VOLUME 2 • ISSUE 1

Canadian Rheumatology Today

Spring 2025

ISSN 2818-2588 (print)
ISSN 2818-2596 (online)

Editorial Board

May Choi, MD, MPH, FRCPC

Associate Professor, Cumming School of Medicine
University of Calgary, Calgary, AB
Associate Director of MitogenDx Laboratory
Associate Director of Research for the University of Calgary Lupus Centre of Excellence

Nigil Haroon, MD, PhD, DM, FRCPC, FRCP, MBA

Clinician Scientist, University Health Network
Senior Scientist, Schroeder Arthritis Institute, Krembil Research Institute
Associate Professor of Medicine and Rheumatology, University of Toronto

Janet Pope, MD, FRCPC

Professor of Medicine and Rheumatologist, University of Western Ontario, London, ON
Schulich School of Medicine

Table of Contents

Canadian Rheumatology Today is published 3 times per year.

To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, canadianrheumatologytoday.com.

To subscribe to Canadian Rheumatology Today and more open access scientific specialty journals published by Catalytic Health, please visit catalytichealth.com/crt.

The content of this journal qualifies for Section 2 (self-learning) CPD credits under the Royal College's Maintenance of Certification (MOC) program. For more information on how journal articles can meet your CPD needs, please consult the Royal College's website. For more personalized support, please contact the Royal College Services Centre (1-800-461-9598) or your local CPD Educator.

catalytic health
medical minds meet here

Medical minds gather here.

As the largest independent medical publisher in Canada, our peer-reviewed open access scientific journals are a practical resource for Canadian healthcare practitioners. We currently publish specialty journals in the areas of allergy & immunology, dermatology, hematology, ophthalmology, diabetes & endocrinology, gastroenterology, primary care, women's health, rheumatology, oncology, respirology and our press is constantly growing with new titles planned.

About the Authors

Roko P.A. Nikolic, MD

Dr. Roko Nikolic is currently completing his residency in internal medicine at the University of Calgary, where he will also begin his rheumatology residency training in July 2025. Dr. Nikolic studied biochemistry at the University of Victoria and completed his medical education at the University of Calgary. His interests include systemic autoimmune rheumatic diseases, nailfold video capillaroscopy, clinical practice guidelines, patient-centred care, and medical education. He has contributed to the development of several national clinical practice guidelines in rheumatology with the Canadian Rheumatology Association.

Affiliations: University of Calgary Division of Rheumatology, Calgary, Canada

Maggie Larché, MBChB, PhD, MRCP (UK)

As the director of the Canadian Scleroderma Research Group, a clinician-scientist, and a Professor at the University of Calgary, Dr. Maggie Larché has successfully established and maintained educational and research initiatives in systemic sclerosis (SSc) across Canada. With over 15 years of experience treating patients with SSc, she is well-placed to understand the need for improved biomarkers, including video nailfold capillaroscopy.

Affiliations: University of Calgary Division of Rheumatology, Calgary, Canada
Arthritis Research Canada, Vancouver, Canada

doi.org/10.58931/crt.2025.2157

Mohammed Osman, MD, PhD, FRCPC

Dr. Osman is a Clinician-Scientist, Associate Professor, and Consultant Rheumatologist with a focus in Immunology within the Division of Rheumatology at the University of Alberta. Prior to his recruitment (March 2019), he earned a PhD in immunology (2007), a Doctor of Medicine (2011) and completed clinical training in internal medicine (2014), and rheumatology with a focus on clinical immunology (2016), all at the University of Alberta. He also completed a postdoctoral research fellowship in translational research (2018) and advanced vascular imaging fellowships in systemic sclerosis at the University of Genoa in Italy and the University Medical Centre of Groningen in the Netherlands. He regularly performs nailfold video capillaroscopy (NVC) and has founded the first Microvascular Clinic in Western Canada. He utilizes NVC to better risk-stratify patients with systemic autoimmune rheumatic diseases (in general) and systemic sclerosis (in particular). Leading his translational research team, he aims to provide solutions for the complex problems faced by his patients.

Affiliations: University of Alberta Division of Rheumatology, Edmonton, Canada
Li Ka Shing Institute of Virology
Women and Children's Health Research Institute

Capillaroscopy in Systemic Autoimmune Rheumatic Diseases: A Clinical Tool Linking Diagnosis and Pathogenesis

Roko P.A. Nikolic, MD
Maggie Larché, MBChB, PhD, MRCP (UK)
Mohammed Osman, MD, PhD, FRCPC

Introduction

Systemic autoimmune rheumatic diseases (SARDs) including systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and idiopathic inflammatory myopathies (IIMs) are multisystemic, potentially life-threatening autoimmune diseases. These diseases are associated with the highest frequency of disease-associated morbidity and mortality among rheumatic diseases, largely because their complex pathophysiology remains poorly and incompletely understood.[1,2] Mortality in SARDs is associated with profound vascular dysfunction ranging from cardiovascular disease to more discreet localized vascular complications including Raynaud's phenomenon (RP), digital ulcers, and pulmonary arterial hypertension (PAH). These vascular complications stem from damage to endothelial cells caused by immune complex deposition,[3] platelet activation,[4] autoantibodies that promote thrombosis (e.g., antiphospholipid antibodies),[5] and immune dysregulation.[6]

The relationship between endothelial cell dysfunction and SARDs was first recognized by Maurice Raynaud in the 19th-century, particularly in the context of localized digital ischemia and gangrene.[7] RP is a frequently-encountered

problem in clinical practice, with a prevalence in the general population ranging from approximately 5–18%.[7-10] While most cases of RP are not associated with SARDs, patients with SARDs commonly experience RP.[7,9] This underscores the importance of vasculopathy related to endothelial dysfunction in the pathogenesis of SARDs.

RP is the earliest presenting feature in up to 20% of patients with SARDs.[7] Indeed, greater than 95% of patients with SSc experience RP.[11] Patients with SLE, IIMs including anti-synthetase syndrome (ASyS), and Sjögren's disease are also commonly affected.[12] Hence, a closer evaluation for microvascular changes is paramount in the clinical assessment of patients with SARDs. This article will review how nailfold video capillaroscopy is emerging as a valuable point-of-care tool for diagnosis and risk stratification by providing a window into the underlying endothelial dysfunction observed in these conditions.

Microvascular Dysfunction in SARDs is Intimately Linked to Pathogenesis

To date, the triggers of immune dysregulation and vasculopathy in SARDs remain unknown, and the pathogenesis is likely multifactorial. Contributing risks include environmental factors (e.g., viral infections,[13] silicone implants,[14] and silica[15]), genetic and epigenetic factors (e.g., defective angiogenesis[16,17] and DNA methylation[1]), genomic instability/malignancies,[18-20] and ischemic injury.[21] These factors can damage the endothelium either directly or indirectly via aberrant angiogenesis and fibroblast activation, along with an exaggerated immune response.

One of the earliest indicators of aberrant immune dysregulation in patients with SARDs is a tendency toward releasing elevated type I (e.g., alpha and beta) and/or type III (e.g., lambda) interferons.[22] Interferons are known to contribute to disease progression in SARDs through various mechanisms, particularly those related to endothelial dysfunction.[23] They also directly inhibit the proliferation of endothelial cells, thereby promoting maladaptive vascular remodelling, which further exacerbates vascular dysfunction in these diseases. In patients with various SARDs, more severe manifestations are linked with interferon dysregulation.[24,25]

Interferon signals exert both direct and indirect pleiotropic effects on microvascular endothelial cells.[26] This is relevant, as impaired angiogenesis is one of the hallmark features of SARD-associated endothelial dysfunction.[16] Further, molecules associated with aberrant endothelial cell function, such as apelin, and the soluble receptor for advanced glycation end-products (sRAGE), are elevated in patients with SARDs.[27,28] The release of these molecules promotes endothelial cell damage through pro-inflammatory signals such as high mobility group box 1 (HMGB1).[28,29] This endothelial damage, in turn, potentiates thrombosis through platelet activation and immune cell recruitment.[4]

Upon recruitment, immune cells promote further endothelial cell damage through the release of inflammatory mediators (e.g., cytokines and immune complexes). For instance, specific cytokines such as IP-10 rapidly increase in response to interferon signals, and in turn activate other innate immune cells, including plasmacytoid and myeloid dendritic cells, to promote their differentiation.[30] These cells subsequently facilitate the development of antigen-specific immune responses, ultimately resulting in the formation of immune complexes. These complexes directly activate endothelial cells, and lead to complement activation. In patients with SSc-specific antibodies (i.e., anti-Scl70, anti-centromere, anti-RNA polymerase, and anti-Th/To), autoantibodies are embedded within immune complexes. These complexes can directly activate endothelial cells and promote the release of other inflammatory mediators linked with disease progression.[3] Hence, in patients with SARDs, particularly those with SSc-spectrum disorders, systemic microvasculopathy is associated with a repetitive deleterious cycle of endothelial cell damage, microvascular remodelling, aberrant activation of somatic cells, (e.g., fibroblasts) and immune cells. This cycle directly promotes inflammation and potentiates further organ damage and disease progression. Clinically, this is highlighted by the presence of enriched perivascular inflammatory cells in nearly all patients with SSc, SLE, and IIMs,[31-33] illustrating the intimate relationship between inflammation and vascular dysfunction (**Figure 1**).

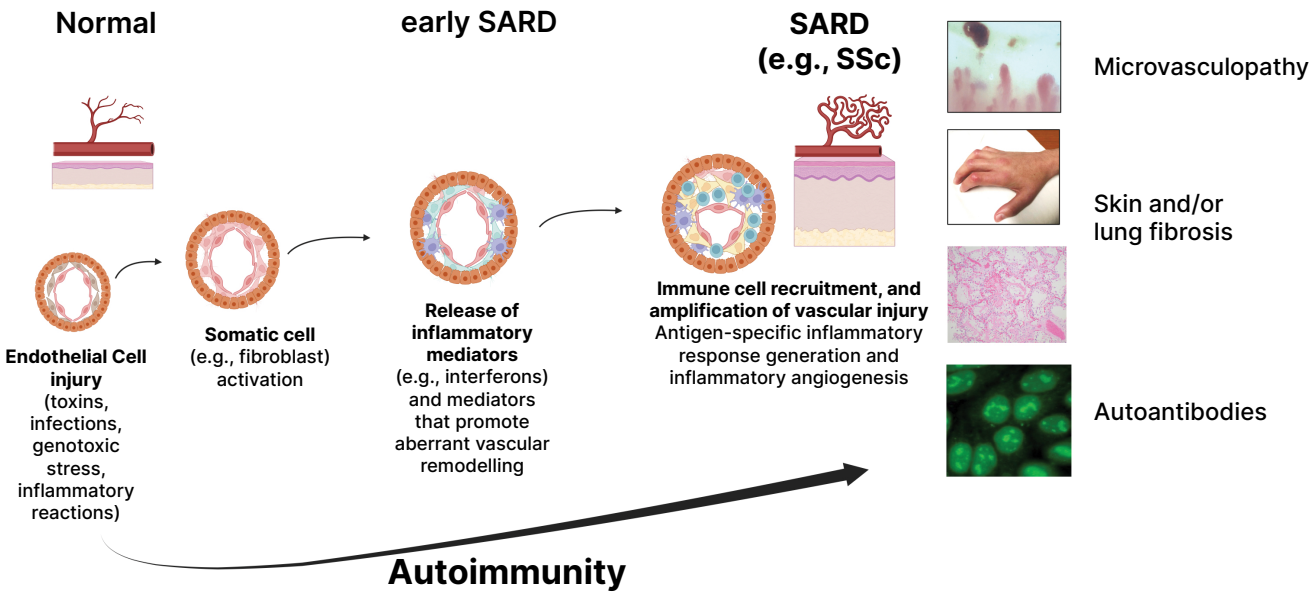

Figure 1. Simplistic overview for evolution of systemic autoimmune rheumatic diseases, (SARDs, particularly systemic sclerosis, SSc). Following vascular and Raynaud's-associated hypoxia-reperfusion injury, somatic cell activation ensues with associated release of inflammatory and vascular mediators. This results in disease amplification of inflammatory signals and disease progression. Nailfold video capillaroscopy is a point-of-care tool that can be utilized for directly visualizing SARD evolution; *created in BioRender*.

Nailfold Capillaroscopy: A Window for the Early Detection of SARDs and Their Complications

Systemic Sclerosis (SSc)

The progressive microvasculopathy observed in SSc patients is most clinically apparent in the distal nailfolds in the upper extremities. The most distal capillaries are directly exposed and positioned perpendicular to the nail bed, making them easily accessible for visualization with point-of-care tools in the clinic. This observation was first noted by Maricq and colleagues using widefield microscopy in the 1970s.[34,35] Since then, the presence of abnormal nailfold capillaries has been proposed as a useful indicator to distinguish idiopathic (primary) RP from RP due to SSc. This so-called "scleroderma pattern" is characterized by giant capillaries, microhemorrhages, and capillary disorganization/loss[36] (**Figure 2**). Individuals exhibiting a scleroderma pattern are much more likely to develop SSc than those without, particularly when SSc-specific autoantibodies are also present.[36-38] Conversely, patients with RP who lack both capillary abnormalities and seropositivity for SSc-specific autoantibodies rarely progress to develop SSc.[38] Thus, nailfold capillaroscopy serves as an indispensable tool for risk stratification of patients presenting with RP, and it is considered part of the standard-of-care in evaluating those with RP and a positive antinuclear antibody. Nailfold capillaroscopy can aid in differentiating primary RP from potentially life-threatening SARDs such as SSc. As a result, it has become an essential component of the clinical evaluation for those with RP.[7,39] Capillaroscopy has also been incorporated into the classification criteria for the very early diagnosis of systemic sclerosis (VEDOSS),[39,40] which may facilitate opportunities for early immunomodulation using antirheumatic medications.[39]

The clinical applications of capillaroscopy extend well beyond RP assessments. In patients with SSc, vascular remodelling parameters (particularly capillary loss) have been linked to disease progression including the development of digital ulcers,[41,42] skin fibrosis,[42] lung fibrosis,[43] and PAH.[42] Moreover, improvements in nailfold

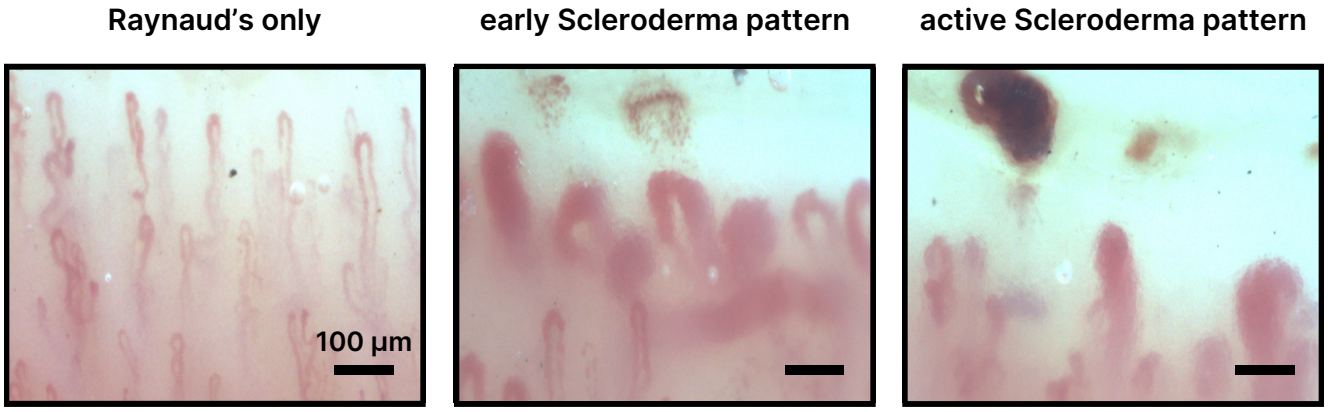

Figure 2. Representative nailfold video capillaroscopy images for a "scleroderma pattern". Images were collected using a DS Medica 2.0 device and a 200X lens. Note the presence of microhemorrhages, giant capillaries (more than 50 microns), and capillary disorganization/dropout with associated capillary loss that are more apparent in an "active scleroderma" pattern (**right**) compared to an "early scleroderma pattern" (**middle**); *courtesy of Roko P.A. Nikolic, MD, Maggie Larché, MBChB, PhD, MRCP (UK), and Mohammed Osman, MD, PhD, FRCPC.*

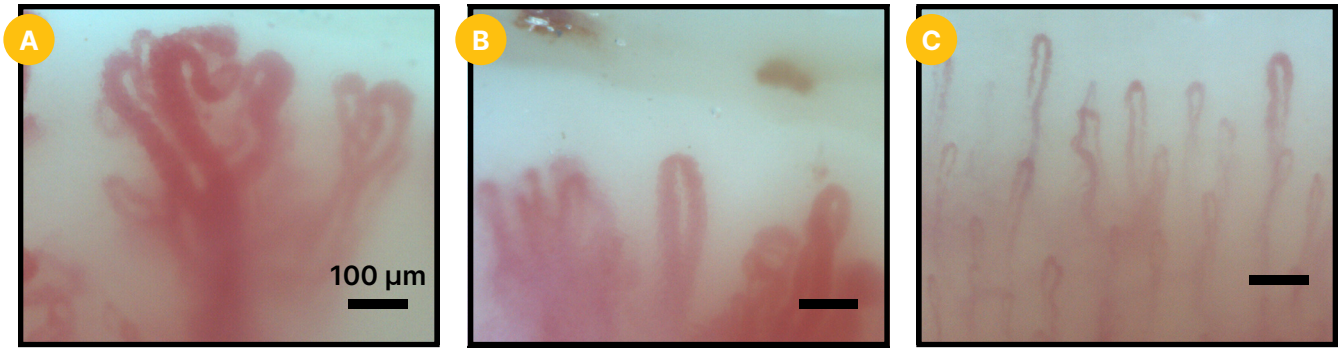

Figure 3. Representative capillary patterns in TIF-1-gamma positive dermatomyositis. Images were collected using a DS Medica 2.0 device and a 200X lens. Note the presence of bushy capillaries **(A)**, and scleroderma-like changes **(B)**. Also note the resolution of these capillary changes (from the same patient) following successful treatment using immunomodulation **(C)**; *courtesy of Roko P.A. Nikolic, MD, Maggie Larché, MBChB, PhD, MRCP (UK), and Mohammed Osman, MD, PhD, FRCPC.*

changes have been linked to the resolution of skin fibrosis in patients treated with autologous stem cell transplant[44] (**Figure 3**), highlighting the connection between nailfold capillary abnormalities and the dynamic disease evolution of SSc.

