclusion of other etiologies via clinical features and investigations (Table 3). Only 21% (6/28) of the studies performed local investigations such as culture and polymerase chain reaction of anterior and/or posterior chamber to support the diagnosis of intraocular TB. There were 6 articles that used response to ATT as a diagnostic criterion for intraocular TB.

3.4. Treatment regime in management of intraocular TB and outcomes

There was a wide heterogeneity in drugs, regimen, and duration of treatment (Table 3). A standard regimen of isoniazid (H), rifampicin or rifampin (R), ethambutol (E), and/or pyrazinamide (Z) for a minimum of 2 months (up to 3–4 months) was used, with subsequent administration of 2-drug therapy, namely isoniazid and rifampicin, for a minimum of 4 months (up to 15 months) in 18 studies. Only 1 study by Agrawal and colleagues² reported use of the second-line ATT drug moxifloxacin (M) instead of ethambutol. Concurrent oral and topical steroid therapy were used in 26 of the studies (93%). Immunosuppressants for severe inflammation were considered in 3 of the studies (11%). Therefore, patients included in this review may have either received “ATT alone,” “ATT + topical/periocular/systemic steroids,” “ATT + immunosuppressant,” or all “ATT + steroids + immunosuppressant.” There was a wide heterogeneity in treatment methodology and duration, and further analysis was not possible. The mean range of follow-up time was 2.1 to 35 months. Outcome measures varied among the studies but mainly consisted of recurrence of inflammation, resolution or progression of inflammation, and visual acuity. There was a generally favorable outcome in all patients who underwent ATT therapy. Twenty-seven of 28 (96%) studies observed a greater proportion of successful outcomes in patients with intraocular TB treated with ATT than those without ATT. There were no significant differences in outcomes between studies conducted in Asian (79.9% favorable outcome) versus non-Asian countries (78.0% favorable outcome) ($P = 0.636$). Clinical phenotypes affecting outcome were not analyzed owing to the wide heterogeneity and lack of detailed data from individual studies.

Our meta-analysis revealed that 84% (95% CI 79–89) of the patients receiving ATT showed nonrecurrence of inflammation during the follow-up period; 69% (95% CI 33–96) showed an improvement in visual acuity; and 92% (95% CI 63–100) showed an improvement in

inflammation (Fig. 3). In contrast, the pooled proportion in the control group of nonrecurrence of inflammation was 58% (95% CI 29–87); 14% (95% CI 8–21) for improvement in visual acuity and 60% (47%–73%) for improvement of inflammation (Fig. 4). Pooled relative risk of ATT for nonrecurrence of inflammation in patients with intraocular TB was 1.42 (95% CI 1.24–1.63); for improvement in visual acuity was 1.66 (95% CI 0.84–3.27); and for improvement of inflammation 1.17 (95% CI 0.74–1.85). A successful outcome was observed in 85% of patients treated with ATT alone (95% CI 25–100); in 82% of patients treated with ATT and systemic steroids (95% CI 73–90); and in 85% of patients treated with ATT and systemic steroids and immunomodulators (95% CI 80–89) (Fig. 5). On the basis of this meta-analysis, we lack evidence to say that there is any difference in outcome between those treated with “ATT alone,” “ATT + topical/periocular/systemic steroid,” “ATT + immunosuppressant,” or all “ATT + steroid + immunosuppressant.”

4. Discussion

The literature on intraocular TB management is dominated by retrospective cohort studies, case series, or case reports. No clinical trials were identified in our literature search. The demographic findings of the studies included in our review were consistent with current literature on nonocular TB, where TB more commonly occurs between ages 15 to 64 years, in men, and among Asians—especially Indians and Chinese, who accounted for 39% of new and recurrent TB cases in 2011.^{13,28}

Most of the studies evaluated 3 of 5 diagnostic methods suggested by Gupta and colleagues³⁵ namely clinical signs, systemic investigations, and exclusion of other possible etiologies (Fig. 6). TST, IGRA, and chest X ray were the most commonly used investigations. The differences in the diagnostic criteria, as well as the inclusion criteria, can be attributed to the fact that some studies focused specifically on choroidal tuberculosis,^{8,34,36,77} whereas others³² focused on retinal vasculitis, leading to the misrepresentation of certain clinical phenotypes of intraocular TB, and hence, the heterogeneity of study population.

The meta-analysis demonstrated high heterogeneity, consistent with the wide range of locations, diagnostic procedures, and treatments in the studies. Nonrecurrence of inflammation was the most common outcome, and our pooled estimate in ATT-treated patients was 84% (95% CI 79–89). Although pooled estimates are possible, more definitive multicenter research is needed to guide treatment. Only 9 of 28 studies had control groups, and although we analyzed these studies separately, the confidence intervals were too wide to allow even tentative conclusions about the efficacy of ATT.

4.1. Current literature on first-line ATT

ATT therapy is a combination of drugs with different mechanisms against MTB. Isoniazid is a prodrug bio-activated by katG in MTB that inhibits mycolic acid synthesis. Isoniazid plays a significant role mainly in the first few days of TB treatment. Among the TB drug regimen, it poses the most potent bactericidal activity at early stages of the treatment.⁶⁹ Rifampicin kills both dividing and dormant bacilli as a result of its bactericidal ability to inhibit b-

subunit of TB RNA polymerase.²⁵ This drug is crucial in the TB regimen because of its rapid onset of action owing to its penetration into macrophages (lipophilic nature) and activity against nonreplicating persisters.^{30,43} When used alone, however, rifampicin can lead to MTB resistance. To avoid this, a combination of ATT is needed. Thus, ethambutol is used in addition to rifampicin for the first 2 months of treatment to avoid rifampicin resistance.^{25,44} Ethambutol exerts its activity by inhibiting arabinogalactan synthesis in MTB cell wall. Another prodrug in the TB regimen is pyrazinamide, which gets activated by an enzyme called pyrazinamidase present in MTB; however, the exact mechanism of action is not known. Its addition to the regimen helps reduce the treatment duration.⁷⁸

As of now, MTB clearly remains the major cause of TB event in humans. Time is a crucial factor for the bacilli to grow and become resistant to the drugs. Attacking the bacilli as soon as possible could lead to successful therapy.¹⁹ To achieve this, a thorough understanding of MTB and the wise use of individual drug regimens are needed. There is no specific drug developed for treating intraocular TB. We rely on the existing TB therapeutics. Ophthalmologists play a crucial role in monitoring ocular disease and drug side effects, but the primary responsibilities and decision making with regard to initiation and subsequent monitoring of systemic ATT is with other physicians in most centers. The amount of free fraction of ATT crossing the blood ocular barriers and reaching various ocular structures is not clearly known, but from the therapeutic outcome and various ocular toxicities exerted by these drugs indicate that they reach the eye to some extent.¹⁵ In addition, the role of ATT in cases where pathogenesis is considered purely immunogenic remains controversial. It is the ophthalmologist's responsibility to monitor drug regimens to avoid ocular toxicity without compromising the ocular therapeutic effect of systemic TB therapeutics.

4.2. Current literature on second-line ATT

A combination of fluoroquinolones, together with ATT, can also be considered when treating intraocular TB. Newer fluoroquinolones such as moxifloxacin are well-tolerated and well-established ocular therapeutics for various ocular diseases.¹⁴ Data from current literature support the use of newer fluoroquinolones as one of the important constituents in drug-resistant TB treatment. Studies from *in vitro*, *in vivo*, and humans support the efficacy of fluoroquinolones (namely levofloxacin and moxifloxacin) against MTB (intracellular and dormant).³⁸ Moreover, fluoroquinolones are also helpful in preventing drug-resistant TB.³⁸ These drugs exert their pharmacological action by targeting DNA gyrase in MTB inhibiting bacterial DNA synthesis, ultimately leading to cell death.⁷³ Interestingly, the combination of levofloxacin and moxifloxacin exerted a synergistic effect when combined with first- and second-line treatment drugs of TB. Levofloxacin and moxifloxacin tend to accumulate in macrophages and granulocytes, with intracellular concentrations exceeding extracellular concentrations at least 4 to 5 fold.

