An excursion into ocular tuberculosis

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Abstract:

Till today, ocular tuberculosis (OTB) presents clinicians with significant challenges in diagnosis and management. There is no one-size-fits-all approach to a heterogeneous disease like OTB, and clinicians often have to consider a multitude of factors when initiating treatment, such as tuberculosis endemicity, the probability of a true OTB diagnosis in the setting of nonspecific ocular features, the effective duration of treatment, and the likelihood of vision-threatening complications in the patient. It is no wonder that treatment protocols are widely varied globally. There have been recent developments in the standardization of nomenclature and therapeutic strategies for OTB, as established by the Collaborative OTB Study Working Group. In this review, we referred to findings in retrospective studies, international clinical guidelines, and OTB consortiums, to explore the clinical presentations, investigations, and updated management principles for patients with presumed tubercular uveitis.

Keywords:

Antitubercular therapy, mycobacteria, ocular tuberculosis, tubercular uveitis

Introduction

Tuberculosis (TB) has been referred to as the second "great imitator," as it commonly mimics other disease processes and confounds clinical decision-making. In Saudi Arabia, TB remains endemic, with an incidence rate of 9.9 cases/100,000 population in 2019, consisting 67.7% pulmonary TB cases and 32.3% extrapulmonary TB cases. Particularly in TB endemic areas, it is important to have a high index of suspicion and be cognizant of atypical presentations of TB, especially in extrapulmonary sites. Although ocular TB (OTB) is an uncommon manifestation of extrapulmonary disease, it should not be underestimated as its potential visual impairment is highly preventable with appropriate treatment.

The management of OTB poses a significant challenge due to atypical and heterogeneous presentations, and a lack of agreement on diagnostic tests or treatment protocols.[1-4] This review aims to provide an updated summary of current perspectives of tubercular uveitis (TBU), discuss new recommendations for management, and highlight potential areas for future exploration.

Methodology

Relevant publications were retrieved through an online database search with keywords of "uveitis," "ocular tuberculosis," "intraocular tuberculosis," and "anti-tubercular therapy." Search results were evaluated for relevance. Journal articles, clinical guidelines, electronic books, web pages, and commentaries published in English were referenced, and studies of the pediatric population were filtered out. References cited within the identified articles were also consulted. The time limit for study inclusion was the year 2000. Information extracted from the publications included definitions, epidemiological data, clinical manifestations, diagnostic methods, management techniques, and treatment outcomes.

Epidemiology

TBU is the most common ocular manifestation of TB[5] and remains prevalent in Saudi Arabia. In a retrospective study of 600 eyes done by Al-Mezaine *et al*., the most commonly identifiable specific diagnosis was presumed TBU,[6] Similarly, Al Dhahri *et al*. found that TBU was among the most frequently diagnosed

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etiology of uveitis.[7] Further studies of TBU prevalence in endemic and nonendemic countries are listed in Table 1.

Definitions

TB is a clinical disease caused by infection with *Mycobacterium* TB (MTB). The Collaborative OTB Study (COTS) Nomenclature Working Group[25] proposed standardization of OTB nomenclature in 2018. The group deemed that OTB represents ocular inflammation attributed to TB, based on positive immunological tests and radiological tests, with or without positive culture or polymerase chain reaction results. Under the umbrella of OTB, TBU represents intraocular inflammation. TBU can be divided into anatomical subgroups, namely tuberculous anterior uveitis (TAU), tubercular intermediate uveitis (TIU), tubercular posterior uveitis (TPU), tubercular panuveitis, and tubercular retinal vasculitis (TRV). The anatomical nomenclature of TBU by COTS is represented in Table 2.

More recently in 2021, the Standardization of Uveitis Nomenclature (SUN) Working Group[26] evaluated 277 cases of TBU by machine learning against other uveitides. Key criteria for TBU were a compatible uveitic syndrome, including (1) anterior uveitis with iris nodules, (2) serpiginous-like tubercular choroiditis, (3) choroidal nodule (tuberculoma), (4) occlusive retinal vasculitis, and (5) in hosts with evidence of active systemic TB, multifocal choroiditis. In addition, evidence of TB was required, including histologically or microbiologically confirmed infection, positive interferon-γ release assay test, or positive tuberculin skin test. The overall accuracy of the diagnosis of TBU in the validation set was 98.2% (95% confidence interval [CI] 96.5–99.1). Hence, the COTS Nomenclature study[25] focused on the clinical consensus of defining anatomical locations of the disease, while SUN[26] focused on automated classification of TBU with data input into an algorithm.

