VOLUME 1 · ISSUE 2

Canadian Rheumatology Today

Summer 2024

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.

About the Authors

Ann E. Clarke, MD, MSc, FRCPC

Dr. Ann Clarke is a Professor in the Division of Rheumatology at the University of Calgary and holds The Arthritis Society Chair in Rheumatic Diseases. She is the Founder and Director of the University of Calgary Lupus/Antiphospholipid Syndrome (APS) Centre of Excellence. Her research focuses on the risk and determinants of malignancy in SLE, the economic burden of SLE, and clinical trials of novel therapeutics. Dr. Clarke has published over 450 manuscripts and is very engaged in the training of the next generation of lupus clinicians and investigators.

Affiliations: Division of Rheumatology, Cumming School of Medicine, University of Calgary

Megan R.W. Barber, MD, PhD, FRCPC

Dr. Megan Barber is a rheumatologist and clinician investigator and the Associate Director of Clinical Trials and Clinical Research for the University of Calgary Lupus Centre of Excellence. Particular research interests include antiphospholipid syndrome and novel lupus therapeutics.

Affiliations: Division of Rheumatology, Cumming School of Medicine, University of Calgary

Bryce Barr, MD, FRCPC

Dr. Bryce Barr is a nephrologist and Assistant Professor in the Department of Medicine at the University of Manitoba. He specializes in glomerulonephritis, with specific interest in lupus nephritis and ANCA-associated vasculitis and is the principal investigator of the Manitoba Glomerular Diseases Registry.

Affiliations: Section of Nephrology, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba

Kim Cheema, MD, FRCPC

Dr. Kim Cheema is a nephrologist in Calgary, Alberta with clinical expertise in glomerular conditions. She completed her internal medicine and nephrology training in Calgary, which was followed by advanced subspecialty training in Lupus and Vasculitis with Professor David Jayne.

Affiliations: Division of Nephrology, Cumming School of Medicine, University of Calgary

doi.org/10.58931/crt.2024.1248

About the Authors

Nicholas L. Li, MD, PhD, FRCPC

Dr. Nicholas Li is a Nephrologist and Clinical Assistant Professor in the Department of Medicine at the University of Calgary. He received his PhD in human immunology from the University of Alberta and his MD from the University of Calgary, where he also completed Internal Medicine and Nephrology. Dr. Li also pursued advanced fellowship training in Lupus, Vasculitis, and Glomerulonephritis at The Ohio State University under the mentorship of Dr. Brad Rovin.

Affiliations: Division of Nephrology, Cumming School of Medicine, University of Calgary

Shifting Paradigms in the Treatment of Systemic Lupus Erythematosus

Ann E. Clarke, MD, MSc, FRCPC
Megan R.W. Barber, MD, PhD, FRCPC
Bryce Barr, MD, FRCPC
Kim Cheema, MD, FRCPC
Nicholas L. Li, MD, PhD, FRCPC

Introduction

For many years, therapeutic options for patients with systemic lupus erythematosus (SLE) have been extremely limited. However, over the past decade, with the approval of new drugs and several promising phase II trials, treatment paradigms are gradually shifting toward multi-targeted therapies for lupus nephritis (LN) and earlier usage of biologics in extra-renal lupus. Below, we will present three patient cases that illustrate how, through a multidisciplinary clinic environment, we have incorporated these shifting treatment paradigms into our delivery of care. Finally, we will conclude with a discussion of emerging therapies, which have the potential to further shift, and ultimately transform, treatment paradigms.

Lupus Nephritis

Patient Case #1

A 25-year-old southeast Asian female with a five-year history of SLE, characterized by alopecia, oral ulcers, and arthritis had been doing well on a treatment regimen of hydroxychloroquine and methotrexate. However, shortly after discontinuation of methotrexate for pregnancy planning, she developed worsening arthritis, and was diagnosed with class III LN with a modified National Institutes of Health (NIH) activity index of 6/24 and a chronicity index of 0/12. Fibrinoid necrosis was observed in one glomerulus and there were no crescents, interstitial fibrosis, or tubular atrophy. Her estimated glomerular filtration rate (eGFR) remained >90 mL/min/1.73m^2 and her peak urine protein:creatinine ratio (UPCR) was 175 mg/mmol with an elevated anti-double-stranded (anti-dsDNA) and a decrease in complement levels. She was started on prednisone at a dose of 0.5 mg/kg/day and mycophenolate mofetil at a dose of 1.5 g twice daily. After three months, her UPCR had decreased minimally to 150 mg/mmol and she experienced ongoing arthritis. After verifying adherence to treatment, belimumab was added to her existing therapy, which resulted in a decrease in her UPCR to 20 mg/mmol, resolution of her arthritis, and discontinuation of prednisone at six months.

Patient Case #2

A 22-year-old Indigenous female was diagnosed two years prior with class IV LN with a modified NIH activity index of 4/24 and a chronicity index of 0/12; there was one fibrocellular crescent, four glomeruli with segmental sclerosis, and no evidence of interstitial fibrosis or tubular atrophy. Her eGFR remained >90 mL/min/1.73m^2 and her peak UPCR was 250 mg/mmol with an elevated anti-dsDNA and a decrease in complement levels. She was started on prednisone at a dose of 0.5 mg/kg/day, mycophenolate mofetil at a dose of 1.5 g twice daily, and hydroxychloroquine. Within six months, she achieved a partial renal response; her UPCR had decreased to 125 mg/mmol and her immune serology had improved. After one year, while on mycophenolate at a dose of 1.5 g twice daily and hydroxychloroquine, her UPCR increased to 500 mg/mmol. Additionally, her eGFR decreased to 60 mL/min/1.73m^2, her anti-dsDNA increased, and her complement levels decreased. Once medication adherence was verified, a repeat renal biopsy was performed and showed class IV LN with a modified NIH activity index of 14/24 and a chronicity index of 2/12 with several glomeruli showing fibrocellular crescents and segmental sclerosis. Prednisone at a dose of 1 mg/kg/day was initiated, and her treatment was switched from mycophenolate mofetil to cyclophosphamide at Euro-Lupus dosing, in combination with belimumab. When the three-month course of cyclophosphamide was completed, she was switched back to mycophenolate mofetil and belimumab was continued. After one year, her UPCR had decreased to 70 mg/mmol, her eGFR had increased to >90 mL/min/1.73m^2, her immune serology had normalized, and prednisone was discontinued.

Induction Treatment of Active Class III or IV LN: A Multi-Targeted Approach

The preceding cases and the treatment algorithms we have developed (**Figures 1 and 2**) illustrate how our group, working in a multidisciplinary lupus/nephrology clinic, applies the recently published clinical practice guidelines (European Alliance of Associations for Rheumatology [EULAR] and Kidney Disease: Improving Global Outcomes [KIDGO])[1,2] for the management of LN.

For both patient cases, mycophenolate was chosen as the initial induction therapy (**Figure 1A**). In case #1, as the patient experienced only a partial renal response after three months, failing to achieve the recommended ≥25% reduction in UPCR[3] (i.e., her UPCR had decreased by 14% from 175 mg/mmol to 150 mg/mmol) and she continued to experience arthritis, belimumab was added to her existing mycophenolate treatment (**Figure 1B**). However, if the patient had experienced no renal response or worsening, we would recommend switching between induction therapies (i.e., cyclophosphamide if the patient had started with mycophenolate or mycophenolate if the patient had started with cyclophosphamide) (**Figure 1C**). Given that the renal pathology is unlikely to have changed significantly within three months, a repeat biopsy would usually not be recommended at this stage.[4] Belimumab, an inhibitor of B-lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF), has shown promising results for the treatment of LN when added to the standard-of-care regimen of either mycophenolate or low-dose (Euro-Lupus) cyclophosphamide. An improved renal response was observed at two years (43% for belimumab vs 32% for placebo, odds ratio [OR], 1.6; 95% confidence interval [CI], 1.0 to 2.3).[5] Post-hoc analyses revealed that belimumab did not significantly improve the renal response in patients with a baseline UPCR of ≥300 mg/mmol, in those with pure class V LN,[6] or when added to cyclophosphamide treatment.[5] However, belimumab reduced the risk of LN flares by 55% (hazard ratio [HR], 0.45; 95% CI, 0.28 to 0.72) across the overall population, including those with class V LN and in combination with cyclophosphamide, and reduced the risk of kidney-related events or death irrespective of baseline proteinuria or treatment regimen.[6] Further, belimumab reduced the risk of a sustained 30% and 40% decline in eGFR.[6]

Voclosporin, a novel calcineurin inhibitor (CNI) which is not available in Canada, when combined with mycophenolate, improved renal response at one year (41% for voclosporin vs 23% for placebo, OR, 2.65; 95% CI, 1.64 to 4.27) with a very rapid decline in proteinuria,[7] which was sustained over the three-year follow-up without a decline in the eGFR.[8] However, given multiple trials showing belimumab's efficacy for extra-renal manifestations,[9,10] we prefer the addition of belimumab for patients who have sub-nephrotic range proteinuria, a partial renal response at three to six months, and persistent mild-to-moderate extra-renal manifestations (as our patient in case #1) (**Figure 1B**). In patients who have nephrotic range proteinuria with a relatively preserved renal

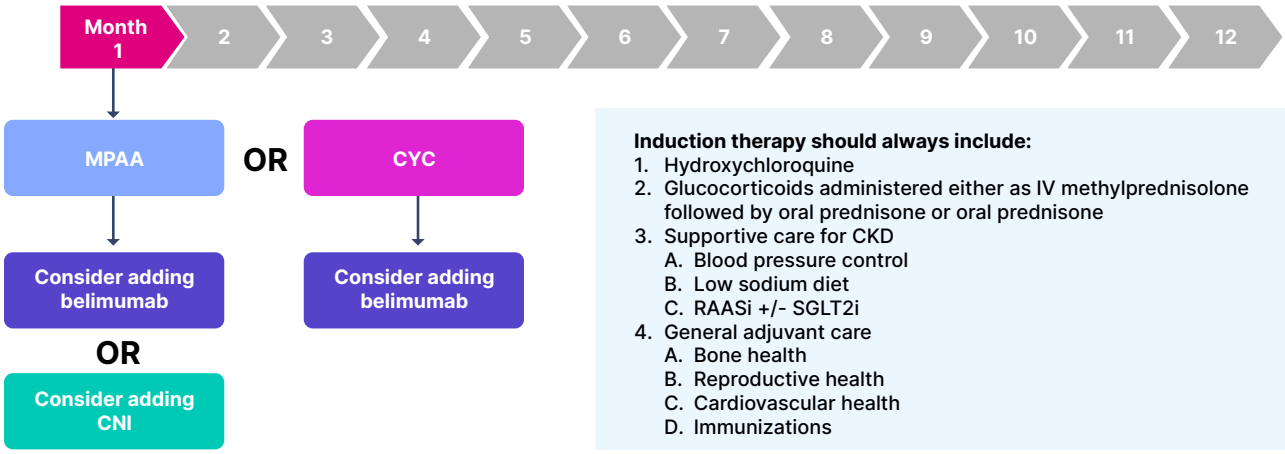


Figure 1A. Induction therapy for active class III or class IV lupus nephritis; *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema, MD, FRCPC, Nicholas L. Li, MD, PhD, FRCPC.*

Initial therapy should include one of the following, in combination with glucocorticoids and hydroxychloroquine: **1)** mycophenolic acid analogue, **2)** cyclophosphamide (usually Euro-Lupus dosing), **3)** mycophenolic acid analogue and belimumab, **4)** mycophenolic acid analogue and a calcineurin inhibitor, or **5)** cyclophosphamide and belimumab. For details on dosing and duration, refer to Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis; 2024.

Abbreviations: CKD: chronic kidney disease, **CNI:** calcineurin inhibitor, **CYC:** cyclophosphamide, **MPAA**: mycophenolic acid analogue (i.e., mycophenolate mofetil or mycophenolic acid), **RAASi:** renin-angiotensin-aldosterone system inhibitors, **SGLT2i:** sodium-glucose cotransporter 2 inhibitors

function (in the voclosporin trial, patients with an eGFR of ≤45 mL/min/1.73m^2 were excluded) and no extra-renal manifestations, we prefer the addition of a CNI (**Figure 1B**). Belimumab is now listed on several provincial formularies for induction therapy in LN (only Quebec also provides public funding for extra-renal indications). Although the trial showing efficacy of belimumab in LN used the intravenous formulation,[5] both the intravenous and subcutaneous formulations have been approved by Health Canada for treatment of LN and we use both interchangeably, largely dependent on patient preference. In Canada, tacrolimus or cyclosporin are used in lieu of voclosporin despite limited data on their effectiveness in combination with mycophenolate.[11,12] The decision whether to initiate belimumab or a CNI at the start of induction or only if the renal response is sub-optimal is a challenging one. Some patients will achieve remission with a single induction agent. For these patients, a multi-targeted approach may be an overtreatment, imposing an unnecessary medication burden, potentially compromising compliance with treatment, and increasing the risk of adverse events. However, in others, particularly those with prior episodes of LN and impaired renal function, delaying the initiation of a multi-targeted approach may prolong the duration of sub-optimal therapies and hasten the accumulation of renal damage. Unfortunately, there are currently no clinical, biochemical, or immunological features that will allow reliable prediction of who will respond to induction with a single agent or who will benefit from the addition of belimumab versus a CNI. In our multidisciplinary lupus/nephrology practice, patients beginning induction are closely monitored to assess the adequacy of their response to treatment, and the decision if, and when, to initiate multi-targeted therapy is shared between the patient and the health care team.

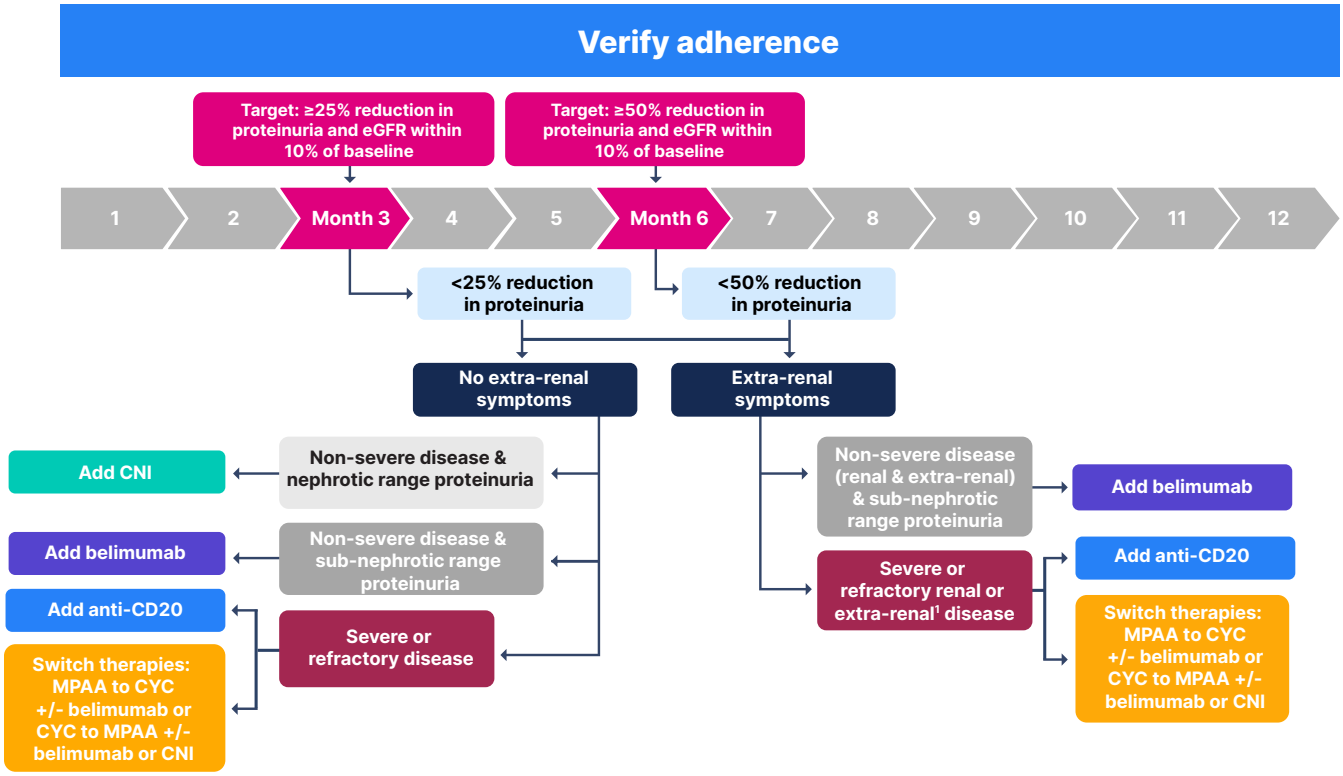


Figure 1B. Recommended approach if a partial renal response is observed at three to six months (in patients starting on monotherapy with either a mycophenolic acid analogue or cyclophosphamide); *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema, MD, FRCPC, Nicholas L. Li, MD, PhD, FRCPC.*

If a partial renal response is observed (defined as a <25% reduction in proteinuria at three months or a <50% reduction in proteinuria at six months, and the eGFR is not within 10% of baseline), in patients with no extra-renal symptoms and non-severe renal disease, the addition of a calcineurin inhibitor or belimumab should be considered. In patients with severe or refractory renal disease, switching between induction therapies or the addition of an anti-CD20 would be appropriate. Adherence should always be verified before modifying the therapy regimen.

In patients with a partial renal response and extra-renal symptoms, we would recommend a similar approach excluding the use of calcineurin inhibitors, as there is limited data on their efficacy in extra-renal lupus. In patients with non-severe renal disease and severe extra-renal disease, therapy should be guided by the severity of the extra-renal disease.[1] In general, the most severe manifestation should guide therapy (e.g., if a patient has thrombocytopenia of $<20 \times 10^9$/L and non-severe renal disease and sub-nephrotic range proteinuria, it would not be appropriate to add belimumab; treatment should be dictated by the thrombocytopenia and the addition of an anti-CD20 would likely be most appropriate).

[1]Severe extra-renal disease refers to major organ-threatening disease such as myelitis, myocarditis, pneumonitis, mesenteric vasculitis, or immune thrombocytopenia with platelets at $<20 \times 10^9$/L

Abbreviations: CNI: calcineurin inhibitor, **CYC:** cyclophosphamide, **eGFR:** estimated glomerular filtration rate, **MPAA;** mycophenolic acid analogue (i.e., mycophenolate mofetil or mycophenolic acid)

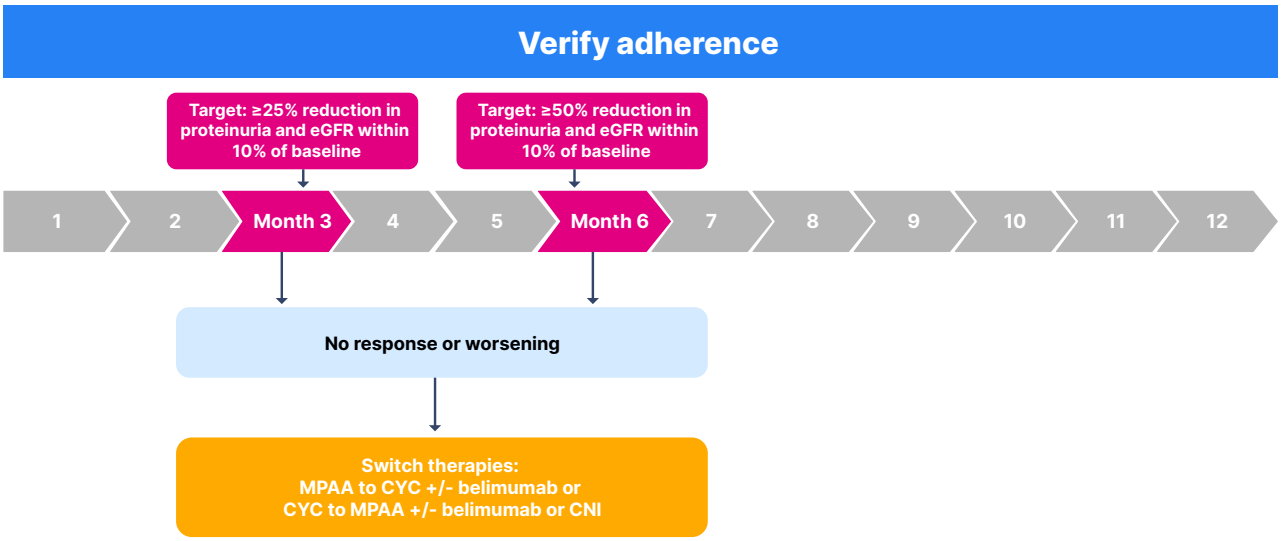


Figure 1C. Recommended approach if no renal response is observed at three to six months (in patients starting on monotherapy with either a mycophenolic acid analogue or cyclophosphamide); *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema, MD, FRCPC, Nicholas L. Li, MD, PhD, FRCPC.*

If no renal response is observed at three to six months (i.e., proteinuria and eGFR show no improvement or worsen), we would recommend switching between induction therapies. Adherence to treatment should always be verified before modifying therapy.

