Title

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Journal

Rheumatic Disease Clinics of North America, 43(4)

ISSN

0889-857X

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Publication Date

2017-11-01

DOI

10.1016/j.rdc.2017.06.009

Peer reviewed

Published in final edited form as:

Rheum Dis Clin North Am. 2017 November ; 43(4): 607–619. doi:10.1016/j.rdc.2017.06.009.

Central nervous system infections associated with immunosuppressive therapy for rheumatic disease

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SYNOPSIS

Patients on immunosuppressive therapy for rheumatic diseases are at elevated risk of opportunistic and non-opportunistic infections. Although infections of the central nervous system (CNS) are relatively less common compared with other sites, patients on broadly immunosuppressive and biologic immunomodulatory agents may be susceptible to more severe, disseminated forms of infection, including of the CNS. Certain key principles regarding infection risk apply across immunosuppressive therapies, including increased risk with higher doses and longer duration of therapy and with combination therapy. Providers caring for patients with rheumatologic conditions should be aware of the infection risk related to immunosuppressant use, including those associated with CNS infections. Recognition of these risks can help guide best practices for screening and prophylaxis.

Keywords

central nervous system infection; immunosuppression; immunomodulatory therapy; rheumatic disease

INTRODUCTION

The risk of opportunistic infections and pathogens that can cause disease in healthy hosts is heightened in patients with rheumatologic conditions treated with immunosuppressive and immunomodulatory agents.[1] In addition, immune dysregulation associated with underlying rheumatic disease may predispose to infectious complications. Infections of the central nervous system (CNS) are particularly important to recognize given high associated

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Disclosures: The authors have no disclosures to report.

morbidity and mortality and the complexity of distinguishing between CNS infections and neurological manifestations of rheumatic disease. In this review, we first present two illustrative cases followed by a discussion of a selection of commonly used agents in the treatment of rheumatic disease and the risk of CNS infections associated with their use.

Case 1

A 25 year-old woman with systemic lupus erythematosus (SLE) presented with 3 weeks of headache, photosensitivity, and vomiting. Her SLE had been treated with varying doses of prednisone, up to 50 mg daily, and azathioprine 200 mg daily. Lumbar puncture demonstrated normal opening pressure. She had a moderate lymphocyte-predominant pleocytosis, mildly elevated protein, and normal glucose. Cryptococcal antigen was positive in the serum and cerebrospinal fluid. She was treated with intravenous amphotericin B liposomal and flucytosine followed by oral fluconazole with complete resolution of her symptoms. She has continued on maintenance fluconazole while on immunosuppression for active SLE.

Case 2

A 61 year-old woman with RA presented with headaches, vertigo and painful paresthesias on the trunk. A brain and spine MRI with contrast demonstrated diffuse ring-enhancing lesions (Figure). She had most recently been treated with rituximab and methotrexate, which were discontinued one year prior to presentation consequent to frequent infections. She had also received glucocorticoids, etanercept, and adalimumab. Lumbar puncture demonstrated no white blood cells, mildly elevated protein, and normal glucose. Serum and urine histoplasma antigen were positive. She was treated with IV amphotericin B liposomal followed by itraconazole for CNS histoplasmosis. She improved clinically with resolution of lesions.

Broadly Immunosuppressive Agents

Glucocorticoids—Glucocorticoids bind to their specific intracellular receptors, leading to down-regulation of the inflammatory response through a broad range of mechanisms.[2–5] Innate immunity is inhibited by depletion of immune cells, impaired migration and phagocytosis, and decreased production of inflammatory cytokines.[6] Adaptive immune function is attenuated through reduction in the number and function of T and B-cells.[7–9] Suppression of innate and adaptive immunity associated with glucocorticoid use increases the risk for virtually all types of infections, many of which can affect the CNS, including pyogenic and intracellular bacteria (e.g., Staphylococcus, Salmonella), mycobacteria (e.g., Mycobacterium tuberculosis), fungi (e.g., Cryptococcus, Candida), viruses (e.g., Herpes viruses), and parasites (e.g., Toxoplasma gondii, Strongyloides).[10] Listeria and Nocardia species are examples of two pathogens with a predilection for the CNS for which glucocorticoid use is a major risk factor.

