Predictive factors for treatment failure in patients with presumed ocular tuberculosis in an area of low endemic prevalence

Rupesh Agrawal[1,2,3]
Julio J. Gonzalez-Lopez[1]
Joao Cardoso
Bhaskar Gupta[4]
Robert Grant[5]
Peter K.F. Addison[1]
Mark Westcott[1]
Carlos E. Pavesio[1,2]

1. Moorfields Eye Hospital, NHS Foundation Trust, London, UK
2. Biomedical Research Centre, UCL Institute of Ophthalmology, London, UK
3. National Healthcare Group Eye Institute, Tan Tock Seng Hospital, Singapore 308433
4. Royal Devon and Exeter NHS Trust, Barrack Road, Exeter, UK
5. Faculty of Health, Social Care and Education, Kingston University and St George's, University of London, UK

Sub- title: Presumed ocular tuberculosis with positive IGRA

Key words: Presumed ocular tuberculosis; positive QFT; IGRA; ATT

Corresponding author:
Mr Carlos Pavesio,
Consultant,
Moorfields Eye Hospital,
City Road,
London EC1V 2PD
Email: carlos.pavesio@moorfields.nhs.uk

Word count: Abstract: 248**,** Manuscript main text: 3400

Abstract:

Aim: To identify factors associated with treatment failure of presumed ocular tuberculosis in an area of low endemic prevalence

Methods: A retrospective cross-sectional study was performed for **213 patients** with presumed ocular tuberculosis from a database from a tertiary referral eye hospital in the UK. A forward conditional logistic regression model was constructed incorporating demographics, baseline characteristics, and different cut offs of QFT to identify significant factors accounting for the variability of the response variable ("failure") across the whole group. Treatment failure was defined as the recurrence of inflammation or inability to taper steroids within six months of completion of anti tubercular therapy (ATT) or after at least 6 months of treatment in the non-ATT group.

Results:126 (65.49%) patients received at least six months of ATT. Within the model, **patients with QFT values >1.50 (OR=0.25, 95% CI=0.11 to 0.56, p=0.001)** had less risk of treatment failure as against those with QFT values between 0.35 and 1.50. Steroid sparing **immunosuppressive agents reduced the chances of treatment success (OR=25.6, 95% CI: 8.7 to 100.8, p<0.001).** This effect persisted even after adjusting for potential confounding factors.

Conclusions: Patients with higher values of QFT (>1.5) are more likely to be associated with treatment success with ATT. In our model, steroid sparing immunosuppressive agents reduced the chances of success, in both ATT and

non ATT treated patients. It is unclear whether this effect reflects the intrinsic underlying severity of disease (i.e. study bias), or whether steroid sparing immmunosuppresive agents mitigate against successful ATT therapy.

Introduction

Tuberculosis (TB) remains a major global health problem with an estimated 8.6 million people who have developed TB and 1.3 million deaths in 2012.[1] Among the developed western countries, the UK has one of the highest incidence rates of 13.9/100,000 reported in 2012. The risk factors include young age, male gender and being born outside of the UK. Increased and rising rates are seen in the population from the Indian subcontinent and in those who have been resident in the UK for long periods of time prior to their TB diagnosis.[2]

The clinical diagnosis of ocular TB is difficult since clinical signs and symptoms can mimic other conditions.[3 4] The ophthalmologist relies on a combination of clinical history, ocular signs, systemic examination by a physician, and screening investigations such as chest radiographs and the tuberculin skin test (TST). [3 4] A definite diagnosis of TB uveitis can be confirmed by performing acid-fast smears, mycobacterial cultures, or polymerase chain reaction-based assays on ocular fluid samples.

Interferon gamma release assays (IGRAs) are new immune-based in vitro tests based on the detection of interferon gamma (IFN-γ) released by sensitized T cells on stimulation with very specific antigens, early secretory antigen target-6 and culture filtrate protein-10, for detecting Mycobacterium tuberculosis (MTb) infection. [5 6] Two commercially available IGRAs include the T-Spot TB test (based on the ELISpot technology to directly count the number of IFN-γ-secreting

T cells) and the Quantiferon TB Gold In-Tube test (QFT: based on the ELISA technology, which measures the concentration of IFN-γ secretion; Cellestis Limited, Carnegie, Victoria, Australia). [7] We examined the predictive failure related to treatment failure or success in a TB-non endemic, cosmopolitan population.

Methods

This was a retrospective review of health records of patients seen at a large tertiary uveitic centre in central London, UK. The study was approved by the institutional review board (ROAD 14/012) and all the research adhered to the tenets of the Helsinki declaration.