Abbreviations: CNI: calcineurin inhibitor, **CYC:** cyclophosphamide, **eGFR:** estimated glomerular filtration rate, **MPAA:** mycophenolic acid analogue (i.e., mycophenolate mofetil or mycophenolic acid)

In case #2, the patient experienced a partial renal response at six months with a decrease in UPCR from 250 mg/mmol to 125 mg/mmol. However, six months later, her UPCR had increased 4-fold to 500 mg/mmol, far exceeding the recommended target of <70–80 mg/mmol at 12 months post initiation of induction,[3,13-15] (**Figure 2**). At this stage, we recommend a repeat renal biopsy to determine if the rising proteinuria reflects ongoing active LN, or an alternative diagnosis (e.g., thrombotic microangiopathy or cryoglobulinemia), or irreversible renal damage (**Figure 2**). Biopsy-guided treatment decisions are preferred, given that clinical features and laboratory tests are often discordant with renal pathology. Basing treatment decisions on laboratory tests alone may result in excessive immunosuppression or organ-threatening treatment delays. In this patient, the repeat biopsy revealed significantly active class IV LN; hence, induction therapy was switched to Euro-Lupus cyclophosphamide in combination with belimumab (**Figure 2**). Although belimumab treatment did not improve the renal response in patients with a baseline UPCR of ≥300 mg/mmol or in combination with cyclophosphamide, post-hoc analysis revealed that it reduced the risk of an LN flare when combined with cyclophosphamide and reduced the risk of kidney-related events or death regardless of baseline proteinuria or treatment regimen.[6] Hence, there may be a long-term benefit in adding belimumab to cyclophosphamide induction, particularly in patients with previous LN flares or declining eGFR (as in this patient case).

The addition of an anti-CD20 (i.e., rituximab) to mycophenolate could also be an option. Although the phase III trial of rituximab added to mycophenolate did not achieve its primary outcome of complete or partial renal response at one year (56.9 % for rituximab vs 45.8% for placebo, p=0.18),[16] the complete renal response at 78 weeks was much higher in rituximab-treated patients who achieved complete peripheral B-cell depletion (47% for those with complete depletion vs 13% for those without, OR, 5.8; 95% CI, 1.2 to 28).[17] In addition, we and others[18,19] have repeatedly observed efficacy in patients who had a sub-optimal response to standard induction therapy. In a Phase II trial,[20] it was found that obinutuzumab, a more

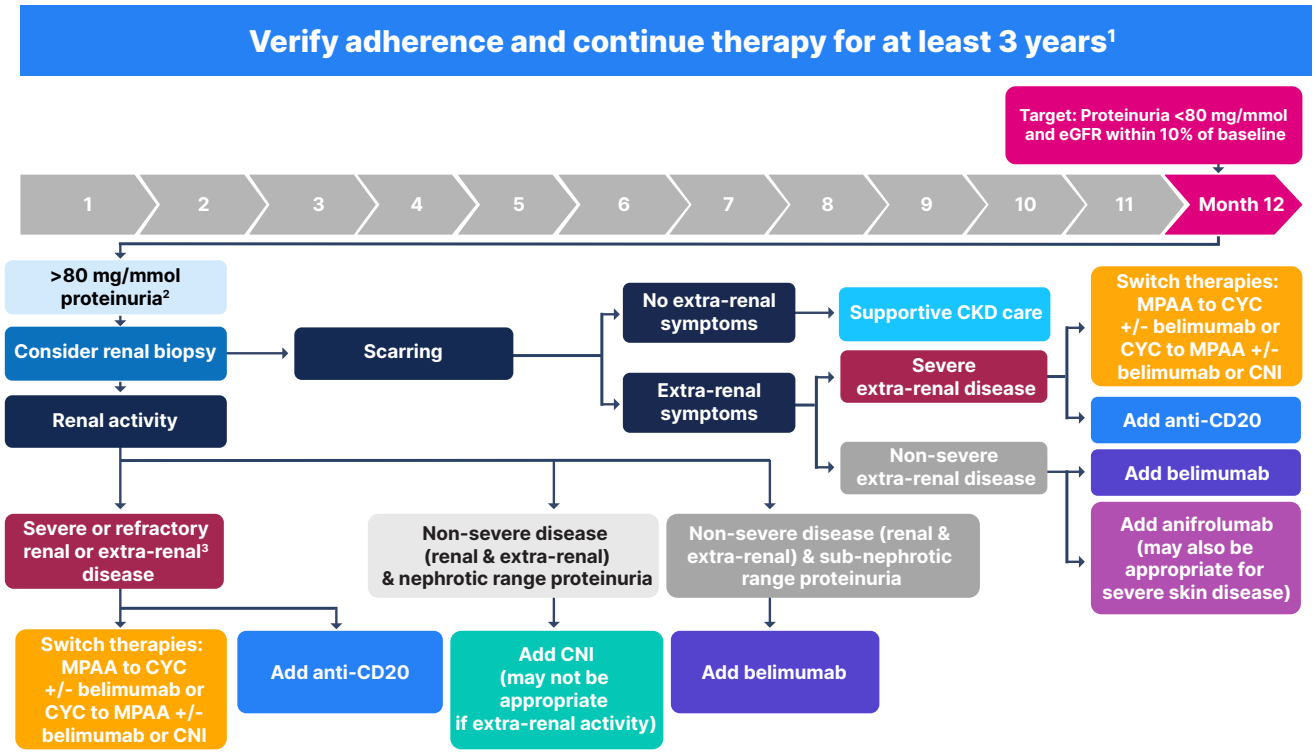


Figure 2. Recommended approach if a partial or no renal response is observed at 12 months (in patients starting on monotherapy with either a mycophenolic acid analogue or cyclophosphamide); *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema, MD, FRCPC, Nicholas L. Li, MD, PhD, FRCPC.*

If a partial or no renal response is observed at 12 months, we would recommend a repeat renal biopsy with therapy guided by the renal pathology. In patients with non-severe renal and extra-renal disease, the addition of a calcineurin inhibitor or belimumab should be considered, whereas in those with severe renal or extra-renal disease, switching between induction therapies or the addition of an anti-CD20 would be appropriate. In patients with scarring, therapy should be guided by the severity of the extra-renal symptoms. If no extra-renal symptoms are observed, supportive chronic kidney disease care (e.g., renin-angiotensin-aldosterone system inhibitors +/- sodium-glucose cotransporter 2 inhibitors) should be initiated or maintained. For non-severe extra-renal disease, either anifrolumab or belimumab could be considered (anifrolumab may also be appropriate for severe skin disease). For severe extra-renal disease, switching between induction therapies or the addition of an anti-CD20 is recommended.

[1] Throughout therapy, adherence should be continuously verified. Once a renal response has been achieved, maintenance therapy should continue for at least three years. Patients initially treated with a mycophenolic acid analogue should continue it; patients initially treated with cyclophosphamide should be switched to a mycophenolic acid analogue. If belimumab or calcineurin inhibitors were used during induction, they can be continued. In patients contemplating pregnancy, azathioprine should be used for maintenance in lieu of a mycophenolic acid analogue. For details on maintenance therapy, refer to Fanouriakis A, *et al*. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update and Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis; 2024.
[2] Patients with nephrotic-range proteinuria at baseline may require an additional 6–12 months to achieve proteinuria of <80 mg/mmol.
[3] Severe extra-renal disease refers to major organ-threatening disease such as myelitis, myocarditis, pneumonitis, mesenteric vasculitis, or immune thrombocytopenia with platelets at <20 × 10^9/L

Abbreviations: CKD: chronic kidney disease, **CNI:** calcineurin inhibitor, **eGFR:** estimated glomerular filtration rate, **MPAA:** mycophenolic acid analogue (i.e., mycophenolate mofetil or mycophenolic acid)

potent B-cell depleting agent than rituximab, when added to mycophenolate, improved renal response at two years (41% for obinutuzumab vs 23% for placebo, difference, 19%; 95% CI, 2.7% to 35%) and in a post-hoc analysis, reduced the risk of LN flares by 57% (HR, 0.43; 95% CI, 0.20 to 0.95) and preserved eGFR.[21] Phase III trials with obinutuzumab are ongoing for both LN and extra-renal lupus. Anifrolumab, which blocks the type 1 interferon receptor (discussed in detail below), has not yet been shown to be effective in LN.[22,23] A phase III LN trial is ongoing; currently, there is no evidence to support its use in LN.

Patients who, upon repeat biopsy, do not have active renal pathology or extra-renal manifestations do not require additional immunosuppressive therapy, and supportive care with agents such as a renin-angiotensin-aldosterone system (RAAS) inhibitor should be maintained or added. The addition of a sodium-glucose cotransporter 2 (SGLT2) inhibitor may also be reasonable in this context for attenuating the progression of chronic kidney disease, though data for their use in LN are limited.[24] In patients without active renal histology but with extra-renal manifestations, the need for additional immunosuppressive therapies should be guided by the severity of these manifestations (**Figure 2**).

Extra-renal Lupus

Patient Case #3

A 63-year-old white female with a 10-year history of SLE had extensive discoid lesions on her scalp, face, chest, back, and extremities, arthritis, thrombocytopenia (>50 × 10^9/L), and a positive antinuclear antibody (ANA) test. Despite treatment with hydroxychloroquine, chloroquine, quinacrine, methotrexate, azathioprine, mycophenolate, belimumab, rituximab, intravenous gammaglobulin, and prednisone, she continued to have diffuse erythematous, scaly lesions with atrophic plaques and follicular plugging (**Photos 1A and 2A**). Anifrolumab was initiated, and after only two treatments, she experienced dramatic improvement in her cutaneous lesions (**Photos 1B and 2B**), which was maintained (**Photos 1C and 2C**). She was able to discontinue prednisone therapy, her arthritis resolved, and her platelets normalized.

Treatment of Extra-Renal Lupus: Earlier Introduction of Biologics

This patient experienced a rapid and sustained response to anifrolumab after failing multiple conventional immunosuppressive therapies and biologics. Anifrolumab was approved by Health Canada for treating extra-renal lupus in 2021 and it has recently been listed on many provincial formularies. In the first of two phase III trials, anifrolumab did not achieve its primary outcome (SLE Responder Index of 4 [SRI-4]) at one year (36% for anifrolumab vs 40% for placebo; difference, -4.2%; 95% CI, -14.2% to 5.8%)[25]; however, informed by the results of this trial and before unblinding, the primary outcome of the second of the phase III trials was changed to the British Isles Lupus Assessment Group (BILAG)-based Composite Lupus Assessment (BICLA). The primary outcome was achieved in this second trial at one year (47.8% for anifrolumab vs 31.5% for placebo, difference, 16.3%; 95% CI, 6.3% to 26.3%). There was a particularly rapid improvement in patients with mucocutaneous involvement (≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at 12 weeks of 49.0% for anifrolumab vs 25.0% for placebo, difference, 24.0%; 95% CI, 4.3% to 43.6%).[26] Accordingly, in our case of severe discoid lupus, we observed a dramatic improvement after only two doses of anifrolumab, which was sustained through 11 months of follow-up and the patient was able to discontinue long-term usage of prednisone. Over a four-year follow-up period,[27] patients receiving anifrolumab experienced greater improvement and lower cumulative glucocorticoid use (as observed in our patient). The most significant safety concerns were a higher incidence of Herpes zoster (13.4% among all anifrolumab-exposed vs 3.6% among all placebo-exposed), mostly occurring during the first year of therapy, latent tuberculosis (4.8% among anifrolumab-exposed vs 1.1% among placebo-exposed), and influenza (6.4% among anifrolumab-exposed vs 3.1% among placebo-exposed).

Although our patient only received biologics after she became refractory to other therapies, recent guidelines[1] recommend that biologics (i.e., belimumab and anifrolumab) can be considered early in patients with mild-to-moderate disease who are not responding to hydroxychloroquine alone or are unable to taper prednisone to ≤5 mg/day (but preferably discontinue). However, the guidelines do

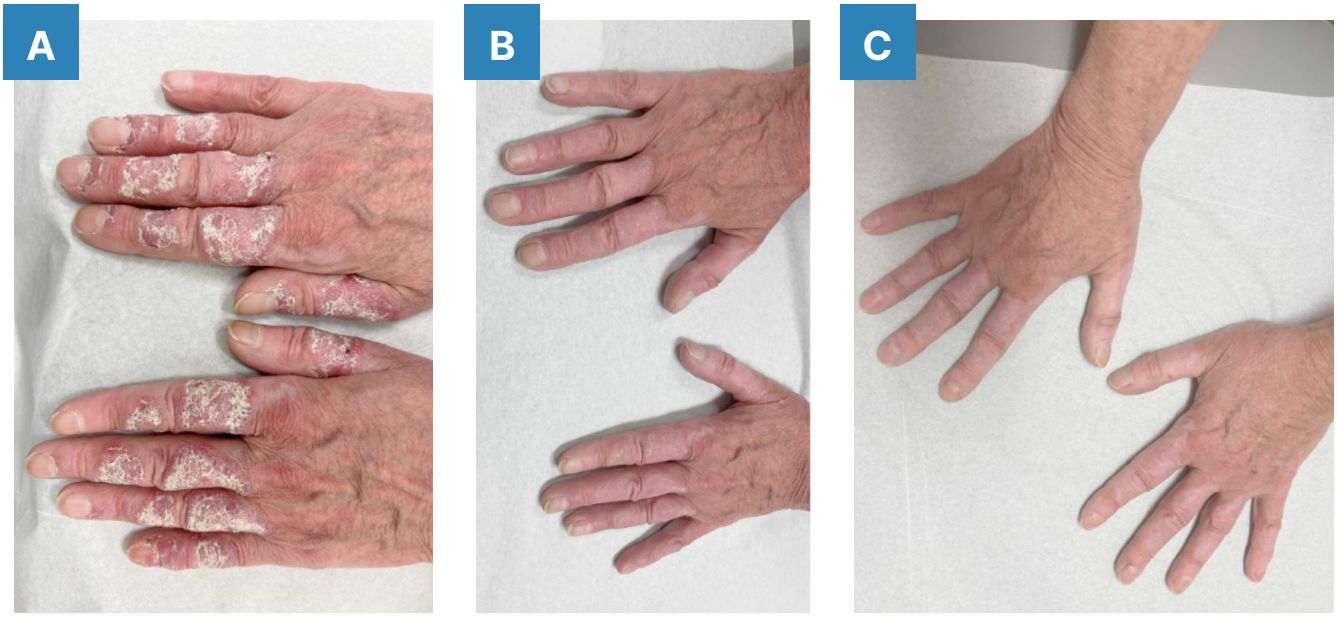


Photo 1A, B, C. Photos taken immediately pre **(A)** and post two doses **(B)** and post 11 doses **(C)** of anifrolumab; *photos courtesy of Megan R.W. Barber, MD, PhD, FRCPC.*

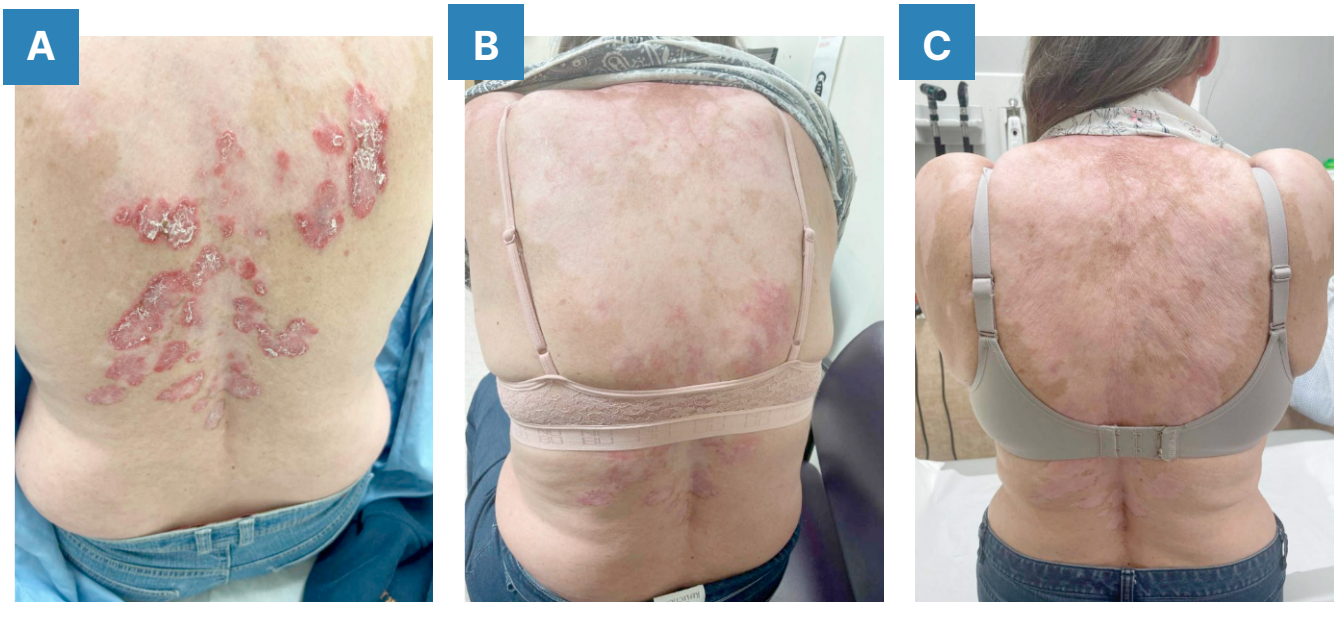


Photo 2A, B, C. Photos taken immediately pre **(A)** and post two doses **(B)** and post 11 doses **(C)** of anifrolumab; *photos courtesy of Megan R.W. Barber, MD, PhD, FRCPC.*

not address the positioning before or after conventional immunosuppressive drugs and the preferred biologic.

Both belimumab and anifrolumab were shown to be effective in patients with predominantly mucocutaneous and musculoskeletal manifestations, although only the anifrolumab trials used a specific instrument to demonstrate mucocutaneous improvement (CLASI), whereas the belimumab trials used generic outcome measures (SRI-4, BILAG). In our practice, decisions regarding the timing and choice of biologic are influenced by both clinical features and biologic reimbursement policies and are shared between the patient and the health care team. In major organ-threatening disease, we may consider adding belimumab or anifrolumab to conventional immunosuppressive therapy, but we never use these therapeutics as the sole immunosuppressive therapy in these cases.

Emerging Therapies: Promising Phase II Results with Ongoing Phase III Trials[28]

B-Cell Inhibition

Telitacicept, an inhibitor of both BLyS and a proliferation-inducing ligand (APRIL), molecules important in B-cell differentiation and maturation, achieved its primary endpoint of an SRI-4 response at 48 weeks across all three doses of telitacicept, (75.8% for 240 mg subcutaneously weekly, 68.3% for 160 mg weekly, 71.0% for 80 mg weekly vs 33.9% for placebo, p<0.001).[29] A Phase III trial (published only as an abstract[30]) demonstrated a similar SRI-4 response rate for the 160 mg dosage of telitacicept at 52 weeks (82.6% for telitacicept vs 38.1% for placebo, p<0.005). The magnitude of the difference between telitacicept and placebo (34% to 45%) is far greater than that observed for belimumab (10% to 14%), which only inhibits BLyS,[9,10] and that observed in most other lupus trials. However, the telitacicept trials have only been conducted in China and a global Phase III trial for extra-renal lupus is ongoing.