In comparison to isoniazid, levofloxacin and moxifloxacin show dose-dependent bactericidal activity. The *in vivo* studies also support the role of moxifloxacin for shortening TB treatment when combined with existing anti-TB drugs.⁴¹ Although there have not been any clinical trials on the use of levofloxacin and moxifloxacin for intraocular TB, their strong bactericidal and sterilizing activity, favorable pharmacokinetics, toxicity profile, and well-

established use in other eye infections could make these drugs more efficacious intraocular TB drugs; however, the various blood ocular barriers may limit their usefulness. Thus, validating that these drugs are effective when administered locally will be necessary.⁶⁷

4.3. Treatment regime

In our review, 19 of 28 studies stated that they consulted a specialist from other departments, namely pulmonologists and infectious disease specialists, before deciding on the treatment regimen. Commonly, a combination of 4 anti-TB drugs (HREZ) was initiated for at least 2 months before instituting a 2-drug regimen (isoniazid and rifampicin) for at least 4 months to avoid development of mycobacterial resistance. The gold standard for dosage of ATT treatment of pulmonary TB is as follows: R (450 mg/day if BW ≤ 50 kg or 600 mg/day if BW > 50 kg), H (5 mg/kg/day), E (15 mg/kg/day), and Z (25–30 mg/kg/day), which has been reported to be adopted by the studies carried out in Singapore, Saudi Arabia, and India. There was only a single study, by Agrawal and colleagues,² that adopted a second-line ATT drug for some patients; moxifloxacin was used in place of ethambutol. Future studies are warranted to understand the application and role of second-line ATT in patients with drug-resistant intraocular TB.

4.4. Treatment duration

The Center for Disease Control and Prevention guidelines recommend ATT for a duration of 6–9 months.^C Most studies included in our analysis prescribed ATT for at least 6 months, with a maximum between 12–19 months. There does not seem to be any correlation between the duration of therapy and the clinical features of the sample population. Other than 5 of the included studies,^{5,26,42,55,77} ATT gave rise to favorable responses, with successful outcome in more than 70% of the patients. Longer duration of ATT may not necessarily reflect better outcome⁶ as there was a higher incidence of recurrence among those who had 12 months or more of ATT. These results need to be interpreted with caution as patients who received more than 12 months of ATT likely had more severe disease. No other study reports significant association between the duration of ATT and ocular outcome.

In studies where patients responded favorably to ATT, improvement was seen within 2 weeks to 3 months of instituting therapy: Gupta and colleagues³² (53.8% within 2 weeks), Ang and colleagues⁵ and Gupta and colleagues³⁶ (most within 2–4 weeks), Moimura and colleagues⁵⁴ (90.0% within 1–2 months), and Zhang and colleagues⁷⁷ (61.1% within 3 months). These results suggest the need for closer monitoring of patients for therapeutic response. Patients who respond within 2 months may benefit with 6 months of total ATT. In patients with no response at 2–3 months, there may be a need to identify second line of therapy or switch treatment on consideration of the overall health of the patient and consultation with an infectious diseases specialist.

4.5. Side effects of ATT

Side effects of ATT were observed in 5 of the studies, and ATT was prematurely discontinued in some patients (Table 7). There were only a few instances of drug discontinuation due to toxicity or intolerance and side effects: 9 patients in study by Ang and colleagues,⁵ 1 in Moimura and colleagues,⁵⁴ 3 by La Distia and colleagues,⁴⁶ 14 by Bansal

and colleagues,⁸ and 2 by Basu and colleagues.⁹ Overall, there was 10.1% (29 of 287 patients), discontinuation rates of ATT. Four studies state no side effects experienced by their patients.^{24,51,64,77} Patients on ATT should be monitored closely for any side effects or complications from its use at every follow-up visit.

4.6. Role of corticosteroids/immunosuppressants

Corticosteroids are often used along with ATT to treat intraocular TB. The addition of steroids may help suppress inflammation caused by infection, although its effects may differ according to the route of administration and the dosages used. Oral corticosteroids are often adopted for patients with posterior segment inflammation, whereas topical steroids are used for those with anterior segment inflammation. Our meta-analysis revealed that the concurrent use of corticosteroids had no significant beneficial effect on treatment outcome. Similar finding was noted by another group who found no role for corticosteroids in improving final visual acuity in patients with tuberculous optic neuropathy.²⁰ Furthermore, Hamade and colleagues³⁷ noted that corticosteroid therapy before initiation of ATT resulted in poorer visual outcome. This is postulated to be the result of corticosteroid-induced immunosuppression and consequent activation of latent TB. In the study by Agrawal and colleagues,² there was higher rate of treatment failure in patients on immunosuppressants.

4.7. Factors influencing outcome

Only 7 studies^{2,5,6,26,37,55,59} reported the factors influencing the outcome of ATT use (Table 4). These include African ethnicity; age >50 years; female gender; longer duration of uveitis; delay in diagnosis (>500 days); presence of intermediate uveitis, posterior uveitis, or panuveitis; higher median QuantiFERON-TB Gold values; administration of corticosteroid therapy before and after administration of ATT. Outcome measures include higher recurrence rate, persistence of inflammation, or poorer visual outcome. Given the lack of information in this area, we propose that more studies need to be undertaken to better evaluate the exact factors that contribute to treatment outcome.

4.8. Pulmonologist' perspective in the management of intraocular TB

The pulmonologist needs to determine if the case being investigated represents latent infection with an unrelated ocular inflammation, an active infection of the ocular compartment, or alternatively a hypersensitivity reaction to remote TB infection. The currently available immunologically based tests—historically used TST, and the more recently adopted IGRAs models—do not distinguish active from latent TB infection. There are no good correlates of disease activity with the magnitude of skin test reactions or IGRA readings. This is even more difficult in countries with higher prevalence of TB and thus likely to have higher incidence of latent TB.

It is therefore important that further investigations are carried out to establish latent or active TB. This requires a careful clinical history and physical examination, combined with a plain chest radiograph, at a minimum. A contact history, past history of treated TB, and of residence in an endemic area could aid clinicians to validate potential exposure risks. Symptoms may alert the physician to target further investigations. Although a plain film may reveal advanced active pulmonary TB, it is now recognized that this may miss significant

mediastinal adenopathy or subtle airway changes only visible on a computerized tomography scan. In microbiologically proven pulmonary TB, up to 10% of cases have “normal” chest radiographs.⁶⁰ The other emerging problem for the clinician is the increasing prevalence of extrapulmonary TB in immunosuppressed patients or in lower incidence countries such as the UK. The emergence of more functional imaging, such as position emission tomography scans, means that we are now able to detect metabolically active TB even in the setting of normal cross-sectional imaging.

Such diagnostic tests allow more directed sampling of extraocular tissue to prove the coexistence of active disease. An important site of disease is now recognized to be mediastinum. Newer techniques such as endobronchial ultrasound allow for nonsurgical sampling of tissue to confirm active TB disease.⁵⁶ This is enhanced by the ability to run polymerase chain reaction tests on small sample sizes over and above traditional smear techniques and the gold standard of culture²¹; however, any body compartment is a potential site for active disease, and approaches need to be tailored to obtain a sample from these sites.