The clinical case definition of presumed intraocular tuberculosis were broad, but entailed all patients with uveitis where the diagnosis of TB uveitis could be considered based on one or more of the broad clinical signs suggested by Gupta et al in 2007.[3] In addition, all patients had had a diagnostic work –up to exclude other diagnoses. Data collected included information on demographics, clinical findings, investigations and therapeutic regimens. Patients at presentation were examined for signs suggestive of ocular tuberculosis by the uveitis team. All patients with presumed TB with a positive QFT were included in the study. All patients with positive QFT and active inflammation suggestive of presumed ocular tuberculosis were further referred to a respiratory physician. **Based on the physician's discretion and the ophthalmologists' reommendations, anti-tubercular therapy (ATT) was initiated. We have taken a "novel" approach to this problem of selection**

bias for instituting ATT by looking at an expanded dataset of patients where the diagnosis of TB uveitis could reasonably be considered, based upon clinical features, demographic risk factors, and where investigations have excluded other diagnoses. By adding patients who do, and do not get ATT treatment we add power to our analysis in the form of a multivariate logistic regression analysis. The decision not to give ATT was not based on intolerance to medications.

Important definitions used were:

QFT: Positivity was assessed according to the Centre for Disease Control (CDC) recommendations.[8] (positive >0.35 IU/m). **The test was not adjusted or considered inappropriate if the patient was on concurrent oral corticosteroids as the CDC has not recommended any specific criteria for assessment of QFT results based on concurrent steroid therapy. However, we acknowledge the fact that oral corticosteroid treatment at the time of asssessment can act as a potential confounder for the QFT value and we hence performed the statistical test to study the impact of the oral steroids or steroid sparing immunosuppressive therapy at time of QFT assessment.**

Definition of failure: Treatment failure was defined as the inability to taper oral corticosteroids to less than 10mg/ day or topical steroids to less than two times per day or the inability to stop the steroid sparing immunosuppressive agent or persistence or recurrence of inflammation within the first six months of completion of ATT. For the patients not on ATT, treatment failure was defined by

the inability to taper medications to the same levels of systemic and topical use **at the same follow up duration as the ATT treated group. The definition was adapted based on the absence of current conventional guidelines for diagnosis and treatment of presumed ocular tuberculosis. The final follow up for assessment of treatment failure or success was based on the inflammation or recurrence within the first six months of completion of ATT or within six months of tapering or stopping oral corticosteroids for the non ATT group.**

Statistical methods: Qualitative variables were expressed as percentages. Quantitative variables were expressed as mean values ± standard deviation (SD) or as median values (range). A binary logistic regression model was built with the treatment failure result as the dependent variable. The selection of variables in the final model was performed by a forward-conditional method, with significance levels of ≤0.05 for inclusion and ≥0.1 for exclusion, and in addition putting age, gender and QFT value into the equation. Overall model fit was assessed by the Nagelkerke R^2 and the C-index. A ROC (Receiver Operating Characteristics) plot was constructed to assess the specificity and sensitivity of the logistic regression variables for treatment failure. Results were considered statistically significant when $p < 0.05$. Data were analysed using Stata／SE, version 13.0 (StataCorp, College Station, TX, USA).

Results

A total of **365** patients were identified from our uveitis database with a diagnosis of presumed ocular tuberculosis. **309 (81.64%) patients underwent QFT out of which 220** (**60.44%)** patients were QFT positive and were included in the study (**Figure 1**). 7 patients had insufficient follow up and were excluded from further analysis. **213** patients with positive QFT were further grouped into those who received ATT **(n=136, 63.85%) or no ATT (n=77, 36.15%) (Figure 1A). Figure 1B** summarises success and failure in each subgroup with and without oral steroids or steroid sparing immunosuppressive therapy.

38 (18.27%) patients were on oral steroids or steroid sparing immunosuppressives at time of QFT. The mean value of QFT was 7.32±6.71 in patients not on prior steroids and/or steroid sparing immunosuppressives and 6.47±5.09 for those on prior corticosteroid and/or steroid sparing immunosuppressives (p=0.816, Mann Whitney test). The mean age of the population was **45.99±15.61** years with a preponderance of males and bilateral presentation **(Table 1)**. Patients receiving ATT were significantly **younger (p<0.001),** and more frequently of Asian (**p=0.016)** descent. There was no statistically significant association between bilaterality and patients receivng **ATT (p=0.269)**

Comparing the clinical phenotypes of patients who received ATT therapy versus those who did not, those with ocular features of retinal vasculitis **(p=0.014),** serpiginous choroiditis **(p=0.015),** and panuveitis **(p=0.009)** in conjunction with positive QFT were more likely to be treated with ATT (**Table 2A**) compared to those without such features. Patients with milder forms of uveitis, such as anterior (**p<0.001)** or intermediate uveitis **(p<0.001)** were proportionally under-represented in the treatment group. There was no specific preference to institute ATT based on qualitative changes suggestive of old healed pulmonary TB seen on chest radiography **(p=0.115)** or quantitative value of the QFT **(p=0.90)** (**Table 2B)**.

