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Clinical science

Relapse in ocular tuberculosis: relapse rate, risk factors and clinical management in a non-endemic country

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ABSTRACT

Aims To assess the risk of uveitis relapse in ocular tuberculosis (OTB) following clinical inactivity, to analyse clinical factors associated with relapses and to describe the management strategies for relapses.

Methods A retrospective study was conducted on a 10-year patient registry of patients with OTB diagnosed at Erasmus MC in Rotterdam, The Netherlands. Time-to-relapse of uveitis was evaluated with Kaplan-Meier curve and risk factors for relapses were analysed.

Results 93 OTB cases were identified, of which 75 patients achieved clinical inactivity following treatment. The median time to achieve uveitis inactivity was 3.97 months. During a median follow-up of 20.7 months (Q1–Q3: 5.2–81.2) after clinical inactivity, uveitis relapse occurred in 25 of these 75 patients (33.3%). Patients who were considered poor treatment responders for their initial uveitis episode had a significantly higher risk of relapse after achieving clinical inactivity than good responders (adjusted HR=3.84, 95% CI: 1.28 to 11.51). 13 of the 25 relapsed patients experienced multiple uveitis relapse episodes, accounting for 78 eye-relapse episodes during the entire observation period. Over half (46 out of 78, 59.0%) of these episodes were anterior uveitis. A significant number of uveitis relapse episodes (31 episodes, 39.7%) were effectively managed with topical corticosteroids.

Conclusions Our results suggest that approximately one-third of patients with OTB will experience relapse after achieving clinical inactivity. The initial disease course and poor response to treatment predict the likelihood of relapse in the long-term follow-up. Topical corticosteroids were particularly effective in relapse presenting as anterior uveitis.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Ocular tuberculosis (OTB) is a significant cause of infectious uveitis. Since detecting the presence of *Mycobacterium tuberculosis* (Mtb) in the eye is challenging, the diagnosis is often relied on systemic investigations. The main treatment approach consists of antitubercular treatment (ATT), especially in cases where the presence of Mtb is confirmed.

WHAT THIS STUDY ADDS

⇒ The relapse rate among patients with OTB following the resolution of uveitis after successfully managing the initial uveitis presentation is presented. Uveitis relapse primarily manifests as anterior uveitis, and most of these episodes were effectively managed using immunosuppressive drugs without the necessity for (re)initiating ATT. Patients who respond poorly to treatment for the initial uveitis (with persistence of ocular inflammation after 6 months of treatment initiation) appear to be a significant predictor of relapse.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Relapse in the context of OTB may support the concept of post-infectious uveitis. Restoration of intraocular hemostasis following infectious uveitis and the underlying pathomechanism of relapses warrant further investigation. Long-term follow-up of patients after the resolution of initial uveitis is necessary, especially among those who were poor responders.

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INTRODUCTION

Tuberculosis (TB) remains a major global health concern, manifesting as active TB disease an estimated 10.6 million individuals globally.[1] While the disease primarily affects the lungs, it can also manifest in extrapulmonary sites, including the eyes. The prevalence of ocular TB (OTB) among uveitis patients varies between 3% in non-high-burden settings and 7%–11% in high-burden settings.[2] The decision to initiate antitubercular treatment (ATT) in presumed OTB cases, based on positive interferon-gamma release assay (IGRA) or tuberculin skin test (TST) results without clinically active systemic TB, remains challenging. Experts recommend starting ATT in patients with tubercular choroiditis, serpiginous-like choroiditis (SLC) or tuberculoma, who also display signs of systemic TB infection based on positive IGRA, TST or chest radiological features suggestive of TB.[3] However, the decision is still challenging when patients present with uveitis manifestations other than the aforementioned phenotypes. In such

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cases, the diagnosis of OTB relies heavily on a positive IGRA/TST result. Meanwhile, reliance on only local or systemic immunosuppressive drugs without ATT to control inflammatory activity in presumed OTB has also been described, even though there are limited data to conclude which subsets of presumed patients with OTB benefit from treatment with immunosuppressant alone.[4 5] A recent study by Alam *et al* explored the application of the Standardised Uveitis Nomenclature (SUN) working group criteria to reclassify presumed patients with OTB.[6] They observed two distinct groups: (1) uveitis patients with ocular clinical phenotypes strongly indicative of OTB based on the SUN criteria, tested positive for *Mycobacterium tuberculosis* (Mtb) PCR from ocular fluid and/or had active TB and (2) those with TST-positive undifferentiated uveitis who did not meet the SUN criteria.[6] Interestingly, the latter group exhibited higher intraocular T lymphocyte cytokine responses, including tumor necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-1 on stimulation with early secreted antigenic target 6 kDa antigen.[6] While the study did not report treatment outcomes, the authors hypothesised that ATT might be beneficial in the OTB group, whereas immunosuppressant therapy, without adjunctive ATT, could be sufficient for managing undifferentiated uveitis cases who showed TB-immunoreactivity.[6]

Relapse and chronic uveitis can occur after the initial successful treatment of infectious uveitis, for instance, in the case of streptococcal infections.[7] However, the occurrence of uveitis relapse after treatment for *Mtb* infection has received limited attention so far. Post-infectious chronic uveitis has been demonstrated in mice after injection of heat-killed *Mtb* in the vitreous cavity of animals with prior systemic exposure to killed *Mtb*.[8] Chronic sterile inflammation, and possibly a uveitis relapse, can arise when the restoration of ocular homeostasis, necessary for maintaining an inflammation-free environment, is compromised by the presence of non-viable Mtb or residual Mtb antigens, along with dysregulated T lymphocytes.[8] It is important to note that the primed mycobacterial uveitis (PMU) model does not accurately mirror the potential scenario of uveitis caused by the initial presence of live replicating Mtb. The model solely assesses the intraocular response to the presence of non-replicating whole Mtb in the eye,[8] which may be closely related to the mechanism occurred in relapse episodes. Several other mechanisms may, theoretically, also contribute to relapses, including the persistence of paucibacillary Mtb within ocular structures or post-infectious autoimmunity due to molecular mimicry or through immune activation in individuals who are prone to develop uveitis.[9] Based on the observed intraocular inflammation occurred in the PMU model,[8] we aimed to investigate the occurrence of recurrent uveitis following treatment in OTB. In our recent small case series study, we recently highlighted that, during a long-term follow-up even after a successful full-course ATT, recurrence occurred in three out of five patients.[10] In order to gain more insights into the risk of uveitis relapse after previous resolution, in a real-world clinical setting, we analysed longitudinal clinical data from all patients with OTB within our 10-year outpatient registry. We then explored clinical factors that may predispose certain patients to a higher likelihood of an uveitis relapse and described the management strategies for relapses.

