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Interstitial Lung Disease for the Rheumatologist: Pearls and Insights

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Introduction

Interstitial lung disease (ILD) is a potentially life-threatening complication of systemic autoimmune rheumatic diseases (SARDs). Its prevalence varies according to the underlying SARD, being highest in anti-synthetase and anti-melanoma-differentiation-associated protein 5 (MDA5) syndromes, but affecting the greatest number of individuals in rheumatoid arthritis due to its higher overall frequency. Because ILD onset may precede, coincide with, or follow SARD diagnosis, rheumatologists may uncover an undiagnosed SARD during ILD evaluation or, conversely, detect ILD through screening of patients with established SARD. The spectrum of SARD-ILD is broad: some patients have mild, stable disease, others experience slowly progressive disease, and some deteriorate rapidly despite treatment, leading to oxygen dependence, lung transplantation, or death. Drug therapies, including immunosuppressive and anti-fibrotic agents, can slow the progression of SARD-ILD.

This article addresses three key clinical questions pertinent to rheumatologists. First, we explore clinical, serological, and morphological features that can aid in diagnosing SARD in patients with ILD, offering practical pearls. Second, we examine screening—covering who to screen, when, how, and at what frequency. Finally, we outline our approach to SARD-ILD management.

1. Reason for Consultation: ILD - Rule Out SARD

Approximately one third of ILD patients have an underlying SARD, making prompt recognition important for guiding management and follow-up.[1] Even subtle extrapulmonary clinical features may provide important diagnostic clues. The challenge is greatest when ILD presents as the first—or even sole—manifestation of SARD. Screening with autoantibody panels is helpful to detect clinically occult SARDs, but careful interpretation of the results is key to avoid misdiagnosis.

Table 1 reviews the prevalence, diagnostic clues, and prognostic risk factors in autoimmune myositis, systemic sclerosis (SSc), mixed connective tissue disease (MCTD), Sjögren disease (SjD), rheumatoid arthritis (RA), anti neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV), and interstitial pneumonia with autoimmune features (IPAF).[2-10]

Pearl #1. *Extrapulmonary features of anti-synthetase syndrome (ASyS) are frequently observed in patients with anti-Jo-1-positive antibodies, but are often absent in those with anti-PL-12 and anti-PL-7 antibodies.*

In the absence of extrapulmonary clinical features, other clues should be sought to strengthen confidence in the diagnosis. These include: a fine speckled cytoplasmic pattern on anti-nuclear antibody (ANA) immunofluorescence (AC-19 or AC-20);[11] concomitant anti-Ro52 antibodies;[12] non-specific interstitial pneumonia (NSIP) and organizing pneumonia (OP) patterns on high resolution computed tomography (HRCT); and a scleroderma-like pattern on nailfold capillaroscopy (e.g., with giant, ramified, or bushy capillaries), which may be present even in patients without Raynaud's phenomenon.[13] In the absence of any of these supporting features, a false-negative anti-synthetase antibody result should be suspected, especially if antibody titers are low.[3]

SARD	ILD Prevalence	Clinical Clues	SerologiCAL CLUES	HRCT Clues	POOR Prognostic factors
Autoimmune myositis	70–100% of anti-synthetase and -MDA5 syndromes Up to 20–25% in other myositis subtypes	• Mechanic's hands • Arthritis/arthralgia • Raynaud's phenomenon • Myositis • Dermatomyositis rash • Nailfold capillaries showing scleroderma-like pattern • Palmar papules, skin ulcerations (MDA5)	• AntiJo1, PL7, PL12, EJ, OJ, KS, Ha, Zo • Anti-MDA5 • Cytoplasmic ANA (AC19/20) • Anti-Ku • Anti-Pm/Scl • Anti-Ro52 • *Other myositis antibodies have lower ILD risks	• NSIP/OP > DAD/AIP > UIP	**Predictors of anti-MDA-5 RP-ILD:** • High anti-MDA5 titre, serum ferritin, LDH, and C-reactive protein • Male sex • Age >50 years
Systemic sclerosis	50% of diffuse SSc 30% of limited SSc	• Raynaud's phenomenon • Skin thickening • Sclerodactyly/puffy fingers • Telangiectasia • Calcinosis • Digital ulcers or pitting scars • Salt and pepper pigmentation • Nailfold capillaries showing scleroderma pattern • Esophageal reflux/dysmotility • Myositis	• Antitopoisomerase I (-Scl70) • Nucleolar ANA • Anti-U1 RNP • If scleroderma panel available: anti-RNA polymerase III, -Th/To, -fibrillarin, -Pm/Scl, -Ku, -Ro52 • If immunoprecipitation available: Anti-U11/U12 RNP (or RNPC3), -RuvBL1/2 (cytoplasmic) • *Anticentromere antibodies have lower ILD risks (< 20%)	• NSIP > UIP • Lower esophageal dilatation • Pulmonary artery enlargement	**Predictors of severe disease:** • Male sex • African descent • Diffuse cutaneous subtype • Anti-topoisomerase I antibodies • Severe GERD • Myositis/myocarditis **Predictors of progressive disease:** • HRCT extent >20% • Lower baseline FVC • Elevated C-reactive protein • Elevated serum KL-6
Mixed connective tissue disease	Up to 40%	• SSc clinical features • Raynaud's phenomenon • Myositis • Arthritis/arthralgia • Dysphagia	• Anti-U1RNP • Speckled ANA	• NSIP	**Predictors of progressive disease:** • Male sex • Elevated anti-U1RNP titres • Presence of anti-Ro52 antibodies • Absence of arthritis • Presence of digital ulcers
Sjögren disease	Up to 20%	• Xerostomia (especially with high caries burden) • Parotid swelling • Older age • Lymphopenia • Raynaud's phenomenon	• AntiSSA/SSB • Rheumatoid factor • Speckled ANA • Anti-Ro52 • Polyclonal hypergammaglobulinemia • L	• NSIP > UIP > OP, LIP	**Predictors of progressive disease:** • Older age • Male sex • Non-sicca onset • Reticular pattern on HRCT • High baseline LDH • Lower baseline FVC

SARD	ILD Prevalence	Clinical Clues	SerologiCAL CLUES	HRCT Clues	POOR Prognostic factors
Rheumatoid arthritis	Up to 20%	• Symmetrical small joint polyarthritis • Risk factors for developing ILD: ◦ High disease activity ◦ Longer RA duration ◦ Male sex ◦ Older age ◦ Cigarette smoking ◦ Obesity	• Rheumatoid factor (high titres) • AntiCCP+ (high titres)	• UIP > NSIP > OP	**Predictors of progressive disease:** • Cigarette smoking • Older age • Male sex • High HRCT ILD extent • Rheumatoid factor >200 RU/ml • High titre anti-CCP (3x) • Reduced DLCO • UIP Pattern
Anca-associated vasculitis	20–45%	• Renal, skin, neurological, and ear/nose/throat manifestations	• Anti-MPO + (or p-ANCA) > Anti-PR3 (c-ANCA)	• UIP > NSIP	**Mortality risk factors:** • Older age • UIP pattern • Microscopic polyangiitis • Cigarette smoking
IPAF	100%	• Distal digital fissuring (i.e., "mechanic's hands") • Distal digital tip ulceration • Inflammatory arthritis or polyarticular morning joint stiffness ≥60 min • Palmar telangiectasia • Raynaud's phenomenon • Unexplained digital oedema • Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	• ANA ≥1:320 titre, diffuse, speckled, homogeneous patterns *or* ◦ ANA nucleolar pattern (any titre) or ◦ ANA centromere pattern (any titre) • Rheumatoid factor ≥2× upper limit of normal • Anti-CCP • Anti-dsDNA • Anti-SSA/SSB • Anti-ribonucleoprotein • Anti-Smith • Antitopoisomerase I (-Scl70) • Anti-PM-Scl • Anti-tRNA synthetase (e.g., Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS) • Anti-MDA5	• NSIP and/or OP, LIP • (may be UIP if meet criteria for clinical and serological domains) • Pleural or pericardial effusion/ thickening • Airways disease • Pulmonary vasculopathy	**Predictors of progressive ILD:** • Male • UIP pattern on HRCT

Table 1. Prevalence, diagnostic clues, and prognostic risk factors of SARD-ILDs; *courtesy of Laurence Poirier-Blanchette, MD, FRCPC, Océane Landon-Cardinal, MD, FRCPC, and Sabrina Hoa, MD, MSc, FRCPC*.