The gold standard of proving TB by culture is difficult as hypersensitivity or active ocular infections can occur in paucibacillary settings; therefore, the clinician will frequently have to rely on a clinicopathological diagnosis to initiate treatment even in the absence of positive microbiology.

International guidance on the duration of TB therapy indicates that most presentations of active TB should respond sufficiently to 6 months of ATT. Even the more prolonged durations used in CNS disease (if we assume direct infection with retinal involvement is identical to CNS disease) are still unclear, but most would advocate a treatment of at maximum 12 months in fully sensitive CNS disease.⁶⁸ Therefore, 6 months of treatment should suffice in ocular manifestations when the bacterial load is still generally low.

Clinicians may also look to modify regimes so that moxifloxacin is used in preference to ethambutol as the fourth drug during the intensive phase of standard regimes. Optic neuropathy from ethambutol in the presence of active eye disease may be masked, making it difficult to distinguish the cause of any visual changes.

5. Conclusion

We provide an evidence-based algorithm for the management of intraocular TB and highlight clinical predictors of treatment outcome. In spite of this, there still exists great uncertainty regarding the diagnosis and treatment of intraocular TB. Our review is limited by several factors, notably that we cannot rule out selection, attrition, performance, detection, reporting, or publication biases. Furthermore, it was not clear whether the articles reviewed used intention-to-treat or per-protocol analysis. There was also a lack of data available in the full texts from some of the included studies included, such as the details of immunosuppressants and so forth. This limited our analysis on the use and benefits of immunosuppressants in patients with intraocular TB. In addition, we found much heterogeneity in the diagnosis and case definition, outcome definition, as well as length and

type of treatment of instituted for intraocular TB. Although this highlights a need for better quality evidence, current available studies support the administration of ATT for intraocular TB.

Further studies are required to establish standardized diagnostic criteria for intraocular TB to allow future longitudinal studies and clinical trials to identify a suitable treatment regimen. Given that there is a low incidence of intraocular TB around the world, a multicenter approach would be beneficial. These studies will improve our understanding of this growing health problem, enabling us to provide appropriate care to minimize the disease burden and avoid the sight-threatening complications of intraocular TB.

Moreover, we also note that there are no known models or studies looking at ATT delivery locally to eyes. Local administration of ATT could overcome the potential limitations of systemic therapy in management of intraocular TB. There are potential barriers to these models with intact ocular tissues that limit ocular penetration; however, other drug delivery systems such as long-acting intravitreal pellets or suprachoroidal drug delivery⁷¹ may help to overcome some of the limitations.

We have hence embarked on the first ever multicenter collaborative study—Collaborative Ocular Tuberculosis Study—analyzing clinical features associated with intraocular TB and treatment outcome for intraocular TB using Web-based encrypted data entry. The collaborative effort will look at constructing a predictive model for diagnosis of intraocular TB. The aim of Collaborative Ocular Tuberculosis Study is to

1. Construct a predictive model of intraocular TB through an international multicenter prospective study—this will identify diagnostic clinical features, to enhance the study of management outcomes and treatment algorithms of intraocular TB as discussed previously. Future initiatives include the identification of novel biomarkers and transcripts for diagnosis of intraocular TB.
2. Pioneering initiative to create a comprehensive international data set of its own kind—high user-reported satisfaction rates with the online encrypted data collection platform.

We hypothesize that a predictive model of intraocular TB will improve productivity by streamlining the process of diagnosing this elusive condition and address the lack of reproducible diagnostic criteria. It will also identify clinical tests that are useful and differentiate them from those that are not, thereby reducing health care costs. The model will deliver value to patients by reducing the incidence of missed and delayed diagnoses so that patients are started on targeted therapy promptly and receive early workup for systemic TB. This will deliver population-wide benefits through reduction of airborne spread of this increasingly prevalent infectious disease. This pioneering initiative to create an international data set will improve productivity by setting new standards for data collection and international collaborations, as well as highlighting a means to achieve them. It will deliver value to the broader medical community far beyond the field of ophthalmology by validating a means to collect high-quality, reproducible data conveniently across geographical boundaries.

To understand how a predictive model of intraocular TB will meet the needs of the future health care system, we have to first understand the future of health care. Technology has oiled the wheels of information flow and paved the way for a new health care consumer—one who has greater insight and awareness of current evidence and literature. A multicenter prospectively derived predictive model of intraocular TB will not only serve physicians in their clinical practice, but also help address the increasing demands of today's well-informed patients. It will also allow clinicians to provide a high level of evidence to justify our clinical decisions.

6. Methods of literature search

1. Eligibility criteria for considering studies for this review

Given the scarce literature on treatment outcomes of ATT in ocular TB, and the aim of evaluating safety as well as efficacy, we set wide inclusion criteria. The literature search included as follows: observational studies (including retrospective and prospective cohort studies, case-control studies, cross-sectional, case series, and clinical studies) that examine ATT use and its outcome on intraocular tuberculosis. Exclusion criteria were the following: studies whose primary aim does not include evaluation of outcome of ATT use; sample size <10; studies conducted earlier than 1990.

2. Search methods for identifying studies

We searched the PubMed database in April 2015 using the search terms “ocular [All Fields],” “intraocular [All Fields],” and “uveitis [All Fields]” which were matched with “tuberculosis [All Fields].” Articles published between January 1990 and April 2015 were reviewed, and reference lists of included articles were handsearched. Articles citing the included articles were retrieved using Web of Science, and handsearched for possible inclusion.

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Fig. 1.

Flowchart representing diagnostic and treatment conundrum in management of intraocular tuberculosis. HRCT, high-resolution chest tomography scan; IGRA, immunoglobulin release assay; PCR, polymerase chain reaction; PET, position emission tomography; Q-Gold, QuantiFERON-TB Gold In-Tube; TB, tuberculosis; TST, tuberculin skin test.

Fig. 2.
Study selection for systematic review. ATT, anti-tubercular therapy.

Fig. 3.

Forest plot showing the result of the random-effect meta-analysis of the effect size (ES) showing the proportion of patients with ocular tuberculosis that experimented a successful outcome following anti-tubercular therapy, by outcome.

Fig. 4.

Forest plot showing the result of the random-effect meta-analysis of the proportion of patients with ocular tuberculosis not receiving any anti-tubercular therapy that experimented a successful outcome, by outcome.

Fig. 5. Forest plot showing the result of the random-effect meta-analysis of the proportion of patients with ocular tuberculosis treated with anti-tubercular therapy (ATT) that experimented a successful outcome, by treatment regime. ES, effect size.

Fig. 6.
Aspects of diagnostic criteria considered across the studies. ATT, anti-tubercular therapy;
TB, tuberculosis.

