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ORIGINAL PAPER

Treatment outcome in patients with presumed tubercular uveitis at a tertiary referral eye care centre in Singapore

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Abstract
Aim To report the clinical features and outcome of patients with presumed tubercular uveitis (TBU).
Methods Retrospective analysis of patients with presumed TBU at a tertiary referral eye care centre in Singapore between 2007 and 2012 was done. Main outcome measures were failure of complete resolution of uveitis or recurrence of inflammation.
Results Fifty three patients with mean age of 44.18 ± 15.26 years with 54.72% being males were included. 19 (35.85%) had bilateral involvement, with panuveitis and anterior uveitis being the most common presentations. 36 (67.92%) patients received antitubercular therapy (ATT), and 28 received concurrent systemic steroids. 15 (28.30%) eyes of 11 (30.55%) patients in the ATT group and 4 (21.05%) eyes of 3 (17.64%) patients in the non-ATT group had treatment failure (p value = 0.51).
Conclusion The use of ATT, with or without concurrent corticosteroid, may not have a statistically significant impact in improving treatment success in patients with presumed TBU.

Keywords Antitubercular therapy · Panuveitis · Tubercular uveitis · Steroids · Tuberculosis

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Introduction

Tuberculosis (TB) is a systemic infectious disease with a significant global health burden. The World Health Organisation (WHO) reported in 2013 a prevalence of 9 million people infected with *Mycobacterium tuberculosis* (MTB) worldwide, accounting for 1.5 million deaths around the world [1]. While up to 90% of individuals infected with MTB may remain asymptomatic throughout life, the remaining 10% may have clinical manifestations of this disease [2].

Tubercular uveitis or TB-related uveitis (TBU) can arise secondary to active ocular infection by MTB or as a consequence of presumed immune-mediated inflammatory reaction to latent TB and the tubercle

bacillus, [3] with the incidence reported to be as high as 18% in patients with systemic TB [4]. Definitive diagnosis of intraocular TB requires demonstration of acid-fast bacilli on direct smear of intraocular fluid, growth of MTB in culture medium, or the presence of MTB DNA via polymerase chain reaction (PCR) [3, 5]. However, given the invasiveness and inherent risk of complications of obtaining intraocular fluid associated with low sensitivity of PCR, the diagnosis of TBU is often a clinical one based on suggestive clinical features and corroborative laboratory findings [3, 6, 7]. Suggestive investigations can include lesions suggestive of old healed pulmonary tuberculosis on chest X-ray, positive tuberculin skin test (TST), or interferon gamma release assay (IGRA).

The ocular manifestations of TB are extremely varied. It typically presents as a posterior uveitis, panuveitis, or a chronic granulomatous anterior uveitis, but it can affect any anatomic location of the eye, even masquerading as an ocular tumour [3, 8, 9]. In the recent decade, a number of studies have advocated the use of antitubercular therapy (ATT) in conjunction with steroids, for the treatment of TBU [10–12]. While there is still no consensus on the exact duration of treatment with ATT, duration of at least 6 months is generally recommended, while some studies suggest an even longer course of 9 months [13].

This study aimed to evaluate the treatment outcome in patients with presumed TBU in high endemic setting in Singapore. In addition, we will analyse the factors that may contribute to treatment failure, including patient demographics, clinical phenotypes, or investigations used to diagnose presumed TBU.

Methods

We conducted a retrospective review of all patients referred to the uveitis service from January 2007 to December 2012 at a tertiary centre in Singapore. Ethics approval was obtained from the National Healthcare Group Domain Specific review board.

All procedures performed in the current study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No formal patient consent was required for this retrospective cohort study.

The diagnosis of presumed intraocular TB was made in accordance with existing accepted guidelines [3, 12]. The inclusion criteria for this study were as follows:

1. Active uveitis with clinical features of TBU;
2. Exclusion of other infectious and non-infectious uveitic etiologies that may mimic the given clinical presentation of TBU;
3. A positive TST (induration >10 mm) following intradermal injection of 5 tuberculin units read 48–72 h after injection or a positive response to IGRAs, namely T-SPOT.TB test (Oxford Immunotec, Abingdon, UK); and
4. A follow-up and assessment at least twelve months from the end of treatment.