The sensitivity of capillaroscopy in predicting SSc is powerful and has been applied to other indications as well. Nailfold capillaroscopy can aid in differentiating sclerodermoid skin diseases that mimic SSc (e.g., pansclerotic morphea, eosinophilic fasciitis) from true SSc, as capillaroscopy usually appears normal in the former.[45] Importantly, some patients with morphea may also develop antinuclear antibodies, which can make the diagnosis without capillaroscopy more challenging.[46] Furthermore, the management of these scleroderma-mimicking conditions often relies upon corticosteroids.[46] However, this approach could be potentially harmful if the ultimate diagnosis is diffuse cutaneous SSc, as high doses of corticosteroids in such cases may be associated with the development of scleroderma renal crisis.[47]

Microvascular abnormalities observed in patients with SSc can also be detected in patients with other SARDs and offer prognostic value. Nailfold changes are more frequently observed in those with SARD-related interstitial lung disease than in those with interstitial pneumonia with autoimmune features or idiopathic pulmonary fibrosis.[48]

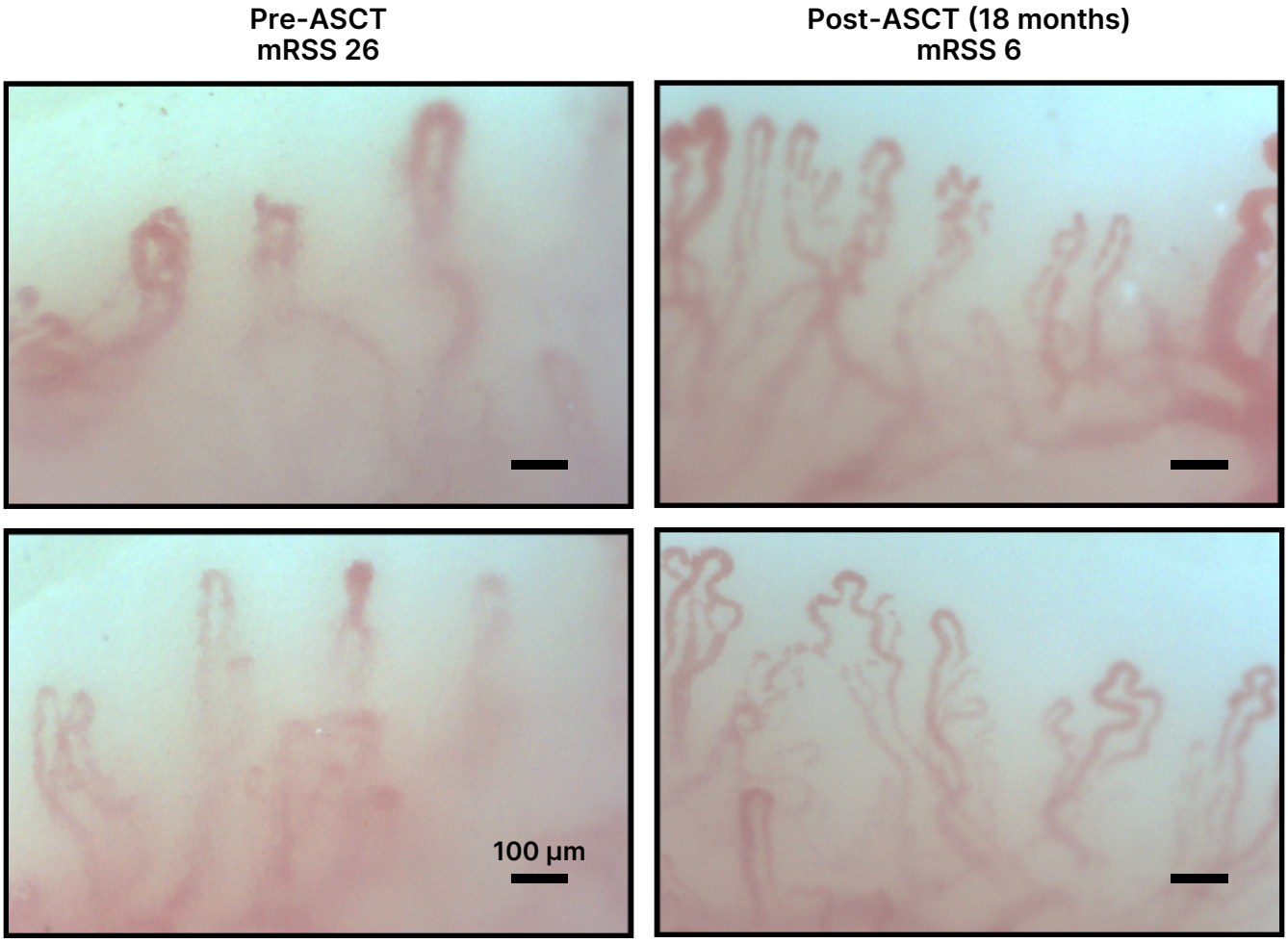

Figure 4. Capillary abnormalities in systemic sclerosis improve with autologous stem cell transplantation. Note improvement capillary density (and resolution of pericapillary edema) that correspond to marked improvement in skin fibrosis as measured using the modified Rodnan skin score (mRSS). Images were collected using a DS Medica 2.0 device and a 200X lens in a patient before autologous stem cell transplantation (ASCT), and approximately 18 months after transplantation; *courtesy of Roko P.A. Nikolic, MD, Maggie Larché, MBChB, PhD, MRCP (UK), and Mohammed Osman, MD, PhD, FRCPC.*

Idiopathic Inflammatory Myopathies: Dermatomyositis, Anti-synthetase Syndrome, and Juvenile Dermatomyositis

Diverse nailfold capillary changes can be observed in patients with IIMs – particularly those with dermatomyositis (DM) (**Figure 4**). These capillary changes range from "bushy capillaries" (reflecting profound vascular angiogenesis) to scleroderma-like changes (i.e., capillary dilation, giant capillaries, and microhemorrhages). Although these capillary changes are potentially similar to those seen in patients with SSc, the changes observed in patients with IIMs are dynamic and reversible.[49-51] The prevalence of nailfold capillary abnormalities in patients with IIMs is also quite variable. While one study identified capillary abnormalities in only 26.9% of patients with DM, a more recent study reported that 55.7% of all patients with pooled IIMs exhibited capillary changes.[50] Of note, capillary abnormalities are infrequently present in patients with acute necrotizing myositis.[52] Capillary abnormalities are frequently seen in patients who are seropositive for anti-MDA5 and anti-TIF1γ autoantibodies.[49,50,53] In one study, 87.5% of those seropositive for anti-MDA5 demonstrated these changes.[50] Additionally, changes may also be more frequently observed in those with Gottron's papules and the heliotrope sign,[50] and they correlate with skin and lung involvement.[51,54]

Nailfold changes in patients with DM are remarkably dynamic, correlating with overall disease activity and improving with immunosuppressive treatment.[50,51] In fact, microvascular changes may even normalize with the use of immunomodulators.[51] Capillary scores may correlate with interferon scores[49] and may also serve as prognostic indicators in those with IIM-associated ILD.[53] As a result, we and others have proposed that microvascular changes, particularly capillary density, may indeed be associated with global disease activity in DM.[49,51] This principle is not limited to adult patient populations. Indeed, capillary abnormalities are highly prevalent (greater than 80%) in pediatric patients with juvenile dermatomyositis (JDM).[55,56] Similar to adult DM, capillary density in JDM reflects overall disease activity and appears to respond to immunomodulation.[55,57]

Curiously, capillary abnormalities are not observed as frequently in patients with ASyS.[49,50] Nonetheless, patients with ASyS may develop giant (enlarged) capillaries associated with capillary disorganization, particularly when visceral involvement is apparent.[58] Thus, inflammatory angiogenesis may be an important contributor to the progression of lung fibrosis in IIMs and particularly in patients with RP, including those with ASyS and anti-MDA5 DM.

Systemic Lupus Erythematosus

The nailfold changes observed in patients with SLE are often termed "non-specific."[36,59] This means that while abnormal, these changes do not strictly fulfill the criteria defining the scleroderma-like pattern appreciable in those with systemic sclerosis.[36,41,60] Capillaroscopy in those with SLE may be associated with reduced capillary density, particularly when visceral organs are affected, as well as increased capillary tortuosity, corkscrew-shaped capillaries, microhemorrhages, and heterogeneity in capillary size.[59,61,62] One study reported that nailfold capillary abnormalities in those with SLE were significantly more common in those with RP, and were predictive of seropositivity for anti-U1-RNP and anticardiolipin antibodies.[61] Further, only 6% of those with SLE demonstrated "scleroderma-like" changes.[61] Hence, nailfold changes may be useful in discerning between the two SARDs in patients presenting with RP. Nailfold abnormalities correlate with disease activity and anti-dsDNA titers in patients with SLE.[59,63,64] They have also been suggested as predictors of SLE-associated ILD,[65] and the presence of normal capillaries can help reduce the likelihood of lupus nephritis.[66] Nonetheless, the potential relationship between nailfold abnormalities and organ involvement in SLE remains to be clarified.[59]

Other Autoimmune Rheumatic Diseases

Capillaroscopy is increasingly being used to assess patients with other autoimmune rheumatic diseases including rheumatoid arthritis, psoriatic arthritis,[67] and Sjögren's disease.[68] However, its role in assessing patients with these conditions remains less defined. Although uncommon, scleroderma-like nailfold changes can be observed in patients with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, where capillary abnormalities may similarly correlate with disease activity.[69]

Challenges Associated with Capillaroscopy: Standardization and Implementation

Despite the diagnostic and prognostic information available through nailfold video capillaroscopy for patients with SARDs, most clinicians have not yet incorporated this technique in routine clinical practice. As a result, international efforts have been made to standardize nailfold video capillaroscopy.[36] Further, newer devices, equipped with software that uses machine learning to semi-automatically identify abnormal capillaries, including detecting scleroderma-associated capillary changes, have been developed.[70] Newer and less expensive alternatives for nailfold video capillaroscopy have made capillary assessment much more accessible.[71] Introductory basic training in capillaroscopy is now available through the European Alliance of Associations for Rheumatology.[36] The significant diagnostic value of this technique has warranted myriad efforts to enhance its accessibility and standardization.

Conclusions and Future Directions

Nailfold capillaroscopy has emerged as an accessible and invaluable point-of-care tool for diagnosing, prognosticating, and managing patients with SARDs. By enabling a sensitive and direct assessment of the microvascular changes observed in patients with these conditions, capillaroscopy bridges the clinical manifestations of SARDs with their underlying pathophysiology. As a prognostic tool, capillaroscopy facilitates accurate differentiation between patients with primary RP who are at low risk for systemic complications, those with scleroderma-mimicking features, and those with RP that may indicate potentially life-threatening SARDs.[36-38,45,46] This differentiation aids in directing further investigation and follow-up. The utility of capillaroscopy in monitoring of SSc and IIM[44,51] holds promise for expanding its role in the tailored and personalized care of patients with these SARDs in the future. Further research may better characterize the utility of capillaroscopy in predicting outcomes for patients with SSc, SLE, and IIM, with respect to other systemic manifestations.

Correspondence

Mohammed Osman, MD, PhD, FRCPC
Email: mosman@ualberta.ca

Financial Disclosures

R.P.A.N: None declared.
M.L.: Director of the Canadian Scleroderma Research Group.
M.O.: None declared.

References

1. Choi MY, Costenbader KH, Fritzler MJ. Environment and systemic autoimmune rheumatic diseases: an overview and future directions. Front Immunol. 2024;15:1456145. doi:10.3389/fimmu.2024.1456145
2. Bournia VK, Fragoulis GE, Mitrou P, Mathioudakis K, Tsolakidis A, Konstantonis G, et al. All-cause mortality in systemic rheumatic diseases under treatment compared with the general population, 2015-2019. RMD Open. 2021;7(3). doi:10.1136/
3. Raschi E, Privitera D, Bodio C, Lonati PA, Borghi MO, Ingegnoli F, et al. Scleroderma-specific autoantibodies embedded in immune complexes mediate endothelial damage: an early event in the pathogenesis of systemic sclerosis. Arthritis Res Ther. 2020;22(1):265. doi:10.1186/s13075-020-02360-3
4. Ramirez GA, Franchini S, Rovere-Querini P, Sabbadini MG, Manfredi AA, Maugeri N. The role of platelets in the pathogenesis of systemic sclerosis. Front Immunol. 2012;3:160. doi:10.3389/fimmu.2012.00160
5. Merashli M, Alves J, Ames PRJ. Clinical relevance of antiphospholipid antibodies in systemic sclerosis: A systematic review and meta-analysis. Semin Arthritis Rheum. 2017;46(5):615-624. doi:10.1016/j.semarthrit.2016.10.004
6. Chizzolini C, Brembilla NC, Montanari E, Truchetet ME. Fibrosis and immune dysregulation in systemic sclerosis. Autoimmun Rev. 2011;10(5):276-281. doi:10.1016/j.autrev.2010.09.016
7. Maverakis E, Patel F, Kronenberg DG, Chung L, Fiorentino D, Allanore Y, et al. International consensus criteria for the diagnosis of Raynaud's phenomenon. J Autoimmun. 2014;48-49:60-65. doi:10.1016/j.jaut.2014.01.020
8. Garner R, Kumari R, Lanyon P, Doherty M, Zhang W. Prevalence, risk factors and associations of primary Raynaud's phenomenon: systematic review and meta-analysis of observational studies. BMJ Open. 2015;5(3):e006389. doi:10.1136/bmjopen-2014-006389
9. Choi E, Henkin S. Raynaud's phenomenon and related vasospastic disorders. Vasc Med. 2021;26(1):56-70. doi:10.1177/1358863X20983455
10. Frech TM, Murtaugh MA, Amuan M, Pugh MJ. The frequency of Raynaud's phenomenon, very early diagnosis of systemic sclerosis, and systemic sclerosis in a large Veteran Health Administration database. BMC Rheumatol. 2021;5(1):42. doi:10.1186/s41927-021-00209-z

11. Haque A, Hughes M. Raynaud's phenomenon. Clin Med (Lond). 2020;20(6):580-587. doi:10.7861/clinmed.2020-0754
12. Maciejewska M, Sikora M, Maciejewski C, Alda-Malicka R, Czuwara J, Rudnicka L. Raynaud's phenomenon with focus on systemic sclerosis. J Clin Med. 2022;11(9). doi:10.3390/jcm11092490
13. Moroncini G, Mori S, Tonnini C, Gabrielli A. Role of viral infections in the etiopathogenesis of systemic sclerosis. Clin Exp Rheumatol. 2013;31(2 Suppl 76):3-7.
14. Lercara A, Sulli A, Pizzorni C, Gotelli E, Paolino S, Cere A, et al. Do cosmetic silicone implants trigger systemic sclerosis? Ann Rheum Dis. 2022;81:1495. doi:10.1136/annrheumdis-2022-eular.4801
15. Tang B, Shi Y, Zeng Z, He X, Yu J, Chai K, et al. Silica's silent threat: contributing to skin fibrosis in systemic sclerosis by targeting the HDAC4/Smad2/3 pathway. Environ Pollut. 2024;355:124194. doi:10.1016/j.envpol.2024.124194
16. Patnaik E, Lyons M, Tran K, Pattanaik D. Endothelial dysfunction in systemic sclerosis. Int J Mol Sci. 2023;24(18). doi:10.3390/ijms241814385
17. Luo Y, Khan A, Liu L, Lee CH, Perreault GJ, Pomenti SF, et al. Cross-phenotype GWAS Supports shared genetic susceptibility to systemic sclerosis and primary biliary cholangitis. medRxiv. 2024. doi:10.1101/2024.07.01.24309721
18. Hill CL, Nguyen AM, Roder D, Roberts-Thomson P. Risk of cancer in patients with scleroderma: a population based cohort study. Ann Rheum Dis. 2003;62(8):728-731. doi:10.1136/ard.62.8.728
19. Vijayraghavan S, Blouin T, McCollum J, Porcher L, Virard F, Zavadil J, et al. Widespread mutagenesis and chromosomal instability shape somatic genomes in systemic sclerosis. Nat Commun. 2024;15(1):8889. doi:10.1038/s41467-024-53332-z
20. Gniadecki R, Iyer A, Hennessey D, Khan L, O'Keefe S, Redmond D, et al. Genomic instability in early systemic sclerosis. J Autoimmun. 2022;131:102847. doi:10.1016/j.jaut.2022.102847
21. Pacholczak-Madej R, Kuszmiersz P, Bazan-Socha S, Kosalka-Wegiel J, Iwaniec T, Zareba L, et al. Endothelial dysfunction in patients with systemic sclerosis. Postepy Dermatol Alergol. 2020;37(4):495-502. doi:10.5114/ada.2019.83501
22. Hinchcliff M, Khanna D, De Lorenzis E, Di Donato S, Carriero A, Ross RL, et al. Serum type I interferon score as a disease activity biomarker in patients with diffuse cutaneous systemic sclerosis: a retrospective cohort study. Lancet Rheumatol. 2025. doi:10.1016/S2665-9913(24)00403-X
23. Yin H, Distler O, Shen L, Xu X, Yuan Y, Li R, et al. Endothelial response to Type I interferon contributes to vasculopathy and fibrosis and predicts disease progression of systemic sclerosis. Arthritis Rheumatol. 2024;76(1):78-91. doi:10.1002/art.42662
24. Di Donato S, Ross R, Karanth R, Kakkar V, De Lorenzis E, Bissell LA, et al. Serum Type I Interferon Score predicts clinically meaningful disease progression in limited cutaneous Systemic Sclerosis. Arthritis Rheumatol. 2025. doi:10.1002/art.43120
25. Mai L, Asaduzzaman A, Noamani B, Fortin PR, Gladman DD, Touma Z, et al. The baseline interferon signature predicts disease severity over the subsequent 5 years in systemic lupus erythematosus. Arthritis Res Ther. 2021;23(1):29. doi:10.1186/s13075-021-02414-0
26. Gomez D, Reich NC. Stimulation of primary human endothelial cell proliferation by IFN. J Immunol. 2003;170(11):5373-5381. doi:10.4049/jimmunol.170.11.5373
27. Aozasa N, Asano Y, Akamata K, Noda S, Masui Y, Yamada D, et al. Serum apelin levels: clinical association with vascular involvements in patients with systemic sclerosis. J Eur Acad Dermatol Venereol. 2013;27(1):37-42. doi:10.1111/j.1468-3083.2011.04354.x
28. Yoshizaki A, Komura K, Iwata Y, Ogawa F, Hara T, Muroi E, et al. Clinical significance of serum HMGB-1 and sRAGE levels in systemic sclerosis: association with disease severity. J Clin Immunol. 2009;29(2):180-189. doi:10.1007/s10875-008-9252-x
29. Dong Y, Ming B, Dong L. The role of HMGB1 in rheumatic diseases. Front Immunol. 2022;13:815257. doi:10.3389/fimmu.2022.815257
30. Carvalheiro T, Zimmermann M, Radstake T, Marut W. Novel insights into dendritic cells in the pathogenesis of systemic sclerosis. Clin Exp Immunol. 2020;201(1):25-33. doi:10.1111/cei.13417
31. Bruni C, Frech T, Manetti M, Rossi FW, Furst DE, De Paulis A, et al. Vascular leaking, a pivotal and early pathogenetic event in systemic sclerosis: should the door be closed? Front Immunol. 2018;9:2045. doi:10.3389/fimmu.2018.02045
32. Stull C, Sprow G, Werth VP. Cutaneous involvement in systemic lupus erythematosus: a review for the rheumatologist. J Rheumatol. 2023;50(1):27-35. doi:10.3899/jrheum.220089
33. Amato AA, Greenberg SA. Inflammatory myopathies. Continuum (Minneap Minn). 2013;19(6 Muscle Disease):1615-1633. doi:10.1212/01.CON.0000440662.26427.bd
34. Maricq HR, Spencer-Green G, LeRoy EC. Skin capillary abnormalities as indicators of organ involvement in scleroderma (systemic sclerosis), Raynaud's syndrome and dermatomyositis. Am J Med. 1976;61(6):862-870. doi:10.1016/0002-9343(76)90410-1
35. Maricq HR. Wide-field capillary microscopy. Arthritis Rheum. 1981;24(9):1159-1165. doi:10.1002/art.1780240907
36. Smith V, Herrick AL, Ingegnoli F, Damjanov N, De Angelis R, Denton CP, et al. Standardisation of nailfold capillaroscopy for the assessment of patients with Raynaud's phenomenon and systemic sclerosis. Autoimmun Rev. 2020;19(3):102458. doi:10.1016/j.autrev.2020.102458
37. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28(7):1573-1576.

