Ocular Tuberculosis: Where are we today?

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Abstract

Diagnosis and management of ocular tuberculosis (OTB) poses a significant challenge. Mixed ocular tissue involvement and lack of agreement on best practice diagnostic tests together with the global variations in therapeutic management contributed to the existing uncertainties regarding the outcome of the disease. The current review aims to update recent progress on OTB. In particular, the Collaborative Ocular Tuberculosis Study (COTS) group recently standardized a nomenclature system for defining clinical phenotypes, and also proposed consensus guidelines and an algorithmic approach for management of different clinical phenotypes of OTB. Recent developments in experimental research and innovations in molecular diagnostics and imaging technology have provided a new understanding in the pathogenesis and natural history of the disease.

1. Introduction

Tuberculosis (TB) represents a global health challenge. According to the World Health Organization (WHO), TB is one of the top ten causes of death worldwide and the leading cause of death from a single infectious agent, with one third of the world's population infected with *Mycobacterium tuberculosis* (MTB), and thus at risk of developing the disease.[1]

TB can affect multiple organs throughout the body. Ocular TB (OTB) is a rare extrapulmonary form of the disease, not to be underestimated considering its potential impact on visual loss in patients diagnosed with the disease. OTB still represents a major diagnostic and therapeutic challenge, due to its heterogeneous clinical manifestations, mixed ocular tissue involvement, lack of diagnostic criteria and gold standard tests, and lack of international agreement on the therapeutic approach **(Figure 1)**.[2-6] As a result, the reported prevalence of tubercular uveitis (TBU) is characterized by a wide variability worldwide, ranging from 0.2% to 2.7% in regions where TB is not endemic, including USA, Europe or Japan, to 5.6%-10.5% in highly endemic areas such as India.[5,9]

Majority of the patients are diagnosed with presumed ocular TB, based on local epidemiology, consistent ocular phenotypes and positive corroborating tests, such as purified protein derivative (PPD) skin test and/or interferon gamma release assays (IGRAs). Patients are commonly referred for initiating antitubercular therapy (ATT) based on the positivity of the immunologic test results, with no pathological findings on chest imaging and no active clinical signs of systemic disease.[3-6] Other causes excluded, clinical signs consistent with TBU play a significant role in the diagnostic process even in the presence of negative corroborating investigations, contributing to the increase in the uncertainty regarding diagnosis and management.[3,6,7]

The gold standard for the diagnosis of OTB is the direct demonstration of the MTB in tissues or fluids, but positive results are difficult to obtain by culture or smear from ocular samples due to the low yield of MTB and the small size of specimens.[4,5,7] In the setting of a paucibacillary disease, polymerase chain reaction (PCR) techniques were expected to be extremely useful for the detection

of MTB. However, recent data from the Collaborative Ocular Tuberculosis Study (COTS) -1 suggested how positive or negative results do not influence the management of the disease in the real-world scenario, because of the low sensitivity and lack of standardization.[8]

In view of these observations, diagnosis of TBU is mostly based on clinical phenotype and immunologic investigations. However, although these techniques are frequently used to reach a presumptive diagnosis, they have limitations related to sensitivity and specificity, and that implies that some caution is required in their interpretation.[3,5-8] In the absence of clinical findings suggestive of TBU, it might be risky for uveitis specialists to rely on a positive immunologic test result as indication for diagnosis, due to a low pre-test probability in cases of low clinical suspicion, and the possibility of latent TB in a patient with ocular inflammation not TB related.[3,10] Screening for OTB, thus, should be discouraged in low risk groups, and positive corroborating test results should be considered for the initiation of ATT only in the context of a strong clinical suspicion.

2. Clinical features and nomenclature of ocular tuberculosis

OTB can affect any tissue of the eye and manifests most commonly as TBU. Different ocular phenotypes have been attributed to TBU. However, the lack of a general agreement among uveitis experts regarding the disease and its etiopathogenesis resulted in the ambiguity of non-standardized terminology. Recently, the Collaborative Ocular Tuberculosis Study (COTS) group worked together with the International Uveitis Study Group (IUSG), International Ocular Inflammation Society (IOIS) and Foster Ocular Immunology Society (FOIS) in the 'Standardization of Nomenclature for Ocular Tuberculosis' project, with the aim to address the ambiguity related to the terminology of OTB, and to promote uniform scientific seamless communication amongst the clinicians worldwide.[11]

