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Shifting Paradigms in the Treatment of Systemic Lupus Erythematosus

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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

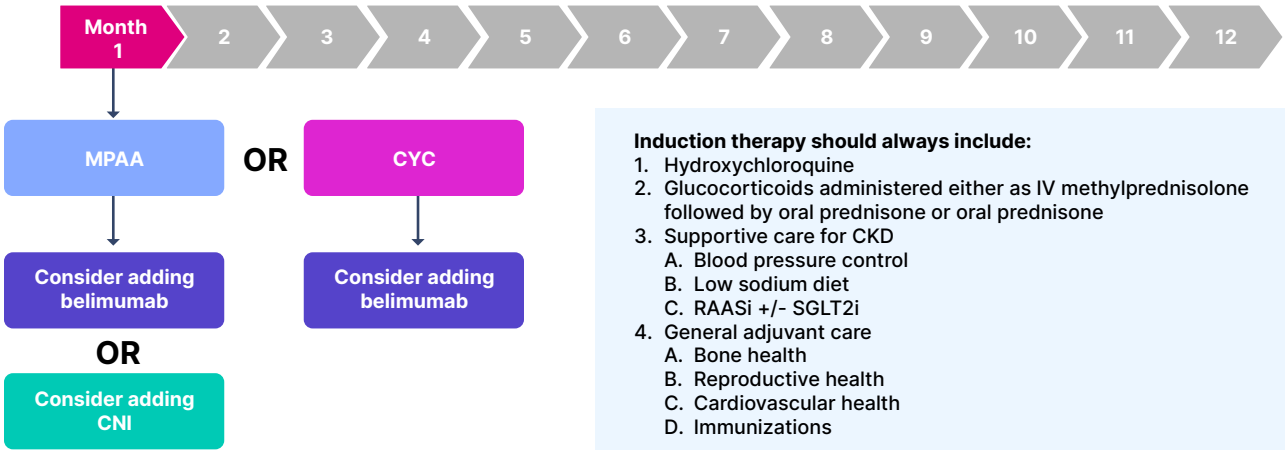

Figure 1A. Induction therapy for active class III or class IV lupus nephritis; *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema, MD, FRCPC, Nicholas L. Li, MD, PhD, FRCPC.*

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.

