Antitubercular Therapy Use in Patients with Ocular Inflammatory Diseases in an Ophthalmology Tertiary Center in Portugal

Uso de Antituberculostáticos em Doentes com Doenças Inflamatórias Oculares num Centro Terciário de Oftalmologia em Portugal

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ABSTRACT

INTRODUCTION: Ocular tuberculosis (OTB) is a rare extrapulmonary form of tuberculosis (TB). Diagnosis is usually presumptive, based on local epidemiologic factors, ocular phenotype, and corroborating immunologic tests: tuberculin skin test (TST), interferon-gamma release assay (IGRA) or both. The aim of this study was to characterize patients who were treated with antitubercular therapy (ATT) for OTB or latent tuberculous infection (LTBI) at an uveitis clinic in a tertiary referral hospital.

METHODS: Patients seen in our uveitis clinic between 2015 and 2021 that had ATT were included and divided into OTB group and LTBI group. Clinical data was analyzed with SPSS statistics®.

RESULTS: We included 38 patients with OTB with a mean age of 53.39 years old. A percentage of 21.1% were immigrants and 2.6% were HIV+. A positive IGRA and/or a TST≥15 mm was found on 97.38%. The most prevalent form of OTB was panuveitis (36.8%), followed by posterior uveitis (21.1%), anterior uveitis (13.2%), intermediate uveitis (13.2%), retinal vasculitis (7.9%), scleritis (5.3%) and episcleritis (2.6%). ATT on 81.6% of patients was a combination of rifampin (RIF), isoniazid (INH), ethambutol and pyrazinamide for the first 2 months followed by INH+RIF. The mean duration of treatment was 8.7 months. The group of LTBI had 16 patients, 18.8% were immigrants and none was HIV+. The diagnosis of 93.75% of patients was based on a positive IGRA and/or TST≥15 mm. The majority (93.75%) were tested and treated prophylactically before starting immunosuppression.

CONCLUSION: TB incidence in Portugal it is still one of the highest in the European Union. Immigrants represented 24.6% of cases in 2019, which is similar to the prevalence found in our study. Conversely, 9% of TB patients in 2019 were HIV+, which is higher than what was found. Almost every patient with ocular inflammation followed in our uveitis clinic is tested for TB and the threshold to start ATT is low, but positive test results should be considered for the initiation of ATT only in the context of a strong clinical suspicion.

KEYWORDS: Antitubercular Agents; Interferon-gamma Release Assay; Latent Tuberculosis; Tuberculin Test; Tuberculosis, Ocular.

RESUMO

INTRODUÇÃO: A tuberculose ocular (TBO) é uma forma rara de tuberculose (TB) extrapulmonar. O diagnóstico é normalmente presuntivo, com base em fatores epidemiológicos locais, fenótipo ocular e testes imunológicos concordantes: teste cutâneo de tuberculina (Mantoux), IGRA ou ambos. O objetivo deste estudo foi analisar os doentes tratados com antibacilares por TBO ou infeção tuberculosa latente (ITBL) na consulta de uveítes de um hospital terciário de referência.

MATERIAL E MÉTODOS: Foram incluídos neste estudo os doentes observados entre 2015 e 2021 na consulta de uveítes e que foram tratados com antibacilares. Foram divididos em 2 grupo: o grupo de TBO e o grupo de ITBL. Os dados colhidos foram analisados com o SPSS statistics®.

RESULTADOS: Foram incluídos 38 doentes com TBO com uma média de 53,39 anos de idade dos quais 21,1% eram imigrantes e 2,6% eram HIV+. Encontrou-se um teste IGRA positivo e/ou teste de Mantoux≥15 mm em 97,38%. A forma mais prevalente de TBO foi a panuveíte (36,8%), seguida da uveíte posterior (21,1%), uveíte anterior (13,2%), uveíte intermédia (13,2%), vasculite retiniana (7,9%), esclerite (5,3%) e episclerite (2,6%). Em 81,6% dos casos usou-se rifampicina (RIF), isoniazida (INH), etambutol e pirazinamida durante os primeiros 2 meses, seguido de INH + RIF. A duração média total do tratamento foi de 8,7 meses. O grupo de ITBL incluiu 16 doentes dos quais 18,8% eram imigrantes e nenhum era HIV+. Em 93,75% dos casos o diagnóstico foi baseado num IGRA positivo e/ou teste de Mantoux ≥15 mm. A maioria (93,75%) foi testada e tratada profilaticamente antes do início de imunossupressão.