Tubercular posterior uveitis (TPU), and more precisely tubercular choroiditis (TBC), is the most common manifestation of TBU.[4,11] Different phenotypes characterize the choroidal involvement in the disease. Tubercular serpiginous-like choroiditis (TB SLC) manifests as multifocal, initially discrete and later confluent, yellowish lesions, characterized by slightly raised edges, showing active

edge wave-like progression and central healing. In most cases lesions are non-contiguous to the optic disc.[7,11-13] The diffuse plaque-like choroiditis is a distinctive pattern of TB SLC, characterized by a solitary placoid lesions with an amoeboid spread **(Figure 2)**. TB SLC can be unilateral or bilateral, and it is commonly associated with mild vitritis. On fundus fluorescein angiography (FA) active inflammatory lesions typically show early hypofluorescence and late hyperfluorescence, with atrophic areas revealing window defects **(Figure 3)**. Indocyanine green angiography (ICGA) is characterized by hypofluorescent lesions in the early phase, remaining hypofluorescent in the late phase. Fundus autofluorescence (FAF) is a non-invasive essential tool for monitoring the progression of the disease. Active lesions initially show a diffuse hyperautofluorescent. As they begin to heal, they show marginal hypoautofluorescence with hyperautofluorescent in the center. When completely healed, lesions become hypoautofluorescent throughout, indicating damage to the RPE and outer retina, and consequently loss of visual function (see ancillary imaging section). [7,11-13]

TBC can manifest as tubercular multifocal choroiditis (TB MC) or tubercular focal choroiditis (TB FC), involving choroiditis phenotypes not resembling TB SLC, such as idiopathic multifocal choroiditis or acute posterior multifocal placoid pigment epitheliopathy (APMPPE) in case of multifocal manifestation **(Figure 4, 5, 6)**.[11,14] Choroidal tubercles have been classified as part of TB MC phenotype.[11] Representing ocular manifestations of disseminated TB indicating haematogenous spread of MTB, tubercles usually appear as multiple, small, grayish-yellowish nodules, unilateral or bilateral, predominantly located at the posterior pole. When lesions are active, borders are indistinct due to the surrounding rim of inflammation, resulting in pigmented scars when healed.[7,11] As per inflammatory lesions, on FA active tubercles appear hypofluorescent in the early phase and hyperfluorescent in the late phase. On ICGA the lesions show hypofluorescence during early and intermediate phases, and become isofluorescent in the late phase, since they are located deeper in the choroid, not involving the choriocapillary.

Tuberculoma is a well-known phenotype and a prototype of the choroidal manifestation of the disease.[7] It manifests as a single or multiple, yellowish, subretinal lesion with fuzzy borders,

surrounded by exudative fluid **(Figure 7A)**. Typically located in the posterior pole or in the mid-periphery at the level of choroidal stroma, it is characterized by oval hyporeflectivity on optical coherence tomography (OCT), better detected on enhanced depth imaging (EDI) – OCT **(Figure 7B)**, and by hypofluorescence in the early and intermediate phase, and isofluorescence in the late phase of ICGA **(Figure 7C)**.[15,16]

Among TPU, tubercular retinal vasculitis (TRV) is characterized by an occlusive phenotype, manifesting as retinal periphlebitis with primarily involvement of the veins rather than the arteries. It typically appears as perivascular sheathing with exudates and retinal haemorrhages **(Figure 8 and 9)**.[7,17] The presence of perivascular choroidal pigment or small choroiditis patches is highly suggestive of tubercular aetiology **(Figure 8)**.[18] Complications include macula oedema and, given the occlusive nature of the vasculitis, retinal or optic disc neovascularization, resulting in vitreous haemorrhage, tractional retinal detachment, iris neovascularization, and neovascular glaucoma **(Figure 4 and 6)**. The term Eales' disease, which by original definition is an idiopathic form of vasculitis, indicates a disorder characterized by occlusive retinal periphlebitis with high risk of retinal neovascularization and related sequelae, usually occurring in healthy young male individuals coming from TB endemic areas, has been strongly correlated to an immune-mediated reaction to MTB.[7,17] Uveitis experts agreed on the use of the term TRV to be preferred to Eales'disease in those cases of TB-related retinal vasculitis, since there is no pathological distinction between the two entities.[11]

The most common manifestation of TBU after TBC is tubercular panuveitis (TPU), characterized by anterior chamber, vitreous, and retina and/or choroid involvement, followed by tubercular anterior uveitis (TAU).[7,17] TAU is typically a granulomatous form of anterior uveitis, unilateral or bilateral, characterized by large mutton-fat keratic precipitates and broad-based posterior synechiae.[7,17] In severe cases nodules on pupillary border or iris surface can be detected. Cataract is a common complication of TAU due to both chronic inflammation and prolonged use of topical corticosteroids.[7,17] The term intermediate uveitis represents a subtype of uveitis where the vitreous is the primary site of inflammation.[17] Tubercular intermediate uveitis (TIU) manifests as low grade,

chronic intraocular inflammation, characterized by vitritis, inferior snowballs, peripheral vascular sheathing, often complicated by cystoid macular oedema.[7,19,20]

Clinical features and nomenclature of ocular tuberculosis are illustrated in **Table 1**. To summarize, TBU accounts for a wide and heterogeneous spectrum of clinical manifestations, including anterior uveitis, intermediate uveitis, retinal vasculitis and chroroiditis. Therefore, the diagnosis of TBU, especially in regions non endemic for TB, still poses a significant challenge, and different entities mimicking similar phenotype must be always considered in the differential diagnosis, together with patient's region of origin and investigations results.

