Global Variations and Challenges With Tubercular Uveitis in the Collaborative Ocular Tuberculosis Study

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PURPOSE. The aim of this study was to examine regional variation management practices and outcomes for tubercular uveitis (TBU).

METHODS. In this retrospective multinational cohort study, patients from 25 international eye care centers diagnosed with TBU with a minimum follow-up of 1 year were included. The geographic variation in treatment outcomes on survival analysis in patients with TBU were analyzed. Treatment failure is defined as a persistence or recurrence of inflammation within 6 months of completing antitubercular therapy, the inability to taper oral corticosteroids to less than 10 mg/d or topical corticosteroid drops to less than 2 drops daily, and/or recalcitrant inflammation necessitating corticosteroid-sparing immunosuppressive therapy.

RESULTS. Records of 945 patients (1485 eyes) with TBU were analyzed. The mean age was 41.3 ± 15.0 years (range, 4–90 years), with more males (52.9%, n = 500/945) and predominant Asian ethnicity (74.4%, n = 690/927). Most patients had no symptoms (92.0%, n = 655/712) or history (76.7%, n = 604/787) suggestive of pulmonary tuberculosis (TB). Some patients had evidence of inactive pulmonary TB on chest X-rays (26.9%, n = 159/604) or chest computed tomography (68.6%, n = 109/159). Patients with western geographic origin (log-rank = 6.47, P = 0.010), African or Hispanic ethnicity (log-rank = 6.87, P = 0.001), and positive immigrant status (log-rank = 4.89, P = 0.027) had poorer survival outcomes.

CONCLUSIONS. This is a first-ever multinational analysis of TBU that highlights regional differences in treatment outcomes for this elusive form of extrapulmonary TB. Our findings will help in the design of future collaborative studies together with internists to develop best practice guidelines for this early opportunity to address TB infection and strategies to target at-risk groups such as immigrants.

Keywords: tuberculosis, ocular, uveitis, antitubercular therapy, corticosteroids

Tuberculosis (TB) is a major infectious disease threat1–3 and has been among the most common causes of death worldwide since the 1990s.4 International efforts led by the World Health Organization have been successful in tampering the spread of TB in recent history.1,5,6 However, several unresolved limitations have enabled the reemergence of both pulmonary and extrapulmonary TB in neglected populations of developed and developing countries alike. These include deficiencies in case detection,6,7 resurgence of drug-resistant TB,5 and reservoirs of infection in neglected populations.5,6,8 These challenges have prompted a call for international data to facilitate the improved diagnosis of TB, especially extrapulmonary TB in the asymptomatic population; additionally, there is a push for a realignment of priorities from passive to active case-finding, with an aim to eliminate the pool of TB in the asymptomatic population.6,9

Extrapulmonary TB accounts for 15% of the health burden of TB and increases to 50% in the subpopulation of patients with HIV coinfection.5 Ocular involvement most often manifests as uveitis, and it has been reported in up to one-fifth of patients with culture-proven TB,10–12 along with significant associated ocular morbidity and visual loss.12–14 It is initially asymptomatic in most patients10–15 and can be the first presentation of TB infection.16 given that affected patients may not have symptoms of active pulmonary TB.17–19 However, despite progress in coordinated efforts to address pulmonary TB, the approach to manage tubercular uveitis (TBU) remains controversial due to a lack of robust data.20–26 In a recent review of index TB in India, a country endemic for TB, ocular TB was excluded due to lack of evidence.27 This has resulted in barriers for physicians to initiate antitubercular therapy (ATT) in these patients.
Global Challenges With Tuberculoc uveitis

The difficulty in the management of TBU is contributed by its ability to affect any tissue in the eye, the need for cautious interpretation of investigations, and the need for targeted therapy and poorer treatment outcomes that are further compounded by a lack of consensus on the management approach for TBU. This group of 25 ophthalmic centers performed an analysis of the largest cohort of TBU cases under the Collaborative Ocular Tuberculosis Study (COTS)-1 group. The first report from the COTS-1 group evaluated the clinical signs associated with TBU based on treatment outcomes in patients with TBU that were treated with ATT. The current investigation describes regional differences in the management practices and outcomes for all patients diagnosed with TBU regardless of whether they were treated with ATT. This was done to understand current practice patterns, with an aim to facilitate the designing of standardized protocols in future investigations to address uncertainties in TBU.