All of the included patients underwent a thorough systemic review and were co-managed with a specialist in Infectious Disease, who evaluated patients and directed ATT. Data collected included age, race, gender, country of origin, history of previous TB or contact with any person with active TB, travel history, Bacillie Calmette-Guerin (BCG) status, duration of symptoms, presence of immunosuppression such as human immunodeficiency status (HIV) or consumption of long-term immunosuppressants as well as the presence of any constitutional and systemic symptoms. A complete examination was performed which included the assessment of visual acuity and intraocular pressures, slit lamp examination, and dilated fundus examination. Standardization of uveitis nomenclature (SUN) working group recommendations for anatomical classification of uveitis and grading of anterior chamber inflammation was employed [14], and all ocular features and description of uveitis at initial presentation and subsequent follow-up visits were documented accordingly.

In addition, we recorded all investigations done for the patients during the period under our follow-up. This included any combination of the following blood tests—full blood counts, inflammatory markers (erythrocyte sedimentation rate, C-reactive protein), serum angiotensin-converting enzyme levels, syphilis screen, and other relevant tests for inflammatory conditions. Imaging and diagnostic tests included chest radiographs, thoracic CT scans, microscopy

examinations for acid-fast bacilli, TST, and T-SPOT.TB test.

Treatment failure was defined as one of the following:

1. Non-resolution of inflammation, or failure of complete clinical resolution of the primary lesion in cases of retinitis or choroiditis, at 12 and 24 months follow-up.
2. Recurrence of inflammation described as a two-step increase in inflammation as defined by the SUN working group criteria for anterior and intermediate uveitis [14].

Our primary outcome measure was to compare the rates of treatment failure in the management of TBU (as defined above) between patients who received steroids and those who received both ATT and steroids. We further evaluated for any relevant factors that may predict treatment outcome, such as demographics, TBU clinical phenotype, or the investigation findings on which TBU diagnosis was based.We also employed a novel approach to categorise and assess the investigation findings that premised diagnosis, in order to assess for features, which may predict treatment response. This was done using a combination of corroborative tests, i.e. CXR, IGRA, and TST with three levels of specificity (level 1, level 2, level 3) for diagnosis of presumed TBU.

Statistical analysis

Descriptive statistics are presented as means, ranges, and percentages. Chi Square test was used for correlating between categorical variables and treatment outcome. Univariate and multivariate regression analyses were used to determine the independent predictors for treatment failure. Results were considered statistically significant with a p value of <0.05. Data were analysed using Stata/SE, version 13.0 (Stata Corp, College Station, TX, USA).

Results

During the 6-year study period, a total of 62 patients were included, with 53 patients (72 eyes) completing the minimum follow-up requirement of 12 months and 26 patients (37 eyes) having follow-up till 24 months.

The mean age of patients was 44.18 ± 15.26 (age range 9–84) years. There were 29 (54.72%) males and 24 (45.28%) females. The majority of the patients were Indian (84.91%), with only 8 (15.09%) being of other races. 34 patients had unilateral involvement, with 20 (37.74%) involving the right eye, 14 (26.42%) involving the left eye, and 19 (35.85%) having bilateral involvement, giving a total of 72 eyes from 53 patients (Table 1).

Of the 72 eyes studied, 41 (56.94%) eyes had anterior uveitis with 26 (36.11%) eyes showing granulomatous features. 8 (11.11%) eyes had intermediate uveitis; 15 (20.83%) eyes had posterior uveitis; 29 (40.28%) eyes had panuveitis; and 5 (6.94%) eyes had anterior scleritis. Snowballs were noted in 6 (8.82%) eyes with associated snowbanking in 3 (4.41%) eyes. Retinal vasculitis was found in 28 (38.89%) eyes and choroiditis in 17 (23.61%) eyes. (Table 2).

Of the investigations performed, 27 patients had CXR done, of which 21 patients (77.78%) had normal CXR findings, while 6 patients (22.22%) had features suggestive of an old, healed pulmonary TB. 23 patients had TST with 3 (13.04%) having indurations less than 10 mm, 5 (21.74%) having indurations between 10 and 15 mm, 12 (52.17%) having indurations between 15 and 20 mm, and 3 (13.04%) having indurations >20 mm; all read between 48 and 72 h after administering the test. 34 patients had T-SPOT.TB performed. Of these, 30 patients (88.24%) had positive results, while 4 (13.33%) were negative (Table 3).