The risk of infection associated with glucocorticoid use increases with higher dosing and longer duration of therapy, along with patient-specific factors including older age, lower functional status, and underlying illness.[11–15] A meta-analysis of 71 clinical trials found the overall rate of infections was higher among patients on glucocorticoid therapy than placebo

(RR 1.6, 95% CI 1.3–1.9). However, infection rates were not increased in patients taking less than 10 prednisone-equivalent mg daily or a cumulative dose of 700 mg. Glucocorticoids used in combination with other immunosuppressants confer greater risk of systemic and CNS infections, particularly at higher cumulative doses (see Case 1).[16] In one series of 23 SLE patients diagnosed with a CNS infection, all were on prednisone doses of 20 to 60 mg/day, with an average dose of 29 mg. Nearly half of patients had recently received pulse cyclophosphamide, and two were on mycophenolate mofetil.[17]

In order to reduce risk of infection, the lowest dose of glucocorticoids should be used for the shortest duration, and concurrent use of other immunosuppression should be avoided when possible. Alternate-day dosing of short-acting glucocorticoids has been suggested to lower associated risks, although evidence of decreased infectious complications is debatable.[18–20] Glucocorticoid dose reduction or discontinuation should be considered while treating infectious complications. Although prophylaxis against infections such as Pneumocystis jiroveci pneumonia for patients requiring long-term glucocorticoid use (e.g., the equivalent of 20 mg or more of prednisone for a minimum of one month) is common practice and can have activity against some CNS pathogens (e.g., Listeria, Nocardia), no data are available regarding the utility of prophylaxis for CNS infections. Clinicians should refer to guidelines regarding the timing of vaccinations for patients on glucocorticoids, as deferral, particularly for live attenuated vaccines (e.g., herpes zoster vaccine), may be required for patients on higher doses.[21]

Methotrexate—Methotrexate (MTX) inhibits dihydrofolate reductase and is a mainstay of treatment of RA and other rheumatic conditions. Current evidence points to adenosine signaling as one primary driver of the anti-inflammatory effects of MTX,[22,23] although other pathways likely contribute to its pleiotropic effects. In general, the safety profile of MTX is viewed as being more favorable than other immunosuppressive agents, with several studies demonstrating minimal, if any, increased risk of serious or opportunistic infections.[24] One prospective observational study evaluated the risk of infection in 77 RA patients treated with MTX compared with 152 RA patients not on MTX, the majority of whom were on either no therapy (37%) or sulfasalazine (20%). Sixty-two percent of the MTX group experienced an infection over one year, with a relative risk of infection compared to the non-MTX group of 1.52 (95% CI 1.04–2.22). None of the infectious complications warranted discontinuation of MTX.[25] Differences in the treatment groups may have accounted for the observed increased risk of infection in MTX users, who had significantly worse functional status. Another study of 7,971 patients with RA from the Consortium of Rheumatology Researchers of North American (CORRONA) registry, in which treatment with MTX and other immunosuppressants were analyzed as time-dependent variables, found an increased rate of infections (e.g., urinary tract infection) associated with MTX use (IRR 1.30, 95% CI 1.12–1.50) compared with other disease-modifying anti-RA treatments (other than tumor necrosis factor antagonists) but no increase in the risk of opportunistic infections.[26]

A recurring theme with immunosuppression is that combination therapy, while potentially more effective in controlling disease activity, may compound infectious risk. Furthermore, use of multiple therapies concurrently or sequentially complicates our ability to pinpoint which agent may be the underlying culprit. Many case reports of CNS infections associated

with MTX are in the setting of concomitant glucocorticoid or other immunosuppressant use.[27–29]

Data addressing the risk of CNS infection associated with MTX are sparse. However, several neurotoxic side effects of MTX related to the dose and route of administration can mimic CNS infections. High-dose systemic MTX is used for CNS inflammatory syndromes, including some rheumatologic diseases, but confers greater risk of toxicities.[30] Attenuating the neurotoxic effects of MTX is an important management principle that relies on leucovorin rescue when high dose MTX is used. Some toxicities, such as aseptic meningitis and posterior reversible encephalopathy syndrome, are generally self-limited and do not necessitate treatment beyond holding MTX.[31,32] Others, like MTX-associated myelopathy, warrant prompt cessation of MTX and consideration of folate metabolites.[33]

Cyclophosphamide—Cyclophosphamide (CYC), an alkylating agent with potent antiproliferative activity, was initially developed as a chemotherapeutic drug. Pulse-dose intravenous CYC is used for severe rheumatologic conditions, including lupus nephritis, CNS lupus, and some vasculitides. Bone marrow suppression from high dose CYC leads to greater susceptibility to infection[16]. However, even in the absence of leukopenia, CYC disrupts both T[34,35] and B cell function[36], resulting in impaired cell-mediated and humoral immunity[37] and elevated infection risk. As with glucocorticoids, cumulative dose and duration are directly tied to toxicity. As a result, curtailing exposure to CYC with pulse regimens is generally associated with fewer adverse effects, including leukopenia,[38] although it is unclear whether this translates into fewer infectious complications.[39]