METHODS

Twenty-five centers listed in Supplementary Material S1 participated in this study of patients with TBU diagnosed between January 2004 and December 2014. The inclusion criteria for this study were patients that satisfied diagnostic criteria detailed in Supplementary Material S2 and received investigations to exclude other potential causes of ocular manifestations. The first report from the COTS-1 group evaluated the clinical signs associated with TBU based on treatment outcomes in patients with TBU that were treated with ATT. The current investigation describes regional differences in the management practices and outcomes for all patients diagnosed with TBU regardless of whether they were treated with ATT. This was done to understand current practice patterns, with an aim to facilitate the designing of standardized protocols in future investigations to address uncertainties in TBU.

RESULTS

A total of 945 patients (1485 eyes) diagnosed with TBU (by uveitis specialists) from 2004 to 2014 were included in this study. The data were entered for 1008 patients, but significant information was missing from 63 patients and, hence, were excluded from further analysis. Patients had a mean age of 41.5 ± 15.0 years (range, 4–90 years), 500 (52.9%, n = 500/945) were males, and many were of Asian ethnicity (74.4%, n = 690/927). Many patients were recruited from centers in Asia (61.5%, n = 581/927), with almost one-fifth of the cohort identified as immigrants (18.1%, n = 168/927) based on the study definition for “immigrant status” in the Methods section. Most patients had no history of immigration (76.7%, n = 604/787) of pulmonary/extrapulmonary TB or symptoms suggestive of the disease, such as chronic cough, hemoptysis, significant weight loss, and night sweats. These clinical features of patients with TBU are further detailed in Table 1. A total of 189 patients with documented results for chest X-rays (26.9%, n = 189/702) and 109 patients with documented results for chest computed tomography (CT) scans (68.6%, n = 109/159) had features consistent with inactive or healed pulmonary TB. Only a few centers conducted chest CT scans and they were not evenly distributed across all the centers. Results of further corroborative investigations are detailed in Table 2.

A total of 799 patients (85.0%, n = 799/940) received corticosteroids, 801 patients (84.6%, n = 801/947) received ATT, and 72 patients (9.0%, n = 72/799) received steroid-sparing immunosuppressive therapy. The severity of anterior chamber and vitreous haze inflammation was outlined in the first report. For the purpose of the COTS-1, a novel data entry platform was conceived to address the heterogeneous nature of this disease. The secure encrypted web-based platform was programmed as a smart form that provided users with explanations and prompts for questions and reinforced information such as inclusion criteria and treatment failure definitions. The form omitted patient identifiers and standardized data entry. This minimized the need for data processing and associated transcript errors. Trivial data entry errors from open-ended entries into the form were manually corrected. For this report, immigrant status was arbitrarily assigned to individuals with an ethnicity foreign to the region of recruitment. This includes all patients that were not Middle Eastern recruited from the Middle East, patients that were not Caucasian recruited from Australia/West (European/American countries, e.g., London, Switzerland, USA, etc.) and patients that were not Asian recruited from Asia. This crude dissection was used for exploratory study based on an “ever an immigrant” status and is not comprehensive. It did not account for the generation of migration nor intraregional migration.

Statistical Analysis

Statistical analysis was conducted using SPSS version 20 (IBM Corp., Armonk, NY, USA) and R-3.2.3 (R foundation for statistical computing) by the coauthors (DVG, DR, and RA). Frequencies were obtained for different study variables and percentages tabulated based on the total number of valid inputs for each variable. Kaplan-Meier plots with log-rank tests were used for univariate survival analysis where log-rank test was used to compare the outcome of time to treatment failure.

Data Collection

For the purpose of the COTS-1, a novel data entry platform was conceived to address the heterogeneous nature of this disease. The secure encrypted web-based platform was programmed as a smart form that provided users with explanations and prompts for questions and reinforced information such as inclusion criteria and treatment failure definitions. The form omitted patient identifiers and standardized data entry. This minimized the need for data processing and associated transcript errors. Trivial data entry errors from open-ended entries into the form were manually corrected. For this report, immigrant status was arbitrarily assigned to individuals with an ethnicity foreign to the region of recruitment. This includes all patients that were not Middle Eastern recruited from the Middle East, patients that were not Caucasian recruited from Australia/West (European/American countries, e.g., London, Switzerland, USA, etc.) and patients that were not Asian recruited from Asia. This crude dissection was used for exploratory study based on an “ever an immigrant” status and is not comprehensive. It did not account for the generation of migration nor intraregional migration.