CONCLUSÃO: A incidência de TB em Portugal continua a ser uma das mais elevadas da União Europeia. Os imigrantes representaram 24,6% dos casos em 2019, o que é semelhante à prevalência encontrada no nosso estudo. Por outro lado, 9% dos doentes com TB em 2019 eram HIV+, o que é mais alto do que o encontrado neste estudo. Quase todos os doentes com uveíte seguidos no serviço são testados para TB e o limiar para início de antibacilares é baixo, mas a testagem e tratamento da TB só devem ser consideradas no contexto de uma forte suspeita clínica.

PALAVRAS-CHAVE: Antituberculosos; Testes de Liberação de Interferon-gama; Teste Tuberculínico; Tuberculose Latente; Tuberculose Ocular.

INTRODUCTION

Ocular tuberculosis (OTB) is a rare extrapulmonary form of tuberculosis (TB), an infection by the *Mycobacterium tuberculosis* that can affect any part of the eye (intraocular, superficial, or surrounding the eye), with or without systemic involvement. It may be an initial presentation of extrapulmonary dissemination of infection.[1,2]

Ocular signs consistent with OTB, namely tubercular uveitis (TBU), are the presence of cells in anterior chamber or vitreous along with broad posterior synechia, retinal perivasculitis with or without discrete choroiditis/scars, multifocal serpiginous-like choroiditis, choroidal granuloma (single or multifocal), optic disk granuloma, and optic neuropathy.[3] TBU can be divided in posterior uveitis, panuveitis, intermediate uveitis, anterior uveitis, and retinal vasculitis.[4] The most common form is tubercula posterior uveitis, more precisely tubercular choroiditis, that can be divided in 4 distinct phenotypes: tubercular serpiginous-like choroiditis, tubercular multifocal choroiditis, tubercular focal choroiditis and choroidal tuberculoma.[2,4] Tubercular anterior uveitis is typically granulomatous, unilateral or bilateral, characterized by large mutton fat keratic precipitates (KPs), iris nodules and posterior synechia.[2,5] Tubercular intermediate uveitis manifests as low grade, chronic intraocular inflammation, characterized by vitritis, inferior snowballs, with or without peripheral choroiditis scars, showing diffuse retinal vasculitis, with or without cystoid macular edema.[2,5] If the inflammation involves the anterior chamber, vitreous, and retina/choroid the patient has tubercular panuveitis. It is classified as tubercular retinal vasculitis if the patient has isolated retinal vasculitis (either periphlebitis and/or arteritis) with/without occlusive disease.[4] Other forms of OTB include both necrotizing and nonnecrotizing diffuse or nodular scleritis, episcleritis, peripheral ulcerative keratitis, and there is also tubercular dacryoadenitis.[6]

OTB is a great mimicker of various uveitis entities and the major limitation in its diagnosis is exclusion of other entities such as sarcoidosis.[3,7] The gold standard for establishing the diagnosis of TBU is the direct demonstration of *Mycobacterium tuberculosis* by performing acid-fast smears, mycobacterial cultures, or polymerase chain reaction (PCR) based assays on ocular fluids. However, the sensitivities of these tests are very low because of the low tissue load of the bacteria and small size of ocular tissue biopsy samples.[2,7,8]

Thus, the diagnosis of OTB remains a challenge and, in most patients, it is presumptive, based on local epidemiology and consistent ocular phenotypes in combination with systemic findings consistent with TB infection and/or positive corroborating immunologic tests. In addition, clinical response to antitubercular therapy (ATT) further supports a presumed diagnosis of OTB.[1,2,7] The immunologic tests available are the tuberculin skin test (TST) and interferon-gamma release assay (IGRA), but these tests may have limitations related to their sensitivity and specificity and neither can differentiate between active and latent TB infection.[7,8]