History Taking

A full past medical history and social history comprises screening for: (1) symptoms of pulmonary TB such as fever, chronic cough, hemoptysis, night sweats, unintentional weight loss, anorexia and (2) potential exposure risks, such as a history of treated TB, HIV status, travel to TB endemic countries and contact with active TB patients. For ocular symptoms, blurred vision and light sensitivity are most commonly reported. Other complaints include flashes, floaters, or eye redness. Patients with posterior segment disease are more likely to be visually symptomatic and seek early medical attention.[27] Importantly, lesions in the peripheral fundus may be asymptomatic and escape medical attention, hence the absence of ocular symptoms does not rule out TBU.

Clinical Signs of Tubercular Uveitis

A patient's clinical manifestation of TBU is a result of his immune system's reaction to the degree of MTB bacterial load. This can account for the wide spectrum of ocular signs. The most common clinical presentation is TPU,[28-30] followed by anterior uveitis, panuveitis, and intermediate uveitis.[1,31] TBU can also manifest as retinitis, optic neuropathy, endophthalmitis or panophthalmitis, although less commonly.[32] An overview of selected TPU subtypes is illustrated in Figure 1.

TPU [Figure 4] classically presents as TB choroiditis, which is either focal or multifocal, and unilateral or bilateral. Multifocal TB Choroiditis manifests most commonly as choroidal

Table 1: Prevalence of tuberculous uveitis in different countries with different tuberculosis burden

Author	Year	Country*	Cases with uveitis	Percentage uveitis cases attributed to TB (%)	Incidence of pulmonary TB (per 100 000 people)†
Biswas *et al*.[8]	2018	South India	352	79 (22.4)	193
Nguyen *et al*.[9]	2017	Vietnam	212	19 (9)	176
Pathanapitoon *et al*.[10]	2008	Thailand	200	3 (2.2)	150
Yang *et al*.[11]	2005	China	1752	13 (0.7)	58
Siak *et al*.[12]	2017	Singapore	1249	84 (6.7)	41
Khairallah *et al*.[13]	2007	Tunisia	472	5 (1.1)	35
Kazokoglu *et al*.[14]	2008	Turkey	761	3 (0.3)	16
Kianersi *et al*.[15]	2015	Iran	2016	4 (0.2)	13
Nakahara *et al*.[16]	2015	Japan	468	7 (1.5)	13
Abdulaal *et al*.[17]	2015	Lebanon	209	12 (5.7)	13
Amin *et al*.[18]	2019	Egypt	414	20 (4.4)	12
Al Dhahri *et al*.[7]	2015	Saudi Arabia	642	114 (17.8)	10
Al-Mezaine *et al*.[6]	2010	Saudi Arabia	351	99 (28.2)	10
Llorenç Bellés *et al*.[19]	2012	Spain	416	25 (6)	9
Sanghvi *et al*.[20]	2011	UK	2368	45 (1.9)	8
Luca *et al*.[21]	2018	Italy	990	56 (5.7)	7
Zagora *et al*.[22]	2017	Australia	1165	49 (4.2)	7
Vos *et al*.[23]	2013	Netherlands	585	66 (11.3)	5
Ducommun *et al*.[24]	2012	Switzerland	654	12 (1.8)	5

*Tuberculosis-endemic regions are highlighted in bold, †Most recent year of documentation: 2019