3. Etiopathogenesis

The etiopathogenesis of OTB - intraocular infection with MTB, should be implied in the terminology itself. Yet the association between the disease and its causative organism has remained tenuous, owing largely to the rarity of microbiological and molecular evidence of MTB in clinical samples obtained from patients. This uncertainty has led to the pathogenic mechanisms of OTB being divided putatively into direct and indirect mechanisms, the latter being those mechanisms that may not require the presence of live/replicating mycobacteria within the eye. In this section, we will review existing literature supporting either direct or indirect mechanisms, and how these might influence decision making in diagnosis and treatment of OTB. Broadly, the supporting literature for either of these mechanisms can be divided into clinical observations, histopathological and cytological studies of human OTB, and animal models of the disease.

3.1 Direct mechanisms

The direct effect of MTB infection in etiopathogenesis of OTB is supported foremost by the beneficial role of ATT in resolution or non-recurrence of inflammation in OTB.[2,21,22] However, the therapeutic efficacy of ATT is not sufficient to distinguish if the infection is latent or involves active/replicating bacilli. Further support for direct role of MTB is obtained from histopathological studies that demonstrate granulomatous inflammation in different ocular tissues with giant cells and areas of

necrosis.[23,24] Very few acid-fast bacilli (AFB) are found. Such studies are generally available from enucleated specimens, though biopsy studies from human eyes are also reported.[25,26] Finally, multiple animal models of OTB are available, that demonstrate the dissemination of MTB from the peripheral circulation to cause granulomatous inflammation in the eye.[27-30] While most models including rabbit, mouse and zebrafish have used intravenous infection with mycobacteria, the guinea pig model used aerosol infection of lungs to produce granuloma in the eye. Together, the beneficial effect of ATT, with demonstration of granulomatous inflammation and AFB in human disease and animal models provides strong support to direct effect of MTB in etiopathogenesis of OTB.

3.2 Indirect mechanisms

The indirect effect of MTB is mostly supported by general lack of microbiological/ molecular evidence of MTB in ocular fluid samples and therapeutic response of clinically diagnosed OTB to corticosteroid therapy alone.[21] Further support is provided by analysis of intraocular T-cells from vitreous samples of OTB that revealed presence of autoreactive (retinal antigen specific T-cells) in addition to the TB-specific T-cells.[31] The autoreactive cells were more pro-inflammatory and survived longer potentially leading to chronic inflammation. Finally, intravenous injection of dead MTB into rabbits was found to produce all forms of intraocular inflammation except retinal vasculitis.[32] Even experimental autoimmune uveitis models in mice requires the addition of Freund's adjuvant containing dead MTB to retinal antigens to produce retina-specific immune response.[33] Additional complexity into the intraocular immune response might be derived from decrease in regulatory T-cells, at least in the peripheral circulation.[34]

It is likely that both direct and indirect mechanisms co-exist in the etiopathogenesis of human OTB. However, the relative contribution of each mechanism to individual phenotypes such as retinal vasculitis or serpiginous-like choroiditis or different stages of disease may vary and should be addressed by future studies. Direct mechanisms could dictate focus on bacteriological diagnosis and therapy, and indirect mechanisms on primary anti-inflammatory therapy with adjunctive ATT.

4. Ancillary Imaging

Recent advances in technology established the role of multimodal imaging in the diagnosis and management of OTB. Detecting a phenotype suggestive of OTB is essential to make a presumptive diagnosis and monitoring the course of the disease plays a key role in the correct therapeutic management. Techniques, such as FA, ICGA, and OCT, together with novel imaging modalities, including FAF, ultra-wide field (UWF) imaging, and optical coherence tomography angiography (OCT-A), supplement each other and provide useful information on the natural course and therapeutic response of the disease.