In clinical practice most patients are considered for initiating ATT after a positive immunologic test, even in the absence of active clinical or radiologic systemic disease and ambiguity still exists among ophthalmologists and internists about the minimum set of criteria to recommend ATT in patients with OTB.[7] The role of ATT in OTB is still controversial, but active ocular disease with evidence of tuberculosis infection deserves treatment and potentially may impact public health measures in the management of extrapulmonary tuberculosis.[2,5] There is no standard treatment regimen for OTB, but it is generally treated under the same guidelines for active pulmonary and extrapulmonary TB,[1] consisting of an initial quadruple therapy for 2 months with isoniazid (INH), rifampin (RIF), ethambutol and pyrazinamide. Thereafter, INH and RIF are continued for an additional period of at least 4 months.[9] There is currently no consensus on the duration of the ATT, but a decision to start treatment implies that it is maintained for a total period of at least 6 months, even if there seems to be no clinical response after 2 months. This lack of response can be due to an immune reaction that needs anti-inflammatory treatment.[3,9] To treat the inflammatory response in TBU, therapy with corticosteroid and immunosuppressive drugs may be required in addition to ATT. Oral corticosteroids should be started concomitantly with or soon after the initiation of ATT.[7] In case of recurrent inflammation while tapering the dose of oral corticosteroids in patients with tubercular posterior uveitis, initiating systemic corticosteroid-sparing immunosuppressive therapy may be justified.[7]

Immunosuppression increases the risk of reactivation of latent tuberculous infection (LTBI) but the need for prophylactic ATT in case of systemic immunosuppression is not well defined.[8,10] In general, in patients being considered for immunosuppressive therapy that have another identified etiologic cause for their uveitis and have positive immunological tests such as TST or IGRA, or evidence of untreated past tuberculosis, ATT should be considered.[3] Most recommendations suggested the use of INH-based therapies for LTBI, with 9 months being the preferred duration of treatment. Treatment of LTBI should be initiated prior to the use of immunosuppressive therapies.[10]

The aim of this study was to characterize patients who were treated with ATT for OTB or LTBI at the uveitis unit in a tertiary referral hospital.

MATERIAL AND METHODS

This is a retrospective study of a tertiary ophthalmological center. All patients followed on the uveitis unit of our institution, between 2015 and 2021 were included and those who had ATT were selected and divided in 2 groups that were analyzed separately: one with patients diagnosed with presumed OTB and the other with LTBI. Patients' archives were searched for demographic information, TB history, ocular findings, diagnostic procedures, treatment options and outcomes. Data was analyzed with SPSS statistics®.

RESULTS

On the OTB group we included 38 patients with ocular tuberculosis, with a mean age of 53.39 (±18.0) years old. The youngest patient was 1-year-old and the oldest was 80 years old. A total of 60.5% were women and 39.5% men. A percentage of 21.1% were immigrants and only 2.6% were HIV+ (Table 1). Past history of pulmonary TB was present on 5.3% of patients and 7.9% had a prior history of LTBI prophylactically treated.

Table 1. Demographic characteristics of OTB patients

Parameter	Value
Number of patients	38
Sex	
F	60.5%
M	395.%
Mean age	53.39 (±18)
HIV+	2.6%
Immigrants	21.1%
Laterality	
Right eye	18.4%
Left eye	21.1%
Bilateral	60.5%

Regarding TB investigations 97.4% had a positive IGRA and/or a TST ≥15 mm. One patient (2.6%) had both these tests negative but had a biopsy of a pulmonary nodule that confirmed the diagnosis of tuberculosis. Only 3 patients (7.9%) had systemic TB, 2 of them had pulmonary TB and 1 had miliary TB (the 1-year-old baby).

Ocular involvement was bilateral on 60.5% of patients, in the right eye on 18.4% and in the left eye on 21.1%. The most prevalent manifestations were panuveitis (36.8%) and posterior uveitis (21.1%), followed by anterior uveitis (13.2%), intermediate (13.2%), retinal vasculitis (7.9%), scleritis (5.3%) and episcleritis (2.6%) (Table 1). Furthermore, patients had some specific clinical features (Table 2) such as: cystoid macular oedema (39.5% of patients), that was mostly present in patients with panuveitis but also in patients with poste-