METHODS

Study design and cohort description

This is a retrospective cohort study based on medical records of all presumed patients with OTB treated in the uveitis outpatient clinics of Erasmus University Medical Centre, Rotterdam, The Netherlands, between January 2012 and December 2021. All uveitis patients diagnosed with a presumed OTB or a positive TST or IGRA test were screened using the inclusion and exclusion criteria according to the COTS study.[11] These criteria specify uveitis characteristics compatible with OTB, including: (1) anterior uveitis (granulomatous or nongranulomatous), iris nodules and ciliary body granuloma; (2) intermediate uveitis (with or without snowballs); (3) anterior and intermediate uveitis (granulomatous, characterised by the presence of iris nodules or mutton-fat keratic precipitates alongside clinically significant vitreous inflammation, or nongranulomatous); (4) posterior and panuveitis, choroidal tubercle, choroidal granuloma, subretinal abscess and SLC; (5) retinitis, retinal vasculitis and neuroretinitis or (6) sclerouveitis. In addition, the patients had to meet positive result from corroborative investigations indicative of Mtb infection (TST, IGRA or evidence of TB infection on chest radiography).

Data collection

Data on all medical records were entered into an encrypted predesigned online-based study form in Castor Electronic Data Capture (EDC) by an ophthalmologist (IP) and accessible for validation by the other investigators (JCEMtB and SMR). Patients' names, initials or medical record number were not entered in Castor EDC to preserve anonymity. Data evaluated in this analysis included demographic characteristics, ocular features at the initial visit, laboratory and ancillary investigation results, medications received during the entire follow-up period and longitudinal data until the last clinic visit until the end of data collection (21 February to 15 March 2023). Best-corrected visual acuity (BCVA) values were categorised according to the WHO—International Classification of Disease (ICD-11, 2018) for distance vision impairment classification.[12] The grade of anterior chamber (AC) cells and anatomical site of uveitis were classified according to the SUN working group nomenclature.[13] In terms of baseline clinical features analysed in this study, we chose the more severe presentation between the first referral visit and the final diagnosis before initial treatment was assigned. Treatment could be ATT with or without local steroids, ATT with the combination of systemic corticosteroid (CS)/immunosuppressive drugs (IMT) or local/systemic CS/IMT without ATT.

In our centre, ATT prescription was determined by a designated pulmonologist, specialised in TB. ATT typically involved a combination of three or four drugs, namely isoniazid, rifampicin and ethambutol, with the optional addition of pyrazinamide. This was administered for a duration of 2 months (initial phase), followed by the continuation phase, which comprised isoniazid and rifampicin, with or without pyrazinamide, for an additional 4 months. The administration of systemic CS (oral prednisolone 0.5–1 mg/kg daily) with an individualised tapering schedule as well as immunosuppressive drugs (IMT) was always monitored by a clinical immunologist. Local steroid therapy, including topical, periocular and intravitreal steroids, was tailored to each patient's specific needs.

Definitions

Patient group

We applied the recently established classification criteria for OTB developed by the SUN working group to categorise our patients.[14] Those who fulfilled the SUN classification criteria and/or had active systemic TB were classified as patient group 1. Patients who met our inclusion and exclusion criteria (COTS criteria) but did not fulfil the SUN classification criteria for OTB

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were categorised as patient group 2 (undifferentiated uveitis with TB-immunoreactivity).

Treatment group

We defined three treatment groups in this study: treatment group A: ATT (±local steroids), for patients treated without oral CS/IMT during the ATT course; treatment group B: combined ATT and CS/IMT, for those received CS/IMT during the ATT course for the initial uveitis presentation and treatment group C: without ATT, if no ATT was being given and the patient was only treated with local and/or systemic IMT. IMT involved a range of therapeutic drugs, including steroids, disease-modifying anti-rheumatic drugs (ie, methotrexate, azathioprine or mycophenolate mofetil) and biologics (ie, anti-TNF and anti-IL-6 therapies) that was prescribed in a stepwise manner.

Good and poor responders

We assessed inflammatory activity at 6 months following treatment initiation for the initial uveitis in all patients. Good responders were defined as patients who met all of the following criteria at the first 6 months of treatment for initial uveitis episode: (1) absence of active inflammation in the retina, choroid, episclera or sclera, with both eyes showing ≤0.5+ AC or vitreous cells; (2) oral prednisone or its equivalent reduced to <10 mg daily; (3) topical 1% prednisolone acetate (or equivalent) reduced to no more than two drops daily and (4) discontinuation of immunosuppressant therapy with the exception of prednisone use <10 mg daily. Patients who did not achieve these criteria were considered as poor responders.

Clinical inactivity

Clinical inactivity in this context was determined by a period of at least 90 days where both eyes exhibited AC cells ≤0.5+, vitreous cells/haze ≤0.5+ and the absence of any other form of clinically active uveitis, such as retinal or choroidal lesions. This assessment was conducted by the attending uveitis specialist, based on slit lamp examination and considering the results of any multimodal imaging modalities that were performed. In line with this definition, our study included patients who fulfilled the 'remission' criteria established by SUN,[13] as well as those who achieved clinical inactivity while maintaining their anti-inflammatory/immunosuppressive medication, reflecting the scenarios encountered in real-world clinical practice.

Main outcome measure

The primary objective of this study was to evaluate the risk of uveitis relapse in patients with OTB and to identify potential predictors for such relapses. Uveitis relapse was defined as any worsening of ocular inflammation (including two-step increase of AC/vitreous cells) or clinically new inflammatory activity (including choroidal or retinal lesion), that needs modification of local or systemic uveitis treatment after a minimum of 90 days of uveitis inactivity and completion of ATT course (for patients receiving ATT) at patient level. Time-to-relapse was calculated from the first visit showing inactive uveitis until the first notification of uveitis relapse.

Statistical analysis

Numerical values were presented as mean with SD for normally distributed data and as median (Q1–Q3) for data with non-normal distribution. Categorical variables were presented as frequency and percentages. Overall risk of relapse was calculated as the incidence of relapse per person-year. Kaplan-Meier curves were generated to evaluate the time-to-inactivity and time-to-relapse. Assessment of proportional hazard assumption of selected variables was conducted through evaluation of the Kaplan-Meier curves of the clinical predictors. Potential risk factors at the patient level for uveitis relapse were evaluated on the basis of HRs and adjusted HRs (with 95% CIs) generated using univariate and multivariate Cox regression, respectively. The final multivariate model included variables with an initial p value <0.20 at univariate analysis. We considered a p value <0.05 to be statistically significant. All statistical analyses were performed using IBM SPSS Statistics V.28.0.1.0 (142) for Windows (SPSS).

