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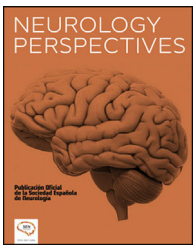

REVIEW

Multiple sclerosis and rheumatic diseases: Rheumatoid arthritis, antiphospholipid syndrome, and systemic lupus erythematosus

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Treatment;
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Abstract
Introduction: Multiple sclerosis (MS) may be associated with a range of rheumatic diseases. Rheumatoid arthritis is a chronic inflammatory disease typically affecting small- and medium-size joints. MS has been associated with antiphospholipid syndrome.
Development: The treatment of these patients must be carefully established, considering the presence of neurological symptoms or central nervous system comorbidities. Patients with MS and rheumatoid arthritis should not be treated with TNF inhibitors, as these may exacerbate the neurological symptoms. Most biological drugs may favour opportunistic infections of the central nervous system; therefore, patients developing neurological symptoms should undergo comprehensive examination, and biological treatment should be adapted according to the results.
Conclusions: We summarise the main recommendations for the treatment of patients with MS associated with rheumatic diseases.

PALABRAS CLAVE
Artritis reumatoide;
Esclerosis múltiple;
Síndrome antifosfolípido;
Lupus eritematoso sistémico;

Esclerosis múltiple y enfermedades reumatológicas: Artritis reumatoide, síndrome antifosfolípido y lupus eritematoso sistémico

Resumen
Introduccion: La Esclerosis Multiple (EM) se puede asociar a varios enfermedades reumatológicas. La artritis reumatoide (AR) es una enfermedad inflamatoria crónica caracterizada por una afectación de las articulaciones de pequeño y mediano tamaño. La EM, se ha asociado más frecuentemente al Sd antifosfolipidico.

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Tratamiento;
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Desarrollo: El tratamiento en estos pacientes debe ser cuidadosamente seleccionado teniendo en cuenta la aparición de cualquier manifestación neurológica o la existencia de comorbilidades del SNC. Pacientes con EM y Artritis Reumatoide no deberían ser tratados con anti-TNF, dado que éstos pueden exacerbar la sintomatología neurológica. La mayoría de los fármacos biológicos pueden favorecer las infecciones oportunistas del SNC, por lo que, ante la aparición de sintomatología neurológica, debe realizarse un examen exhaustivo, adaptando el tratamiento biológico a los resultados del examen.
Conclusiones: Se exponen las principales recomendaciones para el tratamiento de pacientes con EM asociada a enfermedades reumatológicas

Rheumatoid arthritis and multiple sclerosis

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterised by symmetrical involvement of small- and medium-size joints. From an anatomical pathology viewpoint, it is characterised by persistent synovitis accompanied by synovial hyperplasia with invasion of adjacent tissues and pannus formation and is caused by abnormal immune system activation as a result of loss of self-tolerance; it may therefore be classified as an autoimmune disease. These mechanisms are partly responsible for the development of extra-articular manifestations and comorbidities in the context of systemic involvement in RA.[1]

Its global prevalence is 0.5–1%; the condition most frequently affects middle-aged women. According to the Spanish Society of Rheumatology's 2016 EPISER prevalence study, the prevalence of RA in Spain is 0.82%, with a mean age of 60 years.

Central nervous system (CNS) involvement is less frequent in RA than in other autoimmune diseases such as Sjögren syndrome and systemic lupus erythematosus. However, RA involves a systemic inflammatory process that may have direct or indirect effects on the CNS. Direct effects include aseptic meningitis, cerebral vasculitis, and rheumatoid nodules, and indirect effects include cerebrovascular events and neurodegenerative disorders. Furthermore, patients with RA may present CNS diseases, including demyelinating diseases, infections, and neoplasms; the development of these comorbidities is caused by prolonged systemic inflammation and the effect of the treatments used to block the different inflammatory pathways.[1]

The onset of neurological symptoms following biological treatment is highly variable; long-term follow-up of these patients is therefore recommended. In addition to laboratory analyses, MRI is useful in differentiating inflammatory diseases from infections. Furthermore, levels of antibodies against JC virus, varicella zoster virus, cytomegalovirus, and Epstein-Barr virus should be determined before starting immunosuppressant or biological treatment, and vaccination should be recommended.