Treatment details: For the patients in the ATT treated group: ATT was instituted by the respiratory physicians. Based on the preference of the physician, different ATT regimes was instituted. Out of 136 patients in ATT treated group, there were 53(39.0%) patients with six months of ATT, 19(14.0%) and 54(39.7%) with 9 and 12 months of ATT respectively highlighting the heterogeneity in the treatment preference by the physicians. Also, 10(7.3%) patients had only three months of Isoniazid and Rifampicin prophylaxis (like Directly Observed Therapy –DOT- short course therapy for TB) before initiating steroid or steroid sparing immunosuppressive therapy. Due to relentless clinical progression, steroid sparing immunosuppressive agents were given in 15 (11.0%) patients. While 93 (68.38%) patients received conventional ATT regimen comprising of two months of Rifampicin (10mg/kg/day), Ethambutol (25mg/kg/day),

Isoniazid (5mg/kg/day) and Pyrazinamde (25mg/kg/day) followed by six to ten months of Rifampicin (10mg/kg/day) and Isoniazid (5mg/kg/day), 43 (21.62%) patients had 2 months of Rifampicin, Isoniazid, Pyrazinamide and Moxifloxacin (7.5-10mg/kg/day) followed by Rifampicin, Isoniazid and Moxifloxacin as advised by one of the treating chest physicians. This was noted to be a change in practice from the regimen most commonly used in 2009/10 when moxifloxacin was rarely used. The type of regimen did not had any statistically significant impact on the treatment outcome.

Bivariate and logistic regression analysis was done to identify the risk factors for treatment failure for the entire cohort of **213** patients. **Oral corticosteroids did not have any influence on the failure or success of therapy on bivariate analysis (p=0.109) and hence was taken in the multivariate regression analysis.** The model for logistic regression analysis after inputing selective variables (as listed in **Table 3**) from bivariate analysis was accurate **(C index = 0.796, 95% CI = 0.718 to 0.874, pHosmer Lemeshow = 0.445)** (**Table 3)**. Patients receiving steroid sparing immunosuppressive agents had statistically high chances of failure **(OR=25.6, 95% CI: 8.7 to 100.8, p<0.001)** across the whole cohort.

Mean QFT value for ATT group was 7.13 ((±5.96) and for non ATT group was 7.02 (±7.22). As the conventional cut off for QFT is 0.35, we explored newer cut off values starting from 1.00 to 3.00. After analysing different cut off

values at 1.00, 1.50, 2.00, 2.50 and 3.00 of QFT**, patients with QFT values >1.50 (OR=0.25, 95% CI=0.11 to 0.56, p=0.001)** had less risk of treatment failure as against those with QFT values between 0.35 and 1.50. ESR was a significant factor in univariate analysis but not in regression analysis possibly due to the difference in age of the patients in the treatment group (patients without ATT were older = **50.91±17.62 years** compared to those who had ATT **43.21±13.65 , p=0.001**).

We further compared the cohort of patients who received steroid sparing immunosuppressive agents with the group who did not have (**Table 4**). Patients with bilateral disease and panuveitis were more likely to receive steroid sparing immunosuppressive agents, while patients with anterior uveitis were less likely to receive oral corticosteroids therapy **(p<0.067).** 15 patients **(11.03%)** were on concurrent steroid sparing immunosuppressive agents and ATT.

