Progress in Retinal and Eye Research 95 (2023) 101189

Contents lists available at ScienceDirect

Progress in Retinal and Eye Research

journal homepage: www.elsevier.com/locate/preteyeres

The immune response in tubercular uveitis and its implications for treatment: From anti-tubercular treatment to host-directed therapies

Ikhwanuliman Putera [a,b,c,d,*], Benjamin Schrijver [c], Josianne C.E.M. ten Berge [a], Vishali Gupta [e], Rina La Distia Nora [c,d], Rupesh Agrawal [f,g,h,i,j], P. Martin van Hagen [b,c], Saskia M. Rombach [b,1], Willem A. Dik [c,1]

[a] Department of Ophthalmology, Erasmus University Medical Center, Rotterdam, the Netherlands
[b] Department of Internal Medicine, Section Allergy and Clinical Immunology, Erasmus University Medical Center, Rotterdam, the Netherlands
[c] Laboratory Medical Immunology, Department of Immunology, Erasmus University Medical Center, Rotterdam, the Netherlands
[d] Department of Ophthalmology, Faculty of Medicine, Universitas Indonesia, Cipto Mangunkusumo Hospital, Jakarta, Indonesia
[e] Retina and Uvea Services, Post Graduate Institute of Medical Education and Research (PGIMER), Chandigarh, India
[f] National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore
[g] Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[h] Ophthalmology and Visual Sciences Academic Clinical Program, Duke NUS University, Singapore
[i] Singapore Eye Research Institute, Singapore
[j] Moorfields Eye Hospital, London, United Kingdom

ARTICLE INFO

Keywords:
Anti-tubercular treatment
Autoimmunity
Host-directed therapies
Tubercular uveitis
Tuberculosis

ABSTRACT

Tubercular uveitis (TB-uveitis) remains a conundrum in the uveitis field, which is mainly related to the diverse clinical phenotypes of TB-uveitis. Moreover, it remains difficult to differentiate whether *Mycobacterium tuberculosis* (*Mtb*) is present in the ocular tissues, elicits a heightened immune response without *Mtb* invasion in ocular tissues, or even induces an anti-retinal autoimmune response. Gaps in the immuno-pathological knowledge of TB-uveitis likely delay timely diagnosis and appropriate management. In the last decade, the immunopathophysiology of TB-uveitis and its clinical management, including experts' consensus to treat or not to treat certain conditions with anti-tubercular treatment (ATT), have been extensively investigated. In the meantime, research on TB treatment, in general, is shifting more toward host-directed therapies (HDT). Given the complexities of the host-*Mtb* interaction, enhancement of the host immune response is expected to boost the effectiveness of ATT and help overcome the rising burden of drug-resistant *Mtb* strains in the population. This review will summarize the current knowledge on the immunopathophysiology of TB-uveitis and recent advances in treatment modalities and outcomes of TB-uveitis, capturing results gathered from high- and low-burden TB countries with ATT as the mainstay of treatment. Moreover, we outline the recent progress of HDT development in the pulmonary TB field and discuss the possibility of its applicability to TB-uveitis. The concept of HDT might help direct future development of efficacious therapy for TB-uveitis, although more in-depth research on the immunoregulation of this disease is still necessary.

1. Introduction

Tuberculosis (TB) is a major infectious uveitis cause, especially in countries with high TB endemicity.(Tsirouki et al., 2018) Tubercular uveitis (TB-uveitis),(Agrawal et al., 2019) the term used to describe intraocular inflammation due to proven and presumptive *Mycobacterium tuberculosis* (*Mtb*) infection, is responsible for about 22.9–48.0% of infectious uveitis in India and Indonesia.(La Distia Nora et al., 2018a; Putera et al., 2022; Tsirouki et al., 2018) The visual morbidity of TB-uveitis can be severe. It has been reported that the best visual acuity of nearly one-third of TB-uveitis patients was worse than 3/60.(Basu et al., 2014) Another report found that uveitic macular edema and

* Corresponding author. Department of Ophthalmology and Internal Medicine, Section Allergy and Clinical Immunology, Erasmus University Medical Center, Dr. Molewaterplein 40, 3015 GD, Rotterdam, the Netherlands.
E-mail address: i.putera@erasmusmc.nl (I. Putera).
[1] Shared last authorship.

https://doi.org/10.1016/j.preteyeres.2023.101189
Received 7 March 2023; Received in revised form 23 May 2023; Accepted 24 May 2023
Available online 25 May 2023

secondary glaucoma might develop in around 30% of TB-uveitis patients.(Gunasekeran et al., 2018) Meanwhile, the prevalence of TB-uveitis, based on positive interferon-gamma release assay (IGRA) results and exclusion of other entities in non-endemic countries, is low. (Alli et al., 2022) However, the proportion of unknown causes of uveitis was higher in IGRA-positive than in IGRA-negative individuals (59% vs 39%).(Groen-Hakan et al., 2020) This stresses the difficulty of assigning a definitive diagnosis of TB-uveitis to a patient presenting with active uveitis and a positive IGRA but without other ancillary tests or findings supportive of TB infection.

There has been a significant advancement in TB-uveitis diagnosis during the past decade, as indicated by the emergence of new criteria and expert consensus.(Agrawal et al., 2021a; Jabs et al., 2021) However, the dilemmatic aspect of TB-uveitis diagnostics has still not come to an end, particularly when facing patients with the absence of active pulmonary or other extrapulmonary TB.(Testi et al., 2020) Caseating granuloma formation in ocular tissue has been described.(Basu et al., 2015; Wroblewski et al., 2011) Yet, the pathomechanisms underlying TB-uveitis are so far incompletely understood. It was proposed that ocular inflammation can be caused by: (1) direct *Mtb* infection of ocular tissues, (2) the induction of specific anti-retinal immune responses or an immunological reaction toward *Mtb* antigen (without live *Mtb* in the eye) or (3) a combination of those mechanisms. Although the different underlying mechanisms of TB-uveitis may benefit from different treatment approaches, it is so far not possible to clinically distinguish between the different pathomechanisms that may underlie TB-uveitis. (Agrawal et al., 2021c; Basu et al., 2015, 2020; Ludi et al., 2023) This clearly emphasizes that improved pathophysiological knowledge of TB-uveitis is required to optimize diagnostic and treatment approaches for the future.

The conundrum of underlying pathogenesis and diagnostics in TB-uveitis reflects its management approach. Anti-tubercular therapy (ATT) remains the mainstay treatment for TB-uveitis.(Agrawal et al., 2021b) In many clinical circumstances, prescribing ATT is a dilemma when the diagnosis is still in doubt.(Agrawal et al., 2021b) Interestingly, systemic corticosteroid treatment without ATT may also resolve TB-uveitis in a fraction of patients who present without active pulmonary/extrapulmonary TB.(Kee et al., 2016) Moreover, the combination of ATT and systemic corticosteroid treatment is often necessary to obtain optimal treatment results.(Betzler et al., 2021; Kee et al., 2016) Another rising concern is the duration of ATT, which has not been standardized in TB-uveitis.(Ang and Chee, 2017) Some reports described the benefit of prolonging the ATT duration beyond six months.(Agrawal et al., 2015; Ang et al., 2012b) In many clinical scenarios, the lack of proof of *Mtb* presence from ocular samples in suspected TB-uveitis patients raises the possibility of an autoimmune response.(Bigdon et al., 2022) Given the long duration and potential adverse reactions to ATT, patient-specific inflammatory processes need to be understood. Patients can be treated appropriately and in a balanced way between enhancing *Mtb* clearance in ocular tissue and dampening excessive immune responses, including autoimmunity. Despite continuous efforts to advent more effective anti-TB drugs,(Singh and Mizrahi, 2017) host-directed therapy (HDT) has emerged to overcome the unresolved quest for antibiotics in TB. HDT specifically targets the host immune response to either (1) enhance *Mtb* elimination through modulation of host immunity against *Mtb,* such as by increasing efficiency of intracellular *Mtb* killing mechanisms, improving T-cell responses, and strengthening granuloma to limit *Mtb* dissemination, or (2) limit immunopathology caused by an exacerbated *Mtb*-directed immune response.(Kolloli and Subbian, 2017; Young et al., 2020) Although there is still limited available (pre-)clinical evidence,(Kiran et al., 2016; Young et al., 2020) HDT seems applicable to TB-uveitis. In this review, we will give an overview of the immunopathophysiology of TB-uveitis and summarize achievements made within current TB-uveitis management, including HDT and its possible future application for TB-uveitis.

2. Overview of immunopathophysiology of TB-uveitis

The current understanding of TB-uveitis pathogenesis relies on the concept that ocular inflammation relates to infection of ocular tissue by *Mtb* and anti-retinal autoimmune responses that may even occur without apparent ocular *Mtb* infection. A detailed description of these concepts has been provided previously.(Agrawal et al., 2021c; Basu et al., 2020) Here, we summarize relevant basic knowledge on pathogenesis with specific emphasis on the role of retinal pigment epithelium (RPE) in regulating the immune response in TB-uveitis.

2.1. The RPE in TB-uveitis

RPE is a monolayer of specialized epithelial cells that is located between the neurosensory retina and choroid (Fig. 1). It originates from the neuroectoderm and serves many physiological functions, including the transport of nutrients and metabolites between the adjacent layers and recycling retinol for the proper function of photoreceptors, for which the RPE cells also exhibit phagocytic activity with the routine task of clearing photoreceptor outer segment fragments.(Yang et al., 2021) Moreover, RPE constitutes the outer blood-retinal barrier (BRB). The latter function is critical for ocular immune privilege as the tight junctions between the RPE cells maintain the physical barrier toward externally eliciting stimuli, such as infectious pathogens (Fig. 1).(Yang et al., 2021)

Besides their regular physiological functions, RPE cells serve a pivotal immunological function by orchestrating innate and adaptive immune responses within the eye. Human RPE cells express toll-like receptors (TLRs), a set of conserved sensing receptors that play a crucial role in innate immunity by recognizing pathogen-associated molecular patterns derived from various microbes. Recognition of pathogens by TLRs initiates inflammatory cascades leading to the generation of pro-inflammatory cytokines and chemokines, including interleukin (IL)-6, IL-8 (chemokine C-X-C motif ligand (CXCL)-8), monocyte chemoattractant protein (MCP)-1, ICAM-1, CXCL9, CXCL10 and vascular endothelial growth factors (VEGF).(Detrick and Hooks, 2020) In addition, RPE cells express the C3a and C5a complement receptors. Activation of these receptors leads to the production of IL-1β, IL-6, IL-8, (MCP-1/CCL2), and granulocyte-macrophage colony-stimulating factor (GM-CSF).(Detrick and Hooks, 2020) RPE cells are also involved in regulating adaptive immune responses as they express human leukocyte antigens (HLA) classes I and II that can present non-self and self-antigens to T-lymphocytes.(Detrick and Hooks, 2020) Besides this, several lines of evidence point at an immunoregulatory function for RPE. For example, RPE can secrete interferon (IFN)-β, a type 1 IFN family member, that can suppress immune reactivity and exert a retinal protective effect to control the potentially detrimental effects of excessive inflammation.(Detrick and Hooks, 2020) Also, IFN-β suppresses CXCL-9 and intercellular adhesion molecule (ICAM)-1 expression in RPE. These IFN-β driven effects reduce BRB permeability during inflammation and limit the migration of immune cells, including T-lymphocytes and natural killer (NK) cells, into the eye.(Detrick and Hooks, 2020) Moreover, RPE cells can secrete α-Melanocyte-stimulating hormone and neuropeptide Y that enhance the apoptosis of activated effector T-lymphocytes.(Taylor et al., 2021).

2.2. Direct infection of Mtb in TB-uveitis

Mtb can reach ocular tissue through hematogenous dissemination from distant infection foci.(Agrawal et al., 2021c; Basu et al., 2020) Further investigation using a zebrafish model revealed that *Mtb* could seep into the eye despite an intact BRB. This was followed by monocyte infiltration and subsequent granuloma formation in retinal tissue. (Takaki et al., 2018) Another study showed that the capability of *Mtb* to enter retinal tissue by extracellular route is dependent on the mycobacterial ESX-1 secretion system.(Damera et al., 2021) The localized *Mtb*

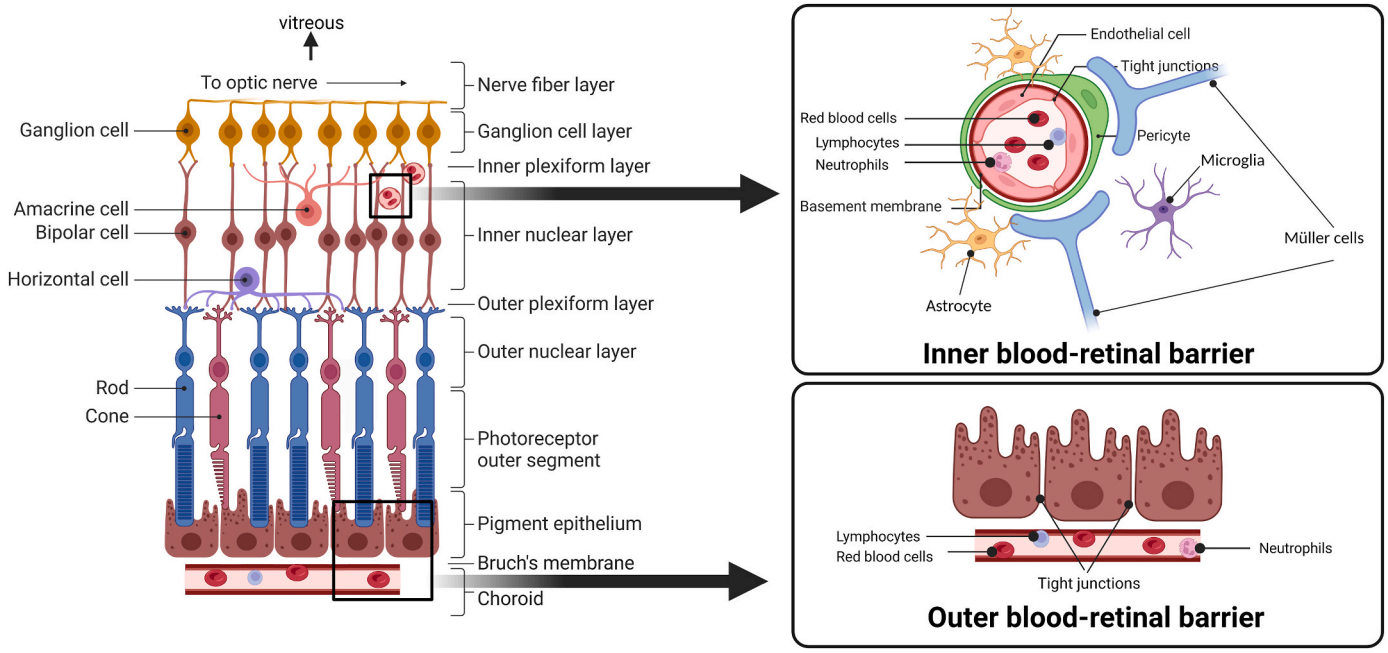

Fig. 1. Cellular components of retinal layers and blood-retinal barriers (BRB). Inner BRB, which regulate permeability of intraretinal capillaries, is composed by retinal endothelial cells, pericytes, and glial cells. Outer BRB, which control permeability of choriocapillaries, consists of tight junctions of retinal pigment epithelial cells. (Created with BioRender.com).

would result in granulomatous inflammation. It has been demonstrated that such inflammation could occur in cases where only a single *Mtb* bacillus was detected in the ocular specimen, particularly in the RPE layer.(Wroblewski et al., 2011) Another histopathological study also confirmed the presence of *Mtb* in necrotic RPE of the eye clinically seen as tuberculoma (choroidal granuloma) and serpiginous-like choroiditis. (Rao et al., 2006) RPE cells phagocytose the invading *Mtb* in the posterior segment of the eye (Fig. 2). TLR-2 and TLR-4 appear critical for *Mtb* infection, as blockage of these TLRs suppresses *Mtb* growth and proliferation in RPE.(Nazari et al., 2014) *Mtb*-infected RPE secrete various cytokines and chemokines (including IL-1β, IL-6, IL-8, tumor necrosis factor (TNF)-α, IFNs, CXCL9, CXCL10, and CXCL11 and attract immune cells, including neutrophils, NK cells, and T lymphocytes. (Agrawal et al., 2021c; Detrick and Hooks, 2020; La Distia Nora et al., 2018d) *Mtb*-infected RPE appeared to be more immunoregulatory than

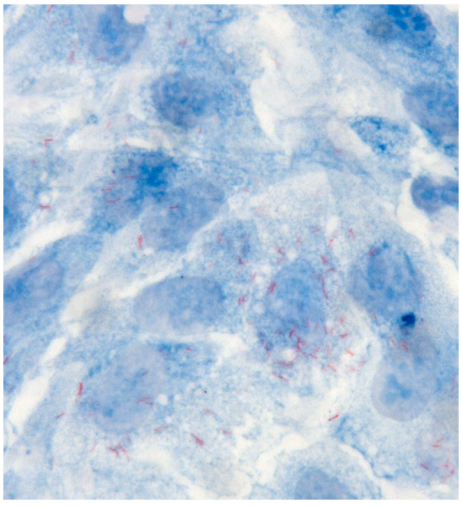

Fig. 2. Microscopy image of retinal pigment epithelial cells (OZR1 cells) being infected by *Mycobacterium tuberculosis* H37Rv in cell culture (using Kinyoun staining).

Mtb-infected macrophages.(La Distia Nora et al., 2018d) A previous study demonstrated that *Mtb*-infected RPE cells had a dominant type 1 IFN (IFNα/β) signaling response and displayed enhanced expression of genes involved in the regulation of cell-death and survival that are important in limiting retinal damage due to inflammation.(La Distia Nora et al., 2018d) Both IFN-α and β bind to IFNAR1 and IFNAR2 subunit receptors, which signal through STAT1 and STAT2.(Moreira-Teixeira et al., 2018) As discussed elsewhere, type 1 IFN signalling can be either protective or detrimental to TB disease. Type 1 IFN primes the secretion of protective cytokines IL-12 and TNF-α. On the other hand, it promotes the production of IL-10 which represses macrophage/monocyte responsiveness to the antibacterial effects of IFN-γ and therefore is associated with disease progression.(Moreira-Teixeira et al., 2018) It was postulated that the highly activated type 1 IFN signalling in RPE benefits the early stage of *Mtb* infection by reducing potential local tissue damage through its immunoregulatory effect and may inhibit *Mtb* outgrowth by eliminating *Mtb* through activated cell-death signalling pathways.(La Distia Nora et al., 2018d) However, chronic infection or *Mtb* latency in the RPE might be expected to happen in the later stage, possibly causing prolonged ocular inflammation. Furthermore, IFN-γ-activated RPE can activate retinal antigen-specific T-lymphocytes by enhanced expression of HLA class II molecules.(Sun et al., 2003) Several reports have shown that active TB is associated with specific activation of type-1 IFN-stimulated genes (ISGs) in peripheral blood cells. The more severe the TB disease, the higher the expression levels of ISGs.(Berry et al., 2010; La Distia Nora et al., 2018b) In line with these observations and the significant activation of IFN signalling upon *in vitro* infection of RPE,(La Distia Nora et al., 2018d) our group also showed that peripheral blood cell expression of ISGs can be of use to stratify QFT-positive patients with uveitis of unknown cause into a group with a high likelihood of having active TB-uveitis (high ISG expression) or a low likelihood of having active TB-uveitis (low ISG expression).(La Distia Nora et al., 2018b) Consequently, it was proposed that this approach may prevent patients with low ISG expression from unnecessary ATT treatment, thus preventing them from possible severe side effects associated with this treatment.(La Distia Nora et al., 2018b)

Interestingly, discrete granuloma formation within the nerve fiber

layer adjacent to the retinal vasculature without RPE involvement can also occur. This intraretinal granuloma lacks multinucleated giant cells but harbours elongated cells that share morphological similarity to activated microglia.(Basu et al., 2012) It seems that the interaction between pericytes and retinal endothelial cells, independent of RPE, controls this intraretinal granuloma formation. Currently, studies regarding the role of various cells other than RPE in the formation of TB-uveitis granulomas are lacking. Moreover, the composition and interactions between BRB constituent cells, namely retinal endothelial cells, microglia, Müller cells, pericytes, and RPE, in TB infection have not been extensively explored.(O'Leary and Campbell, 2023) It is necessary to have a complete *in vitro* model of inner BRB-*Mtb* interaction to gain an in-depth look at the mechanisms that underlie TB-uveitis granuloma formation.

