RHEUMATOLOGY NURSE PRACTICE

THE BIOLOGIC REVOLUTION IN SYSTEMIC LUPUS ERYTHEMATOSUS:

Why It Matters to Our Patients

Inside this Issue

ISSUE **8** | VOLUME **3**

- What evidence supports the use of traditional mainstay therapies for the treatment of systemic lupus erythematosus (SLE)? What are their limitations?
- Why has the development of new drugs for the treatment of SLE historically been such a challenge?
- How do biologic therapies fit into the future SLE treatment landscape?
- What steps can providers take to help patients whose SLE is spiraling out of control?

RELEASE: APR 30, 2018 / EXPIRES: APR 30, 2019

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Support for this activity has been made possible through an educational grant from GSK

Release date: **April 30, 2018**

Expiration date: **April 30, 2019**

Activity URL: **rnsnurse.org/rnpce**

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ACTIVITY DESCRIPTION

In this issue of *Rheumatology Nurse Practice*, we'll take a look at how the treatment landscape in SLE is evolving, why the development of new therapies has historically been so frustrating, and how new breakthroughs are giving hope to the latest generation of patients with SLE.

LEARNING OBJECTIVES

After participating in the activity, learners should be better able to:

- Discuss the evidence supporting and limiting the use of traditional mainstay therapies for the treatment of SLE
- Identify the most common and significant side effects associated with traditional therapies used to treat SLE
- Assess the appropriate utilization of biologic therapies among patients with SLE being treated in your practice
- Analyze the potential utility of new therapies under late-stage investigation for the treatment of SLE

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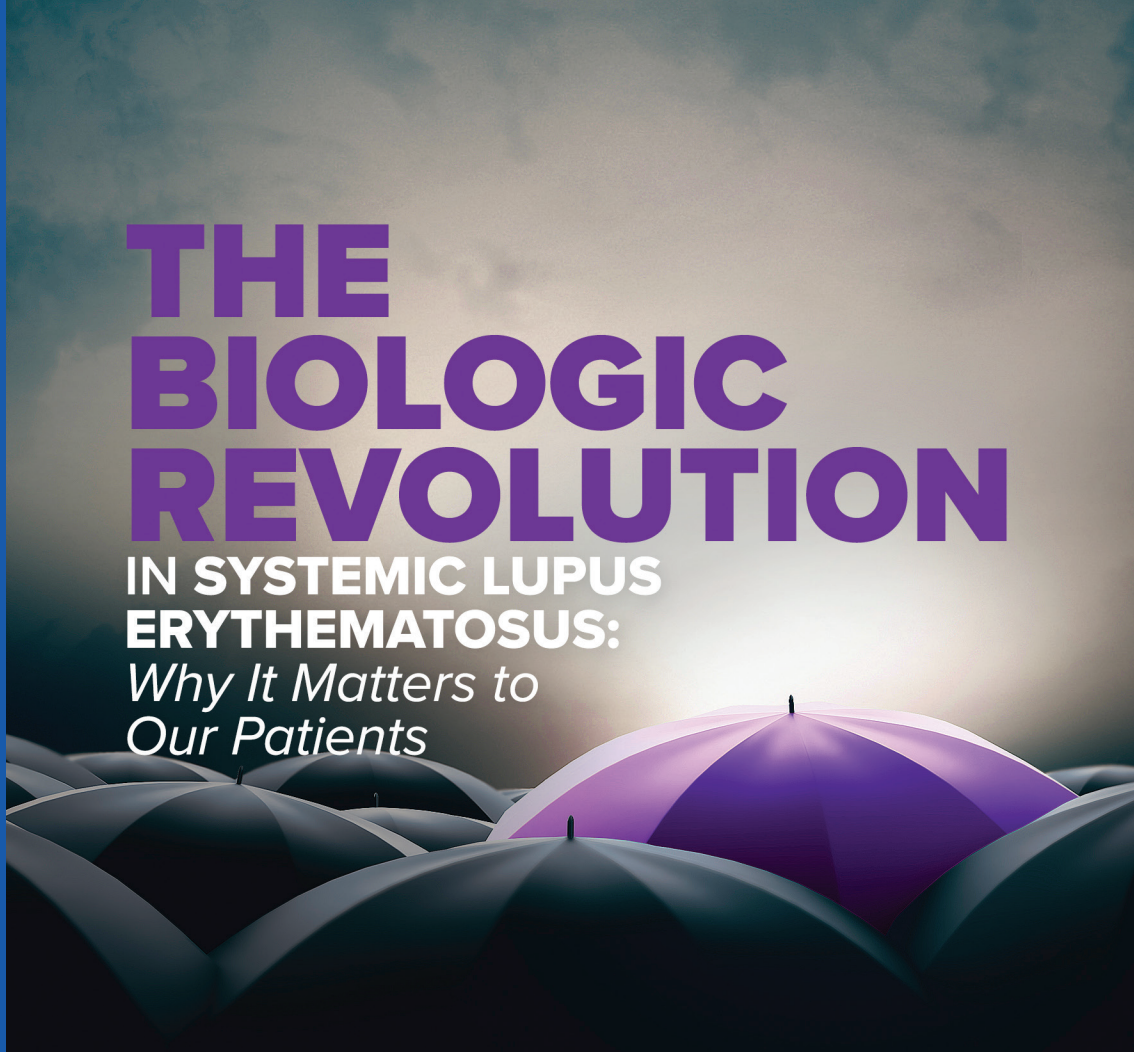


