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

Rupesh Agrawal,1–3 Dinesh Visva Gunasekeran,1,2,4 Dhananjay Raje,5 Aniruddha Agarwal,6 Quan Dong Nguyen,7 Onn Min Kon,8 Carlos Pavesio,2 and Vishali Gupta6; for the Collaborative Ocular Tuberculosis Study Group

1National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
2Moorfields Eye Hospital, National Health Service Foundation Trust, London, United Kingdom
3Singapore Eye Research Institute, Singapore
4School of Medicine, National University of Singapore, Singapore
5MDS Bio-Analytics, Nagpur, India
6Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India
7Byers Eye Institute, Stanford University, Palo Alto, California, United States
8Chest and Allergy Clinic, St. Mary’s Hospital, Imperial College Healthcare National Health Service Trust, London, United Kingdom

Correspondence: Vishali Gupta, Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India; vishalisara@yahoo.co.in.

RA and DVG contributed equally to the work presented here and should therefore be regarded as equivalent authors.

See the appendix for the members of the Collaborative Ocular Tuberculosis Study Group.

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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 = 189/702) 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 = 19.9, 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 reported 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.1,9,10

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.
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The difficulty in the management of TBU is contributed by its ability to affect any tissue in the eye\textsuperscript{20,29–31} and the need for cautious interpretation of investigations.\textsuperscript{32–41} This leads to delay in targeted therapy and poorer treatment outcomes\textsuperscript{24,42} that are yet further compounded by a lack of consensus on the management approach for TBU.\textsuperscript{20,21,24} 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.\textsuperscript{15} 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.\textsuperscript{15} The inclusion criteria for this study were patients that satisfied diagnostic criteria detailed in Supplementary Material S2\textsuperscript{22} and received investigations to exclude other potential causes of ocular manifestations (at the discretion of the attending uveitis specialist). All patients had at least one year of follow-up and medical records with details of ophthalmic examinations. It was a retrospective study where data retrieval was done by the coinvestigators themselves or with help from an institutional medical records department. The study was ethically approved by each respective institute.\textsuperscript{15}

Treatment failure was defined at any time of the follow-up as a persistence or recurrence of inflammation within 6 months of completing ATT, inability to taper oral corticosteroids to <10mg/day (oral prednisone) or topical steroid drops to <2 drops/day, and/or recalcitrant inflammation necessitating steroid-sparing immunosuppressive therapy. The severity of anterior chamber and vitreous haze inflammation was described in accordance with the Standardization of Uveitis Nomenclature definitions. This was assessed at standardized 6-month time intervals from initial diagnosis: 6, 12, 18, and 24 months. Detailed methodology for the COTS-1 has been outlined in the first report.\textsuperscript{15}

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.\textsuperscript{15} 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.

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 did not have good follow up data 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 (76.7%, n = 604/787) of pulmonary/extrapulmonary TB or symptoms (92.0%, n = 655/712) 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-
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Evidence for the use of different treatment regimens by region, along with their use of 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 = 151/805), 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.

Treatment 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 = 0.372, 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 were not started on corticosteroids or ATT 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.

### 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 (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>Race (total 927 valid)</td>
<td>Asian</td>
<td>690 (74.4)‡</td>
</tr>
<tr>
<td></td>
<td>African</td>
<td>56 (6.0)‡</td>
</tr>
<tr>
<td></td>
<td>Middle Eastern</td>
<td>61 (6.8)‡</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>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 (25.6)‡</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 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>Hemoptyisis</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.

### Table 2. Investigations and Management in Patients With TBU

<table>
<thead>
<tr>
<th>Variable</th>
<th>Subvariable</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray result (total 702 valid)</td>
<td>No suggestive</td>
<td>657*</td>
</tr>
<tr>
<td></td>
<td>Pulmonary lesion</td>
<td>549 (76.0)*</td>
</tr>
<tr>
<td></td>
<td>Suggestive pulmonary lesion present</td>
<td>260*</td>
</tr>
<tr>
<td>CT thorax result (total 159 valid)</td>
<td>Negative</td>
<td>64/76, 80%</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>109 (68.6)*</td>
</tr>
<tr>
<td>Mantoux result (total 651 valid)</td>
<td>Negative</td>
<td>82 (13.0)‡</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>549 (87.0)‡</td>
</tr>
<tr>
<td>TSpot.TB result (total 76 valid)</td>
<td>Not reactive</td>
<td>33 (57.9)*</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>64 (91.0)*</td>
</tr>
<tr>
<td>Quantiferon Gold result (total 305 valid)</td>
<td>Negative</td>
<td>274 (88.9)*</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>654 (11.1)*</td>
</tr>
<tr>
<td>TB PCR (total 57 valid)</td>
<td>Negative</td>
<td>24 (42.1)‡</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>33 (57.9)*</td>
</tr>
<tr>
<td>Sputum culture (total 67 valid)</td>
<td>Negative</td>
<td>66 (91.0)*</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>8 (11.0)‡</td>
</tr>
<tr>
<td>Elevated serum angiotensin-converting enzyme (total 398 valid)</td>
<td>Normal</td>
<td>175 (24.1)‡</td>
</tr>
<tr>
<td></td>
<td>Missing/unknown</td>
<td>546*</td>
</tr>
<tr>
<td>ATT (total 930 valid)</td>
<td>No</td>
<td>129 (13.9)‡</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>801 (86.1)‡</td>
</tr>
<tr>
<td>Corticosteroids (total 725 valid)</td>
<td>No</td>
<td>124 (13.4)‡</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>799 (86.6)‡</td>
</tr>
<tr>
<td>Steroid vs ATT combination (total 927 valid)</td>
<td>Neith</td>
<td>42 (6.2)‡</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids only</td>
<td>94 (10.1)‡</td>
</tr>
<tr>
<td></td>
<td>ATT only</td>
<td>99 (10.4)‡</td>
</tr>
<tr>
<td></td>
<td>Both ATT and corticosteroid</td>
<td>705 (76.0)‡</td>
</tr>
<tr>
<td>Use of steroid-sparing immunosuppressive agents (total 799 valid)</td>
<td>Unknown/missing</td>
<td>8*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>727 (91.0)‡</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>72 (9.0)‡</td>
</tr>
</tbody>
</table>