Treatment for these conditions should be established according to the aetiopathogenic mechanism: while corticosteroids and immunosuppressants are useful in the management of CNS diseases related to RA, they may be harmful in other clinical scenarios. The use of immunosuppressants counteracts the direct and indirect effects of the inflammatory process, decreasing the incidence of thrombotic events, dementia, and neuropsychiatric disorders. However, prolonged use is associated with an increased risk of stroke and cognitive impairment. On the other hand, such demyelinating diseases as multiple sclerosis (MS) have rarely been described in patients with RA receiving non-biological treatments.

Like immunosuppressants, tumour necrosis factor (TNF) inhibitors do not seem to increase the risk of cerebrovascular events or neurodegenerative conditions. However, these drugs have been associated with an increase in the incidence of such demyelinating diseases as MS, affecting both the CNS and the peripheral nervous system. The incidence of demyelinating events in patients with RA under treatment with TNF inhibitors is estimated at 30%.[1] Symptoms usually reverse upon treatment withdrawal, but may also progress to an established demyelinating disease in isolated cases. The association between TNF inhibitors and the onset of demyelinating disease is unclear, but may be linked to infectious processes or an abnormal immune response. TNF inhibitors are unable to cross the blood-brain barrier (BBB) or decrease levels of TNF-α in the cerebrospinal fluid and may alter the cytokine balance towards greater production of IL-12 family cytokines, trigger latent infection, and, paradoxically, increase autoreactive T cell activity.

On the other hand, the use of these drugs is also associated with opportunistic CNS infections, such as those caused by *Mycobacterium tuberculosis*, *Listeria monocytogenes*, *Cryptococcus*, and JC virus.

The different TNF inhibitors present a similar safety profile, although golimumab seems to be associated with an increased risk of infection, demyelinating disease, and lymphoma.[2]

Little evidence is available on the use of drugs other than TNF inhibitors (abatacept, rituximab, tocilizumab, anakinra), with the available data mainly being from small cohorts with short follow-up periods.

Abatacept and rituximab are not associated with increased risk of demyelinating disease; on the contrary, they have shown beneficial effects in 2 pivotal studies reporting promising results in MS. Rituximab is safe in patients who develop neurolupus following treatment with TNF inhibitors,

and even in patients with lymphoproliferative disorders affecting the CNS.[3]

However, rituximab has been associated with progressive multifocal leukoencephalopathy secondary to JC virus infection. Patients treated with different biological therapy lines also present a greater risk of JC virus infection.

The available evidence is insufficient to recommend abatacept for the treatment of MS.[4] Tocilizumab, on the other hand, has shown variable results, and recent studies suggest that it is a promising treatment option for neuromyelitis optica.

Treatment algorithm for multiple sclerosis and rheumatoid arthritis

The treatment of patients with RA must be carefully selected, considering the presence of neurological symptoms or CNS comorbidities.

Patients with MS should not be treated with TNF inhibitors, as these may exacerbate the neurological symptoms.

Such biological treatments as abatacept, rituximab, tocilizumab, and anakinra are preferred in the case of comorbid MS, as they seem to be safer.

All biological drugs may favour opportunistic infections of the CNS; therefore, patients developing neurological symptoms should undergo comprehensive examination, and biological treatment should be adapted accordingly.

Antiphospholipid syndrome and multiple sclerosis

Antiphospholipid antibodies (APAs) may be detected in patients with MS; the most frequently studied are anticardiolipin antibodies, lupus anticoagulant, and anti–ß2 glycoprotein I (β2GPI) antibodies. Their exact prevalence and pathogenic role in MS are yet to be determined. The reported frequency of APA positivity in MS ranges from 2% to 88%, with predominance of IgM over IgG.[5]

Filipodou et al.[6] analysed serum samples from 127 patients with MS and 92 healthy controls to detect IgM and IgG antibodies against cardiolipin (CL), β2GPI, and domain I (DI), and found higher levels of anti-CL IgM and IgG antibodies in patients with MS than in controls. Anti-CL IgM antibody levels were higher in patients with secondary progressive and primary progressive MS than in those with a relapsing-remitting course. Patients with MS tested positive for anti-DI antibodies, which could act as a trigger factor for inflammatory-thrombotic events in MS. These findings underscore the need for further research into the role of these antibodies as a risk factor for thromboembolic events in MS.