Ianalumab also has a dual mechanism of action, binding to the BAFF receptor and inhibiting BAFF-receptor signalling, and eliminating B cells by enhancing the ability of natural killer cells to mediate antibody dependent cellular cytotoxicity. In a Phase II study, the primary endpoint, which was the SRI-4 response and a sustained reduction in prednisone, was achieved at 28 weeks (44% for ianalumab vs 9% for placebo, difference, 34.5%; 90% CI, 19.2% to 49.4%). In addition, fewer flares and a greater attainment of the lupus low disease activity state (LLDAS) were also observed.[31] Although the sample was small (ianalumab n=34, placebo n=33) and follow-up was short, these results were considered sufficiently promising to initiate phase III trials of ianalumab for both LN and extra-renal lupus.

Intracellular Signalling

Deucravacitinib, an oral inhibitor of tyrosine kinase and downstream signalling mediated by type 1 interferon, interleukin (IL)-12, and IL-23, achieved its primary endpoint of the SRI-4 response at 32 weeks (58% for deucravacitinib 3 mg twice daily vs 34% for placebo, OR, 2.8; 95% CI, 1.5 to 5.1) as well as all of its secondary endpoints at 48 weeks (SRI-4, BICLA response, LLDAS, CLASI, and joint count).[32] Phase III trials of deucravacitinib for extra-renal lupus are ongoing.

In a multi-armed trial assessing upadacitinib, an oral Janus kinase (JAK) inhibitor (30 mg/day) alone, elsubrutinib, a Bruton's tyrosine kinase inhibitor [BTKi] (60 mg/day) alone, and in combination (upadacitinib 30 mg/day + elsubrutinib 60 mg/day or upadacitinib 15 mg/day + elsubrutinib 60 mg/day), upadacitinib 30 mg alone or in combination achieved its primary endpoint of SRI-4 response and steroids ≤10 mg/day at 24 weeks (54.8% for upadacitinib 30 mg alone vs 37.3% for placebo, p<0.05).[33] Key efficacy endpoints of SRI-4, BICLA, LLDAS, and flare rate were also met at 48 weeks in these groups. Upadacitinib 30 mg/day as monotherapy in extra-renal lupus is being pursued in Phase III trials. It should be noted that baracitinib, another JAK inhibitor,[34,35] and several BTKi[36,37] have had inconsistent efficacy in SLE, therefore, further development of these therapies has been halted. Despite the concerns of malignancy and major adverse cardiovascular events associated with JAK inhibitors in rheumatoid arthritis, there were no significant safety signals in either the deucravacitinib or upadacitinib phase II trials.

Co-Stimulation

Dapirolizumab targets the CD40 ligand (CD40L) on T-cells, inhibiting the interaction between the CD40L and CD40 receptor on antigen-presenting cells and B cells. Early studies with this agent were suspended due to increased rates of thromboembolism, potentially resulting from the functional Fc domain, which promoted platelet activation and aggregation. In a phase II trial

with modified dapirolizumab, the primary objective of establishing a dose-response relationship based on the BICLA response at 24 weeks was not met, but improvements were observed across multiple clinical measures and thrombosis was not increased.[38] Phase III studies assessing dapirolizumab for extra-renal lupus should be concluding shortly.

Plasmacytoid Dendritic Cells

Litifilimab targets plasma dendritic cells, suppressing the generation of interferon and other inflammatory cytokines. Treatment with litifilimab improved both musculoskeletal (change from baseline to 24 weeks in number of active joints: -15.0 for litifilimab vs -11.6 for placebo, difference, -3.4; 95% CI, -6.7 to -0.2)[39] and mucocutaneous manifestations (percent change from baseline to 16 weeks in the CLASI-activity score ranged from -38.8% to -47.9% across three doses of litifilimab vs -14.5% with placebo).[40] However, most secondary endpoints were not met in either trial and there was an increased incidence of herpetic infections. Phase III trials with litifilimab are ongoing for both extra-renal and cutaneous lupus.

Cellular Therapies

Cellular therapies have the potential to revolutionize the treatment of SLE leading to an immunological reset with subsequent prolonged discontinuation of all lupus therapies. The first case series of successful treatment of five refractory SLE patients with autologous anti-CD19 chimeric antigen receptor (CAR) T-cells appeared in 2022.[41] A recent study that included up to 29 months of follow-up reported a durable and medication-free remission.[42] The cytokine release and immune effector cell-associated neurotoxicity syndromes usually observed in the treatment of B-cell-derived malignancies with CAR T-cells were less severe and less frequent, likely related to a reduced target-cell burden. CAR T-cells are produced by leukapheresis of lymphocytes from the SLE patients' blood, T lymphocyte transfection with a viral vector encoding the CAR directed against CD19, followed by in-vitro expansion, and reinfusion.[43] Prior to leukapheresis, immunosuppressive therapies must be stopped, and corticosteroids reduced to <10 mg/day to allow for the development of functional lymphocytes. Prior to reinfusion, preconditioning (usually with cyclophosphamide and fludarabine) is required to facilitate in-vivo CAR T-cell proliferation and survival. After infusion, there is a rapid expansion of CAR T-cells, followed by a deep B-cell depletion, and the reappearance of B-cells after a mean of 112 days. Although B-cell depletion is relatively brief, the reconstituted B-cells are naïve and do not produce SLE-specific antibodies and complete remission is achieved by three months.

Interest in cellular therapies for SLE has exploded with at least 20 ongoing Phase I/II trials. Future strategies may include alternative or combination targets (such as B-cell maturation antigen), synthesis of CARs on alternative cells (such as natural killer cells or macrophages), virus-free CAR engineering, and allogenic off-the-shelf T-cells. Allogenic cells would shorten the wait time pre-infusion, eliminate the need to cease immunosuppressive therapy pre-leukapheresis (as there is no apheresis), and potentially obviate the need for pre-conditioning and hospitalization.

Conclusion

The advent of multi-targeted therapies and the earlier initiation of biologics (as illustrated in our patient cases), combined with the numerous promising phase II trials and burgeoning interest in cellular therapies, have facilitated a shift and potentially a transformation in the treatment paradigms for SLE. Given the complexity of the disease and its evolving treatments, it is optimal, where possible, to deliver care in consultation with an experienced team in a multidisciplinary clinic environment. If a multidisciplinary clinic is not available, the treating rheumatologist should make every effort to consult with the relevant specialists at times of crucial clinical decisions.

Correspondence

Ann E. Clarke, MD, MSc, FRCPC
Email: aeclarke@ucalgary.ca

Financial disclosures

A.C.: Consulting/Advisory Boards/Honoraria: AZ, BMS, GSK, Roche, Otsuka **Research Funding:** GSK
M.B.: Abbvie, AstraZeneca, GSK, Janssen, and Sanofi-Genzyme
B.B.: Consultancy/honoraria: Otsuka, GSK, and Novartis
K.C.: Alexion, Novartis, Otsuka, GSK
N.L.: Advisory board: GSK

References

1. Fanouriakis A, Kostopoulou M, Andersen J, Aringer M, Arnaud L, Bae SC, et al. EULAR recommendations for the management of systemic lupus erythematosus: 2023 update. Ann Rheum Dis. 2024;83(1):15-29. doi: 10.1136/ard-2023-224762.
2. Kidney Disease: Improving Global Outcomes (KDIGO) Lupus Nephritis Work Group. KDIGO 2024 Clinical Practice Guideline for the Management of Lupus Nephritis. Kidney Int. 2024;105(1S):S1-S69. doi: 10.1016/j.kint.2023.09.002
3. Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations for the management of lupus nephritis. Ann Rheum Dis. 2020;79(6):713-723. doi: 10.1136/annrheumdis-2020-216924
4. Malvar A, Alberton V, Lococo B, Lourenco M, Martinez J, Burna L, et al. Remission of lupus nephritis: the trajectory of histological response in successfully treated patients. Lupus Sci Med. 2023;10(1):e000932. doi: 10.1136/lupus-2023-000932
5. Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-year, randomized, controlled trial of belimumab in lupus nephritis. N Engl J Med. 2020;383(12):1117-1128. doi: 10.1056/NEJMoa2001180
6. Rovin BH, Furie R, Teng YKO, Contreras G, Malvar A, Yu X, et al. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney Int. 2022;101(2):403-413. doi: 10.1016/j.kint.2021.08.027
7. Rovin BH, Teng YKO, Ginzler EM, Arriens C, Caster DJ, Romero-Diaz J, et al. Efficacy and safety of voclosporin versus placebo for lupus nephritis (AURORA 1): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. Lancet. 2021;397(10289):2070-2080. doi: 10.1016/S0140-6736(21)00578-X
8. Saxena A, Ginzler EM, Gibson K, Satirapoj B, Santillan AEZ, Levchenko O, et al. Safety and efficacy of long-term voclosporin treatment for lupus nephritis in the phase 3 AURORA 2 clinical trial. Arthritis Rheumatol. 2024;76(1):59-67. doi: 10.1002/art.42657
9. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011;377(9767):721-731. doi: 10.1016/S0140-6736(10)61354-2
10. Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzova D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011;63(12):3918-3930. doi: 10.1002/art.30613
11. Liu Z, Zhang H, Liu Z, Xing C, Fu P, Ni Z, et al. Multitarget therapy for induction treatment of lupus nephritis: a randomized trial. Ann Intern Med. 2015;162(1):18-26.
12. Zhou T, Zhang X, Lin W, Lin S. Multitarget Therapy: An Effective and Safe Therapeutic Regimen for Lupus Nephritis. J Pharm Pharm Sci. 2019;22(1):365-375. doi: 10.7326/M14-1030
13. Moroni G, Gatto M, Tamborini F, Quaglini S, Radice F, Saccon F, et al. Lack of EULAR/ERA-EDTA response at 1 year predicts poor long-term renal outcome in patients with lupus nephritis. Ann Rheum Dis. 2020;79(8):1077-1083. doi: 10.1136/annrheumdis-2020-216965
14. Tamirou F, Lauwerys BR, Dall'Era M, Mackay M, Rovin B, Cervera R, et al. A proteinuria cut-off level of 0.7 g/day after 12 months of treatment best predicts long-term renal outcome in lupus nephritis: data from the MAINTAIN Nephritis Trial. Lupus Sci Med. 2015;2(1):e000123. doi: 10.1136/lupus-2015-000123
15. Dall'Era M, Cisternas MG, Smilek DE, Straub L, Houssiau FA, Cervera R, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. Arthritis Rheumatol. 2015;67(5):1305-1313. doi: 10.1002/art.39026
16. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012;64(4):1215-1226. doi: 10.1002/art.34359
17. Gomez Mendez LM, Cascino MD, Garg J, Katsumoto TR, Brakeman P, Dall'Era M, et al. Peripheral blood B cell depletion after rituximab and complete response in lupus nephritis. Clin J Am Soc Nephrol. 2018;13(10):1502-9. doi: 10.2215/CJN.01070118.
18. Alshaiki F, Obaid E, Almuallim A, Taha R, El-Haddad H, Almoallim H. Outcomes of rituximab therapy in refractory lupus: a meta-analysis. Eur J Rheumatol. 2018;5(2):118-126. doi: 10.5152/eurjrheum.2018.17096
19. Arora S, Rovin BH. Expert Perspective: An Approach to Refractory Lupus Nephritis. Arthritis Rheumatol. 2022;74(6):915-926. doi: 10.1002/art.42092
20. Furie RA, Aroca G, Cascino MD, Garg JP, Rovin BH, Alvarez A, et al. B-cell depletion with obinutuzumab for the treatment of proliferative lupus nephritis: a randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2022;81(1):100-107. doi: 10.1136/annrheumdis-2021-220920
21. Rovin BH, Furie RA, Ross Terres JA, Giang S, Schindler T, Turchetta A, et al. Kidney Outcomes and preservation of kidney function with obinutuzumab in patients with lupus nephritis: a post hoc analysis of the NOBILITY trial. Arthritis Rheumatol. 2024;76(2):247-254. doi: 10.1002/art.42734
22. Jayne D, Rovin B, Mysler EF, Furie RA, Houssiau FA, Trasieva T, et al. Phase II randomised trial of type I interferon inhibitor anifrolumab in patients with active lupus nephritis. Ann Rheum Dis. 2022;81(4):496-506. doi: 10.1136/annrheumdis-2021-221478
23. Jayne D, Rovin B, Mysler E, Furie R, Houssiau F, Trasieva T, et al. Anifrolumab in lupus nephritis: results from second-year extension of a randomised phase II trial. Lupus Sci Med. 2023;10(2) :e000910. doi: 10.1136/lupus-2023-000910

24. Wang H, Li T, Sun F, Liu Z, Zhang D, Teng X, et al. Safety and efficacy of the SGLT2 inhibitor dapagliflozin in patients with systemic lupus erythematosus: a phase I/II trial. RMD Open. 2022;8(2):e002686. doi: 10.1136/rmdopen-2022-002686
25. Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KC, Vital EM, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol. 2019;1(4):e208-e219. doi: 10.1016/S2665-9913(19)30076-1
26. Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of anifrolumab in active systemic lupus erythematosus. N Engl J Med. 2020;382(3):211-221. doi: 10.1056/NEJMoa1912196
27. Kalunian KC, Furie R, Morand EF, Bruce IN, Manzi S, Tanaka Y, et al. A randomized, placebo-controlled phase iii extension trial of the long-term safety and tolerability of anifrolumab in active systemic lupus erythematosus. Arthritis Rheumatol. 2023;75(2):253-265. doi: 10.1002/art.42392
28. Papachristodoulou E, Kyttaris VC. New and emerging therapies for systemic lupus erythematosus. Clin Immunol. 2024;263:110200. doi: 10.1016/j.clim.2024.110200
29. Wu D, Li J, Xu D, Merrill JT, van Vollenhoven RF, Liu Y, et al. Telitacicept in patients with active systemic lupus erythematosus: results of a phase 2b, randomised, double-blind, placebo-controlled trial. Ann Rheum Dis. 2024;83(4):475-487. doi: 10.1136/ard-2023-224854
30. Wu D, Li J, Xu D, Wang L, Fang J, Ross D, et al. Telitacicept, a human recombinant fusion protein targeting b lymphocyte stimulator (BlyS) and a proliferation-inducing ligand (APRIL), in systemic lupus erythematosus (SLE): results of a phase 3 study. ACR Convergence 2022; 2022 Nov 14; Philadelphia, USA. Available from: https://acrabstracts.org/abstract/telitacicept-a-human-recombinant-fusion-protein-targeting-b-lymphocyte-stimulator-blys-and-a-proliferation-inducing-ligand-april-in-systemic-lupus-erythematosus-sle-results-of-a-phase-3-study/
31. Shen N, Ignatenko S, Gordienko A, Hernández JC, Agmon-Levin N, Narongroenknawin P, et al. Phase 2 safety and efficacy of subcutaneous (s.c.) dose ianalumab (VAY736; Anti-BAFFR mAb) administered monthly over 28 weeks in patients with systemic lupus erythematosus (SLE) of moderate-to-severe activity. ACR Convergence 2023; 2023 Nov 14; San Diego, USA. Available from: https://acrabstracts.org/abstract/phase-2-safety-and-efficacy-of-subcutaneous-s-c-dose-ianalumab-vay736-anti-baffr-mab-administered-monthly-over-28-weeks-in-patients-with-systemic--lupus-erythematosus-sle-of-moderate-to-severe/
32. Morand E, Pike M, Merrill JT, van Vollenhoven R, Werth VP, Hobar C, et al. Deucravacitinib, a tyrosine kinase 2 inhibitor, in systemic lupus erythematosus: a Phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2023;75(2):242-252. doi: 10.1002/art.42391
33. Merrill J, Tanaka Y, D'Cruz D, Vila-Rivera K, Siri D, Zeng X, et al. Efficacy and safety of upadacitinib or elsubrutinib alone or in combination for patients with systemic lupus erythematosus: a phase 2 randomized controlled trial. Arthritis Rheumatol 2024; doi:10.1002/art.42926
34. Morand EF, Vital EM, Petri M, van Vollenhoven R, Wallace DJ, Mosca M, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-I). Lancet. 2023;401(10381):1001-1010. doi: 10.1016/S0140-6736(22)02607-1
35. Petri M, Bruce IN, Dorner T, Tanaka Y, Morand EF, Kalunian KC, et al. Baricitinib for systemic lupus erythematosus: a double-blind, randomised, placebo-controlled, phase 3 trial (SLE-BRAVE-II). Lancet. 2023;401(10381):1011-1019. doi: 10.1016/S0140-6736(22)02546-6
36. Isenberg D, Furie R, Jones NS, Guibord P, Galanter J, Lee C, et al. efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a Phase II, randomized, double-blind, placebo-controlled trial. Arthritis Rheumatol. 2021;73(10):1835-1846. doi: 10.1002/art.41811
37. Wallace DJ, Dorner T, Pisetsky DS, Sanchez-Guerrero J, Patel AC, Parsons-Rich D, et al. Efficacy and safety of the Bruton's tyrosine kinase inhibitor evobrutinib in systemic lupus erythematosus: results of a Phase II, randomized, double-blind, placebo-controlled dose-ranging trial. ACR Open Rheumatol. 2023;5(1):38-48. doi: 10.1002/acr2.11511
38. Furie RA, Bruce IN, Dorner T, Leon MG, Leszczynski P, Urowitz M, et al. Phase 2, randomized, placebo-controlled trial of dapirolizumab pegol in patients with moderate-to-severe active systemic lupus erythematosus. Rheumatology (Oxford). 2021;60(11):5397-5407. doi: 10.1093/rheumatology/keab381
39. Furie RA, van Vollenhoven RF, Kalunian K, Navarra S, Romero-Diaz J, Werth VP, et al. Trial of Anti-BDCA2 antibody litifilimab for systemic lupus erythematosus. N Engl J Med. 2022;387(10):894-904. doi: 10.1056/NEJMoa2118025
40. Werth VP, Furie RA, Romero-Diaz J, Navarra S, Kalunian K, van Vollenhoven RF, et al. Trial of Anti-BDCA2 antibody litifilimab for cutaneous lupus erythematosus. N Engl J Med. 2022;387(4):321-31. doi: 10.1056/NEJMoa2118024
41. Mackensen A, Muller F, Mougiakakos D, Boltz 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
42. Muller F, Taubmann J, Bucci L, Wilhelm A, Bergmann C, Volkl 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
43. Schett G, Mackensen A, Mougiakakos D. CAR T-cell therapy in autoimmune diseases. Lancet. 2023;402(10416):2034-2044. doi: 10.1016/S0140-6736(23)01126-1

When your patient presents with active psoriatic arthritis,

SAY TREMFYA®[1]

TREMFYA® and TREMFYA ONE-PRESS®: Provincial and federal funding are now available in most provinces for adult patients with PsA.[1-10*]

Restrictions may apply. Refer to your respective provincial and federal listings for full coverage details and restrictions.[2-10*]

TREMFYA®/TREMFYA ONE-PRESS® (guselkumab injection) is indicated for the treatment of adult patients with active psoriatic arthritis. TREMFYA®/TREMFYA ONE-PRESS® can be used alone or in combination with a conventional disease-modifying antirheumatic drug (cDMARD) (e.g., methotrexate).[1]

TREMFYA®/TREMFYA ONE-PRESS® is also indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.[1]

JANSSEN BIO ADVANCE® Program

ONE dedicated BioAdvance® Coordinator supports your patients with reimbursement assistance so they can get started on TREMFYA®/TREMFYA ONE-PRESS®.

Learn more at Janssenpro.ca

Please consult the Product Monograph at www.janssen.com/canada/our-medicines for important information relating to warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use that has not been discussed in this piece.

The Product Monograph is also available by calling 1-800-567-3331.

PsA=psoriatic arthritis.

* Alberta, Saskatchewan, Manitoba, New Brunswick, Newfoundland and Labrador, Nova Scotia, Ontario (EAP), Prince Edward Island, and Non-Insured Health Benefits (NIHB). Please refer to the respective listings for coverage information and restrictions.

References: 1. TREMFYA®/TREMFYA ONE-PRESS® (guselkumab injection) Product Monograph. Janssen Inc. January 17, 2024. **2.** Alberta Health. Drug benefit list. Formulary Search Results. October 13, 2023. **3.** Manitoba Pharmacare. Manitoba Drug Benefits Formulary Bulletin #129. December 21, 2023. **4.** New Brunswick (NB) Drug Plans Formulary Update. Bulletin #1122. December 18, 2023. **5.** Newfoundland and Labrador Prescription Drug Program Bulletin #234. December 13, 2023. **6.** Nova Scotia Formulary November 16, 2023. **7.** Ontario Ministry of Health. Exceptional Access Program Reimbursement Criteria for Frequently Requested Drugs. December 18, 2023. **8.** Health PEI. PEI Pharmacare Formulary. November 2023. **9.** Saskatchewan Drug Plan. Formulary Search Results. November 16, 2023. **10.** Non-Insured Health Benefits (NIHB) Program. Drug Benefit List. November 30, 2023.