Table 1 Demographics of patients with tuberculous uveitis

Age (years)	44.18 + 15.26 (9–84)
Gender [*N* (%)]	
Male	29 (54.72%)
Female	24 (45.28%)
Race [*N* (%)]	
Indian	45 (84.91%)
Others	8 (15.09%)
Laterality [*N* (%)]	
Unilateral, right	20 (37.74%)
Unilateral, left	14 (26.42%)
Bilateral	19 (35.85%)

N number of patients

Table 2 Clinical features of eyes with tuberculous uveitis

Anterior uveitis [*N* (%)]	
Granulomatous	26 (36.11%)
Ocular manifestations [*N* (%)]	
Anterior scleritis	5 (6.94%)
Anterior uveitis	15 (20.83%)
Intermediate uveitis	8 (11.11%)
Posterior uveitis	15 (20.83%)
Panuveitis	29 (40.28%)
Snow balls [*N* (%)]	
Yes	6 (8.82%)
No	66 (91.7%)
Snow banking [*N* (%)]	
Yes	3 (4.16%)
No	69 (95.8%)
Retinal vasculitis [*N* (%)]	
Yes	28 (38.89%)
No	44 (61.11%)
Choroiditis [*N* (%)]	
Yes	17 (23.61%)
No	55 (76.39%)

N number of eyes

Table 3 Investigations for patients with tuberculous uveitis

Chest X-ray done [*N* (%)]	
Yes	27 (50.9%)
No	26 (49.1%)
Chest X-ray suggestive of old, healed pulmonary TB [*N* (%)]	
Yes	6 (22.22%)
No	21 (77.78%)
Tuberculosis skin test (TST) done [*N* (%)]	
Yes	23 (43.4%)
No	30 (56.6%)
TST induration [*N* (%)]	
<10 mm	3 (13.04%)
10–15 mm	5 (21.74%)
15–20 mm	12 (52.17%)
>20 mm	3 (13.04%)
T-SPOT.TB done [*N* (%)]	
Yes	34 (64.2%)
No	19 (35.8%)
T-SPOT.TB result [*N* (%)]	
Positive	30 (88.24%)
Negative	4 (11.76%)

TB tuberculousis, *TST* tuberculin skin test, *N* number of patients

Table 4 Management of patients with tuberculous uveitis

Topical steroids [*N* (%)]	
Yes	53 (100%)
No	0
Systemic therapy [*N* (%)]	
ATT with systemic steroids	8 (15.1%)
ATT without systemic steroids	28 (52.8%)
Systemic steroids without ATT	5 (9.43%)
Topical steroids alone (No systemic therapy)	12 (22.6%)
Intravitreal/ periocular steroid injection [*N* (%)]	
Yes	0
No	53 (100%)

ATT antitubercular therapy, *N* number of patients

Of the 19 patients who did not have T-SPOT.TB done, they had other corroborative test to support the diagnosis of presumed TBU: 13 had TST performed, with 2 (15.38%) having readings of more than 20 mm, 7 (53.85%) having readings of 15–20 mm, 3 (23.08%) having readings of 10–15 mm, and 1 (7.69%) having less than 10 mm of reading. Of the 6 patients who did not have a positive TST, 4 had T-SPOT.TB positive on repeat testing and 2 had sputum positive for acid-fast bacilli.

With regard to treatment, all 53 patients received topical steroids. In addition, 36 (67.92%) patients received ATT, of whom 28 received systemic steroids concurrently. Amongst the 36 patients, there were 24 (66.66%) patients with posterior or panuveitis, 3 (8.34%) patients with intermediate uveitis, and 9 (25%) patients with granulomatous anterior uveitis. Of the 17 (32.08%) patients who did not receive ATT, 5 received systemic steroids on top of their topical steroids. None of the patients received intravitreal or periocular steroids. The duration of ATT was for a minimum of 6 months, of which patients received quadruple therapy (Rifampicin, Isoniazid (INH), Ethambutol, Pyrazinamide) for the first 2 months followed by a further minimum of 4 months of Rifampicin and INH as guided by the infectious disease specialist based on systemic involvement of tuberculosis (Table 4).

There were 19 (26.39%) eyes of 14 patients and 8 (21.62%) eyes of 6 patients with treatment failure at the end of 12- and 24-month follow-up, respectively. There were 6 eyes that had treatment failure at both the

12- and 24-month follow-up. Six out of the 19 eyes had recurrence between 12 and 24 months of follow-up. Also, of the two patients who initially experienced resolution at the end of 12-month follow-up, two eyes had a recurrence between 12 and 24 months.