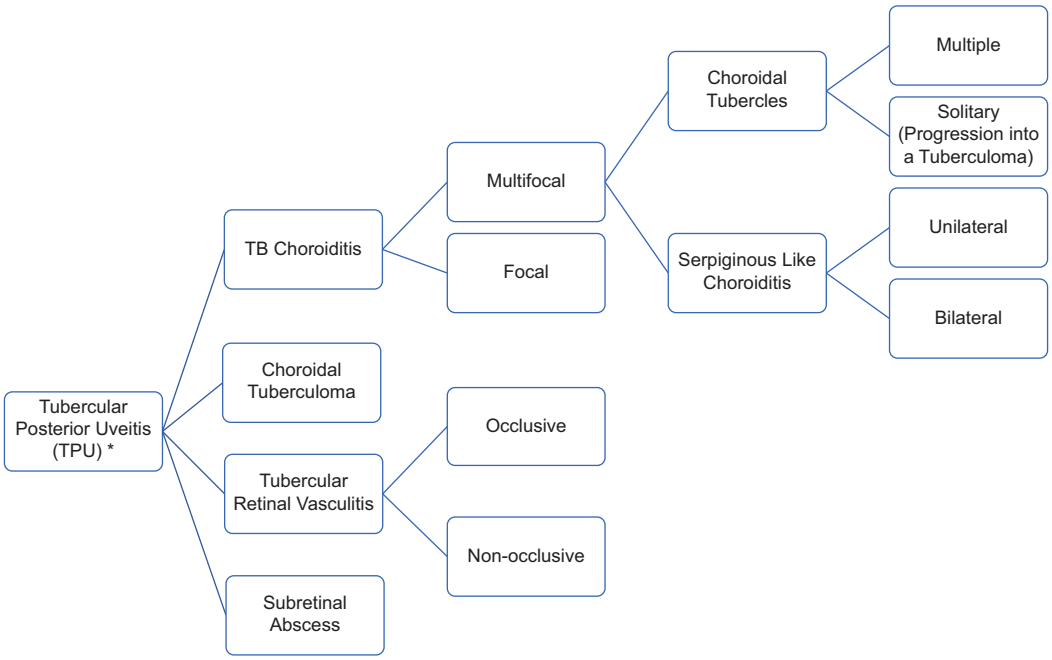

Figure 1: Overview of tubercular posterior uveitis subtypes. *The most common features of tubercular posterior uveitis are highlighted in bold

Table 2: Anatomical nomenclature of tubercular uveitis by collaborative ocular tuberculosis study

Anatomic group	Definition (adapted from Agrawal *et al*.[25])
Tubercular anterior uveitis	Inflammation is confined to the anterior segment, primarily in the anterior chamber: iris and ciliary body
Tubercular intermediate uveitis	Inflammation primarily involves the vitreous (pars plana, posterior ciliary body, and hyalitis)
Tubercular posterior uveitis	Inflammation is primarily involves the retina and/or the choroid
Tubercular panuveitis	Inflammation involves the anterior chamber, vitreous, and retina/choroid

tubercles, which is associated with the hematogeneous spread of TB bacilli.[1] Tubercles are typically small, gray-yellowish nodules at the posterior pole, showing early hypofluorescence and late staining on fluorescein angiography.[33] Choroidal tubercles may progress into larger choroidal tuberculomas, which are yellowish subretinal lesions with indistinct borders and surrounding exudative fluid.[31,34] Other forms of Multifocal TB choroiditis include serpiginous-like choroiditis (SLC) [Figure 3]. SLC is yellowish lesions that start off discrete and progress to a contiguous form, typically with mildly raised and actively advancing edges.[35] Unlike classic serpiginous choroiditis, SLC typically does not extend to the optic disc, is fovea sparing, but is associated with vitritis.[25,36,37] Gupta *et al*. have suggested that SLC represents a hypersensitivity reaction to MTB antigens[1] from a distant focus, such as the lungs.

Another subset of TPU includes TRV, which is almost always a result of the choroidal extension. It is often occlusive and presents as retinal periphlebitis. Often, there is perivascular sheathing – inflammatory exudates around the vessels – and retinal hemorrhages. Retinal vein occlusion creates an ischemic environment, potentially leading to neovascularization that may be further complicated by vitreous hemorrhage, tractional retinal detachment, rubeosis iridis, and neovascular glaucoma.[31]

Tuberculous anterior uveitis (TAU) is usually a granulomatous inflammation with iris nodules, mutton-fat keratic precipitates, and broad-based posterior synechiae. TAU may lead to complications of cataracts, secondary to chronic inflammation and prolonged corticosteroid use.[31] Next, TIU exists as mild-to-moderate vitritis with inferior snowball opacities (clusters of leukocytes), and peripheral vascular sheathing. TIU is frequently complicated by cystoid macular edema.[1,38]

Across the spectrum of anatomical subtypes for TBU, severe visual impairment was found to be largely attributed to vitreous hemorrhage, complicated cataracts, and macular scarring.[39] A breakdown of the prevalence of other TBU complications is shown in Table 3.

Features predictive of visual morbidity

Clinical signs of TBU are useful in predicting visual morbidity at follow-up. If these signs are present at baseline, it may warrant closer monitoring of the patient for disease progression or development of complications. Gunasekeran *et al*.[27] found that clinical phenotypes more likely to be associated with blindness at follow-up were posterior uveitis/panuveitis (7.14%), anterior uveitis (3.67%), and retinal vasculitis (2.40%). This was supported by Basu *et al*.,[39] who found that moderate-to-severe visual impairment was most commonly found in eyes with multifocal serpiginoid choroiditis (100%), panuveitis (80%), and retinal vasculitis (80.6%).