Figure 1. Pie chart showing distribution of patients treated with and without ATT.

Frequencies were obtained for different study variables and percentages tabulated based on the total number of valid inputs for each variable. Kaplan-Meier plots with log-rank tests were used for univariate survival analysis where log-rank test was used to compare the outcome of time to treatment failure.
TABLE 1. Background History of Patients With TBU

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subvariable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>Mean</td>
<td>41.3 (4–90)*</td>
</tr>
<tr>
<td>Sex (total 945 valid)</td>
<td>Female</td>
<td>445 (47.1)†</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>500 (52.9)†</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0‡</td>
</tr>
<tr>
<td>Race (total 927 valid)</td>
<td>Asian</td>
<td>669 (74.4)†</td>
</tr>
<tr>
<td></td>
<td>African</td>
<td>56 (6.04)†</td>
</tr>
<tr>
<td></td>
<td>Middle Eastern</td>
<td>61 (6.80)†</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>115 (12.1)‡</td>
</tr>
<tr>
<td></td>
<td>Hispanic</td>
<td>7 (0.76)†</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>35‡</td>
</tr>
<tr>
<td>Region of recruitment (total 945 valid)</td>
<td>East/Asia</td>
<td>581 (61.5)†</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td>45 (4.76)†</td>
</tr>
<tr>
<td></td>
<td>Middle East</td>
<td>77 (8.1)†</td>
</tr>
<tr>
<td></td>
<td>West</td>
<td>242 (25.60)†</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0‡</td>
</tr>
<tr>
<td>Immigrant status (total 927 valid)</td>
<td>Immigrant</td>
<td>168 (18.1)‡</td>
</tr>
<tr>
<td></td>
<td>Local</td>
<td>759 (81.9)†</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>35‡</td>
</tr>
<tr>
<td>Any known history of systemic TB at the time of diagnosis of TBU (total 787 valid)</td>
<td>None</td>
<td>604 (76.7)†</td>
</tr>
<tr>
<td></td>
<td>Pulmonary</td>
<td>129 (16.4)‡</td>
</tr>
<tr>
<td></td>
<td>Extrapulmonary</td>
<td>50 (6.35)†</td>
</tr>
<tr>
<td></td>
<td>Pulmonary and Extrapulmonary</td>
<td>4 (0.51)‡</td>
</tr>
<tr>
<td></td>
<td>Unknown/Missing</td>
<td>175‡</td>
</tr>
<tr>
<td>Symptoms of systemic TB (total 712 valid)</td>
<td>Chronic cough</td>
<td>20 (2.81)†</td>
</tr>
<tr>
<td></td>
<td>Significant unintended loss of weight/LOW</td>
<td>23 (3.25)‡</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy / LAD</td>
<td>9 (1.26)†</td>
</tr>
<tr>
<td></td>
<td>Night sweats</td>
<td>18 (2.53)†</td>
</tr>
<tr>
<td></td>
<td>Hemoptysis</td>
<td>3 (0.42)‡</td>
</tr>
<tr>
<td></td>
<td>Any one of above symptoms</td>
<td>57 (8.01)‡</td>
</tr>
<tr>
<td></td>
<td>None of above symptoms</td>
<td>655 (92.0)‡</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>250‡</td>
</tr>
</tbody>
</table>

* Values are n (range).
† Values are n (%).
‡ Values are n.

Steroid-sparing immunosuppressive agents (Figs. 1, 2). Large heterogeneity in the usage of individual treatment modalities were identified based on geographic distribution and are further detailed in Figure 5. The proportion of patients that received treatment with both ATT and corticosteroids was highly variable between Asia (80.4%, n = 463/576), Australia (60.0%, n = 27/45), the Middle East (84.2%, n = 64/76), and the West (62.9%, n = 151/240). Treatment failure was reported in 11 patients that did not receive ATT nor oral corticosteroids (18.6%, n = 11/59), 6 patients that received only oral corticosteroids (6.4%, n = 6/94), 7 patients that received ATT only (7.3%, n = 7/96), and 89 patients that received both ATT and corticosteroids (12.6%, n = 89/705). Figure 4 illustrates the use of different treatment regimens by region, along with their respective treatment outcomes.