THE BIOLOGIC REVOLUTION IN SYSTEMIC LUPUS ERYTHEMATOSUS: *Why It Matters to Our Patients*

Systemic lupus erythematosus (SLE) is a disease that affects multiple organ systems, often requiring the use of multiple medications to control disease activity. Therapies used to treat SLE may improve some symptoms while intensifying others, and patients often need the care of a multidisciplinary team to help manage and monitor their disease. These issues make decisions about the timing, duration, and dosing of treatment extremely complex.

Promising results with biologic therapies—the first new drug for SLE in over 50 years was approved by the U.S. Food and Drug Administration (FDA) in 2011—are opening up new targets for therapy that may improve patient adherence, more effectively control disease activity, and limit side effects.

In this issue of *Rheumatology Nurse Practice*, we'll take a look at how the treatment landscape in SLE is evolving, why the development of new therapies has historically been so frustrating, and how new breakthroughs are giving hope to the latest generation of patients with SLE.

Drug Names Included Within This Issue

GENERIC	BRAND
Hydroxychloroquine (HCQ)	Plaquenil
Mycophenolate mofetil (MMF)	CellCept
Belimumab	Benlysta
Rituximab (RTX)	Rituxan
Anifrolumab	TBA
Blisibimod	TBA
Lupuzor	TBA
Voclosporin	Luveniq
Abatacept	Orencia

Treating to a Therapeutic Target in SLE

Recently published treat-to-target recommendations in SLE coincide with the biologic revolution by highlighting the value of targeted management of this complex and chronic disease. Treat to target is already a well-accepted approach for the management of many common chronic diseases. In both hypertension and diabetes, for example, the treatment target is a numeric value for systolic/diastolic blood pressure or blood glucose, respectively. Patients whose treatments are aimed at reaching those targets generally have improvement in their long-term prognosis.[1,2] Treat-to-target approaches have also become popular in the treatment of rheumatoid arthritis in the last decade, with resulting improvements in patient outcomes among individuals driven to specific thresholds of disease activity.[1,3]

In 2014, an international task force of rheumatologists from North America, South America, Southeast Asia, and Australia/Oceania published treat-to-target recommendations for SLE that recognize the complexity of managing a disease that has significant symptomatologies but one where disease activity does not always correlate with disease severity.[1]

The SLE treat-to-target recommendations are based on several core principles:[1]

1. Decisions about SLE disease management should be shared between the patient and healthcare provider
2. Treatment of SLE should aim to ensure long-term survival, prevent organ damage, and improve quality of life
3. Treatment of SLE will most likely require a multidisciplinary approach
4. Long-term monitoring and review and/or adjustment of therapy are vital to the long-term health and well-being of the patient with SLE

The treat-to-target recommendations are designed to highlight strategies that aim for disease remission and curtail the acceleration of end-organ damage.[2] The full list of published strategies is included in Table 1.[1]

Mainstay Treatments for SLE

Although there is no cure for SLE, several mainstay therapies can reduce symptom burden, limit damage to vital organs, and decrease the risk of disease flares.[4] The most commonly used of these agents, typically used in addition to nonsteroidal anti-inflammatories (NSAIDs), are hydroxychloroquine (HCQ), mycophenolate mofetil (MMF), glucocorticoids such as prednisolone and prednisone, cyclophosphamide, azathioprine, and methotrexate (MTX). The following section gives an overview of how each of these drugs fits into the treatment armamentarium for SLE and highlights information from research about their side effects and ability to control the disease.

