EXPERT REVIEWS

How do we manage and treat a patient with multiple sclerosis at risk of tuberculosis?

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Tuberculosis continues to be a serious health problem worldwide. The disease continues to be underdiagnosed and not properly treated. In conditions that affect the immune system, such as multiple sclerosis (MS), latent tuberculosis may thrive and reactivate during the use of immunomodulatory and immunosuppressive drugs. Among the best treatment options for patients with latent or active tuberculosis who have MS are IFN-β, glatiramer acetate and mitoxantrone. Drugs leading to a reduced number and/or function of lymphocytes should be avoided or used with caution. Tuberculosis must always be investigated in patients with MS and treated with rigor.

KEYWORDS: fingolimod • fumarate • glatiramer acetate • IFN-β • multiple sclerosis • natalizumab • teriflunomide • tuberculosis

Multiple sclerosis (MS) is a chronic neurological disease characterized by demyelination, multifocal inflammation, reactive gliosis and axonal/neuron losses [1]. All treatments for MS are immunological modulators or suppressors, due to the intense inflammatory reactions in the CNS of patients. IFN-β, glatiramer acetate, corticosteroids, azathioprine, fingolimod and natalizumab are all currently used for the treatment of MS [2]. Newer treatments are all potentially immunosuppressive and have a more severe profile of adverse events [2]. There are recommendations for first-, second- and third-line therapies for MS depending on the tolerability and efficacy profiles of the drugs to be chosen for different degrees of disease aggressiveness [3,4].

Notwithstanding neurologists' present knowledge of and confidence in the management of MS, occasionally some patients arrive with an extra condition that may complicate matters considerably. A typical example of this situation is the patient with MS who has a previous or present history of tuberculosis. How can we treat a patient with previous or present tuberculosis with immunomodulatory and immunosuppressive drugs? The aim of this review is to present data on tuberculosis and each of the treatments currently used for MS, discussing both diseases in the light of the present knowledge. To perform a comprehensive evaluation of the matter and its implications, the epidemiology and immunology of tuberculosis are initially discussed. Other diseases that may be affected by the concomitant presence of *Mycobacterium tuberculosis* infection are also mentioned briefly. The subject under study was presented for this paper by a group of experts who comprehensively reviewed the literature without a specific start date up to 15 February 2014.

Epidemiology of tuberculosis

Tuberculosis is an infectious-contagious disease caused by *M. tuberculosis* (Koch's bacillus) [5]. Although human tuberculosis may also be due to other mycobacteria, such as *M. bovis* [6], *M. africanum* [7] and *M. microti* [8], these are very exceptional and beyond the scope of the present discussion.

Tuberculosis continues to be a serious health problem in many countries. Cases may be underdiagnosed and not treated, leading to the presence of infected individuals in public

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and closed places. Infected subjects may travel around the country in public and private transport and, indeed, anywhere in the world, before receiving diagnosis and treatment. Thus, in a world in which migration and travel have become easier, tuberculosis may be present in previously 'low-prevalence areas' [9]. In addition, increasing rates of drug-resistant tuberculosis now threaten to undermine the gains made by worldwide tuberculosis control programs [10].

In the year 2000, 8.3 million new cases of tuberculosis were registered, and 1.8 million people died because of this disease [11]. The rate of infection is of the order of one person per second and eradication of the disease is not a possibility in the foreseeable future [12]. Tuberculosis is the second greatest cause of death due to an infectious agent, only behind HIV [11,13]. The sad reality is that these numbers may be even higher, since many cases of tuberculosis are not diagnosed or reported. The efficacy of the BCG vaccine is 80% at the most [14] and it lasts only for 10–20 years [15]. However, revaccination is not a common practice in the world and more people than we think may be at risk.

To complicate matters, latent tuberculosis can be found in asymptomatic individuals and be reactivated if the person is infected with a more virulent strain of the bacillus [16] or undergoes treatments that modulate and/or suppress immunity (as is the case with MS).