Abbreviations: AIP: acute interstitial pneumonia; **ANA:** anti-nuclear antibody; **Anti-CCP:** anti-cyclic citrullinated peptide; **DAD:** diffuse alveolar damage; **DLCO:** diffusing capacity of the lungs for carbon monoxide; **FVC:** forced vital capacity; **KL-6:** Krebs Von Den Lungen 6; **GERD:** gastroesophageal reflux disease; **HRCT:** high resolution computed tomography; **ILD:** interstitial lung disease; **IPAF:** interstitial pneumonia with autoimmune features; **LDH:** lactate dehydrogenase; **LIP:** lymphocytic interstitial pneumonia; **MDA5:** melanoma-differentiation-associated protein 5; **NSIP:** non-specific interstitial pneumonia; **OP:** organizing pneumonia; **RA:** rheumatoid arthritis; **RP-ILD:** rapidly progressive ILD; **SARD:** systemic autoimmune rheumatic disease; **SSc:** systemic sclerosis; **UIP:** usual interstitial pneumonia.

Pearl #2. *Anti-OJ antibodies have very low sensitivity on line immunoassay and should be suspected when typical ASyS clinical features or a cytoplasmic ANA pattern are present despite a negative myositis panel.*

Line immunoassays have been reported to have 0% sensitivity for detecting anti-OJ antibodies compared to protein immunoprecipitation. This discrepancy is likely explained by the fact that anti-OJ antibodies target conformational and quaternary epitopes within a multi-protein complex, whereas blotting assays rely on denatured antigens that lack these structures. Notably, other rare or newly described anti-synthetase antibodies are not included in commercially available myositis panels. Hence, if ASyS is clinically suspected, further testing with immunoprecipitation may be warranted to confirm the diagnosis and inform management.[14]

Pearl #3. *The presence of palmar papules, skin ulcerations, pneumomediastinum, and marked hyperferritinemia should heighten suspicion for anti-MDA5 syndrome even before serological confirmation.*

As anti-MDA5 syndrome is associated with rapidly progressive ILD, early recognition is key to ensure rapid treatment initiation. This syndrome typically presents with little or no muscle involvement, and can have overlapping features with ASyS, including rapidly progressive NSIP/OP, mechanic's hands, arthritis, Raynaud's phenomenon, fever, profound weight loss, cytoplasmic ANA, and a scleroderma-like pattern. Conversely, painful palmar papules, skin ulcerations, pneumomediastinum, and marked hyperferritinemia are more characteristic and specific to anti-MDA5 syndrome, and are thought to reflect underlying vasculopathy and massive alveolar macrophage activation.[15]

Pearl #4. *The presence of SSc-specific anti-Th/To antibodies should be suspected in patients with ILD and high-titer nucleolar ANA, even in the absence of cutaneous findings and a negative scleroderma panel.*

SSc-specific anti-Th/To antibodies are associated with an increased risk of ILD, but often present with no or very subtle skin thickening, which means that many patients do not meet classification criteria for SSc.[16] Commercially available scleroderma panels (line immunoassays) have limited sensitivity for detecting anti-Th/To antibodies, as they do not include the antigen's most frequently targeted subunit.[17] Despite these limitations, other diagnostic clues include a nucleolar ANA pattern (AC-8), a scleroderma pattern on nailfold capillaroscopy (e.g., giant capillaries, hemorrhages, avascular areas, and neoangiogenesis), and findings such as distal esophageal dilatation and pulmonary hypertension on HRCT. As a general rule of thumb, pulmonary hypertension should be suspected when the main pulmonary artery diameter exceeds that of the adjacent aorta.[18]

Pearl #5. *Lymphoid interstitial pneumonia (LIP) is a less common, but more specific, HRCT pattern observed in SjD-ILD.*

Although SjD-ILD is most commonly associated with NSIP and usual interstitial pneumonia (UIP), the presence of LIP, characterized by hallmark pulmonary cysts, should increase suspicion for an underlying SjD diagnosis. Referral to ophthalmology and oral medicine specialists can help identify objective signs of sicca, even in the absence of overt symptoms. In addition to classical anti-SSA and -SSB antibodies, the presence of positive ANA, rheumatoid factor, polyclonal hypergammaglobulinemia, or hypocomplementemia can also support the diagnosis. Challenges arise when ILD is the sole clinically apparent manifestation, or in seronegative SjD lacking classical autoantibodies. In these situations, biopsy of the minor salivary glands may help confirm the diagnosis and should be considered if it would alter management.[19]

Pearl #6. *RA-ILD can develop prior to the onset of joint symptoms in 10–20% of cases.*

Hence, in ILD patients with high titers of rheumatoid factor and/or anti-CCP antibodies, close monitoring for the subsequent development of arthritis is important.[20] Furthermore, in patients

with arthralgias, joint ultrasound and hand X-rays may be useful to detect subclinical synovitis or erosions, which can sometimes occur despite the absence of significant pain, as seen in *arthritis robustus*, typically observed in men.

Pearl #7. *ANCA-positive ILD may precede the development of AAV in up to 25% of cases.*

ILD affects up to 51% of patients with anti-MPO-positive AAV and 23% of those with anti-PR3-positive AAV, with UIP being the most commonly observed HRCT pattern. Two related entities are described: AAV-ILD (meeting AAV classification criteria) and isolated ANCA-ILD (without systemic features). ANCA-positive ILD may precede the development of AAV in up to 25% of cases, with a mean interval of approximately 2 years between ILD and AAV diagnoses. Hence, the *2020 International Consensus on ANCA Testing beyond Systemic Vasculitis* recommends systematic ANCA screening for all ILD patients, along with longitudinal surveillance for renal, skin, neurological, ear-nose-throat, and other systemic signs of AAV.[21-23]

Pearl #8. *Patients with ILD and autoimmune features who do not meet SARD classification criteria should be considered for IPAF classification.*

Defined by the 2015 ERS/ATS statement on IPAF, this research framework classifies ILD patients as having autoimmune features when they fulfill criteria from at least two out of three domains: clinical, serological, or morphological.[24] Some of these patients later develop a defined SARD, and many respond to immunosuppressive therapy similarly to those with established autoimmune disease, especially among patients with inflammatory ILD phenotypes.

2. Defining the Who, When, How, and Frequency of ILD screening in SARD

Because ILD may be asymptomatic in SARDs, screening is essential for early detection and management. Systematic HRCT and pulmonary function test (PFT) screening at diagnosis is recommended for patients with high-risk conditions such as ASyS and anti-MDA5 syndrome, SSc, and MCTD with SSc features. For RA and SjD, baseline screening should be performed in those with risk factors, while in AAV, it is advised for patients with respiratory symptoms, abnormal PFTs, or chest X-ray findings.[25–27]

If baseline screening is negative, continued surveillance is warranted given that ILD may develop later in the disease course.[2,28] Surveillance primarily relies on symptoms and physical examination, and PFTs can be repeated annually or more frequently according to the risk profile, although their sensitivity and specificity is limited.[25,26] Emerging tools such as serum KL-6 and lung ultrasonography are being investigated as sensitive, radiation-free alternatives to HRCT for screening purposes.[29]

For patients with confirmed SARD-ILD, disease is monitored using PFTs, ambulatory desaturation testing, and HRCT as indicated. PFTs are typically repeated every 3 to 12 months, with the frequency tailored according to disease duration, severity, and the presence of risk factors for progression (**Table 1**).[2,3,5-10,15]

3. Management of SARD-ILD

Recent guidelines for the treatment of SARD-ILDs have been published by several professional societies and can be consulted for detailed recommendations.[3,26,30,31] Drug interventions are generally recommended in the presence of symptomatic, moderate to severe, or progressive ILD. Glucocorticoids (GC) are often used as first-line induction agents, particularly in inflammatory (NSIP/OP) or rapidly progressive ILD phenotypes, except in SSc where GCs should be used with caution due to the risk of scleroderma renal crisis. Immunosuppressants should be started early to allow prompt GC tapering and minimize toxicity.