Features predictive of tubercular uveitis diagnosis

The diagnosis of TBU can be difficult and it is helpful to look out for features with high specificity for TBU. These include

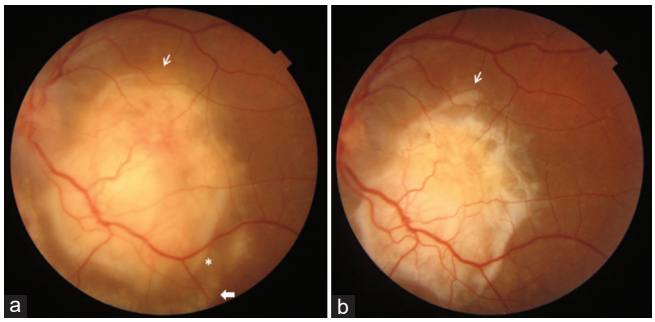

Figure 2: Fundus photograph (Topcon, Tokyo, Japan) of a patient with tubercular choroidal granuloma. At presentation, the lesion had fuzzy margins (white arrow), with surrounding subretinal fluid (asterisk) and exudation (double arrow) (a). The patient was treated with intravitreal Ranibizumab (0.5mg/0.05 ml) injection, oral steroids, and anti-tuberculous therapy. Following treatment, there occurred involution of lesion with margins becoming well defined and resolution of surrounding subretinal fluid and exudation (b)

broad posterior synechiae, occlusive retinal vasculitis, and SLC.[3,41] Furthermore, choroidal granulomas [Figure 2] are the most well-recognized sign of intraocular TB and should raise a high index of suspicion for the diagnosis.[3,42] In the setting of TRV, perivascular choroidal pigment or small choroiditis patches are also suggestive signs of tubercular etiology.[43]

Diagnosis of Tubercular Uveitis

The diagnosis of TBU should be centered on a detailed clinical history and systems review, a full ophthalmologic examination, and laboratory and ancillary tests. A definitive diagnosis of TBU is only made when ocular fluids are positive for the culture of MTB; however, this is rare due to the paucibacillary nature of TBU.[42] In most cases, only a diagnosis of presumed ocular TB can be made, with suggested diagnostic criteria by the COTS Working Group listed in Table 4.

In the absence of definitive evidence of a tubercular etiology, responsiveness to anti-tuberculous therapy (ATT) may also suggest a diagnosis of TBU. In a retrospective study done by Sanghvi *et al*.,[20] recovery of "atypical" uveitis such as nongranulomatous anterior uveitis was observed after ATT, suggesting that TBU cannot be excluded as a differential in the absence of characteristic features. Response to ATT within 6 weeks of initiating therapy without recurrences has been included in the diagnostic criteria of other studies.[1,45]

Investigations

Baseline immunological testing comprises the tuberculin skin test (TST) and interferon-gamma release assay (IGRA). Both tests assess cell-mediated immunity, which usually occurs when the person has had exposure to MTB. TST detects a Type IV hypersensitivity skin reaction toward mycobacterium antigens such as tuberculin, while IGRAs evaluate interferon-ɣ release after *in vitro* stimulation of patients' lymphocytes with MTB-specific antigens. Unfortunately, TST and IGRA do not distinguish active from latent TB. Several studies have reported that IGRAs are more specific than TST, whereas