ROC (Receiver Operating Characteristics) and sensitivity and specificity plots were performed after logistic regression analysis (**Figure 2**) to assess the ability of the regression model to correctly classify patients into treatment success or failure and also to assess the ROC with a new cut off value for QFT. Using different cut off values for QFT as described above, the forward:conditional model included a cut off value of 1.5, as this was found to maximize the predictive ability of the model versus the other values tried (1.0, 2.0, 2.5 and 3.0). **The predicted probability of the model described in table 3 had an area under ROC curve (C-index) of 0.796 (Figure 2A). Patients who received ATT**

and had QFT >1.50 had AUC (Figure 2B) of 0.804 (95% CI=0.690 to 0.924) and those with QFT<1.50 had AUC (Figure 2C) of 0.8469 (95% CI: 0.659 to 1.000). For non ATT group, patients with QFT of >1.50 had AUC (Figure 2D) of 0.646 (95% CI: 0.443 to 0.864) and those with QFT<1.50 had AUC (Figure 2E) of 0.616 (95% CI: 0.354 to 0.846). ATT was not a statistically significant predictor for failure or treatment success. Treatment with ATT or oral corticosteroids alone or in combination in patients with positive QFT and any combinations of clinical signs reduced the likelihood of treatment failure but did not reach statistically significant sensitivity or specificity levels (**Figure 2**).

Discussion

Diagnosis and management of tuberculous uveitis remains a conundrum for most clinicians. It may be a manifestation of a true infection or a hypersensitivity reaction to an extraocular infection. [3] Mycobacterium culture or histopathology remain as gold standard but have inherent limitations due to low test yield and difficulty in obtaining samples due to poor access to ocular tissue. [9] PCR is a well-established technique but its usefulness remains limited. [3] Fundus fluorescein angiography, indocyanine green angiography, ocular coherence topography, ultrasonic biomicroscopy and computed tomography are all used as diagnostic adjuncts to monitor the progress and complications of uveitis but their utility as primary diagnostic tools for tuberculous uveitis remain limited.[10 11 12]

IGRA are considered highly specific for *Mycobacterium tuberculosis* because they are not confounded by prior vaccination for TB. However concerns have

been raised [13] about the sensitivity of QFT for detection of latent TB infection and superiority to traditional tuberculin skin test. [14] Kurup et al [15] reported no demonstrable advantage of QFT over tuberculin skin test for detection of latent TB infection in patients with granulomatous uveitis. Recently, Ang et al recommended Gold In-Tube as the first-line test in preference to T-SPOT.TB [16] but also demonstrated that QFT was not superior to tuberculin skin test in sensitivity as a screening test or first-line study in TB-related uveitis.[17] Similarly, Babu et al showed that QFT is not specific for intraocular TB.[18] QFT was positive in 70% of our presumed ocular tuberculosis patients. It remains a valuable tool in diagnosis and management of disease in regions with low prevalence rates of tuberculosis compared to Singapore and India with high prevalence rates of both pulmonary and extra pulmonary tuberculosis where other ancillary tests are likely to be positive.

The treatment of ocular TB is largely presumptive and there are no randomised, controlled clinical trials or locally recommended guidelines to guide the management of ocular TB. Specifically, **there are no randomised, controlled clinical trials looking at the role of ATT in treatment of ocular TB. This has lead to a wide range of treatment practice patterns which have been reported in the literature. Like in the UK, there are no national TB guidelines about ocular TB diagnosis and treatment in many non endemic regions including Canada and USA. There are conflicting reports and literature on the use of mono versus multiple drug therapy and there is also signifcant debate about treatment duration with ATT (6-18months). Clinical outcomes**

are therefore inconsistent due to lack of a clinical definition for the exact diagnosis of ocular TB, concomitant cortiocosteroid therapy and variation in severity of ocular inflammation prior to initiating treatment [19 20].

In our current study, diagnosis was made by the clinician and only those cases who had positive QFT or strong clinical suspicion of intraocular tuberculosis, were referred to respiratory physicians for further consultation and initiating ATT. Patients with stable or mild anterior uveitis and retinal vasculitis were not referred for ATT due to less visual morbidity, however patients with posterior or pan uveitis or recurrent intermediate uveitis were referred for a therapeutic trial of ATT. The final decision to initiate ATT was based on the discretion of the treating physician. Similar variation in practice occurs in regards to drugs, duration and use of concurrent local or systemic steroids. Systemic steroids have been used and recommended in other forms of extra pulmonary tuberculosis [21 22] ; they are used in ocular tuberculosis uveitis to control persistent inflammation or retinal vasculitis but their role is unproven.

In our study, the use of steroid sparing immuosuppressive therapy increased the likelihood of treatment failure. It is difficult to ascertain the exact cause. One possible hypothesis is that this agents suppress host immune function and this can be disadvantageous in TB infection. In our series, a significant proportion of patients were on prior corticosteroid therapy before ATT was commenced. Clinical phenotypes represented by

positive QFT and those that failed to response to ATT and oral corticosteroid therapy may be the "immune mediated" form and possibly require prolonged immunosuppression and hence steroid sparing immunosuppressives did not have a positive impact on the treatment outcome.