Table 2 outlines our approach to the management of SARD-ILD. Mycophenolate mofetil (MMF) is generally preferred as first-line therapy, supported by evidence from the Scleroderma Lung Study II, which demonstrated similar efficacy but superior safety compared to cyclophosphamide in SSc-ILD.[32] Azathioprine (for mild ILD) or calcineurin inhibitors (CNIs) are suitable alternatives during pregnancy or breastfeeding. CNIs are also often considered in myositis-ILD, as this drug class is also effective for muscle and skin involvement. In anti-synthetase syndrome and anti-MDA5

Disease	First-line Treatment	Second-line Treatment if Progression	Non-pharmaceutical
Anti-synthetase Syndrome	**GC + one of:** MMF or AZA or CNI or RTX **If rapidly progressive: IV GC + 1 or 2 of:** MMF, CNI, JAKi, RTX, or CYC ± IVIg	**Add/switch:** MMF, CNI, JAKi, RTX, CYC and/or IVIg	• Multidisciplinary assessment • Smoking cessation • Pulmonary rehabilitation • Avoid long-term GC • Immunization • GERD Control • Referral for lung transplant when indicated • Referral to tertiary care ILD center when indicated
Anti-MDA5 Syndrome	**GC + one of:** MMF or CNI or JAKi **If rapidly progressive:** IV GC + 1 or 2 of: MMF, CNI, JAKi, RTX, or CYC ± IVIg	**Add/switch:** MMF, CNI, JAKi, RTX, CYC and/or IVIg Consider rescue therapies: basiliximab, plasma exchange, ECMO, or polymyxin-B hemoperfusion	
Systemic Sclerosis	MMF **If contraindication:** AZA	**Add/switch:** RTX, TCZ, NIN, PIR, CYC and/or IVIg Consider AHSCT referral Consider short-term GC at the lowest effective dose if severe disease (use with caution; monitor for renal crisis)	
Mixed Connective Tissue Disease	GC + MMF **If contraindication:** AZA or CNI Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** RTX, TCZ, NIN, CYC and/or IVIg	
Sjögren Disease	MMF **If contraindication:** AZA or CNI Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** RTX, NIN, CYC and/or IVIg	
Rheumatoid Arthritis	**If active joint disease despite csDMARD:** TCZ or RTX **If no active joint disease:** MMF or AZA Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**If active joint disease, add/switch:** TCZ, RTX, JAKi, *or* ABA **If no active joint disease, add/switch:** MMF, NIN, PIR, RTX, or CYC	
Anca-associated Vasculitis	RTX or AZA or MMF Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** RTX, MMF, CYC and/or NIN	
IPAF	MMF **If contraindication:** AZA Consider GC if NSIP/OP with symptomatic or moderate-severe disease	**Add/switch:** CNI, RTX, CYC, NIN and/or IVIg	

Table 2. Our approach to the management of interstitial lung disease in systemic autoimmune rheumatic diseases; *courtesy of Laurence Poirier-Blanchette, MD, FRCPC, Océane Landon-Cardinal, MD, FRCPC, and Sabrina Hoa, MD, MSc, FRCPC.*

Abbreviations: ABA: abatacept; **AHSCT:** autologous hematopoietic stem cell transplant; **AZA:** azathioprine; **CNI:** calcineurin inhibitors; **csDMARD:** conventional systemic disease-modifying anti-rheumatic drugs; **CYC:** cyclophosphamide; **ECMO:** extracorporeal membrane oxygenation; **GC:** glucocorticoids; **GERD:** gastroesophageal reflux disease; **IPAF:** interstitial pneumonia with autoimmune features; **IV:** intravenous; **IVIg:** intravenous immunoglobulins; **JAKi:** Janus kinase inhibitor; **MMF:** mycophenolate; **NIN:** nintedanib; **NSIP:** non-specific interstitial pneumonia; OP: organizing pneumonia; PIR: pirfenidone; **RTX:** rituximab; **TCZ:** tocilizumab.

syndrome with rapidly progressive ILD, early combination therapy is recommended and may include MMF, CNIs, Janus kinase inhibitors (JAKis), rituximab, cyclophosphamide, and/or intravenous immunoglobulin.[33,34]

As second-line treatment in cases of ILD progression, adding or switching to other immunosuppressive drugs is preferred when inflammatory phenotypes (NSIP/OP) ILD are present, or if there are active extrapulmonary SARD manifestations such as myositis, arthritis, inflammatory skin disease, or vasculitis. Among these immunosuppressant agents, rituximab (anti-CD20 monoclonal antibody) was shown to be as effective but safer than cyclophosphamide in the RECITAL trial, which included patients with SSc-, MCTD-, and myositis-ILD.[35] The EVER-ILD trial also showed that combining rituximab with MMF was more beneficial than MMF alone for NSIP.[36] Tocilizumab (anti-IL-6-receptor) was effective in preserving lung function as a secondary outcome in two SSc-ILD trials.[37,38] Cyclophosphamide is generally reserved for severe or refractory disease due to its toxicity.[32,35]

For patients with evidence of progression despite immunosuppressive therapy, particularly those with a fibrotic (UIP) phenotype, antifibrotic agents such as nintedanib or pirfenidone can be added. The SENSCIS and INBUILD trials demonstrated that nintedanib slows forced vital capacity decline in SSc-ILD and progressive pulmonary fibrosis (including SARD-ILDs), respectively.[39,40] Notably, combining nintedanib with MMF produced additive effects on lung function decline, suggesting that targeting both the immune and fibrotic pathways is central to ILD management.[39]

In RA-ILD, methotrexate is considered safe to continue, as large observational studies and meta-analyses have not demonstrated an increased risk of ILD development or progression.[41] However, as rare hypersensitivity pneumonitis may occur, we generally avoid initiating methotrexate in patients with advanced ILD, in whom a drug-induced reaction could have major consequences on lung function.

Finally, some experts advocate for treating subclinical SSc-ILD, particularly when risk factors for progression are present. However, this approach remains heterogeneous and not yet widely adopted; it is currently being evaluated in an ongoing randomized trial in Canada (NCT05785065).[42]

Conclusion

Overall, rheumatologists play a central role in the diagnosis and management of SARD-ILD. Early identification of SARD, appropriate screening for ILD alongside assessment of other target organ involvement, and tailored treatment are key to preserving lung function and quality of life. Future studies should focus on refining screening algorithms, integrating novel biomarkers and imaging modalities into clinical practice, and establishing evidence-based therapeutic approaches through randomized controlled trials, all with the ultimate goal of improving patients' outcomes.

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Latest Developments in Imaging for Axial Disease in Psoriatic Arthritis

Walter P. Maksymowych, MB, ChB, MRCP (UK), FACP, FRCPC

Introduction

Axial disease in psoriatic arthritis (axPsA), affecting the sacroiliac joints (SIJ) and spine, is recognized as one of the domains in the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) treatment recommendations for psoriatic arthritis (PsA).[1] Accurate recognition of this manifestation is crucial for comprehensive management of this disease. It is defined according to both clinical and imaging features. Clinically, inflammatory back pain (IBP) is a key feature; however, findings from a recent Canadian inception cohort study—Screening for Axial Spondyloarthritis in Psoriasis, Iritis, or Colitis Cohorts 1 and 2 (SASPIC1 and 2)—which included patients with psoriasis and undiagnosed back pain, showed no differences in the frequency of IBP or non-steroidal anti-inflammatory drug (NSAID) responsiveness between those diagnosed with axPsA and individuals with other causes of chronic back pain.[2] Similarly, data from the global Axial Involvement in Psoriatic Arthritis (AXIS) cohort revealed only minor numerical differences in NSAID responsiveness or frequency of IBP, according to the ASAS criteria, between participants with and without axial involvement when evaluated by central reviewers.[3] Recent post-hoc studies of clinical trials in PsA have attempted to identify axPsA according to a Bath Ankylosing Spondylitis Disease Activity Index

(BASDAI) threshold of ≥4. However, MRI-based assessment of axPsA in a large European cohort of 581 PsA patients, recruited across 17 European registries within the EuroSpA network, indicated that a BASDAI ≥4 did not discriminate PsA patients with axial disease from those without.[4] Moreover, only 25–45% of patients with radiographic features of axPsA have been reported to have IBP, with some patients being clinically perceived as asymptomatic. Additionally, axSpA-based IBP criteria have demonstrated limited specificity for axPsA.[5,6] Studies using MRI have reported poor correlation between sacroiliitis on imaging and both the presence and type of back pain.[7,8]

Several radiographic features have been described that distinguish axPsA from axSpA based on cross-sectional studies that did not control for age, gender, or symptom duration, all of which may affect the radiographic appearance of the SIJ and spine. These features include less severe SIJ and spinal involvement compared to axSpA, reduced symmetry of sacroiliitis, asymmetry of spondylitis, and more frequent involvement of the cervical spine.[9] Data from the EuroSpA consortium indicated that radiographic sacroiliitis, as defined by the modified New York criteria (mNYc), was present in 29% of patients, which is comparable to the recent findings from the Canadian SASPIC cohorts.[2] Earlier studies had reported radiographic sacroiliitis per mNYc in 37% of Canadian patients with PsA,[10] 24% of British PsA patients,[11] and 29% of German PsA patients.[12] Additional reports included unilateral grade 2 sacroiliitis; using this lower threshold, a Canadian study reported axial involvement in 45% of PsA patients, while a German study reported a radiographic axPsA prevalence of 38%.[12,13] However, the SASPIC data did not demonstrate a significant difference in unilateral sacroiliitis between patients diagnosed with axPsA and those with PsA presenting with other causes of back pain. Moreover, the reliability of detecting low-grade radiographic sacroiliitis is poor, even among experienced musculoskeletal radiologists, making it a suboptimal criterion for defining axPsA.