Table 1

Study details and population demographics

S/N	Study	Study design	Period of study	Origin	Sample size	No. of patients who received ATT	No. of dropouts/lost-to-follow-ups	Control group	No. of control	Age (years); mean $\pm$ SD, (range)	Male gender (%)	Ethnicity/nationality (%)
1	Agrawal (2015); Ocul Immunol Inflamm	Retrospective	-	UK	175	175	0	-	-	44.1 $\pm$ 14.2	61.1	Asian (64.8), white (21.1), African (14.3)
2	Jakob (2014); Ocul Immunol Inflamm	Retrospective	2006–2009	Germany	343	27	?5	-	-	50 (15–86)	38.8	White (62.7), others (21.9), no data (15.5)
3	La Distia Nora (2014); Am J Ophthalmol	Retrospective	-	Netherlands	77	32	8	-	-	46	57.1	Dutch (33.8)
4	Mora (2014); Acta Ophthalmol	Retrospective	2000–2013	Italy, France	30	30	0	-	-	51 (22–87)	-	White (47), African (40), Eastern Asian (13)
5	Tognon (2014); Infection	Retrospective	2007–2010	Italy	62	62	0	-	-	66 ^a (51–79)	45.2	Italian (74.2), others (25.8)
6	Basu (2013); Eye	Retrospective	2008–2010	India	106	106	0	-	-	33.5 ^a (12–60)	60.4	South Asian (100.0)
7	Manousaridis (2013); Eye	Retrospective	2002–2011	UK	21	18	0	-	-	46 (21–82)	71	Asian (52), white (32), African (10)
8	Patel (2013); JAMA Ophthalmol	Retrospective	1995–2010	USA	26	17	3	-	-	47.1 (28–69)	35.3	American (47.1)
9	Vos (2013); Int J Infect Dis	Retrospective	2007–2009	Netherlands	66	10	0	Ocular TB with conventional immunosuppressant treatment (unspecified)	55	46.9 (22–75)	37.9	Dutch (36.4), Indonesian (18.2), Turkish (9.1), Vietnamese (9.1), Curaçaoan (9.1), Algerian (9.1)
10	Ang (2012); Brit J Ophthalmol	Retrospective	2000–2008	Singapore	182	46	18	Ocular TB with systemic/topical steroid	118	45.3 $\pm$ 13.2	42.4	Chinese (50.7), others (49.3)
11	Bansal (2012); Ophthalmology	Retrospective	2002–2010	India	105	93	0	Ocular TB with systemic steroid	12	33 $\pm$ 9.3	71.4	Asian Indian (100)
12	Ducommun (2012); Eur J Ophthalmol	Retrospective	1998–2004	Switzerland	12	10	2	Ocular TB with steroid	-	45.4 (23–73)	50.0	Swiss (33.3), Balkan (25.0), other European (25.0), Asian (16.7)
13	Zhang (2012); Retina	Retrospective	1998–2008	China	18	18	0	-	-	26.9 (8–52)	44.4	-

S/N	Study	Study design	Period of study	Origin	Sample size	No. of patients who received ATT	No. of dropouts/lost-to-follow-ups	Control group	No. of control	Age (years); mean $\pm$ SD, (range)	Male gender (%)	Ethnicity/nationality (%)
14	Doycheva (2011); Br J Ophthalmol	Retrospective	2007–2009	Germany	24	11	4	Ocular TB with systemic steroid $\pm$ immunosuppressant	9	51 $\pm$ 17 (17–76)	62.5	-
15	Gineys (2011); Am J Ophthalmol	Prospective	2007–2007	France	42	25	8	Ocular TB with +ve QFT with no ATT	17	55.0 $\pm$ 16.7	57.7	-
16	Gupta (2011); Am J Ophthalmol	Retrospective	1992–2009	India	84	65	0	Ocular TB with systemic steroid	19	31.2 $\pm$ 9.7 (12–54)	72.6	-
17	Parchand (2011); J Ophthalmol Infect	Retrospective	1996–2009	India	57	42	0	Ocular TB with systemic/topical steroids	15	37.5 $\pm$ 12.1	47.6	-
18	Sanghvi (2011); Eye	Retrospective	1992–2007	UK	27	27	0	-	-	36.1 (3–75)	40.7	Asian (70.4), white (14.8), Afro-Caribbean (14.8)
19	Hamade (2010); Acta Ophthalmol	Retrospective	1997–2007	Saudi Arabia	49	49	0	-	-	45 (12–76)	59.2	-
20	Babu (2009); Ocul Immunol Inflamm	Retrospective	1997–2008	India	51	49	0	-	-	40.5 $\pm$ 11.5 (20–65)	51.9	-
21	Cimino (2009); Int Ophthalmol	Retrospective	-	Italy, Switzerland	35	35	0	-	-	55 ^a (20–70)	40.5	Caucasian (100.0)
22	Al-Mezaine (2008); Int Ophthalmol	Retrospective	1998–2006	Saudi Arabia	51	51	0	-	-	40.1 $\pm$ 11.0 (16–68)	66.7	Saudi Arabian (62.7), Bangladesh (15.7), Indian (13.7), Pakistan (7.8)
23	Bansal (2008); Am Ophthalmol	Retrospective	1991–2005	India	216	216	0	Ocular TB with systemic/topical/periocular steroid	144	34.7 $\pm$ 12.2	48.1	-
24	Gupta (2006); Ocul Immunol Inflamm	Retrospective	2000–2003	India	11	11	0	-	-	30.5 ^a	63.3	-
25	Varma (2006); Eye	Retrospective	-	UK	12	12	0	-	-	48.5 (15–71)	83.3	Pakistani (75.0), Indian (16.7), white (8.3)
26	Morimura (2002); Ophthalmology	Prospective	1998–2000	Japan	10	10	0	-	-	40.7 (27–62)	60.0	Japanese (100)
27	Gupta (2001); Retina	Retrospective	1997–1999	India	13	13	0	-	-	21.7 (11–32)	69.2	Asian Indian (100)
28	Rosen (1990); Eye	Retrospective	-	UK	12	11	0	-	-	35.5 (19–56)	75.0	Indian (58.3), British (25.0), Middle Eastern (8.3), African

S/N	Study	Study design	Period of study	Origin	Sample size	No. of patients who received ATT	No. of dropouts/lost-to-follow-ups	Control group	No. of control	Age (years); mean $\pm$ SD, (range)	Male gender (%)	Ethnicity/nationality (%)
(8.3)												

ATT, anti-tubercular therapy; QFT, QuantiFERON-TB Gold In-Tube; SD, standard deviation; TB, tuberculosis.
All data beyond 2 decimal places have been rounded to 1 decimal place. Demographics (age, gender, ethnicity/nationality) of control group (if any) are not included in this table.

^aMedian.

Table 2

Clinical features of sample population

S/N	Study	Laterality		Phenotypes					Relevant history			Investigations		
		Bilaterality (%)	Right/left (%)	AU (%)	IU (%)	PU (%)	Panuveitis (%)	Retinitis/retinal vasculitis (%)	Neuroretinitis/optic neuropathy (%)	Previous TB (%)	Contact history (%)	Systemic TB (%)	+ve TST/QFT (%)	Positive radiography (CXR or CT) (%)
1	Agrawal (2015)	66.3	-	14.9	21.1	Serpiginous choroiditis (7.4) Nonserpiginous choroiditis (17.1) Choroidal Granuloma (5.1)	38.9	33.1	-	-	-	4.6	-95.4	14.5
2	Jakob (2014)	65.3	-	24.8	24.8	30.0	14.3	-	5.8	-	-	-	-24.2	-
3	La Distia Nora (2014)	-	-	24.7	11.7	Posterior uveitis (37.7) Serpiginous chorioretinitis (14.3)	20.8	44.2	46.6	6.5	22.1	3.9	92.7/41.1	32.9
4	Mora (2014)	67	-	40	8	Serpiginous chorioretinitis (20) Multifocal choroiditis (6) Chorioretinal Granuloma (20)	-	38	16	-	-	-	-	-
5	Tognon (2014)	62.9	-	-	-	54.8	45.2	-	-	-	-	27.4	-100.0	-
6	Basu (2013)	51.9	-	-	-	Chorioretinitis/choroiditis (55%)	-	-	-	-	-	23.8 (pulmonary)/ 2.8 (extrapulmonary)	-	-
7	Manousaridis (2013)	71.4	16.8/83.2	10	-	Serpiginous choroiditis (5) Multifocal choroiditis (10) Choroidal Granuloma (10)	10	57	-	4.8	23.8	38.1	-	28.6
8	Patel (2013)	52.9	-	7.7	-	42.3	34.6	-	-	-	70.6	-	92.3/87.5	26.7 (CXR), 55.6 (CT)
9	Vos (2013)	80.3	-	12.1	6.1	Chorioretinitis (22.7) Choroiditis (1.5)	51.5	47.0	51.5	9.1	12.1	89.4	-	~25
10	Ang (2012)	-	-	49.4	9.8	21.3	19.5	-	-	-	-	-	-	4.4
11	Bansal (2012)	-	-	46.3	-	53.7	-	-	-	-	-	0	36.1/-	11.8