Fundus photography help in documenting clinical signs, pathological involvement and disease extension. However, it is above all in monitoring the course of the disease that it has proved extremely useful, thanks to the possibility of obtaining serial fundus photographs, and allowing to objectively identify and compare progression or resolution of the disease. Recently, novel wide-field and UWF imaging modalities have offered an additional advantage over the conventional techniques. Allowing simultaneous visualization of mid-peripheral and peripheral retina up to a 200° field of view in one single frame, they help detect and monitor peripheral inflammatory lesions beyond the standard 30-60° field of view, providing potential benefits in terms of disease management and therapeutic decisions making.[35,36]

We already showed how FA helps in detecting inflammatory lesions, and how active inflammatory lesions, including TB SLC, choroidal tubercles and tuberculoma, typically show early hypofluorescence and late hyperfluorescence **(Figure 3 and 6)**.[7,12,13,37-39] However, FA is also useful in identifying retinal vasculitis and its complications **(Figure 6 and 9)**. Being TRV an occlusive form of vasculitis, FA is capable of detecting vascular wall staining, extravascular leakage, areas of capillary non-perfusion (CNP) and retinal neovascularization, helping the differential diagnosis between TRV and non-occlusive vasculitis.[7,37,38] In addition, following the recent advent of UWF-FA, additional information on disease extension and peripheral pathological involvement has become available, influencing the therapeutic management of the disease.[40-43]

ICGA is the most useful technique for studying the choroid, and in the context of TBC, choroidal involvement includes both choriocapillaris and choroidal stroma.[44,45] In TB SLC inflammation results in multiple areas of occlusion of the choriocapillaris, manifesting as hypofluorescent lesions in the early phase and remaining hypofluorescent throughout the exam, as the choriocapillaris overlying the stroma is permanently occluded and do not fill with the dye.[12,13] Similarly to TB SLC, full-thickness tuberculomas involving the choriocapillary remain hypofluorescent in the late phases **(Figure 7C)**, whereas partial thickness tuberculomas not involving the choriocapillary show hypofluorescence during early and intermediate phases, but become isofluorescent in the late frames.[37,38] ICGA can also find application in detecting choroidal neovascular membrane (CNV), that can complicate chorio-retinal scars, or retinal angiomatous proliferation (RAP), that can develop in active inflammatory lesions.[7]

FAF in the context of OTB is mainly used to monitor the course of TB SLC. FAF is a non-invasive fundus imaging modality using fluorescent properties of outer photoreceptor segments lipofuscin, that accumulates in the RPE. According to the principle that hypoautofluorescence indicates loss of RPE cells and overlying photoreceptors, and hyperautofluorescence indicates increased metabolic activity and likely progression to loss of function, Gupta et al described four FAF stages of TB SLC.[46] Active lesions show a diffuse hyperautofluorescent halo (stage I), but as they start healing, a thin border of hypoautofluorescence surrounds the active lesions (stage II). The hypoautofluorescence then progresses, and the lesions appear as a mix of autofluorescence with a stippled pattern characterized by increased hypoautofluorescence and decreased hyperautofluorescence (stage III). Once the lesions are totally healed, they appear hypoautofluorescent throughout (stage IV).[46]

Additional information regarding the assessment of chorioretinal tissue and vascular network has been provided by novel OCT imaging modalities, including EDI-OCT and OCT-A.

EDI-OCT allows a good visualization of deep ocular tissue, including choroid and sclera. Choroidal thickness is significantly increased in the active phase of TB SLC, when EDI-OCT shows diffuse choroidal thickening.[47-50] In particular, in acute phases of TB SLC spectral domain (SD)-OCT and EDI-OCT show disruption of ellipsoid and myoid zones with pigment epithelial migration into the outer retinal layers and outer retinal hyperreflectivity, together with increased choroidal thickness with hyperreflectivity in the choroid areas corresponding to active lesions. Once healed, atrophy of outer retinal layers and RPE, with increased choroidal reflectance and choroidal thinning, is detected.[47-51]

EDI-OCT has been proven extremely useful in detecting choroidal granulomas, characterized by a focal area of hyporeflectivity with increased homogeneity, due to the absence of normal vascular pattern **(Figure 7B)**.[15,16] The increased transmission of OCT signal characterizing choroidal granulomas when compared to the surrounding tissue is useful to identify small granulomas and avoid confusion with the large choroidal vessels that can mimic granulomas on EDI-OCT. Invernizzi et al found that tuberculoma are commonly lobulated and less homogeneous than choroidal granulomas of different etiologies, helping in the differential diagnosis.[15,16] Being a non-invasive technique, EDI-OCT can easily be used in the follow-up of choroidal lesions, monitoring the size, choroifal thickness and choroidal vascularity index and hence, response to therapy and recurrence of lesions.[52]

OCT-A is novel non-invasive imaging technique that, providing in vivo quasihistological images of tissues, allows the visualisation of vascular network in retina and choroid.[53] In active TB SLC OCT-A shows areas of flow void representing hypoperfusion of the choriocapillaris, and corresponding to hypofluorescent lesions on ICGA. Once the lesions start healing, atrophy of the choriocapillaris might develop and an intertwined meshwork of vessels, corresponding to choroidal vessels, can be detected in the healed areas.[54-57] OCT-A is extremely useful in detecting retinal capillary areas of non-perfusion in TRV, vascular abnormalities, including non-neovascular tufts and tangled vessels, and CNV.