Table 2. Specific clinical features	
Parameter	**Value**
Cystoid macular oedema	39.5%
Optic disc oedema	31.6%
Non-occlusive vasculitis	23.7%
Hypertensive uveitis	18.4%
Occlusive vasculitis	13.2%
Snowballs	13.2%
Granulomatous keratic precipitates	10.5%
Inoperable retinal detachment	7.9%
Serpiginous-like choroiditis	5.3%
Choroidal tubercles	5.3%
Subretinal abscess	2.6%

rior and intermediate uveitis; optic disc oedema (31.6% of patients), mostly present in panuveitis and posterior uveitis forms, but there was also one case in a patient with intermediate uveitis. Non-occlusive vasculitis (23.7% of patients) was present mostly as part of panuveitis, but also in one case of intermediate uveitis, one case of posterior uveitis and one case of retinal vasculitis alone. Occlusive vasculitis (13.2% of patients) was present as retinal vasculitis alone (Eales' disease-like) but also as a feature of panuveitis, posterior and intermediate uveitis. Two patients (5.3%) had choroidal tubercles, one as part of a panuveitis and in the other as the only ocular finding of a miliary TB. One patient (2.6%) with posterior uveitis also had a subretinal abscess. Other specific clinical features were ocular hypertension (18.4% of patients), snowballs (13.2% of patients), granulomatous keratic precipitates (10.5% of patients), inoperable retinal detachment (7.9% of patients) and serpiginous choroiditis (5.3% of patients). Illustrative images of complementary exams are shown in Fig.s 1 and 2.

The prescribed ATT in 81.6% of patients was a combination of INH, RIF, ethambutol and pyrazinamide for the first 2 months followed by treatment with only INH + RIF. A percentage of 7.9% of patients started with triple therapy, 7.9% with double therapy and 2.6% did only INH for the whole period of the treatment. The mean total duration of treatment was 8.7 (±2.2) months. Every patient also took pyridoxine. In combination with ATT, 55.3% of patients also had systemic corticosteroids, 76.3% had topical corticosteroids, 7.9% had a dexamethasone intravitreal implant and 5.3% needed corticosteroid-sparing immunosuppressive drugs. Four patients have less than 3 months of follow-up after treatment and two others were lost to follow-up before 3 months post-treatment. From the remaining 32 patients, three (9.4%) had a relapse of ocular inflammation and one of them had stopped the treatment after 2 months due to poor tolerance.

On the group of LTBI 16 patients were included with a mean age of 59.9 (±13.7) years. The majority were women (56.3%) and only 18.8% were immigrants, none was HIV+. The diagnosis was based on a positive IGRA and/or TST

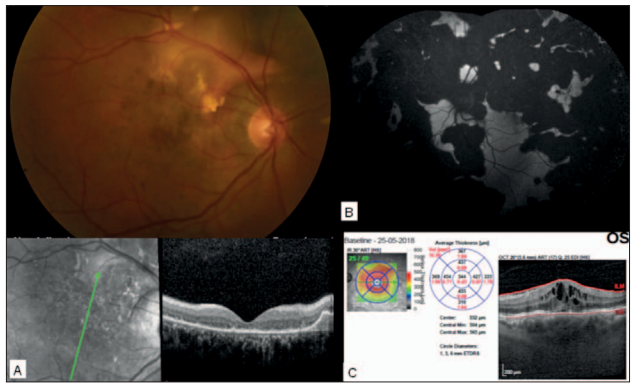

Figure 1. Imaging exams of patients with OTB. A: retinography and OCT of a patient with tubercular posterior uveitis showing a subretinal abscess. B: Fundus auto-fluorescence of tubercular serpiginous-like choroiditis of the left eye. C: Macular oedema in a tubercular intermediate uveitis.

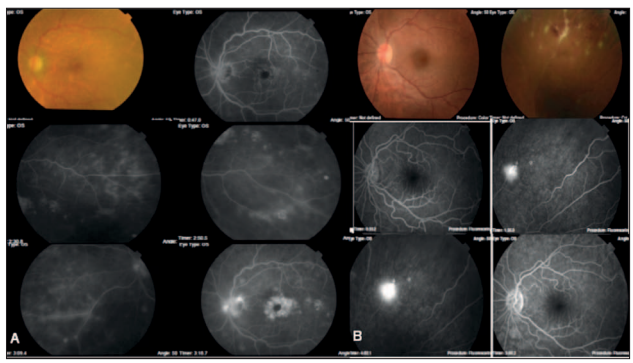

Figure 2. Retinography and fluorescein angiography of patients with tubercular retinal vasculitis. A: non-occlusive vasculitis and macular oedema; B: Occlusive vasculitis.

≥15 mm on 93.75% of patients. One patient had a negative IGRA and a TST of 10 mm but was considered for treatment due to its origin from an endemic country. Prior history of TB was present on 25% of patients (2 pulmonary TB, 1 testicular TB and 1 bone TB).