38. Koenig M, Joyal F, Fritzler MJ, Roussin A, Abrahamowicz M, Boire G, et al. Autoantibodies and microvascular damage are independent predictive factors for the progression of Raynaud's phenomenon to systemic sclerosis: a twenty-year prospective study of 586 patients, with validation of proposed criteria for early systemic sclerosis. Arthritis Rheum. 2008;58(12):3902-3912. doi:10.1002/art.24038
39. Bellando-Randone S, Del Galdo F, Lepri G, Minier T, Huscher D, Furst DE, et al. Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). Lancet Rheumatol. 2021;3(12):e834-e843. doi:10.1016/S2665-9913(21)00244-7
40. Minier T, Guiducci S, Bellando-Randone S, Bruni C, Lepri G, Czirjak L, et al. Preliminary analysis of the very early diagnosis of systemic sclerosis (VEDOSS) EUSTAR multicentre study: evidence for puffy fingers as a pivotal sign for suspicion of systemic sclerosis. Ann Rheum Dis. 2014;73(12):2087-2093. doi:10.1136/annrheumdis-2013-203716
41. Cutolo M, Herrick AL, Distler O, Becker MO, Beltran E, Carpentier P, et al. Nailfold videocapillaroscopic features and other clinical risk factors for digital ulcers in systemic sclerosis: a multicenter, prospective cohort study. Arthritis Rheumatol. 2016;68(10):2527-2539. doi:10.1002/art.39718
42. Avouac J, Lepri G, Smith V, Toniolo E, Hurabielle C, Vallet A, et al. Sequential nailfold videocapillaroscopy examinations have responsiveness to detect organ progression in systemic sclerosis. Semin Arthritis Rheum. 2017;47(1):86-94. doi:10.1016/j.semarthrit.2017.02.006
43. Guillen-Del-Castillo A, Simeon-Aznar CP, Callejas-Moraga EL, Tolosa-Vilella C, Alonso-Vila S, Fonollosa-Pla V, et al. Quantitative videocapillaroscopy correlates with functional respiratory parameters: a clue for vasculopathy as a pathogenic mechanism for lung injury in systemic sclerosis. Arthritis Res Ther. 2018;20(1):281. doi:10.1186/s13075-018-1775-9
44. Santana-Goncalves M, Zanin-Silva D, Henrique-Neto A, Moraes DA, Kawashima-Vasconcelos MY, Lima-Junior JR, et al. Autologous hematopoietic stem cell transplantation modifies specific aspects of systemic sclerosis-related microvasculopathy. Ther Adv Musculoskelet Dis. 2022;14:1759720X221084845. doi:10.1177/1759720X221084845
45. Morgan ND, Hummers LK. Scleroderma mimickers. Curr Treatm Opt Rheumatol. 2016;2(1):69-84. doi:10.1007/s40674-016-0038-7
46. Papara C, De Luca DA, Bieber K, Vorobyev A, Ludwig RJ. Morphea: The 2023 update. Front Med (Lausanne). 2023;10:1108623. doi:10.3389/fmed.2023.1108623
47. Trang G, Steele R, Baron M, Hudson M. Corticosteroids and the risk of scleroderma renal crisis: a systematic review. Rheumatol Int. 2012;32(3):645-653. doi:10.1007/s00296-010-1697-6
48. Umashankar E, Abdel-Shaheed C, Plit M, Girgis L. Assessing the role for nailfold videocapillaroscopy in interstitial lung disease classfication: a systematic review and meta-analysis. Rheumatology (Oxford). 2022;61(6):2221-2234. doi:10.1093/rheumatology/keab772
49. Tang M, Shi J, Pang Y, Zhou S, Liu J, Wu C, et al. Nailfold videocapillaroscopy findings are associated with IIM subtypes and IFN activation. Arthritis Res Ther. 2025;27(1):62. doi:10.1186/s13075-025-03532-9
50. Kubo S, Todoroki Y, Nakayamada S, Nakano K, Satoh M, Nawata A, et al. Significance of nailfold videocapillaroscopy in patients with idiopathic inflammatory myopathies. Rheumatology (Oxford). 2019;58(1):120-130. doi:10.1093/rheumatology/key257
51. Johnson D, van Eeden C, Moazab N, Redmond D, Phan C, Keeling S, et al. Nailfold capillaroscopy abnormalities correlate with disease activity in adult dermatomyositis. Front Med (Lausanne). 2021;8:708432. doi:10.3389/fmed.2021.708432
52. Soubrier C, Seguier J, Di Costanzo MP, Ebbo M, Bernit E, Jean E, et al. Nailfold videocapillaroscopy alterations in dermatomyositis, antisynthetase syndrome, overlap myositis, and immune-mediated necrotizing myopathy. Clin Rheumatol. 2019;38(12):3451-3458. doi:10.1007/s10067-019-04710-2
53. Wakura R, Matsuda S, Kotani T, Shoda T, Takeuchi T. The comparison of nailfold videocapillaroscopy findings between anti-melanoma differentiation-associated gene 5 antibody and anti-aminoacyl tRNA synthetase antibody in patients with dermatomyositis complicated by interstitial lung disease. Sci Rep. 2020;10(1):15692. doi:10.1038/s41598-020-72752-7
54. Selva-O'Callaghan A, Fonollosa-Pla V, Trallero-Araguas E, Martinez-Gomez X, Simeon-Aznar CP, Labrador-Horrillo M, et al. Nailfold capillary microscopy in adults with inflammatory myopathy. Semin Arthritis Rheum. 2010;39(5):398-404. doi:10.1016/j.semarthrit.2008.09.003
55. Schmeling H, Stephens S, Goia C, Manlhiot C, Schneider R, Luthra S, et al. Nailfold capillary density is importantly associated over time with muscle and skin disease activity in juvenile dermatomyositis. Rheumatology (Oxford). 2011;50(5):885-893. doi:10.1093/rheumatology/keq407
56. Bogojevic M, Markovic Vlaisavljevic M, Medjedovic R, Strujic E, Pravilovic Lutovac D, Pavlov-Dolijanovic S. Nailfold capillaroscopy changes in patients with idiopathic inflammatory myopathies. J Clin Med. 2024;13(18). doi:10.3390/jcm13185550
57. Pachman LM, Morgan G, Klein-Gitelman MS, Ahsan N, Khojah A. Nailfold capillary density in 140 untreated children with juvenile dermatomyositis: an indicator of disease activity. Pediatr Rheumatol Online J. 2023;21(1):118. doi:10.1186/s12969-023-00903-x

58. Sebastiani M, Triantafyllias K, Manfredi A, Gonzalez-Gay MA, Palmou-Fontana N, Cassone G, et al. Nailfold capillaroscopy characteristics of antisynthetase syndrome and possible clinical associations: results of a multicenter international study. J Rheumatol. 2019;46(3):279-284. doi:10.3899/jrheum.180355
59. Cutolo M, Melsens K, Wijnant S, Ingegnoli F, Thevissen K, De Keyser F, et al. Nailfold capillaroscopy in systemic lupus erythematosus: A systematic review and critical appraisal. Autoimmun Rev. 2018;17(4):344-352. doi:10.1016/j.autrev.2017.11.025
60. Cutolo M, Sulli A, Pizzorni C, Accardo S. Nailfold videocapillaroscopy assessment of microvascular damage in systemic sclerosis. J Rheumatol. 2000;27(1):155-160.
61. Pavlov-Dolijanovic S, Damjanov NS, Vujasinovic Stupar NZ, Marcetic DR, Sefik-Bukilica MN, Petrovic RR. Is there a difference in systemic lupus erythematosus with and without Raynaud's phenomenon? Rheumatol Int. 2013;33(4):859-865. doi:10.1007/s00296-012-2449-6
62. Tariq S, Tervaert JWC, Osman M. Nailfold capillaroscopy in systemic lupus erythematosus (SLE): a point-of-care tool that parallels disease activity and predicts future complications. Curr Treatm Opt Rheumatol. 2019;5:336-345. doi:https://doi.org/10.1007/s40674-019-00133-x
63. Riccieri V, Spadaro A, Ceccarelli F, Scrivo R, Germano V, Valesini G. Nailfold capillaroscopy changes in systemic lupus erythematosus: correlations with disease activity and autoantibody profile. Lupus. 2005;14(7):521-525. doi:10.1191/0961203305lu2151oa
64. Kuryliszyn-Moskal A, Ciolkiewicz M, Klimiuk PA, Sierakowski S. Clinical significance of nailfold capillaroscopy in systemic lupus erythematosus: correlation with endothelial cell activation markers and disease activity. Scand J Rheumatol. 2009;38(1):38-45. doi:10.1080/03009740802366050
65. Groen H, ter Borg EJ, Postma DS, Wouda AA, van der Mark TW, Kallenberg CG. Pulmonary function in systemic lupus erythematosus is related to distinct clinical, serologic, and nailfold capillary patterns. Am J Med. 1992;93(6):619-627. doi:10.1016/0002-9343(92)90194-g
66. Lee P, Leung FY, Alderdice C, Armstrong SK. Nailfold capillary microscopy in the connective tissue diseases: a semiquantitative assessment. J Rheumatol. 1983;10(6):930-938.
67. Anghel D, Sîrbu CA, Petrache OG, Opriș-Belinski D, Negru MM, Bojincă VC, et al. Nailfold Videocapillaroscopy in patients with rheumatoid arthritis and psoriatic arthropathy on ANTI-TNF-ALPHA therapy. Diagnostics (Basel). 2023;13(12). doi:10.3390/diagnostics13122079
68. Melsens K, Leone MC, Paolino S, Elewaut D, Gerli R, Vanhaecke A, et al. Nailfold capillaroscopy in Sjogren's syndrome: a systematic literature review and standardised interpretation. Clin Exp Rheumatol. 2020;38 Suppl 126(4):150-157.
69. Matsuda S, Kotani T, Wakura R, Suzuka T, Kuwabara H, Kiboshi T, et al. Examination of nailfold videocapillaroscopy findings in ANCA-associated vasculitis. Rheumatology (Oxford). 2023;62(2):747-757. doi:10.1093/rheumatology/keac402
70. Lledo-Ibanez GM, Saez Comet L, Freire Dapena M, Mesa Navas M, Martin Cascon M, Guillen Del Castillo A, et al. CAPI-detect: machine learning in capillaroscopy reveals new variables influencing diagnosis. Rheumatology (Oxford). 2025. doi:10.1093/rheumatology/keaf073
71. Ma Z, Mulder DJ, Gniadecki R, Cohen Tervaert JW, Osman M. Methods of assessing nailfold capillaroscopy compared to video capillaroscopy in patients with systemic sclerosis-a critical review of the literature. Diagnostics (Basel). 2023;13(13). doi:10.3390/diagnostics13132204

BIMZELX IS THE **FIRST AND ONLY** IL-17A AND IL-17F INHIBITOR.*[1,2]

AN OPPORTUNITY TO CHALLENGE PSA AND AXSPA WITH BIMZELX

BIMZELX is indicated for the treatment of adult patients with:[1]

- moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy
- active psoriatic arthritis. BIMZELX can be used alone or in combination with a conventional non-biologic disease-modifying antirheumatic drug (cDMARD) (e.g., methotrexate)
- active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy
- active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs)

Conditions of clinical use:
BIMZELX is not authorized for use in pediatrics (<18 years of age).

Relevant warnings and precautions:

- Inflammatory bowel disease
- Serious hypersensitivity reactions
- Vaccinations
- Infections, including tuberculosis
- Pregnant or nursing women
- Women of childbearing potential

For more information:
Please consult the Product Monograph at ucb-canada.ca/en/bimzelx for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece. The Product Monograph is also available by calling 1-866-709-8444.

* Comparative clinical significance is unknown.

1. BIMZELX Product Monograph. UCB Canada Inc. November 27, 2024. **2.** Data on file, UCB Canada Inc.

Inspired by patients. Driven by science.

REVIEWED BY PAAB

Pr Bimzelx® (bimekizumab)

About the Authors

Jill Trinacty, MD

Dr. Trinacty is originally from Nova Scotia, where she obtained her Bachelor of Science (Honours) degree at Saint Francis Xavier University in Antigonish. She completed her medical degree at Dalhousie University. Dr. Trinacty completed residency in Internal Medicine and specialization in Endocrinology and Metabolism at The Ottawa Hospital. She is a diplomate of the American Board of Obesity Medicine. She practices at LMC Ottawa, Queensway Carleton Hospital, and Bariatric Medical Institute. She is a consultant and affiliate researcher with Bruyere Continuing Care. She is presently a lecturer at the University of Ottawa. She also serves as Vice Chair of the Endocrinology Section for the OMA and is an editor of the journal Canadian Diabetes and Endocrinology Today.

Affiliations: Clinician, LMC Ottawa
Clinician, Bariatric Medical Institute
Clinician, Queensway Carleton Hospital
Consultant and Affiliate Researcher, Bruyère Continuing Care
Lecturer, University of Ottawa

Krista Rostom, MD

Dr. Rostom obtained her Bachelor of Science in Engineering at Queen's University and her medical degree at Dalhousie University. Dr. Rostom completed her residency in Internal Medicine and her Rheumatology fellowship at The University of Ottawa and The Ottawa Hospital. She is a community Rheumatologist practicing in her general rheumatology outpatient clinic as well as seeing patients in hospital as a consultant.

Affiliations: Clinician, West Ottawa Specialty Care
Clinician, Queensway Carleton Hospital

doi.org/10.58931/crt.2025.2158

Glucagon-like-peptide 1 (GLP-1) Receptor Agonists in Rheumatologic Disease

Jill Trinacty, MD
Krista Rostom, MD

Obesity

Obesity is a complex chronic disease that increases the risk of long-term medical complications and reduces lifespan due to excess body fat or adiposopathy. As of 2016, obesity affects 8.3 million (26.4%) of the Canadian population. Severe obesity, defined as a body mass index (BMI) >35 kg/m^2, affects an estimated 1.9 million Canadians. The financial burden of obesity, including both direct and indirect costs, was estimated to be $7.1 billion in 2010.[1] The pathophysiology of obesity is complex and involves a combination of genetic, metabolic, behavioural, and environmental factors. The hypothalamus regulates appetite and energy expenditure, while the mesolimbic area controls the emotional, pleasurable, and rewarding aspects of eating. The frontal lobe is responsible for overriding the hedonic drive of the mesolimbic system. Adipose tissue itself contributes to its regulation through the release of leptin in proportion to fat mass. Leptin binds to receptors in the hypothalamus to reduce appetite and increase energy expenditure. Similarly, insulin binds to receptors in the arcuate nucleus of the hypothalamus also reducing appetite and increasing energy expenditure.[1]

Prevalence of Obesity in Rheumatologic Disease

The prevalence of obesity in rheumatoid arthritis (RA) has been examined in multiple studies. One cross-sectional cohort study of patients conducted at three Brazilian teaching hospitals has shown that 26.9% of patients had BMI-defined obesity, which was associated with age, hypertension, and dyslipidemia.[2] Another cross-sectional analysis found that obesity was prevalent in 33.4% of patients with RA compared to 31.6% of control patients.[3] This suggests that obesity seems to be as prevalent in patients with RA, if not more so. Several studies have shown higher rates of obesity in psoriatic arthritis,[4] with obesity being more prevalent in those with psoriatic arthritis than in patients with RA or psoriasis.

Treatment of Obesity

Glucagon-like-peptide 1 (GLP-1) is an endogenous incretin hormone secreted by intestinal L-cells in response to food intake. Glucagon-like peptide receptor agonists (GLP-1RAs) are a class of medications which historically have been used for diabetes and weight management, given their ability to modulate glucose levels, insulin secretion, and appetite control.[5] Currently, GLP-1RAs are indicated for treating both type 2 diabetes and obesity. This pharmacologic category of medications continues to evolve, with the recent addition of tirzepatide to the market. Tirzepatide is a single molecule that acts as an antagonist to both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), an incretin synthesized in the K-cells of the duodenum and jejunum. GIP has also been shown to impact both insulin secretion and appetite, and dual agonism with GLP-1 results in greater impacts on glucose control and weight management. Currently, tirzepatide is indicated for treating type 2 diabetes. The future of this therapy continues to evolve, with multiple studies looking at co-agonism with amylin analogues and glucagon analogues.[5] The currently available incretin-based therapies are listed in **Table 1**.

However, the mechanisms of GLP-1RAs are complex, and thus their future therapeutic potential goes beyond their historical indications. Recent studies have been looking at a broad range of diseases which could be impacted by

Drug	Administration		Dose (*mg*)	Effect on A1c	Effect on Weight	Weight Loss Indication	CV Benefit
	Route	Frequency					
Exendin-based GLP-1 Receptor Agonists							
Exenatide	SC	BID	5–10	↓↓	↓↓	No	No
Lixisenatide	SC	Daily	10–20	↓↓	↓	No	No
Human GLP-1-based GLP-1 Receptor Agonists							
Liraglutide	SC	Daily	0.6–1.8*	↓↓	↓↓↓	Yes	Yes
Dulaglutide	SC	Weekly	0.75–1.5	↓↓	↓↓	No	Yes
Semaglutide	SC	Weekly	0.25–2*	↓↓↓	↓↓↓	Yes	Yes
	Oral	Daily	3–14	↓↓↓	↓↓↓	No	Yes
Dual GLP-1/G1P Receptor Agonists							
Tirzepatide	SC	Weekly	2.5–15	↓↓↓↓	↓↓↓↓	No	Pending

Table 1. Comparison among incretin-based therapies; *used with permission from Druce, I. (2025). GLP-1 Receptor Agonist Use in Pregnancy. Canadian Diabetes & Endocrinology Today, 3(1), 31–37. https://doi.org/10.58931/cdet.2025.3139.*

*Doses indicated for weight loss are higher than those listed, all listed dosages are for the indication of glycemic management.

Abbreviations: BID: twice daily, **CV:** cardiovascular, **GIP:** glucose-dependent insulinotropic polypeptide, **GLP-1:** glucagon-like peptide 1, **SC:** subcutaneous

GLP-1 therapy including cardiovascular disease, non-alcoholic fatty liver disease, chronic kidney disease, degenerative neurologic diseases, as well as musculoskeletal and inflammatory diseases.[6]

Possible Mechanisms of GLP-1RA in Arthritis

There are multiple potential mechanisms through which GLP-1RAs could affect rheumatologic diseases. First, visceral adipose tissue releases inflammatory mediators such as tumour necrosis factor (TNF)-α, interleukin (IL)-6, and leptin, which can drive multiple inflammatory pathways.[7] Therefore, it is unsurprising that obesity can affect clinical outcomes in various subtypes of inflammatory arthritis. In the context of RA, obesity is a risk factor for poor response to treatment in early RA and reduces the odds of achieving remission in established RA.[8-11] Similarly, in psoriatic arthritis, obese patients experience worse outcomes in terms of remission, and an elevated BMI is a risk factor for developing the condition.[12,13] In ankylosing spondylitis, obesity is associated with worse clinical outcome measures including the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and the Axial Spondyloarthritis Disease Activity Score (ASDAS).[14] Conversely, studies in both RA and psoriatic arthritis that looked at the effect of weight loss on clinical outcomes have shown positive effects.[15-17] However, similar data supporting weight loss to improve outcomes in ankylosing spondylitis is currently lacking.

