Collaborative Ocular Tuberculosis Study (COTS) Consensus Guidelines on the Management of Tubercular Uveitis – Report 2: Guidelines for Initiating Anti-Tubercular Therapy in Anterior Uveitis, Intermediate Uveitis, Panuveitis and Retinal Vasculitis

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Abstract

Topic: The Collaborative Ocular Tuberculosis Study (COTS), supported by the International Ocular Inflammation Society, International Uveitis Study Group and Foster Ocular immunological society, set up an international, expert-led consensus project to develop evidence and experience-based guidelines for the management of tubercular uveitis (TBU).

Clinical relevance: The absence of international agreement on the use of anti-tubercular therapy (ATT) in patients with TBU contributes to a significant heterogeneity in the approach to the management of this condition.

Methods: Consensus statements for the initiation of ATT in TBU were generated using a two-step modified Delphi technique. In Delphi step 1, a smart web-based survey based on background evidence from published literature, was prepared to collect the opinion of 81 international experts on the use of ATT in different clinical scenarios. The survey included 324 questions related to tubercular anterior uveitis (TAU), intermediate uveitis (TIU), panuveitis (TPU) and retinal vasculitis (TRV) administered by the experts after which the COTS group met in November 2019 for a systematic and critical discussion of the statements in accordance to the second round of the modified Delphi process.

Results: Forty-four consensus statements on the initiation of ATT in TAU, TIU, TPU and TRV were obtained, based on ocular phenotypes suggestive of TBU and corroborative evidence of tuberculosis (TB), provided by several combinations of immunological and radiological test results. Experts agreed on initiating ATT in TAU (recurrent episodes), TIU, TPU and active TRV in the presence of positive results for any one of the immunologic tests along with radiologic features suggestive of TB. In cases with first episode of TAU, and patients with inactive TRV, consensus to initiate ATT was reached only if both immunological tests and radiological tests were positive.

Conclusions: COTS consensus guidelines were generated based on the evidence from published literature, specialists' opinion and logic construction, to address the initiation of ATT in TBU. The guidelines also should inform public policy by adding specific types of TBU to the list of conditions which should be treated as TB.

Introduction

Diagnosis and management of tubercular uveitis (TBU) pose a significant challenge due to the lack of specific diagnostic criteria and disagreement among uveitis specialists on initiation of anti-tubercular therapy (ATT).[1-5] The Collaborative Ocular Tuberculosis Study (COTS) was designed with the aim of addressing the knowledge gaps related to the diagnosis and management of TBU.[1,6-9] The COTS-1 was a retrospective study that highlighted geographical variations in the management practices and regional differences in treatment outcomes and thus, the need for global uniform guidelines.[7] Subsequently, the COTS consensus (CON) has been designed as a survey-based clinical study, supported by International Ocular Inflammation Society, International Uveitis Study Group and Foster Ocular immunological society, with the aim of consolidating expertise of uveitis specialists from different regions of the world on the management of TBU.[10-14] The first report from COTS CON illustrated seventy consensus statements addressing the initiation of ATT in the three different subtypes of tubercular (TB) choroiditis, namely serpiginous-like choroiditis, tuberculoma and multifocal or unifocal choroiditis.[15]

While the first report of COTS CON addressed some of the distinctive phenotypes of TBU, entities such as anterior uveitis, intermediate uveitis, panuveitis, and retinal vasculitis are more challenging when it comes to initiating ATT.[15] This was evidenced by the COTS-1, where in a lack of global consensus to intiate ATT has been previously highlighted. In panuveitis attributed to TB, higher treatment failure rates were observed.[1] In addition, in a subet analysis of patients with retinal vasculitis attributed to TB, a definitive conclusion on the role of ATT could not be ascertained.[9] Moreover, analysis of the COTS-1 showed significantly higher hazard ratios of treatment failure associated with phenotypes of intermediate uveitis, anterior uveitis, and panuveitis compared to TB choroiditis.[1]