A total of 93.75% of these patients were tested and treated prophylactically before starting immunosuppression, but 1 patient (6.25%) had a diagnosis of herpetic uveitis after he had started ATT for suspected TBU, but he still completed the treatment for LTBI. The treatment of choice was INH for the total length of treatment on 81.3% of patients,

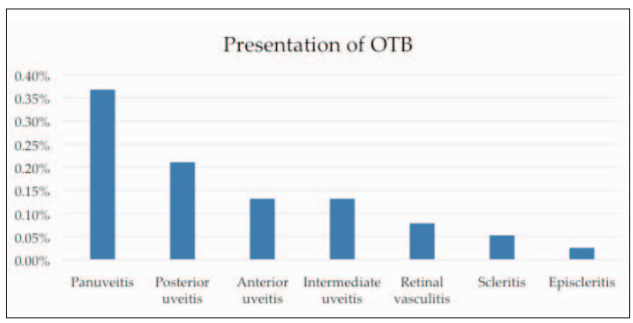

Figure 3. Forms of presentation of OTB.

but 12.5% started with 2 months of quadruple therapy and 6.3% started with double therapy. The mean duration of prophylactic treatment was 9 (±1.1) months. Table 3 shows the ophthalmological diagnosis of these patients.

Table 3. Ocular diagnosis of patients on the LTBI group

Parameter	Value
Anterior uveitis associated to HLA B27+	31.3%
Idiopathic anterior uveitis	12.5%
Birdshot chorioretinopathy	6.3%
Vogt-Koyanagi-Harada Syndrome	6.3%
Multifocal choroiditis	6.3%
Serpiginous choroiditis	6.3%
Idiopathic nodular scleritis	6.3%
Idiopathic panuveitis	6.3%
Idiopathic vasculitis	6.3%
Post-Surgical anterior uveitis	6.3%
Herpetic uveitis	6.3%

DISCUSSION

One third of the world's population is infected with Mycobacterium tuberculosis, and thus at risk of developing disease.[2] There is an ongoing decline in the incidence of TB in Portugal, but it is still one of the highest in the European Union. Immigrant population remains disproportionately affected with a progressive increase in the proportion of cases, representing 24.6% of TB cases in Portugal in 2019, which is similar to the prevalence found in this study. In 2019, 9% of TB patients in Portugal also had HIV, which is very different from what was found now.[11] Also contrary to what was found in this study, two-thirds of TB cases in Portugal in 2018 and 2019 occurred in men. The mean age of these patients was 49 years old, a little lower than that of our patients.[11]

The exact prevalence of TBU is not known, but it is reported to be 0.2% to 10.5% among all uveitis patients at tertiary referral eye care centers around the world.[7] In accordance with previous reports[12] bilateral presentation was the most common on our study, but the most common phenotype was panuveitis, which is not in line with what has been described in literature of posterior uveitis being the most frequent clinical presentation.[12] Surprisingly, only 10.5% of our study patients had granulomatous KPs, which indicates that there were patients with the diagnosis of anterior uveitis and panuveitis that did not mention this kind of precipitates. Knowing that typical anterior uveitis is granulomatous, it indicates that there was possibly an overdiagnosis or patients' registries were incomplete.

Gupta[13] proposed a classification of OTB divided in confirmed OTB, probable OTB and possible OTB. According to this classification, in our OTB group we had 3 cases of probable OTB (7.9% of patients) and the remaining 92.1% were all possible OTB. This fact could also agree with a possible overdiagnosis of TB in our patients. Also considering this classification, we have 4 patients in the LTBI group that could fit in the group of possible OTB (multifocal choroiditis, serpiginous choroiditis, vasculitis and panuveitis.

One of the most significant challenges in the diagnosis and management of OTB is differentiating it from similar-appearing diseases, such as ocular sarcoidosis.[6] We found that almost all patients with ocular inflammation followed on our uveitis department were tested for TB and the threshold to start ATT was low in the presence of a positive immunologic test and absence of other etiologic cause. Literature research tells us that screening for TB should be discouraged in low-risk groups. In the absence of clinical findings suggestive of OTB, it might be risky to rely on a positive immunologic test result as indication for diagnosis, due to a low pretest probability in cases of low clinical suspicion, and the possibility of LTBI in a patient with ocular inflammation not TB related.[2] TST has a low positive predictive value and a high false negative rate in the absence of systemic disease, whereas IGRA, although more specific, has a high false positive rate.[2] So, these tests should only be used in selected cases of high suspicion for OTB that have increased pre and post-test probability, and positive results should be considered for the initiation of ATT only in this context of a strong clinical suspicion.[2,8]