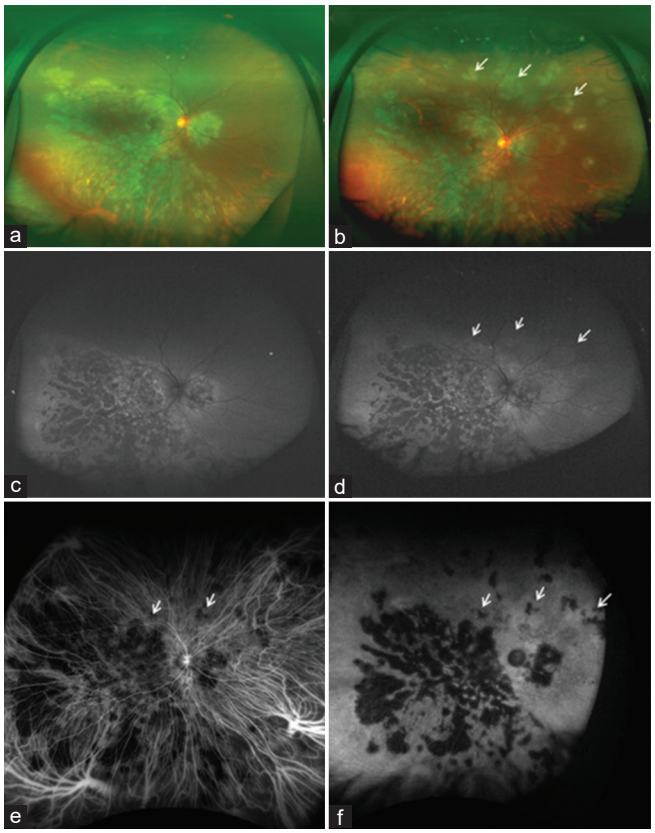

Figure 3: A 19-year-old Asian Indian male, diagnosed with tubercular Serpinginous Like Choroiditis (a) developed paradoxical worsening while on treatment with ATT and oral steroids. Fresh choroiditis lesions are seen superiorly and nasally (b) (white arrows) (Optos California ultra-widefield imaging 200 DTx icg, Scotland, United Kingdom). Corresponding fundus autofluorescence (FAF) (c) shows hyperautoflourescence (d). Indocyanine Green Angiography shows hypocyanescent lesions (e) which remain hypocyanescent in later phases of angiogram (f) (white arrows)

there were varied results when comparing the sensitivities of IGRA and TST. In India, a country with a high TB burden, QFT was superior to TST in both specificity and sensitivity.[46] On the contrary, in a country with an intermediate TB burden like Singapore, Ang *et al*. reported that TST has a higher sensitivity, while T-SPOT. TB has a higher specificity for TBU. They recommended using both tests in tandem to increase the positive predictive value for TBU.[47]

Limitations of laboratory investigations

There is currently no gold standard diagnostic laboratory test; the presence of a compatible form of uveitis and a positive TST or IGRA test is taken as a presumptive diagnosis of TBU. However, this approach is potentially problematic in TB-endemic areas. For instance, 40% of the population in India have positive TST or IGRA results, with most having either latent TB or cleared TB. In patients with uveitis, latent TB may merely be an unrelated and confounding association, and other etiologies of uveitis may have yet to be detected.[48] Moreover, false-positive rates are an issue in both TST and IGRA. TST is limited by a high

Table 3: Complications of intraocular tuberculosis in different countries

Author	Year	Country	CME, *n* (%)	Cataract, *n* (%)	Glaucoma, *n* (%)	Epiretinal membrane, *n* (%)	Retinal vein occlusion, *n* (%)	Choroidal neovascular membrane, *n* (%)	Total (*n*)
Gunasekeran *et al*.[27]	2018	United Kingdom	107 (30.5)	71 (20.1)	99 (28.1)	28 (7.91)	13 (3.67)	6 (1.7)	354 patients
Al-Qarni *et al*.[30]	2019	Saudi Arabia	47 (33.3)	20 (14.2)	11 (7.8)	NA	NA	4 (2.8)	141 eyes
Al Dhahri *et al*.[7]	2015	Saudi Arabia	53 (24.9)	41 (19.2)	18 (8.5)	13 (6.1)	3 (1.4)	2 (0.9)	213 eyes
Basu *et al*.[39]	2014	India	5 (7.5)	10 (15)	2 (3)	2 (3)	NA	NA	61 eyes
La Distia Nora *et al*.[40]	2014	Netherlands	34 (45)	12 (16)	18 (24)	NA	NA	8 (10)	77 patients
Llorenç Bellés *et al*.[19]	2012	Spain	13 (22.4)	23 (39.6)	14 (24.1)	NA	NA	10 (17.2)	58 eyes

NA: Not applicable, CME: Cystoid macular edema

Table 4: Diagnostic criteria for intraocular tuberculosis (Adapted from Agrawal *et al*.[44])

Patients have to satisfy 1 and 2, along with either 3 or 4
Clinical signs suggestive of ocular tuberculosis
Exclusion of other etiologies of uveitis - based on epidemiology, history, and physical examination
Investigations documenting mycobacteria
AFB shown on microscopy, or MTB grown in culture of ocular fluid
Positive PCR from ocular fluid for IS 6110 or other conserved sequences in the mycobacterial genome
Evidence of active pulmonary or extrapulmonary tuberculosis on microscopy or culture of tissue involved
Corroborative investigations
Positive TST
Positive IGRA
QuantiFERON-TB Gold (QFT) (Cellestis, Australia) or
ELISpot assay (T-SPOT.TB) (Oxford Immunotec, Oxford, UK)
Evidence of healed or active TB on Chest X-ray