Ophthalmologists may take decisions to initiate ATT based on purified protein derivative (PPD) skin test and/or interferon gamma release assays (IGRAs), but these tests may have limitations related to their sensitivity and specificity.[2,4,5,16,17] The decision to treat with ATT may be further complicated in case these immunological tests are discordant, or the chest radiology does not reveal any pathology. The phenotypes of tubercular anterior uveitis (TAU), tubercular intermediate uveitis (TIU), tubercular panuveitis (TPU) and tubercular retinal vasculitis (TRV) represent a spectrum of TBU which need universally acceptable guidelines on initiating ATT. This second report of COTS CON explores the consensus-based guidelines for the initiation of ATT in patients with TAU, TIU, TPU and TRV.

Methods

A smart online form builder (Cognito Form, Columbia, South Carolina, USA) was used to create a web-based survey and collect opinions from 81 uveitis specialists (see credit roster). A total of 324 questions related to TAU (108 questions), TIU (54 questions), TPU (54 questions) and TRV (108 questions) were prepared (**Appendix 1**), and binarized as endemic or non-endemic, according to TB endemicity for geographical area of origin of patients (**Appendix 2**, published previously).[15] Ethical clearance for COTS was obtained when the retrospective arm (COTS-1) (NK/2447/Study/2729) was conducted, and the amendment to design the survey-based study without the use of patient data was then obtained (NK/5695/Study/402). All the research adhered to the tenets of the declaration of Helsinki.

In the index study, different scenarios for the various phenotypes of TBU together with the results of the immunological tests and/or radiologic tests were formed and discussed. Immunologic tests were defined as TST (specified as positive for induration of 10 mm or more) and IGRAs (QuantiFERON-TB Gold, Quigen, Germantown, MD; or T-Spot TB, Oxford Diagnostic Laboratories, Memphis, TN). Radiologic tests were defined as chest radiography (CXR) or computed tomography (CT), suggestive of pulmonary TB infection or past exposure (not active disease).[18] ATT was defined as multidrug therapy that typically consisted of 4 drugs, including isoniazid, rifampicin, ethambutol, and pyrazinamide, according to the health policy of each country and local variation management practices.

The detailed methodology has been published previously.[15] The design of the study is shown in **Figure 1**. The experts were asked to provide their input based on their clinical experience and relevant scientific evidence. The participants were given all the available literature including published literature and provided their level of evidence based on the Oxford scale. Since the available literature did not have guidelines on laterality and visual acuity, these were not included as parameters in the administered survey. For evidence supporting each single clinical case scenario see **Appendix 3**. The consensus meeting related to the second round of the modified Delphi technique was held on November 13th, 2019 in Kaohsiung, Taiwan.

Results

All consensus statements required an ocular phenotype suggestive of TBU, other possible diagnosis mimicking TBU excluded.[16] **Table 1, 2** and **3** indicate clinical scenarios that achieved a consensus based on the median score of 5 with IQR width of 0-3 for TAU, TIU and TPU, and TRV, respectively. **Appendix 4** shows how the statements that achieved a median score of 4 during the first round of the Delphi process changed through the systematic and critical discussion that occurred in the second round of the modified Delphi technique. A summary of the consensus statements related to initiation of ATT in TAU, TIU, TPU and TRV is presented **in Figures 2 to 4 and Table 4.**

<u>Tubercular Anterior Uveitis (TAU)</u>

Absolute consensus (median score=5, IQR=0) to start ATT was achieved in patients from both endemic and non-endemic regions with recurrent episodes of anterior uveitis (**Table 1**, **Figure 2, Table 4**) when both the immunological (PPD and IGRAs) and radiological (CXR/CT) tests were positive. However, there was moderate consensus (median score=5, IQR=1) to initiate ATT in a patient with first episode of anterior uveitis, even when all three tests were positive, irrespective of the endemicity. Moderate consensus (median score=5, IQR=1) was also achieved for patients coming from an endemic region with recurrent episodes of anterior uveitis and one immunological test positive (either PPD or IGRA) supported by positive radiological findings. For non-endemic region, the consensus reached was moderate (median score=5, IQR=1) in patients with recurrent episodes of anterior uveitis and one immunological test positive (either IGRA with PPD both negative or not done/not available or PPD with IGRA not done/not available) and positive radiological findings, but it was weak (median score=5, IQR=2) when PPD and radiological test were positive and IGRA was negative.