Autoantibodies play a crucial role in MS pathogenesis. Over the past decade, significant efforts have been made to characterise the antibody profiles of patients with MS, with a view to identifying early predictors of disease onset and progression. However, despite extensive research, no antibody specificity associated with MS has been identified that can discriminate between patients with MS and controls on an individual basis. APAs are among the most commonly studied autoreactive antibodies in MS. Such autoimmune disorders as antiphospholipid syndrome (APS) and systemic lupus erythematosus (SLE) are characterised by persistent APA positivity. APAs react not only with phospholipids but also with phospholipid-binding proteins, with β2GPI being the most important antigenic target. Furthermore, the IgG subtype seems to be more strongly associated with clinical manifestations than IgM or IgA. While all β2GPI domains act as targets for APA, most studies point to anti-DI antibodies as the most significant.[7]

Although the formal diagnostic criteria for these 2 autoimmune syndromes appear to be mutually exclusive, many patients with subcortical white matter lesions exhibit characteristics of both MS and APS. However, a more detailed analysis of clinical and laboratory findings reveals fundamental differences: while MS is characterised by diffuse white matter involvement, APS presents a more patchy lesion distribution.

Acute, isolated neurological syndromes represent the greatest diagnostic challenge, as these are the most common manifestations of MS but may also appear as the sole or initial manifestation of APS, before such typical manifestations as thrombosis or miscarriages. Patients with atypical MS show a significantly higher prevalence of APA positivity than patients with classical MS, as well as slower disease progression.[8] The presence of spinal cord lesions is highly suggestive of MS. On the other hand, a diagnosis of MS rules out other diagnoses that may explain demyelination, ruling out cases in which APS is causally involved.

A number of potential pathophysiological mechanisms have been identified that may explain the neurological dysfunction associated with APA. It has been proposed that these antibodies target antigens in the BBB, compromising its integrity. Other hypotheses suggest that APA may alter the structure of the proteins involved in inflammatory-thrombotic processes, as well as a phenomenon of molecular mimicry between the antigenic targets of APA and myelin and brain phospholipids, which may lead to cross-reactivity.[9]

Treatment for multiple sclerosis and antiphospholipid syndrome

APS may present in isolation (primary APS) or secondary to SLE or other rheumatic or systemic diseases. No study has specifically addressed the use of APS therapies in MS.

Treatments used in MS but contraindicated in APS

One of the most widely used treatments for MS is interferon beta–1a (Avonex or Rebif) or beta–1b (Betaferon). Interferon can exacerbate APS.[10] Anticoagulants, the cornerstone of APS treatment, may increase the risk of bleeding in patients undergoing frequent subcutaneous administration, as is the case with interferon (3–4 times/week), or intramuscular administration. Therefore, interferon is not recommended in these cases.

Treatments used in APS and MS

Azathioprine is a purine analogue immunosuppressant that has been used in MS for over 25 years. It primarily reduces relapse frequency and, to a lesser extent, slows disability progression. A meta-analysis[11] of 5 studies comparing

azathioprine against placebo found a 20% relative risk reduction in relapses and a modest effect on disability progression. The safety profile of azathioprine is acceptable, and the associated risk of cancer seems to be linked to treatment duration longer than 10 years.

Azathioprine may be indicated for APS following corticosteroid therapy. The dosage should be maintained based on treatment response. Few studies have clearly demonstrated its efficacy.[12] Given its risk/benefit profile, azathioprine may be a treatment alternative in these patients; however, level A evidence from clinical trials is still lacking.

Rituximab is a chimeric monoclonal antibody specifically targeting CD20 on B cells. A review of several trials demonstrated that rituximab controls inflammatory activity both clinically (decreasing the relapse rate) and radiologically (preventing the appearance of new or active lesions). However, its effects in slowing disability progression remain controversial. No remarkable safety concerns were reported. Rituximab appears to be an effective and safe treatment option for MS.

Several studies have shown that rituximab decreases APA titres due to its regulatory effects on B cells.[13] Furthermore, the drug has been shown to improve a range of vascular manifestations of APS. Based on the currently available evidence, rituximab seems to be a good option for patients with MS who present APA.

Treatments used in APS but contraindicated in MS

TNF-α inhibitors block the proinflammatory cytokine TNF-α. APA can increase TNF-α expression by stimulating monocytes, which may lead to increased tissue factor production. In vitro studies have shown that adalimumab, a TNF-α blocker, completely inhibits TNF expression induced by anti-β2GPI antibodies in monocytes. Anti-TNF therapy is associated with an increased risk of developing MS and is therefore contraindicated in patients with the condition.[14]

Treatments indicated in APS and with no known contraindications in MS

Obinutuzumab is a type II anti-CD20 monoclonal antibody that induces potent direct apoptosis by disrupting lysosomes. The drug has been found to be more effective than rituximab in inducing B cell lysis, even in the presence of high levels of B cell activating factor (BAFF). This suggests that obinutuzumab may be a valid treatment option for patients with APS who do not respond to rituximab. No study has analysed the use of obinutuzumab in MS, but its action mechanism does not seem to constitute a contraindication in this condition.