CYC is associated with bacterial, viral, and opportunistic infections related to various pathogens.[16] In one retrospective study of 65 rheumatologic patients receiving CYC, infection occurred in 37%, none of which involved the CNS.[40] Risk of infection may be exacerbated by combination therapy as CYC is typically given in conjunction with glucocorticoids. In a controlled trial of 82 lupus nephritis patients randomized to pulse methylprednisolone, CYC or combination therapy, approximately 7% of the methylprednisolone group, 25% of the CYC group, and 33% of the combination therapy group had at least one infectious complication.[41] Among 100 SLE patients on CYC and glucocorticoids, infections occurred in 45% of patients receiving combination therapy versus 12% of a separate group of SLE patients on glucocorticoid monotherapy.[16] Several infections with CNS involvement were documented in patients on CYC, including *Cryptococcus neoformans* and *Nocardia asteroides*. Risk factors for infection were leukopenia nadir ≤3,000/uL and use of sequential intravenous and oral CYC.

Biologic immunomodulatory therapies

In contrast to the broadly immunosuppressive agents discussed above, biologic therapies for rheumatic diseases are more targeted in hopes of establishing therapeutic efficacy while minimizing off-target complications. While biologics generally do not cause global immunosuppression, they still modulate immune function and can confer an increased risk of infectious complications. We will focus on infections of the CNS associated with select, commonly used biologic immunomodulatory agents in the rheumatologists' toolbox.

TNF inhibitors—Tumor necrosis factor (TNF) is synthesized by various immune cells and is integral to phagosome activation, macrophage differentiation, and granuloma formation and maintenance.[42] Granulomatous infections, including mycobacterial, fungal (e.g., cryptococcosis,[43,44] histoplasmosis,[45] coccidiomycosis,[46] aspergillosis[43] and candidiasis) and parasitic infections (e.g., toxoplasmosis[43]) warrant special consideration given the role of TNF in granulomatous reactions.

Tuberculosis (TB) is a well-known infectious complication of TNF antagonists.[47–50] Data are lacking from population-based studies on the incidence of CNS TB associated with TNF inhibitors. Not all TNF inhibitors are equivalent in terms of the risk of reactivation of TB, with etanercept, a soluble TNF receptor fusion protein, carrying a lower risk than the monoclonal TNF antibodies (e.g., infliximab, adalimumab).[48] As with TB related to other causes of immunosuppression,[51] patients on TNF inhibitors are more likely to develop extrapulmonary and disseminated disease.[48,52] The most common CNS syndrome of TB is meningitis, which has a tropism for the base of the brain and may be complicated by infarcts and hydrocephalus. Tuberculomas have been described with and without pulmonary involvement in the setting of TNF antagonism.[53–55]

When CNS TB occurs, prompt diagnosis and treatment are critical. Every effort should be made to demonstrate definitive microbiological or histological evidence of tuberculosis.[56] The diagnostic yield of acid-fast bacilli (AFB) examination in CSF ranges from 37% with one sampling to as high as 87% with up to four serial examinations,[57] although the yield is exceedingly technician dependent and better sensitivities are typically in high-prevalence settings with exceptionally well-trained and experienced personnel. If initial testing is unrevealing but the suspicion remains high, additional lumbar punctures for cultures and AFB staining should be considered. Clinicians should collect a large volume of CSF (i.e., 10 ml) in the final tube to maximize capture of bacilli at the base of the brain and should communicate with the laboratory about the suspected diagnosis to optimize sample processing. CSF mycobacterial nucleic acid amplification testing and adenosine deaminase may add to the diagnostic evaluation.[58] While the World Health Organization recommends Xpert MTB/Rif (Xpert) testing as the initial diagnostic test for TB from CSF when sample volume is low, limitations of Xpert for the diagnosis of CNS TB should be recognized.[59] Studies of the use of Xpert MTB/Rif Ultra (Ultra), a next-generation assay that is more sensitive than Xpert, for improved diagnostic accuracy for CNS TB are eagerly awaited.