RESULTS

93 patients who presented with OTB were documented in our outpatient clinic during the study period. In our cohort, the diagnosis of OTB relied on clinical presentation, positive IGRA test and exclusion of other possible causes of uveitis. Among the patients, five were diagnosed with active systemic TB at baseline uveitis presentation (one with active pulmonary TB and four with extrapulmonary TB other than the eye). Out of the 28 patients who underwent ocular fluid analysis, Mtb PCR testing was performed on five samples, but none yielded a positive result. None of our patients showed active keratitis (eg, deep peripheral interstitial keratitis) at baseline presentation.

Out of 93 patients in our cohort, 12 patients were lost-to-follow-up after the initial visit without any follow-up data. Three patients did not have a well-documented date of clinical inactivity (these patients were initially assessed at our centre, had follow-up for treatment elsewhere and returned to our clinic with clinical inactivity after 1–6 years since initial assessment). Three patients did not achieve clinical inactivity until the last visit. The remaining 75 patients had well-documented clinical inactivity data. The flow of patient inclusion for this study is summarised in online supplemental figure.

The characteristics of the 75 patients included in risk of uveitis relapse analysis are summarised in table 1. The overall median time to achieve uveitis inactivity was 3.97 months (95% CI: 2.21 to 5.72; figure 1A). Based on the SUN classification for OTB, there was no difference in terms of time-to-uveitis inactivity between OTB (patient group 1) and the undifferentiated uveitis (patient group 2) (log-rank test, p=0.732; figure 1B). All patients in group 1 were initially treated with ATT±systemic CS/IMT. There was a trend towards a longer time period to achieve uveitis inactivity in patients treated with a combination of ATT and systemic CS/IMT (treatment group B) (log-rank test, p=0.092; figure 1C): however, it is noteworthy that those patients (treatment group B) exhibited a more severe presentation compared with those receiving ATT without systemic CS/IMT (treatment group A) and those treated without ATT (treatment group C, see online supplemental table 1).

Risk of uveitis relapse and its clinical predictors

Uveitis relapse was occurred in 25 out of 75 patients (33.3%). The median total duration of follow-up after the notification of uveitis inactivity and the last clinic visit in our cohort was 20.7 months (Q1–Q3: 5.2–81.2). The incidence rate of the first uveitis relapse episode following uveitis inactivity was 0.18 cases per person-year. Uveitis relapses typically occur in the same eye as the initial uveitis presentation. Out of seven patients initially presenting with unilateral uveitis, six experienced relapses unilaterally in the same eye while one had a bilateral uveitis relapse. Among 18 patients initially presenting with bilateral

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Table 1 Baseline characteristics of the 75 subjects with OTB who were analysed for uveitis relapse

Characteristics	Uveitis relapse, no. patients (%)		
	Yes	No	P value
Age >50 years	17/43 (39.5)	26/43 (60.5)	0.187
Sex: male	8/34 (23.5)	26/34 (76.5)	0.101
History of TB diagnosis/treatment	6/11 (54.5)	5/11 (45.5)	0.164
Laterality of uveitis: bilateral	18/44 (40.9)	26/44 (59.1)	0.097
Diabetes mellitus	4/15 (26.7)	11/15 (73.3)	0.540
Chest X-ray showing TB infection*	1/3 (33.3)	2/3 (66.7)	1.000
Laboratory values at initial presentation			
ESR (median, Q1–Q3)	21.0 (9.0–38.0)	15.0 (5.2–28.0)	0.547
Leucocytes ($\times 10^3$/µL, mean±SD)	7.4±2.2	8.3±2.4	0.202
QFT level† (median, Q1–Q3)	5.8 (1.2–12.7)	5.6 (1.2–10.3)	0.830
QFT >5.0†	11/30 (36.7)	19/30 (63.3)	1.000
Patient group			
Group 1 (compatible with SUN classification for OTB)	4/16 (25.0)	12/16 (75.0)	0.425
Group 2 (undifferentiated uveitis)	21/59 (35.6)	38/59 (64.4)	
Anatomical site of inflammation			
Anterior uveitis	10/28 (35.7)	18/28 (64.3)	0.057
Intermediate uveitis	3/4 (75.0)	1/4 (25.0)	
Posterior uveitis	2/17 (11.8)	15/17 (88.2)	
Panuveitis	9/24 (37.5)	15/24 (62.5)	
Episclero/sclerouveitis	0/1 (0)	1/1 (100)	
Discrepant between right–left eyes	1/1 (100)	0/1 (0)	
BCVA category of the worst involved eye‡			
No–mild vision impairment	17/45 (37.8)	28/45 (62.2)	0.349
Moderate vision impairment	1/10 (10.0)	9/10 (90.0)	
Severe vision impairment	0/1 (0)	1/1 (100)	
Blindness	5/14 (35.7)	9/14 (64.3)	
Presence of eye(s) with			
Granulomatous AC inflammation (mutton-fat KPs and/or iris nodules)	1/6 (16.7)	5/6 (83.3)	0.657
Posterior synechiae	6/14 (42.9)	8/14 (57.1)	0.531
AC cells ≥2+§	4/13 (30.8)	9/13 (69.2)	1.000
Active vitreous cells	10/32 (31.3)	22/32 (68.8)	0.741
Retinal vasculitis	6/17 (35.3)	11/17 (64.7)	0.845
Non-glaucomatous optic nerve involvement	4/12 (33.3)	8/12 (66.7)	1.000
Retinal lesions	3/7 (42.9)	4/7 (57.1)	0.680
Serpiginous-like choroiditis (SLC)	1/3 (33.3)	2/3 (66.7)	1.000
Choroidal granuloma/tuberculoma	2/4 (50.0)	2/4 (50.0)	0.597
Other type of choroidal lesions	3/11 (27.3)	8/11 (72.7)	0.742
Macular oedema	7/21 (33.3)	14/21 (66.7)	1.000
Initial treatment group			
Treatment group A: ATT±local steroid without systemic CS/IMT	9/35 (25.7)	26/35 (74.3)	0.273
Treatment group B: ATT±local steroid with systemic steroid/IMT	9/19 (47.4)	10/19 (52.6)	
Treatment group C: without ATT (local±systemic CS)	7/21 (33.3)	14/21 (66.7)	