While GLP-1RAs can produce significant weight loss, which in turn may affect outcomes in inflammatory arthritis patients, this is not the only mechanism by which these medications are postulated to exert their effects. GLP-1R expression is present in chondrocytes in osteoarthritis (OA), macrophages and fibroblast-like synoviocytes in RA, as well as in osteoblasts, osteocytes, and osteoclasts.[6] Therefore, GLP-1RAs potentially operate through various mechanisms to affect inflammation and suppress cytokine release, including inhibiting the

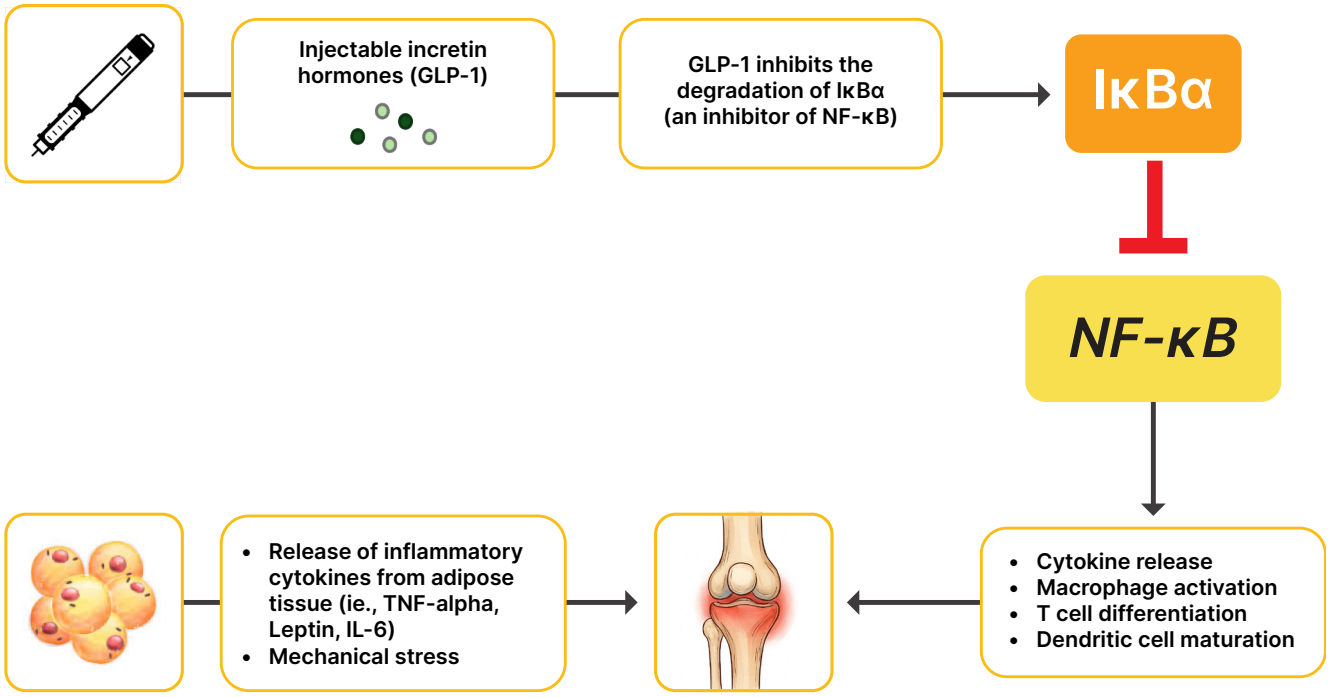

Figure 1. A proposed mechanism of GLP1 mechanisms in rheumatoid arthritis: **1)** Immune: IκBα inhibits nuclear translocation of NF-κB, and thus the downstream inflammatory effects of the NF-κB pathways. GLP1 receptor agonists inhibit phosphorylation and degradation of IκBα, therefore, allowing IκBα to maintain its inhibition on NF-κB pathway and decreasing its downstream inflammatory effects. **2)** Adipose tissue releases inflammatory adipokines which can also contribute to inflammation. **3)** Mechanical stress from adipose tissue; *adpated from Karacabeyli D, Lacaille D. Glucagon-like peptide 1 receptor agonists in patients with inflammatory arthritis or psoriasis: a scoping review J Clin Rheumatol. 2024;30(1):26-31. doi:10.1097/RHU.0000000000001949.*

nuclear factor-kappa B (NF-kB) pathway.[6] In RA, one mechanism is via IκBα, an inhibitor protein that keeps NF-kB transcription factors inactive in the cytoplasm.[18] GLP-1RAs inhibit phosphorylation and degradation of IκBα, which in turn inhibits nuclear activation of the NF-kB pathway, thus blocking its downstream inflammatory effects.[18]

Current Evidence for GLP-1RAs in OA

Currently, the strongest evidence supporting the use of GLP-1RAs is found in OA. OA is the most common degenerative joint disease, and its incidence is higher in obese patients. Studies have shown that weight loss in these patients can both improve symptoms and reduce the risk of developing knee OA.[19] In a recent large randomized controlled trial comparing once weekly semaglutide to a placebo in obese patients with knee OA, those taking semaglutide experienced a significant reduction in pain scores and improved function compared to those taking a placebo.[20] Additionally, the semaglutide group showed a greater reduction in the use of non-steroidal anti-inflammatory drugs compared to the placebo group. Given that the patients in the treatment arm achieved significant weight loss during the trial, it is unclear whether the improved outcomes were soley due to the metabolic effect of GLP-1RAs, or if cellular level effects also played a role.

Current Evidence for GLP-1RAs in Inflammatory Arthritis

The current evidence supporting the use of GLP-1RAs in inflammatory arthritis is less robust compared to OA. There are no published randomized controlled trials for GLP-1RAs in RA, psoriatic arthritis, or ankylosing spondylitis. However, a retrospective cohort study of RA patients on GLP-1RAs reported improvements in the erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and pain scores.[21] Additionally, in a study of 15 patients with

type 2 diabetes and active rheumatoid or psoriatic arthritis, nine patients treated with liraglutide achieved improvement in Disease Activity Score-28 (DAS-28) scores.[18] These patients also showed superior A1c and weight reduction.[22] Currently, there is no evidence for the use of GLP-1RAs in ankylosing spondylitis.

Cardiovascular Risk Reduction

Cardiovascular disease (CVD) is prominent in RA. One study showed that 39.6% of deaths among patients with RA were attributable to CVD.[23] In addition, RA has been associated with a 48% increased risk of cardiovascular events. Patients with RA also face a 50% higher risk of cardiovascular-related mortality compared to the general population.[24,25] The mechanism of increased risk of CVD in patients with RA appears to be related to risk factors including obesity, diabetes, smoking, and hypertension, as well as inflammatory mechanisms. It is suggested that pro-inflammatory cytokines, which contribute to the disease course of RA, may also contribute to the development of atherogenesis.[26] GLP-1RAs have shown a reduction in cardiovascular events in patients with diabetes and in those with obesity. For patients with type 2 diabetes, risk reduction was observed both in those with known cardiovascular disease and those at high risk.[27,28] For patients with obesity, semaglutide has been shown to reduce the risk of major adverse cardiovascular events in those with pre-existing cardiovascular disease.[29] Notably, this cardiovascular benefit was independent of weight loss.

While GLP-1RAs have not been directly studied in patients with RA and CVD, a population-based cohort study of patients in British Columbia assessed the risk of all-cause mortality and major adverse cardiovascular events (MACE) in patients with immune-mediated inflammatory diseases and type 2 diabetes newly initiating GLP-1RAs versus dipeptidyl peptidase-4 inhibitors (DPP-4is).[30] Rates of both mortality and MACE were lower in patients who initiated GLP1-RA therapy compared to those who initiated DPP-4i therapy. This study included patients with comorbid diabetes and therefore the effect in patients with immune-mediated inflammatory disease without diabetes is not yet known.

Conclusion/Future Directions

The potential benefits of GLP-1RAs in rheumatology extend beyond their historical use as weight loss medications, showing promising effects seen on inflammation, immune responses, and direct effects on tissue. While obesity has been shown to be a risk factor for worse outcomes, such as remission in inflammatory arthritis, the link between GLP-1RA medications and better outcomes has yet to be established. Further clinical research is required to demonstrate both the clinical efficacy and safety of GLP-1RAs in inflammatory arthritis patients. As the landscape of GLP-1RAs continues to evolve, more robust evidence is needed before they can be considered a viable treatment strategy for managing chronic inflammatory arthritis.

Correspondence

Jill Trinacty, MD
Email: jill.trinacty@lmc.ca

Financial Disclosures

J.T.: Grants/Research Support: Amgen, Abbott, NovoNordisk, Eli Lilly; **Speakers Bureau/Honoraria:** Abbott, Boehringer Ingelheim, CCRN, CME Away, CPD Network, Dexcom, Eli Lilly, EOCI, Humber River Hospital, Intellectures, Novo Nordisk; **Consulting Fees/Ad Board:** Abbott, Bayer, Eli Lilly, HLS Therapeutics, Novo Nordisk, Tandem

K.R.: Speakers Bureau/Honoraria: AbbVie, UCB, Novartis, Janssen, Lilly; **Consulting Fees/Ad Board:** AbbVie, Novartis, Amgen, Sandoz

References

1. Wharton S, Lau DC, Vallis M, Sharma AM, Biertho L, Campbell-Scherer D, et al. Obesity in adults: a clinical practice guideline. CMAJ. 2020;192(31):E875-E891. doi:10.1503/cmaj.191707
2. Guimarães MF, Rodrigues CE, Gomes KW, Machado CJ, Brenol CV, Krampe SF, et al. High prevalence of obesity in rheumatoid arthritis patients: association with disease activity, hypertension, dyslipidemia and diabetes, a multi-center study. Adv Rheumatol. 2019;59(1):44. doi:10.1186/s42358-019-0089-1
3. Dar L, Tiosano S, Watad A, Bragazzi NL, Zisman D, Comaneshter D, et al. Are obesity and rheumatoid arthritis interrelated Int J Clin Pract. 2018;72(1): 10.1111/ijcp.13045. doi:10.1111/ijcp.13045
4. Maas F, Arends S, van der Veer E, Wink F, Efde M, Bootsma H, et al. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. J Rheumatol. 2016;43(2):383-387. doi:10.3899/jrheum.150648
5. Drucker DJ. Efficacy and safety of GLP-1 medicines for type 2 diabetes and obesity. Diabetes Care. 2024 Nov 1;47(11):1873-1888. doi:10.2337/dci24-0003
6. Zheng Z, Zong Y, Ma Y, Tian Y, Pang Y, Zhang C, et al. Glucagon-like peptide-1 receptor: mechanisms and advances in therapy. Signal Transduct Target Ther. 2024;9(1):234. doi:10.1038/s41392-024-01931-z
7. Williams JC, Hum RM, Rogers K, Maglio C, Alam U, Zhao SS. Metabolic syndrome and psoriatic arthritis: the role of weight loss as a disease-modifying therapy. Ther Adv Musculoskelet Dis. 2024;16:1759720X241271886. doi:10.1177/1759720X241271886
8. Dubovyk V, Vasileiadis GK, Fatima T, Zhang Y, Kapetanovic MC, Kastbom A, et al. Obesity is a risk factor for poor response to treatment in early rheumatoid arthritis: a NORD-STAR study. RMD Open. 2024;10(2):e004227. doi:10.1136/rmdopen-2024-004227
9. Levitsky A, Brismar K, Hafström I, Hambardzumyan K, Lourdudoss C, van Vollenhoven RF, et al. Obesity is a strong predictor of worse clinical outcomes and treatment responses in early rheumatoid arthritis: results from the SWEFOT trial. RMD Open. 2017;3(2):e000458. doi:10.1136/rmdopen-2017-000458
10. Liu Y, Hazlewood GS, Kaplan GG, Eksteen B, Barnabe C. Impact of obesity on remission and disease activity in rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken). 2017;69(2):157-165. doi:10.1002/acr.22932
11. Abuhelwa AY, Hopkins AM, Sorich MJ, Proudman S, Foster DJ, Wiese MD. Association between obesity and remission in rheumatoid arthritis patients treated with disease-modifying anti-rheumatic drugs. Sci Rep. 2020;10(1):18634. doi:10.1038/s41598-020-75673-7
12. Kumthekar A, Ogdie A. Obesity and psoriatic arthritis: a narrative review. Rheumatol Ther. 2020;7(3):447-456. doi:10.1007/s40744-020-00215-6
13. Leung YY, Eder L, Orbai AM, Coates LC, De Wit M, Smolen JS, et al. Association between obesity and likelihood of remission or low disease activity status in psoriatic arthritis applying index-based and patient-based definitions of remission: a cross-sectional study. RMD Open. 2023;9(3):e003157. doi:10.1136/rmdopen-2023-003157
14. Maas F, Arends S, van der Veer E, Wink F, Efde M, Bootsma H, et al. Obesity is common in axial spondyloarthritis and is associated with poor clinical outcome. J Rheumatol. 2016;43(2):383-387. doi:10.3899/jrheum.150648
15. Ranganath VK, La Cava A, Vangala S, Brook J, Kermani TA, Furst DE, et al. Improved outcomes in rheumatoid arthritis with obesity after a weight loss intervention: randomized trial. Rheumatology (Oxford). 2023;62(2):565-574. doi:10.1093/rheumatology/keac307
16. Kreps DJ, Halperin F, Desai SP, Zhang ZZ, Losina E, Olson AT, et al. Association of weight loss with improved disease activity in patients with rheumatoid arthritis: a retrospective analysis using electronic medical record data Int J Clin Rheumtol. 2018;13(1):1-10. doi:10.4172/1758-4272.1000154
17. Klingberg E, Bilberg A, Björkman S, Hedberg M, Jacobsson L, Forsblad-d'Elia H, et al. Weight loss improves disease activity in patients with psoriatic arthritis and obesity: an interventional study. Arthritis Res Ther. 2019;21 (1):17. doi:10.1186/s13075-019-1810-5
18. Karacabeyli D, Lacaille D. Glucagon-like peptide 1 receptor agonists in patients with inflammatory arthritis or psoriasis: a scoping review J Clin Rheumatol. 2024;30(1):26-31. doi:10.1097/RHU.0000000000001949
19. Huffman KF, Ambrose KR, Nelson AE, Allen KD, Golightly YM, Callahan LF. The critical role of physical activity and weight management in knee and hip osteoarthritis: a narrative review. J Rheumatol. 2024;51(3):224-233. doi:10.3899/jrheum.2023-0819
20. Bliddal H, Bays H, Czernichow S, Uddén Hemmingsson J, Hjelmesæth J, Hoffmann Morville T, et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. N Engl J Med. 2024;391(17):1573-1583. doi:10.1056/NEJMoa2403664
21. Dente E, Kellner D, Tran V, Welsh T, Tran V, Saha A, et al. Effects of anti-obesity medications in RA patients. [abstract]. Arthritis Rheumatol. 2024;76 (suppl 9). https://acrabstracts.org/abstract/effects-of-anti-obesity-medications-in-ra-patients. Accessed April 28, 2025.

22. Sullivan C, Gaoatswe G, Gibney J, Healy ML, Doran M, Kane D, et al. Treatment with the glucagon-like peptide-1 analogue liraglutide is associated with amelioration of disease activity in a prospective cohort study of patients with inflammatory arthritis. [abstract]. Arthritis Rheumatol 2013;65:S630-S631. Accessed April 28, 2025
23. Sokka T, Abelson B, Pincus T. Mortality in rheumatoid arthritis: 2008 update. Clin Exp Rheumatol. 2008;26(5 Suppl 51):S35-S61.
24. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis. 2012;71(9):1524-1529. doi:10.1136/annrheumdis-2011-200726
25. Aviña-Zubieta JA, Choi HK, Sadatsafavi M, Etminan M, Esdaile JM, Lacaille D. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum. 2008;59(12):1690-1697. doi:10.1002/art.24092
26. England BR, Thiele GM, Anderson DR, Mikuls TR. Increased cardiovascular risk in rheumatoid arthritis: mechanisms and implications. BMJ. 2018;361:k1036. doi:10.1136/bmj.k1036
27. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med . 2016;375(19):1834-1844. doi:10.1056/NEJMoa1607141
28. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121-130. doi:10.1016/S0140-6736(19)31149-3
29. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes N Engl J Med. 2023;389(24):2221-2232. doi:10.1056/NEJMoa2307563
30. Karacabeyli D, Lacaille D, Lu N, McCormick N, Xie H, Choi HK, Aviña-Zubieta JA. Mortality and major adverse cardiovascular events after glucagon-like peptide-1 receptor agonist initiation in patients with immune-mediated inflammatory diseases and type 2 diabetes: A population-based study. Plos one. 2024 Aug 8;19(8):e0308533.

doi.org/10.58931/crt.2025.2159

About the Author

Marvin J. Fritzler, MD, PhD

Dr. Marvin Fritzler is Professor Emeritus of Medicine, University of Calgary. He is the Founder of Mitogen Diagnostics Corporation and has held the Arthritis Society Research Chair for 14 years. He has published more than 560 peer-reviewed manuscripts, and his work has been cited more than 43,000 times (H index 96).

Affiliations: Professor Emeritus, Cumming School of Medicine, University of Calgary, Calgary, Alberta

The Past, Present and Future of Antinuclear Antibody (ANA) Testing

Marvin J. Fritzler, MD, PhD

This article is in memory of Dr. Eng M. Tan (Emeritus: The Scripps Research Institute) and acknowledges the remarkable mentorship and tremendous contributions to our understanding of anti-nuclear antibodies (ANA). Dr. Tan passed away in 2024 at the age of 97.