It is worth mentioning that the current understanding of TB-uveitis is limited to posterior segment inflammation. From the clinical perspective, the involvement of anterior segment inflammation in TB-uveitis, reflected by the presence of iris nodules, large keratic precipitates (KPs), and profound anterior chamber cells without any posterior segment involvement, could not be explained simply by breached BRB. BRB disruption would be followed by ocular inflammation, but the reverse is not necessarily true.(Forrester et al., 2018)

2.3. Autoimmune response in TB-uveitis

Since detection of *Mtb* or its genome in the eye is challenging and often remains undetectable, uveitis is often assumed to be associated with systemic TB infection based on IGRA or tuberculin skin test (TST) positivity, even in cases without systemic abnormalities. The Collaborative Ocular Tuberculosis Study (COTS) group endorsed using the general term "tubercular uveitis" without the necessity of *Mtb* presence in ocular tissue/fluid.(Agrawal et al., 2019) However, there is a grey area in diagnosing latent TB-uveitis in patients without systemic TB disease. Patients with immunoreactivity against TB, based on IGRA/TST, have a higher risk of developing active TB disease later. Some experts challenge the term "latent" as *Mtb* may keep replicating and is not "dormant" before progressing to active TB. Moreover, with the possibility of an undetected paucibacillary state, an increased immune response may also contribute to ocular inflammation.(Basu, 2022)

Given that some pieces of evidence suggest that uveitis might result from direct infection of the eye, recent investigations also suggest that there is plausible autoimmunity involved in the development of uveitis among individuals with latent TB (Fig. 3). The autoimmune process may involve hypersensitivity to ocular antigens due to immune cell priming that cross-reacts with *Mtb* antigens outside the eye. One report described a case of anterior uveitis in a patient following intravesical Bacille-Calmette-Guérin treatment for bladder carcinoma. This patient presented with mutton-fat KPs and the Koeppe nodule, which resembled granulomatous anterior uveitis typically found in TB-uveitis. The authors evaluated the potential of antigenic mimicry as the underlying cause of uveitis. Peripheral T-lymphocytes had high IL-2, IFN-γ, and TNF-α production in response to purified protein derivative (PPD) stimulation. Similarly, an elevated cytokine response towards three retinal autoantigens (retinal soluble antigen, interphotoreceptor retinoid-binding protein (IRBP), and cellular retinal-binding protein) was found.(Garip et al., 2009)

Moreover, a considerably lower frequency and aberrant function of peripheral T regulatory cells (Tregs) might contribute to TB-uveitis.

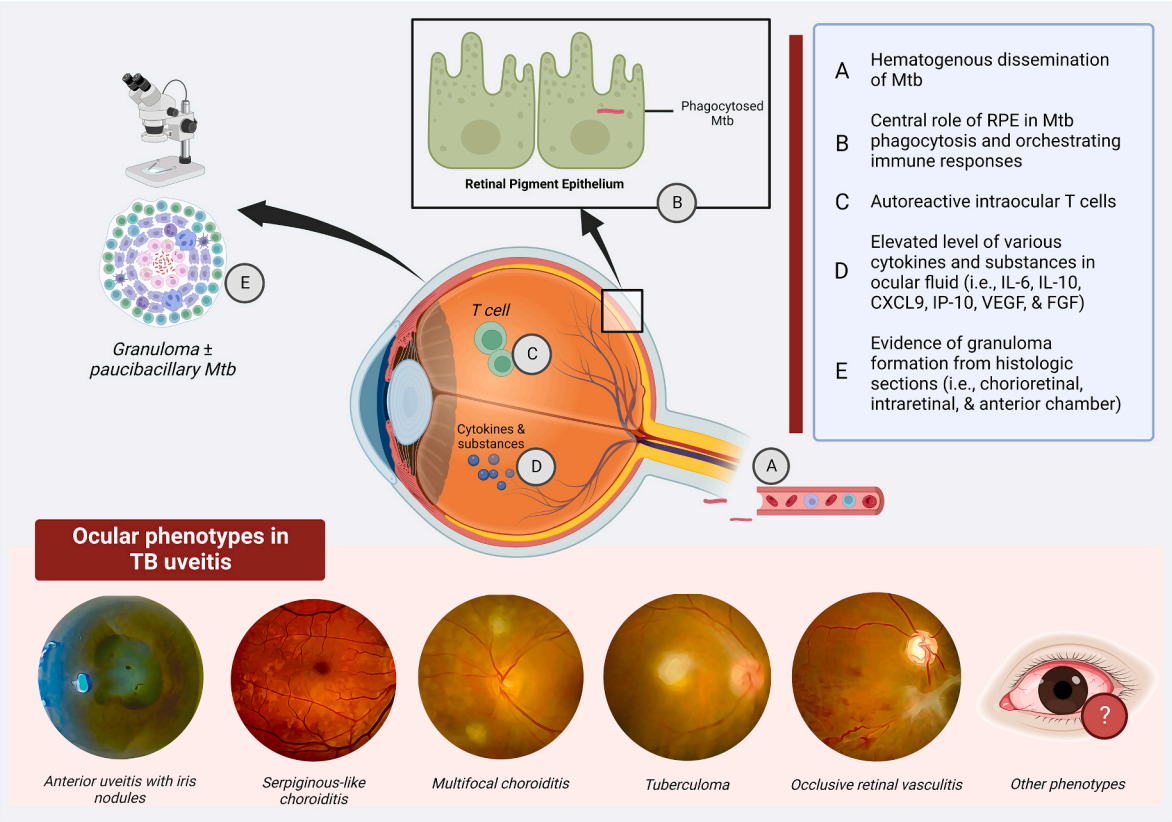

Fig. 3. Proposed pathogenesis of TB-uveitis with the associated clinical phenotypes.
Note: CXCL (chemokine (C-X-C motif) ligand), FGF (fibroblast growth factor), IL (interleukin), IP (IFN-γ inducible protein), *Mtb* (*Mycobacterium tuberculosis*), RPE (retinal pigment epithelium), VEGF (vascular endothelial growth factor).
RPE may harbor disseminated *Mtb* resulting in ocular inflammation (A–E). An alternative hypothesis is a profound inflammation in the absence of *Mtb* in the ocular tissue (C and D ± E) (Created with BioRender.com).

(Sharma et al., 2018a) Intraocular cytokine analysis from TB-uveitis patients showed a higher level of autoimmune-associated cytokines, such as IL-2, IL-12, CXCL9, and TNF-α, than in idiopathic/unknown uveitis.(Ang et al., 2012a) Together, these data support the dysfunction of Treg immunity and strong T-helper (Th)-1 polarisation as contributing factors to TB-uveitis.(Malek, 2003)

Intraocular T-lymphocyte responses upon stimulation with the *Mtb* protein Early Secreted Antigenic Target-6 (ESAT-6) or the retinal autoantigen IRBP was compared in patients stratified for being TB-uveitis (using new Standardization of Uveitis Nomenclature (SUN) classification criteria (see Table 1) or positive *Mtb* polymerase chain reaction (PCR) from ocular fluid), latent TB uveitis (not fulfilled SUN criteria despite being TST+), and non-TB-uveitis patients. T-lymphocytes of latent TB uveitis patients elicited the highest TNF-α, IL-17A, and IFN-γ polyfunctional responses (cells expressing ≥2 cytokines) upon ESAT-6 stimulation.(Alam et al., 2022) Whereas phenotyping of peripheral T lymphocyte showed no difference between TB-uveitis patients presenting with granulomatous versus non-granulomatous uveitis, presence versus absence of chest radiological changes suggestive of pulmonary TB, and between different anatomical sites of uveitis.(Hutchinson et al., 2021) Interestingly, intraocular IRBP-specific T-lymphocyte cytokine responses were equally observed among QFT positive patients with uveitis of unknown cause and patients with uveitis associated with pulmonary TB.(Alam et al., 2022) Tagirasa et al. identified intraocular autoreactive T-lymphocytes that responded to *Mtb*-derived ESAT-6 and crude retinal extract antigens.(Tagirasa et al., 2017) However, autoreactive T-lymphocytes towards crude retinal extract could not be detected in peripheral blood from patients with TB-uveitis, which was suggested to be related to a low frequency of retina-specific T-lymphocytes in peripheral blood.(Schrijver et al., 2021; Tagirasa et al., 2017)

Ocular autoimmunity can be associated with the presence of anti-retinal autoantibodies (ARAs).(Adamus, 2018) In further support of an

Table 1
Criteria for tubercular uveitis case definition.

Criteria/Author (year)	Inclusion criteria		Exclusion criteria	Specific conclusion
	Phenotypes/clinical signs	Recommended investigations (without a necessity to be all fulfilled/performed)		
The SUN working group (2021)(Jabs et al., 2021)	1. Anterior uveitis with iris nodules 2. Serpiginous-like tubercular choroiditis 3. Choroidal nodule (ie, tuberculoma) 4. In individuals with active systemic tuberculosis, multifocal choroiditis 5. Occlusive retinal vasculitis	Evidence of infection with Mtb, either: 1. Histologically or microbiologically confirmed infection with Mtb, OR 2. Positive IGRA, OR 3. Positive TST	1. Positive serology for syphilis using a treponemal test 2. Positive biopsy for sarcoidosis (and therefore an absence of histologic or microbiologic confirmation of infection with Mtb) 3. Uveitic syndrome compatible with either sarcoidosis-associated uveitis or tubercular uveitis and bilateral hilar adenopathy on chest imaging without histologic or microbiologic confirmation of the diagnosis of infection with Mtb	–
The COTS group – inclusion and exclusion criteria (2017)(Agrawal et al., 2017)	1. Anterior uveitis (granulomatous or nongranulomatous), iris nodules, and ciliary body granuloma. 2. Intermediate uveitis (granulomatous or non granulomatous with exudates in the pars plana, with or without snowballs). 3. Posterior and panuveitis, choroidal tubercle, choroidal granuloma, subretinal abscess, and serpiginous-like choroiditis. 4. Retinitis, retinal vasculitis, neuroretinitis, optic neuritis, endogenous endophthalmitis, panophthalmitis, and scleritis.	Fulfil at least one of criteria A or B: A. Investigations that document the Mtb or its genome: 1. Demonstration of acid-fast bacilli by microscopy or culture of Mtb from ocular fluid. 2. PCR from ocular fluid for IS 6110 or other conserved sequences in Mtb genome. 3. Evidence of confirmed active extrapulmonary TB (by microscopic examination or culture of a tissue sample from the affected tissue). B. Corroborative investigations: 1. TST (Mantoux) 2. IGRA, such as QuantiFERON TB Gold 3. Chest radiography showing evidence of healed or active TB	Other uveitic entities, where relevant, based on clinical manifestations of disease and regional epidemiologic findings (not specified)	–
Gupta et al (2015)(A. Gupta et al., 2015)	Presence of cells in anterior chamber or vitreous along with: 1. Broad posterior synechiae 2. Retinal perivasculitis with or without discrete choroiditis/scars 3. Multifocal serpiginoid choroiditis 4. Choroidal granuloma (single or multifocal) 5. Optic disc granuloma 6. Optic neuropathy	Ocular fluid 1. Demonstration of acid-fast bacilli smear/culture of Mycobacterium tuberculosis 2. Mtb detection from the ocular fluids 3. Positive PCR from ocular fluids for IS6110 or other conserved sequences in MTB genome Systemic 1. Positive TST (or IGRA) 2. Evidence of healed or active TB lesion on chest radiography 3. Evidence of extrapulmonary tuberculosis diagnosed by demonstration of tubercular granuloma/acid-fast bacilli/culture of Mtb	Other etiologies excluded (not specified)	Depending on the result of the investigation: 1. Confirmed 2. Probable 3. Possible (For details, please see (A. Gupta et al., 2015))

COTS = The Collaborative Ocular Tuberculosis Study, IGRA = Interferon-Gamma Release Assays, Mtb = *Mycobacterium tuberculosis*, PCR = polymerase-chain reaction, TB = tuberculosis, TST = tuberculin skin test.

autoimmune component in TB-uveitis is the higher prevalence of serum ARA in active and latent TB-uveitis in comparison to healthy controls. (La Distia Nora et al., 2018c; Ten Berge et al., 2016) Although the pathogenic relevance of ARA in TB-uveitis is unclear, it has been proposed that they are formed secondary to the response of inflammation-induced retinal damage and further support the occurrence of a T-lymphocyte-dependent anti-retinal immune response in a substantial number of TB-uveitis cases.(Schrijver et al., 2021)

Furthermore, a recent animal study showed that panuveitis could occur following the injection of heat-killed *Mtb* (hk*Mtb*) in the vitreous humor. Compared to mice without previous systemic exposure to hk*Mtb* (unprimed mice), a significantly higher number of ocular T lymphocytes, NK cells, and macrophages were observed in primed mice. Also, higher levels of IL-17, VEGF, CXCL9, CXCL10, IL-12p40, and macrophage inflammatory protein-1α (MIP-1α/CCL3) were observed. Only the primed mice developed chronic uveitis.(Pepple et al., 2022) Whether these observations are related to an excessive immune response to TB-antigens, an induction of an anti-retinal immune response, or both, is unclear.

3. Clinical perspective of tubercular uveitis: From diagnosis to treatment initiation

TB-uveitis can present with unilateral or bilateral intraocular inflammation at various ocular locations: anterior, intermediate, posterior, as well as panuveitis. The presence of large-mutton fat KPs, iris nodule in the pupillary margin (Koeppe nodule) or anterior mid-iris (Busacca nodule), and broad-based synechia indicate anterior ocular granulomatous inflammation. The formation of cataract is common in chronic inflammation. Significant snowball or snowbanking with peripheral vasculitis is frequently present in tubercular intermediate uveitis. Tubercular posterior uveitis typically presents with retinal and choroidal inflammation. Chorioretinal lesions include choroidal tubercle/tuberculoma, multifocal choroiditis, serpiginous-like choroiditis, or lesions mimicking other entities. Tubercular retinal vasculitis can also manifest as an occlusive periphlebitis. Even though it is rarely reported, optic nerve involvement (papilitis, optic neuritis, or optic nerve tubercle) may also be present.(Betzler et al., 2021; V. Gupta et al., 2015)

In practice, diagnostic delay was variably reported across the globe as the diagnosis of TB-uveitis often relies on the presence of clinically granulomatous inflammation, the exclusion of other possible entities, and the corroborative evaluation of systemic TB infection (based on chest radiography, IGRA, or tuberculin skin test (TST)).(Betzler et al., 2021) As a granulomatous disease, TB-uveitis shares similarities with other diseases, such as sarcoidosis.(Mochizuki et al., 2019; Mortaz et al., 2016) The current diagnostic approach for TB-uveitis implies the challenge of directly detecting *Mtb* or its genome in ocular tissue/fluid. PCR has gained popularity as this method provides an easy and quick result for *Mtb* detection. However, based on our systematic review, the overall PCR positivity for detecting *Mtb* was only 55% with poor specificity when we set the response to ATT as the reference.(La Distia Nora et al., 2021) In India, where TB is highly prevalent, the reported positivity could be as high as 70%, particularly when the *MPB64* primer was used, which is characterised by a lower detection limit.(Balne et al., 2014) Due to the challenge of *Mtb* detection in ocular tissue/fluid in TB-uveitis, direct *Mtb* detection in ocular samples is not consistently implemented,(Agarwal et al., 2019) although it remains essential and irreplaceable. Moreover, a recent statement by the British Thoracic Society (BTS) mentioned that ocular fluid analysis could be an option to help diagnose TB-uveitis in patients presenting with atypical ocular inflammation and a positive IGRA, particularly in those with high risk of TB, (Kon et al., 2022) even though a negative result will still be a clinical dilemma.

In 2015, Gupta et al. proposed a classification of intraocular TB based on direct and indirect evidence of TB infection (Table 1).(A. Gupta et al., 2015) However, this classification was not based on the pathogenesis of TB-uveitis but rather on the amount of clinical evidence. Generally applied, many patients frequently fulfil the probable and possible intraocular TB classifications. In these cases, a clear response towards ATT makes the diagnosis very likely. Considering the problem of making the decision to start ATT, the COTS group published a consensus on when to initiate ATT in patients without proven active pulmonary or extrapulmonary TB. The consensus is based on the country's endemicity of TB, location, type of ocular inflammation, and ancillary test results (chest radiography, IGRA, and TST).(Agrawal et al., 2021b) In brief, the consensus is mainly achieved when at least chest radiography shows evidence of TB infection with one or both IGRA and TST positive results in countries with a high TB-burden. Based on the presenting phenotype, only serpiginous-like choroiditis and choroidal tuberculoma phenotypes need to be either TST or IGRA positive without evidence of a chest radiological TB lesion to start ATT.(Agrawal et al., 2021b) Recently, the SUN working group has developed a set of criteria for TB-uveitis (Table 1).(Jabs et al., 2021) These criteria have strong discriminative properties to differentiate TB-uveitis from the other entities. The criteria emphasise several phenotypes that are strongly compatible with TB: anterior uveitis with iris nodules, serpiginous-like tubercular choroiditis, choroidal nodule (i.e., tuberculoma), in individuals with active systemic tuberculosis showing multifocal choroiditis, and occlusive retinal vasculitis. However, the authors stated that the applicability of the classification criteria in the clinical setting is limited as it was mainly developed for research purposes. The classification system uses relevant clinical appearances in the best agreement between experts on TB-uveitis diagnosis. The authors acknowledged that the criteria are more restrictive than the COTS guidelines described previously, however, the latter might be more suitable for clinical care. For instance, even though intermediate uveitis is not considered a phenotype strongly suggestive of TB-uveitis, a study by Sreenivasan et al. in an endemic TB country reported and highlighted the benefit of adding ATT in addition to systemic immunosuppressive medication for the treatment of intermediate uveitis patients with positive *Mtb* PCR from ocular fluid.(Sreenivasan et al., 2022) In light of systemic biomarkers, the combination of a peripheral blood type-1 IFN gene signature and serum C1q measurements may provide additional diagnostic value in classifying QFT + uveitis of unknown cause without apparent systemic TB disease. (Schrijver et al., 2020) In this situation, uveitis patients showing low serum C1q and low type-1 IFN signature score may not need ATT as they have a low likelihood of having active TB disease (Fig. 4).(Schrijver et al., 2020) However, further prospective validation is required before clinical implementation.

4. Current treatment modalities and the outcomes

4.1. Systemic treatment

ATT, the mainstay treatment of TB-uveitis, has been studied across different populations (Table 2). The ATT regimen often employs a combination of four drugs (isoniazid [H], rifampicin [R], pyrazinamide [Z], and ethambutol [E]) during the initial 2-month intensive phase, followed by a combination of two or three drugs (HR ± Z) for a minimum of 4 months. The World Health Organization currently has also introduced a 4-month ATT regimen consisting of isoniazid, rifapentine [P], moxifloxacin [M], and pyrazinamide (2HPMZ/2HPM)(*WHO consolidated guidelines on tuberculosis Module 4: Treatment - drug-susceptible tuberculosis treatment*, 2020) that may be further applied and tested for TB-uveitis. The benefit of prolonging the total ATT duration beyond six months has been reported.(Agrawal et al., 2015; Ang et al., 2012b) It is recommended to commence a more extended treatment (9–12 months) for those with initial severe inflammation or poor early response to ATT.(Kon et al., 2022) Meanwhile, the role of ATT in treating TB-uveitis patients remains controversial. Resolution of inflammation is also achieved among patients treated without ATT, both in countries with high and low TB burdens (Table 2). On the other hand,

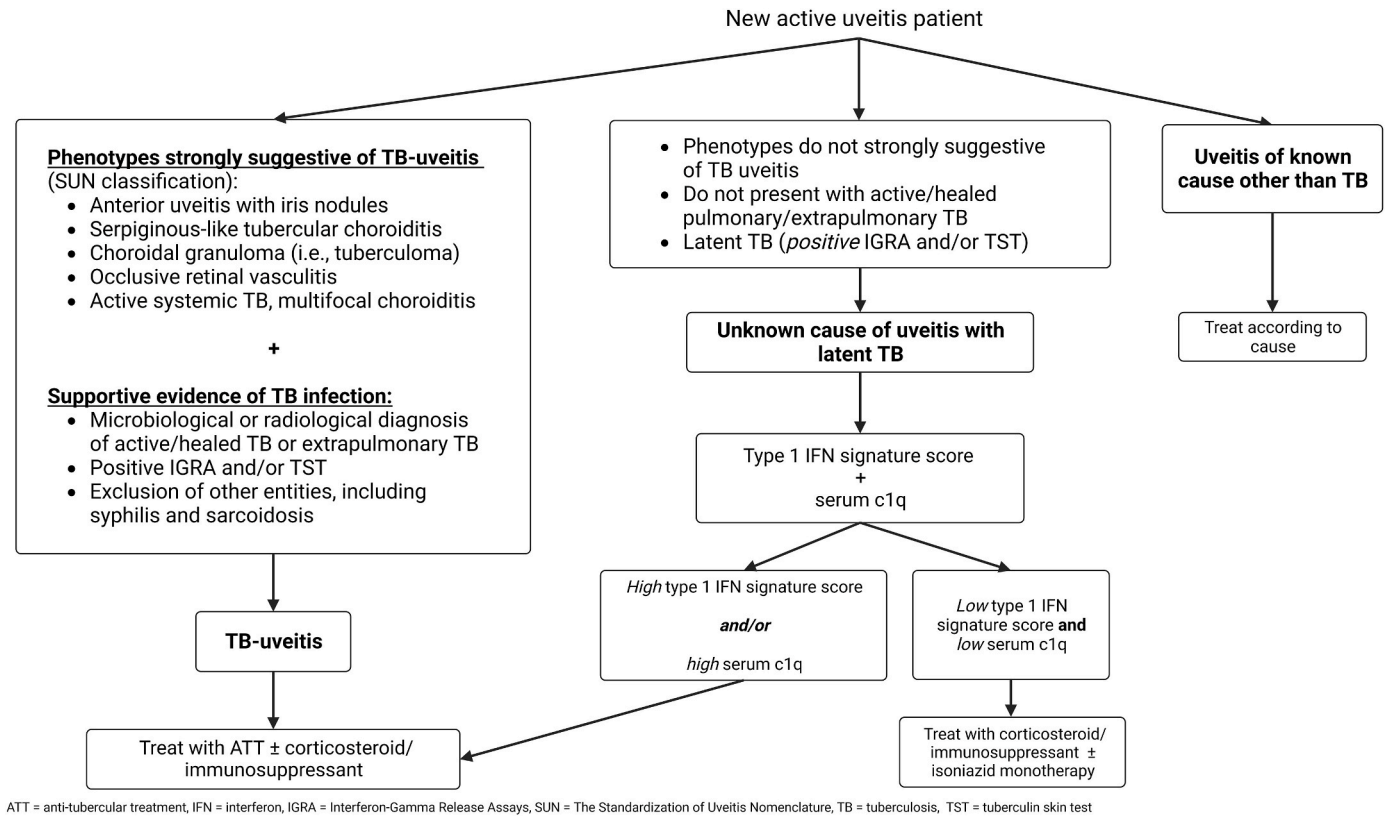

Fig. 4. Proposed algorithm for TB-uveitis diagnostic workup and initial management. (Created with BioRender.com).

a considerable risk of latent TB reactivation or progression with the use of systemic corticosteroid alone has been described.(Betzler et al., 2021; Jick et al., 2006) Overall, the proportions of patients who achieved resolution of uveitis treated with ATT in high and low TB-burden countries were 80–100% and 23.9–100%, respectively. Of note, treatment responses vary considerably among studies, taking into consideration that TB-uveitis lacks a gold standard diagnostic test and can present with diverse ocular inflammatory phenotypes. Therefore, high caution is needed to interpret the treatment response based on a heterogeneous group of patients (see Supplementary Table). Therefore, the development of reliable laboratory tests to objectively monitor treatment response, TB-reactivation, or progression would be of great benefit.