Tremfya® (guselkumab) | Tremfya® (guselkumab) One-Press® | JANSSEN BIO ADVANCE®

The image depicted contains models and is being used for illustrative purposes only.

Janssen Inc. 19 Green Belt Drive | Toronto, Ontario | M3C 1L9 | **www.janssen.com/canada**

doi.org/10.58931/crt.2024.1249

About the Author

Melinda Gooderham, MSc, MD, FRCPC

Dr. Gooderham, Dermatologist and Medical Director at SKiN Centre for Dermatology, is also an Investigator at Probity Medical Research, Assistant Professor at Queens University, and Consultant Physician at Peterborough Regional Health Centre. A fellow of the Royal College of Physicians and Surgeons of Canada, she has been an investigator in over 200 clinical trials focusing on inflammatory skin diseases including psoriasis and atopic dermatitis. Beyond clinical practice, Dr. Gooderham actively contributes to dermatology publications as an author, associate editor and reviewer, with authorship of over 200 articles. Her passion for education extends to global audiences through engaging lectures on innovative therapies for skin diseases.

Affiliations: SKiN Centre for Dermatology, Peterborough, ON
Probity Medical Research, Waterloo, ON
Queen's University, Kingston, ON

Exploring Newer Topical Therapies for Inflammatory Skin Diseases: A Guide for Rheumatologists

Melinda Gooderham, MSc, MD, FRCPC

Introduction

Understanding the pathogenesis of many inflammatory skin diseases and their associated signalling pathways has revealed multiple promising therapeutic targets. Given the chronic nature of many of these conditions, products with long-term safety and efficacy are desired. While topical corticosteroids have been the mainstay of topical therapies for years, they are burdened by concerns over long-term safety (i.e., atrophy, striae, telangiectasias), risk of absorption with systemic glucocorticoid side effects, and patient apprehension regarding steroid use. Similarly, topical calcipotriol and retinoids may be ineffective and can cause irritation. Although topical calcineurin inhibitors (i.e., pimecrolimus, tacrolimus) have been approved for atopic dermatitis, their off-label use for many inflammatory conditions may be limited by tolerability issues such as stinging and burning, and lack of effectiveness. The emergence of newer targeted small molecules for topical application, including topical phosphodiesterase-4 inhibitors (PDE4i), topical Janus kinase inhibitors (JAKi), and a therapeutic aryl hydrocarbon modulating agent (TAMA), offer promising new options and will be reviewed here and summarized in **Table 1.**

Phosphodiesterase-4 Inhibitors (PDE4i)

Cyclic adenosine monophosphate (cAMP) serves as the principal secondary messenger governing the regulation of immune responses. Phosphodiesterase 4 (PDE4) stands out as the key enzyme responsible for cAMP degradation and is present in both immune cells and non-immune cells such as keratinocytes.[1] Inhibitors targeting PDE4 can extend or amplify the effects of cAMP, which can lead to the suppression of both Th1 and Th2 immune responses, thereby making this an attractive target for managing inflammatory skin diseases.[1,2]

Class	Product	Indication	Trade name
Calcineurin inhibitors			
Pimecrolimus	**Pimecrolimus 2% cream BID**	Mild-to-moderate atopic dermatitis	Elidel cream
Tacrolimus	**Tacrolimus 0.03%, Tacrolimus 0.1% ointment**	Moderate-to-severe atopic dermatitis	Protopic ointment
PDE4 inhibitors			
Crisaborole	**Crisaborole 2% ointment BID**	Mild-to-moderate atopic dermatitis, ages 3 months and above	Eucrisa ointment
Roflumilast	**Roflumilast 0.3% cream OD**	Plaque psoriasis, ages 9 years and above	Zoryve cream 0.3%
	Roflumilast 0.3% foam	Seborrheic dermatitis	Zoryve foam 0.3%
	Roflumilast 0.15% cream* OD	Atopic dermatitis	Zoryve cream 0.15%
JAK inhibitors			
Delgocitinib	Delgocitinib 20mg/g cream* BID	Chronic hand eczema	Unknown
Ruxolitinib	Ruxolitinib 1.5% cream** BID	Atopic dermatitis and vitiligo, ages 12 years and above	Opzelura cream
AhR modulating agents (TAMA)			
Tapinarof	Tapinarof 1% cream** OD	Plaque psoriasis Atopic dermatitis	Vtama cream

Table 1: Summary and indications of non-steroidal topical agents for inflammatory skin diseases; *courtesy of Melinda Gooderham, MSc, MD, FRCPC.*

Abbreviations: BID: twice a day, **OD:** once daily

Bolded medications are approved by Health Canada
* Not yet approved by Health Canada
** Not yet approved and under review by Health Canada

This mechanism of action is well proven with the oral PDE4i, apremilast, which is approved for use in moderate-to-severe psoriasis, psoriatic arthritis, and Behçet's disease.[3] Topical PDE4i are also approved for use in inflammatory skin diseases. Specifically, topical crisaborole 2% ointment is approved for atopic dermatitis for ages three months and above,[4] and more recently, topical roflumilast 0.3% cream has been approved for plaque psoriasis in individuals 12 years and above.[5]

Roflumilast, a highly potent PDE4i, has been approved as an oral therapy for chronic obstructive pulmonary disease since 2011.[2] In 2023, Health Canada approved topical roflumilast 0.3% cream, for treating plaque psoriasis, including intertriginous psoriasis for ages 12 and older.[5] This topical formulation of roflumilast is an elegant, moisturizing, water-based cream that is applied once daily. Notably, it exhibits superior potency compared to other PDE4 inhibitors, ranging from 25 to 300 times more potent than apremilast or crisaborole, depending on the specific comparator and PDE4 isoform.[2]

The phase 3 trials, DERMIS-1 and DERMIS-2, included 881 participants aged 2 years and above with plaque psoriasis covering 2–20% of their body surface area. These multicentre trials evaluated the daily use of roflumilast 0.3% cream over an 8-week period. Roflumilast showed significant improvements in key outcomes, including the primary outcome of Investigator Global Assessment (IGA) success (achieving an IGA of clear or almost clear and at least a 2-grade

improvement from baseline) and a key secondary outcome, 75% improvement in Psoriasis Area Severity Index (PASI-75). Pruritus also improved with the use of roflumilast, showing a reduction of at least 4-points in the Worst Itch Numeric Rating Scale (WI-NRS) scores observed as early as week 2, and this improvement was more prominent by week 8. Adverse events associated with roflumilast were comparable between roflumilast and vehicle (placebo) groups which were uncommon and likely unrelated to treatment.[6]

Future approvals and formats of topical roflumilast include a roflumilast 0.3% foam for once daily use to treat seborrheic dermatitis,[7] which is already approved by the FDA for use in ages 9 years and above in the United States. The roflumilast foam product has also been studied in scalp and body psoriasis (NCT05028582) and may have a future indication for the use of roflumilast. A topical roflumilast 0.15% cream is being investigated for use in atopic dermatitis,[8] and was approved by the FDA in July 2024.

Janus Kinase Inhibitors

The Janus kinases (JAKs), including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2), are predominantly found in hematopoietic cells, residing on the cytoplasmic side of Type I and II cytokine receptors.[9] Upon cytokine binding, JAKs activate signal transducers and activators of transcription (STATs). This activation process leads to the phosphorylation of the STATS. Once phosphorylated, they dimerize and translocate to the nucleus to regulate gene transcription. Inhibition of this pathway, which plays a crucial role in immune defence, has shown promise in treating multiple immune-mediated diseases. JAKi, which are small molecules that modulate immune responses by uncoupling cytokine receptor signalling from downstream STAT transcription activation; and, can be effective also as topical preparations.[9] Ruxolitinib 1.5% cream is the first topical JAKi that targets JAK1 and JAK2, which is currently approved by the FDA for use in atopic dermatitis and vitiligo.[10]

The atopic dermatitis pivotal trials, TRuE-AD1 and TRuE-AD2, involved 1249 participants aged 12 years and above with mild-to-moderate atopic dermatitis (IGA 2 or 3) covering 3–20% of their body surface area.[11] These multicentre trials evaluated the use of ruxolitinib 1.5% cream twice daily over an 8-week period. The findings of these trials demonstrated significant improvements of ruxolitinib cream in key outcomes, including the primary outcome, IGA treatment success (IGA-TS), and a 75% improvement in the Eczema Area Severity Index (EASI-75). A treatment effect was noted as early as week 2 in both studies. Pruritus also showed significant improvement with the use of ruxolitinib cream, with at least a 4-point reduction in the Itch Numeric Rating Scale (NRS) scores that were observed as early as day 2 of treatment, with a clinically significant difference at week 2, and the improvement was more prominent by week 8 of treatment in both studies. The most commonly reported adverse events were comparable between the ruxolitinib and vehicle groups, and included nasopharyngitis, upper respiratory tract infection, and headache.[11] There were no reported adverse events associated with systemic JAK absorption.

The pivotal trials in vitiligo, TRuE-V1 and TRuE-V2, included 674 participants 12 years of age or older who had non-segmental vitiligo covering 10% or less of their body surface area.[12] Participants applied either ruxolitinib 1.5% cream twice daily or vehicle to all involved areas for a 24-week period. After this time point, all patients, regardless of their initial group assignment, applied ruxolitinib cream until the 52-week time point. The primary endpoint was a 75% improvement in the Facial Vitiligo Area Scoring Index (F-VASI75) at week 24. The study found significantly greater repigmentation in the ruxolitinib group, with approximately one-third of participants achieving this target, compared to the vehicle group by week 24.[12] Other secondary endpoints included a 50% improvement in the total VASI (T-VASI50), which was significantly greater in the ruxolitinib group and achieved in approximately one-fifth on active treatment with ruxolitinib. After 52 weeks of topical ruxolitinib application, adverse events were infrequent and included acne, nasopharyngitis, and application site pruritus.[12] Topical ruxolitinib 1.5% cream is also currently being studied for conditions such as mild hidradenitis suppurativa (NCT05635838) and prurigo nodularis (NCT05755438, NCT05764161).

Another JAKi, delgocitinib, is a topical pan-JAK inhibitor that is under investigation for chronic hand eczema. Delgocitinib is approved for use in atopic dermatitis in Japan in a 0.5% ointment formulation.[13] The phase 3 pivotal trials, DELTA-1 and DELTA-2, included 960 participants aged 18 years and above who were treated with twice daily delgocitinib cream 20 mg/g or vehicle for 16 weeks.[14,15] The most common reported adverse effects were nasopharyngitis, dermatitis, and

Inflammatory Skin Condition	PDE4 Inhibitors	JAK Inhibitors	AhR Modulating Agent
Psoriasis	**Roflumilast 0.3% cream OD**		Tapinarof 1% cream** OD
Atopic Dermatitis	**Crisaborole 2% ointment BID** **Roflumilast 0.15% cream* OD**	Ruxolitinib 1.5% cream** BID	Tapinarof 1% cream* OD
Chronic Hand Eczema		Delgocitinib 20 mg/g cream* BID	
Seborrheic Dermatitis	Roflumilast 0.3% foam* OD		
Vitiligo		Ruxolitinib 1.5% cream** BID	

Table 2: Approved and upcoming indications for topical therapies; *courtesy of Melinda Gooderham, MSc, MD, FRCPC.*

Abbreviations: BID: twice a day, **OD:** once daily

Bolded medications are approved by Health Canada
* Not yet approved by Health Canada
** Not yet approved and under review by Health Canada

headache. DELTA-3 was a 36-week extension trial that evaluated the long-term safety and efficacy of delgocitinib cream. The results showed good maintenance of effect and no new safety concerns over 36 weeks of as-needed use.[16]

Aryl hydrocarbon receptor antagonists

Aryl hydrocarbon receptor (AhR), a ligand-dependent transcription factor, regulates gene expression in immune and epithelial cells, and is necessary for maintaining skin homeostasis.[17] Through heterodimerization with the AhR nuclear translocator (ARNT), an AhR-ARNT complex is formed that binds to specific DNA sites, to control the transcription of AhR-responsive genes. Activation by different ligands can induce a variety of biological responses, making AhR a suitable therapeutic target for inflammatory skin diseases due to its role in regulating inflammation and homeostasis.[17] For instance, topical inhibition of the AhR pathway, by tapinarof, a topical Therapeutic Aryl hydrocarbon receptor-Modulating Agent (TAMA), is a novel way to target skin inflammation.[17]

In the pivotal trials for topical tapinarof, PSOARING-1 and PSOARING-2, 1025 participants aged 18 to 75 years with a physician global assessment (PGA) score of at least mild (2) and a body surface area of 3 to 20% affected by psoriasis were treated with tapinarof 1% cream or vehicle once daily for 12 weeks.[18] PGA response, reflected by the PGA score (clear [0] or almost clear [1] with at least a 2-point improvement from baseline) was the primary trial endpoint. Other key endpoints, such as the PASI-75 score, were met in a significantly greater proportion of patients in the tapinarof 1% cream arm than in the vehicle arm. Also, long-term efficacy was observed in the PSOARING-3 trial; a long-term extension study. In this trial, participants with a PGA score of 1 or greater applied tapinarof 1% cream for an additional 40 weeks, observing that some patients achieved a remittive effect (the maintenance of clear or almost clear while off therapy). Adverse events such as folliculitis, headache, back pain, and pruritus were most commonly reported.[18] Tapinarof is also being assessed for its use in atopic dermatitis (NCT05014568, NCT05032859).

Future Directions

The need for safe, long-term therapies continues in chronic inflammatory skin conditions. Current treatment options may have cumulative toxicities or tolerability issues, which underscores the excitement surrounding the emergence of novel topical therapies. The recent approval of topical roflumilast 0.3% cream, which offers a convenient once-daily treatment for plaque psoriasis, including the intertriginous areas, opens a promising new avenue for patients to manage their condition. The imminent approvals of other topical treatments, including PDE4i, JAKi, and TAMA for conditions such as psoriasis, atopic dermatitis, seborrheic dermatitis, and vitiligo, with hopefully many more conditions being added to this list adds to therapeutic topical treatments for many patients with inflammatory skin conditions (**Table 2** which

lists various diseases where the new topical agents are being studied). These and other treatments continue to improve outcomes for patients.

Correspondence

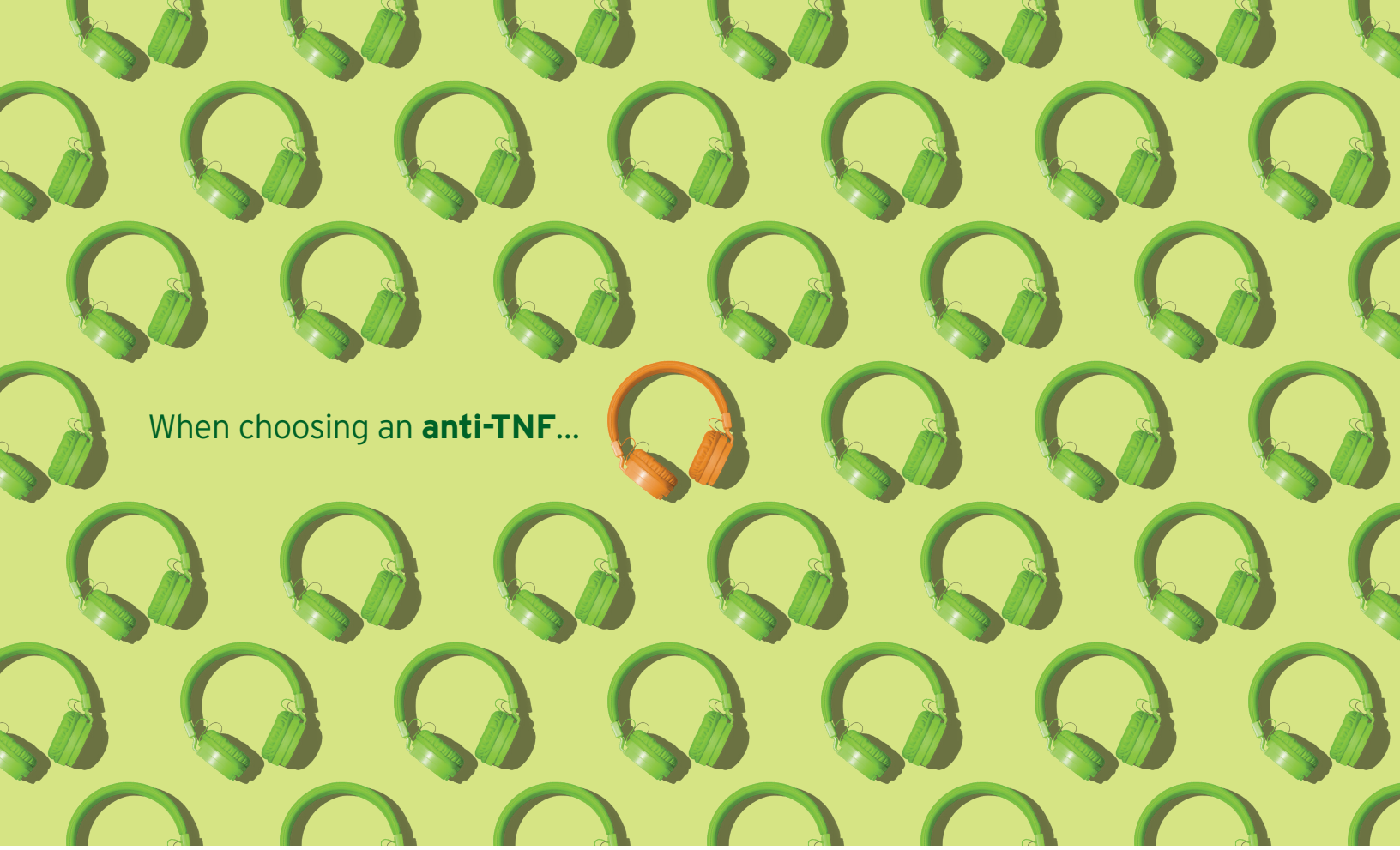
Melinda Gooderham, MSc, MD, FRCPC
Email: mgooderham@centrefordermatology.com

Financial Disclosures

Investigator/speaker and/or advisor: AbbVie, Acelyrin, Amgen, Akros, Arcutis, Aristea, AnaptysBio, Apogee, Bausch Health, BMS, Boehringer Ingelheim, Cara, Dermira, Dermavant, Eli Lilly, Galderma, GSK, Incyte, InMagene, JAMP Pharma, Janssen, Kyowa Kirin, LEO Pharma, MedImmune, Meiji, Merck, Moonlake, Nimbus, Novartis, Pfizer, Regeneron, Roche, Sanofi Genzyme, Sun Pharma, Tarsus, Takeda, UCB, Union and Ventyx.