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S/N	Study	Laterality		Phenotypes					Relevant history			Investigations		
		Bilaterality (%)	Right/left (%)	AU (%)	IU (%)	PU (%)	Panuveitis (%)	Retinitis/retinal vasculitis (%)	Neuroretinitis/optic neuropathy (%)	Previous TB (%)	Contact history (%)	Systemic TB (%)	+ve TST/QFT (%)	Positive radiography (CXR or CT) (%)
12	Ducommun (2012)	33.3	62.5/37.5	-	-	Serpiginous choroiditis (16.7) Multifocal choroiditis (83.3)	-	-	-	-	-	-	100.0/75.0	41.7
13	Zhang (2012)	11.1	37.5/62.5	-	-	Serpiginous choroiditis (5.6) Multifocal choroiditis (5.6) Choroidal tuberculoma (72.2) Choroidal tubercle (5.6)	-	5.6	-	11.1	-	66.7	?/-	-
14	Doycheva (2011)	-	-	4.2	-	Serpiginous choroiditis (50.0) Multifocal choroiditis (8.3) Posterior uveitis (4.2)	8.3	25.0	-	-	-	-	-	12.5
15	Gineys (2011)	66.7	-	21.4	23.8	21.4	45.2	-	-	-	42.9	-	68.4/100.0	-
16	Gupta (2011)	-	-	-	-	-	-	-	-	-	-	-	-	-
17	Parchand (2011)	64.9	-	-	100.0	-	-	-	-	-	-	-	-	-
18	Sanghvi (2011)	77.8	66.7/33.3	11.1	14.8	Serpiginous choroiditis (3.7) Multifocal choroiditis (7.4)	48.1	14.8	-	-	51.9	11.1	-	-
19	Hamade (2010)	61.2	-	22.4	-	30.6	47.0	-	-	-	-	-	-	12.2
20	Babu (2009)	56.9	-	-	-	-	-	-	-	-	-	5.9	96.1/1-	27.5
21	Cimino (2009)	-	-	2.7	-	21.6	75.7	-	-	-	-	-	-	-
22	Al-Mezaine (2008)	43.1	-	17.9	-	Multifocal choroiditis (20.5)	79.5	35.6	-	-	-	-	-	9.8
23	Bansal (2008)	62.9	-	-	-	-	-	-	-	-	-	-	-	-
24	Gupta (2006)	54.5	-	-	-	Chorioretinitis (33.3)	-	33.3	-	-	-	81.8	63.6/-	100.0
25	Varma (2006)	-	-	25.0	8.3	Choroidal tuberculoma (16.7) Multifocal choroiditis (8.3) Serpiginous choroiditis (8.3)	41.7	-	-	-	-	-	100.0/-	-

S/N	Study	Laterality		Phenotypes					Relevant history			Investigations		
		Bilaterality (%)	Right/left (%)	AU (%)	IU (%)	PU (%)	Panuveitis (%)	Retinitis/retinal vasculitis (%)	Neuroretinitis/optic neuropathy (%)	Previous TB (%)	Contact history (%)	Systemic TB (%)	+ve TST/QFT (%)	Positive radiography (CXR or CT) (%)
26	Morimura (2002)	50.0	60.0/40.0	-	-	Multifocal/diffuse chorioiditis (40.0) Chorioid/disc nodule (30.0)	30.0	-	-	-	-	-	10.0/-	10
27	Gupta (2001)	53.8	-	-	100.0	-	-	-	-	-	-	-	-	85
28	Rosen (1990)			8.3	-	Chorioid tubercle (16.7)	-	75.0	-	8.3	16.7	50.0	100.0/-	-

AU, anterior uveitis; CT, computerized tomography; CXR, chest X ray; IU, intermediate uveitis; PU, posterior uveitis; QFT, QuantiFERON-TB Gold In-Tube; TB, tuberculosis; TST, tuberculin skin test.
All data beyond 2 decimal places have been rounded to 1 decimal place.

Table 3

Diagnosis, intervention, and outcome

S/N	Study	Diagnosis			Intervention			Outcome						
		Ocular signs	Systemic investigations	Local investigations	Response to ATT	Exclusion of other etiologies	Consultation with other specialists	ATT	Steroid	Immunosuppressant	Mean follow-up time (months)	Outcome measure	Successful outcome ^d (%)	Successful outcome (%) in controls
1	Agrawal (2015)	TB uveitis	QFT/TB T-spot/CXR	Biopsy	-	+	+	HREZ (2 months) → 2 of HREZ drugs OR HRMZ (2 months) → 2 of HREZ drugs ± M	±Systemic (60 mg/day × 1 week → taper) ±Topical	±		Dosage of corticosteroid/immunosuppressants; recurrence of inflammation	80.6	-
2	Jakob (2014)	-	-	-	-	-	-	HREZ (2 months) → HR (4 months) OR 3 of HREZ drugs	±Systemic ±Peritocular	-	6	Improvement in visual acuity, grade of inflammation, presence of macular edema and subjective symptoms	63.0	-
3	La Distia Nora (2014)	TB uveitis	QFT/TST/CXR	-	-	-	-	HRZ ± E (2 months) → HR (4 months OR 7 months)	±Systemic	±	2.1	Improvement in inflammation and visual acuity	90.6 (P = 0.004)	P < 0.001 improvement in VA
4	Mora (2014)	-	-	-	-	-	-	HREZ/HRE/HR/H (mean 7.8 months)	±Systemic ±Topical	-	12.7	Recurrence of inflammation	62.5	-
5	Tognon (2014)	Ocular TB	QFT/TST/CXR/sputum analysis/extrapulmonary TB findings	Culture /PCR	+	+	-	HREZ (2 months) → HR (7 months)	±Systemic	-	23	Recurrence of inflammation; visual acuity	92.1	-
6	Basu (2013)	Ocular TB	IGRA/TST (10 mm)/extrapulmonary or pulmonary TB findings	-	+	+	+	HREZ (2 months) ^b → HR (4 months)	±Systemic ±Topical ±Peritocular	-	20 ^c	Progression of inflammation (increase in level of inflammation/appearance of new lesions)	75.5	-
7	Manousaridis (2013)	Active/latent TB	QFT/TST/CXR/CT	Culture /PCR	-	+	-	HREZ (2 months) → HR (4 months)	-	-	-	Recurrence of inflammation; visual acuity	100.0	-

