aggressive intervention, about a quarter of patients continue to progress to end stage renal disease (ESRD).¹

There is considerable diversity in the definition of 'refractory lupus nephritis' depending on the treatment protocol, physician's subspecialty, and histopathologic findings. Molecular biomarkers further show potential as surrogates to kidney biopsies in predicting renal outcomes and long-term prognosis.² The factor of drug adherence, however, may draw the fine distinction between refractory (or resistant) and relapsing LN, with the latter substantially more common than the former.³ Nearly half of patients with proliferative LN who initially achieve a complete response to immunosuppressive therapy will have a relapse or renal flare following cessation or reduction of immunosuppression. Other risk factors for refractoriness include genetics and comorbidities like hypertension, diabetic nephropathy and antiphospholipid antibodies, each of which must be effectively addressed in the overall management of these patients.

Treatment options for refractory LN include switching or multitargeted therapy with immunosuppressives cyclophosphamide, mycophenolate derivatives and calcineurin inhibitors (cyclosporine A, tacrolimus, and recently voclosporin).⁴ Literature abounds with the use of rituximab in refractory LN including trials exploring the sequential use of rituximab plus cyclophosphamide followed by belimumab.⁵ Other modalities such as extracorporeal treatment (plasma exchange or immunoadsorption) and stem cell transplantation may be tried in special situations. Novel insights of LN pathogenesis have led to the development of new or re-purposed drugs including obinutuzumab, itolizumab, and igturatimod which can significantly prevent progression to ESRD. Finally, the timely, aggressive and highly individualised management of LN which reinforces strict patient adherence is key to enhanced outcomes.

Learning Objectives

- Define refractory and/or relapsing LN
- Identify risk factors for refractoriness among LN patients
- Describe the management approach to refractory LN
- Describe advances in drug development for LN

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REFRACTORY LUPUS CYTOPENIAS

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The aim of this presentation is to provide concise information regarding diagnosis and management of immune mediated hematological manifestations of systemic lupus erythematosus (SLE), specifically autoimmune hemolytic anemia (AIHA), immune mediated thrombocytopenia and immune mediated leukopenia.^{1–5}

Studies on hematological manifestations of SLE are scarce and with low quality of evidence, therefore most existent guidelines are supported by hematological data from non-SLE patients. Of note, SLE patients have some peculiarities that must be taken into consideration when choosing the best treatment approach for their hematological conditions.

The key points of each cytopenia are:

- a. Autoimmune hemolytic anemia (AHAI) in SLE is usually mediated by warm antibodies (IgG). First-line treatment is glucocorticoid, but there is no consensus to guide second-line therapy. Rituximab and immunosuppressive drugs can be used in refractory cases.
- b. Immune thrombocytopenia is an important prognostic indicator of survival in SLE patients. Treatment is usually indicated for patients with a platelet count $<30 \times 10^9/\text{mm}^3$. First-line therapy remains glucocorticoids (dexamethasone is the hematologists 1st choice), but sustained response after glucocorticoid discontinuation in SLE patients is unlikely to happen. Rituximab and immunosuppressive drugs can be used in refractory cases. Thrombopoietin agonists and splenectomy should be avoided due to high risk of infection and thrombosis
- c. Neutropenia may be severe and can lead to morbidity and mortality from increased susceptibility to infection. Severe neutropenia can be successfully treated with granulocyte colony-stimulating factor. Lymphopenia is most often related to drug toxicity and disease activity. Severe lymphopenia may require the use of prophylactic therapy to prevent opportunistic infections. For all cytopenias an extensive evaluation of other causes, particularly drugs and infection should be performed.