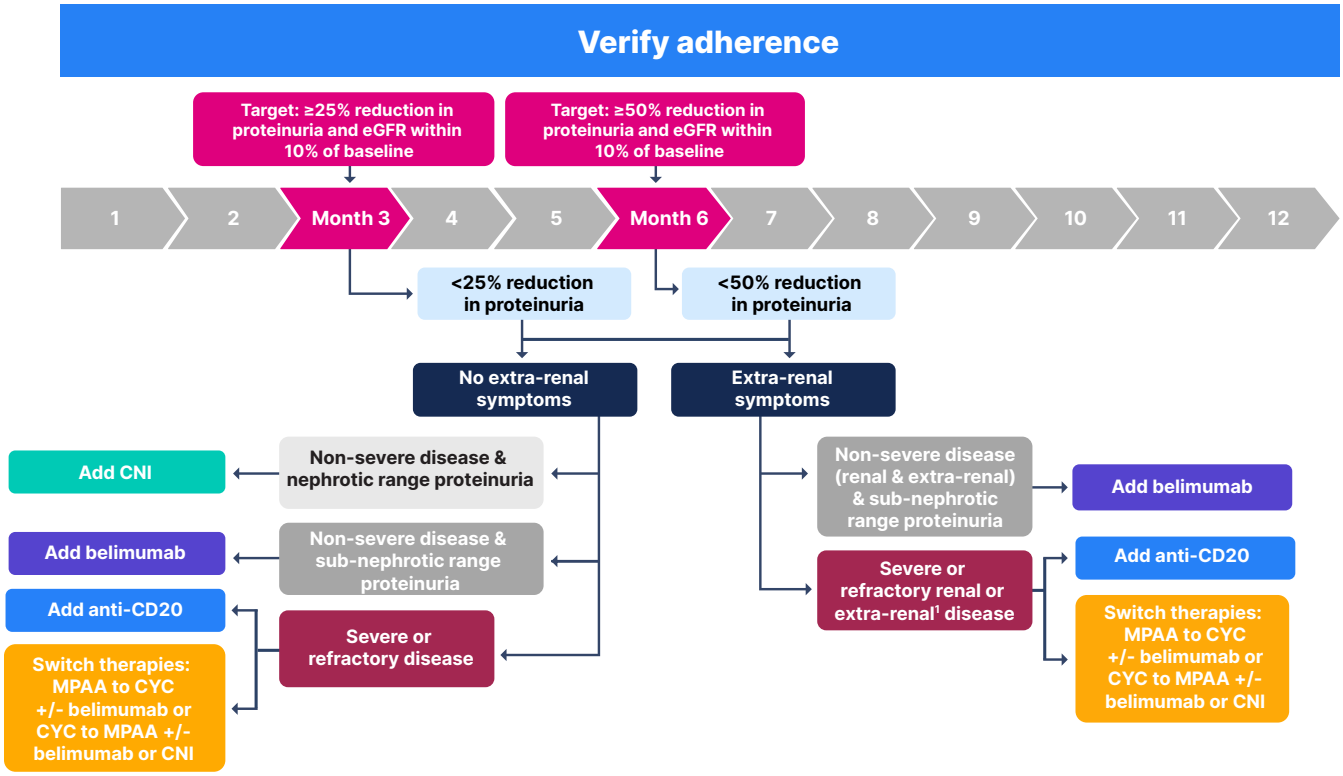

Figure 1B. Recommended approach if a partial renal response is observed at three to six months (in patients starting on monotherapy with either a mycophenolic acid analogue or cyclophosphamide); *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim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

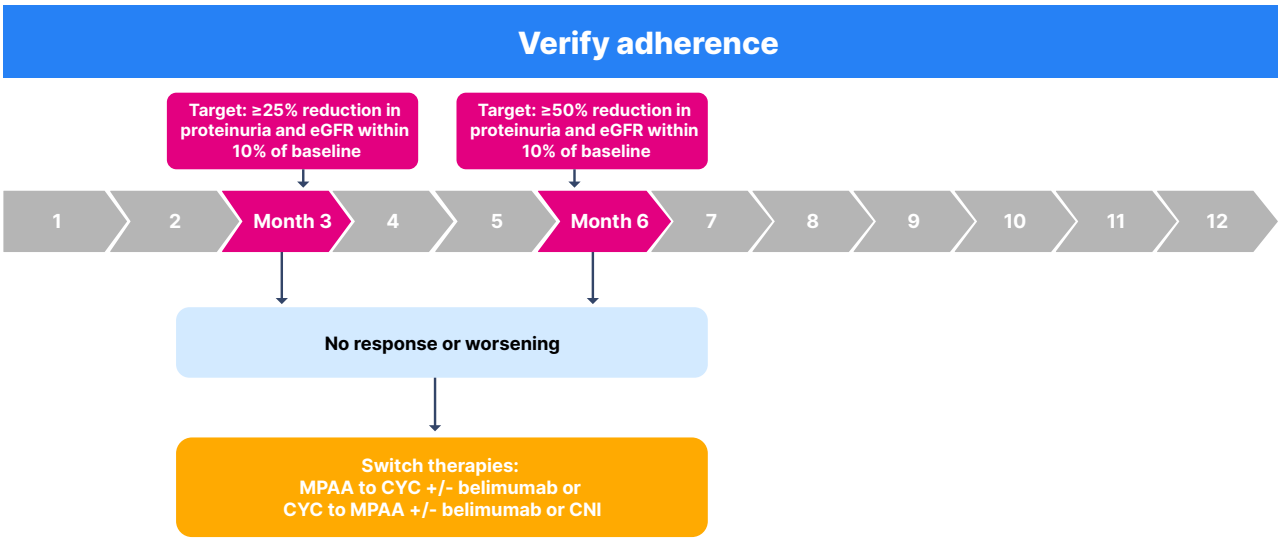

Figure 1C. Recommended approach if no renal response is observed at three to six months (in patients starting on monotherapy with either a mycophenolic acid analogue or cyclophosphamide); *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema,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