Introduction

More than 70 years have passed since the discovery of the lupus erythematosus (LE) cell and the development of the LE cell test, which led to the 'tipping point' for the discovery of antinuclear antibody (ANA), or what should more correctly be referred to as anti-cellular antibodies (ACA).[1] Paralleling the evolution of ANA testing based on the indirect immunofluorescence assay (IFA) on cryopreserved organ sections in the 1960s and through the early 1970s was an 'explosion' in the spectrum of ANA and a remarkable transition in technologies used to detect ANA. This included the transition to IFA on HEp-2 cell substrates beginning in the late 1970s.[2] While some of the 'octogenarian' immunoassays such as double immunodiffusion, hemagglutination, complement fixation, radioimmunoassay, and counterimmunoelectrophoresis are fading into oblivion, the ANA IFA has prevailed because of its world-wide use as a screening test for systemic autoimmune rheumatic diseases (SARD), diagnostic criteria for autoimmune hepatitis, a risk factor for the development of uveitis in juvenile idiopathic arthritis, and the entry criterion for classification of systemic lupus erythematosus (SLE).[1,3] ANA testing, once regarded the domain of rheumatologists and clinical immunologists, has witnessed a widening spectrum of clinicians using these tests because of its links to a growing spectrum of autoimmune and autoinflammatory conditions.[2] All of this is set against the background of remarkable advances in autoantibody detection, especially the emergence of newer high-throughput (i.e., faster turn-around-time for results), multi-analyte array technologies (MAAT). These technologies use comparatively small serum or plasma volumes and provide higher specificity while detecting a broad range of SARD autoantibodies.[4]

Over 180 autoantibodies have been described in SLE, more than 30 in systemic sclerosis, and greater than 20 in autoimmune inflammatory myopathies (AIM). The ongoing discovery and expanding spectrum of autoantibodies in SARD

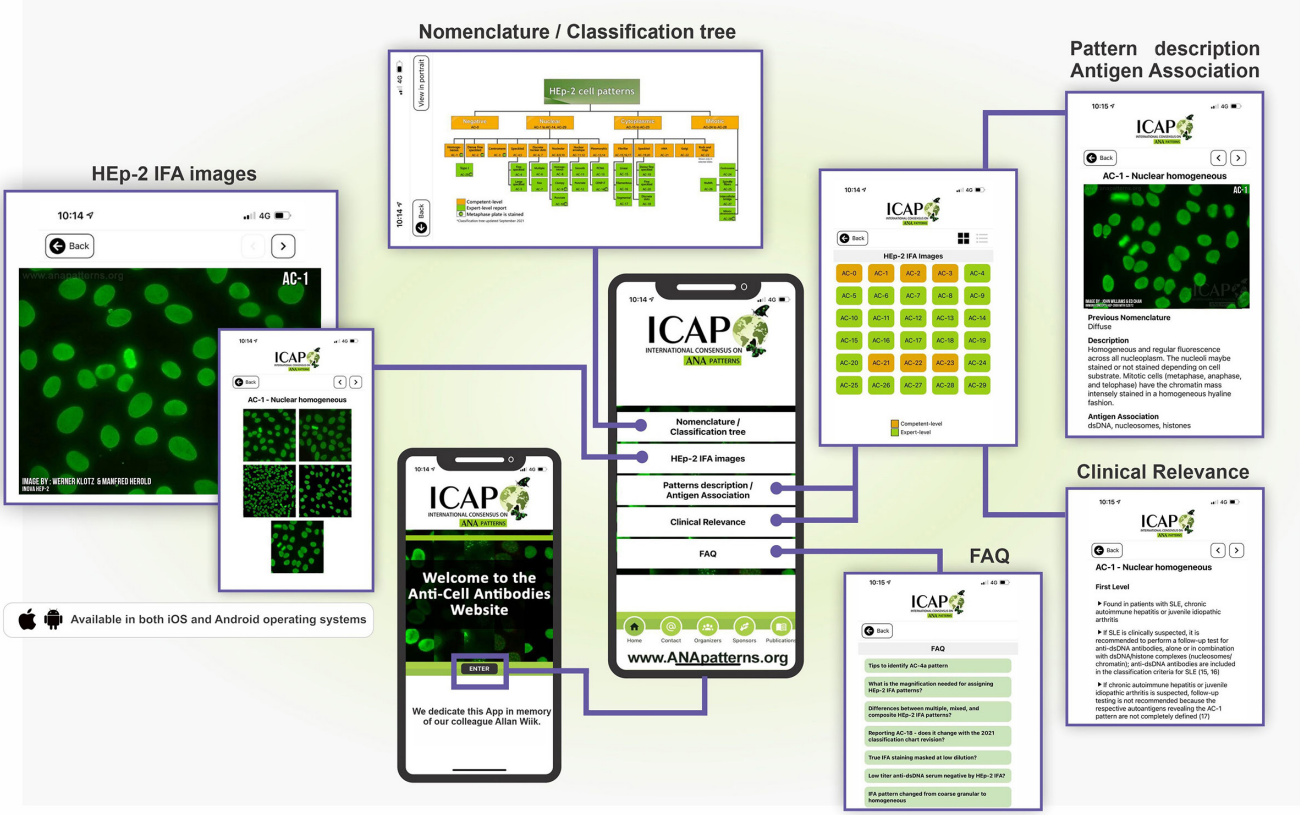

Figure 1. A wealth of information on the nomenclature and related clinical features associated with a wide spectrum of anti-nuclear antibodies (ANA) is available on the **Consensus on Autoantibody Patterns (ICAP) website** and can be easily accessed through this ICAP app available free of charge; *courtesy of Marvin J. Fritzler, MD, PhD.*

might be considered as unnecessary but a primary rationale for these efforts is to identify new and clinically actionable ANAs that close the 'seronegative gap' in SARD.[5]

Despite over half a century of 'progress', one of the major challenges continues to be the standardization and harmonization of ANA testing.[6] The history of this problem is extensive and still plagued by significant limitations despite the concerted efforts of various global committees representing world-wide input. These include the Serology Sub-Committee of the International Union of Immunology Societies, which has provided easily-accessed reference sera containing the major autoantibody specificities, and an extension of those efforts by the International Consensus on Autoantibody Patterns (ICAP) to standardize the nomenclature of the main ANA patterns and ANA test reports.[3,7] Clinicians should take advantage of the wealth of ANA information on the **ICAP website** that can be easily accessed with the ICAP "app" (**Figure 1**).

Another major challenge to the clinical use and interpretation of ANA testing is evidence showing that the prevalence of positive ANAs in the general population is increasing, with some studies reporting rates higher than 30%.[8] This increase has been attributed to several factors including environmental agents and exposure to xenobiotics, climate change, high sensitivity and low specificity of many ANA methodologies, and pandemics including COVID-19.[9,10]

It is important to understand that for an accurate interpretation of the ANA test results, both the titers and IFA patterns are very important.[7] Although there are geographic variations in ANA IFA pattern reporting with some regions restricting reports to 'nuclear' staining patterns, many laboratories also report IFA staining of cytoplasmic and mitotic components cells.[1,7] Many sera also demonstrate more than one AC pattern (e.g., mixed patterns) or have an IFA pattern not currently characterized by ICAP that then receives an AC-XX designation followed by a descriptor.[7]

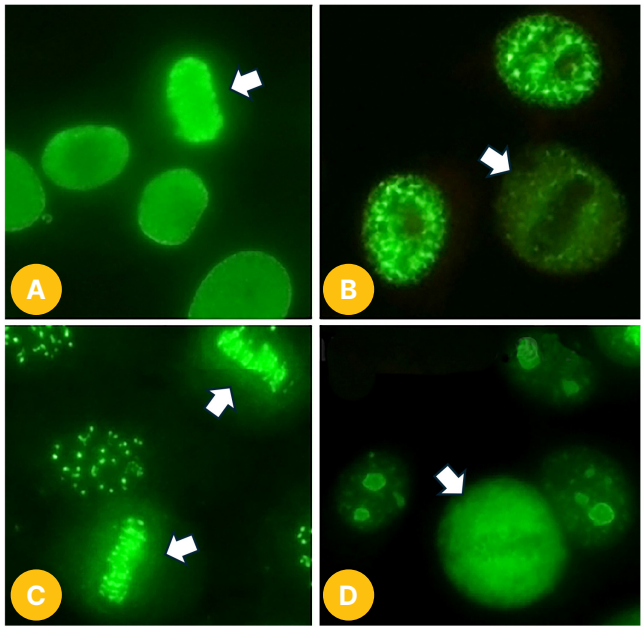

Figure 2. Common HEp-2 indirect immunofluorescence assay (IFA) patterns observed in systemic autoimmune rheumatic diseases (SARD) sera: **a)** homogeneous/diffuse nuclear staining (AC-1) associated with antibodies to dsDNA and nucleosomes; **b)** speckled nuclear staining (AC-4, AC-5) associated with antibodies to Sm and other nuclear ribonucleoproteins (RNP); **c)** discrete speckled nuclear staining (AC-3) associated with anti-centromere antibodies and limited cutaneous systemic sclerosis; **d)** anti-nucleolar antibodies (AC-8, AC-9, AC-10) associated with diffuse cutaneous systemic sclerosis (SSc); *courtesy of Marvin J. Fritzler, MD, PhD.*

In general, SARD are characterized by high titer (>1:320) ANA, with the most specific HEp-2 IFA patterns (**Figure 2**) including AC-1 (anti-dsDNA, anti-nucleosomes), AC-3 (anti-centromere in limited cutaneous systemic sclerosis [SSc]), AC-4 and AC-5 (anti-Sm and U RNPs in SLE and mixed connective tissue disease), AC-8, AC-9, AC-10 (nucleolar autoantibodies characteristic of diffuse cutaneous SSc [dcSSc]), AC-29 (associated with anti-topoisomerase I/Scl-70 in dcSSC), and AC-30 (anti-Ro60 and anti-nucleosomes observed in Sjögren disease [SjD] and SLE). From this overview, it appears that SARD autoantibodies typically stain and target the HEp-2 nuclei. Nevertheless, other IFA patterns are occasionally observed in SARD, and often point to overlapping conditions, inflammatory and infectious diseases, malignancy, or even the absence of overt disease.

For example, the AC-2 HEp-2 IFA pattern, when confirmed as monospecific (e.g., no other known autoantibodies detected) anti-DFS70 antibodies by an antigen-specific immunoassay, rules out the diagnosis of SARD in >95% of cases,[11] while the AC-1, AAC-4, and AC-30 IFA patterns, which are similar to AC-2, -3 tends to "rule in" a SARD diagnosis. It needs to be appreciated that despite the high sensitivity of the HEp-2 IFA test for SARD, the approximate frequency of a negative ANA is 5% in SLE, 3% in SSc, 1% in MCTD, 25% in SjD and 40 % in the broad spectrum of autoimmune inflammatory myopathies (AIM). In addition, many of the HEp-2 IFA patterns observed in AIM are not closely correlated with the specific routinely-detected autoantibodies (e.g., anti-Jo1, anti-MDA5, anti-HMGCR). To summarize, the clinician should not rely on HEp-2 IFA screening when a diagnosis of SjD or AIM is being considered.

As evidenced by the Choosing Wisely recommendations endorsed by the Canadian Rheumatology Association in 2015, and 'consensus' statements of the American College of Rheumatologists and the American College of Pathologists, the use and abuse of ANA testing is the subject of considerable criticism.[12] There is general agreement that once a SARD diagnosis has been established the ANA should not be repeated. However, there are exceptions in which a repeat ANA may be helpful, such as in SARD patients who develop features of another or overlapping condition, with an example being limited cutaneous SSc patients who develop anti-mitochondrial antibodies suggesting the presence or onset of primary biliary cholangitis. Recently, the Effective Health Care (EHC) Program stated that there is a "broad clinical consensus that ANA testing (including ANA sub-serologies) should not be used to screen for SARDs in primary care," Therefore, "there is no clinical uncertainty that a new systematic review could potentially address."[13] In other words, despite evidence to the contrary[12], this evidence indicates that ANA testing must be curtailed (particularly in primary care) because of its "poor positive and negative predictive values (positive predictive value [PPV] 29%, negative predictive value [NPV] 77%), leading to increased health care costs with unclear clinical benefit." With these issues in mind, my perspectives on the future of ANA testing are summarized in four questions.

First, what should be done with well-known evidence that some ANA and related autoantibodies antedate the diagnosis of SARD by up to 20 years?[14] Unfortunately, the proclamations from Choosing Wisely and the EHC arise from a rather myopic perspective that ANA testing should be limited to patients with a high PPV/low NPV for SARD. Clearly, because the frequency of a positive ANA test approaches 30% in the population, ANA testing should not be done on patients without any clear evidence of a SARD.

Second, the circular logic is difficult to rationalize because, if the suspected SARD patient has a high PPV, why should the ANA test be performed at all? Some argue that this is necessary for suspected SLE individuals to fulfill the ACR/EULAR classification criteria. However, it is important to remember that these are classification criteria, not diagnostic criteria. An important aspect that seems to be overlooked is that when conventional diagnostic and an 'intent to treat' approach to ANA testing is used, the diagnosis of SARDs is delayed. As a result, a considerable proportion of patients have active disease and end organ damage at the time of or shortly after the diagnosis is made.[12] This delay in diagnosis is associated with remarkably high direct and indirect health care costs.[15] Conditions such as renal disease, pulmonary fibrosis, hypertension, and irreversible joint damage, to name a few, require much more intensive and expensive care. This leads to a decreased health-related quality of life and additional increased indirect costs. These observations are prompting many clinicians to reconsider their approach to SARDs, making concerted efforts to achieve much earlier diagnoses, as exemplified by studies of undifferentiated connective tissue disease[16] and the Very Early Diagnosis of Systemic Sclerosis (VEDOSS) cohort.[17] It needs to be appreciated that achieving an earlier diagnosis is currently primarily in the domain of primary health care providers, who serve as the SARD 'case finders'.[12] Screening tests such as ANA for SARD are used as part of 'case finding'. Then, based on clinical acumen, patients are referred to subspecialists for evaluation and appropriate management. In my view, it is quite unfortunate that some rheumatologists are unhappy when they receive a referral for an ANA-positive individual who has "nothing". I think that this situation is a win-win for the patient, the physician, and the health care system. In my view, a much clearer and proactive approach is needed for assuring these apparently 'healthy' individuals that a positive ANA is not a diagnostic of a disease. It is beyond the scope of this brief overview to cite the growing literature that other biomarkers can be used as predictors of disease in ANA-positive individuals that might have a low pre-test probability of a SARD. This approach will be more realistic and actionable when artificial intelligence (AI) (discussed briefly below) is used to weigh and sort various aspects of an individual's health to predict an emerging SARD or other condition.

Third, if primary care physicians and 'nurse' practitioners are not the early SARD case finders in the real world when there is a severe shortage of tertiary care rheumatologists, who is?

Fourth, given the documented and perceived limitations of the ANA IFA test as a screen for SARD,[18] what should replace it? As a succinct reply to this question, some modern laboratories are migrating to ANA immunoassay platforms that are highly automated and digital,[2] as well as to MAAT, which offer higher throughput and faster turn-around-times.[4] Recent evidence indicates that the best approach for ANA testing is to screen with the relatively inexpensive HEp-2 IFA ANA and then reflex to a MAAT.[2,19] Some laboratories use solid phase ANA tests, which, despite earlier limitations, now have performance that is comparable to, if not better than, the HEp-2 IFA when used in a reflex test setting.[19] Similarly, the digital automated ANA test systems referred to above have superior performance characteristics compared to 'manual' systems, offering hope that this is an important step toward harmonization of the ANA test.

Many clinicians often find the wealth of laboratory investigation and imaging results overwhelming and confusing (e.g., low titer ANA, obscure ANA IFA patterns, and MAAT results), making it unclear how they are clinically actionable. There is considerable optimism that AI and machine learning approaches will help clarify this by combining testing data into likely diagnoses and subsets of SARD, while also recommending actionable approaches and prognostic considerations for managing patients.[20]

Key Considerations in Ordering and Interpreting ANA tests
The ANA test is not standardized or harmonized; hence, there are differences in results generated by different labs.
Up to 30% of the general population can have a positive ANA.
Useful and clinically actionable ANA tests should be performed on individuals with a moderate-to-high pre-test probability of a SARD.
Both the titer and immunofluorescence patterns should be reported because they are important in interpreting the results.
It is recommended that a positive ANA be followed by testing for specific targets using multi-analyte arrays.
Unless there is a change in the clinical features of the patient, the ANA should not be repeated once the diagnosis of SARD is established.
In the future, ANA results will only be one input considered as artificial intelligence will analyze and 'interpret' multiple inputs to more accurately inform the clinician's diagnostics.

Conclusion

In summary, despite its long history, there is a strong need for evidence-based approaches to ANA testing. Future laboratory testing needs to consider the importance of disease prevention fostered by 'case finding' and the attenuation of significant morbidity and health care expenditures.[12,18] As MAATs improve and decrease in price, it is possible that the ANA test will no longer be the SARD screening assay of choice. In the meantime, the judicious use of the ANA test should focus on making an early and accurate diagnosis of SARD, with the best 'value' of the ANA test being in individuals with a moderate pre-test probability of the disease. Given the high frequency of ANA in the general population, individuals with either a high or low pre-test probability are unlikely to benefit from the test. Individuals with a high pre-test probability will likely gain more benefit from proceeding directly to MAAT analysis of autoantibodies.

Correspondence

Marvin J. Fritzler, MD, PhD
Email: fritzler@ucalgary.ca

Financial Disclosures

M.J.F: Medical Director of and an employee of Mitogen Diagnostics Corporation; **Consultant or Advisory Role:** Aesku Group, BioRad, Werfen International, Alexion Canada; **Honoraria:** Aesku Group, Werfen International, Alexion Canada.

Acknowledgements: I have had outstanding collaborators in Canada and from around the world and my career has benefited from brilliant consultants, graduate students, and post-doctoral fellows.

References

1. Damoiseaux J, von Mühlen CA, Garcia-De La Torre I, Carballo OG, de Melo Cruvinel W, Francescantonio PL, et al. International consensus on ANA patterns (ICAP): the bumpy road towards a consensus on reporting ANA results. Auto Immun Highlights. 2016;7(1):1. doi:10.1007/s13317-016-0075-0
2. Mahler M, Meroni PL, Bossuyt X, Fritzler MJ. Current concepts and future directions for the assessment of autoantibodies to cellular antigens referred to as anti-nuclear antibodies. J Immunol Res. 2014;2014:315179. doi:10.1155/2014/315179
3. Andrade LEC, Klotz W, Herold M, Musset L, Damoiseaux J, Infantino M, et al. Reflecting on a decade of the international consensus on ANA patterns (ICAP): accomplishments and challenges from the perspective of the 7th ICAP workshop. Autoimmun Rev. 2024;23(9):103608. doi:10.1016/j.autrev.2024.103608
4. Fritzler MJ, Mahler M. Redefining systemic lupus erythematosus - SMAARTT proteomics. Nat Rev Rheumatol. 2018;14(8):451-452. doi:10.1038/s41584-018-0035-3
5. Fritzler MJ, Choi MY, Satoh M, Mahler M. Autoantibody discovery, assay development and adoption: death valley, the sea of survival and beyond. Front Immunol. 2021;12:679613. doi:10.3389/fimmu.2021.679613
6. Van den Bremt S, Schouwers S, Van Blerk M, Van Hoovels L. ANA IIF automation: moving towards harmonization? Results of a multicenter study. J Immunol Res. 2017;2017:6038137. doi:10.1155/2017/6038137

7. von Mühlen CA, Garcia-De La Torre I, Infantino M, Damoiseaux J, Andrade LEC, Carballo OG, et al. How to report the antinuclear antibodies (anti-cell antibodies) test on HEp-2 cells: guidelines from the ICAP initiative. Immunol Res. 2021;69(6):594-608. doi:10.1007/s12026-021-09233-0
8. Dinse GE, Parks CG, Weinberg CR, Co CA, Wilkerson J, Zeldin DC, et al. Increasing prevalence of antinuclear antibodies in the United States. Arthritis Rheumatol. 2022;74(12):2032-2041. doi:10.1002/art.42330
9. Miller FW. The increasing prevalence of autoimmunity and autoimmune diseases: an urgent call to action for improved understanding, diagnosis, treatment, and prevention. Curr Opin Immunol. 2023;80:102266. doi:10.1016/j.coi.2022.102266
10. Choi MY, Costenbader KH, Fritzler MJ. Environment and systemic autoimmune rheumatic diseases: an overview and future directions. Front Immunol. 2024;15:1456145. doi:10.3389/fimmu.2024.1456145
11. Bossuyt X. DFS70 autoantibodies: clinical utility in antinuclear antibody testing. Clin Chem. 2024;70(2):374-381. doi:10.1093/clinchem/hvad181
12. Fritzler MJ. Choosing wisely: review and commentary on anti-nuclear antibody (ANA) testing. Autoimmun Rev. 2016;15(3):272-280. doi:10.1016/j.autrev.2015.12.002
13. Agency for Healthcare Research and Quality. Effective health care anti-nuclear antibodies (ANA) screening in community populations: Evidence-Based Practice Centers; 2018 [updated 2018 Oct 2, cited 2025 Feb 13]. Available from: https://effectivehealthcare.ahrq.gov/system/files/docs/ana-testing-topic-disposition.pdf.
14. Brunekreef TE, van den Heuvel HB, Limper M, Leavis H, van Laar JM, Otten H. The predictive value of antinuclear antibodies in patients with suspected connective tissue disease for the development of connective tissue diseases. Clin Exp Rheumatol. 2024;42(1):24-29. doi:10.55563/clinexprheumatol/k2xvu8
15. Yee J, Feldman CH, Oakes EG, Ellrodt J, Guan H, Choi MY, et al. Cost-related medication behaviors for patients with and without systemic autoimmune rheumatic diseases. Arthritis Care Res (Hoboken). 2024. doi:10.1002/acr.25442
16. Radin M, Cecchi I, Barinotti A, Wilson Jones G, Arbrile M, Miraglia P, et al. Identifying subsets of patients with undifferentiated connective tissue disease: results from a prospective, real-world experience using particle-based multi-analyte technology. Autoimmun Rev. 2023;22(5):103298. doi:10.1016/j.autrev.2023.103298
17. Bellando-Randone S, Del Galdo F, Lepri G, Minier T, Huscher D, Furst DE, et al. Progression of patients with Raynaud's phenomenon to systemic sclerosis: a five-year analysis of the European Scleroderma Trial and Research group multicentre, longitudinal registry study for Very Early Diagnosis of Systemic Sclerosis (VEDOSS). Lancet Rheumatol. 2021;3(12):e834-e843. doi:10.1016/s2665-9913(21)00244-7
18. Fritzler MJ. The antinuclear antibody test: last or lasting gasp? Arthritis Rheum. 2011;63(1):19-22. doi:10.1002/art.30078
19. Tonutti E, Bizzaro N, Morozzi G, Radice A, Cinquanta L, Villalta D, et al. The ANA-reflex test as a model for improving clinical appropriateness in autoimmune diagnostics. Auto Immun Highlights. 2016;7(1):9. doi:10.1007/s13317-016-0080-3
20. Zhan K, Buhler KA, Chen IY, Fritzler MJ, Choi MY. Systemic lupus in the era of machine learning medicine. Lupus Sci Med. 2024;11(1). doi:10.1136/lupus-2023-001140

doi.org/10.58931/crt.2025.2160

About the Author

Akihiro Nakamura, MD, PhD

Dr. Nakamura is an Assistant Professor and Clinician Scientist at Queen's University. He completed his rheumatology fellowship training and PhD program at the Schroeder Arthritis Research Institute in Toronto and the University of Toronto, respectively. He co-discovered the immunological roles of macrophage migration inhibitory factor (MIF) and hypoxia-inducible factor (HIF) in spondyloarthritis (SpA). He holds two international and U.S. patents related to these discoveries. Dr. Nakamura has authored numerous high-impact publications, including first-author basic/translational research articles in *Science Translational Medicine, Annals of the Rheumatic Diseases, and Cellular & Molecular Immunology* (Nature). He joined Queen's University in 2022 and serves as the Director of the Queen's Research Program for Spondyloarthritis (QURE-SpA).