Immunology of tuberculosis

Transmission of *M. tuberculosis* occurs via the airways, leading to an inflammatory and immunological response in the alveoli. An unspecified reaction occurs, in which neutrophils try to phagocytize the bacilli. Three weeks later, a more specific reaction occurs when mononuclear cells reach the focus of the infectious lesion. This will modulate granuloma formation [17,18]. The granulomatous reaction is characterized by cell-mediated hypersensitivity in response to components of the wall structure of *M. tuberculosis*, especially cord factor and lipoarabinomannan [19]. CD4+ and CD8+ T cells, epithelioid monocytes and giant multinucleated cells participate in granuloma formation [20]. Granulomas are dynamic structures used by *M. tuberculosis* to subvert the immune response, replicate and spread to other locations [21].

The resistance mechanism in tuberculosis involves a great number of cellular interactions, and different T-cell populations are required for successful control of the bacilli. CD4+ and CD8+ T cells recognize specific parts of *M. tuberculosis* and secrete cytokines, which activate macrophages [22]. CD4+ T cells that are specific for *M. tuberculosis* mediate a protective response via IFN-γ and TNF-α (anti-TNF-α) [23]. CD8+ T cells contribute to the protective response by recognizing the bacteria burden [23]. CD8+ T cells preferably recognize cells heavily infected with *M. tuberculosis* and the magnitude of the CD8+ response correlates with the bacilli load [24]. In addition to the role of CD4+ and CD8+ cells, the natural killer cells also play a crucial role in killing *M. tuberculosis.* The natural killer cells seem to recognize the mycobacteria and induce an array of adaptive responses, including direct bacilli lysis [21,25].

Apart from the efficacy of the human response to the infection, the virulence of the bacillus is also important and it is determined by its genome sequence [26]. The genome of *M. tuberculosis* comprises 4,411,529 base pairs, containing around 4000 genes, with a very high guanine + cytosine content, which is reflected in the biased amino acid content of the proteins. This bacillus differs radically from other bacteria in that a very large portion of its coding capacity is devoted to the production of enzymes involved in lipogenesis and lipolysis [27].

M. tuberculosis is a slow-growing mycobacterium with a doubling time of 12–24 h under optimal conditions, and with a peculiar cell wall structure that provides an exceptionally strong impermeable barrier to noxious compounds and drugs and plays a fundamental role in virulence [27]. It possess an outer membrane, functionally similar to what is seen in gram-negative bacteria, consisting of an asymmetrical lipid bilayer made of long fatty acids in the inner leaflet (mycolic acids) and of glycolipids and waxy components in the outer layer. The outer and inner membranes form a periplasmic space, with the presence of a thin layer of peptidoglycan in the innermost side covalently linked to arabinogalactan and lipoarabinomannan, which in turn are bound to mycolic acids [28]. The waxy surface of the cell wall resists destaining of carbolfuchsin by acid alcohol, retaining a red color [29].

Pathogenic mycobacteria require type VII secretion systems to transport virulence factors across their complex cell envelope. These bacteria have up to five of these systems, termed ESX-1 to ESX-5 [30,31]. ESX1 secretes antigens that interfere with the integrity of the phagosomal membrane, leading to phagosomal rupture and bacterial emission into the cytosol. The virulence of *M. tuberculosis* is given by EX1 secretion, and this is lost in attenuated vaccine BCG [32]. ESX3 is involved in zinc and iron uptake and homeostasis and, as such, it is essential for growth. The roles of ESX2 and ESX4 remain unknown. ESX-5 mediates the secretion of PE_PGRS proteins, thus indicating that ESX-5 is a major secretion pathway in this important pathogen.

M. tuberculosis senses the harsh environment in macrophages and granulomas, characterized by low oxygen and nutrient depletion, and responds by activating a dormant state, whereby the bacillus stops multiplying, downregulates central metabolism and activates anaerobic metabolism, with induction of stress proteins, the Rel toxin-antitoxin [33]. Hence, *M. tuberculosis* persists in host tissues under different metabolic states, with important implications from the pathogenetic and clinical practical perspectives [34]. If patients are subjected to conditions of altered immune responses (diseases or treatments), latent tuberculosis can be reactivated.

