Collaborative Ocular Tuberculosis Study (COTS) Consensus Guidelines on the Management of Tubercular Uveitis – Report 1: Guidelines for Initiating Anti-Tubercular Therapy in Tubercular Choroiditis

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Abstract

Topic: An international, expert-led consensus initiative organized by the Collaborative Ocular Tuberculosis Study (COTS), along with the International Ocular Inflammation Society (IOIS) and the International Uveitis Study Group (IUSG) systematically developed evidence- and experience-based recommendations for the treatment of tubercular choroiditis.

Clinical relevance: The diagnosis and management of tubercular uveitis pose a significant challenge. Current guidelines and literature are insufficient to guide physicians regarding the initiation of anti-tubercular therapy (ATT) in patients with tubercular uveitis.

Methods: An international expert steering subcommittee of the COTS group identified clinical questions and conducted a systematic review of the published literature on the use of ATT for tubercular choroiditis. Using an interactive online questionnaire, guided by background knowledge from published literature, 81 global experts (including ophthalmologists, pulmonologists and infectious disease physicians) generated preliminary consensus statements for initiating ATT in tubercular choroiditis, utilizing Oxford levels of medical evidence. In total, 162 statements were identified around when to initiate ATT in patients with tubercular serpiginous-like choroiditis, tuberculoma and tubercular focal or multifocal choroiditis. The COTS group members met in November 2018 to refine these statements by a two-step modified Delphi process.

Results: Seventy consensus statements addressed the initiation of ATT in the three subtypes of tubercular choroiditis and in addition 12 consensus statements were developed on the use of adjunctive therapy in tubercular choroiditis. Experts agreed on initiating ATT in tubercular choroiditis in the presence of any one of the positive immunological tests along with radiological features suggestive of TB. For tubercular serpiginous-like choroiditis and tuberculoma, even one positive immunological test was considered sufficient to recommend ATT even if there are no radiological features suggestive of TB.

Conclusions: Consensus guidelines were developed to guide the initiation of ATT in patients with tubercular choroiditis, based on the published literature, expert opinion and practical experience, to bridge the gap between clinical need and available medical evidence.

Introduction

There is lack of agreement amongst the uveitis experts on the use of anti-tubercular therapy (ATT) and adjunctive therapies, including systemic corticosteroids in the management of tubercular uveitis (TBU).[1-5] The exact prevalence of TBU is not known, but is reported to be 0.2-10.5% amongst all uveitis patients at tertiary referral eye care centers in the world.[2,4,5,6] The gold standard for establishing the diagnosis of TBU is the detection of Mycobacterium *tuberculosis* (MTB) in ocular tissues or fluids. However, demonstration of the bacillus by smear or culture from ocular samples is seldom achieved, due to the low tissue load of MTB and small size of ocular tissue biopsies.[3,4,6] Diagnosis of TBU is usually presumptive, based on local epidemiology, ocular phenotype and corroborating immunological tests [Tuberculin skin test (TST) and/or interferon-gamma release assays (IGRAs)]. The majority of patients are considered for initiating ATT following a positive immunological test (either TST or IGRA positive) even in the absence of active clinical or radiological infectious disease.[2-5] Polymerase chain reaction (PCR)-based detection methods applied to small volume ocular tissue samples has low sensitivity to be reliably used for diagnosing TBU in the real world settings.[7] Consequently, uveitis specialists rely heavily on the characteristic features and ancillary investigations (such as chest radiography, TST, and IGRAs) when making the diagnosis of TBU, despite the limitations related to sensitivity and specificity of these tests.[2,4,5,6,8]

Based on an approximate 75% reduction in the rate of disease recurrences, the role of ATT is established in tubercular choroiditis.[9] However, there is still ambiguity amongst ophthalmologists and internists about the minimum set of criteria to recommend ATT in patients with tubercular uveitis. Moreover, there has been discordance amongst the uveitis experts on the use of ATT in the spectrum of clinical subtypes representing tubercular choroiditis. These subtypes include tubercular serpiginous-like choroiditis (TB SLC), tuberculoma and tubercular focal choroiditis or tubercular multifocal choroiditis.[4,9,10,11] There is wide heterogeneity in decision-making around the initiation of ATT, based on local prevalence of TB and regional differences in diagnostic work-up and treatment practices. There is also lack of consensus on the role of concurrent use of oral corticosteroid and

immunomodulatory therapies in patients with TBU, including tubercular choroiditis.[4,9,10,11] The decision to initiate ATT is usually taken by the ophthalmologist, in collaboration with pulmonologists and infectious disease physicians, based on local management protocols.[9-12] These observations, together with the uncertainty associated with the interpretation of immunological tests, indicate an unmet medical need in the approach in the management of tubercular choroiditis.