References

1. Bäumer W, Hoppmann J, Rundfeldt C, Keitzmann M. Highly selective phosphodiesterase 4 inhibitors for the treatment of allergic skin diseases and psoriasis. Inflamm Allergy Drug Targets. 2007;6(1):17-26. doi: 10.2174/18715280778007731
2. Crowley EL, Gooderham MJ, Phosphodiesterase-4 Inhibition in the management of Psoriasis. Pharmaceutics. 2023;16(1):23. https://doi.org/10.3390/pharmaceutics16010023
3. Otezla [package insert]. Mississauga (ON): Amgen Canada Inc; 2020. [Cited 2024 Jun 10]. Available from: https://pdf.hres.ca/dpd_pm/00054839.PDF
4. Eucrisa [package insert]. Kirkland (QC): Pfizer Canada ULC; 2021.[Cited 2024 Jun 10]. Available from: https://pdf.hres.ca/dpd_pm/00060960.PDF
5. Zoryve [package insert]. Westlake Village (CA): Arcutis Biotherapeutics Inc.; 2023. [Revised 2024 Jan]. [Cited 2024 Jun 10]. Available from: https://www.arcutis.com/wp-content/uploads/USPI-roflumilast-cream.pdf
6. Lebwohl MG, Kircik LH, Moore AY, Stein Gold L, Draelos ZD, Gooderham MJ, et al. Effect of roflumilast cream vs vehicle cream on chronic plaque psoriasis. JAMA. 2022;328(11):1073. https://doi.org/10.1001/jama.2022.15632
7. Zirwas MJ, Draelos ZD, DuBois J, Kircik LH, Moore AY, Gold LS, et al. Efficacy of roflumilast foam, 0.3%, in patients with seborrheic dermatitis: a double-blind, vehicle-controlled phase 2a randomized clinical trial. JAMA Dermatol. 2023;159(6):613–620. doi:10.1001/jamadermatol.2023.0846
8. Gooderham M, Kircik L, Zirwas M, Lee M, Kempers S, Draelos Z, et al. The safety and efficacy of roflumilast cream 0.15% and 0.05% in patients with atopic dermatitis: randomized, double-blind, phase 2 proof of concept study. J Drugs Dermatol. 2023;22(2):139-147. doi:10.36849/JDD.7295 .
9. Kontzias A, Kotlyar A, Laurence A, Changelian P, O'Shea JJ. Jakinibs: a new class of kinase inhibitors in cancer and autoimmune disease. Curr Opin Pharmacol. 2012;12(4):464-470. doi:10.1016/j.coph.2012.06.008
10. Opzelura [package insert]. Wilmington (DE): Incyte Corporation; 2022. [Cited 10 Jun 2024]. Available from: https://www.opzelura.com/opzelura-prescribing-information
11. Papp K, Szepietowski JC, Kircik L, Toth D, Eichenfield LE, Leung DYM, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol. 2021;85(4):863-872. doi:10.1016/j.jaad.2021.04.085
12. Rosmarin D, Passeron T, Pandya AG, Grimes P, Harris JE, Desai SR, et al. Two phase 3, randomized, controlled trials of ruxolitinib cream for vitiligo. N Engl J Med. 2022;387(16):1445–1455. https://doi.org/10.1056/nejmoa2118828
13. Corectim Ointment 0.5% [package insert]. Tokyo, Japan: Japan Tobacco Inc.; 2019. [Cited 2024 Jun 10]. Available from: https://www.torii.co.jp/en/release/2021/20210526_E1.pdf
14. Bissonnette R, Warren R, Stingeni L, et al. Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema: results of the Phase 3 DELTA 1 trial. Presented at: Late Breaking Research: presentation on 18 March 2023 at the 81st Annual Meeting of the American Academy of Dermatology (AAD) in New Orleans, LA, USA
15. Schliemann S, Pinter A, Schutterlaar ML, et al. Efficacy and safety of delgocitinib cream in adults with moderate to severe chronic hand eczema: results of the Phase 3 DELTA 2 trial. Poster presentation at: The 32nd Annual Congress of the EADV, 11-14 October 2023. Berlin, Germany
16. Gooderham M, Molin S, Bissonnette R, et al. Long-term safety and efficacy of delgocitinib cream for up to 36 weeks in adults with chronic hand eczema: results of the Phase 3 open-label extension DELTA 3 trial. Presented at: Late Breaking Research: Session 1. 9 March 2024. The 82nd Annual Meeting of the American Academy of Dermatology (AAD), in San Diego, CA, USA
17. Bissonnette R, Stein Gold L, Rubenstein, DS, Tallman AM, Armstrong A. Tapinarof in the treatment of psoriasis: a review of the unique mechanism of action of a novel therapeutic aryl hydrocarbon receptor–modulating agent. J Am Acad Dermatol. 2021;84(4):1059-1067. doi:10.1016/j.jaad.2020.10.085
18. Lebwohl MG, Stein Gold L, Strober B, Papp KA, Armstrong AW, Bagel J, et al. Phase 3 trials of tapinarof cream for plaque psoriasis. N Engl J Med. 2021;385(24):2219-2229.doi: 10.1056/NEJMoa2103629



Consider CIMZIA®

- The only anti-TNF with a molecular structure that does not contain a fragment crystallizable (Fc) region, which is normally present in a complete antibody[1,2]*
- Over 14 years of clinical experience combined across all indications in:[2]
  - **Rheumatoid arthritis (RA) – 2009; Psoriatic arthritis (PsA) – 2014; Ankylosing spondylitis (AS) – 2014; Plaque psoriasis (PsO) – 2018; and Non-radiographic axial spondyloarthritis (nr-axSpA) - 2019**[1,3]

CIMZIA (certolizumab pegol) in combination with MTX is indicated for:
- reducing signs and symptoms, including major clinical response, and reducing the progression of joint damage as assessed by X-ray, in adult patients with moderately to severely active RA.

CIMZIA alone or in combination with MTX is indicated for:
- reducing signs and symptoms and inhibiting the progression of structural damage as assessed by X-ray, in adult patients with moderately to severely active PsA who have failed one or more DMARDs.

CIMZIA is indicated for:
- reducing signs and symptoms in adult patients with moderately to severely active RA who do not tolerate MTX.
- reducing signs and symptoms in adult patients with active AS who have had an inadequate response to conventional therapy.
- the treatment of adults with severe active nr-axSpA with objective signs of inflammation as indicated by elevated CRP and/or MRI evidence who have had an inadequate response to, or are intolerant to NSAIDs.
- the treatment of adult patients with moderate to severe PsO who are candidates for systemic therapy.

* Comparative clinical significance unknown.
CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; MRI: magnetic resonance imaging; MTX: methotrexate; NSAIDs: nonsteroidal anti-inflammatory drugs; TNF: tumor necrosis factor alpha.

Consult the product monograph at https://health-products.canada.ca/dpd-bdpp/index-eng.jsp for important information about:
- Contraindications in active tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections; and moderate to severe heart failure (NYHA Class III/IV)
- The most serious warnings and precautions regarding serious infections and malignancy
- Other relevant warnings and precautions regarding worsening congestive heart failure and new onset CHF; hepatitis B virus reactivation; hematological reactions; neurologic reactions; use in combination with other biologic medicines; monitoring for patients in surgery and those being switched to another biologic DMARD; hypersensitivity symptoms; latex sensitivity; formation of autoantibodies; administration of live or live-attenuated vaccines; use in patients with severe immunosuppression; possible erroneously elevated activated partial thromboplastin time (aPTT) assay results in patients without coagulation abnormalities; women of childbearing potential; pregnancy and breastfeeding; caution in infants exposed in utero; caution in geriatric patients
- Conditions of clinical use, adverse reactions, drug interactions and dosing instructions

The product monograph is also available through Medical Information Services at 1-866-709-8444.

1. CIMZIA® Product Monograph. UCB Canada Inc. November 13, 2019.
2. Data on file. UCB, Inc.
3. Health Canada Notice of Compliance Database. Available at https://health-products.canada.ca/noc-ac/search-recherche.do;jsessionid=C19864F3D26560FC593BFC094A8B0CD1?lang=en. Accessed October 13, 2022.

CRA-24-006E

cimzia® (certolizumab pegol)

About the Authors

Matthew Wong-Pack, MD

Dr. Matthew Wong-Pack is a Rheumatology fellow at McMaster University. He works with the Ontario Best Practices Research Initiative (OBRI), a research organization aimed at improving the treatment and outcomes of Ontarians living with rheumatoid arthritis.

Affiliations: Department of Rheumatology, McMaster University, Hamilton, Ontario, Canada

Arthur N. Lau, MD, FRCPC

Dr. Arthur Lau is currently an associate professor in the division of rheumatology at McMaster University, Canada and holds the Actavis Chair in Rheumatology for Better Bone Health. He obtained his medical degree from McMaster University. He also completed his internal medicine and rheumatology training at McMaster University. He then completed the clinical investigator program, concurrently obtaining an MSc in health research methodology through McMaster. He is one of the founding partners of the William G. Bensen Centre for Arthritis Excellence and serves as its medical director. His clinical and research interest focuses on the screening and treatment of osteoporosis, and models of care to improve the screening and treatment of inflammatory arthritis.

Affiliations: Department of Rheumatology, McMaster University, Hamilton, Ontario, Canada

doi.org/10.58931/crt.2024.1250

Osteoporosis in 2024: Frequency, Monitoring and Treatment

Matthew Wong-Pack, MD
Arthur N. Lau, MD, FRCPC

Introduction

Osteoporosis is a chronic condition characterized by decreased bone mineral density (BMD) and deterioration of bone architecture, leading to an increased risk of fractures. It is the most common metabolic bone disease globally. It is estimated that more than two million Canadians aged 40 years and older have osteoporosis. Approximately 80% of Canadians who have sustained a fracture due to osteoporosis do not receive appropriate care, leaving them at an elevated risk for subsequent fractures, deconditioning, and premature death.[1] Many clinical practice guidelines exist on the management of osteoporosis and fracture prevention. Several of them have separate definitions for patients deemed very high and high risk for fracture and, as such, have specific criteria for the use of anabolic and antiresorptive treatments.

Patients with Rheumatic Diseases

Patients with rheumatic diseases are at an elevated risk of osteoporosis due to inflammation and immobility, predisposing them to bone loss. Many autoinflammatory diseases and autoimmune diseases result in the dysregulation of the RANKL-RANK pathway or the upregulation of Dickkopf-related protein 1 (Dkk-1) and sclerostin, both of which inhibit the Wnt/β-catenin pathway.[2,3] Upregulation of RANK-L and downregulation of the Wnt signalling are highly associated with deleterious effects on bone health. Furthermore, given that corticosteroids are common medications used in many rheumatic diseases, clinicians should be vigilant for the risks of their patients developing glucocorticoid-induced osteoporosis. Rheumatologists and family physicians should recognize the increased risk of osteoporosis in their patients with rheumatic diseases and ensure they have timely access to diagnostic assessments as well as pharmacotherapy when necessary.

What Should We Start With?

Patients with rheumatic diseases should undergo a fracture risk assessment, which consists of the following steps:

1. A detailed history of the patient's chronic conditions, comorbidities, health status (i.e., diet, smoking, alcohol consumption), fall risk, and medications that contribute to osteoporosis.
2. A physical examination to evaluate subclinical vertebral fractures, as well as frailty and sarcopenia, both of which are highly associated with bone loss.[4,5]
3. Diagnostic studies to exclude secondary causes of osteoporosis, as well as BMD measurement combined with fracture risk stratification tools such as FRAX and CAROC.

A list of secondary causes of osteoporosis from the Osteoporosis Canada 2023 Guidelines is provided in **Table 1**. Patients undergoing osteoporosis evaluation should have baseline measurements of height, rib-to-pelvic distance, and occiput-to-wall distance taken. If there is a history of height loss greater than 6 cm, a prospect of height loss of at least 2 cm, less than 2 fingerbreadths between the rib-to-pelvis distance, or a greater than 5 cm distance from occiput to-wall measurement on physical examination, consider further investigation with x-rays of the spine, including para-spinal views, to rule out vertebral compression fractures.

Baseline investigations to evaluate for secondary causes of osteoporosis include the following: calcium corrected for albumin, phosphate, renal function, liver function tests, thyroid-stimulating hormone, and serum protein electrophoresis (SPEP) for patients with vertebral

Drugs	Endocrine Disorders	Gastrointestinal & Nutritional Disorders
• Glucocorticoid steroids • Aromatase inhibitors • Anticonvulsants (particularly phenytoin, phenobarbital) • GnRH agonists and antagonists • Androgen-deprivation agents • Cancer chemotherapy • Immunosuppressants (eg. cyclosporine)	• Hyperparathyroidism Hyperthyroidism • Hypercortisolism/Cushing's syndrome • Diabetes mellitus (Type 1 & Type 2) • Prolonged premature hypogonadism • Acromegaly	• Inflammatory bowel disease • Celiac disease • Bariatric surgery • Pancreatic insufficiency • Other malabsorptive syndromes • Primary biliary cholangitis • Chronic liver disease • Eating disorder • Malnutrition • Parenteral nutrition • Vitamin D and/or calcium deficiency
Rheumatologic Disorders	**Genetic Disorders**	**Other Disorders**
• Rheumatoid arthritis • Other inflammatory arthritis disorders • Systemic lupus erythematous	• Osteogenesis imperfecta Hypophosphatasia • Other genetic causes of osteomalacia	• Multiple myeloma • Other marrow-related disorders • Idiopathic hypercalciuria • Chronic kidney disease/renal failure • Chronic obstructive pulmonary disease • Organ transplantation • Multiple sclerosis Parkinson's disease • Other neuromuscular disorders • Prolonged immobilization • Paget's disease • Acquired causes of osteomalacia

Table 1. Secondary causes of osteoporosis; a*dapted from Osteoporosis Canada Guidelines (2023).*

fractures, as well as 25-hydroxy vitamin D if risk factors for insufficiency are present or there is consideration for starting antiresorptive therapy.

Choice and Duration of Pharmacotherapy

Numerous treatment options are available for osteoporosis management and fracture prevention (**Figure 1**). Antiresorptive therapies, including bisphosphonates (i.e., alendronate, risedronate and zoledronic acid), denosumab, venlafaxine, and menopausal hormone therapy, are among the options, as well as anabolic therapies such as teriparatide or romosozumab.

Bisphosphonates

The 2023 Osteoporosis Canada guidelines currently recommend bisphosphonates as first-line treatment for osteoporosis and fracture prevention in postmenopausal females and males aged 50. Bisphosphonates are widely utilized for osteoporosis treatment and fracture prevention in Canada, with the first publications on their effects dating back to 1969. With over 50 years of data on their use in various metabolic bone disorders, they have demonstrated a proven record of success and efficacy.

However, a universal recommendation may not be suitable for all patients, particularly those with rheumatic conditions or secondary causes of osteoporosis. Patients at high risk (e.g., FRAX Hip Fracture Risk ≥3%, FRAX Major Osteoporotic Fracture (MOF) Risk ≥20%, prior

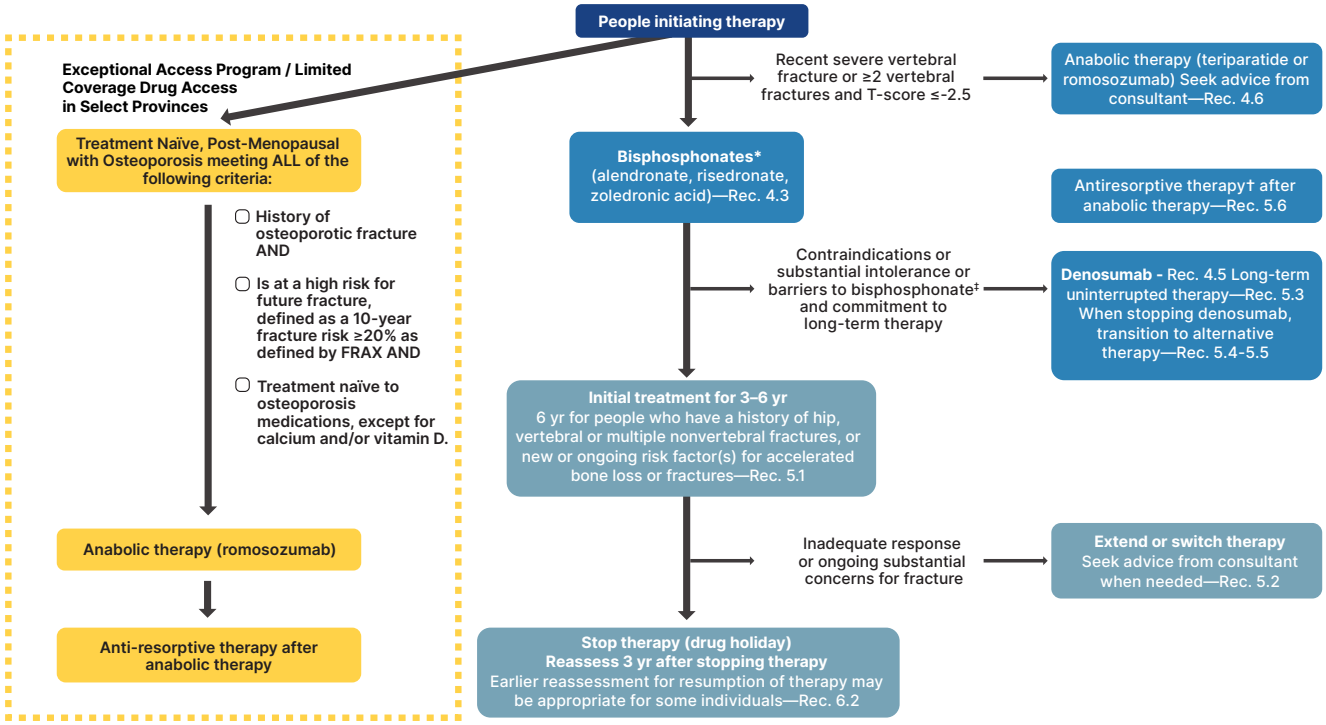


Figure 1. Pharmacotherapy for osteoporosis; *adapted from Osteoporosis Canada Guidelines (2023)*.

spine or hip fracture, or FRAX MOF risk between the upper assessment threshold and very high-risk threshold) or very high risk (e.g., multiple fractures, fracture within the last 12 months, BMD ≤-3.0, fracture while on osteoporosis therapy, FRAX hip fracture risk ≥4.5%, FRAX MOF risk ≥30%) should be considered for alternative antiresorptive therapies (e.g., denosumab) versus anabolic treatments.[6-10]

A systematic review, network meta-analysis, and meta-regression analysis of randomized clinical trials in 2023, involving over 80,000 patients from 69 trials, found that bisphosphonates, parathyroid hormone receptor agonists, and romosozumab all demonstrated a protective effect for clinical fracture prevention. However, bone anabolic treatments were more effective irrespective of baseline risk indicators. Management plans for patients with rheumatic diseases and low bone mass should be individualized and tailored according to the patient's comorbidities and risk profile. Several notable studies comparing newer treatment modalities to bisphosphonates are outlined below.

Denosumab vs Alendronate

A study conducted in 2023 compared the effectiveness of denosumab (n = 90,805) versus alendronate (n = 392,682) among postmenopausal women in the U.S .Medicare program. The study, which focused on treatment naïve patients initiating pharmacotherapy between 2012 and 2018, revealed that the use of denosumab, compared to that of alendronate, resulted in a 36% reduction in hip fractures (RR = 0.64, 95% CI: 0.39–0.90), a 43% reduction in non-vertebral fractures (RR = 0.57; 95% CI: 0.42–0.71), and a 39% reduction in major osteoporotic fractures (RR = 0.61; 95% CI: 0.48–0.74).[11] Overall, the study found that patients who remained on denosumab for extended periods experienced greater reductions in fracture risk compared to those who remained on alendronate, with statistical differences observed as soon as 1 year after pharmacotherapy.

Teriparatide vs Risedronate

The VERO Study (2017) enrolled 680 postmenopausal women with at least 2 moderate or 1 severe vertebral fracture and a BMD T-Score ≤-1.5 in a 24-month double-blind randomized controlled trial. Participants were assigned in a 1:1 ratio to compare the effectiveness of teriparatide vs risedronate in patients with severe osteoporosis. By the end of the 24-month period, the use of teriparatide, compared to risedronate, resulted in a 56% reduction in new vertebral fractures (RR 0.44; 95% CI 0.29–0.68) as well as a lower cumulative incidence of clinical fractures (4.8% vs 9.8%, [HR 0.48; 95% CI 0.32–0.74], P = 0.0009).[12] This demonstrated that teriparatide is associated with a significant reduction in the incidence of vertebral and clinical fractures compared to risedronate.

Romosozumab vs Alendronate

The ARCH Study (2017) enrolled 4093 postmenopausal women with osteoporosis and a fragility fracture in a 24-month double-blinded randomized controlled trial, in a 1:1 ratio, to compare the effectiveness of a regimen initiating romosozumab (12 months) and transitioning to alendronate (12 months) vs treatment with alendronate alone (24 months). By the end of the 24-month period, the romosozumab-to-alendronate group, compared to the alendronate-alone group, showed a 48% lower risk of new vertebral fractures (6.2% [127 of 2046 patients] vs 11.9% [243 of 2047 patients], P<0.001) and a 27% lower risk of clinical fractures (non-vertebral and symptomatic vertebral fracture) (9.7% [198 of 2046 patients] vs 13.0% [266 of 2047 patients], P<0.001).[13] During the first year of treatment, serious cardiovascular adverse events were observed more often with romosozumab compared to alendronate (2.5% [50 of 2040 patients] vs 1.9% [38 of 2014 patients]). Therefore, consideration should be given to the patient's cardiovascular risk profile before considering this treatment. It is contraindicated in patients with a history of previous myocardial infarction or stroke.