Reactivation of tuberculosis

The relation of the immune system with *M. tuberculosis* is very complex and not fully understood yet. The most obscure area of this strange relation is the reactivation of the latent bacillus. The mechanisms by which *M. tuberculosis* exits latency are dependent upon qualitative and quantitative availability of

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CD4+ cells, in association with the availability of TNF-α [21]. Patients undergoing therapies that deplete TNF-α are at a higher risk of bacilli reactivation. Although patients with MS will not fall into this category because TNF-α is not a therapy for MS, they will have alterations in their subset of lymphocytes.

Diagnosis of latent tuberculosis

Diagnostic tools for the identification of active and latent tuberculosis have changed little over the decades [35]. The current diagnostics tests (tuberculin skin test with the purified protein and IFN-γ release assays) poorly predict who will develop active disease [36].

Tuberculosis & the CNS

According to the well-known Rich's formula proposed in 1951 [37], the number and virulence of the bacilli are determinants of the infection, while the host's (natural and acquired) resistance is the determinant of protection against infection [22]. When the bacilli reach the CNS, they accumulate in the parenchyma and the caseous granuloma thus formed may leak into the leptomeninges. These granulomas are rich in bacilli and the subsequent acute and chronic inflammatory reactions lead to vascular and nervous damage. The brain suffers edema, caseous granulomas may undergo necrotic processes, the blood–brain barrier is compromised and fibrotic reactions accumulate in the tissue. Infection of the CNS by *M. tuberculosis* does not occur often, but when it does, the clinical picture is devastating and the treatment is particularly difficult [38].

During immunodepression, patients are more susceptible to developing tuberculosis in the CNS. A whole host of T cells that might avoid this severe infection are compromised by the patients' immune treatment or immunological disease. When the initial disease that led to immunosuppression is MS, observation of the mild signs and symptoms of the initial stages of neurotuberculosis may be confounded with the fluctuating signs and symptoms of MS itself. With the ever-increasing immunosuppression prescribed for patients with MS, it is essential that neurologists should be aware of the possibility of *M. tuberculosis* infection or reactivation, including the potential for infestation of the CNS. It is also important to understand that a tuberculous antigen-mediated demyelination of the CNS may occur [39]. This is different from an MS relapse, although both are demyelinating events of the same area.

Tuberculosis & MS

The relationship between tuberculosis and MS is complex and can be divided into two main axes. First, the risk of tuberculosis reactivation during immunomodulatory and immunosuppressive treatments cannot be ignored. This aspect of the relationship will be discussed in detail for each treatment successively in this text. Second, the potentially intense inflammatory response of the host to infection with *M. tuberculosis* might lead to increased susceptibility to development of autoimmune MS. This second aspect of the relationship is discussed below.

At least for systemic lupus erythematosus, it has been reported that *M. tuberculosis* infection may trigger an autoimmune condition in susceptible populations [40]. The significance of this relationship is yet to be deciphered to understand the role of autoantibodies produced during *M. tuberculosis* infection [41]. Whether the population findings observed in systemic lupus erythematosus cases are also true for MS remains to be established, since only few studies have addressed this subject.

It is interesting to observe that inoculation of the bacillus in BCG vaccination appears to reduce the activity of MS and experimental autoimmune encephalitis by affecting the levels of IFN-γ and altering the Th17 responses [42,43]. Whether BCG may have a protective effect in patients with MS remains to be seen.

Molecular mimicry between antigenic determinants of pathogenic organisms and host proteins could potentially trigger autoimmune reactions [44].

In silico studies have demonstrated homology between epitopes from the chaperone HSP60 (heat shock protein) of *M. tuberculosis* and fragments of HSP60 from patients with MS, particularly in those with the HLAII alleles DRB1*01:01, 03:01, 04:01, 07:01, 11:01, and 15:01 [45]. One particular peptide of this chaperone family promiscuously binds to many alleles including HLA-DRB1*15:01 with high affinity, suggesting that such cross-reactive epitopes may be involved in the pathogenesis of MS [45]. The intense upregulation of HSP60 and HSP70 in the infected host leads to a marked immunological response [46]. When this response is considered in the light of common homologues between the infectious agent and the host, it is not difficult to understand how an autoimmune response could be generated [47].