Amongst the group treated with ATT, 15 (28.30%) eyes of 11 (30.55%) patients had treatment failure, while in the group without ATT, 4 (21.05%) eyes of 3 (17.64%) patients had treatment failure. This difference was not statistically significant by Pearson's x^2 test (p value = 0.511) (Table 5).

We further evaluated the data using univariate regression analyses to study the factors affecting treatment outcome at the minimum 12-month follow-up and found that none of the demographic factors except race ($p = 0.02$) influenced the treatment outcome (Table 6). Likewise, none of the clinical phenotypes or types of TBU had any impact on the treatment outcome (Table 6). Having positive investigative findings of mantoux test, CXR or T-SPOT.TB did not influence the final outcome as well (Table 6). As none of the factors (demographic, clinical phenotypes, laboratory, or radiological investigations) except race had any impact on the final visual outcome ($p > 0.05$), we have not performed the multivariate regression analysis.

We used a novel categorization of our diagnostic tests into 3 levels—level 1 (with all three tests, i.e. CXR, T-SPOT.TB, and TST positive), level 2 (any two of the three positive), and level 3 (any one of the three positive) to further investigate whether the modality of diagnosis had a bearing on treatment failure. The distribution of these patients were 0 eyes in the level 1 category, 19 eyes of 19 (35.84%) patients in level 2 category, and 53 eyes of 34 (64.16%) patients in level 3 category. There were 7 (36.84%) patients in level 2 category and 8 (15.09%) patients in level 3 category with treatment failure at 12-month follow-up with no statistically significant difference in the final treatment outcome (p value = 0.228).

Using scatter plot, we also plotted the logmar visual acuity at baseline and at 12-month follow-up for both

Table 6 Univariate regression analysis for different variables affecting the treatment outcome at 12 months

Univariate regression at 12 months	β[a]	p value
Patient demographics and clinical features		
Age	0.000	0.958
Gender	0.24	0.057
Race (Indian)[b]	−0.13	0.02
Laterality	0.12	0.09
Clinical phenotypes	0.012	0.756
Investigations		
Manoux test	−0.01	0.865
Tb T-spot	0.055	0.353
Chest X-ray	−0.042	0.787
Treatment		
ATT	−0.008	0.946
Duration of ATT	−0.011	0.805
Topical steroids	−0.133	0.471
Oral Steroids	0.196	0.115

[a] Coefficient

[b] Only Indian race had significant treatment failure at 12 months on univariate regression analysis

Table 5 Treatment outcomes in eyes with tuberculous uveitis

Treatment failure at 12 months [N (%)]		
Yes	19 (26.39%)	
No	53 (73.61%)	
Treatment failure at 24 months [N (%)][a]		
Yes	8 (21.62%)	
No	29 (78.38%)	
Treatment Failure [(N (%)), p value]*		
ATT		$p = 0.511$
Yes	15 (28.30%)	
No	38 (71.70%)	
No ATT		
Yes	4 (21.05%)	
No	15 (78.95%)	

N number of eyes

* p value using Pearson's x^2 test

[a] 26 patients (37 eyes) completed the full 24 months of follow-up

ATT and not ATT groups and did not show any statistical significance between the two groups (Fig. 1).

Discussion

TBU can present with myriad of clinical manifestations and poses a diagnostic conundrum [15–17]. Diagnosis is often made presumptively and is based on suggestive clinical features due to the difficulty in isolating the MTB bacilli from intraocular specimens, which is regarded as the gold standard for diagnosis of TBU [18].

Traditional investigations which aid in the diagnosis of presumed TBU include TST and radiographic imaging such as CXR or CT thorax [19]. The advent of IGRAs has brought about a simpler and more specific method of detecting MTB. Though it is unaffected by prior BCG vaccination and atypical mycobacterial infection, IGRAs are still unable to distinguish between latent and active infections [18, 20–22].

Our analysis has shown that the type of investigations used in the process of diagnosing presumed TBU does not influence the risk of treatment failure. While immunological tests have become more accessible, they are costly to perform. In countries with lower socioeconomic status, where the endemic burden of TB is higher, [23] cheaper and widely obtainable tests like TST can be used in conjunction with clinical features to arrive at diagnosis of presumed TBU.

Singapore has a multiracial endogenous population, which is predominantly Chinese. Despite this fact, the majority of patients in our study were of Indian ethnicity, with most being immigrants. This could be attributed to the increase in the local migrant population from the Indian subcontinent over the past decade. This observation is consistent with reports in the UK and US, where most of the patients with TB infection are not indigenous [10, 23]. Therefore, clinicians should have a high index of suspicion of TBU when treating refractory uveitis in patients originating from endemic regions, even when practising in a non-endemic country [24].