Hydroxychloroquine (HCQ)

Once used only to treat or prevent malaria, antimalarials such as HCQ were found effective for treating lupus during World War II as they were found to improve muscle and joint pain, skin rash, pericarditis, pleuritis, fatigue, and fever. Antimalarials, which are thought to work by modulating the immune system, may also help prevent spread of SLE to the kidneys and central nervous system, and have been shown to help reduce flares by as much as 50%. Antimalarials can also protect against ultraviolet light and may improve skin lesions. Finally, they may prevent activation of plasmacytoid dendritic cells.[5]

Antimalarials can be prescribed in combination with other agents for the treatment of SLE, including corticosteroids, immunosuppressives, cytotoxic drugs, and NSAIDs. When an antimalarial is used in combination with prednisone, the steroid dosage needed to control symptoms can sometimes be reduced.[5]

Table 1 *Treat-to-Target Strategies in SLE*

Prevention of flares, especially severe flares, is a realistic target and therapeutic goal.
Prevention of damage accrual is a major therapeutic goal.
Fatigue, pain and depression should be addressed as they negatively influence a patient's quality of life.
Use lowest glucocorticoid dosage for maintenance therapy needed to control disease, and withdraw its use completely if possible.
Aim for remission and, if not achievable, aim for the lowest possible disease activity, measured by a validated lupus activity index and/or by organ-specific markers.
Prevent damage accrual, because damage predicts subsequent damage and death.
Recognize renal involvement early and treat early.
Prevent and treat antiphospholipid syndrome-related morbidity.
Control comorbidities with antihypertensives, lipid-lowering agents, antihyperglycemics, antiplatelet/anticoagulants, immunizations, and bone-protecting agents. There is no evidence to support use of adjunctive therapies or complementary medicines to achieve key therapeutic targets in SLE.
Give serious consideration to use of antimalarials, irrespective of other treatments used.

Research has shown that early use of HCQ—which is considered a disease-modifying anti-rheumatic drug (DMARD)—results in a reduction in cumulative organ damage at 3 years after diagnosis. A systematic literature review published in 2013 found that HCQ use in patients with SLE was associated with less damage at 3 years after diagnosis when regular dose adjustments were made based on disease activity, steroid dose, duration of disease, and calendar year of diagnosis.[6]

HCQ reportedly can have a significant impact on long-term outcomes by reducing low-grade flares and slowing disease progression; it is typically most useful for management of SLE symptoms such as fatigue and fever. HCQ was recently found to be cardioprotective through its ability to reduce total cholesterol and increase HDL cholesterol levels.[7]

HCQ is the most commonly prescribed antimalarial for SLE-related symptoms since it has fewer side effects than other antimalarials such as chloroquine and quinacrine. HCQ is safe to use during pregnancy, with no significant negative effects on the fetus when used at normal doses. It can be used when breastfeeding.[8]

There are, however, some known side effects of antimalarials, including HCQ. Retinopathy has been associated with use of antimalarials and, although rare, may be more common than previously recognized.[9] New research using sensitive screening techniques suggests that HCQ-associated retinopathy increases if the agent is used at high doses and for a long period of time. In one study, the overall prevalence of HCQ-associated retinopathy was 7.5%, though it varied based on dosage and duration of use. Among patients consuming between 4.0–5.0 mg/kg of HCQ daily, the prevalence of retinal toxicity was <2% during the first 10 years of use. The prevalence, however, increased to almost 20% after 20 years of routine HCQ use.[9] Patients taking HCQ should be examined by an ophthalmologist before starting the drug and then have periodic follow-up visits – the American Academy of Ophthalmology suggests annual screening after 5 continuous years of HCQ use.[5,10]

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) is an immunosuppressive drug that was first used to prevent the immune system from attacking and rejecting solid organ transplantation. MMF is used off-label as an alternate immunosuppressant for patients with SLE who may not be able to tolerate or are resistant to other immunosuppressive agents. MMF suppresses T- and B-cell lymphocyte proliferation, key factors in the pathogenesis of SLE.[11]

A study published in 2014 of 135 patients with SLE who were treated with MMF due to renal involvement found an overall good response to the therapy. Patients were

Table 2 *SLE Mainstay Therapies and Pregnancy*

Antimalarials (HCQ)	Considered safe to use during pregnancy
MMF	Avoid during pregnancy: risk of miscarriage, stillbirth, premature delivery, and birth defects. Men should avoid use 3 months prior to trying to conceive.
Glucocorticoids	Use lowest dose possible; risk of premature delivery, lower infant birth weight, pregnancy induced diabetes, and hypertension
Cyclophosphamide	Avoid during pregnancy; associated with infertility and ovarian failure; men should avoid use 3 months prior to trying to conceive
Azathioprine	Considered relatively safe during pregnancy; increased risk of small infant or premature rupture of membranes
Methotrexate	Avoid during pregnancy; linked with miscarriage and birth defects; for potential dads, some experts recommend holding methotrexate for 3 months prior to attempted conception

able to significantly reduce glucocorticoid use from 21.7 mg/day at baseline to 8.3 mg/day after 12 months (an additional 43 patients with systemic vasculitis were also included in these results).[12]