Row percentages are displayed in relapse yes and no columns.
*Chest X-ray was available in 68 patients.
†QFT quantification value was available in 63 patients.
‡BCVA at baseline was available in 70 patients.
§AC cells grade was available in 68 patients.
AC, anterior chamber; ATT, antitubercular treatment; BCVA, best-corrected visual acuity; CS, corticosteroid; ESR, erythrocyte sedimentation rate; IMT, immunosuppressive drugs; KPs, keratic precipitates; OTB, ocular tuberculosis; QFT, QuantiFERON TB Gold test; SUN, Standardised Uveitis Nomenclature; TB, tuberculosis.

uveitis, 13 experienced uveitis relapse as bilateral uveitis, while the other 5 had unilateral uveitis relapses. The distribution of anatomical sites of baseline uveitis presentation with the occurrence of relapse, according to the initial treatment, whether it involved ATT (treatment groups A and B) or not (treatment group C), was presented in online supplemental table 2. While we observed 28 cases of anterior uveitis (28/75, 37.3%) and 4 cases with intermediate uveitis (4/75, 5.3%) at baseline presentation (see online supplemental table 2), none were 'anterior and intermediate uveitis'.

During uveitis relapse, IGRA testing was repeated in 18 patients, of which 9 (50%) still exhibited a positive result and the other 9 (50%) had negative result (online supplemental table 3). Among the nine patients with persistently positive IGRA, five

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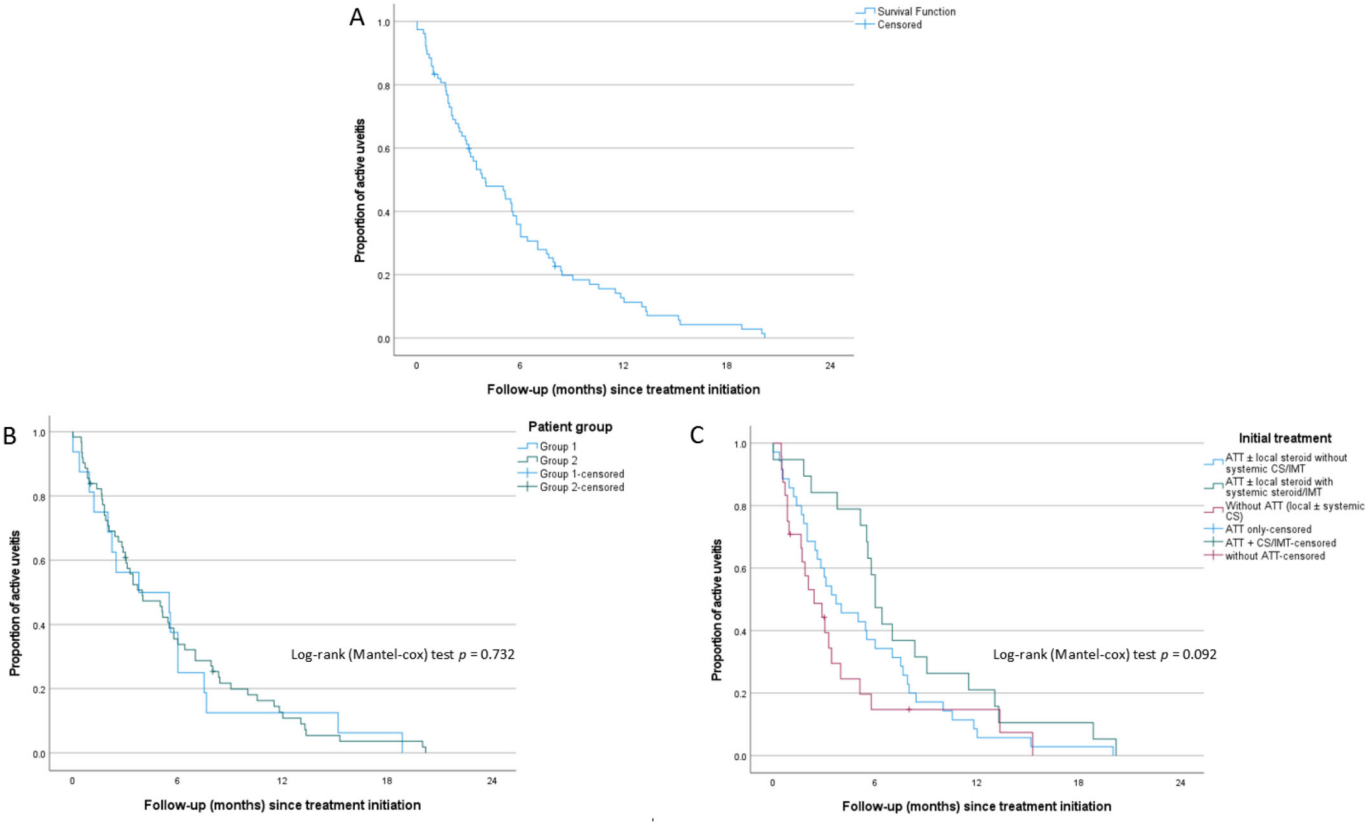

Figure 1 Kaplan-Meier curves for uveitis inactivity. Cumulative rate of uveitis inactivity in all patients (n=78) (A). Sub analyses based on patient group (according to SUN classification) (B) and treatment of initial uveitis (C). Y-axis: cumulative proportion of patients achieving uveitis inactivity, 1.0=100%. X-axis: follow-up since treatment initiation. ATT, antitubercular treatment; CS, corticosteroid; IMT, immunosuppressive drugs.

did not show a decline in IGRA value compared with the initial presentation of uveitis. We did not identify differences in terms of the anatomical site of uveitis at the time of relapse and the timing of relapse between those who remained IGRA positive and those who did not (online supplemental table 3). For assessing the risk of uveitis relapse, only the first episode of relapse is displayed in figure 2. During the total duration of follow-up, 13 out of 25 patients experienced more than one episode of uveitis relapse. The median number of uveitis relapse episodes was 2 (Q1–Q3: 1–3). For the first uveitis relapse episodes, 11 occurred without the use of any topical or systemic medication. Additionally, eight episodes occurred while the patients were solely on topical immunosuppressant drugs and six episodes occurred despite the patients were still receiving systemic immunosuppressant medication (five was still under IMT and one was under oral prednisone). The details of these patients are provided in online supplemental table 3.