* Values are n.  
† Values are n (%).
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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.43,50–57 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 deficits and support the global drive for active case-finding and early initiation of therapy in asymptomatic carriers of TB infection.

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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**APPENDIX**

**COTS-1 Study Group Authors**


1Yong Loo Lin School of Medicine, National University of Singapore, Singapore 2National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore 3Moorefield’s Eye Hospital, National Health Service Foundation Trust, London, England 4Singapore Eye Research Institute, Singapore 5MDS Bio-Analytics, Nagpur, India 6Advanced Eye Centre, Department of Ophthalmology, Postgraduate Institute of Medical Education and Research, Chandigarh, India 7Royal Berkshire Hospital, National Health Service Foundation Trust, Reading, United Kingdom 8Tey Kohli Cornea Institute, Department of Ophthalmology, LV Prasad Eye Institute, Kallam Anji Reddy Campus, Hyderabad, India 9Biomedical Research Centre, Institute of Ophthalmology, University College of London (UCL), London, United Kingdom 10Singapore National Eye Centre, Singapore 11Duke-NUS Medical School, Singapore, Singapore 12Department of Clinical Ophthalmology & Eye Health, Central Clinical School, Save Sight Institute, The University of Sydney, Sydney, Australia 13Ocular Immunology Unit, Azienda USL di Reggio Emilia IRCCS, Reggio Emilia, Italy 14Department of Ophthalmology, Sankara Nethralaya, Chennai, India 15Department of Ophthalmology, Shroff Eye Centre, New Delhi, India 16Department of Ophthalmology, Dr. Shroff’s Charity Eye Hospital Daryaganj, New Delhi, India 17Department of Uveitis and Ocular Immunology, Narayana Nethralaya, Bangalore, India 18Department of Ophthalmology, Fatouma Bourguiba University Hospital, Faculty of Medicine, University of Monastir, Tunisia 19Department of Ophthalmology, University of Manchester, Manchester, United Kingdom 20Istanbul University, Istanbul Faculty of Medicine, Department of Ophthalmology, Turkey 21Prabha Eye Clinic & Research Centre, Department of Ophthalmology, Vittala International Institute of Ophthalmology, Bangalore, India 22LV Prasad Eye Institute, Department of Ophthalmology, Bhubaneswar, India 23Bristol Eye Hospital, Department of Ophthalmology, Bristol, United Kingdom 24King Khaled Eye Specialist Hospital, Department of Ophthalmology, Riyadh, Kingdom of Saudi Arabia 25DHU SightRestore, Department of Ophthalmology, Sorbonne University, Paris, France 26Eye Clinic, Department of Biomedical and Clinical Science “L. Sacco”, Luigi Sacco Hospital, University of Milan, Italy 27Northwestern University, Feinberg School of Medicine, Department of Ophthalmology, Chicago, Illinois, United States
Global Challenges With Tubercular Uveitis

28Centre for Ophthalmic Specialised Care & University of Lausanne, Department of Ophthalmology, Lausanne, Switzerland
29The Centre for Ocular Inflammation and Infection (OCUVAC), Laura Bassi Centre of Expertise Center of Pathophysiology, Infectiology and Immunology, Medical University of Vienna, Vienna, Austria
30Ramón y Cajal University Hospital, Department of Ophthalmology, Madrid, Spain
31Department of Ophthalmology, University of Thessaly, Greece
32Department of Rheumatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
33Department of Microbiology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
34Centre of Ophthalmology, Department of Ophthalmology, University of Tuebingen, Germany
35Faculty of Health, Social Care and Education, Kingston University and St George’s, University of London, London, United Kingdom
36The Department of Ophthalmology, California Pacific Medical Center, San Francisco, California, United States
37The Department of Ophthalmology, Stanford University School of Medicine, Stanford, California, United States
38The Francis I. Proctor Foundation, UCSF School of Medicine, San Francisco, California, United States
39Department of Ophthalmology, Massachusetts Eye and Ear, Harvard Medical School, Boston, Massachusetts, United States
40MCM Eye Unit, MyungSung Christian Medical Center and MyungSung Medical School, Addis Ababa, Ethiopia
41Byers Eye Institute, Stanford University, Palo Alto, California, United States
42Chest and Allergy Clinic, St Mary’s Hospital, Imperial College Healthcare National Health Service Trust, London, United Kingdom