Secondly, the failure in patients treated with steroid sparing immunosuppresives could be attributed to under treatment with corticosteroids or rapid tapering of the oral steroids before the cumulative effect of steroid sparing agents sets in. Also the effective dose of corticosteroid is half the actual dose in the presence of Rifampicin which affects the metabolism of corticosteroids. Rifampicin increases the plasma clearance of prednisolone by 45% and reduces drug bioavailability in tissues by 66% [23] which needs to be considered when deciding the dose of prednisolone. In addition, drug resistance to ATT, reinfection, or immunological response to tubercular antigens released during ATT are other possible reasons for worse outcomes when immununosuppressives were used. Recurrence of disease in up to 25% of cases is a recognised phenomenon and certain clinical phenotypes like intermediate uveitis and retinal vasculitis represent increased risk.[24 25 26] There is a reasonable possibility that these cases irrespective of QFT results were not associated with tubercular uveitis and they represented non infectious posterior uveitis requiring prolonged immunousuppression hence there was failure

to respond to steroid therapy. Our findings that **steroid sparing immunosuppressives in ATT groups increased the likelihood of treatment failure could be an artifactual finding of study bias, and may simply reflect the underlying severity of uveitis.**

According to our model, treatment success as per our definition of succesful steroid taper was optimal with a QFT cut-off of 1.5 IU/ml. A similar trend was seen by Gineys et al [27] in their small cohort but they concluded the cut off value was more than 2 IU/ml. **The authors demonstrated a higher success rate with ATT in patients with highter cut off value (7.67IU/ml v/s 1.22 IU/ml with p=0.026 by Wilcoxon test). The authors included patients with varying degree and types of inflammation in their case series as there were 7 patients with scleritis, 34 patient with panuveitis, 15 patients with posterior uveitis, 14 patients with intermediate uveitis and 15 patients with anterior uveitis. There were 42 patients with positive QFT. 54 patients with negative QFT, 12(29%) patients receiving concurrent oral steroids in the positive QFT group and 14(26%) patients receiving oral steroids in the QFT negative group. The authors evaluated the treatment success based on a therapeutic trial with ATT.** Thus, there is emerging evidence that laboratory cut-off values (0.35 IU/mL) set by the manufacturer are possibly too low for non endemic areas. It may be time to revisit and set up higher cut off values if one is going to recommend ATT treatment based upon a positive IGRA in the context of presumptive clinical signs of tuberculous uveitis.

The ROC curves demonstrated that ATT was not a significant predictor of success in our models and that the ROC curves were comparable in the ATT versus the non ATT treated group in respective subgroups of patients with QFT of <1.50 and QFT of >1.50. The success rate would have been better if we had treated only those patients with QFT > 1.5. This conclusion can only be inferred post analysis. However, the equivalence of success rates between the ATT treated group and the non ATT treated group (presumed non infective) suggests that the clinicians are doing a reasonable job in identifying those patients who will do well with ATT therapy.

In summary, we present one of the largest clinical case cohort studies of presumptive ocular tuberculosis with positive QFT in a population with low endemic prevalence. Positive QFT provides useful information and directs towards the use of ATT in the presence of other clinical signs suggestive of presumptive ocular tuberculosis. However, based on our results, it seems the cut off value of QFT needs further investigation in low endemic regions. Our findings that steroid sparing immunosuppressive therapy increased the likelihood of treatment failure is intriguing. Whilst it could be an artifactual finding, and simply reflect the underyling severity of uveitis, we propose an alternative hypothesis, namely that immunusuppression do increase the likelihood of treatment failure in TB uveitis. This is biologically plausible as immunuosuppressivs suppress host immune function. There are no randomised control trials explicitly looking at the benefit of oral

steroids or steroid sparing immunosuppression in tuberculous uveitis. In fact, the evidence base for the benefit of oral steroids in TB associated uveitis is extremely weak, largely resting on expert opinion and very low quality evidence. [28]

Indeed, this study has inherent limitations of being retrospective in nature with no defined treatment duration. Prospective and idealy randomised control trials are urgently needed in order to investigate this further. Such studies are likley to require a multicentre approach in order to compare results in TB endemic and non endemic counties.