Tubercular Intermediate Uveitis (TIU)

There was moderate consensus (median score=5, IQR=1) amongst the experts to start ATT in patients with TIU **(Table 2, Figure 3, Table 4**) when both immunological (PPD and IGRA) and radiological test (CXR/CT) were positive, irrespective of endemicity. Moderate consensus (median score=5, IQR=1) was also achieved for patients from endemic regions with one of the two immunological tests positive (either PPD or IGRA) and radiological test positive. However, for non-endemic region, moderate consensus (median score=5, IQR=1) was only achieved in patients with both IGRA and radiological test positive and PPD skin test negative, while the consensus reached was weak (median score=5, IQR=2) when PPD skin test and radiological test were positive and IGRA was not performed.

Tubercular Panuveitis (TPU)

There was absolute consensus (median score=5, IQR=0) amongst the experts to start ATT in patients from both endemic and non-endemic region with panuveitis **(Table 2, Figure 3, Table 4**) when both immunological tests (PPD and IGRA) and radiological test (CXR/CT) were positive. Moderate consensus (median score=5, IQR=1) was also achieved for patients with one of the two immunological tests positive (either PPD or IGRA) and radiological test positive, irrespective of endemicity. However, for non-endemic region, the consensus reached was weak (median score=5, IQR=2) when PPD skin test and radiological test were positive and IGRA was negative.

Tubercular Retinal Vasculitis (TRV)

Consensus statements on the management of retinal vasculitis are illustrated in **Table 3** , **Figure 4 and Table 4**. In patients with active retinal vasculitis when both immunological tests (PPD and IGRA) and radiological test (CXR/CT) were positive the consensus to start ATT was absolute (median score=5, IQR=0) in endemic region and weak (median score=5, IQR=2) in non-endemic region. Weak consensus (median score=5, IQR=2) was also achieved for patients in endemic region with both immunological tests positive (PPD and IGRA) and radiological test negative or not performed; however, consensus was poor (median score=5, IQR=3) in non-endemic region and it was reached only in patients with both immunological tests positive and radiological test negative. With one of the two immunological tests positive (either PPD or IGRA) and radiological positive findings the consensus reached was absolute to moderate (median score=5, IQR=0,1) in endemic region and lower (median score=5, IQR=3) in non-endemic area. Further, if retinal vasculitis was inactive, there was weak consensus (median score=5, IQR=2) to start ATT in patients with both immunological tests (PPD and IGRA) and radiological test (CXR/CT) positive.

Tables 4 and Figures 2 to 4 illustrate the consensus statements and the color-coded algorithm for initiation of ATT in patients with TAU, TIU, TPU and TRV. In summary, it is clearly evident that in endemic region, whenever one of the immunological tests is positive along with positive radiography, there was moderate agreement among experts to initiate ATT, specifically when clinical phenotypes were recurrent anterior uveitis, intermediate uveitis and panuveitis. The agreement was less for a patient presenting in a non-endemic region. In case of active TRV, the agreement was absolute to weak for endemic regions and lower for non-endemic areas.

Discussion

The role of ATT in reducing the rate of recurrences in patients diagnosed with TBU has been well established.[1,7,19-45] However, the lack of international agreement on the minimum clinical dataset required to start ATT in a disease characterized by a wide spectrum of phenotypes indicates an unmet medical need in the management of this disease. In November 2019, the COTS CON group met to discuss and define the consensus statements related to the use of ATT in TAU, TIU, TPU and TRV, according to the modified Delphi technique adopted throughout the COTS study. These experts agreed that specific TBU phenotypes and the endemicity for TB of patients' geographical region of origin influenced the decision to start ATT.