Screening for and treatment of latent TB infection is an important early risk reduction strategy when using TNF inhibitors. Screening should include exposure history, physical examination, tuberculin skin test (TST) and/or an interferon gamma release assays (IGRA). Patients who are immunosuppressed (including most patients with rheumatologic illness being considered for anti-TNF therapy) *without* TB risk factors should be screened with an IGRA. For patients *with* risk factors, two screening tests should be performed.[60] An indeterminate IGRA result can be repeated. If screening is positive, further investigation should include chest radiography and sputum examination as indicated, followed by initiation of appropriate treatment. Although screening measures for TB have dramatically decreased the incidence of TB reactivation in the setting of TNF antagonism,[61] the

sensitivity of screening tests is imperfect, and TB should always be considered in patients on TNF inhibitors.

Cryptococcus species are encapsulated fungi commonly found in soil and bird droppings. Diagnosis of CNS cryptococcal infection relies on antigen detection and CSF examination and culture. Effective control of elevated intracranial pressure (ICP) is critical in the management of cryptococcal meningoencephalitis.[62,63] Even in the absence of clinical evidence of elevated ICP,[64] a lumbar puncture should be performed, unless contraindicated, to evaluate the opening pressure, followed by mechanical drainage to reduce the pressure to <20 cm H_2O or by roughly 50% if extremely elevated.[65] Daily therapeutic lumbar punctures may be required to maintain pressure in the normal range, and surgical drainage with placement of a percutaneous lumbar drain may be appropriate. Acetazolamide and glucocorticoids have not been shown to be effective in the management of elevated ICP for HIV-associated cryptococcal meningoencephalitis, and may be harmful.[66,67]

Use of TNF inhibitors also predisposes to infection with endemic mycoses, which can involve the CNS in the form of meningitis, encephalitis and/or myelitis. Histoplasmosis, which is endemic to the Ohio and Mississippi River Valleys, is the most common fungal infection associated with use of TNF inhibitors.[68] and may be more common than TB.[69] As with TB, histoplasmosis infections among patients on TNF inhibitors are generally thought to be more severe and widely disseminated than in immunocompetent patients. In a retrospective study of 98 patients who developed histoplasmosis on TNF inhibitors, with RA as the most common underlying diagnosis, two (2%) had CNS involvement.[70] Combination therapy with glucocorticoids was a risk factor for greater disease severity. Clinicians should inquire about potential exposures and travel to or residence in endemic areas, as well as symptoms of active or recent infection prior to initiation of TNF inhibition therapy. Serologic or antigen screening for histoplasmosis in preparation for starting a TNF inhibitor is not recommended.[45] Depending on the severity of the infection, resumption of TNF inhibitor therapy may be considered after treatment and confirmation of undetectable antigen levels.[70] However, careful clinical and laboratory monitoring is recommended.

Coccidioidomycosis and blastomycosis are two other endemic mycoses with CNS manifestations for which patients on TNF inhibitors are at potentially increased risk, although the frequency of these infections is lower than histoplasmosis.[68,69] Because CNS coccidioidomycosis requires lifelong therapy, experts recommend against resumption of TNF inhibitor therapy in these patients.[71]

When patients develop mycobacterial or invasive fungal infections, TNF antagonists should be held, and the appropriate antimicrobial regimen initiated. Paradoxical immune reconstitution inflammatory syndrome (IRIS), including of the CNS,[72] can occur when immunosuppression is reduced or discontinued. Ironically, TNF antagonists have been used to treat IRIS, including CNS IRIS, in HIV-infected and transplant patients, which speaks to the complexities of IRIS and immune modulation associated with TNF inhibition.[73,74] In addition, some complications of TNF antagonism may mimic CNS infection. For example, autoimmune/granulomatous reactions and demyelinating disease have been reported with these agents.[75]

In addition to more common bacterial infections, including bacterial meningitis,[76] the risk of several intracellular pathogens such as *Listeria* and *Nocardia*, both of which are neurotropic, challenging to diagnose, and associated with high mortality,[77–79] is increased with TNF inhibitors.[80,81] Severe herpesvirus CNS infections have also been reported.[82,83] In one series of TNF inhibitor-associated HSV encephalitis, brain MRI and CSF HSV PCR were initially negative in two of three patients.[84] Although a negative CSF HSV PCR can occur early in HSV encephalitis,[85] empirical antiviral therapy should be continued despite negative testing if clinical suspicion for HSV encephalitis is high, including in patients on TNF inhibitors.

B Cell Targeted Agents—Rituximab is a chimeric anti-CD20 monoclonal IgG1 antibody that depletes peripheral B cells via complement-mediated and antibody-dependent cytotoxicity. Mature plasma cells do not express CD20 and are unaffected by rituximab, as are existing antibody levels.[86] Rituximab is used in the treatment of SLE, RA, and other rheumatic conditions, as well as hematologic malignancies, neuromyelitis optica, and other immune-mediated neurologic conditions.