Belimumab is a monoclonal antibody targeting soluble circulating BAFF. Patients with APS present high BAFF levels. Belimumab may be beneficial for the management of patients with APS presenting high thrombotic risk or those presenting with APA positivity with microthrombotic manifestations. It has also been shown to significantly improve thrombocytopenia in patients with APS who do not respond to corticosteroids or rituximab. At present, no evidence contraindicates its use in MS.

Eculizumab selectively inhibits the human complement C5 protein. Activation of the complement cascade plays a role in APS. When rituximab and immunoglobulins fail to improve platelet count and kidney function, eculizumab may represent an effective treatment alternative. The drug is also a valid option for the management of APS during pregnancy and delivery. At present, no evidence contraindicates its use in MS.

Daratumumab, a monoclonal antibody targeting CD38, depletes long-lived plasma cells. It has been used to treat such autoimmune diseases as APS, SLE, and RA. Clinically significant improvements have been observed in a patient with APS who presented recurrent venous thrombotic events despite standard anticoagulant and immunosuppressant therapy, alongside a significant decrease in APA. No evidence contraindicates its use in MS.

Systemic lupus erythematosus and multiple sclerosis

Both SLE and MS are autoimmune diseases. MS is caused by immune cell infiltration across the BBB, which promotes inflammation, demyelination, gliosis, and axonal degeneration in the white matter of the CNS. SLE, in contrast, is a B cell-mediated disease characterised by the production of autoantibodies targeting nuclear antigens and type III hypersensitivity leading to chronic systemic inflammation and multiorgan damage. While genetic and environmental factors play a role in the pathogenesis of both diseases, their exact aetiology remains unknown.[15,16]

Although an association between SLE and MS has been described in families with multiple members affected by autoimmune diseases,[17] the coexistence of both conditions in a single patient is rare, and diagnosis of MS in a patient with SLE can be challenging.[18,19]

APAs play a crucial role in SLE. The mechanisms by which these antibodies may induce a disease resembling MS in patients with SLE include molecular mimicry with myelin, vasculopathy, and autoimmune vasculitis. Cross-reactions of APA have been observed with myelin, myelin-related proteins, and cerebral antiphospholipids such as thromboplastin and sphingomyelin.

Several risk factors for the development of neurological involvement in SLE have recently been identified, including disease activity itself, high titres of APA (including anti-CL), anti-aβ2GPI, and lupus anticoagulant antibodies. Arthritis and skin alterations are the most frequent systemic manifestations of SLE.

The most common neurological manifestations are optic neuritis and myelitis.[20] Optic neuritis can appear in both MS and SLE. In MS, it presents an acute or subacute course, may be unilateral or bilateral, and is associated with pain that worsens with ocular movement; recovery may be partial or complete. In SLE, however, optic neuritis is rare and is characterised by decreased visual acuity, which progresses to vision loss over the course of several weeks.[21]

In MS, myelitis is asymmetrical, progressing over several hours to days, and is commonly associated with sphincter dysfunction. In SLE, myelitis appears as the first neurological

manifestation in 21% of cases; it is typically extensive and affects the grey matter.[22]

It is essential to determine whether the neurological symptoms and CNS lesions observed on MRI are associated with SLE or relapsing-remitting MS. In patients with SLE, MRI typically reveals focal, punctiform white matter lesions, cortical atrophy, and small-vessel disease. Lesions are oval-shaped and periventricular, frequently subcortical, and affect the corpus callosum, brainstem, and spinal cord.[23]

Treatment for multiple sclerosis

Although several effective treatments are currently available for MS, caution should be exercised when indicating their use in patients with SLE due to differences in the immune response and the potential for drug interactions:

1. Interferons (IFNs) are drugs used to modulate the immune response. In patients with SLE, IFNs promote activation of the immune system and disrupt its regulatory mechanisms, leading to inflammation and tissue damage. It should be noted that SLE associated with APA frequently requires anticoagulant therapy, which may increase the risk of bleeding in patients receiving intramuscular IFN. Drug-induced SLE is defined as a syndrome similar (though not identical) to SLE, related to prolonged exposure to a drug, and which resolves upon withdrawal of the drug. The literature includes some reports of SLE developing in patients with MS treated with IFNs.[24,25] Furthermore, IFN beta has been shown to induce podocyte death and prevent the differentiation of precursor cells into podocytes, representing a contraindication in patients with lupus nephritis.[26,27]
2. Fingolimod is a sphingosine 1-phosphate receptor modulator. Its effects on regulatory B cells or natural killer cells are not fully understood. Fingolimod induces immune dysregulation and T cell imbalance, which may in turn exacerbate autoimmune disease as a result of regulatory T cell inhibition. The hyperactive immune system in SLE may respond inappropriately to the modulation induced by fingolimod, potentially increasing inflammation and immune responses. While there are no absolute contraindications to the use of fingolimod in patients with SLE, other therapeutic options should be considered.[28] Furthermore, concomitant use of fingolimod and other immunosuppressants increases the risk of severe infection.
3. Natalizumab. As occurs with fingolimod, natalizumab (a monoclonal antibody used to prevent inflammatory cell migration into the CNS) may exacerbate SLE. However, there are no absolute contraindications for its use.[29]
4. Mitoxantrone. Several cases of SLE reactivation have been reported with mitoxantrone. Furthermore, as the drug is associated with an increased risk of cardiac toxicity, its use is contraindicated in patients with SLE. Its use in MS is anecdotal.
5. Azathioprine. This immunosuppressant has been used for more than 25 years in the treatment of MS. However, despite its proven efficacy in reducing relapses, the available studies provide modest evidence. Though it might be safe to use in SLE, its efficacy in these patients is yet to be demonstrated.[30]

Treatment of systemic lupus erythematosus

The management of SLE depends on disease severity and the associated neurological and renal manifestations (diffuse proliferative glomerulonephritis). Current recommendations include[31]:

- Mild activity: hydroxychloroquine + non-steroidal anti-inflammatory drugs and analgesics.
- Moderate activity: prednisone + methotrexate, azathioprine, or mycophenolate mofetil (MMF).
- Severe activity without kidney or CNS involvement: cyclophosphamide, leflunomide, or a combination of prednisone + MMF or rituximab.
- Class III glomerulonephritis: induction therapy based on methylprednisolone + cyclophosphamide or MMF, followed by maintenance therapy with MMF, azathioprine, or low-dose cyclophosphamide.[32]
- Severe neurological, haematological, or renal damage: rituximab.

Regarding the treatment of SLE:

1. Corticosteroids, such as prednisone, are frequently used to reduce inflammation and manage symptoms. In MS, corticosteroids are also used to control relapses and reduce CNS inflammation. However, prolonged corticosteroid use may lead to relevant secondary effects, including osteoporosis and immunosuppression.[33]
2. Immunosuppressants, such as azathioprine, methotrexate, and MMF, are used in SLE to suppress immune system activity and prevent inflammation and organ damage. These drugs may have contraindications and require special precautions in patients with MS, as they also act on the immune system and may therefore increase the risk of infection. As mentioned previously, azathioprine may represent a treatment alternative for MS.
3. Rituximab is a chimeric monoclonal antibody targeting CD20 in B cells. In SLE, it is used to deplete B cells in the immune system. It has also been used in MS as a rescue treatment for severe, treatment-resistant cases.[14,34] Few therapeutic options are currently available for the simultaneous treatment of SLE and MS, although rituximab may represent a safe option.
4. TNF-alpha inhibitors, such as daclizumab, are contraindicated in MS, as cases have been reported of increased disease activity.[35]

MMF, azathioprine, methotrexate, and cyclophosphamide have been studied in MS, although their efficacy is not well established, and no phase III studies have compared them with disease-modifying treatments. Other drugs, such as obinutuzumab, belimumab, eculizumab, and daratumumab, have not yet been studied in patients with MS.

Several effective treatments for MS are available, but their contraindications and potential drug interactions should be considered in patients with SLE. Patients with both MS and SLE present great clinical complexity and a different immune response, which affects treatment selection and disease management. Collaboration between different medical specialties, such as neurology and

rheumatology, is essential to ensure an appropriate treatment approach and to minimise the associated risks.

Patient informed consent

No patient data are reported.

Ethical considerations

Not applicable.

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Declaration of conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neurop.2025.100197.

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