Figueira *et al*[3] wrote the Portuguese expert consensus recommendations on the diagnosis and management of OTB. They concluded that the clinician must do a detailed medical history and review of systems that will allow him to establish a complete differential diagnosis before examining the patient. After a complete ophthalmic examination, the classification of the uveitis is very important to develop a list of potential differential diagnosis and then decide the best complementary diagnostic tests. In general, it is important to perform a complete blood count, a metabolic panel, and nonspecific tests for inflammation, such as erythrocyte sedimentation rate or C-reactive protein. Also, screening for syphilis, a chest radiograph and serum angiotensin-converting enzyme levels should be included in the baseline work-up.[3] Other tests such as HLA B27 for anterior uveitis or serologic testing for Lyme disease, Toxocara, toxoplasmosis and cat scratch disease, as well as cerebral magnetic resonance imaging may be important in the setting of an intermediate or posterior uveitis. Other tests must also be done according to clinical findings. Regarding TB screening, it must be done in uveitis of unknown etiology, recurrent or not responding to conventional therapy, in the presence of ocular findings highly suggestive of OTB (broad posterior synechia, retinal perivasculitis with or without discrete choroiditis/scars, multifocal serpiginous-like choroiditis, choroidal granuloma, optic disk granuloma, and optic neuropathy) and before immunosuppression, particularly before biologic agents.[3]

The Collaborative Ocular Tuberculosis Study (COTS) Group has recently published consensus guidelines for the management of TBU that included specific ocular phenotypes, together with the endemicity of TB in patients' geographical regions of origin and investigation results of

immunologic and radiologic tests (chest computed tomography or chest radiography).[5,7] The guidelines depend on the presentation form: regarding tubercular choroiditis, if the phenotype is serpiginous-like choroiditis, a single immunologic test without radiologic evidence is sufficient to initiate ATT in an endemic region, whereas in a nonendemic region, positive IGRA results are a requirement to start the treatment, given its increased specificity. For tuberculoma and tubercular focal or multifocal choroiditis, any immunologic evidence of TB, along with radiologic signs of active or healed pulmonary TB, justifies initiation of ATT.[7] The use of ATT in the management of anterior uveitis is more controversial. There is a moderate consensus for initiating ATT in recurrent anterior uveitis with any immunologic evidence of TB, along with radiologic signs suggestive of pulmonary TB infection, in both endemic and nonendemic regions when other possible causes have been ruled out. However, concerning the first episode of anterior uveitis, consensus to treat was reached only with all immunologic and radiologic tests showing positive results (in endemic regions, isolated positive TST results along with radiologic evidence are sufficient to gain moderate consensus to initiate ATT).[5] The phenotype of intermediate uveitis is less likely to be related to TBU in non-endemic areas but, if radiologic test results were positive, positive IGRA results produced moderate consensus to initiate ATT in most cases, regardless of TST results.[5] Finally, regarding retinal vasculitis, there is a weak consensus for starting ATT in nonendemic areas when all immunologic and radiologic tests are positive. However, for active retinal vasculitis cases in endemic areas, the consensus is moderate to initiate ATT whenever one of the immunologic tests showed positive results along with positive radiologic test results.[5]

LTBI corresponds to the presence of *Mycobacterium tuberculosis* in the body without symptoms, radiological changes or microbiological positivity. Early detection of LTBI through screening of patients at increased risk for TB may provide a window of opportunity for interventions such as treatment to prevent the development of active TB.[10] It must be done when considering the use of biologics such as anti-TNF agents given the evidence of increased risk for systemic, disseminated TB with its use. At the moment there are no standard recommendations for TB screening, treatment, or prophylaxis in patients on anti-metabolites or calcineurin inhibitors.[8] We verified that, in our study, most patients treated for LTBI were on the verge of starting an immunomodulatory biologic agent, but there were also patients treated for LTBI before treatment with other classes of immunosuppressants. We believe that patients must be evaluated individually and in certain cases exceptions can be justified.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia revista em 2013 e da Associação Médica Mundial.

Proveniência e Revisão por Pares: Não comissionado; revisão externa por pares.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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