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Clinical Features and Outcomes of Patients With Tubercular Uveitis Treated With Antitubercular Therapy in the Collaborative Ocular Tuberculosis Study (COTS)–1

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IMPORTANCE Eradication of systemic tuberculosis (TB) has been limited by neglected populations and the HIV pandemic. Whereas ocular TB often presents as uveitis without any prior evidence of systemic TB, the existing uncertainty in the diagnosis of TB uveitis may perpetuate missed opportunities to address systemic TB.

OBJECTIVE To examine the clinical features of TB uveitis and the associations with response to antitubercular therapy (ATT).

DESIGN, SETTING, AND PARTICIPANTS This retrospective multinational cohort study included patients from 25 ophthalmology referral centers diagnosed with TB uveitis and treated with ATT from January 1, 2004, through December 31, 2014, with a minimum follow-up of 1 year.

MAIN OUTCOMES AND MEASURES Treatment failure, defined as a persistence or recurrence of inflammation within 6 months of completing ATT, 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 A total of 801 patients (1272 eyes) were studied (mean [SD] age, 40.5 [14.8] years; 413 [51.6%] male and 388 [48.4%] female; 577 [73.6%] Asian). Most patients had no known history (498 of 661 [75.3%]) of systemic TB. Most patients had bilateral involvement (471 of 801 [58.8%]). Common clinical signs reported include vitreous haze (523 of 1153 [45.4%]), retinal vasculitis (374 of 874 [42.8%]), and choroidal involvement (419 of 651 [64.4%]). Treatment failure developed in 102 of the 801 patients (12.7%). On univariate regression analysis, the hazard ratios (HRs) associated with intermediate uveitis (HR, 2.21; 95% CI, 1.07-4.55; $P = .03$), anterior uveitis (HR, 2.68; 95% CI, 1.32-2.35; $P = .006$), and panuveitis (HR, 3.28; 95% CI, 1.89-5.67; $P < .001$) were significantly higher compared with posterior distribution. The presence of vitreous haze had a statistically significant association (HR, 1.95; 95% CI, 1.26-3.02; $P = .003$) compared with absence of vitreous haze. Bilaterality had an associated HR of 1.50 (95% CI, 0.96-2.35) compared with unilaterality (HR, 1 [reference]), although this finding was not statistically significant ($P = .07$). On multivariate Cox proportional hazards regression analysis, the presence of vitreous haze had an adjusted HR of 2.98 (95% CI, 1.50-5.94; $P = .002$), presence of snow banking had an adjusted HR of 3.71 (95% CI, 1.18-11.62; $P = .02$), and presence of choroidal involvement had an adjusted HR of 2.88 (95% CI, 1.22-6.78; $P = .02$).

CONCLUSIONS AND RELEVANCE A low treatment failure rate occurred in patients with TB uveitis treated with ATT. Phenotypes and test results are studied whereby patients with panuveitis having vitreous and choroidal involvement had a higher risk of treatment failure. These findings are limited by retrospective methods. A prospectively derived composite clinical risk score might address this diagnostic uncertainty through holistic and standardized assessment of the combinations of clinical features and investigation results that may warrant diagnosis of TB uveitis and treatment with ATT.

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Invited Commentary

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Tuberculosis (TB) has persisted as a leading global cause of death for decades,[1-7] with difficulties in its eradication attributed to the neglect of vulnerable populations and the HIV pandemic.[1,8,9] These trends are projected to cause a surge of extrapulmonary TB, given its significantly higher prevalence in patients with TB and HIV coinfection.[1]

Ocular TB is a recognized form of extrapulmonary TB associated with significant morbidity.[4,9-13] Unfortunately, there is a paucity of comprehensive clinical information and agreed-on guidelines for diagnosis, which potentiates the enigma in the diagnosis and management of ocular TB.[14-32] These limitations lead to delayed and even missed diagnoses, resulting in suboptimal clinical outcomes,[18] and may perpetuate missed opportunities to address systemic TB infection early[33,34] because ocular TB often precedes symptomatic evidence of systemic TB.[35-40]

The Collaborative Ocular Tuberculosis Study (COTS)-1 group was created to address these knowledge deficits. The objective of this report is to analyze the role of antitubercular therapy (ATT) in the management of patients with TB uveitis and explore potential correlations of clinical features with treatment response.

Key Points

Questions What are the suggestive clinical features and approach to diagnosis of patients with tubercular (TB) uveitis in a multinational retrospective review?

Findings In this cohort study, clinical features suggestive of TB uveitis were identified through survival analysis of time to treatment failure. Results suggested that accurate diagnosis of TB uveitis required a multipronged approach considering clinical features and investigations as a whole.