With regard to the uveitis phenotypes, COTS reported that the outcomes varied, and ATT was not superior to other treatments (without ATT), which include topical or systemic corticosteroid alone. Clinical resolution of patients treated with and without ATT was comparable in tubercular anterior uveitis (TAU),(Agrawal et al., 2020a) tubercular intermediate uveitis (TIU),(Agrawal et al., 2020b) tubercular panuveitis (TPU),(Agrawal et al., 2020b) TB-uveitis with choroidal involvement (including serpiginous-like choroiditis, tuberculoma, multifocal choroiditis, and ampiginous choroiditis),(Agrawal et al., 2018) and tubercular retinal vasculitis (TRV).(Gunasekeran et al., 2019) However, it is worth noting that there was a tendency to give combination treatments in cases of severe ocular inflammation or significantly reduced visual acuity at presentation. Thus, interpreting treatment success rates in the studies above should be done with caution. A randomised controlled trial recruiting uveitis with positive IGRA who are initially treated with ATT versus corticosteroid is in progress and it is worth waiting for the results (ClinicalTrials.gov registration number: NCT05005637).

The COTS group provides an expert opinion-trained online calculator (https://www.ocularTB.net/cots-calc) to help ophthalmologists decide if ATT is necessary for a given patient. The TB-uveitis phenotypes taken into account by this calculator are TB choroiditis, TAU, TIU, TPU, and TRV. Besides ocular phenotype and country-specific endemicity to TB, individual patient data, including TST, IGRA, and chest X-ray results, are also required by the calculator. The calculator will then display the median score of the survey result, ranging from 1 (very low recommendation to initiate ATT) to 5 (very high recommendation to initiate ATT) and the consensus on this: IQR 0 (absolute consensus achieved) to IQR 3 (poor consensus).(Agrawal et al., 2022)

Even though there is still no well-conducted RCT, the recent BTS statement supports the regular use of a concomitant systemic corticosteroid (1 mg/kg prednisolone or equivalent) with ATT.(Kon et al., 2022) Systemic corticosteroids are expected to further control inflammation, especially in tubercular posterior uveitis.(Betzler et al., 2021; Kon et al., 2022) Increasing the dose of systemic corticosteroid is warranted in cases of paradoxical worsening (clinical or radiological worsening of pre-existing TB lesions or the presence of new lesions in patients who showed initial improvement with treatment) during ATT course, (Basu et al., 2013; Ganesh et al., 2019) which occurs in around a quarter of patients.(Basu et al., 2013) If satisfactory inflammation control is not achieved following a high dose of systemic corticosteroid, another immunosuppressive agent should be considered.(Ganesh et al., 2019) Several reports describe successful control of inflammation and relapse with adjunct immunosuppressive agents (methotrexate, cyclosporine, azathioprine, IFNα2, or a combination of these).(La Distia Nora et al., 2014; Oray et al., 2017; Urzua et al., 2017) The use of immunosuppressive agents and the outcomes are summarised in Table 3.

4.2. Intraocular treatment

Adjunctive intraocular anti-inflammatory treatment in TB-uveitis has a minor role and is supported only by limited studies. Although it is difficult to draw conclusions regarding the success rate, case reports with a limited sample size showed promising results. There was a report on the beneficial effect of a dexamethasone implant for treating secondary cystoid macular edema (success in 10/10 eyes), vitritis (success

Table 2
Summary of studies reporting inflammation resolution following TB-uveitis treatment based on the TB burden category of the country at the study site.

Study	Country	Treatment	ATT regimen	Systemic CS	N[a] treated	N[a] inflammation resolution[b] (%)
Multinational studies (Combined high- and low-burden TB countries)[c]						
COTS (General phenotype)(Agrawal et al., 2017)	Multi-countries (Australia, Austria, France, Greece, India, Italy, Saudi Arabia, Singapore, Spain, Switzerland, Tunisia, Turkey, United Kingdom, United States of America)	ATT ± CS/ immunosuppressive agent	Varied across international centres (Further details were not provided)		801	699 (87.3%)
COTS (TAU-specific phenotype)(Agrawal et al., 2020a)		ATT ± CS/ immunosuppressive agent			165	148 (89.7%)
		CS/immunosuppressive agent (no ATT)			107	94 (87.8%)
COTS (TIU-specific phenotype)(Agrawal et al., 2020b)		ATT			13	13 (100%)
		ATT ± CS/ immunosuppressive agent			109	95 (87.2%)
		CS/immunosuppressive agent (no ATT)			29	25 (86.2%)
COTS (TPU-specific phenotype)(Agrawal et al., 2020b)		ATT			26	25 (96.2%)
		ATT ± CS/ immunosuppressive agent			234	183 (78.2%)
		CS/immunosuppressive agent (no ATT)			29	25 (86.2%)
COTS (Patients with choroidal involvement-specific phenotype)(Agrawal et al., 2018)		ATT ± CS/ immunosuppressive agent			219	185 (84.5%)
		CS/immunosuppressive agent (no ATT)			26	22 (84.6%)
COTS (TRV-specific phenotype)(Gunasekeran et al., 2019)		ATT ± CS/ immunosuppressive agent			228	197 (86.4%)
		CS/immunosuppressive agent (no ATT)			23	18 (78.3%)
High-burden TB countries[c]						
Ghauri et al (2019)(Ghauri et al., 2019)	Pakistan	ATT ± Systemic CS	HRZE 2 months, HR 10 months	Prednisolone was given in a dose of 1 mg/kg given for 3 weeks, then tapered of (only in 3 patients)	40	32 (80.0%)
Elangovan et al (2019)(Elangovan et al., 2019)	India	ATT + Systemic CS	HRZE 2 months, HR 4 months	Used in some patients (based on the clinical judgement). Further details were not reported.	25	21 (84.0%)
Kaur et al (2018)(Kaur et al., 2018)	India	ATT + Systemic CS	HRZE 2 months, HR 10 months	Prednisone (1 mg/kg/day)	27	25 (92.6%)
Sudheer et al (2018) (Sudheer et al., 2018)	India	ATT + Systemic CS	HRZE 2 months, HR 4 months	Oral steroids – unspecified- in tapering doses (0.5–0.75 mg/kg body weight) for the first 4–6 weeks	34	30 (88.2%)
Babu et al (2016) (Babu et al., 2016)	India	ATT	HRZE 2 months, RHZ 4 months, RH 6 months (total 12 months)	Not reported	82	82 (100%)
Basu et al (2013)(Basu et al., 2013)	India	ATT ± Systemic CS	HRZE 2 months, HR 4 months	Oral prednisolone 1 mg/kg/day when required. In some patients (not clearly described) got combination of periocular + oral prednisolone and intravenous + oral prednisolone (details not reported)	106	103 (97.2%)
Gupta et al (2011)(Gupta et al., 2011)	India	ATT + Systemic CS	HRZE	Corticosteroids – unspecified (1–1.5 mg/kg/day)	65	54 (83.1%)
		Systemic CS (No ATT)			19	18 (94.7%)
Low-burden TB countries[c]						
Bigdon et al (2022)(Bigdon et al., 2022)	Germany	Systemic CS + immunosuppressive agent	–	Oral prednisolone 1–2 mg/kg bodyweight at the primary visit, followed by weekly tapering to a maintenance dosage of 7.5 mg/day - 5.0 mg/day. Immunosuppressants: methotrexate/azathioprine/ cyclosporine	6	5 (83.3%)
		Systemic CS + immunosuppressive agent + adalimumab + isoniazid	Isoniazid 300 mg/day for at least 9 months		11	9 (81.8%)
Papasavvas et al (2022)(Papasavvas et al., 2022)	Switzerland	ATT + systemic CS + immunosuppressive agent	HRZE 2 months + HR at least 8 months	Triple therapy among the following agents: prednisone, cyclosporine, azathioprine, mycophenolic acid and infliximab	4	3 (75.0%)
Shirley et al (2020)(Shirley et al., 2020)	United Kingdom	ATT + Systemic CS	HRZE	Systemic corticosteroids (1 mg/kg)	48	29 (60.4%)

(*continued on next page*)

Table 2 (*continued*)

Study	Country	Treatment	ATT regimen	Systemic CS	N[a] treated	N[a] inflammation resolution[b] (%)
Ang et al (2018)(Ang et al., 2018)	Singapore	Systemic CS (No ATT)	–	Further details were not reported	19	15 (78.9%)
		ATT	HRZE 2 months + ≥ 4 months RH		53	38 (71.7%)
Chung et al (2018) (Chung and Li, 2018)	Hong Kong	ATT	HRZ-E/streptomycin 2 months, HR in the continuation phase	Oral prednisolone 1 g/kg/day on initiation and gradually tapered down	6	6 (100%)
		ATT + Systemic CS			8	7 (87.5%)
Al-Qarni et al. (2019) (Al-Qarni et al., 2019)	Saudi Arabia	ATT + Systemic CS	HRZE 2 months, HR 7 months	Systemic corticosteroids-unspecified (1 mg/kg)	141	141 (100%)
Damato et al (2017)(Damato et al., 2017)	United Kingdom	ATT ± Systemic CS	HRZE/HRZ	High-dose oral steroid (usually at least 40 mg daily tapered over several weeks) - unspecified	47	36 (76.6%)
Urzua et al (2017)(Urzua et al., 2017)	Chile & Spain	ATT ± Systemic CS/ Immunosuppressive agent	HRZE/HRZ	Systemic steroid (unspecified) ± methotrexate/cyclosporine/ methotrexate & cyclosporine/ azathioprine & cyclosporine	35	33 (94.3%)
Oray et al (2017)(Oray et al., 2017)	Turkey	ATT + CS ± immunosuppressive agent	HRZE 2 months, HR 10 months	Conventional IMT, interferon or CS monotherapy (further details were not reported)	17	15 (88.2%)
		CS/immunosuppressive agent (No ATT)	–		11	9 (81.8%)
Agrawal et al (2015) (Agrawal et al., 2015)	United Kingdom	ATT	HRZ-E/moxifloxacin 2 months, followed by 2 drugs ± moxifloxacin for rest of the duration of therapy or HR prophylaxis	Oral corticosteroids – unspecified starting at 60 mg/day for 1 week followed by a tapering dose of 40 mg/day 1 week, 30 mg/day 1 week, and eventually slow taper depending on disease activity	55	42 (76.4%)
		ATT + Systemic CS			120	88 (73.3%)
Khochtali et al (2015)(Khochtali et al., 2015)	Tunisia	ATT + Systemic CS	HRZE 2 months + HR 6–10 months	Systemic/periocular corticosteroids - unspecified only in posterior uveitis, panuveitis, or intermediate uveitis (oral prednisone 1 mg/kg/day and then progressively tapered)	20	20 (100%)
		ATT		–	13	13 (100%)
La Distia Nora et al. (2014) (La Distia Nora et al., 2014)	The Netherlands	ATT ± Systemic CS/ Immunosuppressive agent	RHZ 2 months, RH 4 months	Prednisone/immunosuppressive agent (methotrexate, azathioprine, or cyclosporine – further details were not reported)	32	29 (90.6%)
		CS ± Immunosuppressive agent	Isoniazid prophylactic		18	6 (33.3%)
Gineys et al (2011)(Gineys et al., 2011)	France	ATT	HRZ 2 months, HR 4 months	Further details were not reported	12	9 (75%)
		ATT + Systemic CS			18	15 (83.3%)
Doycheva et al. (2011) (Doycheva et al., 2011)	Germany	ATT + Systemic CS/ immunosuppressive drug	RHZ ≥6 months	Further details were not reported	11	9 (81.8%)
Patel et al (2013)(Patel et al., 2013)	United States of America	ATT ± Systemic CS	HRZE	Further details were not reported	26	20 (76.9%)
Manousaridis et al (2013)(Manousaridis et al., 2013)	United Kingdom	ATT ± Systemic CS	HRZE 2 months, RH 4 months	Systemic corticosteroid – further details were not reported (4 patients)	18	18 (100%)
Vos et al (2013)(Vos et al., 2013)	The Netherlands	ATT ± Systemic CS	HRZ ± ethambutol ± moxifloxacin	Further details were not reported	10	7 (70.0%)
		No ATT	–		51	31 (60.8%)
Ang et al (2012) (Ang et al., 2012b)	Singapore	Systemic CS (No ATT)	–	Oral prednisolone 1 mg/kg/day	118	17 (14.4%)
		ATT	HRZE 4 months, HR 2 months		46	11 (23.9%)
Ang et al (2009)(Ang et al., 2009)	Singapore	No ATT	–	Oral prednisolone with a starting dose of 1 mg/kg body weight, tapering slowly over the clinical course	120	99 (82.5%)
		ATT ± Systemic CS	HRZE ≥6 months		37	34 (91.9%)
Al-Mezaine et al. (2008) (Al-Mezaine et al., 2008)	Saudi Arabia	ATT + Systemic CS	RHZ 2 months, RH 4–7 months	Prednisone 1 mg kg-1 day-1 until a clinical effect was seen then a slow reduction	51	51 (100%)

H = Isoniazid, R = rifampicin, Z = pyrazinamide, E = Ethambutol, CS = corticosteroid, TAU = tubercular anterior uveitis, TIU = tubercular intermediate uveitis, TPU = tubercular panuveitis, TRV = tubercular retinal vasculitis.

[a] N = Number of patients or eyes, depending on what was reported in each study.

[b] Resolution of inflammation: Grade 0 cells/no noticeable inflammation (inactive) choroid/retinal/vasculitis lesion(s).

[c] List of high TB burden countries from: https://tbfacts.org/high-burden-tb/(accessed May 28th, 2022).

Table 3
Studies reporting in detail the use of immunosuppressants for tubercular uveitis treatment.

Study	Phenotypes of tubercular uveitis	Reason for immunosuppressants	Immunosuppressant(s)	ATT course	N patients received immunosuppressants	Overall outcome
Bigdon et al (2022) - Germany(Bigdon et al., 2022)	Occlusive and non-occlusive retinal vasculitis with positive IGRA	Recurrences while tapering the systemic corticosteroids ≥10 mg/d (3 patients) or severe inflammation at the first visit (11 patients)	MTX ± AZA ± CsA ± ADA MTX: 10–25 mg/week SC AZA: 150 mg/day CsA: 3 mg/kg/day ADA: 40 mg 2 weekly SC	INH 300 mg/day for at least 9 months	Total: 14 1 CS + CsA 3 CS + MTX 2 CS + AZA 4 CS + MTZ + AZA 2 CS + MTX + ADA 1 CS + MTX + AZA + ADA 1 ADA + low-dose MTX	Remission[a] at last visit: 11/14
Papasavvas et al (2022) - Switzerland(Papasavvas et al., 2022)	Serpiginous choroiditis with positive IGRA	Progressive and severe presentation	1) CsA (starting dose at 4.8 mg/kg/day) + Infliximab (starting dose at 5 mg/kg 1x/4 weeks), or 2) Mycophenolate mofetil (720 mg 2x/day), or 3) Mycophenolate mofetil + CsA	HRZE 2 months followed with HR at least 8 months	4	Progression[b] stopped: 3/4
Urzua et al (2017) – Chile & Spain(Urzua et al., 2017)	Scleritis or tubercular uveitis	Unclear (immunosuppressants were added at least 10 days after initiation of ATT)	MTX, CsA, or AZA	HRZE/HRZ	5 patients 2 CS + MTX 1 CS + CsA 1 CS + MTX + CsA 1 CS + AZA + CsA	1. Final BCVA <20/50: 2/8 eyes 2. Final BCVA <20/200: 1/8 eyes 3. Glaucoma: 3/5 patients 4. Cataract: 0/8 eyes
Oray et al (2017) - Turkey(Oray et al., 2017)	Serpiginous Choroiditis & Multifocal Serpiginoid Choroiditis with latent TB	Unclear	Interferon alpha-2a, AZA, or AZA + CsA	HRZE 2 months, HR 10 months	Group 1 = ATT + immunosuppressants (4 patients) Group 2 = CS ± immunosuppressants (11 patients)	Active inflammation at the final visit: Group 1 = 2/4 Group 2 = 0/11
La Distia Nora et al. (2014) - Netherlands(La Distia Nora et al., 2014)	Uveitis with positive IGRA	Persistence of inflammation	CS ± MTX, AZA, or CsA	RHZ 2 months, RH 4 months	Immunosuppressants + ATT: 12	Not analysed separately

*MTX = methotrexate, CsA = Cyclosporine, AZA = azathioprine, ADA = adalimumab, BCVA = best-corrected visual acuity, H = Isoniazid, R = rifampicin, Z = pyrazinamide, E = Ethambutol, CS = corticosteroid, SC = subcutaneous, IGRA = interferon-gamma release assay, ATT = anti-tubercular therapy.
[a] Remission: Clinically inactive ocular inflammation (further detail was not described).
[b] Progression: clinical worsening of the ocular inflammation, including assessment by multimodal ocular imaging modalities.

in 10/13 eyes), and paradoxical worsening (success in 2/2 eyes) during the ATT course. The timing of a dexamethasone implant varied between 0 and 4 weeks after ATT initiation.(Agarwal et al., 2018) Another report on nine eyes with a specific subset of multifocal serpiginous choroiditis also supported (inflammation control in 8/9 eyes) the use of a dexamethasone implant.(Jain et al., 2018) Besides, dexamethasone implants successfully controlled inflammation among those experiencing a recurrence of inflammation when oral corticosteroids were tapered below 10 mg/day.(Fonollosa et al., 2016) In addition, although only described in a few cases, intravitreal methotrexate(Julian et al., 2013; Sahin and Ziaei, 2014; Tsui et al., 2021) and bevacizumab(Invernizzi et al., 2015) have also been reported to control inflammation satisfactorily.

VEGF is known to be elevated in the serum of active pulmonary TB patients and reflects changes in endothelial function.(Polena et al., 2016; Saghazadeh and Rezaei, 2022) VEGF is involved in the modulation of angiogenesis and granuloma formation, which serves as the niche for *Mtb*.(Saghazadeh and Rezaei, 2022) It is postulated that secreted VEGF is also responsible for monocyte/macrophage accumulation and inflammation. The newly formed blood vessels tend to be fragile and hyperpermeable, potentially involved in *Mtb* dissemination, recruitment of inflammatory cells incapable of *Mtb* elimination or even support its growth, and participation in cell death signalling.(Maison, 2022) *In vitro* studies showed that *Mtb*-infected RPE cells secreted higher amounts of VEGF than uninfected RPE cells.(La Distia Nora et al., 2018d; Singh et al., 2021) In further support of enhanced local ocular VEGF production is the observation that vitreous VEGF level was higher in TB-uveitis than in other uveitis entities. However, available data on this latter was inconsistent.(Singh et al., 2021),(Schrijver et al., 2022) Studies with a significant number of patients are scarce, however, a recently published case report shows the utility of anti-VEGF injection in the resolution of choroidal granuloma.(M. Agarwal et al., 2020) The authors described a TB-uveitis case who received weekly intravitreal bevacizumab injections in combination with moxifloxacin (three injections) along with ATT. With each injection, the vitreous level of VEGF was measured, and a significant decline in its level was observed. Visual acuity improved (from hand movement to 6/9) within one month after the first injection, with noticeable regression of the choroidal granuloma.(M. Agarwal et al., 2020) However, a conflicting case has been reported by Babu et al. where a patient with bilateral choroiditis received bilateral intravitreal ranibizumab injection alongside ATT and systemic corticosteroids. While the injection improved the left eye, the right eye worsened. Subsequent intravitreal injection of moxifloxacin combined with dexamethasone (without anti-VEGF) helped resolve the lesion.(Babu et al., 2022)

Besides anti-VEGF, octreotide (a somatostatin analog) offers an alternative to treat uveitic macular edema. Somatostatin receptors are present in human RPE.(van Hagen et al., 2000) Additionally, macrophages express somatostatin, which is involved in granulomatous inflammation. Somatostatin receptors are upregulated during the differentiation of macrophages from monocytes and the maturation of thymocytes.(Dalm et al., 2003; Ferone et al., 2004) Even though the

precise mechanism of reducing uveitic macular is still unclear, two studies depicted the efficacy of octreotide. A 100 μg subcutaneous injection (three times daily) or a long-acting depot formulation of octreotide acetate (monthly 20-mg intramuscular injection), resolved chronic uveitic macular edema in 7 out of 9 eyes that were unresponsive to prior corticosteroids (local or systemic), oral nonsteroidal anti-inflammatory agents, and acetazolamide.(Kafkala et al., 2006) Another case series further confirmed the potential efficacy of long-acting octreotide as this treatment had a macular edema-reducing effect in 70% of treated episodes.(Missotten et al., 2007) Prospective studies with a larger sample size are warranted to elucidate the potential benefit of additional octreotide treatment for TB-uveitis. Interestingly, octreotide is being developed for local intraocular application by using nanoparticle technology, which brings hope for widespread use in treating macular edema in the upcoming years.(Amato et al., 2020)

5. Treatment monitoring in tubercular uveitis

5.1. Paradoxical worsening

Clinical worsening or progression of the active lesion(s) while on ATT (with or without concomitant corticosteroids) frequently occurs between 3 and 8 weeks after ATT initiation, especially among those showing serpiginous-like choroiditis (SLC)(A. Agarwal et al., 2020b; Esen et al., 2016; Kalra et al., 2022; Mishra et al., 2020) and multifocal choroiditis (MFC).(Aggarwal et al., 2019) The mechanism underlying this worsening in TB-uveitis has not been clearly elucidated. The release of mycobacterial antigens following ATT administration and the occurrence of a delayed-type hypersensitivity reaction have been proposed as the underlying mechanisms. This is partly supported by the higher baseline level of IL-10 as well as increasing levels of IFN-γ, transforming growth factor-β (TGF-β), and TNF-α during treatment among those with paradoxical reactions.(Ganesh et al., 2019) Several clinical factors can help to predict paradoxical worsening, including baseline best corrected visual acuity (BCVA) > 0.7 logMAR, advanced grade of initial lesion opacity, and disc involvement (optic neuritis, disc elevation/edema, or active choroiditis extending to within 1 disc diameter of the optic nerve head).(A. Agarwal et al., 2020b) An algorithm using automated colour fundus image processing showed promising utility in developing an ocular image-based prediction model for paradoxical worsening(Kalra et al., 2022), but this requires further validation in other studies.