Imaging features of TBC are described in **Table 2**. To summarize, multimodal imaging approach has become essential in the diagnosis and management of a disease characterized by multiple phenotypes and different pathological mechanisms. Different imaging modalities complement each other to get the most information on tissue involvement, disease activity, response to therapy and potential complications.

5. Lab and Radiologic Investigations

The gold standard for the diagnosis of OTB is the detection of MTB in tissues or fluids, providing confirmatory evidence of the pathogen through aqueous and/or vitreous sampling. Nucleic acid amplification technique (NAAT), including polymerase chain reaction (PCR), are able to amplify DNA of small genomic sequences. Although in the setting of a paucibacillary disease PCR can be extremely useful for detecting MTB, a definitive diagnosis of OTB is often difficult to obtain due to the low sensitivity of the technique applied to ocular samples characterized by small size and low mycobacterium yield.

Most of the NAATs, including PCR and real-time (RT)-PCR, utilize a single target specific for MTB, namely IS6110 and MPB64. However, IS6110 is absent in 10-40% of MTB samples, especially in endemic areas, where the likelihood of false-negative results is higher, and the reported sensitivity of single gene targets techniques applied to ocular specimens is 37%-58.82%.[58-61] A multi-targeted PCR characterized by simultaneous amplification of three targets specific for MTB, namely IS6110, MPB64, and protein b, has been showed to have enhanced sensitivity. Sharma et al demonstrated a sensitivity and specificity of 77.77% and 100%, respectively, when multiplex PCR (MPCR) is applied to patients with presumed OTB, with a positive and negative predictive value of 100% and 88.88%, respectively.[62]

Most current research has focused on novel techniques of nucleic acid amplification, including GeneXpert MTB/RIF assay and Line Probe Assay (LPA). GeneXpert MTB/RIF assay is based on a

hemi-nested RT-PCR technique, using molecular beacon technology to detect both MTB genome and rpoB gene mutations for rifampicin resistance. Although a report by Sharma et al showed a sensitivity of 22.3% and a specificity of 100% when applied to vitreous samples, the test can provide extremely useful information on drug resistance and thus, explain recurrences despite ATT.[63] LPA, including GenoType MTBDR*plus*, uses a reverse hybridization technique to detect specific mutations in rpoB gene for rifampicin resistance, and InhA and katG genes for isoniazide resistance. Bansal et al utilized three different molecular techniques to detect MTB DNA in the vitreous of 11 eyes with multifocal serpiginoid choroiditis. All eyes were tested with MPCR, Genexpert MTB/RIF assay and GenoType MTBDRplus. Ten eyes resulted positive for MTB DNA using MPCR, 6 eyes were positive for MTB genome using MTBDR Plus, with rifampicin resistance detected in 3 cases, and 4 eyes were positive using GeneXpert, with rifampicin resistance detected in 1 case.[64]

In view of these observations, the diagnosis of OTB is commonly a presumptive diagnosis based on positive immunologic investigations in association with a consistent ocular phenotype. Baseline immunological testing includes PPD skin test and IGRAs. Both tests work on the principle of cell mediated immunity. PPD skin test detects skin hypersensitivity for mycobacterial antigens including purified protein derivate of tuberculin (PPD), while IGRAs test interferon-γ release after in vitro stimulation of patients' lymphocytes with MTB specific antigens (ESAT-6 and CFP-10). Both tests do not distinguish between active and latent disease, and have limitations related to sensitivity and specificity, implying that caution is required in the interpretation.

PPD skin test has a low positive predictive value and a high false negative rate in the absence of systemic disease, whereas IGRAs, although more specific, have a high false positive rate.[3,6,10] Thus, in the absence of clinical findings suggestive of OTB, physicians should not rely on positive IGRA as indication of disease diagnosis.[65] IGRA has a low pre-test probability in cases with low clinical suspicion (approximately 90% of positive IGRAs can be false positives), and the possibility of a latent TB in a patient with ocular inflammation not related to TB must be considered, especially in regions of the world where TB is endemic.[3,6,10] Screening for TB should be thus discouraged in low risk

groups, and immunological tests should be considered for the initiation of ATT only in the context of a strong clinical suspicion. PPD skin test may be positive in patients immunized with Bacillus Calmette-Guerin (BCG) vaccination and in case of atypical mycobacteria. IGRA is a more specific marker of MTB exposure, not affected by prior BCG vaccine and non-tuberculous mycobacteria.[3,6,10] Although more specific, data relating to its sensitivity compared to PPD skin test are variable and still inferior to the ideal. Some authors thus recommended using both the investigations, to enhance sensitivity and specificity in the context of suggestive ocular pehnotype.[3,6,10]