Meaning These results suggest a lack of comprehensive evidence for diagnostic approaches for TB uveitis, with regional inconsistencies in the workup of patients possibly affected.

Methods

COTS-1 is an exploratory retrospective cohort study of patients diagnosed with TB uveitis from January 1, 2004, through December 31, 2014, conducted by 25 multinational centers. The study was conducted with ethical approval obtained by each participating center from their local institutional ethics committee. Participating centers were as follows: National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore; Moorfields Eye Hospital, London, England; Advanced Eye Centre, Postgraduate Institute of Medical Education and Research, Chandigarh, India; LV Prasad Eye Institute, Hyderabad, India; Singapore National Eye Centre, Singapore; Department of Clinical Ophthalmology & Eye Health, Central Clinical School, Save Sight Institute, The University of Sydney, Sydney, Australia; Ocular Immunology Unit, Department of Ophthalmology, Arcispedale-IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy; Sankara Nethrayala, Chennai, India; Shroff Eye Centre, New Delhi, India; Dr Shroff's Charity Eye Hospital Daryaganj, New Delhi, India; Narayana Nethralaya, Bangalore, India; Department of Ophthalmology, Fattouma Bourguiba University Hospital, Faculty of Medicine, University of Monastir, Tunisia; University of Manchester, United Kingdom; Istanbul Faculty of Medicine, Department of Ophthalmology, Istanbul University, Turkey; Prabha Eye Clinic & Research Centre, Vittala International Institute of Ophthalmology, Bangalore, India; LV Prasad Eye Institute, Bhubaneswar, India; Bristol Eye Hospital, Bristol, England; King Khaled Eye Specialist Hospital, Riyadh, Kingdom of Saudi Arabia; University of Pierre and Marie Curie, Paris, France; Luigi Sacco Hospital, University of Milan, Italy; Department of Ophthalmology, Northwestern University, Feinberg School of Medicine, Chicago, Illinois; Centre for Ophthalmic Specialised Care & University of Laussane, Laussane, Switzerland; Medical University of Vienna, Vienna, Austria; Ramón y Cajal University Hospital, Madrid, Spain; and University of Thessaloniki, Thessaloniki, Greece. All centers obtained approval from their institutional review boards, which determined that no informed consent was required because the data were deidentified.

The diagnosis of TB uveitis was established based on the presence of suggestive clinical features identified through a review of current literature and anecdotal evidence from the experts in this study group. The diagnostic criteria for TB uveitis used in COTS-1 are as follows, with patients having to satisfy both criteria 1 and 2 and at least one of criteria 3 and 4:

1. Clinical signs suggestive of TB uveitis, including the following:
   a. Anterior uveitis (granulomatous or nongranulomatous), iris nodules, and ciliary body granuloma.
   b. Intermediate uveitis (granulomatous or nongranulomatous with exudates in the pars plana, with or without snowballs).
   c. Posterior and panuveitis, choroidal tubercle, choroidal granuloma, subretinal abscess, and serpiginous-like choroiditis.
   d. Retinitis, retinal vasculitis (RV), neuroretinitis, optic neuritis, endogenous endophthalmitis, panophthalmitis, and scleritis.
2. Exclusion of other uveitic entities, where relevant, based on clinical manifestations of disease and regional epidemiologic findings.
3. Investigations that document the mycobacteria or its genome:
   a. Demonstration of acid-fast bacilli by microscopy or culture of *Mycobacterium tuberculosis* from ocular fluid.
   b. Positive polymerase chain reaction from ocular fluid for IS 6110 or other conserved sequences in mycobacterial genome.
   c. Evidence of confirmed active extrapulmonary TB (by microscopic examination or culture of a tissue sample from the affected tissue).
4. Corroborative investigations:
   a. Positive Mantoux test result (must be accompanied by information regarding antigen and amount of tuberculin injected, along with institutional practices in interpreting the test).

b. Interferon γ release assay, such as QuantiFERON TB Gold (must be accompanied by information regarding institutional practices in interpreting the test).
c. Evidence of healed or active TB on chest radiography (must be accompanied by information regarding practices by institution radiologists regarding clinical features that are considered evidence in this regard).

Patients who satisfied diagnostic criteria and received treatment with ATT were only recruited for this study if they satisfied the following inclusion criteria: (1) availability of patient medical records with details of ophthalmic examination, (2) ancillary and laboratory investigations performed to exclude relevant differential diagnoses, and (3) completed a minimum follow-up of 1 year.