References

1. WHO Library Cataloguing-in-Publication Data. *Global tuberculosis report* 2013. In: 2013:1-306.

2. Public Health England. *Annual tuberculosis (TB) update*: 2014. In: 2014:1-12.

3. Gupta V, Gupta A, Rao NA. *Intraocular tuberculosis--an update*. Survey of Ophthalmology 2007;52:561-587.

4. Tabbara KF. Tuberculosis. *Current Opinion in Ophthalmology* 2007;18:493-501.

5. Lalvani A, Pareek M. Interferon gamma release assays: principles and practice. *Enfermedades Infecciosas y Microbioligía Clíníca* 2010;28:245-252.

6. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. *Annals of Internal Medicine* 2008;149:177-184.

7. National Institute for Health and Care Excellence. Tuberculosis: Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. In: 2011.

8. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection - United States, 2010. *MMWR Recommendations and Reports* 2010;59:1-25.

9. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technology Assessment* 2007;11:1-196.

10. Doycheva D, Deuter C, Hetzel J, et al. The use of positron emission tomography/CT in the diagnosis of tuberculosis-associated uveitis. British Journal of Ophthalmology 2011;95:1290-1294.

11. Honore-Bouakline S, Vincensini JP, Giacuzzo V, Lagrange PH, Herrmann JL. Rapid diagnosis of extrapulmonary tuberculosis by PCR: impact of sample preparation and DNA extraction. *Journal of Clinical Microbiology* 2003;41:2323-2329.

12. Wolfensberger TJ, Piguet B, Herbort CP. Indocyanine green angiographic features in tuberculous chorioretinitis. *American Journal of Ophthalmology* 1999;127:350-353.

13. Pollock NR, Campos-Neto A, Kashino S, et al. Discordant QuantiFERON-TB Gold test results among US healthcare workers with increased risk of latent tuberculosis infection: a problem or solution? *Infection Control and Hospital Epidemiology* 2008;29:878-886.

14. Mazurek GH, Zajdowicz MJ, Hankinson AL, et al. Detection of Mycobacterium tuberculosis infection in United States Navy recruits using the tuberculin skin test or whole-blood interferon-gamma release assays. *Clinical Infectious Disease* 2007;45:826-836.

15. Kurup SK, Buggage RR, Clarke GL, Ursea R, Lim WK, Nussenblatt RB. Gamma interferon assay as an alternative to PPD skin testing in selected patients with granulomatous intraocular inflammatory disease. *Canadian Journal of Ophthalmology* 2006;41:737-740.

16. Ang M, Wong WL, Kiew SY, Li X, Chee SP. Prospective head-to-head study comparing 2 commercial interferon gamma release assays for the diagnosis of tuberculous uveitis. *American Journal of Ophthalmology* 2014;157:1306-1314.

17. Ang M, Htoon HM, Chee SP. Diagnosis of tuberculous uveitis: clinical application of an interferon-gamma release assay. *Ophthalmology* 2009;116:1391-1396.

18. Babu K, Satish V, Satish S, Subbakrishna DK, Abraham MP, Murthy KR. Utility of QuantiFERON TB gold test in a south Indian patient population of ocular inflammation. *Indian J Ophthalmology* 2009;57:427-430.

19. Varma D, Anand S, Reddy AR, et al. Tuberculosis: an under-diagnosed aetiological agent in uveitis with an effective treatment. Eye 2006; 20:1068-73.

20. Morimura Y, Okada AA, Kawahara S, et al. Tuberculin skin testing in uveitis patients and treatment of presumed intraocular tuberculosis in Japan. Ophthalmology 2002; 109:851-7

21. Ntsekhe M, Wiysonge C, Volmink JA, Commerford PJ, Mayosi BM. Adjuvant corticosteroids for tuberculous pericarditis: promising, but not proven. *QJM* 2003;96:593-599.

22. van de Beek D, de GJ, McIntyre P, Prasad K. Corticosteroids for acute bacterial meningitis. *Cochrane Database Systematic Review* 2007:CD004405.

23. McAllister WA, Thompson PJ, Al-Habet SM, Rogers HJ. Rifampicin reduces effectiveness and bioavailability of prednisolone. *British Medical Journal (Clinical Research Edition).* 1983;286:923-925.

24. Bansal R, Gupta A, Gupta V, Dogra MR, Bambery P, Arora SK. Role of anti-tubercular therapy in uveitis with latent/manifest tuberculosis. *American Journal of Ophthalmology* 2008;146:772-779.

25. Basu S, Nayak S, Padhi TR, Das T. Progressive ocular inflammation following anti-tubercular therapy for presumed ocular tuberculosis in a high-endemic setting. *Eye (Lond).* 2013;27:657-662.

26. Gupta V, Bansal R, Gupta A. Continuous progression of tubercular serpiginous-like choroiditis after initiating antituberculosis treatment. *American Journal of Ophthalmology* 2011;152:857-863.