S/N	Study	Diagnosis					Intervention				Outcome			
		Ocular signs	Systemic investigations	Local investigations	Response to ATT	Exclusion of other etiologies	Consultation with other specialists	ATT	Steroid	Immunosuppressant	Mean follow-up time (months)	Outcome measure	Successful outcome ^a (%)	Successful outcome (%) in controls
8	Patel (2013)	-	-	-	-	-	+	HRZ/HREZ ^d	±Systemic	-	-	Relapse of disease (SUN criteria)	81	-
9	Vos (2013)	TB uveitis	QFT/TST/CXR/CT/sputum	PCR	-	+	+	Not specified (6 or 9 months)	±Systemic ±Topical	±	16.4	Intraocular cell count (SUN Working Group); visual acuity	70.0	60.0
10	Ang (2012)	TB uveitis	QFT/TB T-spot/TST (15 mm)/sputum analysis	-	-	+	+	HREZ (2 months) ^b → HR (4 months)	±Systemic (1 mg/kg → Taper) ±Topical	-	6	Clinical improvement; recurrence of inflammation	24.0	14.4
11	Bansal (2012)	Active TB uveitis	TST (10 mm)	-	-	+	+	HREZ (3 →4 months) ^b → HR (9 →14 months)	±Systemic (1 mg/kg → Taper) ±Topical	±	33.1	Recurrence of inflammation	84.3	25.0
12	Ducommun (2012)	Ocular TB	TST (>15 mm)/TB T-spot	-	-	+	+	H only (6 months) OR HRZ/HREZ (2 months) ^e → HR (4 months)	±Systemic	-	4.5	Relapse of disease	90.0	50.0
13	Zhang (2012)	Ocular TB	TST/CXR/systemic TB findings	-	+	+	+	HREZ (2 months) → HR (4 →10 months)	-	-	33.9	Recurrence of inflammation	53.5	-
14	Doycheva (2011)	-	-	-	-	-	-	HREZ (at least 6 months) except 1 patient (only H)	Systemic	-	-	Recurrence of inflammation	81.8	-
15	Gineys (2011)	-	-	-	-	-	+	HRZ ^f (2 months) → HR (2 months)	±Systemic	-	-	Absence of inflammation or a minimum 2-point decrease in SUN criteria	60.0	-
16	Gupta (2011)	Active serpiginous choroiditis	TST (10 mm)	-	-	-	-	HREZ	Systemic (1 →1.5 mg/kg/day)	-	8.6	Progression of lesion	83.1	94.7
17	Parchand (2011)	TB uveitis	TST (10 mm)	-	-	+	+	Not specified	±Systemic ±Periocular	±	Minimum 12	Recurrence of inflammation	88.1 (P = 0.005)	53.3

S/N	Study	Diagnosis					Intervention				Outcome			
		Ocular signs	Systemic investigations	Local investigations	Response to ATT	Exclusion of other etiologies	Consultation with other specialists	ATT	Steroid	Immunosuppressant	Mean follow-up time (months)	Outcome measure	Successful outcome ^a (%)	Successful outcome (%) in controls
18	Sanghvi (2011)	TB uveitis	γ-interferon test/TST/CXR/ nonocular active or latent TB	-	-	+	-	HREZ (2 months) → HR (4 months)	±Systemic	-	35	Recurrence of inflammation; visual acuity	70.3	-
19	Hamade (2010)	Chorioretinitis; anterior granulomatous uveitis	TST (15 mm)/CT	-	+	+	+	HREZ (2 months) ^b → HR (4 months)	±Topical Systemic stopped if already using	-	12	Clinical improvement (SUN Working Group); resolution of inflammation	100.0	-
20	Babu (2009)	Ocular TB	TST/CXR	-	+	+	+	HREZ (2 months) → HRZ (4 months) → HR (6 months)	±Systemic ±Topical/ peritocular	-	-	Recurrence of inflammation	80.4	-
21	Cimino (2009)	Ocular TB	TST (>15 mm)	-	+	+	+	HREZ ^g (6 months–24 months; mean 10.7 months)	Systemic	±	30.4	Improvement in visual acuity; recurrence of inflammation	91.9 improvement in visual acuity (P < 0.001); 90 no recurrence of inflammation (P < 0.001)	44.4
22	Al-Mezaine (2008)	Ocular TB	TST (15 mm)/CXR/CT/sputum analysis	-	+	+	+	HREZ (2 months) ^a → HR (4 –7 months)	±Systemic (1 mg/kg/day → Taper)	-	28.1	Resolution of inflammation; recurrence of inflammation; visual acuity; macular thickness	100.0	-
23	Bansal (2008)	Active serpiginous choroiditis	QFT/TST (10 mm)/CXR/CT	-	-	+	+	HREZ (3 –4 months) ^b → HR (6 –14 months)	Systemic (1 mg/kg/day → Taper)	-	24.9	Resolution of lesion; recurrence of inflammation	77.4	53.5
24	Gupta (2006)	Ocular TB	TST/CXR/ extrapulmonary TB findings	AFB/culture /PCR	+	+	+	HREZ (3 –4 months) ^b → HR (9 –15 months)	Systemic	-	18.9	Progression of lesion	81.8	-
25	Varma (2006)	-	-	-	-	-	+	Not specified	±Systemic	-	-	Progression of disease; visual acuity	100.0	-

S/N	Study	Diagnosis				Intervention				Outcome				
		Ocular signs	Systemic investigations	Local investigations	Response to ATT	Exclusion of other etiologies	Consultation with other specialists	ATT	Steroid	Immunosuppressant	Mean follow-up time (months)	Outcome measure	Successful outcome ^a (%)	Successful outcome (%) in controls
26	Morimura (2002)	Ocular TB	TST (10 mm)/CXR/CT	-	-	+	+	Not specified	±Systemic	-	-	Improvement in ocular inflammation; visual acuity	90.0	-
27	Gupta (2001)	Ocular TB	TST/CXR	PCR	-	+	+	HREZ (3 months) ^b → HR (9 months) -14 months)	±Systemic	-	9	Recurrence of disease	100.0	-
28	Rosen (1990)	-	-	-	-	-	-	Not specified	±Systemic	-	-	Resolution/inactivity of disease	36.4 (resolved); 36.4 (inactive, with no further therapy needed)	-

CT, computerized tomography; CXR, chest X ray; E, ethambutol; H, isoniazid; M, moxifloxacin; QFT, QuantiFERON-TB Gold In-Tube; R, rifampicin; TB, tuberculosis; TST, tuberculin skin test; Z, pyrazinamide.

All data beyond 2 decimal places have been rounded to 1 decimal place.

^aSuccessful outcome = no recurrence/progression of inflammation, improvement in visual acuity.

^bH 5 mg/kg/day R 450 mg/day if BW 50 kg or 600 mg/day if BW >50 kg E 15 mg/kg/day Z 25–30 mg/kg/day.

^cMedian.

^dH 300 mg/day R 600 mg/day E and Z dosed by weight.

^eH 300 mg/day R 600 mg/day Z 1500 mg/day ± E 800 mg/day.

^fH 5 mg/kg/day R 10 mg/kg Z 25 mg/kg/day.

^gH 300 mg/day R 600 mg/day E 15 mg/kg/day.