Corroborative evidence supporting the diagnosis of TBU is based on commonly performed tests, namely PPD skin test, IGRAs and radiologic tests. For TBU, polymerase chain reaction (PCR)-based tests have proven to be of limited usefulness in real world scenarios.[6] The COTS-1 subset analysis published previously has shown that few clinicians rely on PCR for diagnosing TBU, but do not base their decision on PCR results to treat patients with ATT. In relation to radiologic tests, though it has been shown that CT scan is superior to CXR in detecting features suggestive of pulmonary TB infection, given the international nature of the survey, including countries with no access to CT, we chose not to differentiate in between the two tests grouping them together, and gave the option of not done or not available.[1] All the corroborative tests (such as TST and IGRA) were given equal weightage and survey output was taken into consideration based on experts' opinions on specific clinical phenotypes in presence of different tests permutations and combinations, both in endemic and non-endemic areas. The bias towards specific tests was thus eliminated without affecting consensus guidelines. The survey is restricted to the test commonly performed by clinicians worldwide to achieve the diagnosis of TBU, allowing the physicians to rationalize their treatment strategy based on a minimum dataset.

Addition of ATT to the topical therapy in the management of anterior uveitis has been controversial. From the retrospective analysis of COTS-1 data related to 165 patients affected by TAU (unpublished data), it appeared that the addition of ATT to topical treatment does not have significant impact on treatment outcome of patients with TBU. By contrast, multiple single centres studies highlighted the therapeutic role of ATT in patients diagnosed with TAU.[20,21,24,25,29,38,44-61] Based on overall scientific evidence and experience, uveitis specialists reached good consensus for initiating ATT in recurrent TAU with any immunological evidence of TB, along with radiological signs suggestive of pulmonary TB infection, in both endemic and non-endemic region, when other possible etiologies have been ruled out. However, when it comes to the first episode of anterior uveitis, experts agreed to initiate ATT, irrespective of endemicity, only when both immunological and radiological tests are positive. Our results confirm that patient's region of origin should be considered in the decision-making process. In endemic regions, an isolated positive PPD along with radiological evidence is sufficient to gain moderate consensus to initiate ATT despite a negative IGRA test, indicating that such phenotype in endemic area has a higher pre-test probability of TBU. By contrast, the above clinical scenario in non-endemic region has a lower consensus and a positive IGRA is requested to reach moderate agreement to start the treatment. In both endemic and non-endemic regions, when the other immunological test are not done or not available, it does not influence the pre- or post-test probability of TBU, supporting the initiation of ATT with moderate consensus in the event of one immunological positivity along with radiological findings.

Statements that reached a median score of 4, involving first episode of TAU in both endemic as well as non-endemic region with one immunological test positive along with radiological support, were discussed in details. There was general acceptance that a suggestive phenotype with granulomatous features of TAU, manifesting with iris nodules, keratic precipitates and posterior synechiae, insidious onset and chronicity give additional confidence in starting ATT. Some experts were confident to initiate ATT in the above clinical scenario only in patients from endemic region aiming to eradicate TB, while others preferred to avoid treatment in endemic area in view of the risk of drug resistance, but were likely to start ATT in non-endemic region, given the lower likelihood to have false positive results. However, in relation to the first episode of TAU, consensus to treat was only reached with all immunological and radiological tests positive.