Drugs used to treat MS: how could they affect tuberculosis?

A patient with MS who has active or latent tuberculosis poses an extra challenge for management. There is no doubt that active tuberculosis must be treated with rigor and that latent tuberculosis must be investigated. It is perhaps fortunate that MS does not respond to anti-TNF-α biologicals which, in fact, worsen the disease [48]. However, other agents with potential ability to reactivate tuberculosis are in use for MS.

The regular investigations and therapeutic approaches to tuberculosis in patients with MS should not pose a very complicated problem. However, are we performing this investigation on a regular basis? And how should we treat a patient with MS who has had primary tuberculosis infection and might now have the latent and asymptomatic disease? Considering the immunological aspects of MS and of the immunomodulatory and immunosuppressive treatments, how can we give the patient the most effective and safe treatment? Each of the drugs and the procedure of stem cell transplantation are discussed below.

IFN-β

Unlike other medications that have no natural equivalent in the human body, interferons are secreted by our immunological

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system in response to a variety of immune aggressions. IFN-γ is a product of the cellular immune response and a direct marker of infection or exposure to *M. tuberculosis* [49,50]. IFN-γ is also related to granulomatous reactions [51] and therefore plays a key role in tuberculosis. On the other hand, IFN-β, which is used for treating MS, has never been reported to present associations with tuberculosis infection or reactivation [52].

Glatiramer acetate

Although the mechanism of action of glatiramer acetate has not been fully elucidated yet, it consists mainly of shifting lymphocyte populations toward a more anti-inflammatory environment. Glatiramer acetate affects various levels of the innate and adaptive immune responses by generating deviation from the proinflammatory T-helper-1 (Th1) to the anti-inflammatory T-helper-2 (Th2) pathway [53]. With the shift toward Th2, anti-inflammatory interleukins (IL-4, IL-6 and IL-10) become predominant and inflammatory IL-12 and IFN-γ are decreased, without any concomitant reduction in the number of blood lymphocytes [54,55]. The mechanism of action of this drug neither seems related to the activation of latent tuberculosis nor would it facilitate new *M. tuberculosis* infection. There are no reported cases of tuberculosis during glatiramer acetate use [56].

Fingolimod

Fingolimod acts on the sphingosine-1-phosphate receptor of lymphocytes by holding these cells inside secondary lymphoid tissues. This reduces the number of peripheral lymphocytes, leading to less availability of cells to enter the CNS. Pivotal studies have not shown any infection or reactivation of *M. tuberculosis* [57], and there are no reports of tuberculosis in patients undergoing treatment with fingolimod despite the remarkable induced lymphopenia. It is very important to take into consideration that this drug is not yet available in a number of developing countries and that this panorama may change toward reported cases of tuberculosis, once the populations of particular countries receive fingolimod.

Animal studies have shown that treatment with fingolimod during BCG vaccination reduced vaccine-mediated protection against subsequent infection [58]. However, when the animal had been vaccinated and was exposed to fingolimod and to tuberculosis, there was no infection [58]. No clinical studies have been carried out and there is a crucial lack of data on the subject in the medical literature.

Due to the important lymphopenia derived from the use of fingolimod, patients must undergo careful investigation of possible latent tuberculosis. Patients should be (re)vaccinated prior to use of fingolimod.

Natalizumab

Natalizumab is an α-4-integrin antagonist that inhibits the binding of α-4-integrin to activated leukocytes with its ligand, the vascular cellular adhesion molecule-1 [59]. Inhibition of α-4-integrin–vascular cellular adhesion molecule-1 interactions prevents transmigration of activated lymphocytes into the CNS, which is a critical step in the development of inflammatory lesions in MS. However, its inhibition of leukocyte trafficking is not organ-specific and other organs such as the gut, bone marrow and lungs are also affected. The major concern regarding drug safety is the patient's potential to develop multifocal leukoencephalopathy as a serious opportunistic infection [59]. Differential expansion of α-integrin T cells is important in memory lymphocyte migration to the lungs and other organs following mycobacterial infection [60].