Patients with phlebitis of retinal vasculature were described as having RV with or without occlusive features. There was noninformative right censoring because patients are followed up for 2 years regardless of treatment response. Reasons for incomplete follow-up in some patients include patient transfer to other centers, death, and unavailable for follow-up.

Treatment regimen in terms of the decision to initiate ATT or immunosuppression or duration of ATT or immunosuppression use was directed by attending physicians in collaboration with respiratory or infectious disease physicians as per individual institutional protocols. The route of drug delivery for corticosteroids was guided by clinical phenotype and severity of TB uveitis. Patients with anterior uveitis and mild inflammation received topical corticosteroid eye drops. Patients with intermediate or posterior uveitis and/or severe inflammation received oral corticosteroid therapy in the absence of contraindications. Use of local corticosteroid injections and corticosteroid-sparing immunosuppressive agents was individualized taking into account the treatment response, severity of TB uveitis, and patients' comorbidities on a case-by-case basis.

Treatment failure for individual patients on follow-up was determined using defined criteria based on treatment regimen received. Treatment failure was defined as patients with any of the following: (1) persistence or recurrence of inflammation within 6 months of completing ATT in the involved eyes for patients with unilateral disease or in either eye for patients with bilateral disease, (2) inability to taper oral corticosteroids to less than 10 mg/d or corticosteroid eye drops to less than 2 drops daily, and (3) recalcitrant inflammation that necessitated corticosteroid-sparing immunosuppressive therapy.

Data Collection

A novel data entry platform was conceived to address the heterogeneous nature of this disease. The secure encrypted web-based platform was programmed by 2 of us (D.V.G. and R.A.) as a smart form that provided users with explanations and prompts for questions and reinforced information, such as inclusion criteria and treatment failure definitions used (above). The form omitted patient identifiers and standardized data entry. Given the observational and retrospective nature of the data and the lack of a gold standard diagnostic test, multiple imputation was not attempted.

Patients with ocular manifestations of diseases that could confound the interpretation of clinical features were excluded from this study. These manifestations included comorbidities such as central serous chorioretinopathy, diabetic retinopathy, or hypertensive retinopathy. However, patients with comorbidities that did not confound diagnosis or affect media clarity were not excluded, such as patients with glaucoma or mild cataract. The follow-up variable of treatment failure was assessed at standardized 6-month intervals from initial diagnosis (6, 12, 18, and 24 months).

Statistical Analysis

Percentages were tabulated based on the total number of valid inputs for each variable. In patients with bilateral TB uveitis, the clinical features are described in both eyes. Treatment failure criteria met in either eye was considered as a failure event because management decisions (such as escalating therapy) are tailored based on the response of both eyes.

Visualizations of treatment failure rates were obtained through Kaplan-Meier plots for univariate survival analysis using SPSS statistical software, version 20 (IBM Corp) along with the log-rank test to compare the outcome of time to treatment failure. Multivariate Cox proportional hazards regression analysis was performed to obtain crude and adjusted hazard ratios (HRs) for each clinical sign as an estimate of risk along with 95% CI using R, version 3.2.3 (R Foundation for Statistical Computing). Multicollinearity of independent variables was tested using variance inflation factor. A variable with a variance inflation factor of 4.0 and above was treated as having multicollinearity with one or more independent variables. Because the data included patients with bilateral involvement, a Cox proportional hazards regression model with appropriate extension was used to treat patients as clusters with correlated observations to address interdependency of eyes. Statistical significance was set at a 2-sided $P < .05$. For univariate survival analysis, the significance was determined using the log-rank test. For Cox proportional hazards regression, the significance was determined using the z test.

Results

A total of 801 patients with a diagnosis of presumed TB uveitis who were treated with ATT were included in this study (mean [SD] age, 40.5 [14.8] years; 413 [51.6%] male and 388 [48.4%] female; 577 [73.6%] Asian). Most patients did not have any known history of TB (498 of 661 [75.3%]). Demographics are further described in **Table 1**.

Most patients with TB uveitis had bilateral involvement (471 of 801 [58.8%]). Among these patients, 1272 eyes had descriptions of TB uveitis, which were further analyzed on a per-eye basis (Table 1). On the basis of anatomical distribution of involvement, posterior uveitis (452 of 1249 [36.3%]) was the most common distribution. Clinical signs included vitreous haze (523 of 1153 [45.4%]), disc edema (244 of 1189 [20.5%]), RV (374 of 874 [42.8%]), and choroidal involvement (419 of 651 [64.4%]). Among eyes with descriptions of the type of RV, most had occlusive RV (155 of 378 [41.4%]) (Table 1).