The Collaborative Ocular Tuberculosis Study (COTS) consensus (CON) was a survey-based clinical study that was designed to consolidate the expertise of international uveitis specialists on the approach to the management of TBU, using a two-step modified Delhi technique, supported by International Ocular Inflammation Society (IOIS) and International Uveitis Study Group (IUSG).[13-17] This report presents the consensus-based algorithms for the initiation of ATT and the use of adjunctive therapies in patients with different subtypes of tubercular choroiditis.

Methods

An “interactive” web-based survey form (Cognito Form, Columbia, South Carolina, USA) was generated to gather opinions from 81 uveitis experts (see credit roster). A total of 162 questions related to TB SLC, tuberculoma and tubercular focal or multifocal choroiditis were prepared (**Appendix 1**), and binarized based on regional TB endemicity for patient’s geographical region of origin (endemic or non-endemic) (**Appendix 2;** A TB endemic country was defined as one with an incidence of more than 100 cases of TB per 100,000 persons). Different scenarios for the various tubercular choroiditis subtypes in association with the presence/absence of corroborative evidence for TB infection from immunological tests and/or radiological tests were then formed and discussed **(Figure 1).** The ethics approval for COTS was obtained while conducting the retrospective study (COTS-1) (NK/2447/Study/2729) and the amendment to conduct the survey based on experts’ opinion with no patient data was obtained (NK/5695/Study/402). The study was conducted as per declaration of Helsinki.

Immunological tests were defined as TST (specified as positive for induration of 10 mm or more) and IGRA tests (QuantiFERON TB Gold or T-Spot TB). Radiological tests were defined as chest x-ray (CXR) or computed tomography (CT), suggestive of healed or active pulmonary TB (**Figure 1**).

The experts then scored their likelihood of starting ATT in the different scenarios presented. ATT was multidrug therapy that typically consisted of four drugs including isoniazid, rifampin, ethambutol and pyrazinamide, according to health policy of each country. Scores were recorded on a scale from 1-5 based on a <20%, 21-40%, 41-60%, 61-80% or ≥81%, respectively, with 1 (<20%) representing a very low probability of starting ATT and 5 (≥81%) representing a very high probability to initiate ATT. The scale was in accordance to the five-level Likert scale.[13] The questionnaire was tagged with appropriate Oxford level of evidence (**Appendix 3**) and the experts were asked to provide their inputs based on their experience and after reviewing the evidence supporting each possible clinical scenario (**Appendix 3**).[14] All possible clinical and test results permutations were included in Round 1 questionnaire of the modified Delphi process.[15,16] A total of 81 global experts completed the survey in August 2018. The overall likelihood and the agreement to initiate ATT among experts was quantified in terms of median score and interquartile range (IQR) respectively. The median score indicates the central tendency of experts to initiate ATT. For example, a median score of 5, for a given scenario, indicates overall *high probability* of initiating ATT. An IQR of 0 indicates absolute consensus among experts, while IQR of 1.0 and 2.0 have been referred as moderate and weak consensus indicators.[17] Thus, a notation 5 (0) represents *high probability* to initiate ATT and there is absolute consensus among experts on this choice. Likewise, 5 (1) represents *high probability of initiating* ATT, but with moderate consensus among experts and further 5 (2) represents weak consensus.[17] Statements with median score of 1-3 were considered to indicate absence of consensus and relatively low likelihood for initiating ATT and thus were excluded from further deliberation. Statements with median score of 4 were deliberated in person during the second round of Delphi process, held on November 16, 2018 in Chandigarh, India.

In addition, a total of 16 questions related to the use of adjunctive therapies in conjunction with ATT in patients with different subtypes of tubercular choroiditis were discussed. Adjunctive therapy was defined as the use of oral corticosteroids or

intravitreal steroids or intravitreal methotrexate or systemic non-corticosteroid immunosuppressive therapy. The questions were binarized based on regional TB endemicity and divided based on the use of systemic corticosteroids and immunosuppressive drugs. Consensus for the use of adjunctive therapies was achieved, if more than 75% of the experts agreed on the proposed question (statement).