Earlier studies have reported spondylitis in the absence of sacroiliitis in approximately 15% of cases. Bulky syndesmophytes, non-marginal syndesmophytes, and paravertebral bridging bone are often considered to be characteristic of axPsA compared to axSpA, although comparative data matched for age, gender, and symptom duration remain limited. Notably, the morphology of new bone formation in the spine has raised concerns that some cases designated as axPsA are in fact diffuse idiopathic skeletal hyperostosis (DISH). A Belgian study recently compared radiographic findings of the spine and SIJ in 525 patients (312 with PsA and 213 with SpA). Findings showed that patients with axSpA exhibited more severe spinal disease as indicated by higher modified Stoke Ankylosing Spondylitis (mSASSS) scores. In axPsA, syndesmophytes were more frequently observed in the cervical spine than in the lumbar segment.[14]

MRI is the cornerstone for diagnosis and disease classification in axial spondyloarthritis; however, few studies have systematically compared SIJ and spine findings between axSpA and PsA, especially in cohorts matched for symptom duration, age, and gender; factors which may influence MRI interpretation of the SIJ and spine. In a cross-sectional study of 125 cases from the Toronto cohort with IBP, only 44.6% demonstrated findings on MRI consistent with axSpA.[8] Another cross-sectional observational study from Brazil reported bone marrow edema (BME), enthesitis, erosions, and fat metaplasia on MRI in 37.8% of 45 cases diagnosed with PsA, most of whom were asymptomatic.[15] An Israeli cross-sectional study of 107 patients with PsA reported active sacroiliitis on MRI in 26%, with non-radiographic sacroiliitis evident in 11%.[16] In contrast, a retrospective Canadian cohort of 93 patients with PsA, 65 without axial symptoms and 28 with psoriasis with back pain, showed a lower prevalence of only 13%.[17] None of these studies reported detailed assessments of the type and distribution of MRI lesions.

The MAXIMISE study, a placebo-controlled trial of secukinumab in axPsA, published a secondary analysis in which the axial MRI scans were re-read to include inflammation of the posterior elements and degenerative changes, although no axSpA control group was included.[18] Patients were enrolled based on clinically diagnosed active axial disease (spinal pain ≥40/100 on the visual analogue scale and a BASDAI score ≥4/10). Approximately 60% of the patients had a Berlin BME score ≥1 for the spine and/or the SIJ, but it is unclear what proportion represented BME typical of axial inflammation as opposed to mechanical stress. This study reported inflammation of the spinous processes in 11.1% of axPsA cases (7.2% in the lumbar spine, 5.4% in the thoracic spine, and 2.1% in the cervical spine). In addition, imaging findings compatible with degenerative disease were observed in 64% of

patients, with 21.2% showing only degenerative findings on MRI. For structural lesions, assessment was limited to fat lesions in the spine.

A report from the EuroSpA consortium, which included 17 European registries and 581 patients with PsA, combined both radiographic and MRI evaluation of the SIJ in the routine evaluation of axPsA.[4] Among these, 208 cases (35.8%) had axSpA with psoriasis but without peripheral PsA. Experienced central readers judged the combined evaluation of pelvic radiographs and MRI as compatible with axPsA in 31%. This proportion was somewhat higher than the 23.2% imaging-positive rate for axPsA reported by central readers in the AXIS study[3] and the 17.6% observed in the SASPIC-2 Canadian cohort,[2] where all patients underwent MRI evaluation of the SIJ. These differences are likely due to the differences in study design: AXIS and SASPIC were inception cohorts, AXIS enrolled patients with PsA of <10 years duration and SASPIC included patients with psoriasis and chronic undiagnosed back pain, whereas the EuroSpA study was a convenience sample of PsA cases, nearly one third of whom had axSpA with psoriasis. The Berlin cohort, which had a similar study design as SASPIC-2, reported axPsA in 14% of patients. Among these, only eight had IBP, four showed radiographic sacroiliitis, and five had unilateral sacroiliitis grade ≥2. All cases demonstrated active inflammatory and/or structural (post)inflammatory changes in the SIJ and/or spine on MRI, and five only exhibited axial involvement of the spine.[12]

To date, only the EuroSpA consortium has reported a detailed assessment of the type and distribution of MRI lesions according to central reader evaluations using standardized definitions. Inflammatory lesions typical of axSpA were observed in 21% of patients, while BME overall was present in 44%, indicating that non-specific BME related to other causes, such as mechanical stress, was a common finding. Additional active lesions included inflammation within erosion cavities (8%), enthesitis (5.5%), capsulitis (4%), and joint space fluid (7%) in patients with axPsA. Structural SIJ MRI lesions indicative of SpA were observed in 28% of patients, with erosions (27%) and fat lesions (26%) being the most common. A notable observation that was also reported in the 2009 ASAS classification study of an inception cohort of cases with undiagnosed chronic back pain was the frequent co-occurrence of both inflammatory and structural lesions. Certain types of lesions, such as BME extending ≥1 cm from the subchondral bone, inflammation within an erosion cavity, capsulitis, fat metaplasia in an erosion cavity (backfill), and ankylosis were found almost exclusively in patients with axPsA. MRI findings indicative of SpA, including nearly all types of inflammatory and structural lesions except sclerosis, were more evident in males and HLA-B27 positive patients. Degenerative SIJ changes were observed in 16% of cases and represented the most common differential diagnosis, along with osteitis condensans ilii and mechanical stress-related BME. Multivariable analysis demonstrated that male gender, history of IBP, elevated CRP, and HLA-B27 positivity were independently associated with axPsA. Clinical and radiographic definitions of axial involvement in PsA overlapped only partially with MRI-based definitions, emphasizing the complementary role of clinical and imaging assessments.

Despite imaging data on axPsA remaining quite limited, several themes have emerged in recent years. First, clinical features alone, such as IBP, are not particularly helpful in identifying axial disease in patients with PsA, and only 30–40% of patients with axial disease are positive for HLA-B27. Second, radiography of the SIJ and spine is both insensitive and unreliable, with interpretation often confounded by age- and gender-associated changes, particularly given that axPsA develops later in life than axSpA. Third, MRI of the SIJ and spine is more sensitive than radiography, but interpretation may also be confounded by age, gender, and mechanical stress related to obesity. In particular, focal BME in the antero-inferior region of the SIJ is frequently observed in physically active and/or obese individuals, post-partum women within the first year after delivery, and in disorders such as DISH.

