Title: Twenty-four month outcomes in the Collaborative Ocular Tuberculosis Study Group (COTS) – defining the "Cure" in ocular tuberculosis

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Short title: Two year outcomes in COTS-1

Keywords: Ocular tuberculosis; uveitis; antitubercular therapy; tuberculous; tubercular uveitis; cure

Abstract

Purpose: To report the clinical findings, anatomical features, and treatment outcomes in subjects with ocular tuberculosis (OTB) at 24 months in the Collaborative Ocular Tuberculosis Study (COTS)-1.

Methods: Of the 945 subjects included in the multinational retrospective COTS-1, those who completed 24-month follow-up after completion of treatment were included. Treatment details, anatomical features, and recurrences were noted. The main outcome measure was number of patients with treatment failure (TF).

Results: 228 subjects (120 males; mean age of 42.82±14.73 years) were included. The most common phenotype of uveitis was posterior (n=81; 35.53%), and panuveitis (n=76; 33.33%). 52 patients (22.81%) had TF. Subjects with panuveitis (31.58%) and intermediate uveitis (29.63%) accounted for majority of TF. On univariable analysis, odds of high TF was observed with bilaterality (OR:3.46, p=0.003), vitreous haze (OR:2.14, p=0.018), vitreous cells (OR:2.44, p=0.005), and use of immunosuppressive therapies (OR:5.45, p=0.003).

Conclusions: Majority of subjects (>75%) achieved cure in the COTS-1 at 24-month follow-up. The concept of “cure” maybe a valuable clinical endpoint in trials assessing treatment of OTB.

Introduction

The Collaborative Ocular Tuberculosis Study Group (COTS) has brought together a number of international uveitis experts from various centers globally so that the challenge posed by ocular tuberculosis (OTB) could be tackled.[1,2] The long-term goals in the management of OTB include preservation of visual function and minimizing the relapse of the disease.[2–4] The importance of anti-tubercular therapy (ATT) to improve patient outcomes and reduce the treatment failures has been underlined in the data generated by the COTS group.[5] International experts have agreed that OTB results from direct infection caused by a specific pathogen, *Mycobacterium tuberculosis,* and requires specific anti-microbial therapy in the form of ATT.[6]

The relevance of defining clinical endpoints in the context of OTB cannot be over emphasized . The COTS, in collaboration with the International Uveitis Study Group (IUSG), International Ocular Inflammation Society (IOIS) and Foster Ocular Immunology Society (FOIS) have partly addressed this challenge by publishing the COTS Nomenclature previously.[6] In this nomenclature, experts agreed that the term "*remission"* must be used when OTB is inactive (grade 0 cells/no inflammation) for at least *3 months* after a complete course of ATT. The COTS group also defined "cure" as the disease inactivity 24 months after a complete course of ATT.[6]

The concept of "cure" is often used in the treatment of pulmonary tuberculosis as per the guidelines laid down by the World Health Organization (WHO).[7] For pulmonary TB, "cure" refers to achieving multiple negative bacteriological sputum samples at the end of the treatment.[8–10] In the context of OTB, it is necessary to adjust this concept since ocular disease has significantly different microbiological profile, diagnostic techniques, and endpoints for clinical disease assessment compared to pulmonary disease. It is also imperative to study the data of the patients included in the COTS-1 to determine the activity of the disease at 24-month follow-up after completion of ATT in different phenotypes.

The COTS has creating a platform whereby experts (uveitis specialists, infectious disease specialists and pulmonologists) from all over the world can work together and standardize our reporting of outcomes after treatment with ATT. In this subgroup analysis of the COTS-1, we report the 24-month data in subjects who have completed their course of ATT from the total database of 945 subjects, and define the concept of "cure" in OTB in line with the WHO recommendations.