AFB: Acid-Fast Bacilli, TST: Tuberculin skin test, IFRA: Interferon-gamma release assay, PCR: Polymerase chain reaction, TB: Tuberculosis, QFT: QuantiFERON-TB gold, ELISpot: Enzyme-linked immunosorbent spot

false-positive rate in patients who were immunized with the Bacillus Calmette-Guerin vaccine or patients exposed to nontuberculous mycobacteria.[49] In addition, IGRA has a low pretest probability in settings of low clinical suspicion, and approximately 90% of positive IGRAs can be false positives.[50] To avoid being misled by immunological tests, it is important for treating ophthalmologists to order them selectively and only screen for TB in cases of clinical suspicion: patients with unexplained uveitis and risk factors for TB, and patients with disease that is unresponsive to conventional therapy[31] or associated with multiple recurrences despite corticosteroid treatment.[1] Importantly, stand-alone positive immunological tests without supportive clinical signs should not be taken as an indication of ATT, in view of the high false-positive rates and potential side effects of ATT. Clinicians must guard against over-treating patients with ATT and perpetuating TB drug resistance.

Imaging

TBU commonly occurs without any clinical signs of pulmonary involvement.[28] Nonetheless, chest X-rays are useful in providing evidence of pulmonary TB and guiding the initiation of ATT if positive. In addition, Lee *et al*.[3] reported that a high resolution computed tomography (CT) scan of the chest has increased detection of chest involvement in patients with normal chest

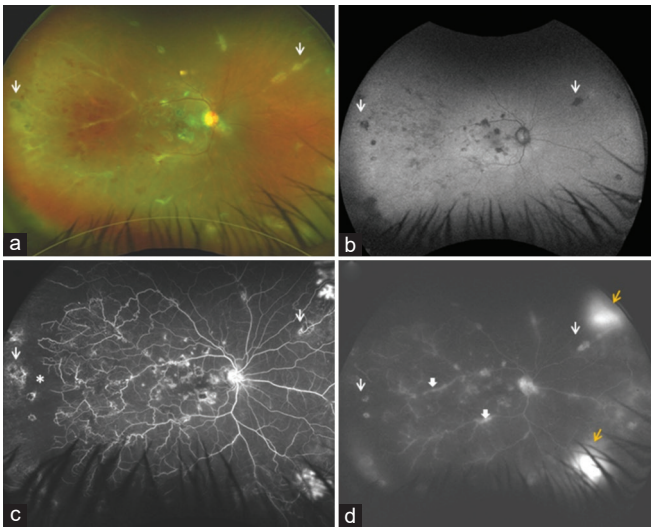

Figure 4: Fundus photograph (Optos California ultra-widefield imaging 200 DTx icg, Scotland, United Kingdom) of a patient with Tubercular Posterior Uveitis showing perivascular choroiditis scars (a) (white arrows) which appear hypoautofluorescent on fundus autofluorescence (b). Fundus fluorescein angiography shows focal phlebitis (double arrows) along with capillary non-perfusion due to occlusive vasculitis (asterisk) and leakage from peripheral neovascularisation (yellow arrows) (c and d). Staining of perivascular choroiditis scars (white arrows) is seen

radiographs and presumed OTB. Chest CT and positron-emission tomography (PET) scans can provide valuable anatomical and functional information, such as the degree of lymphadenopathy or lymph node metabolic activity, that would help identify suitable lesions for biopsy to establish the TB diagnosis and subsequent TBU treatment.[51] Treating ophthalmologists should discuss the indications for CT or PET scans with infectious disease colleagues when clinical suspicions of chest involvement are high. Admittedly, these imaging modalities may not be comparable to chest X-rays in cost-effectiveness.

Treatment

The aim of TBU treatment is to prevent visual loss as a sequela of long-term inflammation. It is advisable to collaborate with an infectious disease expert or pulmonologist in managing the case of TBU. The pulmonologist can help to ascertain the pathogenesis of disease, determining whether the patient's uveitis is (1) unrelated to a concurrent latent TB infection (LTBI), (2) caused by active intraocular

infection of MTB, (3) a hypersensitivity response to distant TB organisms[52] or (4) the result of reactivation of latent ocular MTB infection. There is a possible role for pathogenesis-directed treatment: in cases of direct ocular infection of MTB, typically in patients with choroidal tubercles, treatment would center upon elimination of MTB from the eye via ATT. In hypersensitivity-driven cases, such as in patients with SLC, the goal would be to control the inflammatory response via corticosteroids or other steroid-sparing immunosuppressants.