By applying the SUN classification for OTB, we observed no differences in the risk of relapse between patients classified as group 1 or 2 (log-rank test, p=0.426; figure 2B), neither between patients within treatment group A, B or C (log-rank test, p=0.065; figure 2C). The estimated median time to relapse and annual relapse-free proportions are presented in online supplemental table 4.

Assessment of intraocular inflammation at 6 months from treatment initiation revealed that 48 patients (51.6%) were good responders. Panuveitis as the initial uveitis presentation was associated with poor response (still had ongoing inflammation at 6 month following treatment) when compared with anterior uveitis (OR=5.33, 95% CI: 1.44 to 19.70, p=0.012). Two baseline clinical features, the presence of retinal vasculitis (OR=2.79, 95% CI: 0.92 to 8.43, p=0.070) and choroidal lesions other than SLC/ampiginous choroiditis (OR=3.88, 95% CI: 0.97 to 15.48, p=0.055) demonstrated a trend towards association with becoming poor responders. Multivariate analysis to identify factor associated with uveitis relapse following the achievement of clinical inactivity revealed that poor responder status was the only significant predictor (see table 2 and figure 2D). On stratification by treatment group, our analysis revealed no statistically significant differences between patient group 1 and group 2, as well as between individuals classified as good responders and those classified as poor responders (online supplemental table 5). This may be attributed to the relatively small sample sizes within each category of sub-analysis comparison. Additionally, across all three treatment groups, poor responders demonstrated a higher relapse rate when compared with good responders (online supplemental table 5).

Anatomical site of uveitis relapse and the management of relapse episodes

From 25 patients with a uveitis relapse, a total of 78 eye-relapse episodes were identified until the last follow-up time. Among these episodes, more than half (46 out of 78, 59.0%) presented as anterior uveitis. The number of this recurred anterior uveitis episodes included 19 (19 out of 46) episodes that initially presented as intermediate (n=2), posterior (n=4) and panuveitis (n=13). Distribution and change in anatomical site of uveitis between the initial uveitis presentation and the relapse episodes in each eye are depicted in figure 3A. There were no specific

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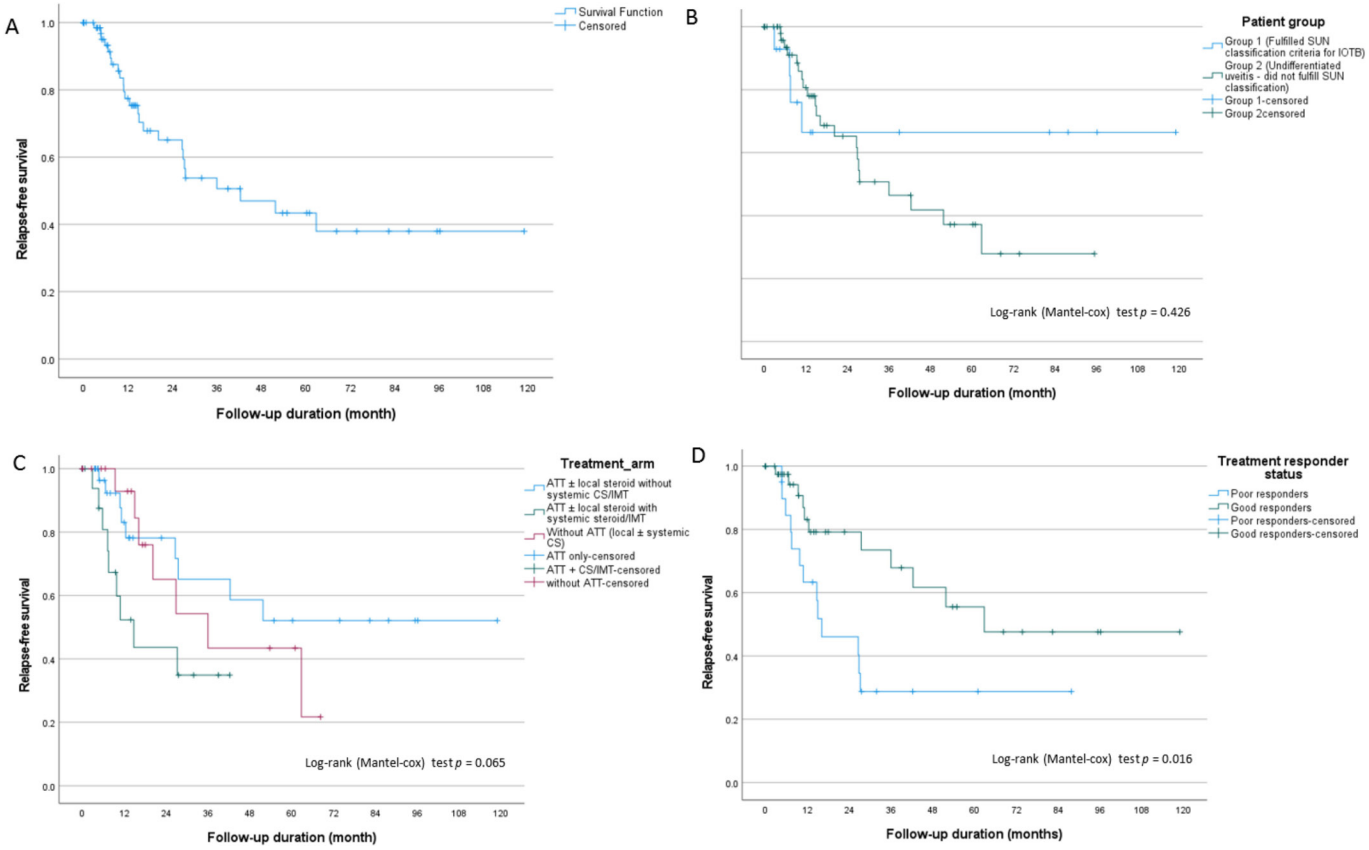

Figure 2 Kaplan-Meier curves showing the overall risk of uveitis relapse after achieving inactivity in the entire study population (n=75) (A) with subsequent subgroup analyses based on SUN classification (B), initial treatment (C) and response to initial treatment (D). Y-axis: cumulative proportion of patients without relapse episode (relapse-free), 1.0=100%. X-axis: follow-up period (calculated from the time uveitis inactivity was achieved). ATT, antitubercular treatment; CS, corticosteroid; IMT, immunosuppressive drugs.