Being an extrapulmonary form of the disease, OTB commonly occurs without any evidence of pulmonary involvement. Although most patients have no clinical signs of active pulmonary disease, radiology can be useful, providing evidence of old healed TB. Results from COTS-1 showed that among 702 patient affected by OTB with documented radiological results, 26.9% had radiologic features suggestive of inactive TB on chest X-ray, and 68.6% had positive findings on chest computed tomography (CT).[66] CT appears to be more a sensitive technique, that can be a valuable diagnostic tool in patients with ocular findings suggestive of OTB and history of exposure with no signs of active infection.

Metha et al studied the role of fluorine-18 fluorodeoxyglucose Positron Emission Tomography Computed Tomography (18-FDG PET/CT) in patient affected by OTB.[67] Of the 27 patients undergoing PET/CT scans, 13 did not show any pathological findings, whereas 14 had evidence of systemic disease. Metabolically active lymphadenopathy was detected in all patients with positive radiologic findings. The most common feature was mediastinal lymphadenitis seen in 12 patients, of which 3 with additional abdominal/pelvic lymphadenopathy and 3 with additional cervical lymphadenopathy. The detected mediastinal involvement can be explained by mediastinal nodes draining the lung parenchyma and being the first nodes to be involved in the lung infection. However, Burger et al analyzed the role of FDG PET/CT and CT in patients with OTB, showing that sensitivity, specificity, positive predictive value and negative predictive value were similar between the two

techniques (33.3%, 100%, 100% and 68%, respectively), demonstrating how PET/CT does not add any additional benefit over chest CT in OTB patients.[68]

6. When to treat?

The role of ATT in OTB is still controversial, and there is no international agreement on therapeutic regimen and treatment duration.[3,5,22,69,70] There is a wide heterogeneity in drugs and regimen adopted, depending on the area of practise, TB endemicity, local diagnostic and therapeutic protocols, and personal experience in treating the disease.

Evidence indicates efficacy of ATT in reducing the rate of disease recurrences in patients with OTB treated with ATT.[2,22,69] A meta-analysis from twenty-eight studies evaluated the effect of ATT on the ocular outcome of 1,917 patients.[22] The results showed that 84% of patients treated with ATT did not experience recurrences of inflammation during the follow-up. Similarly, data from COTS-1 reported a treatment failure rate of 12,6% in patients treated with ATT.[69] However, there is a lack of randomised control trials for treatment of OTB.

The role of concomitant administration of oral corticosteroids and immunosuppressant agents is controversial too, and there is no agreement on their efficacy in patients with TBU treated with ATT.[22,69] Steroid and immunosuppressive agents are supposed to control intraocular inflammation and limit the damage to ocular tissue caused by delayed hypersensitivity reaction, during the active phase of the disease or in case of paradoxical worsening. COTS-1 reported a treatment failure rate in patients receiving ATT alone or in combination with oral steroids of 7.3% and 12.6%, respectively.[69] By contrast, the meta-analysis did not observe significant difference in treatment outcome between the two groups, showing a successful outcome in 85% and 82% of patients receiving ATT alone and ATT together with oral corticosteroids, respectively.[22]

To address the uncertainty in the management of OTB and bridge the gap between clinical need and medical evidence, the COTS group, in collaboration with IUSG, IOIS and FOIS, has recently

developed consensus guidelines for the initiation of ATT for specific clinical phenotypes and proposed guidelines for concomitant adjunctive therapy in patients with TBC.[71] From the study it emerged that specific sub-phenotypes of TBC influence the therapeutic decision of starting ATT, as well as TB endemicity in the geographical region of patient's origin. In TB SLC, tuberculoma and TB MC/TB FC, any immunologic evidence suggestive of TB, namely a positive PPD skin test or IGRA, justifies ATT, when associated with radiologic signs of active or healed pulmonary TB. In TB SLC, given the strong association of the sub-phenotype with MTB, even one positive immunologic evidence, not supported by radiologic findings, is considered enough to start ATT. Similarly, tuberculoma is highly representative of TBU, and therefore, even in this sub-phenotype experts recommended starting ATT in the presence of any single immunologic evidence for TB infection. In addition, if the patient comes from endemic areas, a positive radiologic finding alone justifies starting the treatment regimen in patients affected by tuberculoma. By contrast, TB MC and TB FC are less likely considered TB-related and the administration of ATT in affected patients should always be supported by both immunological and radiological positive findings.