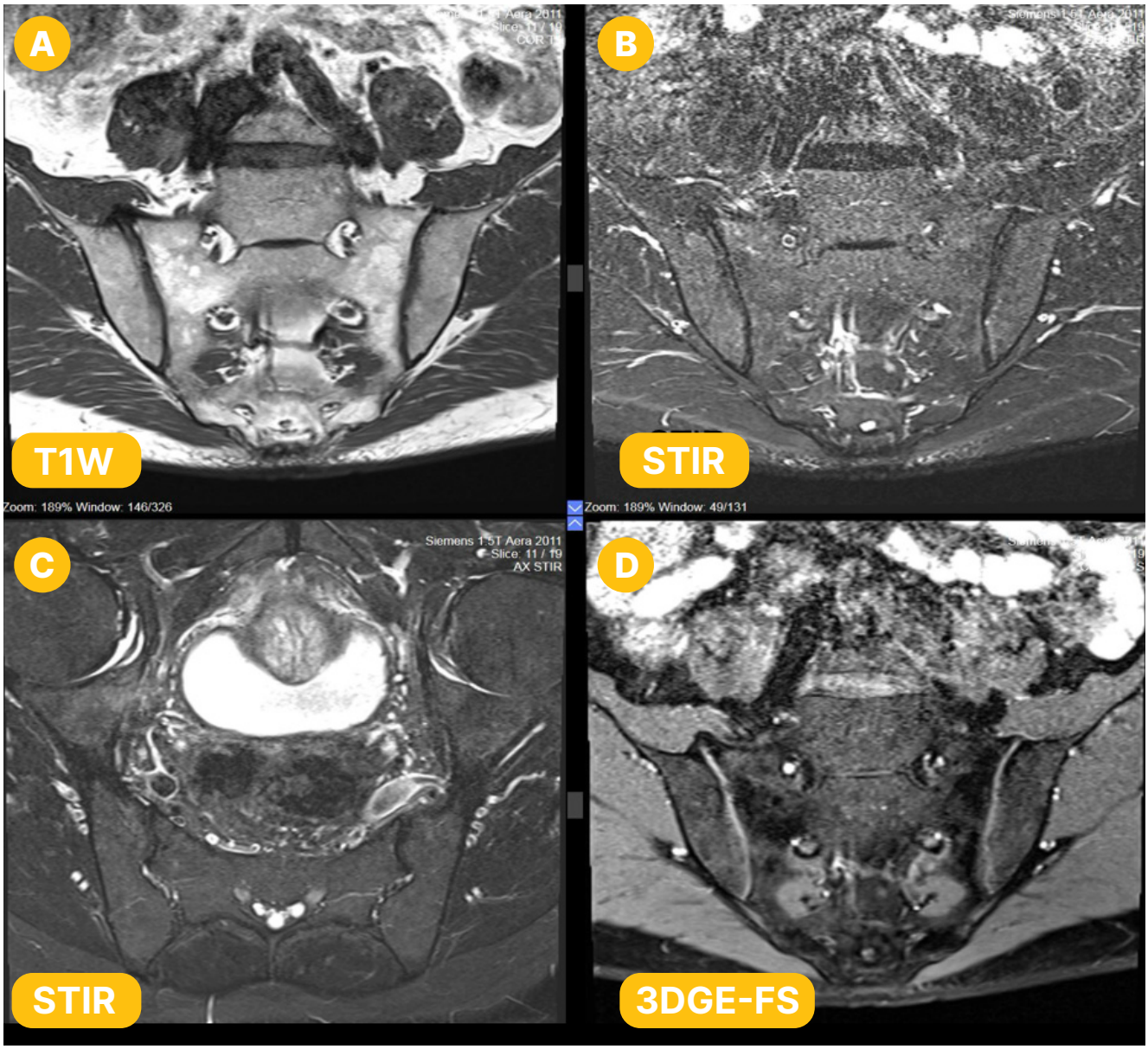

Figure 1. ASAS-SPARTAN standardised image acquisition protocol for diagnostic evaluation of the sacroiliac joints (SIJ).[19] **A)** Semicoronal T1-weighted fat-sensitive sequence. **B)** Short-tau Inversion Recovery (STIR) fluid-sensitive semicoronal sequence. **C)** STIR semiaxial sequence. **D)** Erosion sensitive thin slice sequence e.g. 3D-gradient echo; *courtesy of Walter P. Maksymowych, MB, ChB, MRCP (UK), FACP, FRCPC.*

Conclusion

Recent ASAS-SPARTAN recommendations call for the assessment of BME in both semicoronal and axial orientations using fluid-sensitive sequences that permit precise localization of the region with BME (**Figure 1**).[19] The presence of erosion or fat metaplasia enhances diagnostic specificity, and new MRI sequences are increasingly being implemented into routine evaluation of the SIJ. These thin slice, high-resolution sequences enhance the delineation of subchondral bone relative to the overlying cartilage or joint space, thereby offering superior performance compared to conventional T1-weighted sequences for detecting erosions[20] (**Figure 2**). Moreover, advanced sequences such as zero echo time (ZTE) and processing of data from 3D-gradient echo sequences can generate CT-like images, enhancing detection of both

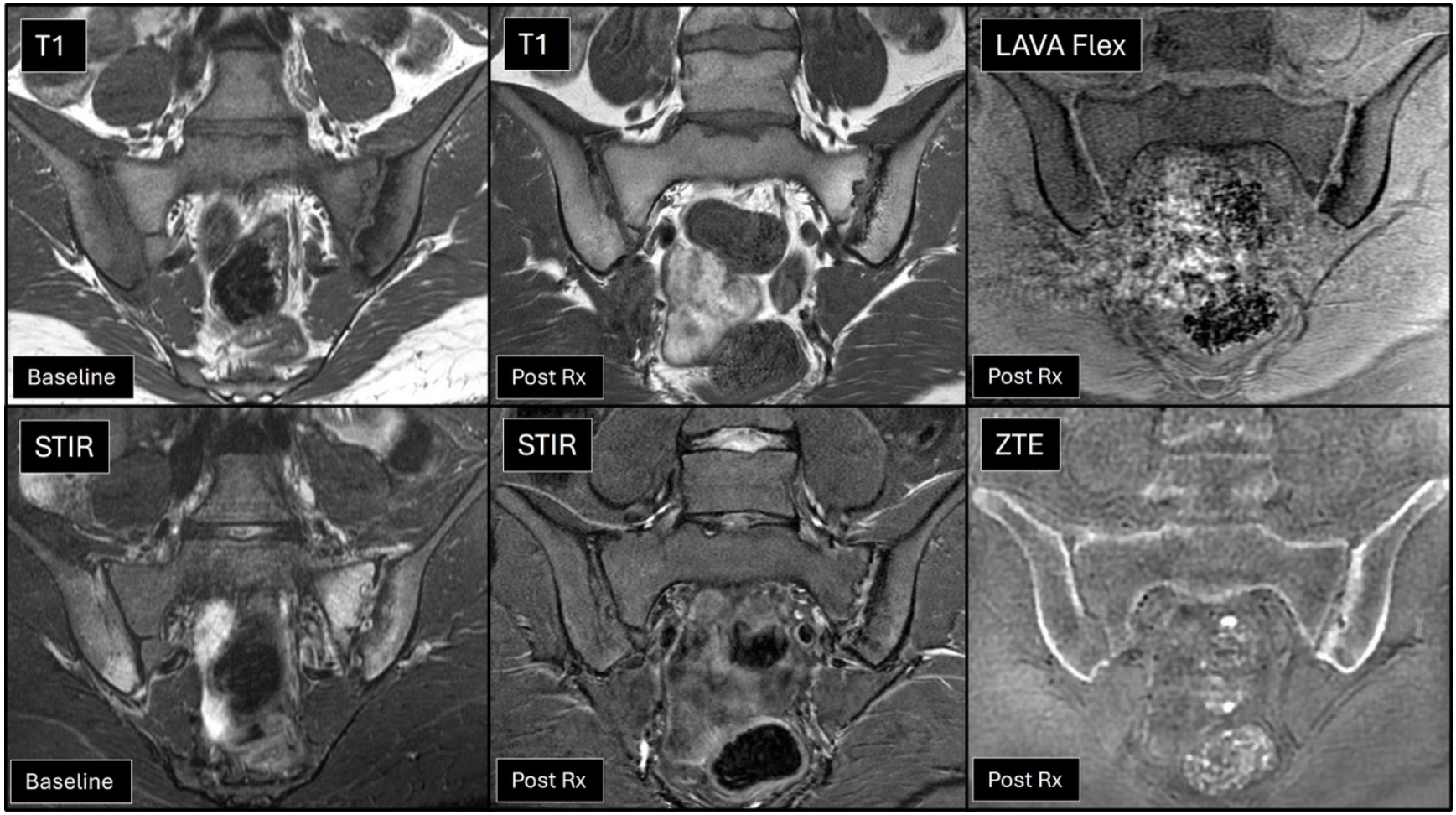

Figure 2. Sacroiliac joint (SIJ) MRI T1W, Short-tau Inversion Recovery (STIR) and 3D high-resolution scans.[20] STIR images confirm the presence of sacroiliitis with improvement in bone marrow edema after biologic therapy. At baseline, erosion is seen in the left iliac cortex that is less evident post-treatment on the T1W scan but more clearly evident on the high-resolution LAVA (liver acceleration volume acquisition) Flex and zero echo time (ZTE) sequences. (Rx: therapy); *courtesy of Walter P. Maksymowych, MB, ChB, MRCP (UK), FACP, FRCPC*.

erosions and new bone formation in the SIJ and spine (**Figure 2**). Increasingly, MRI assessment of the SIJ and spine for both inflammatory and structural lesions should be considered the standard of care in PsA patients with chronic undiagnosed back pain, particularly if the patient is sufficiently symptomatic to warrant consideration of disease-modifying antirheumatic drugs effective for axial disease.

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Management of Adult Patients with Lupus Nephritis: Therapeutic Algorithm Based on the Current Treatment Guidelines

Konstantinos Tselios, MD, PhD

Introduction

Lupus nephritis (LN) is one of the most significant manifestations of systemic lupus erythematosus (SLE) affecting approximately 35–40% of patients in large cohort studies.[1] It is usually diagnosed in the early phases of the disease; among those with LN, approximately 80% are diagnosed at or shortly after disease onset. LN is characterized by histological and clinical heterogeneity and substantially affects survival. A meta-analysis of 18,309 LN patients reported a 10-year risk for the development of end-stage kidney disease (ESKD) of nearly 17% overall and 33% among those with LN class IV (diffuse proliferative form).[2] Early detection and timely management are essential for optimizing outcomes. Given that LN patients are often asymptomatic, it is recommended that all lupus patients, particularly early in the disease course, undergo routine screening every 3–6 months.[3] This includes assessment of proteinuria with urinary protein- or albumin-to-creatinine ratio (and 24 hour urine protein if indicated), urinary sediment and serum creatinine, regardless of disease activity.[3] If abnormal findings that cannot be explained by alternative causes are detected (proteinuria ≥500 mg/day, active urinary sediment with acanthocytes ≥5% or red blood cell casts or white blood cell casts, increased serum creatinine) a renal biopsy should be performed, as it remains the gold standard for confirming the diagnosis, management planning, and informing the prognosis.