Table 1. Demographics and Clinical Features of Patients With TB Uveitis

Variable	Finding[a]
Age, mean (SD) [range], y	40.5 (14.8) [4-90]
Sex (n = 801 patients)	
Female	388 (48.4)
Male	413 (51.6)
Race (n = 784 patients)	
Asian	577 (73.6)
African	44 (5.6)
Middle Eastern	50 (6.4)
White or European	107 (13.6)
Hispanic	6 (0.8)
Missing or unknown	17
Region of recruitment (n = 801 patients)	
East/Asia	489 (61.0)
Australia	42 (5.2)
Middle East	72 (9.0)
West	198 (24.7)
Clinical features of systemic TB (n = 608 patients)	
Chronic cough	14 (2.3)
Loss of weight	19 (3.1)
Lymphadenopathy	9 (1.5)
Night sweats	17 (2.8)
Hemoptysis	3 (0.45)
Any one of the above symptoms	48 (7.9)
None of above symptoms	560 (92.1)
Missing or uknown	193
Any known history of systemic TB at diagnosis of TB uveitis (n = 661 patients)	
None	498 (75.3)
Pulmonary	114 (17.2)
Extrapulmonary	45 (6.8)
Pulmonary and extrapulmonary	4 (0.6)
Missing or unknown	140
Uveitis anatomical distribution (n = 1246 eyes)	
Posterior	452 (36.3)
Intermediate	199 (15.9)
Anterior	155 (12.5)
Panuveitis	440 (35.3)
Missing or unknown	26
Vitreous haze (n = 1153 eyes)	
Absent	630 (54.6)
Present	523 (45.4)
Missing or unknown	119
Snowballs (n = 1175 eyes)	
Absent	985 (83.8)
Present	190 (16.2)
Missing or unknown	97
Snow banking (n = 1170 eyes)	
Absent	1099 (93.9)
Present	71 (6.1)
Missing or unknown	102
Disc hyperemia/edema (n = 1189 eyes)	
Absent	945 (79.5)
Present	244 (20.5)
Missing or unknown	83
Macular edema (n = 1168 eyes)	
Absent	962 (82.4)
Present	206 (17.6)
Missing or unknown	104
RV (n = 374 eyes)	
RV with occlusive features	155 (41.4)
RV without occlusive features	118 (31.5)
RV present but not described	101 (27.0)
Missing or unknown	398
Choroidal involvement (n = 651 eyes)	
Absent	232 (35.6)
Present	419 (64.4)
Missing or unknown	621

Abbreviations: RV, retinal vasculitis; TB, tubercular.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Corroborative investigations produced positive results in 164 of 589 chest radiographs (27.8%), 105 of 149 computed tomographs of the thorax (70.5%), 491 of 559 Mantoux tests (87.8%), 47 of 51 TB-T Spot tests (92.2%), 231 of 259 QuantiFERON-TB Gold In-Tube tests (89.2%), and 30 of 49 TB polymerase chain reactions (61.2%). The serum angiotensin-converting enzyme level was elevated in 78 of 335 patients (23.3%). Among the patients treated with ATT, 705 of 792 patients (89.0%) received concomitant systemic corticosteroid therapy, and 63 of 675 (9.3%) received corticosteroid-sparing immunosuppressive agents. Results of investigations and use of immunosuppressive agents are detailed in **Table 2.**

Treatment failure was defined on a per-patient basis. Of the 801 patients, 699 (87.3%) were successfully treated with ATT. Treatment failure developed in 102 patients (12.7%).

Survival Analysis

Univariate analysis revealed that anatomical distribution had a significant association with time to failure. The HRs associated with intermediate uveitis (HR, 2.21; 95% CI, 1.07-4.55; $P = .03$), anterior uveitis (HR, 2.68; 95% CI, 1.32-5.43; $P = .006$), and panuveitis (HR, 3.28; 95% CI, 1.89-5.67; $P < .001$) were significantly higher compared with posterior distribution. The presence of vitreous haze had a statistically significant association compared with absence of vitreous haze (HR, 1.95; 95% CI, 1.26-3.02; $P = .003$). Bilaterality had an associated HR of 1.50 (95% CI, 0.96-2.35) compared with unilaterality (HR, 1 [reference]), although this finding was not statistically significant ($P = .07$). **Figure 1** illustrates Kaplan-Meier plots for the 2 significant clinical signs. The HRs associated with other factors, such as presence of snowballs (HR, 1.31; 95% CI, 0.76-2.26; $P = .33$), snow banking (HR, 1.83; 95% CI, 0.83-4.02; $P = .13$), disc edema (HR, 0.63, 95% CI, 0.36-1.10; $P = .10$), macular edema (HR, 1.12; 95% CI, 0.66-1.88; $P = .68$), RV with occlusive features (HR, 1.01; 95% CI, 0.52-1.98; $P = .97$), RV without occlusive features (HR, 1.24; 95% CI, 0.64-2.39;