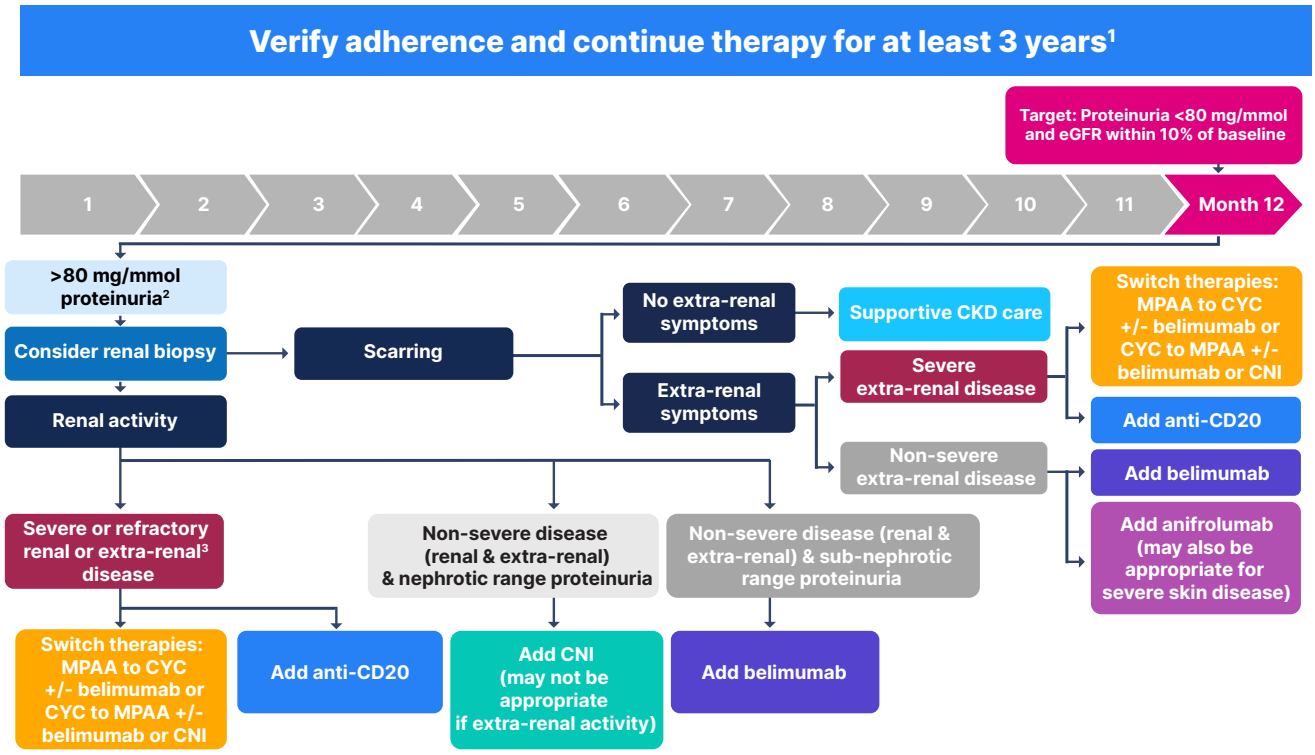

Figure 2. Recommended approach if a partial or no renal response is observed at 12 months (in patients starting on monotherapy with either a mycophenolic acid analogue or cyclophosphamide); *courtesy of Ann E. Clarke, MD, MSc, FRCPC, Megan R.W. Barber, MD, PhD, FRCPC, Bryce Barr, MD, FRCPC, Kim Cheema,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