Because of the current well-described paradoxical reaction, the attending ophthalmologist should stick with the ATT treatment and concomitant use of corticosteroids. However, an alternative differential diagnosis, such as other autoimmune-related uveitis or another infection mimicking TB-uveitis, as a cause for the paradoxical worsening, should be kept in mind. The diagnosis can be revised if the clinical phenotype changes or remains unresponsive to treatment. Further diagnostics, including drug resistance tests (i.e., GeneXpert), are recommended if the continuation of ATT with escalated corticosteroid therapy fails to show improvement beyond the initial 2–3 months of treatment,(Ganesh et al., 2019) although this is practically difficult to test in an ocular fluid sample.

5.2. Current consensus on treatment outcome definition

The COTS nomenclature working group defined remission and cure as the outcomes of TB-uveitis treatment, as stated below. Of note, patients unable to taper systemic corticosteroids to <10 mg/day or topical steroid drops to <2 drops/day and the continuation of steroid-sparing immunosuppressants do not fit into these criteria.(A. Agarwal et al., 2020a; Agrawal et al., 2019)

- Remission: inactive disease (grade 0 cells/no inflammation) for at least 3 months following a complete ATT course.
- Cure: inactive disease (grade 0 cells/no inflammation) 24 months following a complete ATT course.

6. Host-directed therapies for tuberculosis: possible implications on tubercular uveitis treatment

Modulation of host immune cell function against *Mtb* can be achieved via several approaches(Kilinç et al., 2021) (Fig. 5).

1) Enhancing phagolysosome activity and autophagy to improve intracellular killing of *Mtb*,
2) Reducing granulomatous lesions to limit *Mtb* spread,
3) Reducing inflammation-associated tissue damage,
4) Enhancing cellular responses against the infection and associated inflammation, and
5) Skewing T-lymphocytes responses towards Th1 to stimulate cellular immunity.

Knowledge of the underlying immune responses at each stage of TB pathogenesis underpins studies in the development of HDT, mostly from *in vitro* or animal studies on pulmonary TB. This section will focus on selected HDTs that have been applied to human subjects. Of note, none of these mentioned modalities has been applied to TB-uveitis so far. However, as we gain more immune-pathogenic knowledge in TB-uveitis, application of specific HDT for TB-uveitis is to be expected in the future.

6.1. Metformin

Metformin has been repurposed for TB treatment as it may enhance autophagy. It may limit *Mtb* growth by stimulating the formation of reactive oxygen species and phagolysosome fusion.(Guler et al., 2021) In a *Mtb* guinea pig model for granuloma formation, metformin dampened inflammation and significantly reduced lung pathology.(Frenkel et al., 2020) Further study observed the downregulation of genes involved in oxidative phosphorylation, mammalian target of rapamycin (mTOR) signalling, and type I IFN response pathways.(Lachmandas et al., 2019) Meanwhile, genes involved in phagocytosis and the production of reactive oxygen species were upregulated.(Lachmandas et al., 2019) Adjunct metformin, combined with ATT, increased the probability of sputum conversion at two months of treatment.(Yu et al., 2019) It also lowered the mortality rate among people with diabetes, based on a recent systematic review.(Yu et al., 2019) However, another study reported that additional metformin treatment significantly accelerated lung healing but did not accelerate sputum culture conversion.(Padmapriydarsini et al., 2022)

Autophagy is a conserved process that delivers proteins, organelles, and invading pathogens to lysosomes for degradation.(Liang et al., 2017) However, *Mtb* can escape and block the maturation of autophagolysosomes, preventing it from an effective pathogen-killing mechanism.(Liang et al., 2017) Although initial findings showed the benefit of adjunct metformin in TB patients with diabetes mellitus,(Yu et al., 2019) the potential use of metformin for TB-uveitis through its autophagy enhancement needs further investigation. As *Mtb* can infect RPE,(La Distia Nora et al., 2018d) we assume that theoretically, the discovery of an effective drug that enhances the killing of *Mtb* residing in RPE can accelerate clinical improvement and prevent chronic ocular inflammation.

6.2. Phosphodiesterase and mTOR inhibition

Phosphodiesterase inhibitors suppress TNF-α while increasing intracellular signalling pathways involving cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP).(Guler et al., 2021) Autophagy is regulated by the serine/threonine kinase mTOR. Inhibition of mTOR stimulates autophagy in macrophages and has been suggested to enhance intracellular killing of *Mtb*.(Singh and

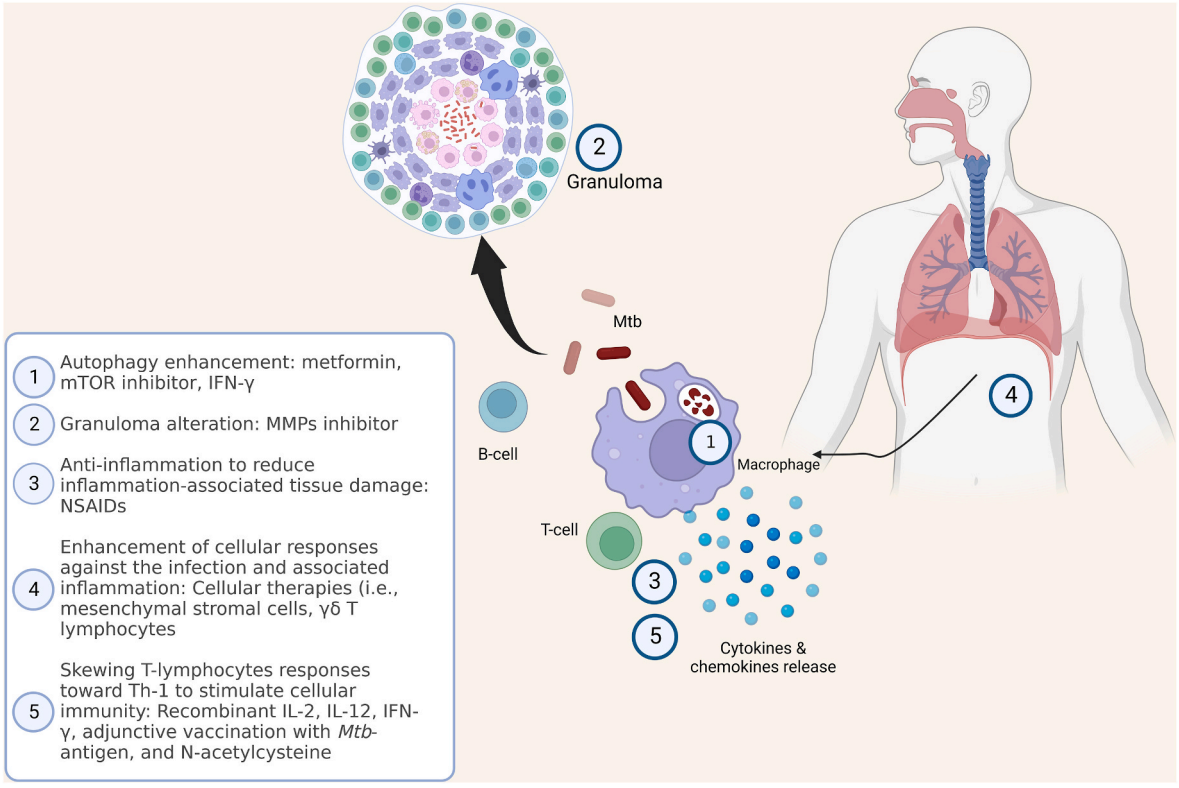

Fig. 5. Schematic strategies of HDT for pulmonary TB based on currently available evidence from clinical trials. These concepts and strategies are potential treatments for TB-uveitis in the future (Created with BioRender.com).

Subbian, 2018) mTORC1 inhibition by nitazoxanide could enhance autophagy and inhibit *Mtb* proliferation *in vitro*.(Lam et al., 2012) A recent trial showed that adjunctive everolimus (mTOR inhibitor) and CC-11050 (type 4 phosphodiesterase inhibitor) had beneficial effects. These compounds were safe and may facilitate lung function recovery but not early sputum culture conversion in pulmonary TB.(Wallis et al., 2021) Similar to metformin, more research is needed to evaluate its potential use in TB-uveitis.

6.3. Matrix metalloproteinases (MMPs) inhibition

TB granuloma is currently thought to be a protective immune response to TB. However, the granuloma can also serve as a potential niche for further *Mtb* replication and dissemination. MMPs are a family of endopeptidases that have properties to degrade extracellular matrix (ECM) components, and their activity is controlled by tissue inhibitors of metalloproteinases (TIMPs).(Sabir et al., 2019)Although the primary function of MMPs is related to ECM degradation and remodelling,(Sabir et al., 2019) these endopeptidases are also involved in angiogenesis, inflammation, and immune responses.(Ohno-Matsui et al., 2003; Xu et al., 2018) During inflammation, the expression and activity of most MMPs increases in immune (including monocytes/macrophages) and non-immune cells, which is controlled by different cytokines and transcription factors, including IFN-γ, IL-12, IL-17, TNF-α, NF-κB, and STAT3.(Sabir et al., 2019) Increased MMP expression, including MMP-1, -3, -9, and -12 and MMP-10, has been demonstrated in TB lung pathology.(Parasa et al., 2017) Furthermore, elevated levels of MMP-1, -2, -7, -8, and -9 have also been detected in circulation.(Kumar et al., 2020) MMP-9, induced by ESAT-6, is involved in monocyte/macrophage recruitment during the initial phase of granuloma formation at the site of infection.(Sabir et al., 2019) Meanwhile, MMP-3, MMP-8, and MMP-13 are more involved in tissue remodelling at the site of granuloma.(Sabir et al., 2019)

To date, doxycycline is the only FDA-approved MMP inhibitor and has been explored as an HDT for TB. Adjunct doxycycline treatment for two weeks at 100 mg twice a day during ATT resulted in reduced pulmonary cavity volumes that, however, did not reach statistical significance compared to the placebo-treated patients.(Miow et al., 2021) Reduced plasma MMP-1, -8, -9, -12, and −13 levels, suppressed degradation of type I collagen and elastin, and reduced blood transcriptional levels of several immune response genes (IRF1, APOL1, FCGR1A, FCGR1B, GBP5, and GBP6) were observed upon doxycycline treatment. (Miow et al., 2021) Although the precise mechanism of granuloma formation and remodelling in TB-uveitis is not fully understood, the additional use of doxycycline (or another MMPs inhibitor) to limit retinal damage in TB-uveitis with posterior segment inflammation warrants further investigation.

6.4. N-acetylcysteine

The biological effect of N-acetylcysteine is attributed to its antioxidant properties. It may also lower inflammatory cytokine production (e.g TNF-α) by replenishing intracellular glutathione, which is decreased in the peripheral blood mononuclear cells of TB patients.(Venketaraman et al., 2008) Furthermore, it may limit *Mtb* growth by its immunomodulatory function, resulting in adequate production of Th1 cytokines (e.g. IL-2, IFN-γ), which are crucial to controlling *Mtb* effectively.(Guerra et al., 2011; Guler et al., 2021) The result of a study on adjunctive N-acetylcysteine seems promising, as it significantly increased glutathione peroxidase levels, accelerated sputum conversion, and enhanced radiological improvement among pulmonary TB patients.(Mahakalkar et al., 2017) Further investigation is warranted, especially in TB-uveitis presenting with clinical pictures strongly suggestive of *Mtb* presence in the eye, such as choroidal tuberculoma and serpiginous-like choroiditis.

6.5. Cyclooxygenase (COX) inhibitor

Non-steroidal anti-inflammatory drugs (NSAIDs), including

ibuprofen, indomethacin, diclofenac, and aspirin, have been explored as candidates for HDT against *Mtb*. It was observed that the inhibition of COX reduces the prostaglandin E2 (PGE2) level, which may inhibit phagocytosis and *Mtb* killing at the late stage of infection.(Kroesen et al., 2017) An *in-vitro* study revealed that indomethacin reduced Treg activity and enhanced Th1 immunity, as shown by the increased production of IL-2, TNF-α and IFN-γ by $CD4^+$ T-lymphocytes.(Tonby et al., 2016) Thereby, it can be expected that COX inhibitor may increase Mtb clearance. Moreover, a hypercoagulable state that may be present in the advanced stage of TB can also be managed with low-dose aspirin. (Kroesen et al., 2017) Although it does not reduce the mortality rate, aspirin significantly reduces the onset of stroke among patients with TB meningitis.(Rohilla et al., 2021) In addition, adjunctive aspirin for treating diabetic patients with pulmonary TB increased the sputum conversion rate (86.7% vs 53.8%; $p = 0.031$).(Wang et al., 2020) The observed beneficial effect of NSAIDs raises the possibility of repurposing these drugs to be used to combat TB.(Kroesen et al., 2017; Maitra et al., 2016) COX inhibitors might be considered an adjunct treatment in TB-uveitis, particularly for those with a clinical picture of retinal vasculitis or patients with an increased risk of cardiovascular complications.

6.6. Cellular therapies

Mesenchymal stromal cells (MSCs) exhibit multipotent differentiation capacity and display tissue repair and immunosuppressive capacities by limiting the proliferation of T lymphocytes ($CD4^+$ and $CD8^+$), B lymphocytes, and NK cells.(Joshi et al., 2015) MSCs also modulate dendritic cells (DC) and induce Tregs.(Joshi et al., 2015) The immunosuppressant properties of MSCs rely on cell-to-cell interactions as well as the secretion of soluble factors, such as TGF-β1, hepatocyte growth factor (HGF), and PGE2.(Joshi et al., 2015) MSCs can phagocytose *Mtb* and restrict *Mtb* growth through autophagy.(Khan et al., 2017) A phase I trial with a single infusion of autologous bone marrow-derived MSCs as an adjunct treatment was conducted in multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB and was found to be safe.(Skrahin et al., 2014) In the follow-up study, the cure rate for patients who received MSCs was three times higher than that for those treated with anti-TB treatment only.(Skrahin et al., 2016)

Circulating Vγ9Vδ2 T lymphocytes represent a major innate-like peripheral T-lymphocyte subset activated by non-protein phosphoantigens derived from microbial pathogens, including mycobacteria.(Poupot and Fournié, 2004) Expansion of the Vγ9Vδ2 T lymphocyte pool occurs following infection with a variety of microbial pathogens, including *Mtb*.(Gay et al., 2022; Poupot and Fournié, 2004) These cells can directly kill infected cells, mainly through the release of lytic molecules, cytokines, and apoptosis but also modulate functions of other innate and adaptive immune cells.(Gay et al., 2022) However, a loss of cytotoxic activity of Vγ9Vδ2 T lymphocytes has also been described in active TB.(Gay et al., 2022) Vγ9Vδ2 T lymphocyte-based immunotherapy could be of interest in treating TB. A preliminary report on the utility of allogeneic Vγ9Vδ2 T lymphocytes treatment in tuberculosis has been recently published (ClinicalTrials.gov registration number: NCT03575299).(Liang et al., 2021) In that study, Vγ9Vδ2 T lymphocytes were obtained from healthy donors, expanded *ex vivo,* and subsequently infused into patients. Based on the published report, this procedure was safe, and lung lesions were reduced in all patients.(Liang et al., 2021) Moreover, CD56 high-expressing NK cells were reduced, while CD56 low-expressing NK cells were increased. (Liang et al., 2021) CD56 low $CD16^+$ high expressing NK cells have a lesser capability in cytokine production than CD56 high CD16 low-expressing NK cells, the former exhibits significantly higher cytotoxic activity.(Poli et al., 2009) This suggests that the anti-TB effect of Vγ9Vδ2 T lymphocytes treatment is, potentially, mediated through a shift in the distribution of NK cell sub-populations and related functions. (Liang et al., 2021) Besides the effect on NK cells, Vγ9Vδ2 T lymphocyte treatment altered the distribution of other immune cell populations in peripheral blood, including increased effector memory T-lymphocytes (both $CD4^+$ effector memory and $CD8^+$ effector memory).(Liang et al., 2021)

To be adopted in TB-uveitis treatment, the ability of cellular therapies to modulate other potential cells contributing to the granulomatous inflammation needs to be investigated. As the inner and outer BRB are important upon *Mtb* infection, cellular therapies that also strengthen the immunological response of microglia, Müller cells, and astrocytes against *Mtb* would be of interest. The integrity of the inner BRB depends upon pericyte-retinal endothelial cell interactions that involve autocrine and paracrine signaling pathways, including the VEGF and TGF-β signaling pathways.(Huang, 2020) Besides, retinal microglia, a resident immune cell involved in immune surveillance and the regulation of neurogenesis, would likely be important in the immune response in uveitis,(Okunuki et al., 2019) but so far, studies on this are limited. Moreover, recently it was demonstrated that IL-1β stimulates the proliferation and reactivity of microglia, which was associated with a reduction in retinal damage.(Todd et al., 2019) Importantly, microglia are crucial to facilitate passage of primed inflammatory cells across the BRB, and the absence of microglia prevents uveitis, as shown in the experimental autoimmune uveitis.(Okunuki et al., 2019) Furthermore, the retinal microenvironment contains cell and molecules involved in the establishment of ocular immune privilege, for instance, through CD95 ligand (CD95L/Fas ligand) that induces apoptosis of infiltrated inflammatory cells.(Keino et al., 2018) RPE cells also have the ability to convert activated T lymphocytes into Tregs via TGF-β signaling and express PD-L1 that suppresses IRBP-specific T lymphocytes exposed to IL-17 and IFN-γ.(Keino et al., 2018) T lymphocyte profiling from the peripheral blood of TB-uveitis patients revealed a low frequency of Tregs and a high CD4+/CD8+ T lymphocyte ratio.(Sharma et al., 2018a, 2018b) However, in vitreous from TB-uveitis patients, comparable $CD4^+$ and $CD8^+$ lymphocyte numbers were observed. (Sharma et al., 2018b) Interestingly, even though T lymphocytes in the vitreous of TB-uveitis were significantly more abundant than in the non-uveitis controls, the percentage of viable T-lymphocytes was significantly lower.(Sharma et al., 2018b) These findings highlight the difference in the composition of the infiltrating T lymphocyte population in the eye compared to the systemic compartment, with a higher proportion of $CD8^+$ T lymphocytes and the immune-privilege associated regulatory mechanisms to which the ocular immune response is exposed in TB-uveitis. Thus, the response of these cells toward cellular therapies warrants further exploration and should be taken into account when deciding on cellular therapies in TB-uveitis that are multipotent for their immunosuppression and retina-specific repair capacities.

6.7. Enhancement of cellular and humoral immune responses

IL-2 is a crucial cytokine within the immune system as it is involved in the activation of T-lymphocytes.(Ross and Cantrell, 2018) Cell-mediated immunity involving $CD4^+$ and $CD8^+$ T lymphocytes is crucial in TB pathogenesis. Treatment with recombinant human IL-2 has been tried to enhance Th1 activity against *Mtb*. Accelerated sputum smear conversion, sputum culture conversion, and pulmonary radiological resolution rates were achieved with IL-2 treatment.(Shen et al., 2015) However, further studies with a large number of patients yielded contradictory results.(Johnson et al., 2003; Nie et al., 2022)

IFN-γ could enhance *Mtb* killing within macrophages via induction of autophagy by counteracting IL-6.(Dutta et al., 2012) Importantly, it was shown that *Mtb* could dampen IFN-γ signalling and inhibit HLA class II-antigen processing, allowing *Mtb* to escape cellular immune surveillance.(Pai et al., 2003) Thus, IFN-γ treatment is expected to improve *Mtb*-antigen presentation. The direct administration of IFN-γ to enhance Th1-mediated immunity has also been explored. Subcutaneous IFN-γ was used in the treatment of MDR pulmonary TB but did not improve the clinical outcome.(Park et al., 2007) Also, aerosolised IFN-γ treatment was not beneficial in the treatment of MDR pulmonary TB, although no

control group was included in this study.(Koh et al., 2004) Furthermore, adjunct treatment with IL-12 (recombinant IL-12, 300 ng/kg body weight subcutaneously twice weekly for three months), an enhancer of IFN-γ, alongside ATT improved the treatment outcome of a patient with multiple site TB abscesses.(Greinert et al., 2001) Unfortunately, the effect of the treatment on Th1 skewing was not explored in those aforementioned studies.