Herein, we present a step-by step approach to the current management of adult LN as recommended by the 2024 American College of Rheumatology (ACR),[4] the 2025 updated European Alliance of Associations for Rheumatology (EULAR),[5,6] as well as the 2024 KDIGO (Kidney

Disease: Improving Global Outcomes)[7] guidelines. New treatment options that will be available in the near future are also discussed briefly.

Should emphasize that the focus is on adult LN approach. The ACR guidelines also discuss children, so I think it should be acknowledged that the focus here is for adults.

If the author is not going to talk about the KDIGO guidelines (which are more recent than the EULAR guidelines), they should be at least acknowledged early on and perhaps just mention some of the differences between ACR/KDIGO as readers it's been a point of debate and discussion at multiple lupus meetings.

Induction Therapy for LN Class III and IV (With or Without V)

Management of LN should begin promptly (even in anticipation of the kidney biopsy if there is no alternative explanation) and based on aggressive immunomodulatory therapy with glucocorticoids and immunosuppressives as well as adjuvant therapies. All guideline sets (2024 ACR, 2025 EULAR, 2024 KDIGO) recommend the use of antimalarials, mainly hydroxychloroquine, in all patients with LN unless contraindicated.[4-7] Hydroxychloroquine has recently been characterized as a disease-modifying drug due to its ability to prevent disease flares, decrease the risk for thrombosis, delay damage accrual, and improve survival.[8]

The use of intravenous methylprednisolone pulses as an initial approach is also recommended by all guideline sets.[4-7] The goal is to achieve rapid suppression of the autoimmune inflammation at the tissue level and allow for the subsequent transition to lower doses of oral prednisone. Dosing strategies are not standardized and depend on the severity of the disease as well as extra-renal manifestations. Most commonly, intravenous methylprednisolone is administered in pulses of 250–1000 mg daily for up to three consecutive days.

Oral glucocorticoids should be administered following the initial intravenous methylprednisolone pulses. In randomized controlled trials (RCTs), oral glucocorticoids have historically been used in various doses (up to 1 mg/kg body weight [BW] or 80 mg/day of prednisone equivalent). However, a recent pooled analysis of nine RCTs showed that low prednisone doses (up to 0.5 mg/kg BW) are equally effective as higher doses (up to 1 mg/kg BW) in achieving overall renal response (defined as combined complete and partial renal responses at 12 months).[9] Moreover, patients who had received lower prednisone doses experienced significantly fewer serious adverse events and serious infections. Consequently, both the 2024 ACR and 2025 EULAR guidelines recommend an initial prednisone dose of ≤0.5 mg/kg BW (maximum daily dose of 40 mg/day) with a tapering schedule targeting ≤5 mg/day at 6 months (ACR) or ≤7.5 mg/day at 3–6 months (EULAR).[4-6] The 2024 KDIGO guidelines suggest 3 different schemes for oral glucocorticoids according to initial disease severity (high-dose scheme with a maximum starting dose of 80 mg/day, a moderate-dose scheme starting at 50 mg/day and a reduced-dose scheme starting at 40 mg/day).[7] Accordingly, the goal is to reduce the daily prednisone dose to ≤5 mg by week 24 from treatment initiation (2.5 mg/day for the reduced-dose scheme). In general, all guideline sets agree that cumulative glucocorticoid exposure should be minimized and a daily prednisone dose of 5 mg at 6 months should be considered as a treatment goal.[4-7]

Immunosuppressive therapy is considered the cornerstone of LN management and should be initiated concomitantly with glucocorticoids. All guidelines strongly recommend the use of mycophenolic acid (MPA), its prodrug mycophenolate mofetil (MMF), or cyclophosphamide (CYC), which are considered equivalent regarding efficacy based on findings from several randomized controlled trials.[10] A recent meta-analysis of 1,989 LN patients demonstrated that MPA/MMF may offer a slight advantage in overall efficacy and substantially less ovarian toxicity compared to CYC.[11] The favourable safety profile of MPA/MMF renders them more appropriate for use in daily practice, particularly given the demographic characteristics of the majority of LN patients (young women). Reflecting this, the ACR conditionally recommends MPA over CYC.[4] The target dose for MPA is 1.44–2.16 g/day (equivalent to 2–3 g/day for MMF). In contrast, CYC is administered in intermittent pulses (preferably 500 mg every 2 weeks for six pulses, Euro-Lupus protocol, or 0.5–0.75 g/m^2 monthly for 6 months in the presence of adverse clinical or histologic features, NIH protocol). In general, lower CYC doses (Euro-Lupus protocol) are preferred (and recommended by the ACR)[4] to prevent long-term side effects such as infertility and malignancies. CYC may be more appropriate in patients who have difficulty adhering or being

intolerant to MPA/MMF or in cases of rapidly progressing glomerulonephritis (2024 ACR).[4]

The combination of glucocorticoids with either MPA/MMF or CYC is considered the minimum standard of care (SoC) for LN. However, given that complete renal remission (CRR) with these regimens is achieved in less than one-third of patients,[12] all recent guidelines recommend triple therapy with the addition of calcineurin inhibitors (CNIs) or B-cell targeted therapies (belimumab, obinutuzumab) as part of the SoC.[4-7]

CNIs have been extensively used in the management of other immune-mediated nephropathies and for preventing transplant rejection. In LN, tacrolimus (TAC) in combination with MMF (in doses of 1 g/day) demonstrated superior efficacy over CYC in Chinese LN patients, particularly those with class IV and V LN, achieving a complete renal response rate of 45.9% versus 25.6%, respectively, at 24 weeks.[13] This approach, termed multi-targeted therapy, emphasized the multiple pathogenetic pathways that participate in LN pathogenesis. In the AURORA-1 trial, voclosporin (plus SoC) performed substantially better versus SoC alone, achieving a complete renal response rate of 41% versus 23% at 52 weeks.[14] Voclosporin is a cyclosporine analog with enhanced metabolic stability and favorable safety profile. Notably, approximately 90% of patients experienced a 50% reduction of their baseline proteinuria within 7–8 months. Concerns about long-term nephrotoxicity were not verified in the AURORA 2 trial, which showed no reduction in estimated Glomerular Filtration Rate (eGFR) after 30 months of voclosporin treatment.[15] CNIs are recommended in combination with MPA/MMF primarily for patients with relatively preserved kidney function and nephrotic range proteinuria (>3 g/24 hours), likely due to extensive podocyte injury, as well as patients who cannot tolerate standard-dose MPA/MMF or are unfit for or will not use CYC-based regimens.[4,7] The maximum dose for TAC is 4 mg/day (divided in two doses), while voclosporin is dosed at 23.7 mg twice daily. It should be mentioned that voclosporin is currently not available in Canada. New-onset hypertension, hyperglycemia, and nephrotoxicity as well as the need for drug level monitoring should also be considered with CNIs.

B cells play a fundamental role in SLE pathogenesis, and targeting them with monoclonal antibodies has led to significant improvements in disease activity. Despite the failure of the LUNAR trial to meet its primary endpoint, rituximab (a type 1 anti-CD-20 antibody) has shown favourable effects in LN, particularly when complete B-cell depletion is achieved.[16] Condon et al. applied a “no oral steroid regime” using rituximab at a dose of 1000 mg on days 1 and 15 with 500 mg of concomitant methylprednisolone followed by MMF, showed substantial efficacy in LN.[17] Belimumab, a B lymphocyte stimulator (BLyS) inhibitor, in combination with SoC demonstrated superior efficacy in the BLISS-LN trial at 104 weeks, achieving a complete renal response rate of 30% versus 20% with placebo plus SoC. This led to belimumab becoming the first biologic to be approved for treating LN.[18] Belimumab is recommended in combination with MPA/MMF or CYC for LN class III or IV, particularly in patients where extra-renal manifestations are prevalent[4-6] or with repeated kidney flares or at high risk for progression to kidney failure due to severe chronic kidney disease.[7] Most recently, obinutuzumab, a type 2 anti-CD20 antibody, demonstrated improved outcomes in the REGENCY trial when added to SoC therapy (glucocorticoids and MMF), achieving a complete renal response rate of 46.4% compared to 33.1% of placebo plus SoC at week 76.[19] Obinutuzumab showed particularly enhanced efficacy in patients with nephrotic-range proteinuria, active lupus serology (abnormal anti-dsDNA and/or low complement C3/C4 levels), and in newly diagnosed patients. Obinutuzumab has been approved by the FDA; it has been included as an alternate therapy for addition to SoC in the new 2025 EULAR guidelines.[6]

Induction Therapy for Pure LN Class V

Management of pure membranous LN (class V) should be guided by the level of initial proteinuria. In patients with proteinuria ≥1 g/day, the 2024 ACR guidelines recommend triple therapy with glucocorticoids, MPA/MMF and CNIs.[4] Regarding glucocorticoids, methylprednisolone pulses should still be applied but, in general, the oral prednisone doses should be lower (maximum of 40 mg/day per ACR or 50 mg/day per KDIGO).[4,7] If ineffective, CYC for less than 6 months or B-cell targeted therapies may be considered.