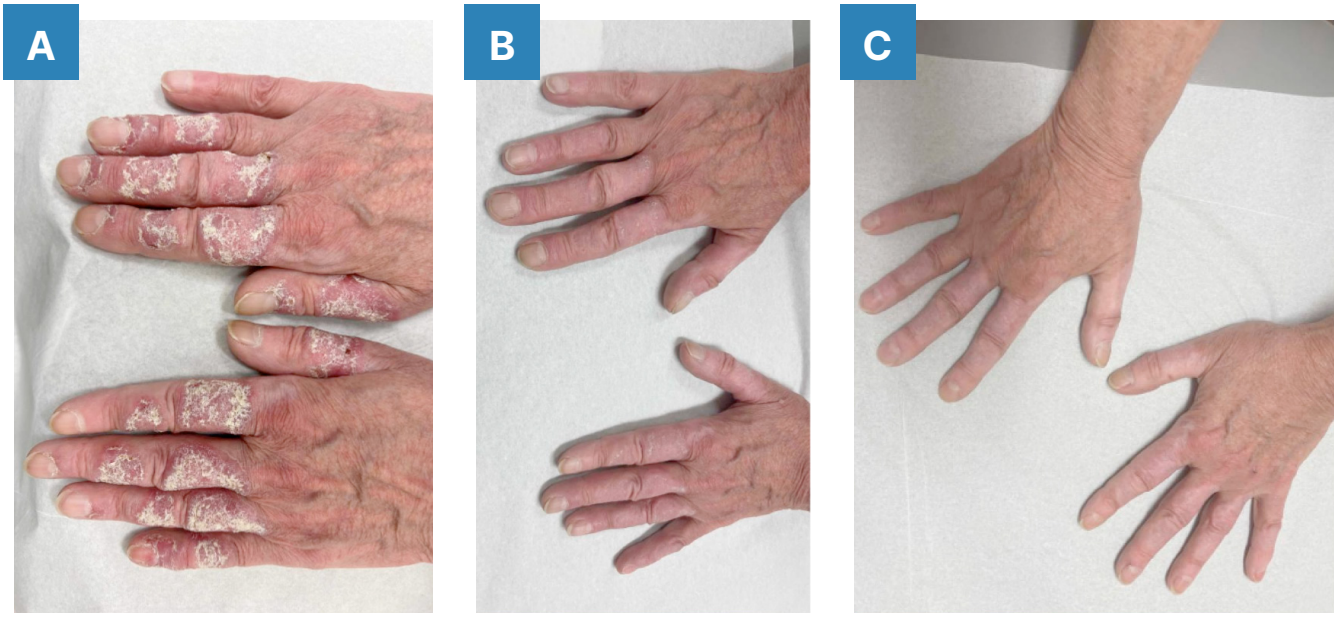

Photo 1A, B, C. Photos taken immediately pre **(A)** and post two doses **(B)** and post 11 doses **(C)** of anifrolumab; *photos courtesy of Megan R.W. Barber, MD, PhD, FRCPC.*

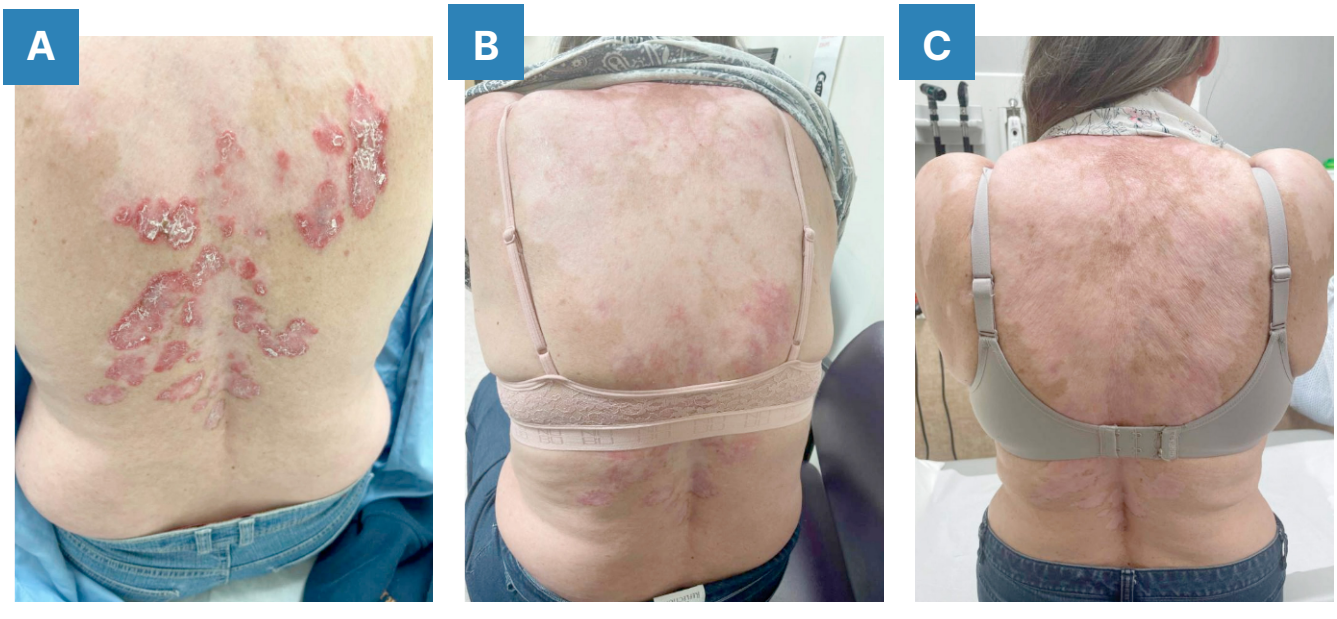

Photo 2A, B, C. Photos taken immediately pre **(A)** and post two doses **(B)** and post 11 doses **(C)** of anifrolumab; *photos courtesy of Megan R.W. Barber, MD, PhD, FRCPC.*

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.

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