Natalizumab treatment does not seem to relate to infection by or reactivation of tuberculosis, although very few studies have directly addressed this matter [61]. Long-term monitoring of infections relating to natalizumab rendered only one report of two cases of pulmonary tuberculosis in women using the drug [62]. Pulmonary tuberculosis in these cases might have been the result of the drug's action on α-4-β-1 integrin activity. However, whether such an effect was due to heightened susceptibility to de novo *M. tuberculosis* infection owing to lack of BCG and potential environmental exposure, or to reactivation of latent tuberculosis, cannot be definitively concluded [62,63].

Corticosteroids

Corticosteroids affect the growth, differentiation and function of monocytes and lymphocytes, distribution of cellular subsets and production of cytokines, and can induce leukocyte apoptosis [64,65]. Although corticosteroids are, *per protocol*, used in the treatment of some forms of tuberculosis [66], prolonged use of 15 mg/day or higher doses has been independently associated with higher risk of tuberculosis infection and reactivation [67–69]. Very few studies have assessed the risk of corticosteroids prescribed as pulse therapy and the risk of tuberculosis, but at least for systemic erythematosus lupus [70] and post-transplantation [71] this association seems to be clear. In countries with low income and absence of other medications to treat MS, corticosteroids are likely to be widely used. Unfortunately, these are exactly the same countries with higher risk of tuberculosis.

It is strongly recommended that patients undergoing pulse therapy (particularly if followed by oral supplementation doses) and other forms of corticosteroid treatments in MS cases should be rigorously and routinely screened for tuberculosis.

Unspecific immunosuppressants

Patients with MS who are candidates for immunosuppressive treatments must be properly screened for tuberculosis before the treatment starts. Unfortunately, immunosuppression is often recommended in very aggressive and fast-progressing cases of MS, and proper investigation for tuberculosis may not be completely done due to the urgency in starting the immunosuppression. Again, unspecific immunosuppressants are more likely to be used in countries without other more expensive alternatives for MS.

Azathioprine – Through the metabolism, azathioprine is converted into 6-mercaptopurine, which is then converted into 6-thioguanine. Subsequently, 6-thioguanine is converted into two metabolites: one that is incorporated into DNA

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(6-thioguanine nucleotide) and one that is incorporated into small GTPases, including GTPase-Rac1. In CD4+ T cells, azathioprine targets Rac1 activation, leading to lymphocyte apoptosis [72]. Azathioprine has an efficacy profile in MS that renders the treatment adequate in several countries [73]. The main concerns relate to the safety profile, due to potential malignancy, liver dysfunction and severe leukopenia [74]. Latent and active tuberculosis are contraindications for use of azathioprine (included in the medication leaflet). It is important to emphasize that azathioprine, just like corticosteroids, is an inexpensive treatment for MS and is more likely to be used in developing countries where the risk of tuberculosis is higher.

Cyclophosphamide – The metabolism of cyclophosphamide generates the metabolites cis- and trans-4-hydroxycyclophosphamide, aldophosphamide (and its hydrate), iminophosphamide, phosphoramide mustard, acrolein and chloroethylaziridine [75]. The drug has potentially serious cytotoxic side effects and it is not specific toward lymphocyte control. Cyclophosphamide cannot be used in association with treatment of tuberculosis. The use of rifampicin (associated with isoniazid or pyrazinamide) increases the conversion of cyclophosphamide into its toxic metabolites through strong activation of the cytochrome CYP2B6 [76].