Affiliations: Department of Medicine, Division of Rheumatology, Queen's University, Kingston, Ontario, Canada.
Faculty of Health Sciences, School of Medicine, Queen's University, Kingston, Ontario, Canada.
Translational Institute of Medicine, Department of Medicine, Queen's University, Ontario, Canada.
Rheumatology Clinic, Kingston Health Science Centre, Kingston, Ontario, Canada.

The Impact of Chimeric Antigen Receptor (CAR) T Cell Therapy: Its Potential to Reshape Rheumatology Practice

Akihiro Nakamura, MD, PhD

In recent years, genetically modified T cell therapy, using chimeric antigen receptor (CAR)-engineered T cells, has revolutionized the field of rheumatology. While CAR T cell therapy is approved by government agencies, including Health Canada, as a standard treatment for B cell lymphoproliferative malignancies, it has also shown remarkable efficacy in refractory cases of rheumatic diseases, including systemic lupus erythematosus, systemic sclerosis, idiopathic inflammatory myopathies, ANCA-associated vasculitis, and rheumatoid arthritis. A single infusion of CAR T cells has demonstrated the potential to induce long-term drug-free remission in most cases. This therapy achieves profound B cell depletion in both blood and tissues—an effect not typically observed with conventional antibody-based B cell-target therapies. Despite its transformative potential, several challenges remain, including questions around long-term safety, high costs, limited accessibility, and the absence of standardized guidelines, which complicate its broader application. Rheumatologists face practical uncertainties, such as determining the optimal timing for treatment, selecting suitable patients, and identifying which diseases might benefit the most from this therapy. This editorial explores the fundamental principles of CAR T cell therapy, highlights the unresolved challenges, and provides insights into how rheumatologists can optimize its use for managing rheumatic diseases. (Please note that this manuscript was written in April 2025. Given the rapid advancements and emerging evidence in this field, there may be updates by the time this article is published.)

Introduction

Since the first report of five refractory cases of systemic lupus erythematosus (SLE),[1] chimeric antigen receptor (CAR) T cell therapy targeting CD19-expressed B cells has garnered considerable attention as a potential treatment capable of inducing long-term remission for autoantibody-driven rheumatic diseases. According to the currently available literature, this therapy has been used in refractory cases of SLE,[1,2] systemic sclerosis (SSc),[3-5] idiopathic inflammatory myopathy (IIM),[5,6] ANCA-associated vasculitis (AAV), and rheumatoid arthritis (RA),[7] with additional reports likely to emerge for other rheumatic conditions. These patients had tried various currently available treatment options but failed to achieve disease control. Remarkably, all but one patient with IIM achieved drug-free remission without recurrence following a single infusion of CAR T cells, as reported in the latest conference update,[8] which included up to 3 years of follow-up in 30 patients with autoimmune diseases.

Although the remarkable effects of CAR T cell therapy have significantly impacted rheumatologists, they have also raised important considerations. Key questions include which types of rheumatic diseases, at what stages, and for which patients this therapy should be used. Additionally, safety concerns, cost, and available facilities remain major factors for many rheumatologists when contemplating the use of CAR T cell therapy in clinical practice.

This editorial provides insights into the fundamental aspects of CAR T cell therapy—such as its mechanism of action, efficacy, and safety—while also discussing its potential impact and practical considerations for rheumatologists to optimize patient outcomes with this groundbreaking treatment.

What is CAR T Cell Therapy and Why is it So Effective?

CAR T cells are genetically engineered by inserting CARs into T cells, typically using viral vectors. These T cells can be obtained from either the same patient (autologous)[1] or a donor (allogeneic).[5] CARs have various subtypes based on their targets and structural differences, with newer generations engineered to maximize their binding affinity to target cells.[4,9,10] In rheumatic diseases, where autoreactive B cell clones are primary targets, CARs targeting B cell surface markers such as CD19 or B cell maturation antigen (BCMA) have been used.[11,12] Once these CAR T cells are expanded and infused back into the patient, they recognize their target B cell lineages and eliminate the cells expressing these targets by releasing T cell-derived cytotoxic enzymes, such as granzymes and perforin.[9] Following administration, CAR T cells undergo dramatic expansion upon activation through interaction with targeted B cells, remain at high levels in the circulation for several weeks, and gradually decline over the next several months.[1,8] The key information on CAR T cells is provided in **Table 1**.

The efficacy of CAR T cells for autoimmune rheumatic diseases has been extensively discussed elsewhere,[1,13] and the results so far appear remarkably promising. Targeting B cells is not a new strategy in autoimmune-driven rheumatic diseases. Why, then, are CAR T cells so effective compared to other antibody-based B cell-targeted therapies, such as rituximab? The short answer lies in the ability of CAR T cell therapy to achieve deep depletion of B cells. As described below, several factors contribute to this superior efficacy.

First, as a "live-cell" therapy, CAR T cells possess the unique ability to migrate into tissues. Unlike rituximab, which primarily depletes circulating B cells, CAR T cells can infiltrate into major organs such as the kidneys, lungs, and even the brain by crossing the blood-brain barrier.[14] Once in the target tissues, CAR T cells bind to, and eliminate B cells, including autoreactive B cell clones, resulting in profound B cell depletion within these tissues. Indeed, a recent study demonstrated that while both CAR T cell therapy and rituximab effectively deplete B cells in the peripheral blood, only CAR T cell therapy achieves a visibly complete B cell depletion in tissues such as lymph nodes, colon, kidneys, and gallbladder.[15] This distinctive feature of CAR T cell therapy is particularly crucial in treating autoimmune diseases because it provides multiple benefits, including:

- Eliminating B cell maturation into plasmablasts or plasma cells that produce autoantibodies
- Reducing B cell-driven cytokine release
- Preventing B cell-mediated antigen presentation to naïve T cells, which could otherwise differentiate into effector T cells and contribute to tissue damage.

Questions	Answers based on currently available reports
What are the sources of CAR T cells?	Autologous (from the patient) or Allogenic (from healthy donors)
Which markers are targeted by CAR T cells?	CD19 and/or BCMA
How are CARs inserted?	Mostly virus-mediated insertion (e.g., lentiviral or retroviral vector)
How long does it take to expand CAR T cells before administration?	Several weeks. The CAR T cells are expanded using cocktails of cytokines, such as IL-2, IL-7, and IL-15
How soon are B cells eliminated from the circulation after CAR T cell infusion?	Within a week (between 3 and 7 days)
How long do CAR T cells remain in the body after infusion?	They are expanded over several weeks and gradually decreased over the following months
Which rheumatic diseases are the best targets for CD19- or BCMA-CAR T cell therapy?	B cell-driven autoimmune diseases, such as SLE, SSc, IIM, RA, SjS, and AAV
What are the common adverse events associated with CAR T cell therapy for rheumatic diseases?	CRS (grade 1*), neutropenia, lymphocytopenia, and infections (ICU cases are uncommon) The risks of ICANS and cancer appear to be very low
When does B cell reconstruction begin to be seen?	Approximately 3 months after CAR T cell infusion
Are newly emerging B cells pathogenic during reconstruction?	Based on currently available evidence, the new B cells appear to be healthy

Table 1. Ten common questions and answers regarding CAR T cell therapy for rheumatic diseases (based on evidence available as of January 2025); *courtesy of Akihiro Nakamura, MD, PhD.*

*Based on the Penn grading scale.[18]

Abbreviations: **AAV:** antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis, **BCMA:** B cell maturation antigen, **CAR:** chimeric antigen receptor, **CD19:** cluster differentiation-19, **CRS:** cytokine releasing syndrome, **ICANS:** immune-cell-associated neurotoxicity syndrome, **IIM**: idiopathic inflammatory myositis, **IL:** interleukin, **RA:** rheumatoid arthritis, **SjS:** Sjögren's syndrome, **SLE:** systemic lupus erythematosus, **SSc:** systemic sclerosis.

Another potential explanation for the deep B cell depletion achieved by CAR T cell therapy is its target, CD19 or BCMA. Unlike CD20, CD19 and BCMA are expressed on a broader range of more matured B cell lineage cells, including plasmablasts and some fractions of plasma cells. This is particularly critical, as they are major sources of autoantibodies. These plasmablasts and plasma cells do not predominantly express CD20 and can therefore persist in the circulation, tissues, or blood after anti-CD20 therapies such as rituximab and obinutuzumab.[15,16]

Another striking feature of CAR T cell therapy is its ability to induce B cell reconstruction. Within 3 to 7 days post-administration, B cells are usually completely eliminated from the circulating blood. However, approximately 3 months after CAR T cell infusion, B cells reemerge in the circulation with a phenotype similar to that of healthy individuals,[1,13] yet autoantibodies remain undetectable. This suggests a "reset" of the B cell population following CAR T cell administration. Importantly, this reset appears to be long-lasting, as patient observations over a span of 2 years have shown no reemergence of detectable autoantibodies.[13] Although the long-term outcomes beyond 2 years remain unknown and need to be monitored, the treatment has thus far produced remarkable results, including the regeneration of seemingly healthy B cells without pathogenic phenotypes.

Practical Considerations for Rheumatologists

Given such astonishing results, CAR T cell therapy holds significant potential for broader use in rheumatic diseases. However, there is currently no specific guidance or evidence for the optimal

use of CAR T cell therapy due to the limited number of cases in which it has been applied in rheumatic diseases. For rheumatologists, it is essential to address critical questions to optimize the treatment, including which diseases, at what time points, and for which patients CAR T cell therapy should be prioritized.

Although current evidence is limited, the nature of this therapy targeting B cells makes it clear that B cell-driven, autoantibody-mediated rheumatic diseases are the most suitable targets. In this context, SLE, SSc, IIM, AAV, and RA are reasonable candidates for CAR T cell therapy, as these diseases are driven by autoantibody-mediated inflammation that results in tissue damage. Importantly, recent omics-based phenotypic stratification has revealed substantial heterogeneity within the same disease, highlighting the need to identify patients with strong autoantibody signatures in their circulation and/or tissues. Other B cell-driven diseases, such as Sjögren's disease and IgG4-related disease, are also considered to potentially receive benefits from CAR T cell therapy. These diseases are currently being investigated in clinical trials, primarily based in China, as of January 2025 (**ClinicalTrials.gov** ID: NCT06497361 and NCT06056921). In contrast, diseases primarily driven by non-B cell populations (seronegative diseases), such as psoriatic arthritis and spondyloarthritis,[17] are unlikely to be suitable candidates for B cell-targeted CAR T cell therapy.

The timing of CAR T cell administration also requires discussion. Based on currently available reported cases, all patients have received the therapy after undergoing multiple treatments. This approach is logical at this point, as CAR T cell therapy is not yet a standard treatment for rheumatic diseases, largely due to the limited availability of facilities, its extremely high cost (approximately $350,000 to $500,000 USD per infusion),[9] and unconfirmed long-term safety. However, given the favourable outcomes observed over a period of up to 3 years,[8] and potentially beyond, rheumatologists may need to consider the optimal timing for CAR T cell administration to achieve the best treatment outcomes.

In this context, from my personal perspective, if no major barriers are identified in the future, earlier administration—before exhausting all other available treatments—may need to be considered, as treatment outcomes and prognosis primarily depend on minimizing permanent tissue and organ damage caused by long-term inflammation, vasculopathy, and fibrosis. To achieve this, it is crucial to risk-stratify patients based on various assessments, including the speed of disease progression, histological evaluation, imaging modalities, and functional studies. Once appropriate candidates are identified, a multidisciplinary team comprising of the rheumatologist and other specialists such as hematologists, nephrologists, and respirologists, along with an ethics board, should review the case and consider CAR T cell therapy if it is deemed the best option. Given the complexity of these cases and the need for facilities with access to a range of specialists within a multidisciplinary team, it is most practical to conduct CAR T cell therapy at tertiary academic centres. These centres often have hematologists experienced in using CAR T cell therapy for hematological cancers, therefore making them the most suitable option when Canadian rheumatologists begin using this therapy. Collaborating with hematologists also allows for the monitoring of hematological parameters, such as B cell reconstitution and potential hematological adverse events, after administration.

Safety

The safety of CAR T cell therapy, both in the short-term and long-term, is a major concern when applying it to rheumatic diseases. Given the limited number of cases in rheumatic diseases, any risks associated with CAR T therapies reported in hematological malignancy cases are considered conceivable. Although it is too early to draw definitive conclusions, the current safety profiles in rheumatic diseases appear to be milder than those in cancer treatments.

Major adverse events related to CAR T cell therapy include cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS: a condition caused by systemic inflammation and elevated cytokines, leading to CNS inflammation and can potentially life-threatening cerebral edema), macrophage activation syndrome (MAS), and hematological malignancies. CRS is commonly observed as an early adverse event following infusion, but most instances are grade 1 CRS (based on the Penn grading scale[18]), which is generally manageable with anti-pyretic treatments. Although grade 3 CRS and grade 4 ICANS were recently reported in a patient treated with CD19 CAR T cell therapy

for polyrefractory RA,[7] grade 2 or 3 CRS and other conditions, including ICANS and MAS, appear to be very uncommon based on currently available data.[8] This may be attributed to the smaller burden of B cells targeted by CAR T cells in rheumatic diseases compared to cancer, where a larger number of B cells are targeted and destroyed by the therapy. The destruction of B cells, especially in B cell lymphoma, continuously activates not only CAR T cells but also innate immune cells such as monocytes, macrophages, and neutrophils.[19] This activation leads to the release of cytotoxic or inflammatory cytokines that can cause tissue or organ damage. Furthermore, in cancer-related CAR T cell therapy, newly emerged rheumatic diseases have been reported, including RA, palindromic rheumatism, and inflammatory myositis.[20] This may be due to increased neoantigen (cancer cell-derived autoantigen) exposure from destroyed cancer cells to CD4+ T cells, triggering the activation and maturation of B cells that produce autoantibodies. Although new rheumatic diseases secondary to CAR T cell therapy have not been reported in patients with rheumatic diseases, this is theoretically possible. Therefore, careful monitoring—both during hospitalization following the infusion and during outpatient follow-up—is essential following therapy, particularly in distinguishing these conditions from the original rheumatic diseases.

Regarding the risk of infections, it is conceivable that CAR T cell therapy increases this risk. Indeed, severe infections have been reported in 7 out of 35 patients (20%), over an observation period of up to 3 years, including pneumonia related to COVID-19, cytomegalovirus (CMV), or respiratory syncytial virus (RSV).[8] In particular, due to common adverse events such as neutropenia and lymphocytopenia following lymphodepletion with cyclophosphamide and fludarabine prior to CAR T cell infusion, potential infectious risks should always be considered. However, during the observation period of up to 3 years, no cases requiring ICU admission were identified.[8] Additionally, since CAR T cell therapy has the potential to induce drug-free remission for years, the long-term risk of infections—particularly after B cell reconstruction following CAR T cell therapy—may decrease overall in patients with rheumatic diseases. Although infectious risks need to be firmly evaluated in clinical trials compared with control groups, CAR T cell therapy may ultimately reduce overall long-term infectious risks in rheumatic diseases. It is also crucial to maximize vaccination prior to CAR T cell therapy. The immunity acquired following vaccination is likely maintained even after CAR T cell-mediated elimination of CD19-expressing B cells, because long-term plasma cells generally do not express CD19, and they remain in the bone marrow for years.

In terms of malignancies, there are no reports of CAR T cell therapy causing malignancies in rheumatic diseases. Although the risk of T cell malignancy following CAR T cell therapy has raised concerns due to their nature of expansion after infusion, a recent analysis of over 3,000 pediatric and adult patients with hematologic malignancies (with a median observation period of up to 17.7 months) revealed only one case (0.03%),[21] indicating an extremely low risk. This risk appears to be similar for rheumatic diseases.

Future Directions and Conclusions

The excitement surrounding this innovative treatment, which offers the potential for long-term, drug-free remission and represents a significant step toward the ultimate goal of a ‘cure’ for autoimmune-driven rheumatic diseases, is already motivating rheumatologists to take the next steps. However, several critical challenges and uncertainties must be addressed to move forward. First, it is essential to confirm the efficacy and safety of this therapy beyond 3 years to ensure sustainable clinical outcomes without unforeseen adverse effects. As of April 2025, more than 80 clinical trials targeting rheumatic diseases are actively ongoing worldwide, according to the **ClinicalTrials.gov** registry. Most of these studies are being conducted in China, the United States, and various European countries. Currently, no trials are registered in Canada. However, given the approval of CAR T cell therapy for hematologic conditions, there is potential to initiate related clinical trials in Canada in the near future.

Second, as discussed in previous sections, rheumatologists must optimize patient selection and the timing of administration. Ideally, guidelines or recommendations for CAR T cell therapy will be developed in the future, but robust data is required to do so. While such data are unlikely

to be available in the next few years, preliminary guidance for clinicians could be developed in the future if the therapy comes to be regarded as a standard option for refractory patients. Regarding the types of diseases, testing this approach in other rapidly progressive and life-threatening B cell-driven diseases—such as anti-melanoma differentiation-associated protein 5 (MDA5)-positive dermatomyositis and catastrophic antiphospholipid antibody syndrome—should also be considered. This could broaden its applicability and address unmet needs in these critical conditions.