The precise risk of infection associated with rituximab for patients with rheumatologic disease remains uncertain. Many reported cases of serious infections associated with rituximab are in patients who have received multiple prior biologic and non-biologic immunomodulatory agents, including TNF antagonists (see Case 2). Available data suggest that infectious risk associated with rituximab is lower than with TNF inhibitors and may not be increased in this population, unlike in patients with hematologic malignancies or post-transplant.[87] Unlike with TNF inhibitors, an association between rituximab and elevated TB risk has not been demonstrated, and there are no official recommendations to screen for latent TB infection prior to initiation of rituximab.[88]

The best recognized opportunistic CNS infection associated with rituximab is progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the CNS caused by infection of oligodendrocytes by JC virus.[89] The risk of PML in patients with RA treated with rituximab is an estimated 1/25,000 patients,[90] considerably lower than in multiple sclerosis patients on natalizumab,[91] although the mortality rate may be as high as 90% overall.[92] While JC virus antibody screening is an integral risk reduction strategy for patients treated with natalizumab, there is currently no role for screening in patients on rituximab.[91,93] Monitoring patients for clinical signs and symptoms of neurological impairment, including aphasia, visual deficits, and focal weakness, may be a more useful screening tool for emerging PML, which generally has a subacute presentation. Rituximab can also cause hypogammaglobulinemia, particularly with repeated cycles, predisposing to infections that may require immunoglobulin replacement.[94]

CONCLUSIONS

Rheumatologists should be familiar with the risk of CNS infections associated with broadly immunosuppressive and biologic immunomodulatory agents used to treat rheumatic diseases. Awareness of these infectious complications can help guide screening and prophylaxis, when indicated.

Acknowledgments

Funding: This work was supported by NIH/NCATS KL2TR000143 (Chow).

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Key Points

- Rheumatologists should be familiar with CNS infections associated with immunosuppressive therapy, and changes in neurologic function should be queried at every clinic visit
- The risk of infection associated with glucocorticoids increases with dose and duration of therapy and combination regimens likely compound the risk of infection
- Although little data suggest increased risk of CNS infection from methotrexate, rheumatologists should be familiar with the neurotoxic side effects that can develop
- TNF inhibitors increase the risk of granulomatous and bacterial infections and can also cause idiopathic granulomatous or demyelinating reactions
- Rituximab is associated with rare cases of progressive multifocal leukoencephalopathy; patients should be carefully monitored clinically and clinicians should maintain a high index of suspicion

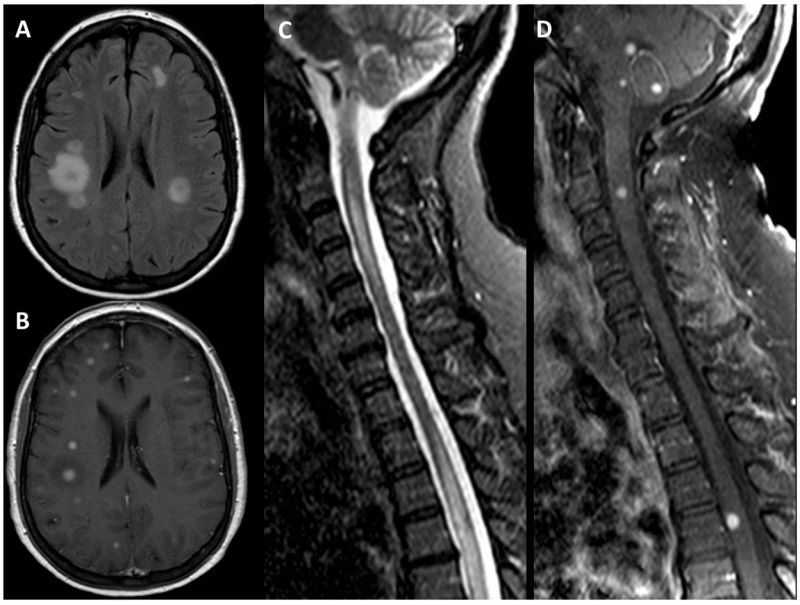

Figure 1.

Histoplasma encephalomyelitis in the setting of prior rituximab and methotrexate use. A) Axial T2-FLAIR brain MRI B) Axial T1 post-contrast brain MRI C) Midsagittal T2 MRI of the spine D) Axial T1 post-contrast MRI of the spine