Table 4

Factors influencing outcome of anti-tubercular therapy

S/N	Demographics				Investigation findings			Intervention			
	Age, OR (95% CI)	Ethnicity, OR (95% CI)	Gender, OR (95% CI)	Laterality, OR (95% CI)	Duration of uveitis, OR (95% CI)	Phenotype, OR (95% CI)	Nonimaging, OR (95% CI)	Imaging, OR (95% CI)	ATT, OR (95% CI)	Steroid, OR (95% CI)	Immunosuppressant, OR (95% CI)
1	n.s.	African ethnicity (higher treatment failure)	n.s.	n.s.	-	Intermediate uveitis, Panuveitis (higher treatment failure) OR 0.54 (0.27–1.06); OR 0.28 (0.15–0.50), respectively	QFT (n.s.)	CXR (n.s.)	n.s.	n.s. ^a	Immunosuppressant (higher treatment failure and persistence of inflammation) OR 3.00 (1.09–8.25)
2	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	n.s.	n.s.	-
5	-	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-
8	>50 years (higher risk of irreversible vision loss) OR 10.5 (1.1–98.9)	-	-	-	Delay in diagnosis >500 days (higher risk of irreversible vision loss) OR 20.0 (1.41–282)	Posterior uveitis (higher risk of relapse) OR 13.1 (1.16–148)	-	-	-	Supplemental systemic steroids after ATT (higher risk of relapse) OR 14.9 (1.40–160)	-
9	-	-	-	-	-	-	-	-	-	-	-
10	n.s.	-	Female (higher recurrence) OR 2.30 (1.18–4.48)	-	-	n.s.	IGRA (n.s.)	-	n.s.	n.s.	-
11	-	-	-	-	-	-	-	-	-	??	-
12	-	-	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-	-	-	-

S/N	Demographics				Investigation findings			Intervention			
	Age, OR (95% CI)	Ethnicity, OR (95% CI)	Gender, OR (95% CI)	Laterality, OR (95% CI)	Duration of uveitis, OR (95% CI)	Phenotype, OR (95% CI)	Nonimaging, OR (95% CI)	Imaging, OR (95% CI)	ATT, OR (95% CI)	Steroid, OR (95% CI)	Immunosuppressant, OR (95% CI)
15	-	-	-	-	-	-	Higher median QFT values (higher success)	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-	-	-	-
19	-	-	-	-	-	Posterior uveitis (poorer visual outcome) OR 9.09 (2.15–38.43)	-	-	-	Corticosteroid therapy before ATT (poorer visual outcome)	-
20	n.s.	-	n.s.	n.s.	Longer duration (higher recurrence)	-	ESR (n.s.)	CXR (n.s.)	12 months versus <12 months (higher recurrence)	-	-
21	-	-	-	-	-	-	-	-	-	-	-
22	-	-	-	-	-	-	-	-	-	-	-
23	-	-	-	-	-	-	-	-	-	-	-
24	-	-	-	-	-	-	-	-	-	-	-
25	-	-	-	-	-	-	-	-	-	-	-
26	-	-	-	-	-	-	-	-	-	-	-
27	-	-	-	-	-	-	-	-	-	-	-
28	-	-	-	-	-	-	-	-	-	-	-

ATT, anti-tubercular therapy; CI, confidence interval; ESR, erythrocyte sedimentation rate; IGRA, interferon-gamma release assay; n.s., statistically not significant; OR, odds ratio; QFT, QuantiFERON-TB Gold In-Tube.

All data beyond 2 decimal places have been rounded to 1 decimal place.

^aOdds ratio not reported but statistically significant P-value.

Table 5

Risk-bias assessment—Newcastle-Ottawa Quality Assessment Scale

Study	Selection (4)			Comparability (2)		Outcome (3)		Total (Max 9)		
	Representativeness	Non-exposed selection	Ascertainment of exposure	Outcome of interest not present at start	One factor	Additional factor	Assessment		Adequate follow up	Adequacy of follow up
1 Agrawal (2015) Cohort study 21 TRU 9Y	Tertiary referral center	No comparison to non-exposed	Drawn from same community although excluded from the study if not on ATT	No available data on impact of ATT on uveitis. It shed light on factors of failure (i.e. immunosuppressive therapy)	Patients identified based on single criteria (Gupta et al)	Not identified	Not blind	6/21 completed at least 6/12 follow up	2/21 follow up less than 6 months (9%) which is adequate	6
2 Jakob (2014) Retrospective N = 19 (19 received full ATT) 3Y	Tertiary referral center	Groups stated but not compared	QFT and clinical examination used	TB is an important diagnostic consideration. Treat less severe early and with full therapy for best results	Groups controlled according to therapy (Full, isoniazid, steroid, ml) – but not analysed	Not identified	Not blind	Mean follow up 6 months	3/43 lost to follow-up	5
3 La Distia Nora (2014) Multi-center retrospective cohort study N = 96 3Y	Tertiary referral center	No comparison to non-exposed	QFT positive plus clinical/ TST findings	Favourable outcome with ATT in QFT + patients	QFT Positive and ATT. 29/32 showed improvement in VA at 1Y	Not identified	Not blind	Mean follow up 2.1 years	All accounted for	6
4 Mora (2014) Retrospective cohort study N = 30 13Y	Tertiary referral center	No comparison to non-exposed	Drawn from same community although excluded from the study if not on ATT	Use of ICG advised to rule out Choroidal granulomas (present in 20%)	TST/QFT performed to include patients	Not identified	Not blind	Minimum 12/12 follow up	30/53 fulfilled criteria for inclusion. No data on the 23 excluded.	5
5 Tognon (2014) Prospective cohort study N = 101 4Y	Tertiary referral center	Comparison of cohort 1 and 2	Microbiological/QFT and according to SUN guidelines	Epidemiology of immigrants in cohort 1	SUN working guidelines used, plus TST/QFT	VA compared	Not blind	Minimum 9/12 follow up	All patients with TB in cohort 1 and 2 accounted for	8
6 Basu (2013) Retrospective cohort study N = 106 13Y	Tertiary referral center	No comparison to non-exposed	SUN guidelines, TST, Interferon test	Paradoxical worsening post ATT (6 months) – usually 9–12 months. 26 progressed following	All TBU	Not identified	Not blind	Minimum 1 year post ATT	All accounted for	5

Study	Selection (4)			Comparability (2)		Outcome (3)		Total (Max 9)		
	Representativeness	Non-exposed selection	Ascertainment of exposure	Outcome of interest not present at start	One factor	Additional factor	Assessment		Adequate follow up	Adequacy of follow up
7	Manousaridis (2013) Retrospective N = 21 10Y	No comparison to non-exposed	QFT, TST, clinical examination	Systemic TB noted in patients with no history. Plus 10/21 CT chests were abnormal	TST/QFT tests performed to include patients	Not identified	Not blind	16/18 completed at least 6 months	2/21 did not receive ATT (not advised)	6
8	Patel (2013) Retrospective case series N = 17 16Y	No comparison to non-exposed	TST/QFT/SUN guidelines	Poor prognosis with posterior uveitis/delay in ATT and concurrent steroid/ATT	No control	Not identified	Not blind	No details mentioned	No details mentioned	3
9	Vos (2013) Retrospective N = 10 2Y	No comparison to non-exposed	Classification into latent, possible, presumed and confirmed	Not mentioned	Same criteria used to identify presumed TBU	Not identified	Not blind	All completed at least 6 months of ATT	3/10 follow-up less than 6 months following cessation of ATT (30%)	4
10	Ang (2012) Retrospective N = 64 9Y	Comparison with no ATT patients (118)	Drawn from same community although excluded from the study if not on ATT	Not mentioned	Response to ATT – duration greater than 9/12	Not identified	Not blind	Mean follow up 12/12	Mean follow up was 12months (no specifics)	6
11	Bansal (2012) Retrospective cohort study looking into only serpiginous-like choroiditis N = 105 9Y	Compared with corticosteroids alone (12)	From same population as non-exposed. Positive TST /QFT included.	Not mentioned	Recurrence. 9/12 steroids alone. 9/93 recurrence in ATT group	Not identified	Not blind	Minimum 9 month follow up	Mean 29-33 months. Deemed adequate.	6
12	Ducommun (2012) Retrospective N = 12 7Y	No comparison to non-exposed	TST, clinical exam and T Spot Test	Lesion size reduced on ICG – new. Also recurrence due to paradoxical worsening	No control	Not identified	Not blind	Long term follow up 4.5 years	All accounted for	5
13	Zhang (2012) Retrospective non-comparative case series N = 18 10Y	One population (specific selection)	No QFT/TST to diagnose. Only used PPD, clinical examination and response to ATT to diagnose.	Not mentioned	No comparisons made – all one diagnosis and treatment.	Not identified	Not blind	Minimum follow up 6 months	All accounted for	3