baseline clinical features associated with the anatomical site of the uveitis relapse. Interestingly, regardless the anatomical site of initial uveitis, the majority of relapse episodes appeared as anterior uveitis (figure 3A). In cases of intermediate uveitis, most of the relapse were observed as intermediate uveitis as well. A large number of uveitis relapse episodes (31 episodes, 39.7%) were effectively managed with topical CS, especially in cases of an anterior uveitis (see figure 3B). Only one patient received isoniazid monotherapy in combination with topical and oral prednisone and underwent pars plana vitrectomy for the treatment of the relapse. In general, the first uveitis relapse episode displayed a more severe intraocular inflammation, indicated by a higher proportion of eyes with AC cells ≥2+, compared with the initial uveitis presentation (34.2% vs 13.2%, online supplemental table 6). However, visual acuity appeared to remain relatively stable across the initial uveitis episode, the first uveitis relapse episode and subsequent uveitis relapses. With each subsequent relapse episode, there was an increasing tendency to prescribe IMT (online supplemental table 6). The median time required to achieve inactivity in the first, second and third episodes of uveitis relapse was 2.3 months (Q1–Q3: 1.6–4.2), 3.3 months (Q1–Q3: 1.5–5.4) and 1.4 months (Q1–Q3: 0.5–3.5), respectively.

In our cohort, out of the initial five patients who presented with concurrent uveitis and active systemic TB (one case each with pulmonary TB, meningitis TB, Poncet's disease, urogenital TB and lymphadenitis TB) and were initially treated with ATT, two experienced relapses after uveitis resolution. These relapses in the two patients were successfully managed with immunosuppressive treatment without re-initiation of ATT. We did not observe a distinct pattern in the course of uveitis relapse between the two patients who initially presented with concurrent uveitis with active systemic TB and the other 23 patients who were initially diagnosed as OTB based on positive IGRA and the exclusion of other possible uveitis etiologies (online supplemental table 3).

DISCUSSION

In this study, we demonstrate that the cumulative incidence of uveitis first relapse episodes among OTB cases within the low TB-endemic setting in the Netherlands is 33.3% (25 out of 75 cases). The first relapse episodes occurred after a median period of 11.9 months (range 4.7–27.5 months) after treatment and recovery of the initial presenting uveitis. Importantly, we noted that a poor response to treatment for the first presenting uveitis episode is associated with an increased risk of uveitis relapse after achievement of clinical inactivity for the initial uveitis. In line with a prior investigation by the COTS group, which identified choroidal involvement, vitreous haze and retinal vasculitis as clinical signs associated with treatment failure,[11] our findings indicate that panuveitis, non-specific choroidal involvement and retinal vasculitis are also associated with an inadequate response to the initial uveitis treatment.

Until now, comprehensive long-term follow-up data on post-treatment outcomes in patients with OTB are still limited, both in high and low TB endemic areas. Our recent meta-analysis indicated a potential reduction in risk of relapse with ATT.[4] However, cautious interpretation is required due to the inability

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Table 2 Cox-regression analysis for factors predictive to uveitis relapse following clinical inactivity

Factors	Crude HR (95% CI)	Adjusted HR (95% CI)
Age		
≤50 years	1 (reference)	1 (reference)
>50 years	1.82 (0.78 to 4.25)	2.42 (0.83 to 7.02)
Sex		
Female	1 (reference)	1 (reference)
Male	0.53 (0.23 to 1.24)	0.61 (0.21 to 1.75)
History of systemic TB		
Yes	2.09 (0.83 to 5.30)	1.93 (0.60 to 6.23)
No	1 (reference)	1 (reference)
Laterality		
Unilateral	1 (reference)	1 (reference)
Bilateral	1.08 (0.37 to 3.18)	1.12 (0.42 to 3.03)
Anatomical site of uveitis		
Anterior uveitis	1 (reference)	1 (reference)
Posterior uveitis	0.19 (0.04 to 0.90)	0.20 (0.04 to 1.10)
Other anatomical sites of uveitis	0.99 (0.43 to 2.28)	0.91 (0.29 to 2.86)
Treatment group		
With ATT—treatment groups A and B	1.09 (0.46 to 2.62)	2.12 (0.75 to 6.01)
Without ATT—treatment group C	1 (reference)	1 (reference)
Patient group		
Group 1 (fulfilled SUN classification)	0.65 (0.22 to 1.91)	0.69 (0.20 to 2.39)
Group 2 (undifferentiated uveitis with TB-immunoreactivity)	1 (reference)	1 (reference)
Response to treatment for initial uveitis presentation		
Good responders	1 (reference)	1 (reference)
Poor responders	2.69 (1.16 to 5.99)	3.84 (1.28 to 11.51)*

*Statistically significant in multivariable cox-regression analysis (p=0.016).
ATT, antitubercular treatment; SUN, Standardised Uveitis Nomenclature; TB, tuberculosis.

to assess relapse outcomes in a time-sensitive manner (ie, calculation of relapse incidence rate), which could introduce bias from varying study endpoints. A study by Tomkinz-Netzer *et al* reported similar results to the current study, showing a relapse cumulative incidence of 34.9% among patients with OTB during the median follow-up time of 29 months (6–287 months).[15] They observed a lower risk of relapse associated with ATT administration compared with those that were not being treated with ATT[15]; however, our study did not replicate these findings, despite sharing a similar low-endemic TB country setting. It is noteworthy that the baseline characteristics of our patients differed from that study. Most of our patients did not meet the SUN classification criteria for OTB and only a limited number exhibited abnormalities indicative of TB infection in the chest radiographs. In contrast, the aforementioned study included a higher proportion of patients with posterior uveitis manifestations (eg, retinal vasculitis, multifocal choroiditis, SLC) and one-fifth of their patients exhibited evidence of TB infection in chest radiographs.[15] Thus, anti-TB treatment effect might be anticipated to be more beneficial in their study cohort than ours. Moreover, we noted a high prevalence of anterior uveitis in our cohort, in line with findings from two other studies conducted on the UK population.[16 17] Importantly, a study that specifically included tubercular retinal vasculitis also concluded that there was no difference in terms of the occurrence of relapse between patients treated with and without ATT.[18] We hypothesise that geographical variation may contribute to the varying proportions of observed uveitis types in OTB, possibly associated with distinct host-immune responses or variations in Mtb virulence.[19] However, further studies are needed to explore the potential causes behind these phenotypic variations in proportions. Additionally, a study by Multani *et al* conducted in India reported that only 10% (15 out of 156 patients) of patients with OTB experienced a uveitis relapse.[20] Important to note that, comparable to our approach, the majority of uveitis relapse episodes identified in the study by Multani *et al* were managed by immunosuppressive drugs and not by ATT re-initiation.[20]