Evidence supported efficacy of ATT in patients with TIU and TPU.[20-24,26,30,31,38,44,46-63] In patients with TIU and TPU, any immunological evidence of TB, along with positive radiological signs supports the initiation of ATT, irrespective of endemicity. However, comparing results from endemic and non-endemic region, data confirm once again that in endemic area, where the pre-test probability of TBU is higher, experts are more likely to treat patients with an isolated positive PPD despite a negative IGRA test. From the COTS-1 results, it is clearly evident that panuveitis have a stronger predictive value for TBU compared to intermediate uveitis.[1]

Intermediate uveitis was defined as a phenotype characterized by snowballs, with or without peripheral choroiditis scars, showing diffuse retinal vasculitis, with or without cystoid macular edema. Experts considered this phenotype less likely related to TBU and did not agree to start ATT in the event of an isolated positive PPD along with radiological evidence and negative IGRA test. However, weak consensus to treat was reached in the event of an IGRA test not done or not available, indicating that if the second test is not performed, it does not influence the pre- or post-test probability for the diagnosis of TBU, supporting the initiation of ATT in the event of one immunological positivity along with positive radiological findings.

From the COTS-1 analysis of 251 patients diagnosed with TRV and treated with ATT, treatment failure was less frequent in patients who were treated with ATT (13.6%), compared with those who did not (21.7%).[9] Several other studies have supported effectiveness of ATT in patients with TRV.[21,22,24,25,29,31,38,44,46-64] In active retinal vasculitis, any immunological positivity along with radiological support, or immunological evidence, involving both PPD and IGRA positivity without radiological findings, supports the initiation of ATT, irrespective of endemicity. However, from the results, it is evident that in non-endemic regions, the consensus to start ATT was lower. Experts agreed that the phenotype should suggestive of TRV is characterized by occlusive disease, associated perivascular choroiditis patches. In non-endemic settings, other causes of retinal vasculitis including systemic inflammatory diseases, or primary ocular disorders, must be considered and ruled out in the differential diagnosis.[9,65,66]

Inactive TRV was defined as sequelae of occlusive vasculitis, characterized by vitreous hemorrhage, retinal neovascularization and capillary non-perfusion without active phlebitis. There was weak consensus to start ATT in patients with inactive TRV in the endemic setting when both immunological and radiological tests were positive. This is because some experts considered the initiation of ATT in inactive TRV questionable due to

the lack of clinical endpoints for the treatment. Consequently, there was no consensus to start ATT in patients with inactive retinal vasculitis in non-endemic regions if there is a weak evidence of TB from corroborative tests.

In conclusion, the COTS group established consensus guidelines on the use of ATT in patients with TAU, TIU, TPU and TRV, based on the limited available evidence and international experts' opinion and practice. COTS CON guidelines will help address the conundrum in the approach to the management of TBU, guiding ophthalmologists, physicians and regulatory bodies in the therapeutic decision-making process, and representing a potential benefit to the patients' clinical outcome. Since majority of patients with TBU have underlying TB infection, and infectious disease experts may be unwilling to treat these patients with ATT, uveitis experts often face challenges in treating their patients with ATT. These guidelines indicate that active ocular disease with evidence of TB infection deserves treatment, and will potentially impact the public health measures in the management of extrapulmonary TB. The COTS team is preparing simple algorithmic flow charts merging consensus guidelines from COTS CON report 1 and 2, providing a concise review and practical recommendations for readers and clinicians to follow in their real word clinical practice. The COTS CON guidelines will be useful as a basis for prospective clinical studies to evaluate the role of ATT in different phenotypes of TBU, for validating the findings presented in this report and to propose guidelines for health regulatory agencies.

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Figure legend:

Figure 1: The study design for Collaborative Ocular Tuberculosis Study group Consensus guidelines (COTS CON) for tubercular anterior uveitis, intermediate uveitis, panuveitis and retinal vasculitis, using a two-stage modified Delphi technique.

Figure 2: Color Coded algorithm for initiation of antitubercular therapy (ATT) in patients with tubercular anterior uveitis (TAU)

Figure 3: Color Coded algorithm for initiation of antitubercular therapy (ATT) in patients with tubercular intermediate uveitis (TIU) and tubercular panuveitis (TPU)

Figure 4: Color Coded algorithm for initiation of antitubercular therapy (ATT) in patients with tubercular retinal vasculitis (TRV)