In patients with milder proteinuria (<1 g/day), the 2024 ACR guidelines recommend treatment with glucocorticoids (low oral doses) plus an immunosuppressive (MPA/MMF or CNI or azathioprine) and close monitoring of proteinuria.[4] On the contrary, the 2024 KDIGO guidelines state that immunosuppressive treatment should

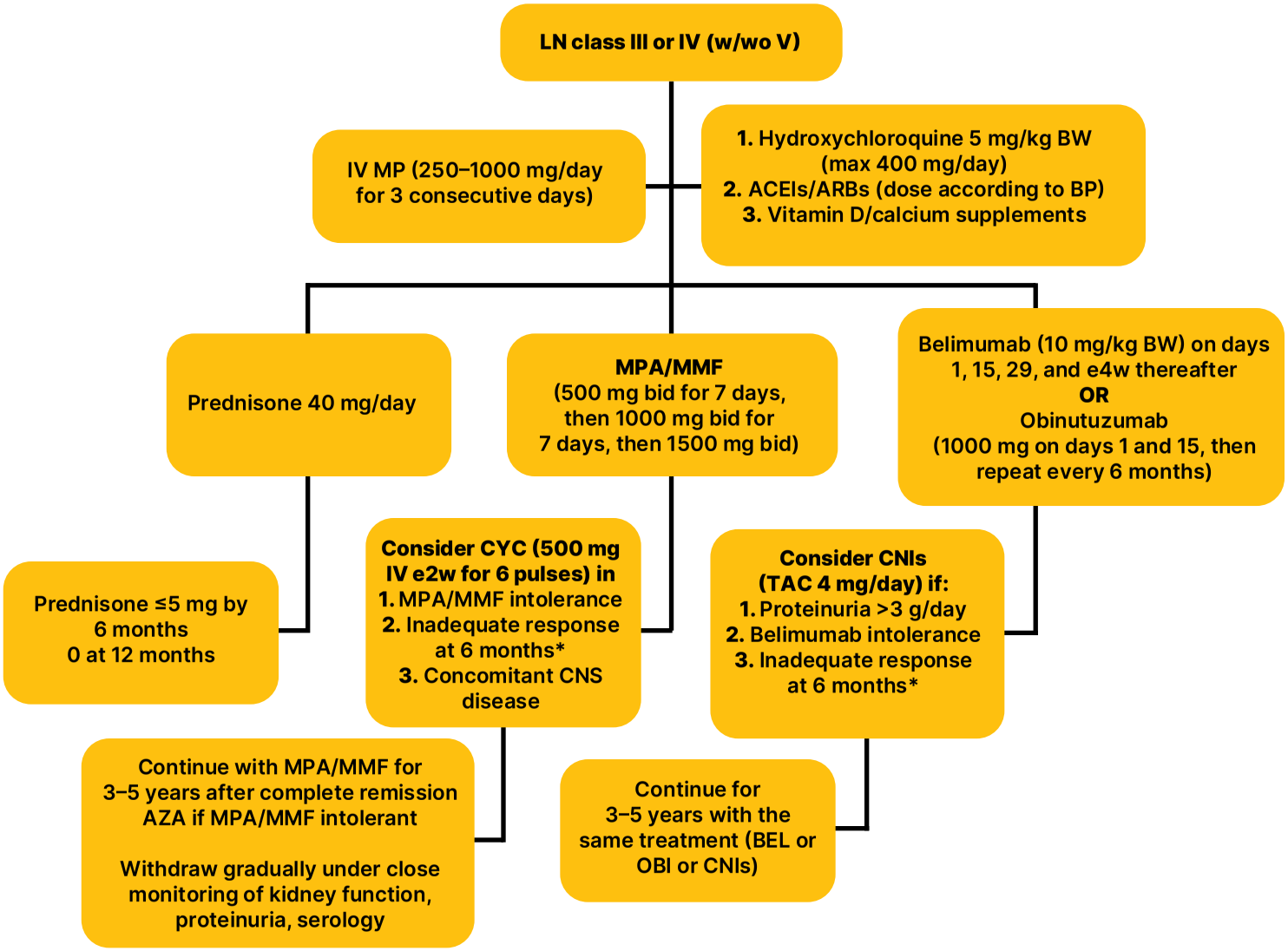

Figure 1. Therapeutic algorithm for LN class III and IV (with or without V); *courtesy of Konstantinos Tselios, MD, PhD.*

*No partial renal response (50% improvement in proteinuria from baseline and stable renal function).

Obinutuzumab was superior to placebo and SoC in the phase III Regency trial.
Voclosporin is not available in Canada and not mentioned in this figure.

Abbreviations: ACEIs: angiotensin-converting enzyme inhibitors; **ARBs:** angiotensin receptor blockers; **AZA:** azathioprine; **BEL:** belimumab; **CNIs:** calcineurin inhibitors; **CNS:** central nervous system; **CYC:** cyclophosphamide; **LN:** lupus nephritis; **MMF:** mycophenolate mofetil; **MP:** methylprednisolone; **MPA:** mycophenolic acid; **OBI:** Obinutuzumab; **TAC:** tacrolimus.

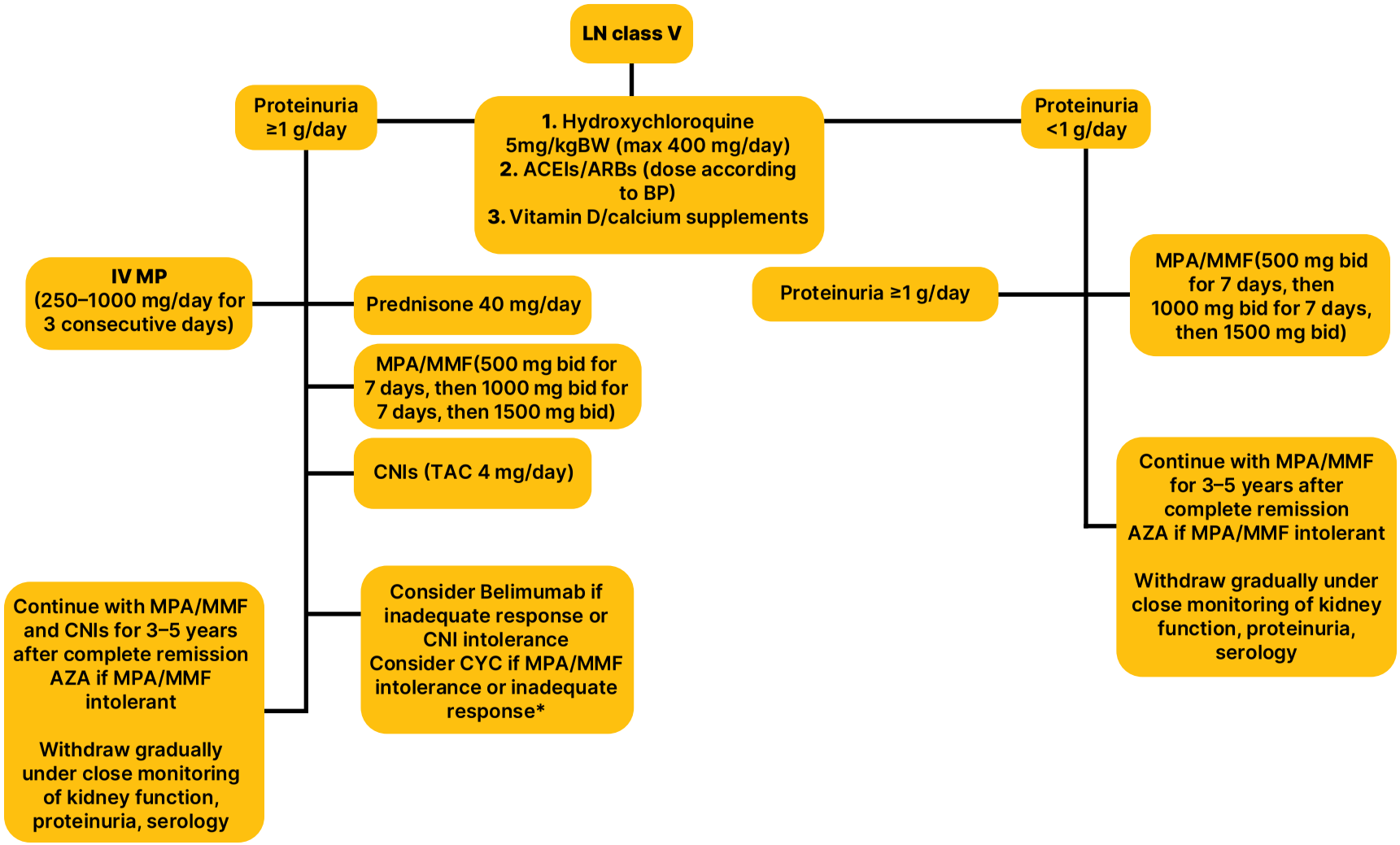

Figure 2. Therapeutic algorithm for LN class V; *courtesy of Konstantinos Tselios, MD, PhD.*

*No partial renal response (50% improvement in proteinuria from baseline and stable renal function).