Methotrexate – This is an anti-folate drug that is already very restricted for use in MS since it is highly teratogenic. The drug is not free from complications for patients with latent tuberculosis and can lead to pulmonary and extrapulmonary tuberculosis [77,78]. Patients with MS may undergo treatment with isoniazid and methotrexate at the same time without a serious risk of worsening the infection, although caution must be exercised. It is essential to regularly monitor hepatic function in patients receiving both drugs, due to the high risk of hepatotoxicity [79].

Mitoxantrone – This is an inhibitor of topoisomerase II and can be used for the treatment of both MS and tuberculosis. *M. tuberculosis* requires PknB (a serine-threonine transmembrane protein kinase) for exponential growth [79]. Mitoxantrone inhibits PknB [80]. At least in theory, since it has never been properly assessed, mitoxantrone would be a very good treatment for MS in a patient at risk of being infected or having reactivation of tuberculosis. If mitoxantrone is properly used and the toxicity risks are carefully monitored, it is a very good therapeutic option for aggressive MS [81]. It is a fairly inexpensive option for countries that do not possess other drug alternatives and may also be endemic for tuberculosis.

Stem cell transplantation

Autologous or allogeneic hematopoietic stem cell transplantation is considered to be a third-line therapy by many neurologists. This procedure is recommended for cases where disease aggressiveness and lack of response to other anti-inflammatory treatments require more energetic measures [82]. Although this procedure is becoming safer and more MS centers are comfortable about recommending this therapeutic approach, tuberculosis remains a problem for patients subjected to severe immunosuppression [83–85]. Mesenchymal stem cell transplantation, an experimental procedure undergoing clinical investigation, which does not require immunosuppression, is likely to be used in the future [86]. For the moment, stem cell transplantation following severe immunosuppression cannot be recommended for patients with a past or present history of tuberculosis.

Recently approved drugs

Three new drugs have been approved for the treatment of MS. These drugs are BG-12 (dimethyl fumarate), teriflunomide and alemtuzumab.

BG-12 – This drug appears to have anti-inflammatory and cytoprotective activities mediated (at least in part) by the antioxidant pathway of the nuclear factor Nrf2 [87]. Although mild-to-moderate leukopenia in patients using BG-12 is known to occur [88], no opportunistic infections have been observed with the use of this drug [89]. The drug is new and it is necessary to observe its safety profile in clinical practice. It is curious to observe that bedaquiline fumarate is a potent drug for the treatment of tuberculosis. Despite the name in the molecule, fumarate has no role in the mechanism of action of this drug.

Teriflunomide – This drug inhibits the T-cell receptor CD3, altering calcium mobilization and T-cell function [90]. In addition, it profoundly affects the interaction between antigen-presenting cells and T cells [91], rendering the drug a potent immunological effect in cellular immunity. It is recommended that patients subjected to treatment with teriflunomide are vaccinated against tuberculosis.

Alemtuzumab – This is a monoclonal antibody targeting CDE52, which is expressed in circulating T and B lymphocytes. Alemtuzumab can be used to treat MS [92,93] and has been recently approved for MS therapy in several countries. Due to the severe depletion of lymphocytes caused by the drug, opportunistic infections may be a problem with alemtuzumab [94]. Of these infections, the reactivation of tuberculosis poses a particular serious problem. Diffuse *M. bovis* infection [95], reactivation of infection with *M. tuberculosis* [96] and tuberculous hepatitis [97] are a few of the potential complications of mycobacteria in patients using alemtuzumab. Extreme caution is recommended if a patient is to receive alemtuzumab regarding the risk of tuberculosis, particularly in endemic areas.

Practical approach to patients with MS & latent tuberculosis

A summary of findings in this review is presented in Table 1. The fact that tools to identify latent tuberculosis are far from ideal does not preclude an investigation in all patients with MS who will undergo immunosuppressive treatments. This has not been done on a routine basis because for many years IFN-β and glatiramer acetate dominated the prescriptions for MS, and these drugs do not pose a problem in the reactivation of tuberculosis. With the arrival of new and very potent drugs, this scenario is about to change. Patients need to be screened with the best means we have, and in some places this means only the

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Table 1. Summary of presently used drugs and treatments for multiple sclerosis and the risk of developing or reactivating tuberculosis.