H56:IC31subunit vaccine, containing the *Mtb* antigens (Ag85B, ESAT-6, and Rv2660c (H56)) was deployed to enhance humoral and cellular immune responses (antigen-specific T lymphocytes).(Aagaard et al., 2011) Jenum et al. conducted a four-arm phase I/II randomised controlled trial using the H56:IC31 vaccine and etoricoxib (a cyclooxygenase-2-inhibitor) in addition to standard ATT (ClinicalTrials.gov registration number: NCT02503839).(Jenum et al., 2021) In the eterocoxib group, there was no significant difference in the level of IFN-γ and IL-2 responses from isolated T-lymphocytes from TB patients in response to H56 fusion protein, Ag85B, or ESAT-6 stimulation. However, patients receiving two doses of H56:IC31 showed increased IFN-γ and IL-2 responses. It was concluded that H56:IC31 vaccination in TB patients resulted in an improved immune response compared to ATT alone, without major safety concerns.(Jenum et al., 2021) Since TB-uveitis patients with a higher QFT level have a greater chance for an ATT response,(Danjou et al., 2021) the induction of the host's IFN-γ and IL-2 responses seems promising to expedite clinical resolution in TB-uveitis. Also, it is important to study the effect of the aforementioned induction of the host IFN-γ and IL-2 responses on retinal glial cells. IFN-γ, for instance, stimulates TNF-α and IL-6 as well as ICAM-1 expression by Müller cells.(Drescher and Whittum-Hudson, 1996) Stimulation of ICAM-1 expression influences the migration of leucocytes in the inflamed tissue.(Drescher and Whittum-Hudson, 1996). Moreover, retinal glial cells not only exert innate and adaptive immune functions but also possess capacity for autophagy and apoptosis, which may also play a role in *Mtb* control and surveillance within the retinal-specific microenvironments.(Lorenz et al., 2021; Qin et al., 2022) Therefore, exploring the contribution of the different retinal cell types to *Mtb* surveillance and TB-uveitis and the role of cytokines such as IFN-γ herein requires further study.

7. The burden of drug-resistant TB

The use of second-line ATT, including the use of alternative ATT combinations to treat potential drug-resistant *Mtb*, has not been widely incorporated in clinics. The extent of drug-resistant *Mtb* strains detected in the ocular fluid/tissue has not been widely explored, as we still face challenges in finding *Mtb* footprints. *Mtb* resistance can be expected in patients from high-burden countries. Rifampicin-resistant *Mtb* can be expected in 14% of the cases.(Zignol et al., 2018) Bansal et al. reported that rifampicin- and isoniazid-resistant *Mtb* was present in their TB-uveitis cohort, with a positive response towards a combination of MDR TB treatment, systemic corticosteroids, and azathioprine.(Bansal et al., 2015) The extent of MDR and XDR problems should be considered among those residing in countries with a high MDR TB burden. It is hoped that TB-uveitis treatment with HDT in the future will also be able to overcome this MDR and XDR problem, which may be currently overlooked.

8. Future directions

The current understanding of intraocular TB infection is especially based on the observation of the RPE response in the presence of *Mtb*. *Mtb* may reach the ocular structure via intra- or extracellular routes, which is argued to explain the diverse phenotypes of TB-uveitis as both routes differ in BRB breaching.(Damera et al., 2021) TLRs on RPE recognise *Mtb* structures.(Nazari et al., 2014) Once phagocytosed, RPE would orchestrate further immune regulation against *Mtb*.(La Distia Nora et al., 2018d; Nazari et al., 2014)

Meanwhile, the current development of HDT for TB is based on lung pathology, mainly involving macrophages, lung alveolar cells, and cytokines involved with the lung lesions.(Guler et al., 2021) Granulomas are important structures in the pathology of TB and are also formed in the ocular structures. Granuloma formation in TB can occur during the primary infection or reactivation phase in a previously latently infected person. As a dynamic structure, classic TB granuloma, as found in the lungs, might be constructed by complex interplay between various types of immune and non-immune cells.(Guirado and Schlesinger, 2013) Formation of TB granuloma involves interaction between macrophages, epithelioid cells, multinucleated giant cells, B and T lymphocytes, neutrophils, and fibroblasts, that results in a central necrotic area within the granuloma where *Mtb* is mainly sequestered.(Cronan, 2022; Guirado and Schlesinger, 2013) Secreted CCL2/MCP-1, CCL12, and CCL13 that bind to the CCR2 receptor lead to early macrophage recruitment in the infected tissue.(Guirado and Schlesinger, 2013) Infected macrophages secrete TNF-α which is essential for appropriate granuloma formation, as altered TNF-α signaling resulted in fatal TB progression with a lack of epithelioid cells, less-organized granuloma formation, and profound mycobacterial replication.(Cronan, 2022; Domingo-Gonzalez et al., 2016; Kindler et al., 1989) This granulomas not only combat *Mtb* but also become a source of inflammation, which warrants further exploration to limit self-tissue damage.(Guler et al., 2021; Kolloli and Subbian, 2017) NK cells also participate in cytokine signaling in response to *Mtb* antigens, induce cell-mediated cytotoxicity, and bridge innate and adaptive immune responses against *Mtb*.(Garand et al., 2018) The adaptive immune response induced by *Mtb* infection is mainly evoked by dendritic cells trafficking to the lymph nodes and subsequent priming of naïve T lymphocytes. This will result in a dominant Th1 response that is characterized by marked IFN-γ secretion by $CD4^+$ T lymphocytes.(Domingo-Gonzalez et al., 2016) In addition, activated $CD8^+$ T lymphocytes can also produce IFN-γ and exert cytotoxic activity.(Guirado and Schlesinger, 2013) Moreover, Th17 cells will secrete IL-17, which then primarily stimulates the production of the G-CSF and IL-8 that subsequently attract neutrophils.(Mourik et al., 2017; Zenaro et al., 2009) Neutrophils also exert *Mtb* killing capacity through nicotinamide adenine dinucleotide phosphatase (NADPH) mechanism.(Yang et al., 2012) However, accumulation of necrotic neutrophils is associated with chronic inflammation and tissue damage.(Hilda et al., 2020) B cells, aside from acting as antigen presenting cells, are also critical in enhancement of Th1 immunity and granuloma formation as they promote the proliferation and capacity of IFN-γ-producing $CD4^+$ T lymphocytes.(Chen et al., 2023) The general view of an adaptive immune response to TB is thus depicted by a dominant Th1 response with robust IFN-γ secretion, although the pathogenesis clearly involves other cellular components, proinflammatory cytokines (such as TNF-α, IL-1β, IL-6, IL-8, and IFN-α/β), as well as anti-inflammatory cytokines (such as TGF-β and IL-10).(Cronan, 2022) The local production of various cytokines thus induces immune cells recruitment and *Mtb* killing. Eventually, a well-regulated balance between pro- and anti-inflammatory mechanisms within TB granulomas will determine whether *Mtb* can be controlled. Within the microenvironment of a granuloma, *Mtb* can persist in the granuloma for a long time, so-called latent TB, which is asymptomatic. Several eliciting stimuli that alter host immunological status, including malnutrition, diabetes, and even aging, can reactivate the contained *Mtb*.(Guirado and Schlesinger, 2013)

Optimization of al HDT development in the setting of TB-uveitis requires further in-depth knowledge on the immunopathogenesis of granuloma formation within the ocular structures. Alternative regulation of ocular granuloma formation can be expected as RPE cells display a lower phagocytic capacity and a different transcriptomic response to *Mtb* infection when compared to *Mtb* –infected macrophages.(La Distia Nora et al., 2018d) This raises the possibility of a specific pathological process involved in granuloma formation within the eye that does not occur in pulmonary/systemic TB.

Even though significant research efforts to improve the

understanding of TB-uveitis pathophysiology have been made, still large gaps in our current knowledge interfere with effective diagnosis and adequate treatment management. With multi-omics approaches, pathways of host-pathogen responses and immunoregulatory processes involved in TB-uveitis might be better understood. Identification of key pathways involved in the pathology of TB-uveitis might uncover novel diagnostic approaches as well as target molecules and/or pathways for disease treatment. Moreover, we consider accurate detection of *Mtb* in ocular tissue and identification of biomarkers that are capable of distinguishing the various subtypes of patients, particularly those who might pose induced immune responses, to be critical for optimal patient-directed treatment.(Ludi et al., 2023)

8.1. A lesson learned from immune checkpoint inhibitor treatment for host directed therapy in TB

Immune checkpoint inhibitors (ICI), such as anti-programmed cell death 1 (PD-1)/programmed cell death ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) signalling, have been used for cancer treatment.(Elkington et al., 2018; Langan et al., 2020) There are concerns about new onset TB disease following such treatment, even though the estimated incidence rate might be low (3/1,144 cancer patients treated with ICI).(Zaemes and Kim, 2020) Despite being used for reversing tolerance to tumor tissue, the development of TB following ICI that enhance effector T lymphocytes seems counterintuitive.(Elkington et al., 2018) However, it is hypothesised that the immune homeostasis within TB granulomas is altered and facilitates *Mtb* spread. As a result of PD-L1 inhibition, augmented cytokine responses could lead to excessive inflammatory cell activation and the destruction of the granuloma-associated extracellular matrix, thereby enhancing *Mtb* growth and spread.(Tezera et al., 2020) Altogether, this data suggests that finding an appropriate HDT is challenging and should take differences between systemic and local (within the granuloma) immune regulation in TB into account.

8.2. Harnessing HDT for tubercular uveitis: Are we there yet?

The applicability of the current HDTs to TB-uveitis patients may be of limited value unless: (1) substantial evidence supports their utility in both pulmonary and extrapulmonary TB, (2) a specific drug target involved in TB-uveitis that dampens various inflammatory pathways relevant to the ocular condition is discovered, and (3) treatment-directed patient classification that focuses on underlying pathological processes despite various clinical spectrums is validated. Many other HDT candidates than those discussed above are being investigated. The drug candidates might serve as an adjunct treatment of ATT for TB-uveitis.

9. Conclusion

TB-uveitis is one of the uveitis entities that leads to diagnostic and treatment problems among clinicians. The diversity of its clinical picture without a reliable single gold-standard diagnostic test makes it challenging to diagnose and treat TB-uveitis accurately. On one side, *Mtb* might be detected in a paucibacillary manner in the ocular tissue, but an autoimmune process without demonstrable presence of ocular *Mtb* might also play a pivotal role. Some conditions where the diagnosis of TB is not straightforward pose difficulties in deciding who needs and who does not need ATT, particularly if one is facing patients with a positive TST or IGRA but without an ocular phenotype strongly suggestive of TB-uveitis or other signs of TB-disease. Meanwhile, successful treatment with ATT was depicted in many studies, even though treatment results without ATT were not immensely inferior; the latter finding should not be overlooked. The long duration and potential adverse reactions to ATT underline the need for further studies to identify those patients in actual need of ATT. Moreover, the current development of HDTs that specifically modulate host responses to *Mtb* without ignoring the importance of antimycobacterial therapy might in the future also prove to be of value for the treatment of TB-uveitis. It is imperative to emphasise the importance of more studies on developing a new approach in TB-uveitis diagnostics and the further development of precise treatment strategies based on the patient-specific underlying inflammatory process. This requires us to greatly increase our understanding of the pathogenesis of TB-uveitis in the coming years.

Author statement

Ikhwanuliman Putera: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing Original Draft/Review/Editing.

Benjamin Schrijver: Conceptualization, Formal analysis, Review & Editing.

Josianne C.E.M. ten Berge: Formal analysis, Review & Editing.

Vishali Gupta: Validation, Editing & Review, Supervision.

Rina La Distia Nora: Formal analysis, Editing & Review, Supervision.

Rupesh Agrawal: Review and Editing (revision stage), validation (revision stage)

P. Martin van Hagen: Conceptualization, Validation, Review & Editing, Supervision.

Saskia M. Rombach: Conceptualization, Editing & Review, Supervision.

Willem A Dik: Conceptualization, Formal analysis, Validation, Writing, Review & Editing, Supervision.

Declaration of competing interest

None.

Data availability

No data was used for the research described in the article.

Acknowledgement

RLDN was supported by Riset Inovatif Produktif - Lembaga Pengelola Dana Pendidikan (RISPRO-LPDP) [RISPRO/KI/B1/KOM/5/15219/4/2020]. The funding source supported the creation of the figures from Biorender.com. The funding source had no involvement in the collection, analysis, interpretation, writing of the report, and decision to submit the article for publication. RA has been supported by National Medical Research Council (NMRC) grants from Ministry of Health (MOH), Singapore (The grant details: MOH-CSAINV19nov-0003 and MOH-CSAINV22jul-0004). The funding source has provided funding to RA to conduct original studies related to ocular TB and nothing to do with this particular publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preteyeres.2023.101189.

References

Aagaard, C., Hoang, T., Dietrich, J., Cardona, P.-J., Izzo, A., Dolganov, G., Schoolnik, G. K., Cassidy, J.P., Billeskov, R., Andersen, P., 2011. A multistage tuberculosis vaccine that confers efficient protection before and after exposure. Nat. Med. 17, 189–194. https://doi.org/10.1038/nm.2285.

Adamus, G., 2018. Are anti-retinal autoantibodies a cause or a consequence of retinal degeneration in autoimmune retinopathies? Front. Immunol. 9, 765. https://doi.org/10.3389/fimmu.2018.00765.

Agarwal, A., Agrawal, R., Gunasekaran, D.V., Raje, D., Gupta, B., Aggarwal, K., Murthy, S.L., Westcott, M., Chee, S.P., McCluskey, P., Ling, H.S., Teoh, S., Cimino, L., Biswas, J., Narain, S., Agarwal, Manisha, Mahendradas, P., Khairallah, M., Jones, N., Tugal-Tutkun, I., Babu, K., Basu, S., Carreño, E., Lee, R., Al-Dhibi, H., Bodaghi, B.,

Invernizzi, A., Goldstein, D.A., Herbort, C.P., Barisani-Asenbauer, T., González-López, J.J., Androudi, S., Bansal, R., Moharana, B., Mahajan, S., Esposti, S., Tasiopoulou, A., Nadarajah, S., Agarwal, Mamta, Abraham, S., Vala, R., Singh, R., Sharma, A., Sharma, K., Zierhut, M., Kon, O.M., Cunningham, E., Nguyen, Q.D., Pavesio, C., Gupta, V., 2019. The collaborative ocular tuberculosis study (COTS)-1 report 3: polymerase chain reaction in the diagnosis and management of tubercular uveitis: global trends. Ocul. Immunol. Inflamm. 27, 465–473. https://doi.org/10.1080/09273948.2017.1406529.

Agarwal, A., Agrawal, R., Raje, D., Testi, I., Mahajan, S., Gunasekeran, D.V., Aggarwal, K., Murthy, S.I., Westcott, M., Chee, S.-P., Mccluskey, P., Ho, S.L., Teoh, S., Cimino, L., Biswas, J., Narain, S., Agarwal, Manisha, Mahendradas, P., Khairallah, M., Jones, N., Tugal-Tutkun, I., Babu, K., Basu, S., Carreño, E., Lee, R., Al-Dhibi, H., Bodaghi, B., Invernizzi, A., Goldstein, D.A., Herbort, C.P., Barisani-Asenbauer, T., González-López, J.J., Androudi, S., Bansal, R., Moharana, B., Esposti, S.D., Tasiopoulou, A., Nadarajah, S., Agarwal, Mamta, Abraham, S., Vala, R., Singh, R., Sharma, A., Sharma, K., Zierhut, M., Kon, O.M., Cunningham, E.T., Kempen, J.H., Nguyen, Q.D., Pavesio, C., Gupta, V., 2020a. Twenty-four month outcomes in the collaborative ocular tuberculosis study (COTS)-1: defining the "cure" in ocular tuberculosis. Ocul. Immunol. Inflamm. 28, 65–73. https://doi.org/10.1080/09273948.2020.1761401.

Agarwal, A., Handa, S., Aggarwal, K., Sharma, M., Singh, R., Sharma, A., Agrawal, R., Sharma, K., Gupta, V., 2018. The role of dexamethasone implant in the management of tubercular uveitis. Ocul. Immunol. Inflamm. 26, 884–892. https://doi.org/10.1080/09273948.2017.1400074.

Agarwal, A., Marchese, A., Rabiolo, A., Agrawal, R., Bansal, R., Gupta, V., 2020b. Clinical and imaging factors associated with the outcomes of tubercular serpiginous-like choroiditis. Am. J. Ophthalmol. 220, 160–169. https://doi.org/10.1016/j.ajo.2020.07.024.

Agarwal, M., Gupta, C., Mohan, K.V., Upadhyay, P.K., Jha, V., 2020c. Correlation of vascular endothelial growth factor with the clinical regression of tubercular granuloma. Indian J. Ophthalmol. https://doi.org/10.4103/ijo.IJO_1261_20.

Aggarwal, K., Agarwal, A., Deokar, A., Singh, R., Bansal, R., Sharma, A., Sharma, K., Dogra, M.R., Gupta, V., 2019. Ultra-wide field imaging in paradoxical worsening of tubercular multifocal serpiginoid choroiditis after the initiation of anti-tubercular therapy. Ocul. Immunol. Inflamm. 27, 365–370. https://doi.org/10.1080/09273948.2017.1373829.

Agrawal, R., Agarwal, A., Jabs, D.A., Kee, A., Testi, I., Mahajan, S., McCluskey, P.J., Gupta, A., Palestine, A., Denniston, A., Banker, A., Invernizzi, A., Fonollosa, A., Sharma, A., Kumar, Amitabh, Curi, A., Okada, A., Schlaen, A., Heiligenhaus, A., Kumar, Atul, Gurbaxani, A., Bodaghi, B., Islam Shah, B., Lowder, C., Tappeiner, C., Muccioli, C., Vasconcelos-Santos, D.V., Goldstein, D., Behra, D., Das, D., Makhoul, D., Baglivo, E., Denisova, E., Miserocchi, E., Carreno, E., Asyari, F., Pichi, F., Sen, H.N., Uy, H., Nascimento, H., Tugal-Tutkun, I., Arevalo, J.F., Davis, J., Thorne, J., Hisae Yamamoto, J., Smith, J., Garweg, J.G., Biswas, J., Babu, K., Aggarwal, K., Cimino, L., Kuffova, L., Agarwal, Mamta, Zierhut, M., Agarwal, Manisha, De Smet, M., Tognon, M.S., Errera, M.-H., Munk, M., Westcott, M., Soheilian, M., Accorinti, M., Khairallah, M., Nguyen, M., Kon, O.M., Mahendradas, P., Yang, P., Neri, P., Ozdal, P., Amer, R., Lee, R., Distia Nora, R. La, Chhabra, R., Belfort, R., Mehta, S., Shoughy, S., Luthra, S., Mohamed, S.O., Chee, S.-P., Basu, S., Teoh, S., Ganesh, S., Barisani-Asenbauer, T., Guex-Crosier, Y., Ozyazgan, Y., Akova, Y., Habot-Wilner, Z., Kempen, J., Nguyen, Q.D., Pavesio, C., Gupta, V., 2019. Standardization of nomenclature for ocular tuberculosis - results of collaborative ocular tuberculosis study (COTS) workshop. Ocul. Immunol. Inflamm. 1–11 https://doi.org/10.1080/09273948.2019.1653933.

Agrawal, R., Betzler, B., Testi, I., Mahajan, S., Agarwal, A., Gunasekeran, D.V., Raje, D., Aggarwal, K., Murthy, S.I., Westcott, M., Chee, S.-P., Mccluskey, P., Ho, S.L., Teoh, S., Cimino, L., Biswas, J., Narain, S., Agarwal, Manisha, Mahendradas, P., Khairallah, M., Jones, N., Tugal-Tutkun, I., Babu, K., Basu, S., Carreño, E., Lee, R., Al-Dhibi, H., Bodaghi, B., Invernizzi, A., Goldstein, D., Herbort, C.P., Barisani-Asenbauer, T., González-López, J.J., Androudi, S., Bansal, R., Moharana, B., Esposti, S., Tasiopoulou, A., Nadarajah, S., Agarwal, Mamta, Abraham, S., Vala, R., Singh, R., Sharma, A., Sharma, K., Zierhut, M., Kon, O.M., Cunningham, E.T., Kempen, J.H., Nguyen, Q.D., Pavesio, C., Gupta, V., 2020a. The collaborative ocular tuberculosis study (COTS)-1: a multinational review of 165 patients with tubercular anterior uveitis. Ocul. Immunol. Inflamm. 1–10 https://doi.org/10.1080/09273948.2020.1761400.

Agrawal, R., Betzler, B.K., Testi, I., Mahajan, S., Agarwal, A., Gunasekeran, D.V., Raje, D., Aggarwal, K., Murthy, S.I., Westcott, M., Chee, S.-P., McCluskey, P., Ho, S.L., Teoh, S., Cimino, L., Biswas, J., Narain, S., Agarwal, Manisha, Mahendradas, P., Khairallah, M., Jones, N., Tugal-Tutkun, I., Babu, K., Basu, S., Carreño, E., Lee, R., Al-Dhibi, H., Bodaghi, B., Invernizzi, A., Goldstein, D.A., Barisani-Asenbauer, T., González-López, J.J., Androudi, S., Bansal, R., Moharana, B., Esposti, S.D., Tasiopoulou, A., Nadarajah, S., Agarwal, Mamta, Abraham, S., Vala, R., Singh, R., Sharma, A., Sharma, K., Zierhut, M., Kon, O.M., Cunningham, E.T., Kempen, J.H., Nguyen, Q.D., Pavesio, C., Gupta, V., 2020b. The collaborative ocular tuberculosis study (COTS)-1: a multinational review of 447 patients with tubercular intermediate uveitis and panuveitis. Ocul. Immunol. Inflamm. 1–11 https://doi.org/10.1080/09273948.2020.1808226.