When to start anti-tuberculous therapy?

There is a current lack of consensus on the therapeutic regimen and the length of treatment of TBU with ATT; management of TBU is still widely heterogeneous and dependent on the country's local management protocols. Recently, the COTS Working group[53] addressed these uncertainties by developing consensus guidelines for the initiation of ATT for specific clinical phenotypes in the setting of different TB burdens. Eighty-one international uveitis experts were consulted. In an endemic region, whenever one of the immunologic tests (TST or IGRA) shows positive results along with a positive radiologic test (Chest X-ray or CT), experts moderately agreed to initiate ATT, particularly for the TBU subtypes of recurrent anterior uveitis, intermediate uveitis, active retinal vasculitis, and panuveitis. Specifically for patients presenting with the first episode of TAU, experts agreed to initiate ATT only if TST, IGRA, and radiographic tests were positive. For patients with TB posterior uveitis, experts agreed to initiate ATT if there was at least one positive immunologic test together with positive radiologic signs, regardless of the country's TB endemicity. Future long-term prospective studies can explore the decision to initiate ATT in the absence of positive radiologic signs but with supportive clinical and immunological evidence, especially in the context of latent TB.

Special considerations for latent tuberculosis

According to the World Health Organization (WHO), LTBI is a state of persistent immune response to stimulation by MTB, without evidence of clinically manifested active TB. Most patients with TBU have isolated positive immunological tests, with no evidence of systemic TB disease[48] and nonspecific signs of ocular inflammation.[41] These patients represent latent TB cases with concomitant uveitis that may or may not be related, and the decision to initiate ATT in these cases is not always straightforward. Often, patients with uveitis and no other underlying disease other than LTBI are still not treated with ATT, after consultation with ID physicians.[54] Currently, the WHO recommends treatment for LTBI to be initiated primarily in populations at-risk of disease activation, such as people living with HIV. In patients with uveitis and latent TB, studies have shown that ATT may still be indicated, even if they do not have risk factors of disease activation. In India, Bansal *et al*. have reported that patients with latent TB and uveitis have benefitted from combined ATT and corticosteroid therapy, with a significantly lower recurrence rate of 15.74%, compared to that of 46.53% for the group receiving only corticosteroid therapy.[48] Notably, 15 out of 216 patients included in the combined therapy group had manifest systemic TB. Likewise, in Singapore, Ang *et al.* found that patients with uveitis and latent TB who received ATT for at least 9 months had an 11-fold reduction in the likelihood of recurrence.[54] Similar findings are documented in TB nonendemic countries such as the Netherlands[40] and the United Kingdom (UK).[20] A possible mechanism for the effectiveness of ATT in treating uveitis with latent TB is its ability to limit MTB load within the eye or in distant sites, thereby reducing hypersensitivity reactions and recurrences of intraocular inflammation. Ultimately, the long-term outcome of patients with uveitis who receive the full course of anti-tubercular therapy for latent TB remains unknown and warrants further exploration.

How long to treat for?

The recommended standard 4-drug regimen includes isoniazid, rifampicin, ethambutol, and pyrazinamide daily for 2 months, followed by both isoniazid and rifampicin for 4 months.[55] Till date, there is a lack of consensus on the ideal duration of ATT and the endpoint of treatment. In most studies, ATT is administered for at least 6 months, with some centers extending treatment up to 18 months.[48] The Centers for Disease Control and Prevention recommends prolonged ATT of at least 9 months in (1) patients with disease affecting extra-pulmonary sites with slower response to therapy, such as in OTB, and (2) in patients with a higher risk of relapse, indicated by the presence of cavitary pulmonary disease and/or sputum culture-positivity after 2 months of treatment.[56] A study done in the UK reported that a longer duration of ATT of at least 9 months was associated with a lower treatment failure rate.[57] This is supported by Ang *et al*., who found that shorter, 6-month treatment duration was less effective in reducing recurrences after ATT cessation. Even though many of their patients had quiescent inflammation and could be weaned off ATT at 6-months, recurrences were seen months after stopping ATT.[54] Further studies of recurrence rates and associated treatment duration are reflected in Table 5.