Finally, to achieve the best outcomes from this therapy, and minimize the risk of adverse events, such as graft-versus-host disease, further refinements in CAR structure (targeting different molecules beyond CD19 and BCMA), delivery systems (e.g., CRISPR technology), and exploration of alternative cell sources, such as γδ T cells and natural killer (NK) cells, are necessary. Additionally, employing allogeneic CAR T cells to bypass the need for T cell collection from patients, along with scaling production and marketing efforts, could significantly reduce costs and improve access to this transformative therapy.

While this therapeutic approach offers unprecedented promise, its widespread adoption and success will depend on addressing several challenges. Advances in technology, clinical validation of long-term safety, and innovative solutions to cost barriers will be critical in making this therapy a practical and sustainable option for patients with autoimmune rheumatic diseases. With continued research and collaboration, this treatment could pave the way for a new era in medicine, reshaping treatment strategies driven by rheumatologists.

Correspondence

Akihiro Nakamura, MD, PhD
Email: Akihiro.Nakamura@queensu.ca

Financial Disclosures

A.N.: None declared.

References

1. Mackensen A, Müller F, Mougiakakos D, Böltz S, Wilhelm A, Aigner M, et al. Anti-CD19 CAR T cell therapy for refractory systemic lupus erythematosus. Nat Med. 2022;28(10):2124-2132. doi:10.1038/s41591-022-02017-5
2. Mougiakakos D, Krönke G, Völkl S, Kretschmann S, Aigner M, Kharboutli S, et al. CD19-Targeted CAR T cells in refractory systemic lupus erythematosus. N Engl J Med. 2021;385(6):567-569. doi:10.1056/NEJMc2107725
3. Bergmann C, Müller F, Distler JHW, Györfi AH, Völkl S, Aigner M, et al. Treatment of a patient with severe systemic sclerosis (SSc) using CD19-targeted CAR T cells. Ann Rheum Dis. 2023;82(8):1117-1120. doi:10.1136/ard-2023-223952
4. Merkt W, Freitag M, Claus M, Kolb P, Falcone V, Röhrich M, et al. Third-generation CD19.CAR-T cell-containing combination therapy in Scl70+ systemic sclerosis. Ann Rheum Dis. 2024;83(4):543-546. doi:10.1136/ard-2023-225174
5. Wang X, Wu X, Tan B, Zhu L, Zhang Y, Lin L, et al. Allogeneic CD19-targeted CAR-T therapy in patients with severe myositis and systemic sclerosis. Cell. 2024;187(18):4890-4904.e4899. doi:10.1016/j.cell.2024.06.027
6. Pecher AC, Hensen L, Klein R, Schairer R, Lutz K, Atar D, et al. CD19-targeting CAR T cells for myositis and interstitial lung disease associated with antisynthetase syndrome. Jama. 2023;329(24):2154-2162. doi:10.1001/jama.2023.8753
7. Lidar M, Rimar D, David P, Jacoby E, Shapira-Frommer R, Itzhaki O, et al. CD-19 CAR-T cells for polyrefractory rheumatoid arthritis. Ann Rheum Dis. 2024. doi:10.1136/ard-2024-226437

8. Hagen M, Muller F, Wirsching A, Tur C, Krickau T, Metzler M, et al. Safety and long-term efficacy of CD19-CAR T-cell therapy in 30 patients with autoimmune disease [abstract]. Arthritis Rhematol. 2024;76.
9. Ohno R, Nakamura A. Advancing autoimmune rheumatic disease treatment: CAR-T Cell therapies - evidence, safety, and future directions. Semin Arthritis Rheum. 2024;67:152479. doi:10.1016/j.semarthrit.2024.152479
10. Schett G, Müller F, Taubmann J, Mackensen A, Wang W, Furie RA, et al. Advancements and challenges in CAR T cell therapy in autoimmune diseases. Nat Rev Rheumatol. 2024;20(9):531-544. doi:10.1038/s41584-024-01139-z
11. Qin C, Dong MH, Zhou LQ, Wang W, Cai SB, You YF, et al. Single-cell analysis of refractory anti-SRP necrotizing myopathy treated with anti-BCMA CAR-T cell therapy. Proc Natl Acad Sci U S A. 2024;121(6):e2315990121. doi:10.1073/pnas.2315990121
12. Wang W, He S, Zhang W, Zhang H, DeStefano VM, Wada M, et al. BCMA-CD19 compound CAR T cells for systemic lupus erythematosus: a phase 1 open-label clinical trial. Ann Rheum Dis. 2024;83(10):1304-1314. doi:10.1136/ard-2024-225785
13. Müller F, Taubmann J, Bucci L, Wilhelm A, Bergmann C, Völkl S, et al. CD19 CAR T-cell therapy in autoimmune disease - a case series with follow-up. N Engl J Med. 2024;390(8):687-700. doi:10.1056/NEJMoa2308917
14. Siddiqi T, Wang X, Blanchard MS, Wagner JR, Popplewell LL, Budde LE, et al. CD19-directed CAR T-cell therapy for treatment of primary CNS lymphoma. Blood Adv. 2021;5(20):4059-4063. doi:10.1182/bloodadvances.2020004106
15. Tur C, Eckstein M, Velden J, Rauber S, Bergmann C, Auth J, et al. CD19-CAR T-cell therapy induces deep tissue depletion of B cells. Ann Rheum Dis. 2024. doi:10.1136/ard-2024-226142
16. Looney CM, Schroeder A, Tavares E, Garg J, Schindler T, Vincenti F, et al. Obinutuzumab effectively depletes Key B-cell subsets in blood and tissue in end-stage renal disease patients. Transplant Direct. 2023;9(2):e1436. doi:10.1097/txd.0000000000001436
17. Remalante-Rayco P, Nakamura A. Year in review: novel Insights in the Pathogenesis of Spondyloarthritis - SPARTAN 2024 Annual Meeting Proceedings. Curr Rheumatol Rep. 2024;27(1):9. doi:10.1007/s11926-024-01176-3
18. Porter D, Frey N, Wood PA, Weng Y, Grupp SA. Grading of cytokine release syndrome associated with the CAR T cell therapy tisagenlecleucel. J Hematol Oncol. 2018;11(1):35. doi:10.1186/s13045-018-0571-y
19. Moreno-Castaño AB, Fernández S, Ventosa H, Palomo M, Martinez-Sanchez J, Ramos A, et al. Characterization of the endotheliopathy, innate-immune activation and hemostatic imbalance underlying CAR-T cell toxicities: laboratory tools for an early and differential diagnosis. J Immunother Cancer. 2023;11(4). doi:10.1136/jitc-2022-006365
20. Gómez-Puerta JA, Monegal A, Ponce A, Peris P, Martínez-Cibrian N, Sarmiento-Monroy JC, et al. Rheumatologic complications of CAR-T Cell therapy. Experience of a single center. Semin Arthritis Rheum. 2024;71:152610. doi:10.1016/j.semarthrit.2024.152610
21. Dulery R, Guiraud V, Choquet S, Thieblemont C, Bachy E, Barete S, et al. T cell malignancies after CAR T cell therapy in the DESCAR-T registry. Nat Med. 2025. doi:10.1038/s41591-024-03458-w

doi.org/10.58931/crt.2025.2161

About the Author

Denis Poddubnyy, MD, PhD, MSc (Epi)

Dr. Denis Poddubnyy holds the position of Professor of Medicine at the University of Toronto and serves as a Senior Scientist at the Schroeder Arthritis Institute within the University Health Network in Toronto. His research focuses on the early diagnosis, treatment, and outcomes of patients with spondyloarthritis, including psoriatic arthritis. Dr. Poddubnyy is a member of the Executive Committee of the Assessment of SpondyloArthritis International Society (ASAS) and the Steering Committee of the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA).

Affiliations: Division of Rheumatology, University of Toronto
Schroeder Arthritis Institute, University Health Network, Toronto, Canada.

Imaging for Diagnosis and Differential Diagnosis of Axial Spondyloarthritis

Denis Poddubnyy, MD, PhD, MSc (Epi)

Introduction

Spondyloarthritis refers to a group of inflammatory rheumatic diseases characterized by shared clinical features, such as inflammatory involvement of the axial skeleton, a specific pattern of peripheral joint involvement (usually asymmetric mono- or oligoarthritis, predominantly involving the lower extremities), enthesitis, and dactylitis.[1] Common extra-musculoskeletal manifestations include acute anterior uveitis, psoriasis, and inflammatory bowel disease (Crohn's disease and ulcerative colitis).

Axial spondyloarthritis (axSpA) denotes the subset of spondyloarthritis with predominant involvement of the spine and sacroiliac joints. The term axSpA encompasses both non-radiographic disease (no definite structural damage on X-rays of the sacroiliac joints) and radiographic disease, which has historically been referred to as ankylosing spondylitis. In clinical practice, these entities represent a spectrum. axSpA may initially present without X-ray changes and in some patients, may later progress to classic ankylosing spondylitis.

In this article, we will review the approach to diagnosing (versus classifying) axSpA and examine the role of imaging modalities in diagnosing axSpA and distinguishing it from common mimics.

Epidemiology

AxSpA typically begins in early adulthood, most commonly in the third decade of life. The prevalence of axSpA in the general population ranges from 0.3–1%, with variations depending on ethnicity and prevalence of the HLA-B27 gene. Notably, there is a sex difference between non-radiographic and radiographic axSpA: radiographic axSpA (ankylosing spondylitis) shows a male predominance (~2:1), whereas non-radiographic axSpA affects men and women almost equally.[1] A hallmark problem in axSpA care has been diagnostic delay. Historically, patients have waited many years from symptom onset to diagnosis, with global estimates placing the average delay at approximately 6–8 years.[2]

Such delays occur mainly due to attribution of back pain to mechanical/degenerative causes and a lack of awareness about the condition. Although increased awareness and the availability of magnetic resonance imaging (MRI), which supports early diagnosis, have begun to shorten the diagnostic delay in some regions, it remains unacceptably prolonged for many patients.

Paradoxically, while delayed diagnosis remains an issue, overdiagnosis of axSpA has emerged as a concern in recent years. Heightened awareness and reliance on MRI have led some patients with mechanical or degenerative back pain to be incorrectly diagnosed with axSpA. A recent interim report from a German telemedicine project (IMPROVE-axSpA) found that approximately one-third of patients carrying a diagnosis of axSpA were reclassified as not having the disease after expert re-evaluation, with other conditions deemed the cause of their symptoms.[3] Overdiagnosis is often driven by misinterpretation of imaging. For example, overcalling nonspecific bone marrow edema (BME) on MRI as evidence of axSpA. Both delayed diagnosis and overdiagnosis can be harmful: delayed diagnosis allows the progression of inflammation and structural damage, whereas overdiagnosis can expose patients to unnecessary treatments and psychological burden. Recognizing this dual challenge, clinicians must use a balanced approach to diagnosing axSpA, carefully integrating clinical and imaging findings.

Diagnosis and Classification

When evaluating a patient for possible axSpA, it is crucial to distinguish diagnostic criteria from classification criteria.[4] Diagnosis is the process by which a clinician, using all available information (history, exam, laboratory tests, imaging), determines whether an individual patient has axSpA with a certain level of probability. Classification criteria, on the other hand, are standardized definitions used primarily in research to create homogeneous study populations. The modified New York criteria for ankylosing spondylitis, established in 1984, require definite sacroiliitis visible on X-ray plus at least one clinical criterion.[5] This means that in traditional practice, a patient needed to have established structural damage in the sacroiliac joints to fulfill the “AS” criteria. In 2009, the Assessment of SpondyloArthritis International Society (ASAS) proposed new classification criteria for axSpA to promote the new spondyloarthritis concept and to enable recognition of earlier stages of the disease. Notably, patients can be classified as axSpA either by the imaging arm (active sacroiliitis on MRI or definite radiographic sacroiliitis, plus at least one SpA feature) or by the clinical arm (HLA-B27 plus at least two other SpA features).[6] These criteria introduced MRI as the method of visualizing active inflammation, aiming to identify axSpA before irreversible structural changes occur.

It is important to remember that meeting the ASAS classification criteria does not automatically equate to a clinical diagnosis; clinicians must still exclude other causes and consider the total clinical picture. Conversely, a patient who does not neatly fulfill classification criteria may still be diagnosed with axSpA by an expert clinician. In summary, while classification criteria are useful guides, and have improved early recognition, a practical diagnostic approach must remain individualized.

To apply the ASAS classification criteria, patients must first have an established diagnosis of axSpA. In practice, diagnosing axSpA is a clinical decision that is supported by investigations. Clues such as chronic back pain starting before age 45, the inflammatory character of back pain (improvement with exercise, no improvement with rest, night pain, morning stiffness of more than 30 minutes, and alternating buttock pain), peripheral arthritis, enthesitis, acute anterior uveitis, psoriasis, inflammatory bowel disease, a positive HLA-B27, and elevated C-reactive protein levels all increase suspicion. However, none of these features is specific or diagnostic on its own. Indeed, even the concept of “inflammatory back pain” has limitations, as many patients with mechanical back issues can experience inflammatory-type back pain symptoms.[7] Likewise, HLA-B27 is prevalent in ~5–15% of the healthy population, thus, while it greatly increases the pre-test probability in a patient with compatible symptoms, it is not a definitive test. Given the lack of a single clinical or lab “gold standard” for axSpA, imaging plays a pivotal role by providing objective evidence of inflammation or structural change in the sacroiliac joints and spine. Imaging findings, when interpreted within the proper clinical context, can confirm the diagnosis of axSpA or suggest alternative pathologies. The diagnostic approach, therefore, relies on a synthesis of clinical assessment, laboratory results, and imaging studies.

Role of Imaging in axSpA

Imaging undeniably plays an important role in diagnosing and assessing axSpA, often being the only possibility to objectively confirm the presence of inflammatory involvement of the sacroiliac joints or spine.[8]

X-rays

The typical imaging evaluation for suspected axSpA begins with conventional X-rays of the pelvis (sacroiliac joints).[9] X-rays have been used for decades to detect structural changes consistent with axSpA, such as erosions, sclerosis, changes of the joint space, and eventual ankylosis. If the initial X-rays are normal or equivocal and clinical suspicion remains high, MRI of the sacroiliac joints is the next step. The stepwise approach of performing X-rays followed by MRI is reflected in recommendations and represents a practical strategy to maximize diagnostic yield. However, in settings where MRI and X-rays are equally available, X-rays can be omitted due to their limitations outlined below.

Radiographic changes take time to develop, and in the early stages of axSpA (the first few years of symptoms), X-rays are often normal. In fact, a significant proportion of axSpA patients, especially women, may never develop advanced radiographic sacroiliitis even after many years, remaining in the non-radiographic category. Therefore, the sensitivity of X-rays for detecting early disease is quite low.[10] Even when structural changes exist, they can be subtle, and inter-reader reliability for grading sacroiliitis on X-ray is only moderate at best. Changes such as sclerosis can also be due to other causes (for example, osteitis condensans ilii [OCI] or degenerative changes in general), which can confuse interpretation. Therefore, a normal X-ray does not rule out axSpA, and an abnormal X-ray with mild changes is not always definitive. Because of these issues, radiography is increasingly seen as an initial screening tool. If it shows definite changes, a diagnosis of radiographic axSpA can be made; however, if the findings are negative or equivocal, further imaging is warranted.

Magnetic Resonance Imaging

MRI has revolutionized the diagnosis of axSpA by allowing the visualization of active inflammation in the sacroiliac joints and spine. The hallmark MRI finding in active axSpA is BME in the subchondral bone on fat-suppressed T2-weighted sequences, such as Short Tau Inversion Recovery (STIR).[11] This appears as bright areas in the usually dark bone marrow and represents osteitis (**Figure 1**). MRI can also show capsulitis, enthesitis, and inflammatory signals in the joint space or in the erosion cavity in the sacroiliac joints, as well as inflammatory lesions in the spine, such as spondylitis, facet arthritis, costovertebral or costotransverse arthritis, and enthesitis. In addition to inflammation, MRI can depict structural lesions, including erosions (appearing as dark defects in the bright marrow fat), subchondral fat deposition (bright signal on T1), sclerosis (low signal on both T1 and T2), and ankylosis. One specific structural lesion visualized by MRI is the phenomenon of "backfill", which is the replacement of an erosion cavity by tissue with fat signal. This appears as a high T1 signal filling the joint space where bone has eroded (**Figure 1**). Backfill is considered a reparative change and is a specific sign of chronic axSpA damage, often preceding new bone formation across the joint.

An important aspect of practical imaging application is the standardization of protocols and reporting. Recently, an international task force, a collaboration between ASAS and the Spondyloarthritis Research and Treatment Network (SPARTAN), developed a standardized MRI protocol for the sacroiliac joints to maximize diagnostic utility.[12] The consensus recommended that MRI to evaluate the sacroiliac joints for signs of axSpA should include at least four sequences, as depicted in **Figures 1 and 2**:

1. A semi-coronal T1-weighted sequence to assess structural damage,
2. A semi-coronal T2-weighted fat-suppressed sequence, such as STIR, to detect active inflammation,
3. An erosion-sensitive sequence in the semi-coronal plane to enhance visualization of cortical bone erosions, which can be a T1 fat-suppressed gradient echo, known as Volumetric Interpolated Breath-hold Examination (VIBE), Liver Acquisition with Volume Acceleration (LAVA), or T1 High-Resolution Isotropic Volume Examination (THRIVE), depending on the MRI manufacturer, and
4. An additional T2-weighted fat-suppressed semi-axial sequence for further evaluation of inflammatory lesions.

Most MRI scanners now can accommodate these sequences within a single exam of a reasonable duration.