What to Monitor in Patients with Osteoporosis

During each follow-up assessment, it is recommended to reassess the risk for fracture, patient adherence to pharmacotherapy, and whether treatment needs to be continued or modified. Ideally, BMD measurements should be repeated three years after initiating pharmacotherapy, but shorter intervals may be necessary for patients with secondary causes of osteoporosis, new fractures or clinical risk factors associated with rapid bone loss. Patients with rheumatic diseases are at an elevated risk for bone loss compared to the general population, so repeat BMD testing every 1–2 years may be considered for this group.

Pharmacotherapy should be re-evaluated, and consideration given to a drug holiday at 5–6 years for patients taking oral bisphosphonates due to the risk of cumulative exposure and the development of atypical femoral fractures. If there is an inadequate response or if there are ongoing concerns for future fractures, extending or switching treatment modalities may be necessary, with guidance from a specialist in osteoporosis, if required. Patients with contraindications or potential intolerance to bisphosphonates should be considered for denosumab or anabolic therapy depending on their fracture risk. For those on denosumab, long-term uninterrupted therapy is recommended. The treatment duration for anabolic therapies (romosozumab and teriparatide) is 1 year, after which the patient should transition to an antiresorptive agent (either bisphosphonates or denosumab) to maintain bone density gains.

Conclusion

Osteoporosis is a disease that clinicians should closely monitor, especially in those with autoimmune rheumatic diseases. Several treatment options exist for fracture prevention. However, it is essential to carefully evaluate the patient's comorbidities, medications and risk profile to determine the appropriateness of the chosen pharmacotherapy based on the patient's circumstances.

Correspondence

Arthur N. Lau, MD, FRCPC
Email: arthur.lau@medportal.ca

Financial Disclosures

Matthew Wong-Pack: None declared.
Arthur Lau: Honorarium/Speaker Bureau: AbbVie, Amgen, BMS, Celgene. Eli Lilly, Merck, Novartis, Janssen, Pfizer, Roche, Sanofi, UCB
Clinical Trials: AbbVie, Amgen, Janssen, UCB

References

1. Public Health Agency of Canada. Osteoporosis and related fractures in Canada: report from the Canadian Chronic Disease Surveillance System. Ottawa ; 2020.
2. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modelling and remodeling. Arch Biochem Biophys. 2008;473(2):139-46.
3. Rossini M, Gatti D, Adami S. Involvement of WNT/β-catenin signaling in the treatment of osteoporosis. Calcif Tissue Int. 2013;93(2):121-32.
4. Yu X, Sun S, Zhang S, et al. A pooled analysis of the association between sarcopenia and osteoporosis. Medicine. 2022;101(46: e31692.
5. Li G, Thabane L, Papaioannou A, et al. An overview of osteoporosis and frailty in the elderly. BMC Musculoskelet Disord. 2017;18(1):46.
6. Kanis JA, Harvey NC, McCloskey E, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int. 2020;31(1):1-12.
7. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis 2020 Update. Endocr Pract. 2020 May 1;26(5):564-70.
8. Shoback D, Rosen CJ, Black DM, et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J Clin Endocrinol Metab. 2020 Mar 1;105(3):587-94.
9. Khan AA, Alrob HA, Ali DS, et al. Guideline No. 422g: Menopause and Osteoporosis. JOGC. 2022 May 1;44(5):527-536.e5.
10. North American Menopause Society. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021;28(9):973-7.
11. Curtis J, Arora T, Liu T, et al. Comparative effectiveness of denosumab versus alendronate among postmenopausal women with osteoporosis in the U.S. Medicare program. In: ACR Convergence 2023. San Diego: American College of Rheumatology; 2023.
12. Kendler DL, Marin F, Zerbini CAF, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. The Lancet. 2018 Jan 20;391(10117):230-40.
13. Saag KG, Petersen J, Brandi ML, et al. Romosozumab or alendronate for fracture prevention in women with osteoporosis. N Engl J Med. 2017 Sep 11;377(15):1417-27.

About the Authors

Shadi Akhtari, MD, MSc

Dr. Akhtari is a staff cardiologist at Women's College Hospital, Assistant Professor in the Department of Medicine, and a Clinician in Quality and Innovation, University of Toronto. She specializes in advanced cardiac imaging. Apart from clinical practice of general cardiology and multi-modality cardiac imaging, her other areas of interest are prevention, diagnosis, and management of coronary artery disease, particularly in those with underlying inflammatory disease. She runs the cardio-rheumatology clinic at WCH, directed at improving quality of cardiac care offered to patients with rheumatic disease.

Affiliations: Division of Cardiology, Women's College Hospital, University of Toronto, Toronto, Ontario, Canada

Bindee Kuriya, MD, SM

Dr. Kuriya is an expert in rheumatoid arthritis, and her research primarily focuses on important co-morbidities such as cardiovascular disease. She is a member of the University of Toronto's Cardio-Rheum Program, which is aimed at primary CVD prevention for patients living with inflammatory arthritis.

Affiliations: Division of Rheumatology, Sinai Health System, University of Toronto, Toronto, Ontario, Canada

doi.org/10.58931/crt.2024.1251

Screening and Management of Atherosclerotic Cardiovascular Disease in Inflammatory Arthritis: A Comprehensive Approach for the Rheumatologist

Shadi Akhtari, MD, MSc
Bindee Kuriya, MD, SM

Inflammatory arthritis (IA) is associated with an increased risk of atherosclerotic cardiovascular disease (ASCVD) and contributes to significant morbidity and mortality. Early identification and treatment of conventional cardiovascular disease (CVD) risk factors are pivotal in mitigating ASCVD risk among the IA population. Equally crucial is the proactive management of inflammatory disease, necessitating a thorough discussion of the risks and benefits, particularly regarding the use of some advanced therapeutic agents indicated for IA, which may carry an increased risk of CVD in high-risk subgroups.

This article reviews the current evidence for optimal CVD screening in IA. We underscore the importance of a holistic approach that incorporates conventional risk assessment tools, biomarkers, imaging techniques, and interdisciplinary cooperation.

Section 1: The Scope of the Problem–Epidemiology, Mechanisms, and Gaps in Conventional Cardiovascular Disease Care

Rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) are the most common types of inflammatory arthritis (IA), affecting up to 5% of Canadians. The use of highly effective disease-modifying antirheumatic drugs (DMARDs), especially when administered early and aggressively, can effectively curb inflammation, safeguard against joint damage, and prevent disability. However, IA conditions are not confined to causing joint inflammation, and their systemic nature can extend to other organ systems, including the cardiovascular system. This involvement encompasses various cardiovascular diseases, including arrhythmias, valvular disease, pericarditis, myocarditis, and heart failure. Notably, epidemiological research reveals a 1.5- to 2-fold increased risk of incident atherosclerotic cardiovascular disease (ASCVD) events in those with IA when compared to the general population, and CVD-related death continues to be the primary cause of premature mortality in IA patients.[1]

This heightened risk of ASCVD in IA stems from the pathophysiological mechanisms intertwining inflammation and vascular dysfunction. The inflammatory hypothesis of ASCVD underscores the role of chronic inflammation as a pivotal player in atherogenesis, promoting endothelial dysfunction, plaque formation, and eventually plaque rupture, leading to total arterial occlusion. Inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), contribute to systemic inflammation and accelerate atherosclerosis progression.[2]

Patients with poorly controlled IA, or those who have experienced a long disease duration with several episodes of active disease, are at a high risk for adverse CVD outcomes. In addition, factors such as male sex, older age, elevated inflammatory marker levels, and erosive disease are predictors of accelerated CVD.[1] For RA

specifically, factors such as high titre rheumatoid factor or anti-citrullinated peptide antibody (ACPA) and the presence of extra-articular manifestations are also associated with a higher risk of ASCVD.[3] Studies exploring the contribution of IA characteristics suggest that up to 30% of the ASCVD risk may be attributed to disease specific variables and may be modified with aggressive treatment of the underlying IA.[4] However, this highlights the point that most of the ASCVD risk stems from non-IA factors. Traditional CVD risk factors, including hypertension, dyslipidemia, cigarette smoking, and diabetes have increased prevalence in patients with IA. Patients with PsA and AS are more frequently male and have a higher burden of metabolic syndrome than patients with RA.[4] These same metabolic risk factors are frequently underdiagnosed and undertreated in individuals with IA, further exacerbating their cardiovascular vulnerability. A number of barriers to optimal screening and control of metabolic risk factors have been identified.[5] Patients with IA often receive focused care primarily targeting their joint symptoms, leading to inadequate attention to their CVD risk factors. Additionally, symptoms of IA may overshadow other comorbidities, leading to an under-recognition and underestimation of their significance. Furthermore, rheumatology providers may lack comfort in determining the best screening modalities to use, and they may also lack the time and resources to serially screen IA patients for metabolic conditions. Rheumatologists may also not be equipped to medically manage these comorbidities or provide advice on lifestyle. Additionally, there is the issue of potentially encroaching on each other's roles, and it remains uncertain whether this task should fall under the purview of the primary care physician, other health care providers, or the rheumatologist.[6] Thus, the synergistic effect of systemic inflammation and suboptimal management of traditional risk factors increases the ASCVD risk, which emphasizes the importance of a comprehensive CVD risk assessment and management strategies in this high-risk population.

Section 2: Improving CVD Screening–Who? When? and How?

Several publications support enhanced CVD screening in patients with IA. First, they recognize that IA represents an above average at-risk population, with some suggesting that IA be considered a CVD risk-equivalent akin to diabetes.[7] Second, the majority of guidelines support that the rheumatologist (despite some of the barriers cited above) has a central role in the evaluation of CVD risk.

One of the earliest recommendations came from the European League Against Rheumatism (EULAR). In 2009, EULAR formulated 10 recommendations for CVD risk management in patients with chronic inflammatory rheumatic diseases.[8] This guideline recommends a risk assessment for CVD in all patients with systemic autoimmune rheumatic diseases, including IA, at least once every 5 years, and reconsideration after major changes to their DMARD therapy.[8] If the patient is found to be at low risk after the initial screening, then a 5-year routine risk assessment is reasonable, unless there is a significant change in clinical status. If the initial screening puts the patient in a low-intermediate or intermediate risk category, then an earlier reassessment of risk may be considered. For those patients who are found to be at a high CVD risk based on the initial evaluation, institution of specific treatments to lower the ASCVD risk such as statin therapy or antihypertensive therapy would be indicated, along with follow up as needed to ensure targets of therapy have been reached.[8]

However, accurate ASCVD risk stratification in patients with IA can be challenging. The commonly used ASCVD risk calculators such as the Framingham Risk Score (FRS) including a **Canadian calculator**, the Systematic Coronary Risk Evaluation (**SCORE**), and the American College of Cardiology/American Heart Association (ACC/AHA) **ASCVD Risk Calculator** provide a snapshot assessment incorporating various traditional risk factors including age, sex, smoking status, blood pressure, lipid profile, and diabetes.[9] The benefits of these tools include familiarity, as many healthcare providers (particularly primary care) have these tools integrated into their electronic medical records. In addition,

they involve simple calculations based on readily available patient data. These tools also provide a systematic method to stratify patients into different risk categories (low, moderate, and high), to aid in guiding treatment decisions for primary prevention interventions. However, when these tools are applied to IA, they may not accurately reflect the cumulative exposure to dynamic risk factors in patients with a chronic, remitting and relapsing condition, and most do not account for systemic inflammation or incorporate inflammatory markers. Furthermore, most of these tools have not been validated in populations with IA, which can lead to inaccurate risk estimations. Lastly, traditional risk assessment tools do not account for risk factors that behave paradoxically in the presence of inflammation. For example, lipid levels may appear falsely favourable in the inflammatory milieu but start rising with better control of the underlying inflammation, known as the so-called 'lipid paradox'. These lipid levels are best assessed when inflammation is well controlled.[10]

Efforts to include non-traditional risk factors, disease-specific parameters, multipliers, and biomarkers have not yet been as successful at improving risk estimates in this population.[9] In the absence of validated disease-specific risk estimators, most societies continue to recommend the use of national guidelines for CVD risk estimation. The 2017 EULAR update recommended using a multiplication factor of 1.5 for all patients with RA, which is based on a consensus opinion.[8] This is in contrast to the 2009 EULAR guidelines that had recommended a multiplication factor of 1.5 for patients with RA who met specific criteria, which included a longer disease duration >10 years, rheumatoid factor (RF)/ACPA positivity, and the presence of extra-articular manifestations. This recommendation was based on the concern that using the selective approach would underestimate the risk.[8,11]

Despite these recommendations, multiple studies have demonstrated that using the general risk predictors often results in an underestimate and at times an overestimate of cardiovascular risk in IA, and that applying the multiplication factor does not significantly improve risk prediction.[9,12,13] Newer approaches that incorporate non-invasive imaging of subclinical atherosclerosis such as coronary artery calcium (CAC) scoring show promise for a more accurate ASCVD risk stratification in individuals in whom the ASCVD risk level remains unclear.[14] The presence of coronary calcifications on cardiac CT scans is a strong predictor of ASCVD risk. Further, increases in CAC scores are directly proportional to increases in the risk of ASCVD. Generally, a CAC score >100 is an indication for intensive CV risk reduction. The use of other biomarkers, including the evaluation of Lipoprotein(a) [Lp(a)], an LDL-like atherogenic lipid molecule shown to be causally related to ASCVD, can be helpful in further stratifying patients into appropriate risk categories.[14]

There are currently no specific Canadian guidelines for CVD screening in IA. Nevertheless, a set of CVD quality indicators tailored for RA was developed by Barber *et al*. in collaboration with rheumatologists, cardiologists, and patient representatives.[15] These include communicating the above-average risk for CVD in IA to primary care providers, conducting regular CVD risk assessments in the same patient over time, addressing modifiable risk factors such as smoking, obesity, hypertension, diabetes, and dyslipidemia, and promoting healthy lifestyle recommendations (**Table 1**).[15] Notably, the guidelines also underscore the importance of minimizing corticosteroid and non-steroidal anti-inflammatory drug (NSAID) use, a consideration not typically addressed in conventional CVD primary prevention guidelines. A follow-up study that evaluated the ease of applying these quality indicators in clinical practice found several gaps in CVD care. The quality indicators that focused on screening for risk factors or formal CVD risk estimation showed a poor performance, but documentation for the intent to taper steroids/NSAIDs was universally high among rheumatologists.[16] As expected, rheumatologists may feel more at ease managing IA, but may be less inclined to address or take action on conventional CVD risk factors. These findings highlight the necessity for quality improvement initiatives to close this gap, including enhanced coordination of care among rheumatology, primary care, and cardiology. Each specialty possesses unique expertise, and collaborative efforts are essential to ensure comprehensive and effective management.

Section 3: Management of Traditional CVD Risk Factors–What Rheumatologists Can Learn About Treatment Targets

The importance of a heart healthy lifestyle including total smoking cessation, adherence to a heart-healthy diet, weight management, and regular physical activity should be emphasized to

Recommendations	Comments
Traditional Risk Factor Screening and Management	
Perform CVD risk assessment	• Communicate regularly that IA is a risk factor for CVD with both the PCP and patient • The formal CVD risk assessment tool should be used at least once within the first 2 years of diagnosis • If low risk, repeat the risk assessment every 5 years • If intermediate risk or higher, treat the modifiable risk factors • Repeat the assessment any time there is a sustained change in disease activity
Measure the lipid panel	• Recommended once within 2 years of diagnosis and then annually • Interpretation of lipid levels should be performed with caution when the disease is active, it is recommended to check lipid levels once the disease activity is low or ~12 weeks after DMARD initiation/changes • If lipid levels are abnormal, relay the results to the PCP for management or refer to the appropriate health care professional
Screen for diabetes	• Check HbA1C and fasting glucose levels once within 2 years of diagnosis and annually
Measure blood pressure	• Record annually • Communicate abnormal blood pressure results (systolic blood pressure ≥140 and or diastolic blood pressure ≥90) to primary care or refer to the appropriate health care professional • If repeated blood pressure assessments are high, treatment should be initiated, or current anti-hypertensive medications should be adjusted
Perform CVD risk score	• Perform annually or any time there is a change in the disease status
Smoking	• Document smoking status annually • Smoking cessation should be encouraged at every visit • Explore smoking cessation options by liaising with primary care
Weight	• Record body mass index and waist circumference annually • If overweight or obese, counsel on lifestyle interventions and communicate this with the PCP or appropriate health care professional
Exercise	• Benefits of physical activity and recommended Canadian guidelines for exercise should be discussed annually

Recommendations	Comments
Management of IA Risk Factors	
Disease activity should be as low as possible	• Treatment should target low disease activity or remission in IA
Limit exposure to corticosteroids	• Discourage chronic use of corticosteroids and discuss the possible CVD risks with the patient • If needed for flares, use the lowest effective dose and for the shortest duration possible • Discuss the intent to taper corticosteroids if used long term
Limit exposure to NSAIDs	• Use NSAIDs at lowest effective dose and for the shortest duration possible • Discourage chronic use and discuss the possible CVD risks with the patient
Therapeutic DMARD Considerations	
The goal of DMARD therapy is to suppress systemic inflammation	• Use of csDMARDs (most evidence is in support of methotrexate) and bDMARD have overall net cardioprotective benefits
DMARD therapy may alter traditional CVD risk factors	• Be aware of the "lipid paradox" and optimal timing to check lipids and anticipated changes in the lipid profile pre- and post-treatment • No clear evidence that DMARD therapy independently increases the risk of diabetes or hypertension
A suitable therapeutic alternative to tsDMARD should be considered in patients with history or risk factors for ASCVD	• Consider for males, and for those aged >65 years
If no suitable treatment alternatives are available for a patient with high ASCVD risk, a JAKi can be considered	• Refer to cardiology for assessment ideally before starting JAKi to optimize reversible ASCVD risk factors and for ongoing monitoring as indicated

Table 1. Approach to ASCVD risk assessment and management in patients with IA; *adapted from Barber et al* [15]*. and Avouac* [21] *et al.*

Abbreviations: ASCVD: atherosclerotic cardiovascular disease, **bDMARD:** biologic disease modifying antirheumatic drug, **csDMARD:** conventional synthetic disease modifying antirheumatic drug, **HbA1C:** hemoglobin A1C, JAKi: Janus kinase inhibitor, **PCP:** primary care physician, **NSAIDs:** nonsteroidal anti-inflammatory drugs, **tsDMARD:** targeted synthetic disease modifying antirheumatic drugs

all patients. Providing a recommendation for total smoking cessation at every visit, and a referral to smoking cessation programs for individuals who feel ready to quit smoking should be considered at each clinical encounter. Adherence to a diet rich in vegetables, fruits, legumes, nuts, whole grains, and fish along with reduced amounts of dietary cholesterol, particularly saturated and trans fats, refined carbohydrates, and sodium is recommended to reduce ASCVD risk. The **Mediterranean diet** can improve both CV risks (cholesterol, blood pressure) and can also slightly improve inflammatory arthritis so it can be suggested to patients with IA and CVD risk factors.

Patients should engage in at least 150 minutes per week of moderate-intensity exercise, or 75 minutes per week of vigorous-intensity aerobic physical activity to reduce ASCVD risk.[17] Achieving these physical activity targets can be particularly challenging for individuals with IA due to joint limitations; thus, activities such as swimming or other water-based sports, which are generally easier on the joints, should be considered.

The current EULAR recommendation for the management of individual CVD risk factors in IA, including hypertension and dyslipidemia, is to follow the recommendations set for the general population. For patients with dyslipidemia who are at a high ASCVD risk, the typical recommendation is to reduce LDL-cholesterol to <2.0 mmol/L in the primary prevention setting and to <1.8 mmol/L in the secondary prevention setting, with the use of optimal dosing of statins as first-line therapy (especially rosuvastatin or atorvastatin), and additional lipid lowering therapies as needed, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors.[18] The specific targets of therapy for hypertension vary somewhat between different sets of guidelines set for the general population, however, in general, a target blood pressure of 130/80 mmHg is recommended for individuals at a high ASCVD risk. This target is usually achieved with the use of angiotensin converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, or diuretics as typical first-line agents. Individuals who have diabetes as an additional risk factor should undergo careful evaluation with their primary care physician or endocrinologist to achieve the best possible glycemic control to prevent microvascular and macrovascular complications.