Materials and Methods

Study Participants and Procedures

The COTS-1 was a retrospective study conducted at 25 international centers with participation of over 30 international uveitis experts.[1,2,5] All the participating centers have been listed in **Appendix 1.** The data was collected from patients diagnosed with OTB between January 2004 to December 2014. For all the subjects, details such as demographic data, clinical findings such as visual acuities, anatomical location of the uveitis, disease phenotype, investigations and laboratory tests, management, and outcomes were noted. The data collection was performed on a data entry platform created for this purpose considering the complex and heterogenous nature of the disease. The study adhered to the tenets of the Declaration of Helsinki, and Institutional Ethics

Committee/ Institutional Review Board approval was obtained from all the participating centers for the conduct of the study.

The diagnostic criteria of OTB have been described in previous publications from the COTS group.[2,5,11,12] These have been provided in **Appendix 2.** Briefly, these included (1) clinical features compatible with OTB including anterior, intermediate, posterior and panuveitis, retinal vasculitis and optic neuritis; (2) exclusion of other uveitic entities based on clinical manifestations and laboratory tests; (3) positive investigations such as direct detection of acid fast bacilli, polymerase chain reaction tests, immunological tests such as Mantoux, interferon gamma release assay, and radiological tests such as computerized chest tomography. The specific inclusion criteria for this study were completed follow-up of 24 months after completion of ATT, availability of patient records including complete examination findings and visual acuity, and availability of information regarding patient outcomes and complications.

Study Subject Treatments

The regimen of ATT was directed by the individual clinical protocols and availability of drugs based on the advice of respiratory or infectious disease physicians. In addition, the subjects received concomitant systemic corticosteroid/immunosuppressive therapies based on the anatomical location of the disease, severity, response to therapy, and complications as per the decision of the treating uveitis expert. The COTS-1 defined treatment failure (published previously) if the patient experienced any of the following: (1) Persistent/recurrent inflammation within 6 months of completing ATT; (2) Inability to taper systemic (oral) corticosteroids to <10mg/day or topical steroid drops to <2 drops/day; and (3) Recalcitrant inflammation necessitating steroid-sparing immunosuppressive therapies.

Study Variables and Analysis

For this subset analysis from COTS-1, the study data variables analyzed included demographic factors such as gender, age, and race, among others, anatomical location of uveitis, laterality of the disease, features such as disc/macular edema, retinal vasculitis and choroiditis, treatment protocols and strategies, and complications if any. Data collection was done at 6-monthly time intervals from initial diagnosis - 6 months, 12 months, 18 months, and 24 months. Any recurrences during these intervals were noted.

Statistical Analysis

The data analysis for the COTS-1 was performed using IBM SPSS software (IBM, Armonk, NY, USA). The frequencies were obtained for different study variables. Non-parametric survival analysis was performed using Kaplan-Meier plots for the development of treatment failures among different clinical phenotypes. The statistical significance of the difference in the survival rates across phenotypes was determined using log-rank test, based on the predefined criteria. The analysis considered a significant p value if it was less than 0.5.

Results

Of the 945 patients included in the COTS-1 from 25 international centers, 303 subjects had visual acuity details until 24 months. Of these, 228 (24.13%) patients had complete clinical and treatment records at months 6, 12 and 24 after completion of ATT.

The mean age of these 228 subjects was 42.82 ± 14.73 years. There were 120 males (52.63%) included in the study. Most of the subjects were Asians in the cohort (154 subjects; 67.54%). The geographical origin was also predominantly Asian (125 subjects; 54.82%). The demographic details of the subjects included in this substudy is provided in Table 1.

A majority of the subjects included in the study had bilateral disease (152 subjects; 66.67%). The distribution of the anatomical location of uveitis was as follows: anterior uveitis (41 subjects – 17.98%); intermediate uveitis (27 subjects – 11.84%); posterior uveitis (81 subjects – 35.53%); and panuveitis (76 subjects – 33.33%). Retinal vasculitis was observed in 71.49% subjects, and choroidal involvement was observed in 28.51% subjects. Macular edema was present in 17.54% subjects. Vitreous haze and cells were a significant finding observed in over 64% subjects in the cohort. The clinical details of subjects with OTB included in this study are listed in Table 1.

In this series, most of the subjects were treated with a combination of ATT and corticosteroids (143 subjects; 62.72%). Thirty subjects (13.16%) received additional immunosuppressive therapies. In addition, 24 subjects (10.53%) received only ATT without concomitant corticosteroid/immunosuppressive therapy (Table 2).