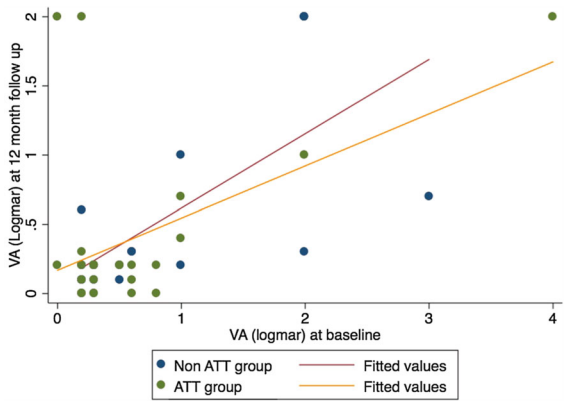

Fig. 1 Scatter plots for visual acuity at baseline and at 12 months follow-up for both Antitubercular therapy (ATT) group and non-ATT group

In our study, we analysed the outcome of patients at both 12- and 24-month intervals. In the 37 eyes (of 26 patients) that completed follow-up to the 2-year mark, all except 2 eyes (of 2 patients) showed similar outcomes at 12 and 24 months. Such time intervals were chosen because most trials use a failure at treatment completion and relapse within 24 months as a measure of treatment efficacy [25]. Furthermore, the recommended treatment duration for multi-drug-resistant TB or patients needing alternative treatment regimes from first-line drugs is 18–24 months [26]. Therefore, by analysing our treatment outcomes at 24 months, we were able to capture patients with delayed relapses. As a significant proportion of these patients are immigrants, these findings would emphasize the importance of ensuring continuity of care should they return to their home country.

Various studies have reported the benefits of using ATT in conjunction with steroids in the management of TBU, resulting in fewer recurrences than the use of steroids alone [6, 12, 27, 28]. Our study had 28.9% of patients in the ATT group with treatment failure, and this was similar to the group not receiving ATT. Several reasons may account for this. First and foremost, the small numbers in our study may account for this bias. Next, TB is known to mimic uveitis of other etiologies, occasionally leading to an incorrect diagnosis of TBU [29]. Also, there has been little consensus on the optimal duration of ATT use in the treatment of presumed TBU, which may play a role in treatment failure. Some studies followed the WHO guidelines for extra-pulmonary TB of 6 months of ATT [29, 30], while studies that tailored the duration of their treatment to the clinical response have proposed longer treatment periods [13, 16], some in excess of 18 months [12]. Moreover, the increasing incidence of drug-resistant TB may have accounted for some of the treatment failures [31, 32].

We recognize the other limitations in our study. Given the retrospective nature of our study, we were unable to control for confounders such as demographics or standardize diagnostic tests or treatment regimes for TBU. Also, as Singapore has a low endemic incidence of TB and TBU, our sample size was limited. Our study also recruited patients with presumed, but not confirmed, TBU due to the difficulty in obtaining histopathological or microbiological samples of intraocular specimens. Nevertheless, we used standards, which are well recognized in diagnosing TBU and employed by numerous other studies. [12, 13] We also treated all patients with topical steroids, as all of them had some degree of anterior chamber inflammation. We recognize that this may not be because of a true uveitis and may be a spillover from a posterior uveitis, but it was still sufficient for the clinician to feel that it was warranted. Lastly, while we had a robust number of patients followed up at 12 months, a significant proportion were lost at 24 months. This is likely due to the significant number of migrant patients who might have left the country before the completion of our study.

Conclusion

In conclusion, while this study found no statistically significant difference in treatment failure amongst patients who had or had not received ATT, it was retrospective and there was a lack of standardization on treatment. Nevertheless, more prospective studies are required to determine if this is truly feasible as it would negate the side effects of ATT when managing presumed TBU, and we suggest a longer follow-up duration of 24 months, as this may affect treatment adequacy. We propose that treatment comprising solely of steroids can be considered in selected patients with presumed TBU only if they can be monitored closely and have ATT started if their condition worsens.

Author's contributions LA was involved in the conceptualization of the study, data acquisition, analysis of data, and drafting and writing up of the manuscript. AK, YTH, and VGD were involved in the acquisition and analysis of the data. HSL, ST, and RA were involved in conceptualization of the study, writing up and editing of the manuscript.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

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