Section 4: The Role of DMARDs/Biologics in ASCVD Risk Reduction

DMARDs and biologics offer potential benefits beyond the joints and have been shown to lower ASCVD risk. However, achieving aggressive control of inflammation is imperative to unlock these cardioprotective effects. There is substantial evidence supporting the cardioprotective properties of methotrexate and TNF inhibitors (TNFi), which have been associated with a reduced risk of myocardial infarction, stroke, and heart failure (HF) development among patients with IA.[19] Methotrexate and cytokine inhibitors have made headlines for their ability to lower the CVD risk, possibly even in non-rheumatic populations (for biologics such as IL-1i), by targeting the pivotal role that inflammation plays in CVD development.[20]

In contrast, the use of NSAIDs can have undesirable CVD effects, including hypertension, myocardial infarction, stroke, and HF. Glucocorticoid use is similarly associated with a variety of adverse CVD effects including hypertension, fluid retention, premature atherosclerosis, myocardial infarction, arrhythmias, and HF. NSAIDs and glucocorticoids should be prescribed with extreme caution, especially for those with known CVD or multiple CVD risk factors. All guidelines, irrespective of patient age, recommend limiting the dose and duration to prevent CVD events and the multiple other adverse effects associated with these medications.[8,15,21]

Furthermore, while certain biologics such as tocilizumab may lead to anticipated increases in lipid levels due to their mechanism of action, the interplay between lipids and inflammation in this scenario is intricate. During active disease states, lipid levels paradoxically tend to be low. Although lipid levels may rise as disease control improves, not all of this increase is driven by highly atherogenic particles. Indeed, biologics may have a favourable impact on “good cholesterol” by enhancing the structure and function of high-density lipoprotein (HDL), while concurrently reducing the levels of other “bad” CVD biomarkers such as serum amyloid A and Lp(a).[22] Consequently, the timing of lipid assessment becomes critical, and is typically performed at baseline and then approximately 12 weeks after treatment initiation, or upon reaching a state of low disease activity. Should lipid levels remain elevated or concerning despite adequate disease

control, adherence to national guidelines for dyslipidemia management is recommended over withholding potentially effective biologic therapy.[18] Moreover, newer lipoprotein markers (Lp(a), Apolipoprotein B), are less susceptible to inflammation-induced fluctuations, and offer a more dependable means of CVD risk assessment in patients undergoing biologic treatment. However, interpretation and treatment based on these parameters likely warrants collaboration with a cardiologist or another experienced health care provider. Additionally, a head-to-head CVD outcomes trial in active RA patients failing MTX demonstrated that CV events were not different between etanercept (a TNFi) and tocilizumab.[23]

The ORAL Surveillance study sparked significant controversy regarding the safety of Janus kinase inhibitors (JAKi). The study observed an increased number of major adverse CVD events (MACE) and malignancies in JAKi-treated patients compared to TNFi-treated patients over the age of 50 years with at least one CVD risk factor.[24] This finding substantially changed many rheumatology practices and prescribing patterns due to the implementation of warnings on all JAKi, and concerns of a potential "class effect", despite the study being conducted only on tofacitinib.

A number of post-hoc analyses of the ORAL Surveillance study indicate an elevated MACE risk in RA patients with prior CVD events or multiple risk factors, which include males, older age (>65 years), and current smokers.[25,26] In contrast, trials of baricitinib and upadacitinib have not shown a distinctly increased risk of MACE at the doses approved for RA treatment, compared to TNFi or placebo.[26] Real-world data suggests that this overall risk remains generally low, however, there are trends toward higher CVD event rates in patients who are similar to those included in the ORAL Surveillance study.

Overall, the risks from JAKi treatment are clearly influenced by the baseline CVD risk, and documentation of this risk can aid clinical decision making and counselling. This risk is also influenced by multiple factors, which include the following: the specific indication for using the JAK (disease severity, extra-articular manifestations), other known comorbidities, previous response to therapy, the availability of alternative treatments, the type and dose of the JAKi chosen, and other risk-benefit considerations, including the ability to minimize the use of NSAIDs and corticosteroids.[25] When faced with limited treatment options, prioritizing effective inflammation control should be paramount, even in the face of potential risks associated with JAKi therapy. To address this challenge, we recommend implementing regular and focused screening when considering any IA treatment changes. Additionally, for high-risk patients, a proactive referral to a cardiologist for a comprehensive evaluation and management can ensure optimal CVD care alongside IA treatment strategies. Thus, personalized assessment and monitoring are crucial to optimize treatment outcomes while minimizing potential adverse effects with JAKi or any advanced therapeutic (**Table 1**).

Section 5: Interdisciplinary Collaboration: The Emergence of Cardio-Rheumatology

The emerging discipline of 'Cardio-Rheumatology' represents a collaborative multidisciplinary approach to addressing the complexities involved in the cardiovascular care of patients with underlying systemic inflammatory disease. Despite the high degree of awareness about this elevated risk among rheumatologists, a high percentage of patients with IA remain underdiagnosed and undertreated with regards to CVD risk factors, and a lack of care coordination has been identified by rheumatologists and primary care providers as a large barrier to optimized CVD risk management.[27] As such, a dedicated cardiac assessment of these patients with the use of advanced biomarkers and imaging modalities, including CAC scoring, can help with the early identification and treatment of CVD and associated risk factors. Knowledge about the effect of medications, including anti-inflammatory therapies, corticosteroids, and DMARDs, on the cardiovascular system is crucial. Cardiologists in these clinics review this aspect very carefully to ensure optimal patient care. For example, considering the CVD safety signals brought forward by the ORAL Surveillance trial, a more careful ASCVD risk stratification might be required for a subset of patients being considered for targeted synthetic disease-modifying antirheumatic drug (tsDMARD) therapy. This can inform risk/benefit discussions and potentially lead to more aggressive risk management approaches in those who require the use of such medications. A number of other benefits of coordinated care have been identified, including the importance of patient education and advancing research opportunities to include

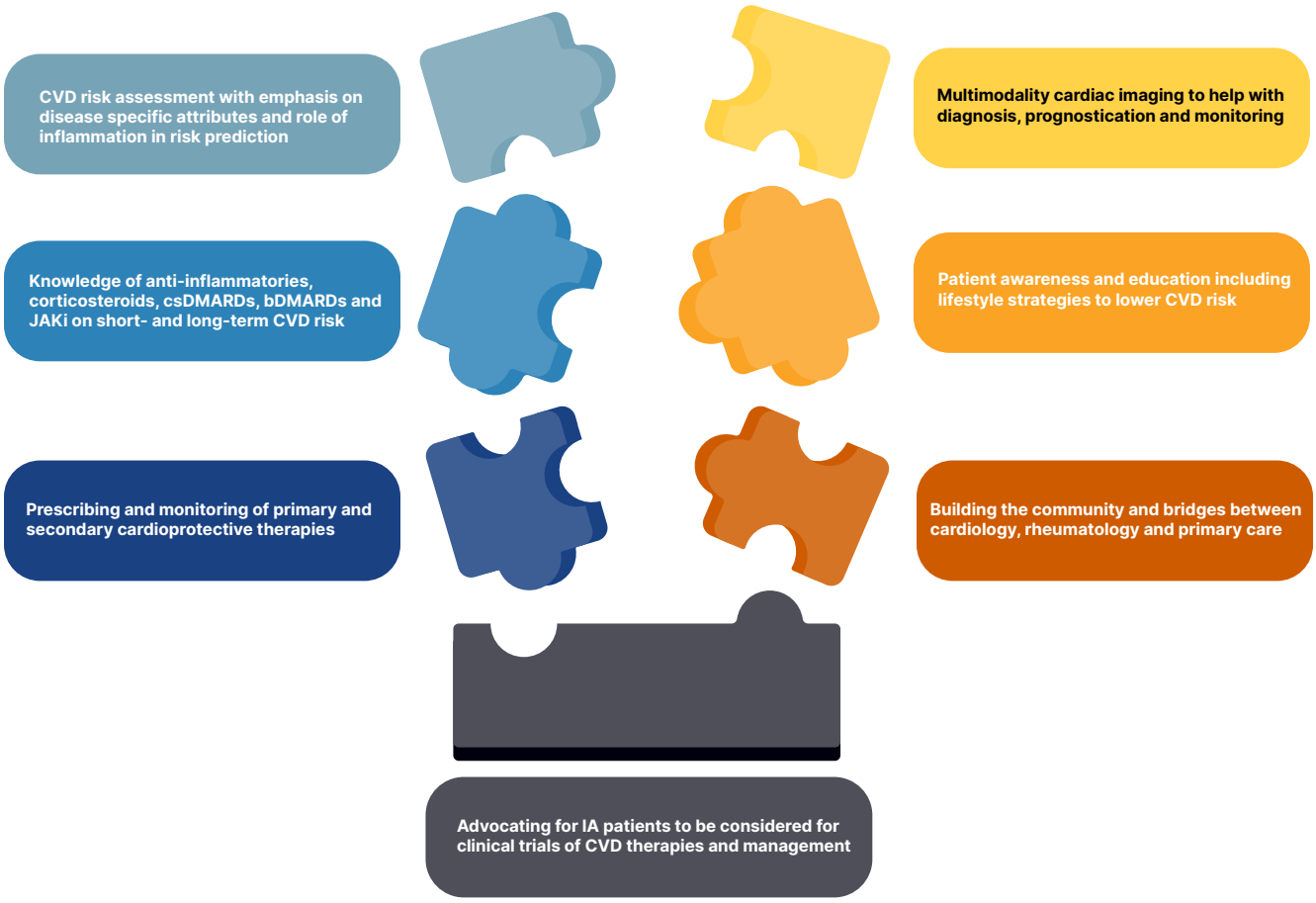


Figure 1. How cardio-rheumatology models of care can improve overall CVD risk stratification and management in IA; *adapted from Weber et al.*[29]

this underrepresented population in clinical trials (**Figure 1**).

To date, a number of cardio-rheumatology clinics have emerged in Europe and North America. To our knowledge, the University of Toronto hosts the first and largest such program in Canada. Established in 2017, the program aims to improve primary CVD prevention for patients with IA. Close to 700 patients have undergone screening at this program which involves nurses, rheumatologists, cardiologists, and radiologists. Using newer lipoprotein parameters and coronary CT scans, we have significantly enhanced the risk assessment in most patients. Notably, nearly half of asymptomatic IA patients have been identified as eligible for statin/lipid-lowering therapies according to Canadian dyslipidemia guidelines.[28] Moreover, this initiative boasts strong patient acceptance and relies on readily accessible tests and procedures that cardiologists can request and act upon. We view this as a scalable model that can be replicated in other centres and community hospitals and may help close the previously identified care gaps.

Conclusion

Patients with IA are at an increased risk of cardiovascular morbidity and mortality. Effective control of inflammation, careful cardiovascular screening, and aggressive management of cardiovascular risk factors are key in reducing this risk. A practical approach to helping assess and treat CVD risk factors in patients with IA is to document the risks and facilitate investigation and management by routinely adding the increased CV risk in your notes to the primary care physician and to treat the targets at least using a risk calculator and even considering the risks similar to type II diabetics and using established targets for HTN, hyperlipidemia and type 2 diabetes mellitus.

Cardio-Rheumatology, a multidisciplinary collaboration between rheumatologists and cardiologists, is crucial for the design and delivery of an integrated care plan that considers the intricacies involved in providing care to this complex patient population. Such collaborations can also help combine research efforts between the two disciplines and help fill current knowledge gaps and improve the quality of cardiovascular care offered to all patients living with rheumatic diseases.

Correspondence

Bindee Kuriya, MD, SM, FRCPC
Email: Bindee.Kuriya@sinaihealth.ca

Financial Disclosures

B.K.: Advisory Board: AbbVie, Pfizer
S.A.: None declared.

References

1. Heslinga M, Nielen MMJ, Smulders Y, Simsek S, Nurmohamed MT. Amplified prevalence and incidence of cardiovascular disease in patients with inflammatory arthritis and coexistent autoimmune disorders. Rheumatology (Oxford). 2020. doi:10.1093/rheumatology/kez650
2. Mason JC, Libby P. Cardiovascular disease in patients with chronic inflammation: mechanisms underlying premature cardiovascular events in rheumatologic conditions. Eur Heart J. 2015;36(8):482-489c. doi:10.1093/eurheartj/ehu403
3. Hajiesmaeili Y, Tamhankar P, Stranges S, Barra L. Factors associated with incident cardiovascular disease in patients with rheumatoid arthritis: a scoping review. Autoimmun Rev. 2024;23(5):103539. doi:10.1016/j.autrev.2024.103539
4. Crowson CS, Rollefstad S, Ikdahl E, Kitas GD, van Riel PLCM, Gabriel SE, et al. Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. Ann Rheum Dis. 2018;77(1):48-54. doi:10.1136/annrheumdis-2017-211735
5. Bartels CM, Roberts TJ, Hansen KE, Jacobs EA, Gilmore A, Maxcy C, et al. Rheumatologist and primary care management of cardiovascular disease risk in rheumatoid arthritis: patient and provider perspectives. Arthritis Care Res (Hoboken). 2015. doi:10.1002/acr.22689
6. Chodara AM, Wattiaux A, Bartels CM. Managing cardiovascular disease risk in rheumatoid arthritis: clinical updates and three strategic approaches. Curr Rheumatol Rep. 2017;19(4):16. doi:10.1007/s11926-017-0643-y
7. Agca R, Hopman LHGA, Laan KJC, van Halm VP, Peters MJL, Smulders YM, et al. Cardiovascular event risk in rheumatoid arthritis compared with type 2 diabetes: a 15-year longitudinal study. J Rheumatol. 2020;47(3):316-324. doi:10.3899/jrheum.180726
8. Agca R, Heslinga SC, Rollefstad S, Heslinga M, McInnes IB, Peters MJ, et al. EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. Ann Rheum Dis. 2017;76(1):17-28. doi:10.1136/annrheumdis-2016-209775
9. Colaco K, Ocampo V, Ayala AP, Harvey P, Gladman DD, Piguet V, et al. Predictive utility of cardiovascular risk prediction algorithms in inflammatory rheumatic diseases: a systematic review. J Rheumatol. 2020;47(6):928-938. doi:10.3899/jrheum.190261
10. Gonzalez-Gay MA, Gonzalez-Juanatey C. Inflammation and lipid profile in rheumatoid arthritis: bridging an apparent paradox. Ann Rheum Dis. 2014;73(7):1281-1283. doi:10.1136/annrheumdis-2013-204933
11. Peters MJ, Symmons DP, McCarey D, Dijkmans BA, Nicola P, Kvien TK, et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis. 2010;69(2):325-331. doi:10.1136/ard.2009.113696

12. Navarini L, Margiotta DPE, Caso F, Currado D, Tasso M, Angeletti S, et al. Performances of five risk algorithms in predicting cardiovascular events in patients with psoriatic arthritis: an Italian bicentric study. PLoS One. 2018;13(10):e0205506. doi:10.1371/journal.pone.0205506
13. Arts EE, Popa CD, Den Broeder AA, Donders R, Sandoo A, Toms T, et al. Prediction of cardiovascular risk in rheumatoid arthritis: performance of original and adapted SCORE algorithms. Ann Rheum Dis. 2016;75(4):674-680. doi:10.1136/annrheumdis-2014-206879
14. Misra DP, Hauge EM, Crowson CS, Kitas GD, Ormseth SR, Karpouzas GA. Atherosclerotic cardiovascular risk stratification in the rheumatic diseases: an integrative, multiparametric approach. Rheum Dis Clin North Am. 2023;49(1):19-43. doi:10.1016/j.rdc.2022.07.004
15. Barber CE, Marshall DA, Alvarez N, Mancini GB, Lacaille D, Keeling S, et al. Development of cardiovascular quality indicators for rheumatoid arthritis: results from an international expert panel using a novel online process. J Rheumatol. 2015;42(9):1548-1555. doi:10.3899/jrheum.141603
16. Barber CE, Esdaile JM, Martin LO, Faris P, Barnabe C, Guo S, et al. Gaps in Addressing cardiovascular risk in rheumatoid arthritis: assessing performance using cardiovascular quality indicators. J Rheumatol. 2016;43(11):1965-1973. doi:10.3899/jrheum.160241
17. Canada HaSFo. Canadian Physical Activity Guidelines Canadian Sedentary Behaviour Guidelines [Available from: https://www.heartandstroke.ca/healthy-living/stay-active.
18. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, et al. 2021 Canadian Cardiovascular Society Guidelines for the management of dyslipidemia for the prevention of cardiovascular disease in the adult. Can J Cardiol. 2021. doi:10.1016/j.cjca.2021.03.016
19. Roubille C, Richer V, Starnino T, McCourt C, McFarlane A, Fleming P, et al. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis. 2015;74(3):480-489. doi:10.1136/annrheumdis-2014-206624
20. Ridker PM. Closing the loop on inflammation and atherothrombosis: why perform the CIRT and CANTOS trials? Trans Am Clin Climatol Assoc. 2013;124:174-190.
21. Avouac J, Fogel O, Hecquet S, Daien C, Elalamy I, Picard F, et al. Recommendations for assessing the risk of cardiovascular disease and venous thromboembolism before the initiation of targeted therapies for chronic inflammatory rheumatic diseases. Joint Bone Spine. 2023;90(5):105592. doi:10.1016/j.jbspin.2023.105592
22. Liao KP, Playford MP, Frits M, Coblyn JS, Iannaccone C, Weinblatt ME, et al. The association between reduction in inflammation and changes in lipoprotein levels and HDL cholesterol efflux capacity in rheumatoid arthritis. J Am Heart Assoc. 2015;4(2). doi:10.1161/JAHA.114.001588
23. Giles JT, Sattar N, Gabriel S, Ridker PM, Gay S, Warne C, Musselman D, Brockwell L, Shittu E, Klearman M, Fleming TR. Cardiovascular Safety of Tocilizumab Versus Etanercept in Rheumatoid Arthritis: A Randomized Controlled Trial. Arthritis Rheumatol. 2020 Jan;72(1):31-40. doi: 10.1002/art.41095. PMID: 31469238.
24. Ytterberg SR, Bhatt DL, Connell CA. Cardiovascular and Cancer Risk with Tofacitinib in Rheumatoid Arthritis. Reply. N Engl J Med. 2022;386(18):1768. doi:10.1056/NEJMc2202778
25. Yang V, Kragstrup TW, McMaster C, Reid P, Singh N, Haysen SR, et al. Managing Cardiovascular and cancer risk associated with JAK inhibitors. Drug Saf. 2023;46(11):1049-1071. doi:10.1007/s40264-023-01333-0
26. Misra DP, Pande G, Agarwal V. Cardiovascular risks associated with Janus kinase inhibitors: peering outside the black box. Clin Rheumatol. 2023;42(2):621-632. doi:10.1007/s10067-022-06415-5
27. Navarro-Millan I, Cornelius-Schecter A, O'Beirne RJ, Morris MS, Lui GE, Goodman SM, et al. Views of primary care physicians and rheumatologists regarding screening and treatment of hyperlipidemia among patients with rheumatoid arthritis. BMC Rheumatol. 2020;4:14. doi:10.1186/s41927-020-0112-5
28. Kuriya B, Akhtari S, Movahedi M, Udell JA, Lawler PR, Farkouh ME, et al. Statin use for primary cardiovascular disease prevention is low in inflammatory arthritis. Can J Cardiol. 2022;38(8):1244-1252. doi:10.1016/j.cjca.2022.04.002
29. Weber B, Garshick M, Liao KP, Di Carli M. Sore, Hot, and at Risk: The Emerging Specialty of Cardio-Rheumatology. J Am Heart Assoc. 2023;12(11):e027846. doi:10.1161/JAHA.122.027846

doi.org/10.58931/crt.2024.1252

About the Author

Sherry Rohekar, BSc, MD, FRCPC, MSc (Clin. Epi)

Dr. Sherry Rohekar completed medical school at the University of Western Ontario, and then went on to train in general internal medicine at Queen's University and rheumatology at the University of Toronto. She also has a Master's of Clinical Epidemiology from UWO. She is now an Associate Professor in the Department of Medicine, Division of Rheumatology at UWO. Her research and clinical interest is spondyloarthritis, including ankylosing spondylitis and psoriatic arthritis. She is currently on the executive committee the SPondyloArthritis Research Consortium of Canada, and member of the International Psoriasis and Arthritis Research Team, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis and the SPondyloArthritis Research & Treatment Network.