Results

The study design for the Delphi process is illustrated in **Figure 1**. The consensus statements presupposed an ocular picture consistent with TB (**Figure 2**) and the exclusion of other possible forms of uveitis masquerading as TBU. **Table 1** illustrates the different permutations and combinations of test results that reached a consensus according to the median score of 5 with IQR width of 0-2 for TB SLC, tuberculoma and tubercular focal or multifocal choroiditis. **Figure 3** shows the minimum set of criteria to consider ATT in each subtype of tubercular choroiditis. **Table 2** illustrates how the statements that reached a median score of 4 during Delphi round 1 changed after systematic and critical deliberation during the second round of the Delphi process. Summary of the consensus statements related to initiation of ATT in tubercular choroiditis are presented in **Table 3**.

Tubercular serpiginous-like choroiditis

Absolute consensus was reached amongst the experts to initiate ATT in patients (endemic or non-endemic region for TB) with TB SLC (**Figure 2A and Table 3**) when both immunological tests (TST and IGRAs) and radiological tests (CXR/CT) were performed and positive. Absolute consensus (IQR=0) was also achieved for patients from endemic regions with one of the two immunological tests (Either TST or IGRA) and radiological test positive. However, for non-endemic regions, the consensus reached was moderate (IQR=1). When both immunological tests were positive without any radiological evidence, there was relatively lower consensus to initiate ATT in both endemic and non-endemic regions. For remaining scenarios with only one of the three tests (TST/IGRA/Radiological tests) being positive, the median score indicated higher likelihood to initiate ATT, but with weak to moderate consensus among experts (IQR≥1).

Tubercular Unifocal or Multifocal Choroiditis

There was moderate consensus amongst the experts to initiate ATT in patients with unifocal or multifocal choroiditis **(Figure 2B, 2C and Table 3)**. Absolute consensus (IQR=0) was reached amongst the experts to initiate ATT in patients (endemic or non-endemic region for TB) when both immunological tests (TST and IGRAs) and radiological tests (CXR/CT) were positive. Moderate consensus was achieved among experts (IQR=1.0) if either one of the immunological tests was positive and supported with positive radiological finding. The general opinion to initiate ATT was almost similar in both endemic and non-endemic regions.

Tuberculoma

Consensus statements on the management of tuberculoma are presented in **Figure 2D** and **Table 3**. Again, absolute consensus (IQR=0) was achieved to initiate ATT in patients with tuberculoma when both immunological tests (TST and IGRAs) and radiological tests (CXR/CT) were positive. When both immunological tests were positive but radiological evidence was negative, the consensus in endemic region was absolute (IQR=0); however, in non-endemic region, it was moderate (IQR=1). Further, if any of the two immunological tests were positive and there was positive radiological evidence, in an endemic region there was absolute consensus to initiate ATT (IQR=0); however, the perception differed in non-endemic region (IQR=1). If either of the immunological test was positive and there was no radiological support, the consensus to initiate ATT was again moderate (IQR=1) in both the regions. The observation was similar in the absence of immunological evidence but positive radiological finding (IQR=1).

Table 3B and **Figure 3** represents a guide and an algorithm based on the minimum set of criteria required to initiate ATT in patients with tubercular choroiditis. In summary, it is clearly evident from **Table 3B and Figure 3** that in an endemic region, whenever one of the immunological tests is positive along with positive radiography, there was agreement among experts to initiate ATT, specifically when clinical subtypes were TB SLC and Tuberculoma. The agreement was less for non-endemic regions. In case of uni- or multifocal choroiditis, the agreement was moderate for both endemic and non-endemic regions. Furthermore, in an endemic region, if any of

the immunological tests were positive but without radiological support, there was moderate to weak consensus to initiate ATT for TB SLC and Tuberculoma subtypes. This observation was more or less the same in non-endemic regions for these subtypes. Blank cells corresponding to different diagnostic outcomes for different clinical sub-types indicates lesser likelihood of initiating ATT.

Adjunctive Therapy

Consensus was obtained for concomitant use of oral corticosteroids with or shortly after the initiation of ATT in patients from both endemic and non-endemic regions with TB SLC. In patients with tuberculoma (with no associated systemic infectious disease), there was a strong agreement to institute ATT with adjunctive therapy. However, in patients with tubercular multifocal or unifocal choroiditis, though there was consensus on use of adjunctive therapy, there was rather mixed opinion on timing of initiation of oral corticosteroids. Systemic immunosuppressive therapy was recommended by experts for patients with recurrent inflammation (on tapering oral corticosteroids) in the patients with TB SLC and Uni- or multifocal choroiditis. Consensus statements on the adjunctive therapy with corticosteroids and immunosuppressive drugs in patients with tubercular choroiditis are presented in **Table 4**.