Table 2. Investigations and Management in Patients With TB Uveitis

Variable	No. (%) of Patients
Chest radiography result (n = 589 patients)	
No suggestive pulmonary lesion	425 (72.2)
Suggestive pulmonary lesion	164 (27.8)
Thorax computed tomography result (n = 149 patients)	
Missing or unknown	212
No	44 (29.5)
Yes	105 (70.5)
Mantoux or TB skin test results (n = 559 patients)	
Missing or unknown	652
Negative	68 (12.2)
Positive	491 (87.8)
Missing or unknown	242
TB-T Spot test result (n = 51 patients)	
Negative	4 (7.8)
Positive	47 (92.2)
Missing or unknown	750
QuantiFERON-TB Gold In-Tube test result (n = 259 patients)	
Negative	28 (10.8)
Positive	231 (89.2)
Missing or unknown	542
TB polymerase chain reaction (n = 49 patients)	
No	19 (38.8)
Yes	30 (61.2)
Missing or unknown	752
Sputum culture (n = 58 patients)	
No	52 (89.7)
Yes	6 (10.3)
Missing or unknown	743
Serum ACE test result (n = 335 patients)	
Normal	257 (76.7)
High	78 (23.3)
Missing or unknown	466
Use of corticosteroids (n = 792 patients)	
No	87 (11.0)
Yes	705 (89.0)
Missing or unknown	9
Use of corticosteroid-sparing Immunosuppressive agents (n = 675 patients)	
No	612 (90.7)
Yes	63 (9.3)
Unknown or missing	126

Abbreviations: ACE, angiotensin-converting enzyme; TB, tubercular.

P = .52), RV present but not described (HR, 1.36; 95% CI, 0.60-3.06; P = .46), and choroidal involvement (HR, 1.30; 95% CI, 0.72-2.36; P = .38) had no statistically significant differences from their respective reference levels.

The adjusted HRs were obtained using the multivariate Cox proportional hazards regression model (**Table 3**). Inclusion of all the variables in the Cox model revealed multicollinearity of anatomical distribution with vitreous haze and choroidal involvement. Thus, a model with vitreous haze and choroidal involvement along with other variables was considered, whereas the variable of anatomical distribution was ignored. The resulting variance inflation factor of variables was smaller than 2.0, indicating absence of multicollinearity. The model revealed that presence of vitreous haze had an adjusted HR of 2.98 (95% CI, 1.50-5.94; P = .002), presence of snow banking had an adjusted HR of 3.71 (95% CI, 1.18-11.62; P = .02), and presence of choroidal involvement had an adjusted HR of 2.88 (95% CI, 1.22-6.78; P = .02). The risk of event increases significantly with the presence of these 3 clinical features (ie, vitreous haze, snow banking, and choroidal involvement). Of 24 cases with these signs, 22 (91.7%) had panuveitis, indicating a more extensive form of this disease.