Of the 228 subjects included in this series, 52 patients (22.81%) were diagnosed with treatment failure based on the pre-defined criteria at 24 months follow-up. Of the 52 subjects with treatment failure, 24 had panuveitis (46.15%), and 12 subjects (23.07%) had posterior uveitis. However, taking into account the total number of subjects of a particular phenotype at month 24, the subgroup of patients which had the highest percetange of treatment failures were those with panuveitis and intermediate uveitis (31.58% and 29.63%, respectively). The subgroup diagnosed with posterior uveitis had the least percentage of subjects with treatment failure (14.81%).

Based on the univariable analysis, the baseline factors that favored treatment failure 24 months after completion of ATT included bilaterality of the disease (OR: 3.46, CI:1.54 – 7.8; p=0.003), vitreous haze (OR: 2.14, CI:1.14 – 4.02; p=0.018) and vitreous cells (OR: 2.44, CI:1.3 – 4.59; p=0.005). The presence of choroiditis was also associated with higher odds of treatment failure, though it did not reach statistical significance (OR: 1.82, CI: 0.95 – 3.2; p=0.07). Patients who were treated with ATT, corticosteroids and received additional immunosuppressive therapies also had higher odds of treatment failure in the univariable analysis (OR: 5.45, CI:1.73 – 17.16; p=0.003) (Table 3).

Multiple regression model assessing the odds of treatment failure showed that only bilaterality was associated with higher odds of failure (OR: 2.84, CI: 1.19 – 6.75; p=0.02). We compared the unilateral versus bilateral cases of the 24 month cohort with the complete cohort of COTS-1. The number of bilateral cases in the original COTS cohort were 555/945 patients (58.73%). Chi square analysis revealed a significantly higher proportion of bilateral cases in the 24 month cohort ($\chi^2 = 4.83$; p=0.03). The use of immunosuppressive therapies was associated with higher odds of treatment failure, though it did not reach statistical significance (OR: 3.18, CI: 0.95 – 10.64; p=0.06) (Table 3).

Kaplan-Meier survival analysis considering treatment failure as an event, the effect of several variables found significant in the univariable and multivariable analysis are shown in Figure 1.

Discussion

The COTS-1 provided the largest collective database of patients with OTB from various international centers shedding light on the strategies used by experts for the treatment of OTB, and the overall treatment failure. In the COTS-1 analysis published previously, the results have shown that overall treatment failure based on the same predefined clinical criteria was approximately 12%.[5] The COTS-1 manuscripts have provided important data on the relevance of various patient factors (such as age, gender, race, geographic origin, and immigrant status, among others), and clinical features (such as anatomical location of uveitis, laterality of the disease, findings of choroiditis, vitritis, vasculitis, and optic nerve involvement, among others).[1,2] It is imperative to understand the long-term implication of these factors, and understand features that favor recovery and recurrence-free follow-up from this large cohort.

In our subgroup analysis of 228 subjects, the overall treatment failure was higher (i.e. 22.81%). There could be several reasons for this observation. The most likely reason could be that patients who had persistent inflammation, or recurrences during their follow-up continued their clinical visits whereas those who had healed/quiescent disease may have ceased their hospital visits. In the previously published COTS-1 study analyzing the treatment failure among subjects who received ATT, bilateral disease was observed in 58.73% subjects,[5] in contrast to the index study where bilaterality was observed in 66.67% eyes (p=0.03). Patients with bilateral disease may have more severe manifestations, and required longer follow-up with high risk of treatment failure. Thus, long-term data may overestimate subjects with treatment failures, because this subset of the cohort may represent more difficult-to-treat patients.[13] Despite this bias, it is encouraging to note that more than 75% subjects can achieve “cure” at the end of 2 years of treatment.