The term 'post-infectious uveitis' has emerged to describe uveitis relapse following successful resolution of initial infectious uveitis.[7 21] We highlight that patients with OTB who were poor responders for the treatment of their initial uveitis episode might have a higher likelihood of uveitis relapse, after clinical inactivity has been achieved. It is now known that dynamic properties within the AC actively control the content of the aqueous humour. This involves not only the breach of iris vasculature but also the strong influence of iris stromal epithelium that actively controls the content of the aqueous humour.[22] Nevertheless, little is known about how the blood-aqueous barrier and iris epithelium regain their hemostasis, as well as how the inflammatory immune response in prior uveitis influences subsequent reactions and how these could contribute to the phenomenon of 'post-infectious uveitis'.[23] Additionally, dysregulation in the AC seems to influence the predominance of anterior uveitis in relapse episodes we observed. When evaluating uveitis relapse in OTB, two important questions arise: (1) Is a uveitis relapse associated with reinfection of ocular structures with Mtb or due to reactivation of a previously dormant residual Mtb that necessitates ATT re-initiation?, (2) Is the uveitis relapse due to a dysregulated immune responses (ie, autoimmune or autoinflammation) within ocular structures rather than related to reinfection/

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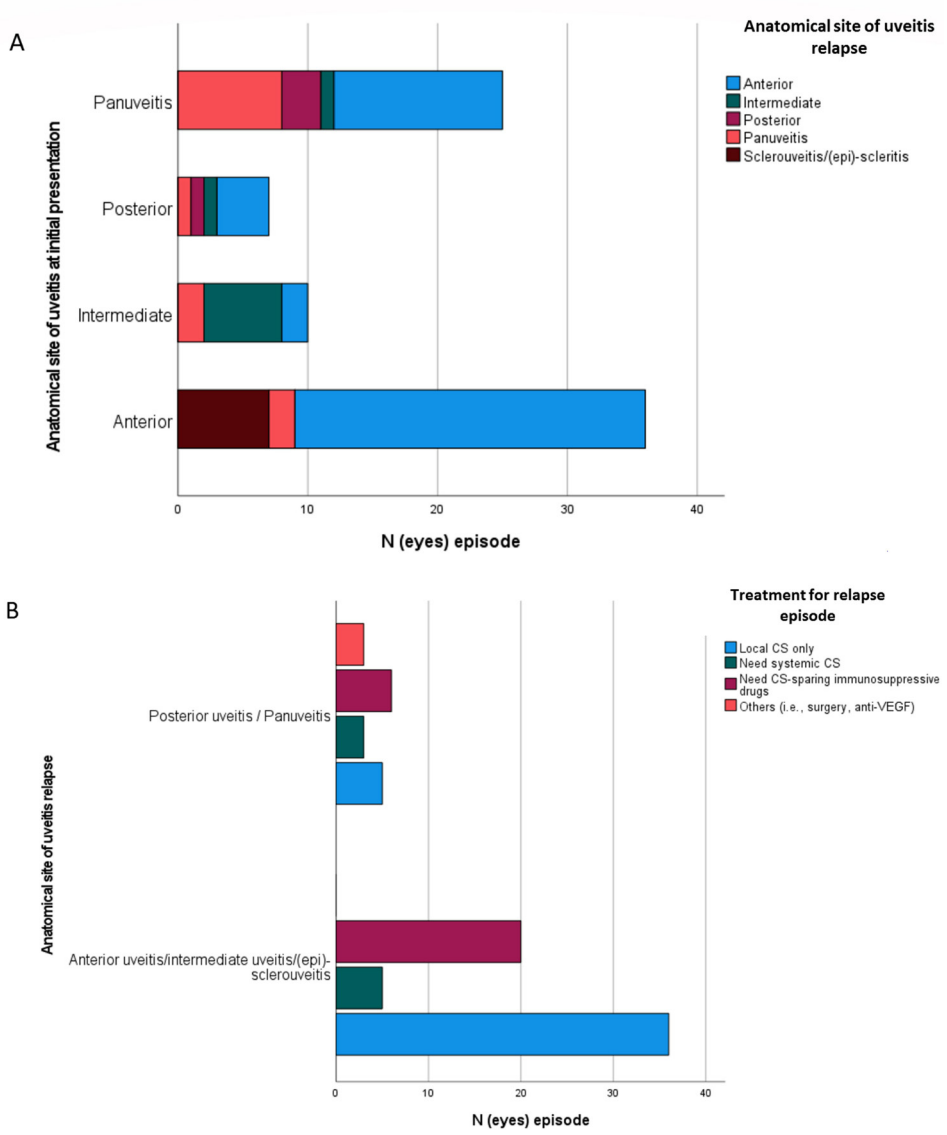

Figure 3 Anatomical site of uveitis relapse. The changing pattern of anatomical site of uveitis relapse according to the anatomical site of initial uveitis (A) and the treatment of relapse episodes according to the anatomical site of uveitis relapse (B). CS, corticosteroid; VEGF, vascular endothelial growth factor.

reactivation and thus treatable solely with immunosuppressant drugs? Regarding the possibility of reinfection in TB, endogenous reactivation is more prevalent than reinfection.[24 25] Of note, from the observation in pulmonary TB, the occurrence of recurrent disease in patients residing in low-endemic TB settings is low (1.8%),[25] which can also be extrapolated to our OTB cohort. Clinical clues to delve into the mechanism underlying uveitis relapse in OTB include the anatomical site of relapses and the treatment commenced for relapse episodes, as described in current study. Anterior uveitis is the most dominant anatomical site in relapse episodes. This aligns with findings by Multani *et al* describing that even in patients initially presenting with posterior uveitis or panuveitis, uveitis relapse primarily also manifests as anterior or intermediate uveitis.[20] They discussed the possibility of viable versus non-viable Mtb triggering intraocular inflammation following treatment, with viable Mtb having a greater propensity to cause posterior segment involvement (eg, retinal vasculitis and SLC) than non-viable Mtb.[8 20] However, conflicting evidence arises as successful retinal vasculitis management can solely depend on a treatment approach using either ATT or CS/IMT,[5 26] raising a debate whether one can discriminate viable versus non-viable Mtb as the cause of the inflammation primarily based on clinical signs and anatomical site of uveitis. Intriguingly, an animal model supports the notion that the presence of non-viable Mtb in the intraocular compartment could induce chronic intraocular inflammation.[8] If this phenomenon also occurs in relapse episodes encountered in patients with OTB, immunosuppressive treatment alone, without the need to re-initiate ATT, might suffice to treat the relapse episode.[6] Align with that hypothesis, we observed that most uveitis relapse episodes in OTB can be effectively managed with immunosuppressant drugs alone, either topically or systemically, with a fraction of patients requiring IMT.