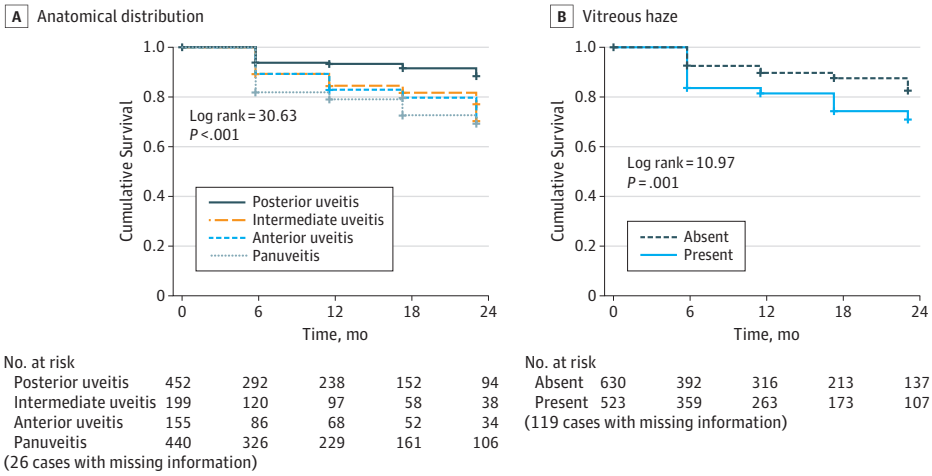
Discussion

Clinical features of patients with TB uveitis from a multinational cohort are described in this diverse multinational study of ocular TB, which is to our knowledge, the first such study. There was a predominance of male and Asian patient demographics, consistent with a previous report.[19] The existing literature on the clinical features of TB uveitis includes isolated descriptions in regional cohorts and is limited by inconsistency in the criteria used for inclusion and treatment failure.[4,14-21,29,30] The current study of TB uveitis in a large and international cohort addresses these limitations. Results of regression analysis suggest that individual signs or suggestive investigations taken in isolation are not sufficient to warrant a diagnosis of TB uveitis. This finding emphasizes the need for a holistic and standardized approach considering clinical features and investigation results together. This concept is consistent with anecdotal recommendations in the current literature,[16,22,23,41] with the use of the Apgar score in pediatrics providing an excellent example of the utility of such a score.[42]

Survival analysis using clinical features and investigation results based on the outcome of time to treatment failure was conducted. On multivariate regression analysis, the presence of choroidal involvement with vitreous haze and snowballs in patients with panuveitis was associated with a higher risk of recurrence. This finding is not consistent with the current literature, which suggests improved treatment outcomes for patients with TB uveitis who have intermediate uveitis or panuveitis[17] or positive QuantiFERON-TB Gold In-Tube test results.[43] It is apparent from the current results that prospective data and advanced statistics, such as elastic net regression, might be of value to generate a composite clinical score to address diagnostic uncertainties in TB uveitis.

The current study also describes the incidence of treatment failure in groups of patients stratified by the results of TB immunologic investigations and use of corticosteroids in **Figure 2**. Overall, Figure 2 suggests that patients treated with corticosteroids may have had poorer outcomes than those who were not. This finding contradicts a recent meta-analysis[19] that reported no significant difference in treatment outcomes with or without systemic corticosteroid use in patients treated with ATT. The same report,[19] how-

Figure 1. Survival Plots for Clinical Signs With Significant Difference Across Levels as Observed Through Univariate Analysis



No. at risk

Posterior uveitis	452	292	238	152	94
Intermediate uveitis	199	120	97	58	38
Anterior uveitis	155	86	68	52	34
Panuveitis	440	326	229	161	106

(26 cases with missing information)

No. at risk

Absent	630	392	316	213	137
Present	523	359	263	173	107

(119 cases with missing information)