27. Gineys R, Bodaghi B, Carcelain G, et al. QuantiFERON-TB gold cut-off value: implications for the management of tuberculosis-related ocular inflammation. *American Journal of Ophthalmology* 2011;152:433-440.

28. Guyatt GH, Haynes RB, Jaeschke RZ, et al. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA : the journal of the American Medical Association 2000;**284**(10):1290-6

Competing interest:

JJGL has received study grants from Alcon, Novartis and Merck, and has provided unpaid consultancy to Bayer. RA is on NMRC overseas research training fellowship at Institute of Ophthalmology and Moorfields Eye Hospital, London. There are no competing interests for any of the authors in this study and there is no funding for this project.

Authors' contribution:

BG had written the first draft of the manuscript and was involved in critical inputs and data analysis and interpretation. RA had edited the first draft of the manuscript and was involved in study design, data collecation, analysis and intellectual inputs. JJGL had contributed to the first draft of the manuscript and did statistical analysis. RG assisted in statistical analysis. CP, PA and MW were directly involved in patient care and edited the draft and provided intellectual inputs for the study design and data collection.

Acknowledgements:

This work was supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The authors would like to acknowledge support from Margaret Richards who helped in identifying case records with QFT at our centre. The authors will also acknowledge support from Dr Farzana Rahman, Dr Ioanna and Dr Sumita Phatak for their assistance with the data collection.

Legends:

Figure 1A: Distribution of patients with Presumed Ocular Tuberculosis with QGold Positive

Figure 1B: Flow diagram of outcome of cohort of presumed ocular tuberculosis patients with positive QFT.

Figure 2: Receiver operating characteristic curve of the binary logistic regression model for the prediction of treatment failure. **(2A)** Receiver operating characteristic curve of the binary logistic regression model for the prediction of treatment failure in cohort of patients who had ATT and had QFT >1.50. **(2B)** Receiver operating characteristic curve of the binary logistic regression model for the prediction of treatment failure in cohort of patients who had ATT but QFT was <1.50. **(2C)** Receiver operating characteristic curve of the binary logistic regression model for the prediction of treatment failure in cohort of patients who did not have ATT and had QFT >1.50. **(2D)** Receiver operating characteristic curve of the binary logistic regression model for the prediction of treatment failure in cohort of patients who did not have ATT but QFT was <1.50. **(2E)**

Table 1: Baseline patient demographics **(**ATT: Anti Tubercular Therapy**)**

Table 2A: Clinical phenotypes and probability of treatment with Anti Tubercular Therapy (ATT)

Table 2B: Diagnostic and therapeutic characteristics for patients based on Anti tubercular treatment (ATT)

Table 3: Model of logistic regression analysis

Table 4: Subgroup classification by oral corticosteroid therapy

Table 1: Baseline demographics

	Total (N=213)	**ATT -ve (N=77)**	**ATT+ve (N=136)**	**Effect size (95% CI)**	**P**
Age	45.99±15.61	50.91±17.62	43.21±13.65	0.51 (0.22 to 0.79)	0.001
Bilaterality	124(58.2%)	41(53.25%)	83(61.03%)	1.38 (0.78 to 2.42)	0.269
Male Gender	122(57.3%)	42(54.54%)	80(58.82%)	1.19 (0.68 to 2.09)	0.544
Ethnicity					
White	42 (19.7%)	19 (24.68%)	23 (16.91%)	0.62 (0.31 to 1.23)	0.171
Asian	120 (56.3%)	35 (45.45%)	85 (62.50%)	2.00 (1.13 to 3.53)	0.016
African	51(23.9%)	23 (29.87%)	28 (20.59%)	0.61 (0.32 to 1.16)	0.127

ATT: Anti Tubercular Therapy, -ve: negative, +ve: positive

Table 2A: Clinical phenotypes and their likelihood of receiving ATT

	Total (N=213)	No ATT (N=77)	ATT (N=136)	Effect size (CI95)	P
Retinal vasculitis	54(25.4%)	12 (15.6%)	42(30.9%)	2.42 (1.18 to 4.95)	0.014
Serpiginous like choroiditis	10(4.7%)	0 (0.0%)	10 (7.4%)		0.015
Choroiditis	34(16.0%)	11 (14.3%)	23(16.9%)	1.22 (0.56 to 2.66)	0.615
Choroidal granuloma	8(3.8%)	1 (1.3%)	7 (5.1%)	4.12 (0.50 to 34.17)	0.263
Panuveitis	71(33.3%)	17(22.1%)	54 (39.7%)	2.32 (1.23 to 4.40)	0.009
Intermediate uveitis	69 (32.4%)	38 (48.1%)	32(23.5%)	0.33 (0.18 to 0.61)	<0.001
Anterior uveitis	90 (42.3%)	47(61.0%)	43 (31.6%)	0.30 (0.17 to 0.53)	<0.001