Discussion

The management of tubercular choroiditis is unclear due to the lack of high levels of evidence to guide clinicians.[1,2,3,6,9] However, several studies have reported a significant reduction in uveitis recurrences following initiation of ATT in TBU.[1,9,10,18-47] COTS CON, an international, expert-led consensus initiative aimed to develop systematic, evidence- and experience-based recommendations for the treatment of TBU, has consolidated the expertise of international uveitis specialists on the management of tubercular choroiditis using a modified Delphi technique. This report represents a unified view about consensus opinion and practices of experts from both endemic and non-endemic regions, with the aim of improving patients' outcomes by guiding ophthalmologists on when to consider initiating or recommending ATT and how to use corticosteroids or immunosuppressive drugs in this context.

Our uveitis experts concluded that therapeutic decision-making is influenced by specific phenotypes of tubercular choroiditis. Likewise, the TB endemicity in the geographical region where the patient lives, plays a part in the clinician's decision-making process for considering ATT.

In TB SLC, tuberculoma and tubercular focal or multifocal choroiditis, any immunological evidence of TB, along with radiological signs of active or healed pulmonary TB justifies initiation of ATT. In fact, if the phenotype of choroiditis is TB SLC, a single immunological test without radiological evidence is considered sufficient to initiate ATT. The TB SLC phenotype has been assumed to be related to TB for more than a decade.[32-35] In 2003, Gupta et al presented the first report of presumed TB etiology of SLC, describing TB SLC as multifocal progressive choroiditis, discrete and non-contiguous, showing relentless progression with a leading edge, or as diffuse choroiditis, where the initial presentation was a plaque like choroiditis with an amoeboid pattern along with a leading edge.[35] Subsequently, multiple reports established TB as possible cause for SLC, both in endemic and non-endemic settings, with beneficial effect of ATT in reducing recurrences.[36-43] Currently, the identification of the clinical spectrum of SLC is of major relevance in routine clinical practice, particularly in areas endemic for TB, for specifically tailored TB investigations and administration of appropriate treatment. From our results, it emerged that for TB SLC, only one positive immunological test (TST or IGRA) is considered sufficient to start ATT, but the background and origin of the patient must also be considered in the therapeutic approach. In an endemic region, an isolated positive TST is sufficient to initiate ATT despite a negative IGRA test, highlighting the strong predictive value for ocular TB of such phenotype in endemic area (where the pre-test probability of ocular TB is higher), while in a non-endemic region a positive IGRA is a requirement to start the treatment,given its increased specificity. Both in endemic and non-endemic regions, if the second immunological test is not done or not available, it does not influence the pre- or post-test probability for the diagnosis, and physicians can justify initiation of ATT in the event of one positive immunological test. However, a positive TST, but negative IGRA, could indicate atypical MTB infection or BCG vaccination within the past 10 years ago, and these factors should be considered when applying the consensus guidelines. A Bayesian approach for

addressing this issue and potential confounding factors would have been appropriate but previous attempts to resolve this dilemma in TBU with Bayesian analysis were not entirely successful.[44]

TB is also known to also present as a focal lesion in the choroid, with choroidal tubercles and tuberculomas as the most common and best documented clinical presentations.[6,45-50] Results from the current consensus guidelines confirmed that tuberculoma is highly representative of TBU and physicians should consider commencing ATT if there is any corroborative immunological evidence for TB. In addition, in endemic areas, radiological findings alone justify the initiation of ATT. While depending on the radiological features alone may be questionable, it must be understood that chest radiography is generally performed to look for evidence of past infection (as opposed to necessarily active disease). Chest imaging is relevant because it corroborates the presence of latent infection. In contrast to TB SLC and tuberculoma, tubercular focal or multifocal choroiditis phenotypes have relatively weak association with TB and use of ATT must be supported by immunological evidence together with radiological signs suggestive of old healed or active pulmonary TB. In phenotypes that are weakly compatible with TB, judicious use of ATT should be considered given the weak association with TB and the risks of increasing drug resistance with the excessive use of ATT in these cases. Hence, uveitis specialists across the world must exercise caution in prescribing ATT.