Agrawal, R., Gunasekeran, D.V., Agarwal, A., Carreño, E., Aggarwal, K., Gupta, B., Raje, D., Murthy, S.I., Westcott, M., Chee, S.P., McCluskey, P., Ling, H.S., Teoh, S., Cimino, L., Biswas, J., Narain, S., Agarwal, Manisha, Mahendradas, P., Khairallah, M., Jones, N., Tugal-Tutkun, I., Babu, K., Basu, S., Lee, R., Al-Dhibi, H., Bodaghi, B., Invernizzi, A., Goldstein, D.A., Herbort, C.P., Barisani-Asenbauer, T., González-López, J.J., Androudi, S., Bansal, R., Moharana, B., Mahajan, S., Esposti, S., Tasiopoulou, A., Nadarajah, S., Agarwal, Mamta, Abraham, S., Vala, R., Lord, J., Singh, R., Sharma, A., Sharma, K., Zierhut, M., Kon, O.M., Kempen, J., Cunningham, E.T., Rousselot, A., Nguyen, Q.D., Pavesio, C., Gupta, V., 2018. The collaborative ocular tuberculosis study (COTS)-1: a multinational description of the spectrum of choroidal involvement in 245 patients with tubercular uveitis. Ocul. Immunol. Inflamm. 1–11. https://doi.org/10.1080/09273948.2018.1489061.

Agrawal, R., Gunasekeran, D.V., Grant, R., Agarwal, A., Kon, O.M., Nguyen, Q.D., Pavesio, C., Gupta, V., 2017. Clinical features and outcomes of patients with tubercular uveitis treated with antitubercular therapy in the collaborative ocular tuberculosis study (COTS)-1. JAMA Ophthalmol 135, 1318–1327. https://doi.org/10.1001/jamaophthalmol.2017.4485.

Agrawal, R., Gupta, B., Gonzalez-Lopez, J.J., Rahman, F., Phatak, S., Triantafyllopoulou, I., Addison, P.K.F., Westcott, M., Pavesio, C.E., 2015. The role of anti-tubercular therapy in patients with presumed ocular tuberculosis. Ocul. Immunol. Inflamm. 23, 40–46. https://doi.org/10.3109/09273948.2014.986584.

Agrawal, R., Ludi, Z., Betzler, B.K., Testi, I., Mahajan, S., Rousellot, A., Kempen, J.H., Smith, J.R., McCluskey, P., Nguyen, Q.D., Pavesio, C., Gupta, V., 2022. The Collaborative Ocular Tuberculosis Study (COTS) calculator-a consensus-based decision tool for initiating antitubercular therapy in ocular tuberculosis. Eye. https://doi.org/10.1038/s41433-022-02147-7.

Agrawal, R., Testi, I., Bodaghi, B., Barisani-Asenbauer, T., McCluskey, P., Agarwal, A., Kempen, J.H., Gupta, A., Smith, J.R., de Smet, M.D., Yuen, Y. Sen, Mahajan, S., Kon, O.M., Nguyen, Q.D., Pavesio, C., Gupta, V., Agarwal, Mamta, Agarwal, Manisha, Aggarwal, A., Aggarwal, K., Agrawal, M., Al-Dhibi, H., Androudi, S., Asyari, F., Balasundaram, M.B., Murthy, K.B., Baglivo, E., Banker, A., Bansal, R., Basu, S., Behera, D., Biswas, J., Carreño, E., Caspers, L., Chee, S.P., Chhabra, R., Cimino, L., Concha del Rio, L.E., Cunningham, E.T., Land Curi, A.L., Das, D., Davis, J., DeSmet, M., Denisova, E., Denniston, A.K., Errera, M.H., Fonollosa, A., George, A., Goldstein, D.A., Crosier, Y.G., Gunasekeran, D.V., Gurbaxani, A., Invernizzi, A., Isa, H.M., Islam, S.M.d., Jones, N., Katoch, D., Khairallah, M., Khosla, A., Kramer, M., Kumar, Amitabh, Kumar, Atul, La Distia Nora, R., Lee, R., Lowder, C., Luthra, S., Mahendradas, P., Makhoul, D., Mazumdar, S., Mehta, S., Miserocchi, E., Mochizuki, M., Mohamed, O.S., Muccioli, C., Munk, M.R., Murthy, S., Narain, S., Nascimento, H., Neri, P., Nguyen, M., Okada, A.A., Ozdal, P., Palestine, A., Pichi, F., Raje, D., Rathinam, S.R., Rousselot, A., Schlaen, A., Sehgal, S., Nida Sen, H., Sharma, A., Sharma, K., Shoughy, S.S., Singh, N., Singh, R., Soheilian, M., Sridharan, S., Thorne, J.E., Tappeiner, C., Teoh, S., Tognon, M.S., Tugal-Tutkun, I., Tyagi, M., Uy, H., Vasconcelos Santos, D.V., Valentincic, N.V., Westcott, M., Yanai, R., Alvarez, B.Y., Zahedur, R., Zierhut, M., Xian, Z., 2021a. Collaborative ocular tuberculosis study consensus guidelines on the management of tubercular uveitis—report 2: guidelines for initiating antitubercular therapy in anterior uveitis, intermediate uveitis, panuveitis, and retinal vasculitis. Ophthalmology 128, 277–287. https://doi.org/10.1016/j.ophtha.2020.06.052.

Agrawal, R., Testi, I., Mahajan, S., Yuen, Y. Sen, Agarwal, A., Kon, O.M., Barisani-Asenbauer, T., Kempen, J.H., Gupta, A., Jabs, D.A., Smith, J.R., Nguyen, Q.D., Pavesio, C., Gupta, V., 2021b. Collaborative ocular tuberculosis study consensus guidelines on the management of tubercular uveitis-report 1: guidelines for initiating antitubercular therapy in tubercular choroiditis. Ophthalmology 128, 266–276. https://doi.org/10.1016/j.ophtha.2020.01.008.

Agrawal, R., Testi, I., Rousselot, A., Chen, E.J., Lakshminarayanan, R., Singhal, A., Bundele, M., Hutchison, P., Kon, O.M., Gupta, V., Pavesio, C., 2021c. Insights into the molecular pathogenesis of ocular tuberculosis. Tuberculosis 126, 102018. https://doi.org/10.1016/j.tube.2020.102018.

Al-Mezaine, H.S., Al-Muammar, A., Kangave, D., Abu El-Asrar, A.M., 2008. Clinical and optical coherence tomographic findings and outcome of treatment in patients with presumed tuberculous uveitis. Int. Ophthalmol. 28, 413–423. https://doi.org/10.1007/s10792-007-9170-6.

Al-Qarni, A., Abouammoh, M.A., Almousa, A.N., Mousa, A., Abu El-Asrar, A.M., 2019. Presumed tuberculous uveitis in a university-based tertiary referral center in Saudi Arabia. Int. Ophthalmol. 39, 317–333. https://doi.org/10.1007/s10792-017-0815-9.

Alam, K., Sharma, G., Forrester, J.V., Basu, S., 2022. Antigen-specific intraocular cytokine responses distinguish ocular TB from undifferentiated uveitis in TB-immunoreactive patients. Am. J. Ophthalmol. https://doi.org/10.1016/j.ajo.2022.08.029.

Alli, H.D., Ally, N., Mayet, I., Dangor, Z., Madhi, S.A., 2022. Global prevalence and clinical outcomes of tubercular uveitis: a systematic review and meta-analysis. Surv. Ophthalmol. 67, 770–792. https://doi.org/10.1016/j.survophthal.2021.10.001.

Amato, R., Giannaccini, M., Dal Monte, M., Cammalleri, M., Pini, A., Raffa, V., Lulli, M., Casini, G., 2020. Association of the somatostatin analog octreotide with magnetic nanoparticles for intraocular delivery: a possible approach for the treatment of diabetic retinopathy. Front. Bioeng. Biotechnol. 8, 144. https://doi.org/10.3389/fbioe.2020.00144.

Ang, L., Kee, A., Yeo, T.H., Dinesh, V.G., Ho, S.L., Teoh, S.C., Agrawal, R., 2018. Treatment outcome in patients with presumed tubercular uveitis at a tertiary referral eye care centre in Singapore. Int. Ophthalmol. 38, 11–18. https://doi.org/10.1007/s10792-016-0401-6.

Ang, M., Chee, S.P., 2017. Controversies in ocular tuberculosis. Br. J. Ophthalmol. 101, 6–9. https://doi.org/10.1136/bjophthalmol-2016-309531.

Ang, M., Cheung, G., Vania, M., Chen, J., Yang, H., Li, J., Chee, S.P., 2012a. Aqueous cytokine and chemokine analysis in uveitis associated with tuberculosis. Mol. Vis. 18, 565–573.

Ang, M., Hedayatfar, A., Wong, W., Chee, S.-P., 2012b. Duration of anti-tubercular therapy in uveitis associated with latent tuberculosis: a case-control study. Br. J. Ophthalmol. 96, 332–336. https://doi.org/10.1136/bjophthalmol-2011-300209.

Ang, M., Htoon, H.M., Chee, S.-P., 2009. Diagnosis of tuberculous uveitis: clinical application of an interferon-gamma release assay. Ophthalmology 116, 1391–1396. https://doi.org/10.1016/j.ophtha.2009.02.005.

Babu, K., Bhat, S.S., Philips, M., Subbakrishna, D.K., 2016. Review of results of QuantiFERON TB gold test in presumed ocular tuberculosis in a South Indian patient population. Ocul. Immunol. Inflamm. 24, 498–502. https://doi.org/10.3109/09273948.2015.1010094.

Babu, K., Shah, D., Murthy, K., 2022. Refractory bilateral choroiditis due to presumed ocular tuberculosis responding to intravitreal moxifloxacin. Indian J Ophthalmol Case Rep 2, 700–3.

Balne, P.K., Modi, R.R., Choudhury, N., Mohan, N., Barik, M.R., Padhi, T.R., Sharma, S., Panigrahi, S.R., Basu, S., 2014. Factors influencing polymerase chain reaction outcomes in patients with clinically suspected ocular tuberculosis. J. Ophthalmic Inflamm. Infect. 4, 1–6. https://doi.org/10.1186/1869-5760-4-10.

Bansal, R., Sharma, K., Gupta, A., Sharma, A., Singh, M.P., Gupta, V., Mulkutkar, S., Dogra, M., Dogra, M.R., Kamal, S., Sharma, S.P., Fiorella, P.D., 2015. Detection of Mycobacterium tuberculosis genome in vitreous fluid of eyes with multifocal serpiginoid choroiditis. Ophthalmology 122, 840–850. https://doi.org/10.1016/j.ophtha.2014.11.021.

Basu, S., 2022. Absence of evidence as the evidence of absence: the curious case of latent infection causing ocular tuberculosis. Front. Ophthalmol. 2, 874400.

Basu, S., Elkington, P., Rao, N.A., 2020. Pathogenesis of ocular tuberculosis: new observations and future directions. Tuberc 124, 101961. https://doi.org/10.1016/j.tube.2020.101961.

Basu, S., Mittal, R., Balne, P.K., Sharma, S., 2012. Intraretinal tuberculosis. Ophthalmology. https://doi.org/10.1016/j.ophtha.2012.06.003.

Basu, S., Monira, S., Modi, R.R., Choudhury, N., Mohan, N., Padhi, T.R., Balne, P.K., Sharma, S., Panigrahi, S.R., 2014. Degree, duration, and causes of visual impairment in eyes affected with ocular tuberculosis. J. Ophthalmic Inflamm. Infect. 4, 3. https://doi.org/10.1186/1869-5760-4-3.

Basu, S., Nayak, S., Padhi, T.R., Das, T., 2013. Progressive ocular inflammation following anti-tubercular therapy for presumed ocular tuberculosis in a high-endemic setting. Eye (Lond). 27, 657–662. https://doi.org/10.1038/eye.2013.5.

Basu, S., Wakefield, D., Biswas, J., Rao, N.A., 2015. Pathogenesis and pathology of intraocular tuberculosis. Ocul. Immunol. Inflamm. 23, 353–357. https://doi.org/10.3109/09273948.2015.1056536.

Berry, M.P., Graham, C.M., McNab, F.W., Xu, Z., Bloch, S.A., Oni, T., others, 2010. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature 466, 973–977.

Betzler, B.K., Gupta, V., Agrawal, R., 2021. Clinics of ocular tuberculosis: a review. Clin. Exp. Ophthalmol. 49, 146–160. https://doi.org/10.1111/ceo.13847.

Bigdon, E., Steinhorst, N.A., Weissleder, S., Durchkiv, V., Stübiger, N., 2022. Treatment in latent tuberculosis uveitis-is immunosuppression effective or is conventional 3- or 4-drug antituberculosis therapy mandatory? J. Clin. Med. 11 https://doi.org/10.3390/jcm11092419.

Chen, Y., Bharrhan, S., Xu, J., Sharma, T., Wang, Y., Salgame, P., Zhang, J., Nargan, K., Steyn, A.J.C., Maglione, P.J., Chan, J., 2023. B cells promote granulomatous inflammation during chronic Mycobacterium tuberculosis infection in mice. PLoS Pathog. 19, e1011187 https://doi.org/10.1371/journal.ppat.1011187.

Chung, C.Y., Li, K.K.W., 2018. The efficacy of latent tuberculosis treatment for immunocompetent uveitis patients with a positive T-SPOT.TB test: 6-year experience in a tuberculosis endemic region. Int. Ophthalmol. 38, 2273–2282. https://doi.org/10.1007/s10792-017-0716-y.

Cronan, M.R., 2022. In the thick of it: formation of the tuberculous granuloma and its effects on host and therapeutic responses. Front. Immunol. 13, 820134 https://doi.org/10.3389/fimmu.2022.820134.

Dalm, V.A.S.H., van Hagen, P.M., van Koetsveld, P.M., Achilefu, S., Houtsmuller, A.B., Pols, D.H.J., van der Lely, A.-J., Lamberts, S.W.J., Hofland, L.J., 2003. Expression of somatostatin, cortistatin, and somatostatin receptors in human monocytes, macrophages, and dendritic cells. Am. J. Physiol. Endocrinol. Metab. 285, E344–E353. https://doi.org/10.1152/ajpendo.00048.2003.

Damato, E.M., Dawson, S., Liu, X., Mukherjee, C., Horsburgh, J., Denniston, A.K., Moran, E., Dedicoat, M., Murray, P.I., 2017. A retrospective cohort study of patients treated with anti-tuberculous therapy for presumed ocular tuberculosis. J. Ophthalmic Inflamm. Infect. 7, 23. https://doi.org/10.1186/s12348-017-0141-4.

Damera, S.K., Panigrahi, R.K., Mitra, S., Basu, S., 2021. Role of extracellular mycobacteria in blood-retinal barrier invasion in a zebrafish model of ocular TB. Pathogens 10. https://doi.org/10.3390/pathogens10030333.

Danjou, W., Pradat, P., Jamilloux, Y., Gerfaud-Valentin, M., Kodjikian, L., Trad, S., Seve, P., 2021. Usefulness of the QuantiFERON test for the diagnosis of tubercular uveitis and the predictions of response to antituberculosis treatment. Br. J. Ophthalmol. https://doi.org/10.1136/bjophthalmol-2021-318868.

Detrick, B., Hooks, J.J., 2020. In: Klettner, A.K., Dithmar, S. (Eds.), The RPE Cell and the Immune System BT - Retinal Pigment Epithelium in Health and Disease. Springer International Publishing, Cham, pp. 101–114. https://doi.org/10.1007/978-3-030-28384-1_6.

Domingo-Gonzalez, R., Prince, O., Cooper, A., Khader, S.A., 2016. Cytokines and chemokines in Mycobacterium tuberculosis infection. Microbiol. Spectr. 4 https://doi.org/10.1128/microbiolspec.TBTB2-0018-2016.

Doycheva, D., Deuter, C., Hetzel, J., Frick, J.-S., Aschoff, P., Schuelen, E., Zierhut, M., Pfannenberg, C., 2011. The use of positron emission tomography/CT in the diagnosis of tuberculosis-associated uveitis. Br. J. Ophthalmol. 95, 1290–1294. https://doi.org/10.1136/bjo.2010.182659.

Drescher, K.M., Whittum-Hudson, J.A., 1996. Modulation of immune-associated surface markers and cytokine production by murine retinal glial cells. J. Neuroimmunol. 64, 71–81. https://doi.org/10.1016/0165-5728(95)00156-5.

Dutta, R.K., Kathania, M., Raje, M., Majumdar, S., 2012. IL-6 inhibits IFN-γ induced autophagy in Mycobacterium tuberculosis H37Rv infected macrophages. Int. J. Biochem. Cell Biol. 44, 942–954. https://doi.org/10.1016/j.biocel.2012.02.021.

Elangovan, S., Govindarajan, S., Mayilvakanam, L., Gunasekaran, N., 2019. Clinical profile and treatment response of patients with ocular inflammation due to presumed ocular tuberculosis: a retrospective study. Turkish J. Orthod. 49, 188–193. https://doi.org/10.4274/tjo.galenos.2019.05874.

Elkington, P.T., Bateman, A.C., Thomas, G.J., Ottensmeier, C.H., 2018. Implications of tuberculosis reactivation after immune checkpoint inhibition. Am. J. Respir. Crit. Care Med. https://doi.org/10.1164/rccm.201807-1250LE.

Esen, E., Sızmaz, S., Kunt, Z., Demircan, N., 2016. Paradoxical worsening of tubercular serpiginous-like choroiditis after initiation of antitubercular therapy. Turkish J. Orthod. 46, 186–189. https://doi.org/10.4274/tjo.94809.

Ferone, D., van Hagen, P.M., Semino, C., Dalm, V.A., Barreca, A., Colao, A., Lamberts, S.W.J., Minuto, F., Hofland, L.J., 2004. Somatostatin receptor distribution and function in immune system. Dig. liver Dis. Off. J. Ital. Soc. Gastroenterol. Ital. Assoc. Study Liver 36 (Suppl. 1), S68–S77. https://doi.org/10.1016/j.dld.2003.11.020.

Fonollosa, A., Valsero, S., Artaraz, J., Ruiz-Arruza, I., 2016. Dexamethasone intravitreal implants in the management of tubercular multifocal serpiginoid choroiditis. J. Ophthalmic Inflamm. Infect. 6, 31. https://doi.org/10.1186/s12348-016-0101-4.

Forrester, J.V., Kuffova, L., Dick, A.D., 2018. Autoimmunity, autoinflammation, and infection in uveitis. Am. J. Ophthalmol. 189, 77–85. https://doi.org/10.1016/j.ajo.2018.02.019.

Frenkel, J.D.H., Ackart, D.F., Todd, A.K., DiLisio, J.E., Hoffman, S., Tanner, S., Kiran, D., Murray, M., Chicco, A., Obregón-Henao, A., Podell, B.K., Basaraba, R.J., 2020. Metformin enhances protection in Guinea pigs chronically infected with Mycobacterium tuberculosis. Sci. Rep. 10, 16257 https://doi.org/10.1038/s41598-020-73212-y.

Ganesh, S.K., Abraham, S., Sudharshan, S., 2019. Paradoxical reactions in ocular tuberculosis. J. Ophthalmic Inflamm. Infect. 9, 19. https://doi.org/10.1186/s12348-019-0183-x.

Garand, M., Goodier, M., Owolabi, O., Donkor, S., Kampmann, B., Sutherland, J.S., 2018. Functional and phenotypic changes of natural killer cells in whole blood during Mycobacterium tuberculosis infection and disease. Front. Immunol. 9, 257. https://doi.org/10.3389/fimmu.2018.00257.

Garip, A., Diedrichs-Mohring, M., Thurau, S.R., Deeg, C.A., Wildner, G., 2009. Uveitis in a patient treated with Bacille-Calmette-Guerin: possible antigenic mimicry of mycobacterial and retinal antigens. Ophthalmology 116, 1–2.

Gay, L., Mezouar, S., Cano, C., Frohna, P., Madakamutil, L., Mège, J.-L., Olive, D., 2022. Role of Vγ9vδ2 T lymphocytes in infectious diseases. Front. Immunol. 13, 928441 https://doi.org/10.3389/fimmu.2022.928441.

Ghauri, M.I., Iqbal, N., Riaz, S.U., Irfan, M., Kumar, A., Mukarram, M.S., 2019. Visual and treatment outcomes of tubercular uveitis: a prospective case series from a referral hospital in Pakistan. BMC Res. Notes 12, 404. https://doi.org/10.1186/s13104-019-4432-8.

Gineys, R., Bodaghi, B., Carcelain, G., Cassoux, N., Boutin, L.T.H., Amoura, Z., Lehoang, P., Trad, S., 2011. QuantiFERON-TB gold cut-off value: implications for the management of tuberculosis-related ocular inflammation. Am. J. Ophthalmol. 152, 433–440.e1. https://doi.org/10.1016/j.ajo.2011.02.006.

Greinert, U., Ernst, M., Schlaak, M., Entzian, P., 2001. Interleukin-12 as successful adjuvant in tuberculosis treatment. Eur. Respir. J. 17, 1049–1051. https://doi.org/10.1183/09031936.01.17510490.