Half of the patients with OTB in our study that experienced a relapse and were re-tested for IGRA still showed a positive IGRA result (9 out of 18 patients re-tested patients). A cautious approach is recommended when interpreting repeated IGRA testing for uveitis relapse episodes in the context of OTB. It should be kept in mind that IGRA reversion (conversion from positive to negative result) might be caused by several factors,

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including technical aspects associated with the IGRA test itself (ie, reproducibility between tests) and genuinely reflect adequate anti-TB treatment.[27] Generally, IGRA values tend to decline following ATT, indicating an adequate response to treatment.[28] Nevertheless, the considerable variability in the IGRA reversion rate (between 0% and 72%) challenges the reliability and objectivity of using it as a method for monitoring TB treatment, as highlighted in a systematic review.[28] In the current study, repeated IGRA testing was not performed on treatment completion of the initial uveitis episode nor at the time of clinical inactivity. Intriguingly, a report by Kaneko *et al* revealed that while a significant number of patients had IGRA reversion on completion of treatment for pulmonary TB, patients who experienced recurrence later in the follow-up period exhibited non-reversion and even an increased IGRA response towards Mtb antigen at the time of treatment completion.[29] Nevertheless, the explanation for the observed phenomenon in that study remains unclear. Meanwhile, several studies have emphasised that even though substantial patients showed decreasing levels of the QFT value, reversion cannot become a reliable marker for treatment adequacy, as some patients were still QFT positive after successful anti-TB treatment.[30 31] Therefore, it appears that repeated IGRA testing may not directly yield conclusions about the underlying cause of a uveitis relapse in previously treated OTB. Moreover, repeated IGRA testing cannot serve as a decisive tool to (re)initiate ATT for relapse episodes. Higher baseline QFT values would decrease the likelihood of reversion.[31] This aligns with current study (online supplemental table 3), showing that patients with high initial QFT values remained positive at their first uveitis relapse. For patients without reversion at the time of a relapse episode occurrence, new questions arise: (1) Does this relapse episode involve a mechanism different from the initial uveitis presentation?, (2) Was the initial uveitis presentation truly related to TB infection? Although the data obtained in our current study cannot answer these questions, it has been observed that no specific IGRA cut-off for uveitis can be applied to determine true cases of OTB.[32] As one of several plausible underlying mechanisms of uveitis relapse in OTB, recent accumulating evidence suggests that TB infection might induce autoimmune responses,[33] as also discussed separately.[9] Pulmonary TB patients displayed an altered B lymphocytes composition (increased CD24++CD38++subset) in peripheral circulation and a high proportion of patients were positive for autoantibodies to modified citrullinated vimentin.[33] Moreover, in our previous study, we detected that serum antinuclear autoantibodies were more prevalent in OTB than unknown cause of uveitis with negative IGRA.[34] However, the connection of these observations to an autoimmune response occurring in ocular structures as the underlying mechanism of uveitis relapse remains elusive. Altogether, the occurrence of uveitis relapse following clinical inactivity in OTB might reflect impaired ocular hemostasis and warrant close monitoring and treatment with immunosuppressive drugs.

The current study is limited by the retrospective collection of data and the variable length of follow-up. As our study only focused on the tertiary academic referral centre, subsequent follow-up data, if the patients were referred to another hospital, could not be retrieved. The treatment approach for OTB, whether the patients were treated with or without ATT, was based on the severity of initial presentation. However, when comparing patients with and without a relapse, there were no differences in clinical presentation besides the clinical response at 6 months since treatment initiation for their initial uveitis episode (good vs poor responders). It is important to note that in our cohort, the diagnosis of OTB was primarily achieved through corroborative investigations, with only five cases concurrently diagnosed with active systemic TB at baseline presentation. Ocular fluid analysis was infrequently performed in our setting, with only five patients undergoing testing, all of which yielded negative results. Consistent with our findings, a previous report by Gunasekeran *et al* similarly reported no PCR-positive OTB cases in a UK setting.[17] Next, while we have a substantial number of patients in three different treatment groups, we acknowledge that there was a relatively small number of patients belonging to treatment group A (ATT without systemic CS/IMT but with/without local steroids) in our study cohort. While we have presented information on the relapse rate in patients with OTB from a non-endemic setting who were treated with and without ATT, further larger prospective studies with longer follow-up time are necessary to conclusively determine whether ATT can reduce the number and severity of relapses, especially for patients who meet the SUN classification criteria for OTB (patient group 1) without other indications for ATT, such as concurrent active pulmonary or other forms of extrapulmonary TB). It would also be important to conduct a study that recruits undifferentiated uveitis patients (patient group 2) with a comparable sample size and baseline disease severity among those treated with and without ATT. Additionally, we were unable to draw conclusions regarding the appropriate regimen and duration of immunosuppressive drugs required to prevent relapse episodes. While the current guidelines still focus on the utilisation of immunosuppressive drugs for disease-specific non-infectious uveitis other than 'post-infectious uveitis',[35] this field remains open for future investigations. Lastly, conducting studies involving patient samples to explore the potential contribution of autoimmunity and autoinflammation underlying uveitis relapse in OTB is an intriguing avenue to pursue.

In conclusion, among cases of OTB from an academic referral centre in a low TB-endemic setting, uveitis relapse is common, occurring in one-third of cases within a median follow-up period of 20.7 months after inactivity was achieved for the initial presenting uveitis. Uveitis relapse primarily manifested as anterior uveitis. While approximately half of the patients re-tested for IGRA still exhibited IGRA positivity during the first relapse episode, most of these relapse episodes were effectively managed using immunosuppressive drugs without the necessity for (re) initiating ATT. Topical CSs were particularly effective in relapse presenting as anterior uveitis. The intraocular inflammation status at 6 months following treatment initiation for the initial uveitis appeared to be a significant predictor of relapse prognosis. Poor responders for the treatment of initial uveitis episode were at a significantly higher risk of experiencing a relapse after achieving clinical inactivity.

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