In order to treat the inflammatory response in TBU, therapy with corticosteroid and immunosuppressive drugs may be required in addition to ATT.[1,6,9] Oral corticosteroids should be started concomitantly with or soon after the initiation of ATT in patients with TB SLC, tuberculoma (except in the presence of active systemic infection) and tubercular multifocal or unifocal choroiditis. These findings are in keeping with current dogma that, in the presence of intraocular inflammation consistent with a high clinical suspicion of TBU, the prescription of anti-inflammatory drugs should be delayed until initiation of anti-microbial treatment, unless there is a high risk of complications secondary to intense inflammatory reaction. In case of recurrent inflammation while tapering the dose of oral corticosteroids in patients with TB SLC and tubercular multifocal or unifocal choroiditis, physicians may justify initiating systemic corticosteroid-sparing immunosuppressive therapy. It is imperative

for practicing uveitis specialists to be aware of potential drug interactions when combining ATT with the various immunosuppressive therapies.

Limitations of the study include the strong representation from Asia, Oceania, Western Europe, North and South America, with only few experts from Eastern Europe and Africa. In addition, since the level of evidence derived from literature search was not strong for any of the clinical scenarios, uveitis experts' opinions were the primary source of information for some consensus statements. Finally, while the consensus guidelines aimed to be international, regional practice patterns vary and local adaptation of the guidelines may be appropriate. In the future, prospective clinical trials in which patients are treated according to these COTS recommendations would be desirable to validate these COTS consensus statements.

We recognize that the major limitation in the diagnosis of ocular TB is exclusion of other entities such as sarcoidosis. Invasive tests such as lymph node biopsies are not indicated in all patients, and even these tests may not have high sensitivity in diagnosing tuberculosis. The COTS group was formed with the goal of highlighting the global challenge that is faced in establishing the diagnosis, and to bring together experts for formulating diagnostic and management guidelines. This initiative has highlighted the lack of adequate literature supporting appropriate treatment strategy in managing patients with TBU. In addition, or even as a consequence, it is not possible to identify which treatment algorithms would be appropriate for any specific phenotype of TBU or tubercular choroiditis. Nevertheless, the COTS platform has clearly identified the opportunities to collaborate with colleagues and set up a platform for optimal methods of communication and co-management of patients amongst ophthalmologist and fellow physicians. The study included several uveitis experts, as well as pulmonologists and infectious disease specialists from around the world. The study group identified clinicians with more than 10-year experience in clinical practice based on their contribution to the literature. While a strength of our study lies in inclusion of specialists from these fields of medicine for establishing consensus, this professional association needs to be strengthened further in the future.

In conclusion, with the limited available evidence including the lack of randomized controlled trials, the COTS CON's expert consensus is that treatment of patients with features suggestive of tubercular choroiditis with ATT, is potentially of a large benefit to the patients. These guidelines developed along with respiratory physicians, will also help set up concordance amongst ophthalmologists and infectious disease specialists or physicians for managing patients with TBU. These guidelines may be used by the COTS group as a basis for prospective clinical trials to assess the benefit of initiation of ATT in various phenotypes of tubercular choroiditis, and for validation of the findings presented in this manuscript.

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Figure legends:

Figure 1: The study design for collaborative ocular tuberculosis study group consensus guidelines (COTS CON) for tubercular choroiditis using a two stage Delphi process. In round 1 of the Delphi process, there were a total of 162 questions related to antitubercular therapy (ATT) and adjunctive therapy with oral corticosteroids or immunosuppressive agents or intravitreal therapy and in round 2 of Delphi process, there were a total of 71 questions for deliberation.

Figure 2: The composite figure 2 illustrates the spectrum of choroidal involvement in patients with tubercular choroditis. Tubercular choroiditis encompasses all the conditions characterized by choroidal inflammation in tuberculosis (TB). Tubercular serpiginous like choroiditis (TB SLC) was the term refering to discreet yellowish-white fuzzy choroidal lesions with slightly raised edges that show wave-like progression **(A);** tubercular multifocal choroiditis **(B)** was intended for *multifocal* choroiditis lesions with a phenotype similar to idiopathic multifocal choroiditis, acute posterior multifocal placoid pigment epitheliopathy (APMPPE), and other phenotypes that *do not* resemble TB SLC; tubercular unifocal choroiditis **(C)** was intended for unifocal choroiditis lesions that *do not* resemble TB SLC and tuberculoma (D) was

used for tubercular choroiditis represented by a yellowish subretinal lesion with indistinct borders and surrounding exudative fluid.

Figure 3: Figure 3 illustrates a simple alogrithm and guide for specialists and physicians to initiate anti tubercular therapy (ATT) in patients with tubercular choroiditis across all three phenotypes. The flow chart proposes the minimum parameters required for considering ATT in patients with TB SLC, TB uni- or multifocal choroiditis and tuberculoma.