Voclosporin is not available in Canada and not mentioned in this figure.

Abbreviations: ACEIs: angiotensin-converting enzyme inhibitors; **ARBs:** angiotensin receptor blockers; **AZA:** azathioprine; **bid:** twice a day; **CNIs:** calcineurin inhibitors; **CYC:** cyclophosphamide; **LN:** lupus nephritis; **MMF:** mycophenolate mofetil; **MP:** methylprednisolone; **MPA:** mycophenolic acid; **TAC:** tacrolimus.

be based on the extrarenal SLE manifestations while proteinuria should be treated with renin-angiotensin system blockade and blood pressure control.[7]

The EULAR guidelines recommend triple therapy with glucocorticoids, MPA/MMF and CNIs (especially tacrolimus) in cases with nephrotic range proteinuria; CYC can be used as an alternative to MPA/MMF.[5]

Adjuvant Therapies for LN

Adjuvant, non-immunosuppressive, therapies are fundamental in achieving treatment goals in LN. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are conditionally recommended in all LN patients (unless contraindicated) for managing any increase in proteinuria, even at levels <0.5 g/day.[4-7] These recommendations are extrapolated from other proteinuric nephropathies, as their efficacy in pure LN populations has not been confirmed. Nevertheless, they remain important for blood pressure control in LN and are useful in patients where proteinuria is attributed to chronic nephron damage. Sodium-glucose cotransporter 2 inhibitors (SGLT-2) have also demonstrated nephroprotective properties in other kidney diseases and may reduce the risk for chronic and ESKD in patients with LN with concomitant diabetes.[20] Their use might be considered in cases of chronic LN with diabetes or heart failure or chronic kidney disease.[4,7] Other nephroprotective strategies (optimization of blood pressure, low sodium intake <2 g/day and avoidance of high protein diet if eGFR<60 ml/min/1.73m^2) are also recommended by all guidelines.

Other measures to minimize the risk of complications and optimize outcomes include considerations for cardiovascular health (management of hypertension, dyslipidemia, diabetes, smoking cessation, BMI optimization among others), bone health (vitamin D and calcium supplementation and fracture risk assessment with appropriate management), infection control (screening for chronic infections, appropriate vaccinations and consideration of prophylactic therapy for Pneumocystis jirovecii) and reproductive health (contraception methods, gonadotropin releasing hormone agonists in females treated with CYC among others).

Goals of Treatment in LN

Achieving CRR, defined as proteinuria <0.5 g/day and stable kidney function (eGFR±10–15% of the baseline value), is considered the optimal goal of LN management. While there is broad consensus on the importance of stable eGFR, RCTs have used a more lenient threshold for proteinuria, for example, the BLISS-LN trial accepted levels of up to 700 mg/day.[18] The timing of CRR achievement is of paramount importance, as achieving CRR by 12 months offers substantially better long-term prognosis, extending over 20 years, than CRR achieved at 24 or 36 months.[21] The minimum goal of treatment is achieving partial renal remission by 6 months, defined as a reduction in proteinuria of >50% without a significant decrease in renal function (eGFR±10–15% of baseline).[4-7] Moreover, all guidelines now incorporate oral glucocorticoid tapering into treatment goals, recommending a dose of ≤5 mg/day at 6 months[4-6] or even lower (2.5 mg/day if the KDIGO reduced-dose scheme was employed).[7]

What to Do if Goals are Not Achieved?

In cases of refractory disease, medication dose and patient adherence should be assessed regularly as an important first step. In patients who were treated with dual therapy (i.e., glucocorticoids and MPA/MMF or CYC), escalation to triple therapy with the addition of belimumab[4-7] or obinutuzumab[6] or CNIs[4-7] is recommended. In patients who were initially treated with triple therapy, alternate triple therapy should be employed (i.e., belimumab instead of CNIs or vice versa) or addition of an anti-CD20 agent (rituximab, obinutuzumab) on MPA/MMF or low dose CYC.[4] In patients who have failed two standard therapy courses, addition of an anti-CD20 agent or quadruple therapy (glucocorticoids plus MPA/MMF plus belimumab plus CNIs) or investigational therapy should be considered.[4]

In cases of disease relapse after achieving remission, the 2024 KDIGO guidelines recommend the same therapy that initially achieved remission or an alternate recommended therapy.[7]

In patients who develop ESKD, both the 2024 ACR and 2024 KDIGO guidelines recommend pre-emptive kidney transplantation over hemodialysis as this is related to substantially improved survival.[4,7] Clinical and serological

quiescence are not a requirement to proceed with transplantation (as long as there is no other major organ involvement) according to the ACR.[4] In cases where kidney transplant is not an option, hemodialysis or peritoneal dialysis should be initiated in collaboration with Nephrology.[4,7]

Maintenance Therapy

Management of LN should be long-term and aim to reduce the risk of subsequent disease flares that can lead to nephron loss and eventually to chronic kidney disease. All guidelines strongly recommend continuing maintenance therapy with the same immunosuppressive regimen used to achieve CRR, typically MPA/MMF following induction therapy with CYC, for at least 3–5 years (if not more).[4-7] Patients who received more than 3 years of immunosuppressive treatment had substantially better outcomes over a 20-year period compared to those with shorter treatment durations.[21] Based on findings from repeated kidney biopsies, De Rosa et al. showed that LN patients in proteinuric complete remission for 12 months may still have active disease at the tissue level.[22] These patients were at risk for disease flares following the discontinuation of immunosuppressive therapy, highlighting the need for biomarkers that could better characterize the state of LN beyond proteinuria alone. Multiple urinary biomarkers have been identified that may help to predict ongoing histologic activity and may eliminate the need for repeat kidney biopsies in the future.[23]

Withdrawal of immunosuppressive therapy after prolonged complete remission should be individualized and carried out gradually under close clinical and laboratory monitoring. This includes assessments of kidney function, proteinuria, and lupus serology markers (anti-dsDNA antibodies and complement levels [C3/C4]). In the WIN-Lupus trial, maintenance of immunosuppressive therapy for more than 3 years did not demonstrate statistically superior results compared to discontinuation (relapse rates: 12.5% versus 27.3%, difference 14.8%, 95% confidence interval -1.9–31.5).[24] However, the small number of patients did not allow for sound conclusions. Notably, patients who discontinued immunosuppressive therapy developed a significantly higher rate of non-nephritic lupus flares.

Future Prospects: CAR T-Cell Therapy for LN

Chimeric antigen receptor T-cell (CAR T) therapy was first administered to a patient with refractory LN in 2021.[25] The patient had received all available treatments for her LN to no avail; however, a rapid and profound clinical and serologic response was documented shortly after the administration of CD-19 engineered T cells, and has remained in drug-free remission ever since. CAR T-cell therapy has now been successfully administered to more than 50 patients with refractory SLE worldwide, the majority of them with concomitant LN.[26] This approach has also been employed in children and adolescents with LN.[26] Currently, over 60 RCTs in early phases are recruiting patients with systemic autoimmune diseases to evaluate CAR T-cell therapy. The mechanistic basis involves targeting of B cells through molecules such as CD19 or B-cell maturation antigen (BCMA) (or both) that are expressed on the surface of B cells in different stages of their functional maturation. Compared to biologics like rituximab, CAR T-cells have the advantage of deeper and sustained depletion of the B cells given their persistence in the peripheral blood as well as their capacity for tissue penetration and eradication of the B cells that reside in germinal centres within the affected organs. However, the cost of this therapy remains an obstacle to its wide adoption in lupus treatment.

Conclusions

LN treatment should begin promptly and target complete renal remission within 12 months from initiation. All patients should be treated with hydroxychloroquine and glucocorticoids (initially with intravenous pulses and subsequently orally) and aim at a prednisone dose of ≤5 mg/day by 6 months. Immunosuppressive agents (MPA/MMF or low-dose CYC), and biologics (belimumab, obinutuzumab) or CNIs (TAC, voclosporin) should be added for class III–IV and pure class V with proteinuria ≥1 g/day. Early initiation of adjuvant treatments, including ACEIs/ARBs, is recommended. Maintenance therapy with the same immunosuppressive regimen should be continued for at least 3–5 years after remission.

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