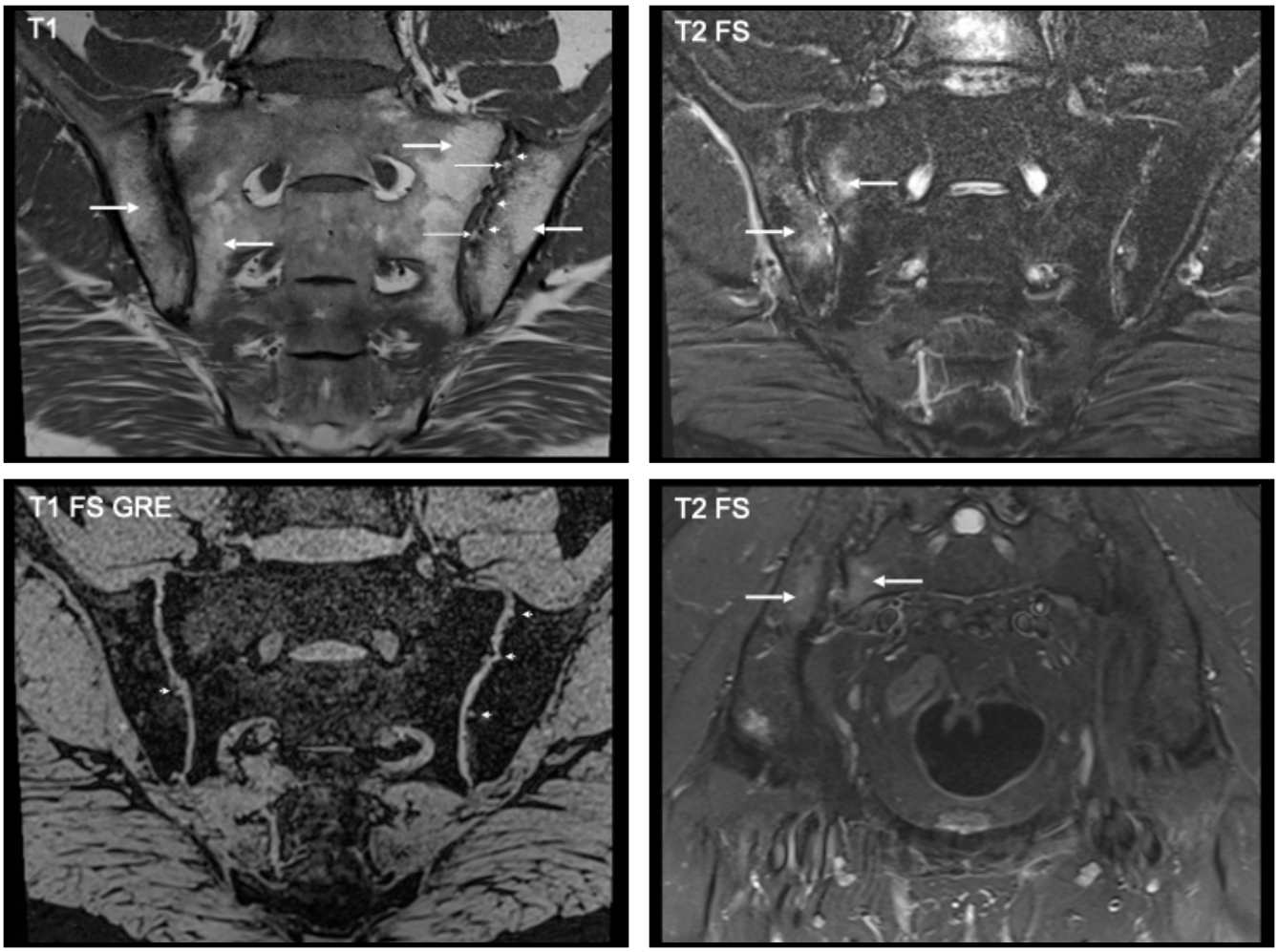

Figure 1. Typical patterns of MRI changes in the sacroiliac joints in axial spondyloarthritis; *courtesy of Denis Poddubnyy, MD, PhD, MSc (Epi)*.

Subchondral bone marrow oedema is observed in the middle part of the cartilaginous compartment of the right sacroiliac joint, indicated by arrows on the T2-weighted sequence with fat suppression (T2 FS). This is accompanied by erosions, indicated by arrowheads on the T1-weighted sequence and the erosion-sensitive T1-weighted fat supressed gradient echo sequence (T1 FS GRE). Additionally, backfill is noted, shown by a thin arrow on T1, along with fat lesions in the bone marrow, indicated by a thick arrow on T1.

Furthermore, the ASAS has recently emphasized the need for optimal communication between rheumatologists and radiologists. They have defined a set of relevant clinical information that should be provided to the radiologist when requesting imaging for patients with suspected axSpA. This information includes the presence of mechanical stress factors, HLA-B27 status, and key clinical features to aid in accurate interpretation.[13]

Likewise, radiologists are encouraged to use structured reporting for sacroiliac joint images. They should note the presence or absence of active inflammation (BME on MRI) and structural lesions (erosions, fat metaplasia, sclerosis, ankylosis). Additionally, they should provide an overall impression of whether the findings are suggestive of axSpA or more consistent with alternative diagnoses.[14]

The strength of MRI is its ability to facilitate early diagnosis. A patient with only a few months of inflammatory back pain can already show definite sacroiliitis on MRI, even though X-rays might remain normal for years. MRI evidence of sacroiliitis, such as active lesions, especially if paired with structural lesions like small erosions, greatly increases the probability of axSpA. Thus, MRI has become the key

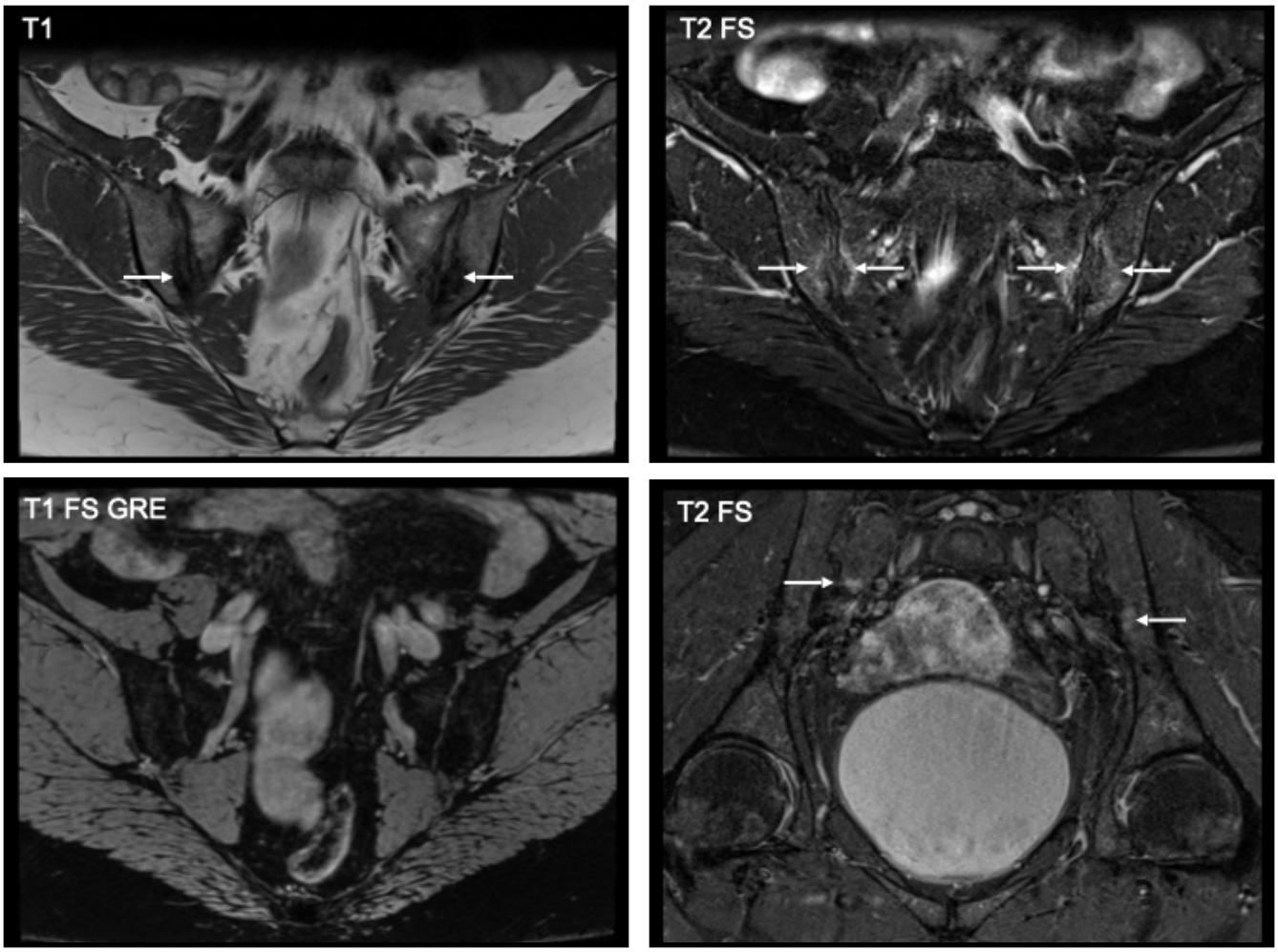

Figure 2. Typical patterns of MRI changes in the sacroiliac joints in osteitis condensans; *courtesy of Denis Poddubnyy, MD, PhD, MSc (Epi)*.

The pattern of mechanically induced changes includes bone marrow oedema in the ventral part of both sacroiliac joints, indicated by arrows on the T2-weighted sequence with fat suppression (T2 FS). This is accompanied by sclerosis, indicated by arrows on the T1-weighted sequence and the erosion-sensitive T1 FS GRE sequence. Of note, there is no evidence of erosive damage.

to identifying non-radiographic axSpA. Additionally, MRI is useful in difficult cases (e.g., young patients with persistent symptoms but normal X-rays,) as it can help re-classify these patients as having axSpA if the findings are positive.

Despite its benefits, MRI has challenges and pitfalls. The specificity of MRI changes, particularly BME, is limited. Mechanical stress on the sacroiliac joints can also produce BME lesions that mimic inflammation. Healthy athletes, postpartum women, and individuals with heavy physical workloads have been found to exhibit sacroiliac joint BME on MRI in the absence of axSpA.[15,16] Typically, these mechanical lesions occur at predictable locations (known as "mechanical load zones") in the sacroiliac joint. These zones include the anterior-inferior (ventrocaudal) corners of the joint and areas adjacent to the ligamentous part of the joint. Furthermore, mechanically induced lesions are not associated with erosive damage, backfill, or ankylosis, which differentiates them from axSpA-compatible lesions. Therefore, when interpreting MRI for suspected axSpA, it is important to look for the coexistence of active inflammation with structural changes, such as erosions or backfill or ankylosis, to confirm the true inflammatory nature of the lesions.

One of the most important differential diagnoses for axSpA is OCI.[17] OCI is a benign condition often observed in women, classically

postpartum, and is considered a prototype disease with mechanically induced changes in sacroiliac joints. On pelvic X-rays, OCI appears as triangular areas of sclerosis on the iliac side of the sacroiliac joints, usually bilateral and symmetric. On MRI, OCI can confuse matters by also displaying subchondral BME, as shown in **Figure 2**. In fact, studies have demonstrated that OCI can present with BME in the sacroiliac joints, sometimes quite extensively. However, the key distinguishing MRI features are the predominant localization of edema in the ventral mechanical load zone and the virtual absence of erosions.

Computed Tomography

Computed tomography (CT) provides exquisite bone detail and is considered the gold standard for visualizing structural changes in the sacroiliac joints. CT can confirm the presence of erosions and ankylosis with far greater sensitivity and specificity than X-rays.[18] Traditionally, CT has not been used routinely in axSpA diagnosis because of the high radiation dose a standard pelvic CT imparts, which is significantly higher than that of X-rays or MRI. However, recent advances in low-dose CT techniques and protocols have significantly reduced radiation exposure while preserving diagnostic yield. Modern low-dose CT of the sacroiliac joints can be performed with a radiation dose comparable to that of a set of X-rays, making it a feasible option for imaging these joints. Studies have shown that low-dose CT is more sensitive than X-rays for detecting sacroiliac erosions and offers excellent reliability, as the 3D detail of CT eliminates the projectional ambiguities of X-rays. For example, small erosions or posterior joint fusions that are not visible on X-rays can be readily identified on CT.

Therefore, CT could be used when MRI is contraindicated, such as in pacemaker patients, or when MRI is unavailable. CT can also be a problem-solver when MRI and X-ray findings conflict. For instance, if a patient has suggestive MRI changes, but normal X-rays, a CT scan can verify the presence of subtle erosions. Despite these advantages, CT is limited to showing chronic changes and does not reveal active inflammation. In addition, the availability of low-dose CT protocols might be limited. Thus, while CT is a valuable adjunct in difficult cases, current recommendations place it as a second-line option.

Future Directions

The landscape of imaging in axSpA continues to evolve, with ongoing efforts to improve diagnostic precision and reduce errors. One key direction is education and training, as the increased use of MRI has made it clear that accurate interpretation requires specific expertise. Misinterpretation of sacroiliac joint MRIs has contributed to overdiagnosis. To address this issue, rheumatology and radiology communities are emphasizing training in axSpA imaging. The ASAS group has developed an interactive online case library featuring MRI examples that span the spectrum of axSpA and its mimics. Clinicians can use this resource to hone their interpretative skills, with cases that include classic active sacroiliitis, OCI, degenerative joints, and more. This resource is available **here**. Such educational tools, along with workshops and courses on MRI reading, aim to standardize the identification of positive MRI findings for axSpA.

Another promising avenue is the use of artificial intelligence (AI) in imaging analysis. AI algorithms, particularly deep learning models, are being developed to detect sacroiliitis on radiographs and MRIs.[19,20] In the future, a trained algorithm might assist radiologists by flagging suspicious lesions or even quantifying inflammation. AI could also help reduce inter-reader variability, providing more consistent interpretations. While these tools are still in the research stages, they may eventually integrate into clinical practice as decision support systems.

Additionally, improvements in imaging technology itself are on the horizon.

Conclusion

In conclusion, imaging in axSpA is a dynamic field where improvements in technology, technique, and training are converging. For clinicians today, the focus should be on using the available imaging tools wisely: adhering to recommended approaches, being aware of pitfalls, and seeking expert input when in doubt. By doing so, rheumatologists can diagnose axSpA at the earliest appropriate time and thereby initiate therapy for those who need it while sparing those who do not. Ongoing research and innovation promise to make this balance easier to achieve, moving us toward an era of even more precise and personalized care in axSpA.

Correspondence

Denis Poddubnyy, MD, PhD, MSc (Epi)
Email: Denis.Poddubnyy@uhn.ca

Financial Disclosures

D.P.: Research support: AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; **Consulting fees:** AbbVie, Eli Lilly, Greywolf Therapeutics, Janssen, Merk, Moonlake, Novartis, Pfizer, and UCB; **Speaker fees:** AbbVie, Canon, Eli Lilly, Janssen, Medscape, Novartis, Peervoice, Pfizer, and UCB.

References

1. Sieper J, Poddubnyy D. Axial spondyloarthritis. Lancet. 2017;390(10089):73-84. doi:10.1016/S0140-6736(16)31591-4
2. Poddubnyy D, Garrido-Cumbrera M, Sommerfleck F, Navarro-Compan V, Bundy C, Makri S, et al. Diagnostic delay in patients from the international map of axial spondyloarthritis: geographic, socio-demographic and disease-related factors. Rheumatology (Oxford). 2025;64(4):1873-1879. doi:10.1093/rheumatology/keae521
3. Poddubnyy D, Kämmerer M, Kremers M, Wiedon A, Redeker I, Baraliakos X. Pos0029 Enhancing the diagnostic accuracy and avoiding overdiagnosis in axial spondyloarthritis through central evaluation of imaging: IMPROVE-axSpA, a nationwide telemedicine project. Ann Rheum Dis. 2024;83(Suppl. 1):476-477. doi:10.1136/annrhumdis-2024-eular.2639
4. Poddubnyy D. Classification vs diagnostic criteria: the challenge of diagnosing axial spondyloarthritis. Rheumatology (Oxford). 2020;59(Suppl4):iv6-iv17. doi:10.1093/rheumatology/keaa250
5. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum. 1984;27(4):361-368. doi:10.1002/art.1780270401
6. Rudwaleit M, van der Heijde D, Landewe R, Listing J, Akkoc N, Brandt J, et al. The development of Assessment of SpondyloArthritis international Society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis. 2009;68(6):777-783. doi:ard.2009.108233
7. Poddubnyy D, Callhoff J, Spiller I, Listing J, Braun J, Sieper J, et al. Diagnostic accuracy of inflammatory back pain for axial spondyloarthritis in rheumatological care. RMD open. 2018;4(2):e000825. doi:10.1136/rmdopen-2018-000825
8. Poddubnyy D, Diekhoff T, Baraliakos X, Hermann KGA, Sieper J. Diagnostic evaluation of the sacroiliac joints for axial spondyloarthritis: should MRI replace radiography? Ann Rheum Dis. 2022;81(11):1486-1490. doi:10.1136/ard-2022-222986
9. Mandl P, Navarro-Compan V, Terslev L, Aegerter P, van der Heijde D, D'Agostino MA, et al. EULAR recommendations for the use of imaging in the diagnosis and management of spondyloarthritis in clinical practice. Ann Rheum Dis. 2015;74(7):1327-1339. doi:10.1136/annrheumdis-2014-206971
10. Diekhoff T, Eshed I, Radny F, Ziegeler K, Proft F, Greese J, et al. Choose wisely: imaging for diagnosis of axial spondyloarthritis. Ann Rheum Dis. 2022;81(2):237-242. doi:10.1136/annrheumdis-2021-220136
11. Maksymowych WP, Lambert RG, Ostergaard M, Pedersen SJ, Machado PM, Weber U, et al. MRI lesions in the sacroiliac joints of patients with spondyloarthritis: an update of definitions and validation by the ASAS MRI working group. Ann Rheum Dis. 2019;78(11):1550-1558. doi:10.1136/annrheumdis-2019-215589
12. Lambert RGW, Baraliakos X, Bernard SA, Carrino JA, Diekhoff T, Eshed I, et al. Development of international consensus on a standardised image acquisition protocol for diagnostic evaluation of the sacroiliac joints by MRI: an ASAS-SPARTAN collaboration. Ann Rheum Dis. 2024;83(12):1628-1635. doi:10.1136/ard-2024-225882
13. Diekhoff T, Giraudo C, Machado PM, Mallinson M, Eshed I, Haibel H, et al. Clinical information on imaging referrals for suspected or known axial spondyloarthritis: recommendations from the Assessment of Spondyloarthritis International Society (ASAS). Ann Rheum Dis. 2024;83(12):1636-1643. doi:10.1136/ard-2024-226280
14. Diekhoff T, Eshed I, Giraudo C, Haibel H, Hermann KGA, de Hooge M, et al. Reporting sacroiliac joint imaging performed for known or suspected axial spondyloarthritis: assessment of SpondyloArthritis International Society recommendations. Radiology. 2024;311(3):e231786. doi:10.1148/radiol.231786
15. Weber U, Jurik AG, Zejden A, Larsen E, Jorgensen SH, Rufibach K, et al. Frequency and anatomic distribution of magnetic resonance imaging features in the sacroiliac joints of young athletes: exploring "background noise" toward a data-driven definition of sacroiliitis in early spondyloarthritis. Arthritis Rheumatol. 2018;70(5):736-745. doi:10.1002/art.40429
16. Ziegeler K, Kreutzinger V, Proft F, Poddubnyy D, Hermann KGA, Diekhoff T. Joint anatomy in axial spondyloarthritis: strong associations between sacroiliac joint form variation and symptomatic disease. Rheumatology (Oxford). 2021;61(1):388-393. doi:10.1093/rheumatology/keab318
17. Poddubnyy D, Weineck H, Diekhoff T, Redeker I, Gobejishvili N, Llop M, et al. Clinical and imaging characteristics of osteitis condensans ilii as compared with axial spondyloarthritis. Rheumatology (Oxford). 2020;59(12):3798-3806. doi:10.1093/rheumatology/keaa175
18. Diekhoff T, Hermann KG, Greese J, Schwenke C, Poddubnyy D, Hamm B, et al. Comparison of MRI with radiography for detecting structural lesions of the sacroiliac joint using CT as standard of reference: results from the SIMACT study. Ann Rheum Dis. 2017;76(9):1502-1508. doi:10.1136/annrheumdis-2016-210640
19. Bressem KK, Adams LC, Proft F, Hermann KGA, Diekhoff T, Spiller L, et al. Deep learning detects changes indicative of axial spondyloarthritis at MRI of sacroiliac joints. [published correction appears in Radiology. 2023 May;307(3):e239007. doi: 10.1148/radiol.239007.]. Radiology. 2022;305(3):655-665. doi:10.1148/radiol.212526
20. Bressem KK, Vahldiek JL, Adams L, Niehues SM, Haibel H, Rodriguez VR, et al. Deep learning for detection of radiographic sacroiliitis: achieving expert-level performance. Arthritis Res Ther. 2021;23(1):106. doi:10.1186/s13075-021-02484-0

Register for future digital and print issues by visiting us at catalytichealth.com/crt

Looking for more?
All back issues are available online at canadianrheumatologytoday.com