Table 3. Cox Proportional Hazards Regression Analysis for Clinical Signs

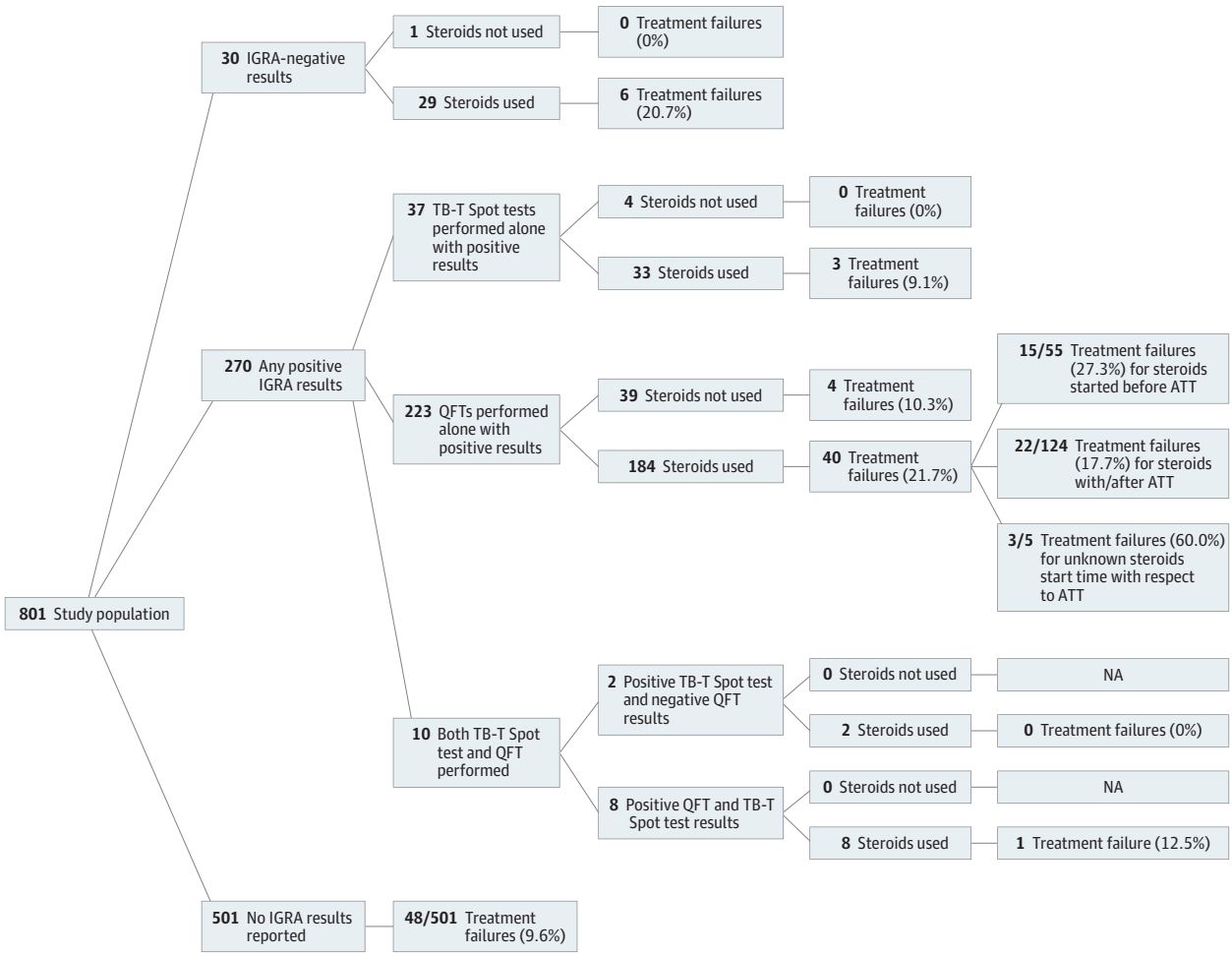
	Hazard Ratio (95% CI)			
Variable	Unadjusted[a]	*P* Value	Adjusted[b]	*P* Value
Laterality				
Unilateral	1 [Reference]	NA	1 [Reference]	NA
Bilateral	1.50 (0.96-2.35)	.07	1.53 (0.72-3.32)	.27
Anatomical distribution				
Posterior	1 [Reference]	NA	NA	NA
Intermediate	2.21 (1.07-4.55)	.03	NA	NA
Anterior	2.68 (1.32-5.43)	.006	NA	NA
Panuveitis	3.28 (1.89-5.67)	.001	NA	NA
Vitreous haze				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	1.95 (1.26-3.02)	.003	2.98 (1.50-5.94)	.002
Snowballs				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	1.31 (0.76-2.26)	.33	1.24 (0.47-3.27)	.66
Snow banking				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	1.83 (0.83-4.02)	.13	3.71 (1.18-11.61)	.02
Disc edema				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	0.63 (0.36-1.10)	.10	0.49 (0.24-1.01)	.055
Macular edema				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	1.12 (0.66-1.88)	.68	1.04 (0.49-2.19)	.92
RV				
None	1 [Reference]	NA	1 [Reference]	NA
RV with occlusive features	1.01 (0.52-1.98)	.97	0.96 (0.38-2.47)	.94
RV without occlusive features	1.24 (0.64-2.39)	.52	1.18 (0.44-3.13)	.74
RV present but not described	1.36 (0.60-3.06)	.46	2.591 (1.11-6.05)	.03
Choroidal involvement				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	1.30 (0.72-2.36)	.38	2.88 (1.22-6.78)	.02

Abbreviations: NA, not applicable; RV, retinal vasculitis.

[a] Univariate Cox proportional hazards regression.

[b] Multivariate Cox proportional hazards regression with multiple observations per patient with laterality. Haze, snowballs, snow bank, disc edema, molecular edema, RV, and choroidal involvement were independent variables in the model.

Figure 2. Results of Interferon γ Release Assays (IGRAs), Corticosteroid Use, and Clinical Outcomes



ATT indicates antitubercular therapy; NA, not applicable; QFT, QuantiFERON-TB Gold In-Tube test.

ever, cited a limitation that there is a lack of control group analysis in the existing literature. A prospective, interventional randomized clinical trial would be the ideal manner to address this management conundrum.

In addition, on closer inspection of Figure 2, it appears that patients with positive QuantiFERON-TB Gold In-Tube test results who received systemic corticosteroids had a distinctly high incidence of treatment failure. This finding was largely contributed by the group that received systemic corticosteroids before initiation of ATT, whereby the percentage of patients with treatment failure reported was almost twice that of the other groups of patients. This finding is consistent with the existing doctrine that physicians should delay prescribing systemic corticosteroids until after initiation of ATT in patients with high clinical suspicion of TB uveitis unless there is a high risk of complications secondary to intense inflammatory reaction. However, the current data do not provide definitive support for this conclusion because of the retrospective methods whereby severity of inflammation at initiation of therapy is a confounding factor that cannot be adjusted for. Controlling for severity of inflammation at initiation of therapy would certainly be pertinent in future interventional trials for TB uveitis.