Affiliations: Associate Professor, Western University, London, Ontario

Axial Spondyloarthritis Treatment Recommendations in 2024: Where Are We Now?

Sherry Rohekar, BSc, MD, FRCPC, MSc (Clin. Epi)

Introduction

As 2024 continues to evolve, so do treatment recommendations for the management of spondyloarthritis (SpA), including ankylosing spondylitis (AS) and non-radiographic axial spondyloarthritis (nr-axSpA). From a Canadian perspective, we eagerly await the publication of the Canadian Rheumatology Association (CRA)/Spondyloarthritis Research Consortium of Canada (SPARCC) Living Treatment Recommendations for the Management of Axial Spondyloarthritis (axSpA), currently in press. Until these recommendations for axSpA treatment with a Canadian perspective arrive – where are we now?

Current AxSpA Treatment Recommendations

There are two major treatment recommendations (or guidelines) for axSpA currently in use. The first is the 2019 Update of the American College of Rheumatology (ACR)/Spondylitis Association of America (SAA)/ Spondyloarthritis Research and Treatment Network (SPARTAN) Recommendations for the Treatment of AS and nr-axSpA.[1] The second is the 2022 update from the Assessment of Spondyloarthritis International Society (ASAS)-European Alliance of Associations for Rheumatology (EULAR) Recommendations for the Management of Axial Spondyloarthritis.[2]

In comparing the ACR and EULAR guidelines, there are some notable similarities and differences.

- ***Disease definition:*** The ACR guidelines divide SpA into distinct categories of AS and nr-axSpA, whereas the EULAR guidelines treats AS and nr-axSpA as part of the same disease spectrum, axSpA.[1,2]
- ***Non-pharmacologic interventions:*** both guidelines recommend regular exercise, patient education, and physiotherapy for maintenance of patient function and quality of life.[1,2]

- ***First-line pharmacologic therapy:*** both guidelines recommend the use of non-steroidal anti-inflammatory drugs (NSAIDs) as first-line therapy for the management of pain and inflammation in axSpA.[1,2]

- ***Biologic therapies:*** tumour necrosis factor inhibitors (TNFi) and interleukin (IL)-17 inhibitors (IL-17i) are recommended for NSAID non-responders.[1,2] In both guidelines, the use of these biologics is based on disease severity and patient-specific factors.[1,2] However, in the ACR guidelines, there is a conditional recommendation for the use of TNFi over IL-17i in adults with active AS.[1] The EULAR guidelines recommend considering the following for patients with continued high disease activity despite conventional treatment, TNFi, IL-17i, or JAK inhibitors (JAKi), with the current practice being to start either a TNFi or an IL-17i.[2] The rationale for this recommendation was the lack of safety data for JAKi at the time.[2]

- ***Biosimilars:*** the ACR guidelines strongly recommend against a mandated switch to a biosimilar TNFi in patients with stable AS.[1] In contrast, the EULAR recommendations do not directly address this issue, but state that "when a choice needs to be made between two drugs with comparable efficacy and safety, then the one with the lowest cost is preferable", noting that the rheumatologist should keep in mind the high cost of biologics to society.[2]

- ***Biologic tapering:*** The ACR conditionally recommends against tapering biologics in those with stable AS or nr-axSpA.[1] On the other hand, EULAR suggests that if a patient is in sustained remission, tapering of a biological disease-modifying anti-rheumatic drug (bDMARD) may be considered.[2]

- ***Disease Monitoring:*** The ACR guidelines conditionally recommend the regular interval use of a validated AS disease measure, but also conditionally recommend against a treat-to-target strategy of using a specific Ankylosing Spondylitis Disease Activity Score (ASDAS) over the physician's assessment.[1] Conversely, the EULAR guidelines emphasize the use of the ASDAS as the most appropriate tool for measuring disease activity, although the guidelines also acknowledged issues with the current knowledge around adopting a treat-to-target strategy.[2] Change in the ASDAS score was used as a measure of response to therapy in the EULAR guidelines' treatment algorithm.[2]

- ***Extramusculoskeletal manifestations (EMMs):*** Both guidelines recommend preferential use of a monoclonal TNFi for those with inflammatory bowel disease or recurrent uveitis, and the EULAR recommendations take a step further to suggest an IL-17i may be preferred in those with significant psoriasis.[1,2]

- ***Re-evaluating the diagnosis:*** The EULAR guidelines note that the "absence of response to treatment should prompt re-evaluation of the diagnosis and consideration of the presence of comorbidities".[2] They highlight the dangers of cycling through immunosuppressants, and the risk of overtreatment, particularly if the patient has comorbidities such as fibromyalgia, depression, or osteoarthritis that may be confounding their clinical picture.[2] They note that the increased awareness of axSpA and the rheumatologists' eagerness to decrease diagnostic delay may be leading to over treatment.[2]

- ***Use of imaging:*** The ACR guidelines conditionally recommend obtaining a spinal or pelvis MRI to assess disease activity in adults with AS or nr-axSpA who have an unclear disease activity status.[1] In the EULAR guidelines, when to re-image is included as part of their research agenda.[2]

- ***Methodology:*** The ACR guidelines use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology.[3] This is a stringent process in which systematic literature reviews (SLRs) are conducted to answer questions using a framework that includes a predetermined clinical population, intervention, comparator, and outcomes, termed PICO. In comparison, the EULAR guidelines derive their levels of evidence and recommendation grades from SLRs, following the standards set by the Oxford Centre for Evidence Based Medicine.[4] Most treatment recommendations tend to use the more stringent GRADE approach.

Implementing Treatment Recommendations in AxSpA

Treatment recommendations are invaluable tools for clinical practice in that they help clinicians make evidence-based decisions when choosing care for their patients. However, whether these recommendations are used in daily practice remains unclear. A recent survey of axSpA treatment recommendations and disease activity monitoring in clinical practice found that though there was general awareness of the importance of disease monitoring as per guidelines, it was rarely implemented.[5] The same study showed that UpToDate ranked higher than the ACR or EULAR guidelines as a source for knowledge regarding the management of patients with axSpA.[5] What are the barriers that may be preventing the implementation of treatment recommendations in daily clinical practice?

- ***Rigidity:*** Clinicians see patients that are unique individuals who do not neatly fit into flowcharts and tables. This leads to the sense that guidelines are too restricting, and therefore not applicable to real-world practice.

- ***Overemphasis on guidelines:*** This is why I prefer to call them "treatment recommendations" – guidelines may seem like a prescriptive set of rules from the "experts" rather than from those who are faced with making day-to-day decisions. Clinicians must be allowed to tailor patient care to their own judgment.

- ***Accessibility and implementation:*** Guidelines often include recommendations that would happen in the ideal world but may be difficult to access in real life. For example, having axSpA patients with undetermined disease activity undergo reimaging with MRI is a recommendation that might be very difficult to achieve in a timely manner in some parts of Canada.

- ***Quality of evidence:*** While some of the recommendations are based on robust clinical trials, others are of low quality and largely grounded on expert opinion or consensus.

- ***Keeping pace with new evidence:*** Traditional guidelines, such as the ACR and EULAR guidelines discussed above, are almost immediately out of date upon publication. Research in axSpA is fast-paced and new modalities of treatment are emerging quickly. This leads to a lag between the guidelines and the reality of treating patients.

Living Guidelines in AxSpA

To address the issue of keeping pace with new evidence, treatment recommendations are increasingly moving to a "living guideline" model. The impending CRA/SPARCC Treatment Recommendations for AxSpA will be living guidelines. The ACR is also in the process of updating their guidelines to a living guidelines model.

What are living guidelines? In comparison to traditional guidelines, where several years pass between updates, living guidelines allow for individual recommendations to be either updated or added on an as needed basis.[6] This creates a set of guidelines that is perpetually relevant and current. In order to establish the living guidelines, a living systematic review is also simultaneously generated.[7] Supplemental journal articles or announcements may be published periodically with major modifications to the treatment recommendations to aid in knowledge dissemination. The living guideline model has already been successfully implemented for other CRA guidelines, such as rheumatoid arthritis, available **here**.[8] The living guidelines will be housed online for ease of access, and clinicians will be able to easily select their clinical question without having to read through an entire paper.

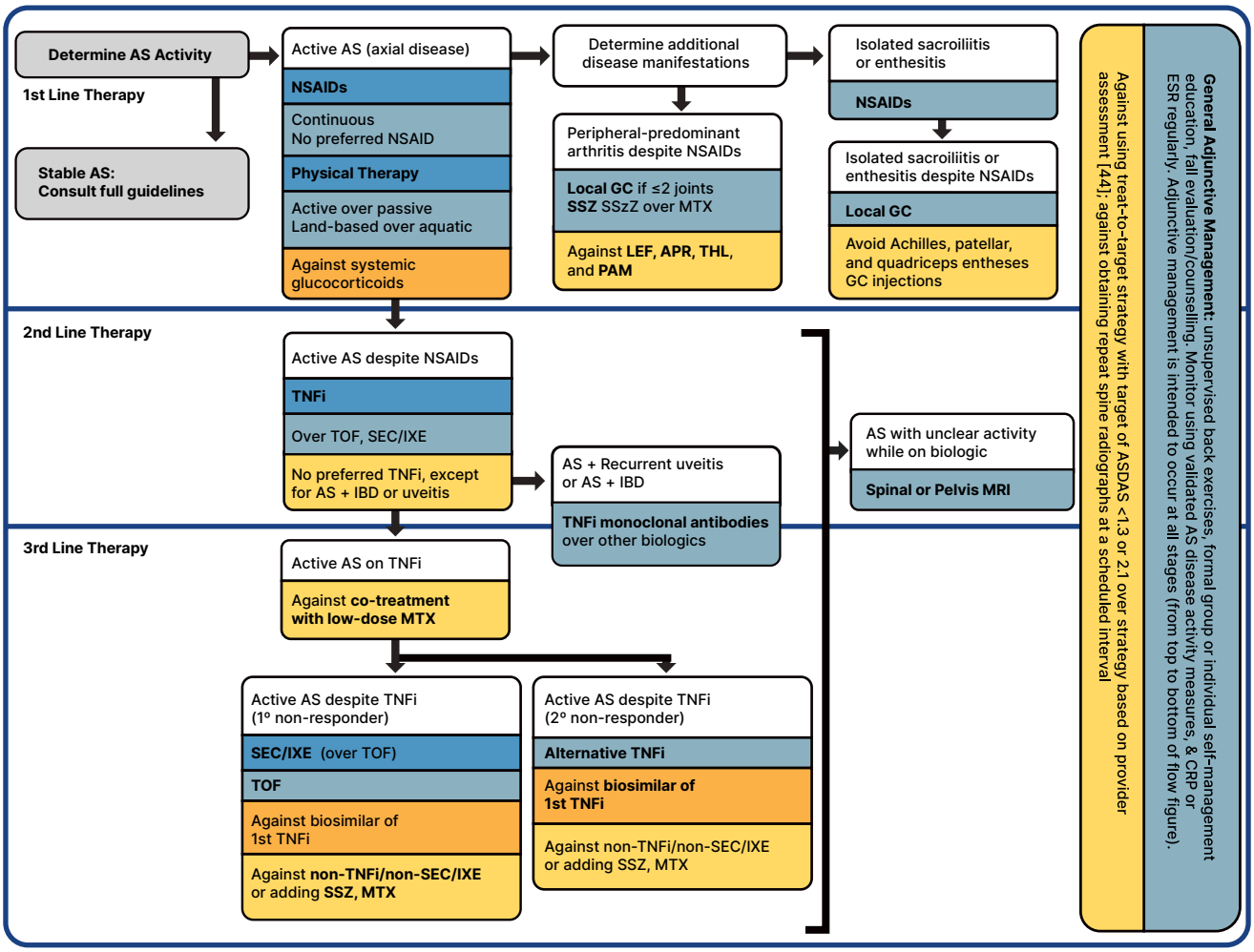


Figure 1. 2019 Update of the ACR/SAA/SPARTAN Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis**.** Summary of the main recommendations for treating patients with active ankylosing spondylitis; *adapted from Ward, MM et al., 2019*.

Abbreviations: AS: ankylosing spondylitis, **NSAIDs:** nonsteroidal antiinflammatory drugs, **GC:** glucocorticoid, **SSZ:** sulfasalazine, **MTX:** methotrexate, **LEF:** leflunomide, **APR:** apremilast, **THL:** thalidomide, **PAM:** pamidronate, **TNFi:** tumor necrosis factor inhibitor, **TOF:** tofacitinib, **SEC:** secukinumab, **IXE:** ixekizumab, **IBD:** inflammatory bowel disease, **csARD:** conventional synthetic antirheumatic drugs, **ESR**: erythrocyte sedimentation rate, **CRP:** C-reactive protein level, **ASDAS:** Ankylosing Spondylitis Disease Activity Score, **MRI:** magnetic resonance imaging, **PICO:** population, intervention, comparison, and outcomes.

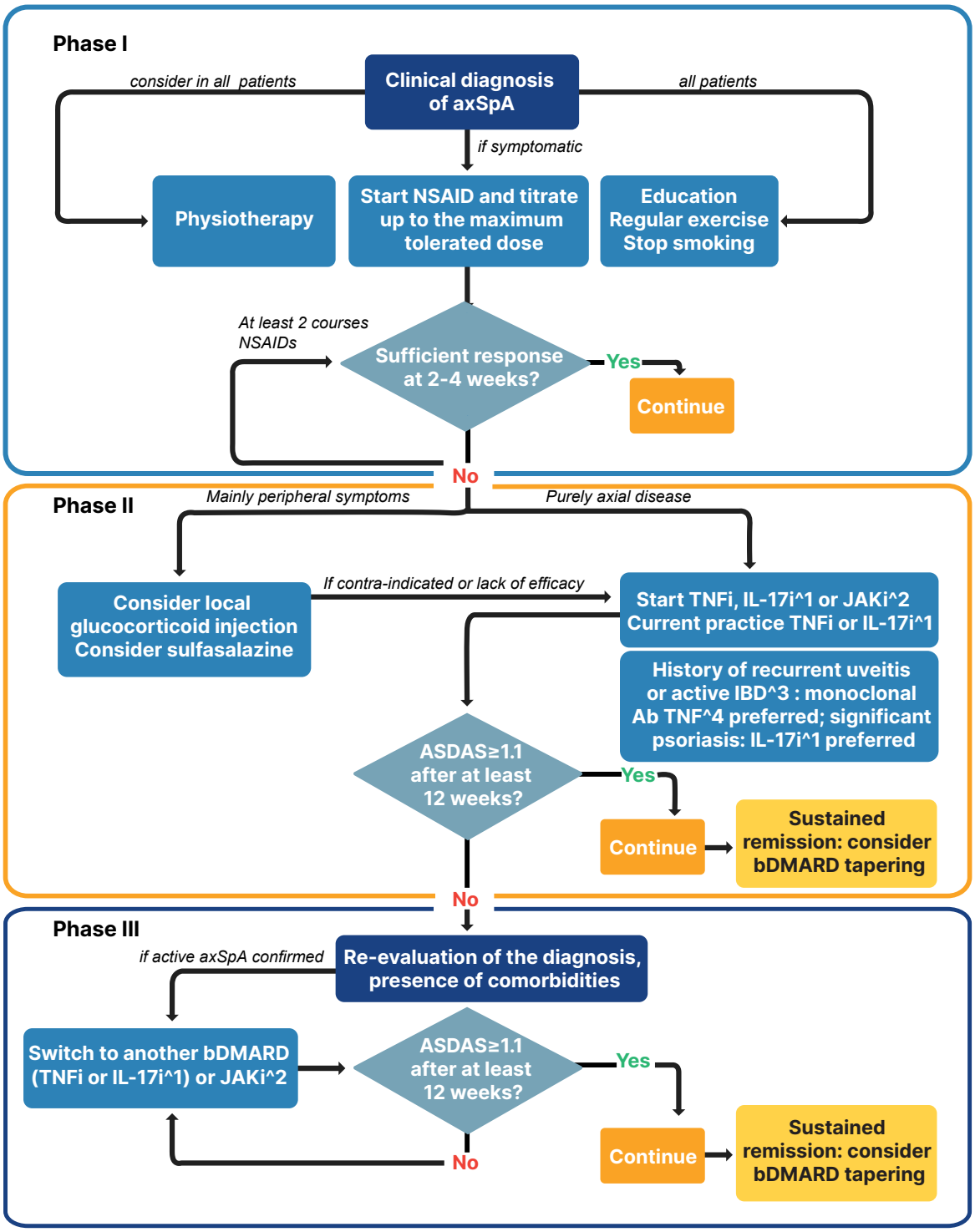


Figure 2. Algorithm based on the ASAS-EULAR recommendations for the management of axial spondyloarthritis (axSpA); *adapted from Ramiro, S et al, 2023.*

Abbreviations: Ab: antibody, **ASAS:** Assessment of Spondylo Arthritis international Society, **ASDAS:** Ankylosing Spondylitis Disease Activity Score, **bDMARD:** biological disease-modifying antirheumatic drug, **IBD:** inflammatory bowel disease, **IL-17i:** interleukin-17 inhibitors, **JAKi:** Janus kinase inhibitors; **NSAID**: non-steroidal anti-inflammatory drug, **TNFi:** tumour necrosis factor inhibitors.

Conclusion

As we progress through 2024, we can reflect on our current position to envision where we are going. Treatment recommendations for the management of axSpA will continue to be highly useful for several reasons. They will allow for standardization of care and an evidence-based approach to diagnosis, treatment, and monitoring, ensuring that clinicians are making the best therapeutic decisions for their patients. Hopefully, this in turn leads to improved patient outcomes, such as better disease control, reduced disease progression, and improved quality of life. Treatment recommendations also lend guidance on the management of comorbidities and non-pharmacologic management for our patients. Finally, they allow us to identify a research agenda by identifying gaps in our knowledge and highlighting areas for further investigation.

Correspondence

Sherry Rohekar, BSc, MD, FRCPC, MSc (Clin. Epi)
Email: sherry.rohekar@sjhc.london.on.ca

Financial disclosures

Honoraria and/or Advisory Boards: AbbVie, Amgen, BioJAMP, BMS, Celgene, Celltrion, Eli-Lilly, Fresenius Kabi, Gilead, Janssen, Merck, Novartis, Organon, Pfizer, Roche, Sandoz, UCB, Viatris

References

1. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al. 2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis. Arthritis Care Res (Hoboken). 2019;71(10):1285–1299. doi: 10.1002/acr.24025
2. Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis. 2023;82(1):19–34. doi: 10.1136/ard-2022-223296
3. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–926. doi: 10.1136/bmj.39489.470347.AD
4. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-Based Medicine:The Oxford 2009 levels of evidence. [Updated: 2024, Cited: 14 Jun 2024]. Available at: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-forevidence-based-medicine-levels-of-evidence-march-2009.
5. Sinnappan S, Forte A, Ermann J. Axial spondyloarthritis treatment recommendations and disease activity monitoring in clinical practice: results of an online survey. J Rheumatol. 2024;51(5):472–478. doi: 10.3899/jrheum.2023-0894.
6. Akl EA, Meerpohl JJ, Elliott J, Kahale LA, Schünemann HJ, Living Systematic Review Network. Living systematic reviews: 4. Living guideline recommendations. J Clin Epidemiol. 2017;91:47–53. doi: 10.1016/j.jclinepi.2017.08.009
7. Elliott JH, Synnot A, Turner T, Simmonds M, Akl EA, McDonald S, et al. Living systematic review: 1. Introduction-the why, what, when, and how. J Clin Epidemiol. 2017;91:23–30. doi: 10.1016/j.jclinepi.2017.08.010
8. Hazlewood GS, Pardo JP, Barnabe C, Schieir O, Barber CEH, Proulx L, et al. Canadian Rheumatology Association living guidelines for the pharmacological management of rheumatoid arthritis with disease-modifying anti-rheumatic drugs [version 2.1]. [Internet]. [cited 25 Nov 2023]. Available from: https://app.magicapp.org/#/guideline/7413

Canadian Rheumatology Today
Science for the Real World

canadianrheumatologytoday.com

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