Treatmen outcomes on survival analysis were superior in patients of Middle Eastern or Asian ethnicity (log-rank = 19.9, P < 0.001), Australian or Asian geographic region of recruitment (log-rank = 6.47, P = 0.010), and if they were not immigrants as defined in this study (log-rank = 4.89, P = 0.027). The survival distributions did not yield differences in outcomes based on age (log-rank = 0.21, P = 0.885) or sex (log-rank = 0.572, P = 0.542). With regards to treatment modalities, treatment outcomes on survival analysis were worse in patients that did not receive ATT nor corticosteroids (log-rank = 4.06, P = 0.044). Survival curves are illustrated in Figure 5.

Survival analysis was repeated based on treatment regimen with the data set stratified by region of origin. Results for survival analysis in patients that did not receive corticosteroids nor ATT were worse for patients in Asia (log-rank = 6.843, P = 0.077) and the West (log-rank = 7.215, P = 0.065), although these were not statistically significant. On the other hand, patients in the West who started on corticosteroids before ATT had the poorest outcome on survival analysis (log-rank = 9.470, P = 0.009), whereas patients in Asia who did not start at corticosteroids had poorer outcomes on survival analysis (log-rank = 7.003, P = 0.030) compared with patients in the West. These stratified survival analyses are depicted in Figure 6.
DISCUSSION

The COTS-1 group presents the largest investigation of demographic data, investigation results, and management outcomes of patients diagnosed with TBU. The descriptive data also concur with previous reports that TBU is often devoid of systemic symptoms of TB16,17 and can be the first presentation of occult TB infection in the affected patients. This study describes regional variations in treatment practices for TBU (Table 2), including the regime, duration of ATT, and concomitant use of corticosteroids and immunosuppressive agents (both systemic and local). Although we have enrolled patients that met the inclusion criteria, there was no defined treatment protocol in the inclusion criteria. Hence, the treatment received by patients in this study is heterogeneous given the retrospective nature of this study and because the treatment in a majority of TBU cases is directed in consultation with the attending pulmonologist/internist based on guidelines that vary depending on the region of their practice. Survival analysis also revealed variation in outcomes between different ethnic groups and geographic regions, as depicted in Figures 5 and 6. These results contradict existing reports that describe similar results among Asian and non-Asian patients.24 However, the lack of standardization in multinational recruitment and treatment outcome definition are significant limitations of existing literature,24 that this study has addressed. Potential explanations for variation in disease expression arise from emerging geographic trends in TB drug resistance2,5 and the use of imperfect tests in populations with varying epidemiological burden of TB etiology for uveitis.43 The current literature on systemic and pulmonary TB also describes age- and sex-related variations in disease activity and severity.8,44–46 However, this study did not find a correlation between these demographic factors and outcomes in TBU.

In the index study, it is worth noting that 76.7% of patients had no history of TB disease, and 92% had no symptoms of TB. Chest CT scans had better sensitivity compared with plain chest radiographs (Table 2). This suggests that chest CT scans have a valuable additional yield in patients with suggestive phenotypes and suspected latent TB. Although there was variable use (Table 2) of the tuberculin skin test, Mantoux test, and either of the immune globulin release assays, immunologic evidence of at least latent TB is relatively high among those tested in this population. Given the variable specificities of these tests, using a combination of them can facilitate early diagnosis of latent TB infection among these patients, in alignment with current global initiatives for active case-finding and treatment of asymptomatic patients with systemic TB infection.5 Microbiologic confirmation was low in this cohort, and bronchoscopy with nucleic acid amplification tests of bronchial washings and/or endobronchial ultrasound could be a useful consideration for patients with indeterminate phenotypes.47

Our study of immigrant status in COTS-1 was inspired by previous reports that highlighted immigrants as a unique subpopulation with a higher risk for TB48,49 and to explore if this phenomenon was replicated in TBU. Our findings concur with these studies but are limited by the crude “ever an immigrant” allocation of immigrant status used. Further study of TBU based on immigrant status is certainly warranted to account for country of origin and “generation of immigration”
via detailed history taking combined with cross-checking with national records.