Learning Objectives

- Identify and manage immune mediated anemia in lupus
- Discuss diagnosis and treatment options for thrombocytopenia in lupus
- Explain the diagnosis and management of leukopenia in lupus

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REFRACTORY MUSCULOSKELETAL MANIFESTATIONS

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Musculoskeletal involvement is one of the most common clinical manifestations of systemic lupus erythematosus (SLE),

being the first presenting symptom in around 50–70% of cases and affecting up to 95% of patients at some point. The most prevalent manifestations are arthralgia and arthritis (95%), follow by myalgia/myositis (17%), tenosynovitis and bursitis (12%). Deformities arise in 5–15% of patients with no radiographic erosions, as the hallmarks of Jaccoud's arthropathy, whereas radiographic erosions may be detected in less than 5% of patients suggesting the overlap between rheumatoid arthritis and SLE referred as rhupus syndrome. Other comorbidities may be present as musculoskeletal involvement, such as: fibromyalgia (6–32%), fragility fractures (8–12%) and avascular osteonecrosis (2–12%).^{1–4}

Recent insights from US studies show that in large numbers of lupus patients with arthralgia, despite subclinical synovitis, clinical assessment underestimates the level of joint and tendon inflammation compared to ultrasound and magnetic resonance imaging. This has implications for therapeutic choice, evaluation of response or treat-to-target protocols. While prevalence of subclinical synovitis is agreed, it is not yet clear whether it should be treated, however imaging studies suggest potential changes to the classification, assessment and management of patients with inflammatory musculoskeletal lupus.

SLE manifestations are considered refractory when patients are unresponsive to-or disease relapses despite-treatment with corticosteroids, antimalarials and/or immunosuppressants. Other key issues are that recurrent flares of disease activity are associated with poor long-term outcomes and longstanding overreliance on corticosteroid therapy, which contributes substantially to damage accrual and patient mortality.

Hydroxychloroquine and corticosteroids remain first-line therapies for musculoskeletal manifestations of SLE; however, patients with refractory musculoskeletal disease may require further management with immunosuppressive (methotrexate, leflunomide) or biologic (belimumab, abatacept, rituximab) agents for inflammatory disease control. Mycophenolate mofetil and, to a lesser degree, azathioprine have shown efficacy in the treatment of inflammatory myositis in SLE patients and have demonstrated a steroid sparing effect. Despite current therapy, musculoskeletal manifestations are major contributors to poor quality of life and work instability. There remains an unmet clinical need in SLE, particularly in patients with disease refractory to conventional immunosuppressive therapies.

Learning Objectives

- Explain the main musculoskeletal manifestations in patients with SLE
- Describe potential changes to the classification of musculoskeletal manifestations
- Describe the current recommendations for the treatment of refractory musculoskeletal manifestations
- Discuss new trends in research on new therapies for musculoskeletal manifestations in patients with SLE

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REFRACTORY AND/OR CATASTROPHIC APS IN SLE

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Antiphospholipid syndrome (APS) is an autoimmune disease characterised by vascular thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies (aPL), mainly lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-β2-glycoprotein I antibodies (anti-β2GPI). Precision Medicine can benefit the specific profiles of patients with refractory thrombotic and/or obstetric APS and those with catastrophic APS.

Hydroxychloroquine and low-dose steroid, alone or combined, may be an option for pregnant APS patients with a previous pregnancy refractory to conventional therapy. Intravenous immunoglobulins and plasma exchange, alone or combined, could be considered in refractory high-risk pregnant APS patients.^{1 2}

Evidence on the management of recurrent thrombosis despite vitamin K antagonists (VKA) treatment is limited. After evaluating other risk factors for thrombosis (e.g., traditional cardiovascular risk factors, cancer, other thrombophilic states) and investigating the adherence to VKA treatment, increase of target international normalised ratio (INR) to 3–4, or INR 2–3 with the addition of low dose aspirin, or switching to low molecular weight heparin may be considered. Adjunctive therapy with antimalarials or statins could also be considered.

Management of catastrophic APS is challenging. The higher recovery rate is achieved by the combination of anticoagulation, plus glucocorticoids, plus plasma exchange and/or intravenous immunoglobulins. New therapeutic approaches include rituximab and eculizumab.

Learning Objectives

- Explain the main unmet needs in the management of the APS in SLE
- Describe the options for the treatment of refractory thrombotic and obstetric manifestations of APS
- Discuss the current recommendations for the management of catastrophic APS cases
- Discuss new trends in research on new therapies for APS

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