Systemic corticosteroids could be initiated concomitantly with or soon after the administration of ATT in patients with TB SLC, tuberculoma with no active systemic infection, and TB MC/TB FC, unless there is a high risk of significant ocular complications due to severe inflammatory reaction.[71] When the inflammation recurs during tapering, systemic corticosteroid-sparing immunosuppressants can be started in patients with TB SLC and TB MC/TB FC.

Local therapy has been recently successfully used in the management of TBU as an optional adjunctive anti-inflammatory therapy.[72-74] Although the experience is limited, patients diagnosed with TIU, TRV and TB SLC have been treated with intravitreal injection of dexamethasone implants in case of corticosteroid intolerance, cystoid macular oedema, and paradoxical worsening. Concomitantly with ATT administration, the device demonstrated its efficacy in the management of macular oedema, vitreous haze, and choroidal lesions.

In conclusion, the decision to treat OTB is usually made by the ophthalmologist. Chest and infectious disease physicians have to rely on the suspicion of TBU of the referring ophthalmologist to start ATT, based on history of exposure, supportive ocular findings and corroborating investigations. A globally unified collaborative effort has been made by the COTS Group to address the uncertainty related to the management of TBU, and consensus guidelines for initiation of ATT will be of significant help for both physicians and patients. Prospective clinical trials are needed to better assess the role of ATT and adjunctive therapy in patients affected by OTB and set up concordance on treatment regimen among the experts worldwide.

Table 1. Spectrum of Ocular Involvement and Nomenclature of Tubercular Uveitis (TBU)

Tubercular posterior uveitis (TPU)

Tubercular choroiditis (TBC)

- Tubercular serpiginous-like choroiditis (TB SLC)
  - *- multifocal, initially discrete and later confluent, yellowish lesions, non-contiguous to the optic disc, with slightly raised edges, showing active edge wave-like progression and central healing*
  - *- diffuse plaque-like variant, characterized by solitary placoid lesions with amoeboid spread*

- Tubercular multifocal choroiditis (TB MC)
  - *- multifocal choroiditis not resembling TB SLC, including idiopathic multifocal choroiditis or acute posterior multifocal placoid pigment epitheliopathy (APMPPE)*

  - \- Choroidal tubercles
  - *multiple, small, grayish-yellowish nodules, with indistinct borders and surrounding rim of inflammation, resulting in pigmented scars when healed*

- Tubercular focal choroiditis (TB FC)
  - *- unifocal choroiditis not resembling TB SLC*

- Tuberculoma
  - *- single or multiple, yellowish, subretinal lesion with fuzzy borders, surrounded by exudative fluid, typically located at the level of choroidal stroma*

Tubercular retinal vasculitis (TRV)
- occlusive periphlebitis, tipically appearing as perivascular sheathing with exudates and retinal haemorrhages, and perivascular choroiditis patches

Tubercular panuveitis (TPU)
- anterior chamber, vitreous, retina and/or choroid involvement

Tubercular anterior uveitis (TAU)
- granulomatous anterior uveitis, with large mutton-fat keratic precipitates, broad-based posterior synechiae, and nodules on pupillary border or iris surface

Tubercular intermediate uveitis (TIU)
- vitritis, inferior snowballs, peripheral vascular sheathing, often complicated by cystoid macular oedema

Table 2. Imaging features of tubercular choroiditis

		FAF	ICG	FA	EDI-OCT	OCT-A
Serpiginous-like choroiditis	Active lesions	Diffuse hyperautofluorescence	Early and late hypofluorescence with fuzzy margins	Early hypofluorescence with late hyperfluorescence	Disruption of ellipsoid and myoid zones with pigment epithelial migration into outer retinal layers, outer retinal hyperreflectivity, increased choroidal thickness with hyperreflectivity of choroid areas corresponding to active lesions	Areas of flow void representing hypoperfusion of the choriocapillaris
	Healed lesions	Uniform hypoautofluorescence	Early and late hypofluorescence with discrete margins	Early and late trasmision hyperfluorescence	Atrophy of outer retinal layers and RPE, with increased choroidal reflectance and choroidal thinning	Intertwined meshwork of vessels due to atrophy of choriocapillaris
Tuberculoma	Full thickness	Depending on outer retinal involvement	Early and late hypofluorescence	Early hypofluorescence with late hyperfluorescence	Focal area of hyporeflectivity with increased homogeneity and increased transmission	Area of choriocapillaris non-flow that colocalizes with ICG hypofluorescence
	Partial thickness	Not detected with FAF since not involving outer retina	Early hypofluorescence with late isofluorescence	Early hypofluorescence with late hyperfluorescence	Focal area of hyporeflectivity with increased homogeneity and increased transmission	Not detected with OCTA at the level of the choriocapillaris

FAF: fundus autofluorescence, ICG: indocyanine angiography, FA: fluorescein angiography, EDI-OCT: enhanced depth imaging optical coherence tomography, OCT-A: optical coherence tomography angiography, RPE: retinal pigment epithelium.