Drug procedure	Mode of action	Indication	Risk of reactivating tuberculosis	Recommendations for screening	Ref.
IFN-β	At immune cells level, it is multifactorial and incompletely understood	RRMS	None reported	None	[100]
Glatiramer acetate	Immune deviation, may therefore have direct CNS effects, still incompletely understood	RRMS	None reported	None	[101]
Fingolimod	Prevents lymphocyte egress from lymphoid tissues, may therefore have direct CNS effects	RRMS	Potential	(Re)vaccinate patients	[102]
Natalizumab	Inhibits immune cell extravasation and inflammation in the CNS	RRMS	Two cases reported	(Re)vaccinate patients	[103]
Corticosteroids	Affect the growth, differentiation and function of lymphocytes, anti-inflammatory and immunosuppressive effects	Relapses	High risk of reactivation	Rigorous and frequent screening for tuberculosis	[64,67]
Azathioprine	Leads to lymphocyte apoptosis	RRMS and SPMS	Very high risk	Do not use it if there is a risk of tuberculosis	[72,74]
Cyclophosphamide	Has cytotoxic side effects and it is not specific toward lymphocytes	Aggressive RRMS	Very high risk and cannot be associated to rifampicin, isoniazid or pyrazinamide	Do not use it if there is a risk of tuberculosis	[76]
Methotrexate	Anti-folate	RRMS	Very high risk	Do not use it if there is a risk of tuberculosis	[77,78]
Mitoxantrone	Inhibits topoisomerase II and can be used for treatment of both MS and tuberculosis	Aggressive RRMS	None	Can be used to treat tuberculosis	[79]
BG-12 (dimethyl fumarate)	Has anti-inflammatory, antioxidant and cytoprotective effects	RRMS	Potentially none	(Re)vaccinate patients, since this is a new drug	[87]
Teriflunomide	Inhibits CD3 and affects calcium mobilization and T-cell function	RRMS	Potential	(Re)vaccinate patients	[90]
Alemtuzumab	Leads to severe depletion of lymphocytes	RRMS	Very high risk	Do not use it if there is a risk of tuberculosis	[94,104]
Stem cell transplantation	Leads to severe immunosuppression	Very aggressive RRMS	Very high risk	Do not use it if there is a risk of tuberculosis	[83–85]

RRMS: Relapsing-remitting multiple sclerosis; SPMS: Secondary progressive multiple sclerosis.

anamneses and the purified protein skin test. If at all possible, the test should also include the IFN-γ release assay and chest image [98]. It would be advisable to have a pneumologist and/or a specialist on infectious diseases who could help neurologists evaluate patients going for more aggressive MS treatments.

If the patient is diagnosed with latent tuberculosis, 6 months of isoniazid or 4 months of rifampicin should be given [98]. Patients undergoing immunosuppressive therapy for MS must continue to be monitored, as recommended in other suppressive treatments [99].

Five-year view

The new drugs used for the treatment of MS can potentially be involved in the reactivation of tuberculosis. Drugs coming in the next 5 years are bound to be even more potent in controlling the inflammation in MS. Therefore, screening for

tuberculosis in patients with MS, both before and during treatment, should become obligatory.

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Key issues

- Tuberculosis and multiple sclerosis (MS) are severe diseases that are increasing worldwide, affecting mainly young adults.
- Drugs used for the treatment of MS are immunomodulatory and/or immunosuppressive. Therefore, these drugs may facilitate the reactivation of tuberculosis.
- Investigation and treatment of active or latent tuberculosis should be considered for all patients undergoing treatment of MS. Despite the idea that tuberculosis is a disease of the underdeveloped world and MS is a disease of developed countries, this cannot be held true for the global situation we live in the 21 century.
- Immunosuppressive drugs should be avoided in patients at risk of tuberculosis. The risk should be tested more than only at the institution of a new therapy.
- The safest drugs to be used in patients with latent tuberculosis are IFN-β, glatiramer acetate and mitoxantrone.

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