Groen-Hakan, F., van Laar, J.A.M., Bakker, M., van Hagen, P.M., Hardjosantoso, H., Rothova, A., 2020. Prevalence of positive QuantiFERON-TB gold in-tube test in uveitis and its clinical implications in a country nonendemic for tuberculosis. Am. J. Ophthalmol. 211, 151–158. https://doi.org/10.1016/j.ajo.2019.11.009.

Guerra, C., Morris, D., Sipin, A., Kung, S., Franklin, M., Gray, D., Tanzil, M., Guilford, F., Khasawneh, F.T., Venketaraman, V., 2011. Glutathione and adaptive immune responses against Mycobacterium tuberculosis infection in healthy and HIV infected individuals. PLoS One 6, e28378. https://doi.org/10.1371/journal.pone.0028378.

Guirado, E., Schlesinger, L.S., 2013. Modeling the Mycobacterium tuberculosis granuloma - the critical battlefield in host immunity and disease. Front. Immunol. 4, 98. https://doi.org/10.3389/fimmu.2013.00098.

Guler, R., Ozturk, M., Sabeel, S., Motaung, B., Parihar, S.P., Thienemann, F., Brombacher, F., 2021. Targeting molecular inflammatory pathways in granuloma as host-directed therapies for tuberculosis. Front. Immunol. 12, 733853 https://doi.org/10.3389/fimmu.2021.733853.

Gunasekeran, D.V., Gupta, B., Cardoso, J., Pavesio, C.E., Agrawal, R., 2018. Visual morbidity and ocular complications in presumed intraocular tuberculosis: an analysis of 354 cases from a non-endemic population. Ocul. Immunol. Inflamm. 26, 865–869. https://doi.org/10.1080/09273948.2017.1296580.

Gunasekeran, D.V., Agrawal, R., Agarwal, A., Carreño, E., Raje, D., Aggarwal, K., Kon, O. M., Nguyen, Q.D., Pavesio, C., Gupta, V., 2019. The collaborative ocular tuberculosis study (COTS)-1: a multinational review of 251 patients with tubercular retinal vasculitis. Retina 39, 1623–1630. https://doi.org/10.1097/IAE.0000000000002194.

Gupta, A., Sharma, A., Bansal, R., Sharma, K., 2015. Classification of intraocular tuberculosis. Ocul. Immunol. Inflamm. 23, 7–13. https://doi.org/10.3109/09273948.2014.967358.

Gupta, V., Bansal, R., Gupta, A., 2011. Continuous progression of tubercular serpiginous-like choroiditis after initiating antituberculosis treatment. Am. J. Ophthalmol. 152 https://doi.org/10.1016/j.ajo.2011.05.004, 857–63.e2.

Gupta, V., Shoughy, S.S., Mahajan, S., Khairallah, M., Rosenbaum, J.T., Curi, A., Tabbara, K.F., 2015. Clinics of ocular tuberculosis. Ocul. Immunol. Inflamm. 23, 14–24. https://doi.org/10.3109/09273948.2014.986582.

Hilda, J.N., Das, S., Tripathy, S.P., Hanna, L.E., 2020. Role of neutrophils in tuberculosis: a bird's eye view. Innate Immun. 26, 240–247. https://doi.org/10.1177/1753425919881176.

Huang, H., 2020. Pericyte-endothelial interactions in the retinal microvasculature. Int. J. Mol. Sci. 21 https://doi.org/10.3390/ijms21197413.

Hutchinson, P.E., Kee, A.R., Agrawal, R., Yawata, N., Tumulak, M.J., Connolly, J.E., others, 2021. Singapore ocular tuberculosis immunity study (SPOTIS): role of T-lymphocyte profiling in patients with presumed ocular tuberculosis. Ocul. Immunol. Inflamm. 29, 1489–1495.

Invernizzi, A., Franzetti, F., Viola, F., Meroni, L., Staurenghi, G., 2015. Optic nerve head tubercular granuloma successfully treated with anti-VEGF intravitreal injections in addition to systemic therapy. Eur. J. Ophthalmol. 25, 270–272. https://doi.org/10.5301/ejo.5000528.

Jabs, D.A., Belfort, R., Bodaghi, B., Graham, E., Gupta, V., Holland, G.N., Lightman, S.L., Oden, N., Palestine, A.G., Smith, J.R., Thorne, J.E., Trusko, B.E., 2021. Classification criteria for tubercular uveitis. Am. J. Ophthalmol. 228, 142–151. https://doi.org/10.1016/j.ajo.2021.03.040.

Jain, L., Panda, K.G., Basu, S., 2018. Clinical outcomes of adjunctive Sustained-release intravitreal dexamethasone implants in tuberculosis-associated multifocal Serpigenoid choroiditis. Ocul. Immunol. Inflamm. 26, 877–883. https://doi.org/10.1080/09273948.2017.1383446.

Jenum, S., Tonby, K., Rueegg, C.S., Rühwald, M., Kristiansen, M.P., Bang, P., Olsen, I.C., Sellæg, K., Røstad, K., Mustafa, T., Taskén, K., Kvale, D., Mortensen, R., Dyrhol-Riise, A.M., 2021. A Phase I/II randomized trial of H56:IC31 vaccination and adjunctive cyclooxygenase-2-inhibitor treatment in tuberculosis patients. Nat. Commun. 12, 6774. https://doi.org/10.1038/s41467-021-27029-6.

Jick, S.S., Lieberman, E.S., Rahman, M.U., Choi, H.K., 2006. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Rheum. 55, 19–26. https://doi.org/10.1002/art.21705.

Johnson, J.L., Ssekasanvu, E., Okwera, A., Mayanja, H., Hirsch, C.S., Nakibali, J.G., Jankus, D.D., Eisenach, K.D., Boom, W.H., Ellner, J.J., Mugerwa, R.D., 2003. Randomized trial of adjunctive interleukin-2 in adults with pulmonary tuberculosis. Am. J. Respir. Crit. Care Med. 168, 185–191. https://doi.org/10.1164/rccm.200211-1359OC.

Joshi, L., Chelluri, L.K., Gaddam, S., 2015. Mesenchymal stromal cell therapy in MDR/XDR tuberculosis: a concise review. Arch. Immunol. Ther. Exp. 63, 427–433. https://doi.org/10.1007/s00005-015-0347-9.

Julian, K., Langner-Wegscheider, B.-J., Haas, A., De Smet, M.D., 2013. Intravitreal methotrexate in the management of presumed tuberculous serpiginous-like choroiditis. Retina 33, 1943–1948. https://doi.org/10.1097/IAE.0b013e318285cdbe.

Kafkala, C., Choi, J.Y., Choopong, P., Foster, C.S., 2006. Octreotide as a treatment for uveitic cystoid macular edema. Arch. Ophthalmol. 124, 1353–1355. https://doi.org/10.1001/archopht.124.9.1353.

Kalra, G., Agarwal, A., Marchese, A., Agrawal, R., Bansal, R., Gupta, V., 2022. Automated lesion segmentation and quantification for prediction of paradoxical worsening in patients with tubercular serpiginous-like choroiditis. Sci. Rep. 12, 5392. https://doi.org/10.1038/s41598-022-09338-y.

Kaur, S., Aggarwal, K., Agarwal, A., Suri, D., Gupta, Anju, Singh, R., Bansal, R., Singh, S., Singh, N., Gupta, Amod, Gupta, V., 2018. Clinical course and outcomes of pediatric tubercular uveitis in north India. Ocul. Immunol. Inflamm. 26, 859–864. https://doi.org/10.1080/09273948.2017.1296579.

Kee, A.R., Gonzalez-Lopez, J.J., Al-Hity, A., Gupta, B., Lee, C.S., Gunasekeran, D.V., Jayabalan, N., Grant, R., Kon, O.M., Gupta, V., Westcott, M., Pavesio, C., Agrawal, R., 2016. Anti-tubercular therapy for intraocular tuberculosis: a systematic review and meta-analysis. Surv. Ophthalmol. 61, 628–653. https://doi.org/10.1016/j.survophthal.2016.03.001.

Keino, H., Horie, S., Sugita, S., 2018. Immune privilege and eye-derived T-regulatory cells. J. Immunol. Res. 2018, 1679197 https://doi.org/10.1155/2018/1679197.

Khan, A., Mann, L., Papanna, R., Lyu, M.-A., Singh, C.R., Olson, S., Eissa, N.T., Cirillo, J., Das, G., Hunter, R.L., Jagannath, C., 2017. Mesenchymal stem cells internalize Mycobacterium tuberculosis through scavenger receptors and restrict bacterial growth through autophagy. Sci. Rep. 7, 15010 https://doi.org/10.1038/s41598-017-15290-z.

Khochtali, S., Gargouri, S., Abroug, N., Ksiaa, I., Attia, S., Sellami, D., Feki, J., Khairallah, M., 2015. The spectrum of presumed tubercular uveitis in Tunisia, North Africa. Int. Ophthalmol. 35, 663–671. https://doi.org/10.1007/s10792-014-9992-y.

Kilinç, G., Saris, A., Ottenhoff, T.H.M., Haks, M.C., 2021. Host-directed therapy to combat mycobacterial infections. Immunol. Rev. 301, 62–83. https://doi.org/10.1111/imr.12951.

Kindler, V., Sappino, A.P., Grau, G.E., Piguet, P.F., Vassalli, P., 1989. The inducing role of tumor necrosis factor in the development of bactericidal granulomas during BCG infection. Cell 56, 731–740. https://doi.org/10.1016/0092-8674(89)90676-4.

Kiran, D., Podell, B.K., Chambers, M., Basaraba, R.J., 2016. Host-directed therapy targeting the Mycobacterium tuberculosis granuloma: a review. Semin. Immunopathol. 38, 167–183. https://doi.org/10.1007/s00281-015-0537-x.

Koh, W.-J., Kwon, O.J., Suh, G.Y., Chung, M.P., Kim, H., Lee, N.Y., Kim, T.S., Lee, K.S., 2004. Six-month therapy with aerosolized interferon-gamma for refractory multidrug-resistant pulmonary tuberculosis. J. Kor. Med. Sci. 19, 167–171. https://doi.org/10.3346/jkms.2004.19.2.167.

Kolloli, A., Subbian, S., 2017. Host-directed therapeutic strategies for tuberculosis. Front. Med. 4, 171. https://doi.org/10.3389/fmed.2017.00171.

Kon, O.M., Beare, N., Connell, D., Damato, E., Gorsuch, T., Hagan, G., Perrin, F., Petrushkin, H., Potter, J., Sethi, C., Stanford, M., 2022. BTS clinical statement for the diagnosis and management of ocular tuberculosis. BMJ open Respir. Res. 9 https://doi.org/10.1136/bmjresp-2022-001225.

Kroesen, V.M., Gröschel, M.I., Martinson, N., Zumla, A., Maeurer, M., van der Werf, T.S., Vilaplana, C., 2017. Non-steroidal anti-inflammatory drugs as host-directed therapy for tuberculosis: a systematic review. Front. Immunol. 8, 772. https://doi.org/10.3389/fimmu.2017.00772.

Kumar, N.P., Moideen, K., Nancy, A., Viswanathan, V., Thiruvengadam, K., Sivakumar, S., Hissar, S., Nair, D., Banurekha, V.V., Kornfeld, H., Babu, S., 2020. Association of plasma matrix metalloproteinase and tissue inhibitors of matrix metalloproteinase levels with adverse treatment outcomes among patients with pulmonary tuberculosis. JAMA Netw. Open 3, e2027754. https://doi.org/10.1001/jamanetworkopen.2020.27754.

La Distia Nora, R., Putera, I., Khalisha, D.F., Septiana, I., Sitompul, R., 2021. The diagnostic value of polymerase chain reaction for ocular tuberculosis diagnosis in relation to antitubercular therapy response: a meta-analysis. Int. J. Infect. Dis. 110, 394–402. https://doi.org/10.1016/j.ijid.2021.07.075.

La Distia Nora, R., Sitompul, R., Bakker, M., Susiyanti, M., Edwar, L., Sjamsoe, S., Singh, G., Martin van Hagen, P., Rothova, A., 2018a. Tuberculosis and other causes of uveitis in Indonesia. Eye 32, 546–554. https://doi.org/10.1038/eye.2017.231.

La Distia Nora, R., Sitompul, R., Bakker, M., Versnel, M.A., Swagemakers, S.M.A., van der Spek, P.J., Susiyanti, M., Edwar, L., Sjamsoe, S., Singh, G., Diah Handayani, R.R., Rothova, A., Martin van Hagen, P., Dik, W.A., 2018b. Type 1 interferon-inducible gene expression in QuantiFERON Gold TB-positive uveitis: a tool to stratify a high versus low risk of active tuberculosis? PLoS One 13, 1–9. https://doi.org/10.1371/journal.pone.0206073.

La Distia Nora, R., Ten Berge, J.C., Rothova, A., Schreurs, M.W., 2018c. Antinuclear and antiretinal antibodies in uveitis associated with active and latent tuberculosis. Acta Ophthalmol. https://doi.org/10.1111/aos.13707.

La Distia Nora, R., van Velthoven, M.E.J., Ten Dam-van Loon, N.H., Misotten, T., Bakker, M., van Hagen, M.P., Rothova, A., 2014. Clinical manifestations of patients with intraocular inflammation and positive QuantiFERON-TB gold in-tube test in a country nonendemic for tuberculosis. Am. J. Ophthalmol. 157, 754–761. https://doi.org/10.1016/j.ajo.2013.11.013.

La Distia Nora, R., Walburg, K.V., van Hagen, P.M., Swagemakers, S.M.A., van der Spek, P.J., Quinten, E., van Velthoven, M., Ottenhoff, T.H.M., Dik, W.A., Haks, M.C., 2018d. Retinal pigment epithelial cells control early Mycobacterium tuberculosis infection via interferon signaling. Invest. Ophthalmol. Vis. Sci. 59, 1384–1395. https://doi.org/10.1167/iovs.17-23246.

Lachmandas, E., Eckold, C., Böhme, J., Koeken, V.A.C.M., Marzuki, M.B., Blok, B., Arts, R.J.W., Chen, J., Teng, K.W.W., Ratter, J., Smolders, E.J., Van den Heuvel, C., Stienstra, R., Dockrell, H.M., Newell, E., Netea, M.G., Singhal, A., Cliff, J.M., Van Crevel, R., 2019. Metformin alters human host responses to Mycobacterium tuberculosis in healthy Subjects. J. Infect. Dis. 220, 139–150. https://doi.org/10.1093/infdis/jiz064.

Lam, K.K.Y., Zheng, X., Forestieri, R., Balgi, A.D., Nodwell, M., Vollett, S., Anderson, H. J., Andersen, R.J., Av-Gay, Y., Roberge, M., 2012. Nitazoxanide stimulates autophagy and inhibits mTORC1 signaling and intracellular proliferation of Mycobacterium tuberculosis. PLoS Pathog. 8, e1002691 https://doi.org/10.1371/journal.ppat.1002691.

Langan, E.A., Graetz, V., Allerheiligen, J., Zillikens, D., Rupp, J., Terheyden, P., 2020. Immune checkpoint inhibitors and tuberculosis: an old disease in a new context. Lancet Oncol. 21 https://doi.org/10.1016/S1470-2045(19)30674-6 e55–e65.

Liang, J., Fu, L., Li, M., Chen, Y., Wang, Y., Lin, Y., Zhang, H., Xu, Y., Qin, L., Liu, J., Wang, W., Hao, J., Liu, S., Zhang, P., Lin, L., Alnaggar, M., Zhou, J., Zhou, L., Guo, H., Wang, Z., Liu, L., Deng, G., Zhang, G., Wu, Y., Yin, Z., 2021. Allogeneic Vγ9Vδ2 T-cell therapy promotes pulmonary lesion repair: an open-label, single-arm pilot study in patients with multidrug-resistant tuberculosis. Front. Immunol. 12, 756495 https://doi.org/10.3389/fimmu.2021.756495.

Liang, M., Habib, Z., Sakamoto, K., Chen, X., Cao, G., 2017. Mycobacteria and autophagy: many questions and few answers. Curr. Issues Mol. Biol. 21, 63–72.

Lorenz, L., Hirmer, S., Schmalen, A., Hauck, S.M., Deeg, C.A., 2021. Cell surface profiling of retinal müller glial cells reveals association to immune pathways after LPS stimulation. Cells 10. https://doi.org/10.3390/cells10030711.

Ludi, Z., Sule, A.A., Samy, R.P., Putera, I., Schrijver, B., Hutchinson, P.E., Gunaratne, J., Verma, I., Singhal, A., Nora, R.L.D., van Hagen, P.M., Dik, W.A., Gupta, V., Agrawal, R., 2023. Diagnosis and biomarkers for ocular tuberculosis: from the present into the future. Theranostics 13, 2088–2113. https://doi.org/10.7150/thno.81488.

Mahakalkar, S.M., Nagrale, D., Gaur, S., Urade, C., Murhar, B., Turankar, A., 2017. N-acetylcysteine as an add-on to Directly Observed Therapy Short-I therapy in fresh pulmonary tuberculosis patients: a randomized, placebo-controlled, double-blinded study. Perspect. Clin. Res. 8, 132–136. https://doi.org/10.4103/2229-3485.210450.

Maison, D.P., 2022. Tuberculosis pathophysiology and anti-VEGF intervention. J. Clin. Tuberc. other Mycobact. Dis. 27, 100300 https://doi.org/10.1016/j.jctube.2022.100300.

Maitra, A., Bates, S., Shaik, M., Evangelopoulos, D., Abubakar, I., McHugh, T.D., Lipman, M., Bhakta, S., 2016. Repurposing drugs for treatment of tuberculosis: a role for non-steroidal anti-inflammatory drugs. Br. Med. Bull. 118, 138–148. https://doi.org/10.1093/bmb/ldw019.

Malek, T.R., 2003. The main function of IL-2 is to promote the development of T regulatory cells. J. Leukoc. Biol. 74, 961–965. https://doi.org/10.1189/jlb.0603272.

Manousaridis, K., Ong, E., Stenton, C., Gupta, R., Browning, A.C., Pandit, R., 2013. Clinical presentation, treatment, and outcomes in presumed intraocular tuberculosis: experience from Newcastle upon Tyne, UK. Eye (Lond). 27, 480–486. https://doi.org/10.1038/eye.2013.11.

Miow, Q.H., Vallejo, A.F., Wang, Y., Hong, J.M., Bai, C., Teo, F.S., Wang, A.D., Loh, H.R., Tan, T.Z., Ding, Y., She, H.W., Gan, S.H., Paton, N.I., Lum, J., Tay, A., Chee, C.B., Tambyah, P.A., Polak, M.E., Wang, Y.T., Singhal, A., Elkington, P.T., Friedland, J.S.,