Regardless of the finalized treatment duration, regular follow-up on the patient's response to ATT is essential, to prevent unwarranted treatment with ATT and avoid unnecessary ATT side effects. In a recent meta-analysis, Kee *et al*. analyzed 28 studies evaluating the effect of ATT on 1917 patients with OTB. They documented that ATT led to successful outcomes in more than 70% of patients and evident improvement within 2 weeks to 3 months. The authors suggest a careful reassessment of the patient after 2–3 months of therapy to determine if treatment is effective. In patients with a lack of response, it may be prudent to identify second-line therapy or consider differential diagnoses,[33] after excluding noncompliance to medication or TB drug resistance.

Phenotypes that increase the risk of treatment failure include vitreous haze, snow banking, and choroidal involvement;[4] conversely, features associated with successful treatment

Table 5: Duration of Treatment and Recurrence Rates

	Year	Population	Duration of treatment (ATT±corticosteroids)	Time post initiation of treatment	Recurrence rate, *n* (%)
Jiang *et al*.[58]	2021	China	12-18 months	12-18 months	2 (3)*
Al-Qarni *et al*.[30]	2019	Saudi Arabia	9 months	4-10 months	2 (2.2)
La Distia Nora *et al*.[40]	2014	Netherlands	6-9 months	3 years	1 (3.13)
Sanghvi *et al*.[20]	2011	United Kingdom	6 months	6 months	6 (22.2)†
Bansal *et al*.[48]	2008	India	15-18 months	6 months	34 (15.74)

*Jiang *et al*. reported that the patients with recurrence only underwent ATT for 6 months as they stopped treatment against the physician's recommendations, †5 patients developed recurrent anterior uveitis at a mean of 0.2 months after ATT cessation. ATT: Anti-tuberculous therapy

include monocular involvement, posterior uveitis, normal chest X-ray, and the absence of vitreous haze.[59]

Steroids

Corticosteroids are given to reverse insult from granulomatous inflammation and to limit intraocular damage caused by delayed-type hypersensitivity to TB antigens.[60] Existing literature has emphasized the importance of combined ATT and corticosteroid therapy, as exclusive use of steroids may induce the reactivation of latent disease or prolong the active growth of MTB in the eye.[1,61] Different routes of corticosteroid administration have been suggested for different anatomical subtypes of TBU, as reflected in Table 6. Al-Qarni *et al*. have documented that combined usage of ATT and systemic corticosteroids resulted in resolution of inflammation and macular edema with significant improvement in visual acuity.[30] Other studies have also reported favorable responses to combined ATT and corticosteroid therapy,[1,62] such as elimination of recurrences of TBU.[45] The benefits of corticosteroid usage ought to be weighed against the risk of developing steroid-associated complications such as cataracts – typically the posterior subcapsular subtype. In addition, the rare phenomenon of paradoxical worsening is a cause for concern – clinicians should monitor for clinical deterioration and the formation of new retinal or subretinal lesions on serial examination. The addition of oral prednisolone 25 mg once daily (followed by slow tapering) in patients with paradoxical worsening might prove useful.

Defining treatment success

Treatment would be deemed a success if there is the elimination of uveitis, prevention of TBU visual morbidity, and no significant treatment toxicity. The COTS Nomenclature Working Group[63] has defined "*remission*" to be inactive disease (grade 0 cells/no inflammation) for at least 3 months after a complete course of ATT. "*Cure*" would entail inactive disease 24 months after a complete course of ATT. These concepts may be a valuable endpoint in future trials of OTB and can potentially be used as discharge criteria for patients.

Conclusion

TBU remains a highly complex but treatable disease, with great potential for preserving ocular function and quality of life. The diagnosis and management of TBU poses a significant challenge and can only be surmounted by tight collaboration between ophthalmologists, and respiratory and infectious disease physicians. Prospective clinical trials are needed to better understand the associations between various phenotypes and treatment outcomes, and whether close follow-up without administration of therapy is a suitable option in mild, nonvision-threatening TBU cases.

Table 6: Recommended route for corticosteroid administration[48,52]

Predominant anatomic subtype	Recommend route
Anterior/intermediate uveitis	Local (topical and/or periocular)
Posterior uveitis	Systemic (oral)*
Panuveitis	Both local and systemic

*Oral dose: 1 mg/kg/day initially, tapered off over 4-6 weeks

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Conflicts of interest

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