Management with ATT has been advocated for all patients with suspected TB uveitis.[4,10,28,32,44-48] There are several possible causes of the poor outcome despite ATT in some of these patients. One possible cause of this could be overdiagnosis of TB uveitis, as suggested above. Overdiagnosis may explain the poorer outcomes in patients with chest radiographic findings suggestive of pulmonary TB as opposed to patients without them. Bronchoscopy for histologic sampling of pulmonary foci could be one way to improve diagnostic accuracy while also establishing drug sensitivity in such patients with suggestive chest radiographic findings.

The possibility of overdiagnosis is also suggested by our finding that patients recruited in the West appear to have poorer outcomes that those from the East. This finding may be attributable to the lower epidemiologic burden of TB in the West and a lower likelihood of TB as a cause of uveitis.[1,6] However, high-incidence countries, such as India, in the East are faced

with a different problem. These countries would inevitably have a lower specificity for a positive interferon γ release assay or Mantoux test result attributable to the higher prevalence of latent TB. Patients with latent systemic TB could potentially have another ocular disease cause but end up diagnosed with TB uveitis because of a positive interferon γ release assay or Mantoux test result. The contribution of these factors to this geographic variation in outcomes can only be determined through prospective analysis with comprehensive and standardized recruitment and treatment protocols.

Another hypothesis for the poor response to ATT noted in some patients is that certain phenotypes of TB uveitis may represent ocular manifestations of autoimmune reaction to molecular mimicry of latent TB, instead of active TB infection of the uvea. In the current study, higher incidence of treatment failure was noted in patients with choroidal involvement associated with vitreous haze. Presence of these clinical features suggests more immunologic reaction and may require a more aggressive regimen for immunosuppressive therapy. These patients cannot be differentiated using the conventional immunologic tests that are used in TB uveitis.[49] Such a pathologic difference may also explain the poorer outcomes reported in patients with predominantly anterior uveitis, a manifestation anecdotally hypothesized to be an autoimmune reaction as opposed to direct infection by TB bacilli.[50] The rationale for this hypothesis is that foci of TB bacilli in secondary sites of infection (such as the eye or spine) typically spread from systemic sites of primary infection (such as the pulmonary or genitourinary systems) via the vasculature.[51-53] In the case of the eye, blood vessels originate posteriorly and extend to the anterior chamber via the choroid. Differentiation between autoimmune and infectious causes of various phenotypes of TB uveitis will greatly improve our understanding of the role of ATT and corticosteroids in the treatment of patients with specific types of presumed TB uveitis. However, this will require histologic studies of ocular samples for confirmation.

Strengths and Limitations

A limitation of this study is the retrospective methods, which lead to a lack of standardization in documentation and hence missing data, such as that for the exact duration of follow-up or ATT use, which are therefore not described. Furthermore, drug resistance of the ocular strain of TB was not ascertained in most patients. This could be a confounding factor for treatment failure if the predominant ocular strain differs from that isolated from systemic TB foci because the systemic strain often guides the choice of ATT.[43] However, drug sensitivity is not typically established in TB uveitis given the associated risks and low yield of cultures and polymerase chain reaction analyses of ocular fluids[49,54-57] and will remain a limitation of prospective analysis in the foreseeable future.[49,58,59] Furthermore, given the lack of control group analysis and specific study of individual phenotypes, these results are not generalizable to all patients with TB uveitis.

Regardless of these limitations, this study had strengths of standardized inclusion and diagnostic criteria and a large and diverse cohort of patients.[4,14-19] The multinational approach of COTS-1 is particularly relevant in improving the understanding of TB uveitis given that previous reports[4,57] have described regional variation in disease expression. This study has also highlighted pertinent considerations for future prospective studies to better define the phenotypes, management, and outcomes of TB uveitis through standardized recruitment and treatment protocol.

Conclusions

A low treatment failure rate is reported in patients with TB uveitis treated with ATT. Patients with choroidal involvement and associated vitreous haze had higher risk of treatment failure. Findings from the current study are limited by retrospective methods. A prospectively derived clinical risk score with holistic and standardized assessment of clinical features and investigation results might be of value to tackle diagnostic uncertainty and to determine the role of ATT in patients with TB uveitis.

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