Study	Selection (4)				Comparability (2)		Outcome (3)			Total (Max 9)
	Representativeness	Non-exposed selection	Ascertainment of exposure	Outcome of interest not present at start	One factor	Additional factor	Assessment	Adequate follow up	Adequacy of follow up	
14	Doycheva (2011) Prospective N = 20 3Y	No comparison to non-exposed	Clinical exam and QFT. 20 had PET	Aware of limitations (11 ATT treated patients, 4 were PET negative)	No control	Not identified	Not blind	No mention of follow up details	No mention of follow up details	3
15	Gineys (2011) Prospective non-randomised clinical lab investigation N = 42 2Y	No comparison to non-exposed	All ocular inflammation given QFT then positives treated only	Higher cut-off needed for QFT to avoid over-treating	All QFT positive treated with ATT (SUN protocol)	Not identified	Not blind	12-24 months	All accounted for	6
16	Gupta (2011) Retrospective case series N = 110 10Y	Grouped by result of TST	TST only	Progression was the outcome (more in ATT than steroid alone)	Comparison of "steroids" and "steroid+ATT" (worsening due to delayed effect)	Not Identified	Not blind	Minimum 18 months (mean 35)	All accounted for	6
17	Parchand (2011) Retrospective case series N = 57 15Y	Comparison between ATT and non ATT groups	TST and clinical findings	Most common cause of IU was TB. ATT reduced recurrence rate as compared to use of steroid alone	Rate of recurrence and VA compared between groups	Not identified	Not blind	Minimum follow up 12 months	All accounted for	7
18	Sanghvi (2011) Retrospective N = 27 15Y	No comparison to non-exposed	TST/QFT used. Also, minimum 6 month ATT therapy used.	Ethnicity (majority Asian population)	TST/QFT used (4 only). Also, minimum 6 month ATT therapy used.	Not identified	Not blind	Minimum 6 months	All accounted for	6
19	Hamade (2010) Retrospective N = 49 10Y	No comparison to non-exposed	TST/ No QFT	Treat with ATT at diagnosis. No steroid without ATT (as can activate dormant TB)	Only 4 week response used to suspect TB Steroid /with no steroid pre ATT	Not identified	Not blind	Minimum 6 months	All accounted for	6
20	Babu (2009) Retrospective N = 51 11Y	No comparison to non-exposed	Use of Mantoux test to determine latent TB and response to ATT	Not mentioned	Use of Mantoux test to determine latent TB and response to ATT	Not identified	Not blind	Mean follow up 24 months	96% completed 1 year course of ATT	4

Study	Selection (4)				Comparability (2)		Outcome (3)		Total (Max 9)		
	Representativeness	Non-exposed selection	Ascertainment of exposure	Outcome of interest not present at start	One factor	Additional factor	Assessment	Adequate follow up			
21	Cimino (2009) Retrospective cohort study N = 35 4Y	Tertiary referral center	Diagnosis at start	TST, clinical findings, rule out other causes	Delay in diagnosis leads to unnecessary steroid use, increased recurrence (when tapering)	ATT regime similar in all groups	Not identified	Not blind	30-month follow up	All accounted for	7
22	Al-Mezaine (2008) Retrospective review N = 51 8Y	Tertiary referral center	No comparison to non-exposed	Response to ATT and positive TST	Not mentioned	OCT changes with ATT	ME and VA – no correlation	Not blind	Minimum follow up 6 (mean 19)	All accounted for	5
23	Bansal (2008) Retrospective case series 14Y	Tertiary referral center	Comparison of ATT with steroids	TST (>10mm) and clinical features of TB	Yes – Addition of ATT to steroids reduced recurrence	Compare ATT with steroids	Not identified	Not blind	Median follow up 24 months	All accounted for	7
24	Gupta (2006) Retrospective case series N = 11 4Y	Tertiary referral center	No comparison to non-exposed	4-part criteria including clinical, ocular, Mantoux and response to ATT over 4 weeks) Steroids also given	ppv to drain granuloma fluid not advised – medical therapy alone is best	No comparison	Not identified	Not blind	Minimum 9 months Follow up	All accounted for	5
25	Varma (2006) Retrospective case series N = 12 1Y	Tertiary referral center	No unexposed group	TST/clinical findings in all patients	Dramatic response to ATT supports its use with high clinical suspicion and positive Mantoux test	No control or details of treatment	Not identified	Not blind	Minimum 6 month follow up in 6 identified cases. The rest not mentioned.	6 follow up accounted for. The rest not mentioned.	3
26	Morimura (2002) Prospective, non comparative interventional case series N = 10 3Y	Tertiary referral center	No comparison to non-exposed	TST, clinical findings used	ATT – only Isoniazid +/-Rifampicin	No steroid-only group to compare	Not identified – untreated patients with positive TST not analysed	Not blind	Only 6 patients completed 6/12 (60%). Small numbers	Unclear follow up details post treatment	2
27	Gupta (2001) Retrospective N = 13 3Y	Tertiary referral center	No comparison to non-exposed	Mantoux, clinical findings	PCR important in order to request only relevant diagnostic tests. 12/13 – no recurrence. 9–12 month course of ATT. Steroid alone	ATT according to World Health Organisation	Not identified	Not blind	Mean follow up 6 months – all showed resolution	All accounted for	6

Study	Selection (4)			Comparability (2)		Outcome (3)			Total (Max 9)
	Representativeness	Non-exposed selection	Ascertainment of exposure	Outcome of interest not present at start	One factor	Additional factor	Assessment	Adequate follow up	Adequacy of follow up
28 Rosen (1990) Retrospective case series N = 12 1Y	Tertiary referral center.	No comparison to non-exposed	TST in all patients	also showed resolution. Retinal vasculitis strongly correlated with positive Mantoux test	No control	Not identified	Not blind	No details mentioned	No details mentioned

ATT, anti-tubercular therapy; CS, case series; ICG, indocyanine green; IU, intermediate uveitis; LTF, lost to follow up; ME, macular edema; OCT, optical coherence tomography; PET, positron emission tomography; PPV, pars plana vitrectomy; QFT, QuantiFERON TB Gold; SUN, standardization of uveitis nomenclature; TB, tuberculosis; TBU, tuberculosis uveitis; TRU, tuberculosis related uveitis; TST, tuberculin skin test; VA, visual acuity.

Table 6

Clinical phenotypes of ocular tuberculosis

Phenotype	Number of studies ^a (%)
Posterior uveitis	
Choroiditis/chorioretinitis	23 (82.1)
Serpiginous	
Nonserpiginous	
Multifocal	
Choroidal tubercle/granuloma/nodule	
Unspecified	
Anterior uveitis	17 (60.7)
Panuveitis	16 (57.1)
Intermediate uveitis	11 (39.3)
Retinitis/retinal vasculitis	11 (39.3)
Neuroretinitis/optic neuropathy	4 (14.3)
Endophthalmitis/panophthalmitis	0 (0.0)

^a Number of studies that included patients with each respective clinical phenotype (out of a total of 28 studies included in this review).

Table 7

Side effects of anti-tubercular therapy

Side effect	Number of patients ^a (%)
Unspecified side effects	16 (5.5)
Liver damage	6 (2.1)
Rash	5 (1.7)
Reduced libido	1 (0.3)
General malaise	1 (0.3)
Total	29 (10.1)

^a Out of 287 patients from the 5 studies (out of a total of 28 studies) which reported side effects secondary to the use of anti-tubercular therapy.