Management with ATT has been advocated for patients with TBU. The current study describes a low rate of treatment failure in patients that received ATT with (12.6%, $n = 89/705$) or without (7.3%, $n = 7/96$) corticosteroids. However, this study is unable to determine the responsiveness of TBU to ATT due to the relatively low proportion of patients that did not receive ATT ($n = 161$) compared with those that did ($n = 801$).

Furthermore, Figures 3 and 4 highlight the regional differences in treatment practices and outcomes in TBU. To date, there are no randomized controlled trials that have defined the diagnosis nor the management of ocular TB. The consequent under-/overdiagnosis of TB etiology may help explain these variations in treatment outcomes. Furthermore, there are no consensus guidelines among the uveitis experts regarding the treatment of ocular TB, including duration of ATT, ATT regime, and also regarding the concurrent use of oral corticosteroids and immunomodulatory therapy (either systemic or local). In addition, there is no multicenter study on TB that highlights differences in practice across the globe. These observations underscore the need for multinational prospective data collection and analysis in collaboration with

**Figure 4.** Shows treatment regimens and outcomes of patients with TBU in the study.
pulmonary and/or infectious disease specialists to direct management and address these uncertainties.

The study is limited by its retrospective methodology, giving rise to an inability to accurately assess treatment adherence and ATT regimen modifications attributed to rare side-effects. Additionally, selection bias can arise given the diagnostic ambiguity in some cases, and there is a lack of a standardized systematic way to identify all patients with TBU over a 10-year period retrospectively. Another limitation is that there were no centers from sub-Saharan Africa due to lack of collaborators. In addition, some clinical information was not available for study, including country of birth of immigrants, generation of immigration, HIV status, and risk factors for poor outcomes in systemic TB, such as alcoholism and diabetes. 58–60

Based on the COTS case definition of ocular TB, patients who have certain clinical manifestations (e.g., optic neuritis) and positive corroborative tests for TB could be diagnosed and treated with ATT by fellow colleagues across the world. Although the Mantoux test and interferon gamma release assays may be positive in some centers due to endemicity of TB in the region, a lack of additional evidence such as imaging (e.g., a contrast-enhanced CT scan of the chest) may result in increased false positive cases of ocular TB (e.g., patients with idiopathic ocular inflammation that happen to have positive Mantoux/immune globulin release assays due to high TB endemicity). Highlighting this diagnostic conundrum associated with ocular TB is one of the key aims of this investigation and could be addressed in future investigations by implementing strict inclusion criteria and prospective investigation. Another limitation of this index study is the retrospective methodology, whereby patients were not classified into possible, probable, or confirmed ocular TB based on the classification proposed by Gupta et al. 61 This classification still needs validation and may be relevant for future prospective studies to explore.

The current study serves to provide a rich overview of TBU and sheds light on global practices. 62 It is the largest data set on TBU that uses standardized criteria for outcomes and combines data from multiple leading international centers. The current evidence for outcomes in TBU is limited by small numbers, isolated studies in demographic subgroups of patients, and lack of standardization in measures of treatment response. 24 The COTS-1 addresses these knowledge gaps through the use of strict criteria for treatment outcomes in patients that have a broad breath of clinical phenotypes. The current study has identified important factors and the need to standardize diagnostic approaches for future prospective analyses in order to derive comprehensive evidence-based guidelines in the approach to TBU management.

Looking Ahead

Future prospective studies are required to address the limitations of this study and standardize treatment regimens and follow-up intervals. This index study concludes that there is no internationally accepted approach to the diagnosis and treatment of TBU. The COTS group aims to address the unanswered questions about TBU, such as clinical features suggestive of TBU and the duration of ATT required. This will be achieved through collaborative prospective analysis with pulmonologists and infectious disease experts in the future to...
develop best practice guidelines for TBU. A prospectively derived clinical risk score will help to improve the diagnosis and management of TBU and potentially serve as a point-of-care screening tool to identify asymptomatic pulmonary TB in carriers. This information will help to address current knowledge deficits20–24,42 and support the global drive for active case-finding and early initiation of therapy in asymptomatic carriers of TB infection.7,9

CONCLUSIONS

The data collected from multiple international centers have highlighted regional variations in management practices and treatment outcomes. Furthermore, the findings from this unique collaborative initiative will help in the design of future prospective studies together with chest physicians to develop best practice guidelines for the proper diagnosis and appropriate management of TBU, along with specific strategies to target at-risk groups such as immigrants.

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References


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