Ong, C.W., 2021. Doxycycline host-directed therapy in human pulmonary tuberculosis. J. Clin. Invest. 131 https://doi.org/10.1172/JCI141895.
Mishra, S.B., Saoji, K., Pathengay, A., 2020. Dual lesion margins on fundus autofluorescence associated with paradoxical worsening following treatment for tubercular serpiginous-like choroiditis. Indian J. Ophthalmol. https://doi.org/10.4103/ijo.IJO_536_19.
Missotten, T., van Laar, J.A.M., van der Loos, T.L., van Daele, P.L.A., Kuijpers, R.W.A.M., Baarsma, G.S., van Hagen, P.M., 2007. Octreotide long-acting repeatable for the treatment of chronic macular edema in uveitis. Am. J. Ophthalmol. 144, 838–843. https://doi.org/10.1016/j.ajo.2007.07.039.
Mochizuki, M., Smith, J.R., Takase, H., Kaburaki, T., Acharya, N.R., Rao, N.A., 2019. Revised criteria of international workshop on ocular sarcoidosis (IWOS) for the diagnosis of ocular sarcoidosis. Br. J. Ophthalmol. 103, 1418–1422. https://doi.org/10.1136/bjophthalmol-2018-313356.
Moreira-Teixeira, L., Mayer-Barber, K., Sher, A., O'Garra, A., 2018. Type I interferons in tuberculosis: foe and occasionally friend. J. Exp. Med. 215, 1273–1285. https://doi.org/10.1084/jem.20180325.
Mortaz, E., Masjedi, M.R., Abedini, A., Matroodi, S., Kiani, A., Soroush, D., Adcock, I.M., 2016. Common features of tuberculosis and sarcoidosis. Int. J. mycobacteriology 5 (Suppl. 1), S240–S241. https://doi.org/10.1016/j.ijmyco.2016.09.031.
Mourik, B.C., Lubberts, E., de Steenwinkel, J.E.M., Ottenhoff, T.H.M., Leenen, P.J.M., 2017. Interactions between type 1 interferons and the Th17 response in tuberculosis: lessons learned from autoimmune diseases. Front. Immunol. 8, 294. https://doi.org/10.3389/fimmu.2017.00294.
Nazari, H., Karakousis, P.C., Rao, N.A., 2014. Replication of Mycobacterium tuberculosis in retinal pigment epithelium. JAMA Ophthalmol 132, 724–729. https://doi.org/10.1001/jamaophthalmol.2014.270.
Nie, W., Wang, J., Zeng, J., Wang, Q., Du, Y., Tan, Q., Xie, W., Deng, Q., Deng, G., Li, X., Li, Z., Zhao, J., Pang, J., Luan, K., Chu, L., Duan, H., Zhang, C., Ji, Q., Chen, X., Chen, J., Wang, N., Chen, Y., Qiu, C., Deng, A., Ren, P., Liu, Y., Li, C., Cao, S., Liu, H., Yan, H., Chu, N., 2022. Adjunctive interleukin-2 for the treatment of drug-susceptible tuberculosis: a randomized control trial in China. Infection 50, 413–421. https://doi.org/10.1007/s15010-021-01698-3.
O'Leary, F., Campbell, M., 2023. The blood-retina barrier in health and disease. FEBS J. 290, 878–891. https://doi.org/10.1111/febs.16330.
Ohno-Matsui, K., Uetama, T., Yoshida, T., Hayano, M., Itoh, T., Morita, I., Mochizuki, M., 2003. Reduced retinal angiogenesis in MMP-2-deficient mice. Invest. Ophthalmol. Vis. Sci. 44, 5370–5375. https://doi.org/10.1167/iovs.03-0249.
Okunuki, Y., Mukai, R., Nakao, T., Tabor, S.J., Butovsky, O., Dana, R., Ksander, B.R., Connor, K.M., 2019. Retinal microglia initiate neuroinflammation in ocular autoimmunity. Proc. Natl. Acad. Sci. U.S.A. 116, 9989–9998. https://doi.org/10.1073/pnas.1820387116.
Oray, M., Zakiev, Z., Çağatay, T., Tuğal-Tutkun, İ., 2017. Treatment results in serpiginous choroiditis and multifocal serpiginoid choroiditis associated with latent tuberculosis. Turkish J. Orthod. 47, 89–93. https://doi.org/10.4274/tjo.37630.
Padmapriydarsini, C., Mamulwar, M., Mohan, A., Shanmugam, P., Gomathy, N.S., Mane, A., Singh, U.B., Pavankumar, N., Kadam, A., Kumar, H., Suresh, C., Reddy, D., Devi, P., Ramesh, P.M., Sekar, L., Jawahar, S., Shandil, R.K., Singh, M., Menon, J., Guleria, R., 2022. Randomized trial of metformin with anti-tuberculosis drugs for early sputum conversion in adults with pulmonary tuberculosis. Clin. Infect. Dis. 75, 425–434. https://doi.org/10.1093/cid/ciab964.
Pai, R.K., Convery, M., Hamilton, T.A., Boom, W.H., Harding, C.V., 2003. Inhibition of IFN-gamma-induced class II transactivator expression by a 19-kDa lipoprotein from Mycobacterium tuberculosis: a potential mechanism for immune evasion. J. Immunol. 171, 175–184. https://doi.org/10.4049/jimmunol.171.1.175.
Papasavvas, I., Jeannin, B., Herbort, C.P.J., 2022. Tuberculosis-related serpiginous choroiditis: aggressive therapy with dual concomitant combination of multiple anti-tubercular and multiple immunosuppressive agents is needed to halt the progression of the disease. J. Ophthalmic Inflamm. Infect. 12, 7. https://doi.org/10.1186/s12348-022-00282-6.
Parasa, V.R., Muvva, J.R., Rose, J.F., Braian, C., Brighenti, S., Lerm, M., 2017. Inhibition of tissue matrix metalloproteinases interferes with Mycobacterium tuberculosis-induced granuloma formation and reduces bacterial load in a human lung tissue model. Front. Microbiol. 8, 2370. https://doi.org/10.3389/fmicb.2017.02370.
Park, S.-K., Cho, S., Lee, I.-H., Jeon, D.-S., Hong, S.-H., Smego, R.A.J., Cho, S.-N., 2007. Subcutaneously administered interferon-gamma for the treatment of multidrug-resistant pulmonary tuberculosis. Int. J. Infect. Dis. 11, 434–440. https://doi.org/10.1016/j.ijid.2006.12.004.
Patel, S.S., Saraiya, N.V., Tessler, H.H., Goldstein, D.A., 2013. Mycobacterial ocular inflammation: delay in diagnosis and other factors impacting morbidity. JAMA Ophthalmol 131, 752–758. https://doi.org/10.1001/jamaophthalmol.2013.71.
Pepple, K.L., John, S., Wilson, L., Wang, V., Van Gelder, R.N., 2022. Systemic prime exacerbates the ocular immune response to heat-killed. Mycobacterium tuberculosis. Exp. Eye Res. 223, 109198 https://doi.org/10.1016/j.exer.2022.109198.
Polena, H., Boudou, F., Tilleul, S., Dubois-Colas, N., Lecointe, C., Rakotosamimanana, N., Pelizzola, M., Andriamandimby, S.F., Raharimanga, V., Charles, P., Herrmann, J.-L., Ricciardi-Castagnoli, P., Rasolofo, V., Gicquel, B., Tailleux, L., 2016. Mycobacterium tuberculosis exploits the formation of new blood vessels for its dissemination. Sci. Rep. 6, 33162 https://doi.org/10.1038/srep33162.
Poli, A., Michel, T., Thérésine, M., Andrès, E., Hentges, F., Zimmer, J., 2009. CD56bright natural killer (NK) cells: an important NK cell subset. Immunology 126, 458–465. https://doi.org/10.1111/j.1365-2567.2008.03027.x.
Poupot, M., Fournié, J.-J., 2004. Non-peptide antigens activating human Vgamma9/Vdelta2 T lymphocytes. Immunol. Lett. 95, 129–138. https://doi.org/10.1016/j.imlet.2004.06.013.
Putera, I., La Distia Nora, R., Utami, N., Karuniawati, A., Yasmon, A., Wulandari, D., Edwar, L., Susiyanti, M., Aziza, Y., Jessica, P., Riasanti, M., Sitompul, R., 2022. The impact of aqueous humor polymerase chain reaction and serological test results for establishing infectious uveitis diagnosis: an Indonesian experience. Heliyon 8, e10988. https://doi.org/10.1016/j.heliyon.2022.e10988.
Qin, M., Xie, Z., Cao, T., Wang, Z., Zhang, Xiaoyu, Wang, F., Wei, W., Jin, M., Ma, J., Zeng, L., Wang, Y., Pei, S., Zhang, Xu, 2022. Autophagy in rat müller glial cells is modulated by the Sirtuin 4/AMPK/mTOR pathway and induces apoptosis under oxidative stress. Cells 11. https://doi.org/10.3390/cells11172645.
Rao, N.A., Saraswathy, S., Smith, R.E., 2006. Tuberculous uveitis: distribution of Mycobacterium tuberculosis in the retinal pigment epithelium. Arch. Ophthalmol. 124, 1777–1779. https://doi.org/10.1001/archopht.124.12.1777.
Rohilla, R., Shafiq, N., Malhotra, S., 2021. Efficacy and safety of aspirin as an adjunctive therapy in tubercular meningitis: a systematic review and meta-analysis. EClinicalMedicine 34, 100819. https://doi.org/10.1016/j.eclinm.2021.100819.
Ross, S.H., Cantrell, D.A., 2018. Signaling and function of interleukin-2 in T lymphocytes. Annu. Rev. Immunol. 36, 411–433. https://doi.org/10.1146/annurev-immunol-042617-053352.
Sabir, N., Hussain, T., Mangi, M.H., Zhao, D., Zhou, X., 2019. Matrix metalloproteinases: expression, regulation and role in the immunopathology of tuberculosis. Cell Prolif. 52, e12649 https://doi.org/10.1111/cpr.12649.
Saghazadeh, A., Rezaei, N., 2022. Vascular endothelial growth factor levels in tuberculosis: a systematic review and meta-analysis. PLoS One 17, e0268543. https://doi.org/10.1371/journal.pone.0268543.
Sahin, O., Ziaei, A., 2014. The role of methotrexate in resolving ocular inflammation after specific therapy for presumed latent syphilitic uveitis and presumed tuberculosis-related uveitis. Retina 34, 1451–1459. https://doi.org/10.1097/IAE.0000000000000080.
Schrijver, B., Dijkstra, D.J., Borggreven, N.V., La Distia Nora, R., Huijser, E., Versnel, M. A., van Hagen, P.M., Joosten, S.A., Trouw, L.A., Dik, W.A., 2020. Inverse correlation between serum complement component C1q levels and whole blood type-1 interferon signature in active tuberculosis and QuantiFERON-positive uveitis: implications for diagnosis. Clin. Transl. Immunol. 9, 1–10. https://doi.org/10.1002/cti2.1196.
Schrijver, B., Hardjosantoso, H., Ten Berge, J., Mwj, S., Van Hagen, P.M., Brooimans, R. A., others, 2021. No evidence for circulating retina specific autoreactive T-cells in latent tuberculosis-associated uveitis and sarcoid uveitis. Ocul. Immunol. Inflamm. 29, 883–889.
Schrijver, B., Kolijn, P.M., Ten Berge, J., Nma, N., van Rijswijk, A., Sma, S., others, 2022. Vitreous proteomics, a gateway to improved understanding and stratification of diverse uveitis aetiologies. Acta Ophthalmol. 100, 403–413.
Sharma, R.K., Gupta, A., Kamal, S., Bansal, R., Singh, N., Sharma, K., Virk, S., Sachdeva, N., 2018a. Role of regulatory T cells in tubercular uveitis. Ocul. Immunol. Inflamm. 26, 27–36. https://doi.org/10.1080/09273948.2016.1196711.
Sharma, R.K., Gupta, V., Bansal, R., Sharma, K., Gupta, A., Sachdeva, N., 2018b. Immune profiling of T cells infiltrating vitreous humor in tubercular uveitis. Immunol. Invest. 47, 615–631. https://doi.org/10.1080/08820139.2018.1470640.
Shen, H., Min, R., Tan, Q., Xie, W., Wang, H., Pan, H., Zhang, L., Xu, H., Zhang, X., Dai, J., 2015. The beneficial effects of adjunctive recombinant human interleukin-2 for multidrug resistant tuberculosis. Arch. Med. Sci. 11, 584–590. https://doi.org/10.5114/aoms.2015.52362.
Shirley, K., Dowlut, S., Silvestri, J., Pavesio, C., Foot, B., 2020. Presumed ocular tuberculosis in the United Kingdom: a British ophthalmological surveillance unit (BOSU) study. Eye (Lond). 34, 1835–1841. https://doi.org/10.1038/s41433-019-0748-9.
Singh, N., Singh, Ravinder, Sharma, R.K., Kumar, A., Sharma, S.P., Agarwal, A., Gupta, V., Singh, Ramandeep, Katoch, D., 2021. Mycobacterium tuberculosis modulates fibroblast growth factor and vascular endothelial growth factor in ocular tuberculosis. Ocul. Immunol. Inflamm. 29, 1445–1451. https://doi.org/10.1080/09273948.2020.1734212.
Singh, P., Subbian, S., 2018. Harnessing the mTOR pathway for tuberculosis treatment. Front. Microbiol. 9, 70. https://doi.org/10.3389/fmicb.2018.00070.
Singh, V., Mizrahi, V., 2017. Identification and validation of novel drug targets in Mycobacterium tuberculosis. Drug Discov. Today Off. 22, 503–509. https://doi.org/10.1016/j.drudis.2016.09.010.
Skrahin, A., Ahmed, R.K., Ferrara, G., Rane, L., Poiret, T., Isaikina, Y., Skrahina, A., Zumla, A., Maeurer, M.J., 2014. Autologous mesenchymal stromal cell infusion as adjunct treatment in patients with multidrug and extensively drug-resistant tuberculosis: an open-label phase 1 safety trial. Lancet Respir. Med. 2, 108–122. https://doi.org/10.1016/S2213-2600(13)70234-0.
Skrahin, A., Jenkins, H.E., Hurevich, H., Solodovnikova, V., Isaikina, Y., Klimuk, D., Rohava, Z., Skrahina, A., 2016. Effectiveness of a novel cellular therapy to treat multidrug-resistant tuberculosis. J. Clin. Tuberc. other Mycobact. Dis. 4, 21–27. https://doi.org/10.1016/j.jctube.2016.05.003.
Sreenivasan, J., Jain, A., Kamalini, P.N., Janani, M.K., Biswas, J., 2022. Polymerase chain reaction confirmed mycobacterium tuberculosis intermediate uveitis - analysis of 22 eyes of 14 cases from a tertiary care centre in South India: a retrospective study. J. Ophthalmic Inflamm. Infect. 12, 23. https://doi.org/10.1186/s12348-022-00296-0.
Sudheer, B., Lalitha, P., Kumar, A.L., Rathinam, S., 2018. Polymerase chain reaction and its correlation with clinical features and treatment response in tubercular uveitis. Ocul. Immunol. Inflamm. 26, 845–852. https://doi.org/10.1080/09273948.2017.1287925.
Sun, D., Enzmann, V., Lei, S., Sun, S.L., Kaplan, H.J., Shao, H., 2003. Retinal pigment epithelial cells activate uveitogenic T cells when they express high levels of MHC

class II molecules, but inhibit T cell activation when they express restricted levels. J. Neuroimmunol. 144, 1–8. https://doi.org/10.1016/s0165-5728(03)00248-0.
Tagirasa, R., Parmar, S., Barik, M.R., Devadas, S., Basu, S., 2017. Autoreactive T cells in immunopathogenesis of TB-Associated Uveitis. Investig. Ophthalmol. Vis. Sci. 58, 5682–5691. https://doi.org/10.1167/iovs.17-22462.
Takaki, K., Ramakrishnan, L., Basu, S., 2018. A zebrafish model for ocular tuberculosis. PLoS One 13, e0194982. https://doi.org/10.1371/journal.pone.0194982.
Taylor, A.W., Hsu, S., Ng, T.F., 2021. The role of retinal pigment epithelial cells in regulation of macrophages/microglial cells in retinal immunobiology. Front. Immunol. 12, 724601 https://doi.org/10.3389/fimmu.2021.724601.
Ten Berge, J.C.E.M., Schreurs, M.W.J., Vermeer, J., Meester-Smoor, M.A., Rothova, A., 2016. Prevalence and clinical impact of antiretinal antibodies in uveitis. Acta Ophthalmol. 94, 282–288. https://doi.org/10.1111/aos.12939.
Testi, I., Agrawal, R., Mehta, S., Basu, S., Nguyen, Q., Pavesio, C., Gupta, V., 2020. Ocular tuberculosis: where are we today? Indian J. Ophthalmol. 68, 1808–1817. https://doi.org/10.4103/ijo.IJO_1451_20.
Tezera, L.B., Bielecka, M.K., Ogongo, P., Walker, N.F., Ellis, M., Garay-Baquero, D.J., Thomas, K., Reichmann, M.T., Johnston, D.A., Wilkinson, K.A., Ahmed, M., Jogai, S., Jayasinghe, S.N., Wilkinson, R.J., Mansour, S., Thomas, G.J., Ottensmeier, C.H., Leslie, A., Elkington, P.T., 2020. Anti-PD-1 immunotherapy leads to tuberculosis reactivation via dysregulation of TNF-α. Elife 9. https://doi.org/10.7554/eLife.52668.
Todd, L., Palazzo, I., Suarez, L., Liu, X., Volkov, L., Hoang, T.V., Campbell, W.A., Blackshaw, S., Quan, N., Fischer, A.J., 2019. Reactive microglia and IL1β/IL-1R1-signaling mediate neuroprotection in excitotoxin-damaged mouse retina. J. Neuroinflammation 16, 118. https://doi.org/10.1186/s12974-019-1505-5.
Tonby, K., Wergeland, I., Lieske, N.V., Kvale, D., Tasken, K., Dyrhol-Riise, A.M., 2016. The COX- inhibitor indomethacin reduces Th1 effector and T regulatory cells in vitro in Mycobacterium tuberculosis infection. BMC Infect. Dis. 16, 599. https://doi.org/10.1186/s12879-016-1938-8.
Tsirouki, T., Dastiridou, A., Symeonidis, C., Tounakaki, O., Brazitikou, I., Kalogeropoulos, C., Androudi, S., 2018. A focus on the epidemiology of uveitis. Ocul. Immunol. Inflamm. 26, 2–16. https://doi.org/10.1080/09273948.2016.1196713.
Tsui, E., Fern, C.M., Goldberg, N.R., 2021. Treatment of refractory tubercular serpigious-like choroiditis with intravitreal methotrexate. Retin. Cases Brief Rep. 15, 169–173. https://doi.org/10.1097/ICB.0000000000000767.
Urzua, C.A., Lantigua, Y., Abuauad, S., Liberman, P., Berger, O., Sabat, P., Velasquez, V., Castiglione, E., Calonge, M., 2017. Clinical features and prognostic factors in presumed ocular tuberculosis. Curr. Eye Res. 42, 1029–1034. https://doi.org/10.1080/02713683.2016.1266663.
van Hagen, P.M., Baarsma, G.S., Mooy, C.M., Ercoskan, E.M., ter Averst, E., Hofland, L.J., Lamberts, S.W., Kuijpers, R.W., 2000. Somatostatin and somatostatin receptors in retinal diseases. Eur. J. Endocrinol. 143 (Suppl. l), S43–S51. https://doi.org/10.1530/eje.0.143s043.
Venketaraman, V., Millman, A., Salman, M., Swaminathan, S., Goetz, M., Lardizabal, A., Hom, D., Connell, N.D., 2008. Glutathione levels and immune responses in tuberculosis patients. Microb. Pathog. 44, 255–261. https://doi.org/10.1016/j.micpath.2007.09.002.
Vos, A.G., Wassenberg, M.W.M., de Hoog, J., Oosterheert, J.J., 2013. Diagnosis and treatment of tuberculous uveitis in a low endemic setting. Int. J. Infect. Dis. 17, e993–e999. https://doi.org/10.1016/j.ijid.2013.03.019.
Wallis, R.S., Ginindza, S., Beattie, T., Arjun, N., Likoti, M., Edward, V.A., Rassool, M., Ahmed, K., Fielding, K., Ahidjo, B.A., Vangu, M.D.T., Churchyard, G., 2021. Adjunctive host-directed therapies for pulmonary tuberculosis: a prospective, open-label, phase 2, randomised controlled trial. Lancet Respir. Med. 9, 897–908. https://doi.org/10.1016/S2213-2600(20)30448-3.
Wang, W., Du, Z., Ni, M., Wang, Z., Liang, M., Sheng, H., Zhang, A., Yang, J., 2020. Aspirin enhances the clinical efficacy of anti-tuberculosis therapy in pulmonary tuberculosis in patients with type 2 diabetes mellitus. Inf. Disp. 52, 721–729. https://doi.org/10.1080/23744235.2020.1778177.
WHO Consolidated Guidelines on Tuberculosis Module 4: Treatment - Drug-Susceptible Tuberculosis Treatment, 2020. World Health Organization, Geneva.
Wroblewski, K.J., Hidayat, A.A., Neafie, R.C., Rao, N.A., Zapor, M., 2011. Ocular tuberculosis: a clinicopathologic and molecular study. Ophthalmology 118, 772–777. https://doi.org/10.1016/j.ophtha.2010.08.011.
Xu, Y., Wang, L., Zimmerman, M.D., Chen, K.-Y., Huang, L., Fu, D.-J., Kaya, F., Rakhilin, N., Nazarova, E.V., Bu, P., Dartois, V., Russell, D.G., Shen, X., 2018. Matrix metalloproteinase inhibitors enhance the efficacy of frontline drugs against Mycobacterium tuberculosis. PLoS Pathog. 14, e1006974 https://doi.org/10.1371/journal.ppat.1006974.
Yang, C.-T., Cambier, C.J., Davis, J.M., Hall, C.J., Crosier, P.S., Ramakrishnan, L., 2012. Neutrophils exert protection in the early tuberculous granuloma by oxidative killing of mycobacteria phagocytosed from infected macrophages. Cell Host Microbe 12, 301–312. https://doi.org/10.1016/j.chom.2012.07.009.
Yang, S., Zhou, J., Li, D., 2021. Functions and diseases of the retinal pigment epithelium. Front. Pharmacol. 12, 727870 https://doi.org/10.3389/fphar.2021.727870.
Young, C., Walzl, G., Du Plessis, N., 2020. Therapeutic host-directed strategies to improve outcome in tuberculosis. Mucosal Immunol. 13, 190–204. https://doi.org/10.1038/s41385-019-0226-5.
Yu, X., Li, L., Xia, L., Feng, X., Chen, F., Cao, S., Wei, X., 2019. Impact of metformin on the risk and treatment outcomes of tuberculosis in diabetics: a systematic review. BMC Infect. Dis. 19, 859. https://doi.org/10.1186/s12879-019-4548-4.
Zaemes, J., Kim, C., 2020. Immune checkpoint inhibitor use and tuberculosis: a systematic review of the literature. Eur. J. Cancer 132, 168–175. https://doi.org/10.1016/j.ejca.2020.03.015.
Zenaro, E., Donini, M., Dusi, S., 2009. Induction of Th1/Th17 immune response by Mycobacterium tuberculosis: role of dectin-1, Mannose Receptor, and DC-SIGN. J. Leukoc. Biol. 86, 1393–1401. https://doi.org/10.1189/jlb.0409242.
Zignol, M., Cabibbe, A.M., Dean, A.S., Glaziou, P., Alikhanova, N., Ama, C., Andres, S., Barbova, A., Borbe-Reyes, A., Chin, D.P., Cirillo, D.M., Colvin, C., Dadu, A., Dreyer, A., Driesen, M., Gilpin, C., Hasan, R., Hasan, Z., Hoffner, S., Hussain, A., Ismail, N., Kamal, S.M.M., Khanzada, F.M., Kimerling, M., Kohl, T.A., Mansjö, M., Miotto, P., Mukadi, Y.D., Mvusi, L., Niemann, S., Omar, S.V., Rigouts, L., Schito, M., Sela, I., Seyfaddinova, M., Skenders, G., Skrahina, A., Tahseen, S., Wells, W.A., Zhurilo, A., Weyer, K., Floyd, K., Raviglione, M.C., 2018. Genetic sequencing for surveillance of drug resistance in tuberculosis in highly endemic countries: a multi-country population-based surveillance study. Lancet Infect. Dis. 18, 675–683. https://doi.org/10.1016/S1473-3099(18)30073-2.