ATT: Anti Tubercular Therapy

Table 2B: Diagnostic and treatment characteristics based on patients receiving Anti Tubercular therapy

	Total (N=213)	No ATT (N=77)	ATT (N=136)	Effect size (95% CI)	P
Chest X-Ray	31(14.6%)	15 (19.5%)	16 (11.8%)	0.54 (0.25 to 1.17)	0.115
ESR	13.60(±11.40)	15.17(±12.17)	12.69(±10.88)	0.22 (-0.06 to 0.50)	0.144
QFT value	7.09 (±6.43)	7.02 (±7.22)	7.13 (±5.96)	-0.02 (-0.30 to 0.26)	0.902
Oral Steroids	123 (57.7%)	30 (39.0%)	93 (68.4%)	3.39 (1.89 to 6.07)	<0.001

ATT: Anti Tubercular Therapy, ESR=Erythrocyte sedimentation rate,

QFT= QuantiFERON Gold in tube test

*** - Chest X ray findings consistent with healed tuberculosis.**

Table 3: Results of binary logistic regression model for factors predicting failure (n = 213; $R^2_{Nagelkerke}$ = 0.357; C-index = 0.822; $p_{Hosmer–Lemeshow}$ = 0.463).

Variable	B	SE of β	OR	95% CI	P
Age in years	-0.009	0.013	0.991	0.97 to 1.02	0.508
Sex (male)	0.369	0.398	1.45	0.66 to 3.16	0.355
ATT	-0.208	0.437	0.812	0.35 to 1.91	0.633
Oral steroids	0.607	0.466	1.835	0.74 to 4.58	0.193
Anterior uveitis	1.253	0.464	3.500	1.41 to 8.69	0.007
Immunosuppressive treatment	3.182	0.650	24.106	6.75 to 86.11	<0.001
QFT Value (>/=1.50)	-1.596	0.437	0.203	0.09 to 0.48	<0.001
Serpinginous-like choroiditis	-0.250	1.067	0.778	0.10 to 6.30	0.814
Panuveitis	0.094	0.447	1.098	0.46 to 2.64	0.834
Constant	-0.394	0.855	0.503	0.03 to 1.76	0.241

OR: odds ratio, 95% CI: 95% confidence interval, ATT: Antitubercular therapy,

QFT=QuantiFERON Gold in tube test.

Table 4: Subgroup classification by oral inmunosuppressive therapy.

	No Immunosupressants (N=191)	Immunosuppressive treatment (N=22)	Effect size (CI95)	P
Age	45.99 ± 15.92	45.95 ± 12.91	0.00 (-0.44 to 0.44)	0.991
Bilaterality	105 (55.0%)	19 (86.4%)	5.19 (1.49-18.12)	0.005
Female gender	78 (40.8%)	13 (59.1%)	2.09 (0.85 to 5.13)	0.101
Retinal vasculitis	50 (26.2%)	4 (18.2%)	0.63 (0.20 to 1.94)	0.605
Serpiginous like choroiditis	7 (3.7%)	3 (13.6%)	4.15 (0.99 to 17.39)	0.071
Choroiditis	30 (15.7%)	4 (18.2%)	1.19 (0.38 to 3.77)	0.760
Choroidal granuloma	7 (3.7%)	1 (4.5%)	1.25 (0.15 to 10.68)	0.588
Panuveitis	59 (30.9%)	12 (54.5%)	2.68 (1.10 to 6.56)	0.026
Intermediate uveitis	62 (32.5%)	7 (31.8%)	0.97 (0.38 to 2.50)	0.951
Anterior uveitis	85 (44.5%)	5 (22.7%)	0.37 (0.13 to 1.04)	0.067
QGold Value	7.05 ± 6.47	7.48±6.21	-0.07 (-0.51 to 0.38)	0.776
QGold Value ≥1.50	143 (78.1%)	18 (90.0%)	2.52 (0.56 to 11.31)	0.381
ATT	121 (63.4%)	15 (68.2%)	1.24 (0.48 to 3.119)	0.655
Oral steroids	101 (52.9%)	22 (100.0)	40.12 (2.40 to 670.97)	<0.001