Table 3. Executive summary

Background

- Diagnosis and management of OTB pose a significant challenge
- Heterogeneous clinical manifestation and mixed ocular tissue involvement
- Lack of agreement on best practice diagnostic investigations
- Global variations in therapeutic management

Where we are? - Key points

- **COTS nomenclature** - standardized nomenclature system for defining clinical phenotypes and promote uniform scientific communication amongst clinicians worldwide

- **New understanding of pathogenic mechanisms** - histopathological and immunopathological studies

- **Multimodal imaging –** novel imaging modalities, including UWF imaging, EDI-OCT and OCT-A, providing new insight in the knowledge of OTB and playing a key role in threapeutic management

- **Advances in molecular techniques** - multi-target PCR,to detect MTB DNA in ocular fluid/tissue with enhanced sensitivity; Gene Xpert MTB/RIF assay and Line Probe Assay, to detect drug resistant tuberculosis

- **COTS consensus guidelines on the initiation of ATT** - to address uncertainty in the management of OTB and bridge the gap between medical evidence and clinical need

Table 1 Spectrum of Ocular Involvement and Nomenclature of Tubercular Uveitis (TBU)

Table 2 Imaging features of tubercular choroiditis

Table 3 Executive summary

Figure 1 Diagnostic and therapeutic conundrum of ocular tuberculosis

Figure 2 (A) Right eye ultra-wide field color fundus photograph of serpiginous-like choroiditis having an active edge with amoeboid spread and a healing center (better seen in the magnified square 1) (B) Right eye ultra-wide field fundus autofluorescence showing hyperautofluorescent active edge.

Figure 3 Ultra-wide field fluorescein angiography of the same eye as in figure 2 showing (A) hypofluorescence in the early phase and (B) hyperfluorescence in the late phase.

Figure 4 Ultra-wide field color fundus photograph of a 38-yr-old Indian man diagnosed with tubercular multifocal choroiditis **Right eye** multifocal inactive lesions distributed in the posterior pole and in the periphery **Left eye** multifocal active lesions (*arrow and circle*), along with old healing lesions, involving the posterior pole and peripheral fundus. **Both eyes** show sequelae of healed retinal vascultitis, including peripheral ischemia and retinal neovascularization.

Figure 5 Ultra-wide field indocyanine angiography of the same patient diagnosed with tubercular multifocal choroiditis **Rigth eye** Healed lesions, showing early and late hypofluorescence **Left eye** showing active lesions (*arrow and circle*), that are hypofluorescent in early phase **(A)** and remain hypofluorescent in late phase **(B),** with fuzzy margins suggestive of activity; and healed lesions, showing early and late hypofluorescence with more discrete margins.

Figure 6 Ultra-wide field fluorescein angiography of the same patient diagnosed with tubercular multifocal choroiditis **Rigth eye** Healed lesions show ealy and late transmission hyperfluorescence **Left eye** Active lesions (*arrow and circle*) that are hypofluorescent in the early phase **(A)**, showing hyperfluorescence in the late phase **(B)**, along with inactive scars showing early and late transmission hyperfluorescence. **Both eyes** show peripheral areas of capillary non perfusion and retinal neovascularization.

Figure 7 (A) Ultra-wide field color fundus photograph of the right eye eye of a 55-year-old Indian man with positive QuantiFERON-TB Gold diagnosed with tuberculoma. (B) EDI-OCT showing large homogenous, hyporeflective choroidal granuloma (star) with subretinal fluid and 'contact sign' (arrow), defined as localized area of adhesion between RPE–choriocapillaris and overlying neurosensory retina, surrounded by an area of exudative retinal detachment. (C) ICGA revealing hypofluorescent lesion in early phase (C, left panel), remaining hypofluorescent in the late phase (C, right panel).

Figure 8 Ultra-wide field color fundus photograph of a patient diagnosed with bilateral tubercular vasculitis, showing vascular sheating involving the veins, with a characteristic perivascular patch of choroiditis in the superior temporal periphery (circle)

Figure 9 Ultra-wide field fluorescein angiography of the same eye as in figure 8 showing bilateral vascular leakage and bilateral leakage into the cystoid spaces suggestive of cystoid macular oedema.

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