Similar to the observations in the previous publications by the COTS group, the subset of patients with panuveitis were found to have the highest percentage of treatment failure at the end of 24 months.[2,5,11] Subjects with vitreous haze and vitreous cells had high odds of treatment failure compared to other disease phenotypes. It is possible that this phenomenon could be linked to higher immunological response, which may be triggered by a high mycobacterial load and therefore, linked to higher treatment failures.[14] Subjects with TB panuveitis, especially when the disease is bilateral, may require more aggressive and long-term therapy with anti-inflammatory agents along with ATT. Similarly, subjects who required additional immunosuppressive therapies also had higher treatment failures, indicative of higher levels of inflammation.

These observations highlight the concept of *cure* in the context of systemic TB. Cure is interpreted as “free of disease” at completion of treatment, while its bacteriological basis is not strictly defined. In pulmonary TB, the cure would be defined based on negative bacteriological sputum testing at end of treatment.[15] In general, the World Health Organization (WHO) considers cure could mean either two or more negative cultures or two or more negative microscopic smear examinations.[7,8] However, these criteria and definitions cannot be applied to OTB, since the clinical profile, immunological basis, and microbiological features are completely different in uveal disease. In order to address this challenge, the COTS group took the an important step in agreeing that *the manifestations of OTB are related directly to the pathogen* (*Mycobacterium tuberculosis*) even if the mycobacteria cannot be isolated/cultured.[6] Therefore, in the context of OTB, a “cure”

should essentially mean that the ocular tissues are "*inflammation-free*", and this augurs well with the criteria of "treatment failure" used in this study.

The experts in the COTS group agreed to define cure at the end of 24 months primarily because TB uveitis is challenging to treat and often requires long-term treatment.[6] Clinical trials in uveitis have highlighted the high impact of uveitis in terms of years of potential vision loss.[16] Large clinical trials such as the Multicenter Uveitis Steroid Treatment (MUST) trial also use an endpoint of 2 years in reported clinical data.[17] In the phase III clinical trials of adalimumab for non-infectious uveitis, the mean duration of uveitis in the treatment arms exceeded 60 months, and the endpoint of time to treatment failure also revealed that subjects in the adalimumab group who experienced treatment failure did so at > 18 months.[18] Thus, in the context of OTB, a timeline of 24 months to define "cure" seemed appropriate to the COTS group participants.

Our current study has a number of limitations. The most important limitation is that being a retrospective study, it is susceptible to several biases, such as selection bias mentioned previously, resulting in a possible overestimation of treatment failures. We had higher number of bilateral cases in our cohort compared to the entire COTS-1 cohort. This may indicate a clinician bias, or possibly that patients with bilateral disease have more severe inflammation and do worse. We had a large number of subjects who had incomplete records, and the attrition rates were high compared to prospective trials. The high attrition rate may potentially distort our findings in this selected population group. The COTS-1 was only a retrospective analysis from various international clinical centers, and thus, the treatment regimens have not been strictly defined. In fact, a number of retrospective analyses of the COTS-1 have helped in formulating guidelines for treatment strategies, such as those for choroiditis.[19] This subset analysis from the largest global database may help define a critical aspect in the treatment of OTB – the clinical endpoint of "cure". We hope that such initiatives may help in further advancing our knowledge and develop strategies to tackle this challenging clinical entity. Other limitations of COTS-1, such as the use of non-standardized investigations (including Mantoux and interferon gamma release assays) and radiological tests, and potential issues with data entries have been mentioned in previous publications.[2,5,11,12,20]

In summary, the diagnosis and management of OTB can be aided by using well-defined clinical endpoints in future prospective studies. Most subjects (>75%) tend to achieve clinical remission at the end of 24 months of treatment with ATT with/without corticosteroids and immunosuppression. Long-term remission after 24 months of completion of ATT in OTB can be considered as "cure" and used as an important clinical endpoint in future prospective studies.

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Figure Legends:

Figure 1: Kaplan Meier (KM) survival plots for clinical signs with significant difference across levels as observed through univariate analysis are shown. (A) KM plot showing cumulative treatment survival in two laterality groups. (B) KM plot showing cumulative treatment survival in two vitreous haze categories. (C) KM plot showing cumulative treatment survival in two vitreous cell categories. (D) KM plot showing cumulative treatment survival as per treatment categories.

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