Studies conducted more than a decade ago indicate that MMF is as effective as IV cyclophosphamide for induction of remission and disease maintenance in patients with lupus nephritis. Data reported in 2010 indicate that MMF and IV cyclophosphamide are both able to reduce nonrenal as well as renal lupus manifestations and can reduce the incidence of disease relapse.[7,13] MMF is now increasingly used for induction and maintenance of remission not only in patients with lupus nephritis but also among those with severe manifestations of SLE.[7]

Side effects related to use of MMF can include diarrhea, nausea, and vomiting, although those effects can be minimized by reducing or splitting the dose. Infections such as cellulitis and herpes zoster have been reported as well,[7] although a recent longitudinal study of Medicaid patients with SLE showed no difference in rates of serious infection and mortality among new users of MMF, azathioprine, or cyclophosphamide.[14]

In 2012, the FDA issued a Risk Evaluation and Mitigation Strategy (REMS) about mycophenolate-containing medicines, warning that they are associated with increased risk of first trimester miscarriage and birth defects if taken during pregnancy. According to this guidance, structural malformations occur in approximately 20% of live-born infants exposed to MMF in utero. The REMS emphasized the need to prevent unplanned pregnancy in patients using MMF and to minimize fetal exposure by informing women of reproductive age about these risks.[15] Men should avoid use of MMF for at least 3 months prior to attempted conception to improve fertility.[8]

Glucocorticoids

Glucocorticoids, particularly prednisone, are considered a mainstay of SLE treatment and management. They rapidly control disease activity in patients with both mild and severe SLE, although their effects may not persist over time, thus requiring the use of additional immunosuppressive agents.[16]

Despite their overall efficacy, glucocorticoids often have severe side effects, particularly when used at high doses. Recent studies have found that glucocorticoids may significantly contribute to morbidity in patients with SLE, especially related to permanent organ damage. The effects of glucocorticoids may depend on dosing. A longitudinal study that observed patients with SLE for 4 years found a strong association with accrual of organ damage in SLE with glucocorticoid use. The most significant adverse effects were associated with patients receiving a time-adjusted mean dose of >7.82 mg/day, but remained significant even among those receiving a lower dose of >4.42 mg/day.[17]

In another study, damage accrual was confirmed in patients with SLE treated with prednisone within the first 5 years following diagnosis; this included multiple cases of cataracts, osteoporotic fractures, avascular necrosis, and diabetes mellitus. Treatment with either prednisone <7.5 mg/d or methylprednisone pulses (an IV administration of high doses of the drug for a limited number of days) was not associated with damage accrual. One suggestion from this study is that efforts should be made to minimize the unwanted

effects of prednisone without giving up the anti-inflammatory potential of glucocorticoids. The following strategies were suggested by the authors to accomplish this goal:[18]

- Use pulse therapy instead of high oral doses of glucocorticoids in periods of disease activity
- Promote the early association of immunosuppressive drugs
- Incorporate HCQ as universal baseline therapy

Due to their potential side effects, glucocorticoids should be taken as directed, at breakfast and with food, and can be taken up to 4 times daily during periods of acute inflammation. Patients should not discontinue glucocorticoids abruptly as the adrenal gland cannot respond adequately to a sudden withdrawal.[19] Use of glucocorticoids at the lowest dose possible is recommended for pregnant women with flares during pregnancy. Glucocorticoids can increase risk of premature rupture of membranes, lower infant birth weight, and pregnancy-induced diabetes and hypertension in the mother.[8]

Other side effects beyond accrual of organ damage may include heartburn, palpitations, agitation, and difficulty sleeping. Over time, additional side effects may include, but are not limited to bruises, hair loss, increased facial hair, impaired wound healing, muscle weakness, osteoporosis, weight gain, cataracts and glaucoma, hypertension, fluid retention, Cushing's syndrome, and greater risk of infection. Patients using glucocorticoids for more than a few weeks should be carefully monitored by their healthcare provider.[19]

Cyclophosphamide

Cyclophosphamide is considered both a potent immunosuppressive agent as well as an alkylating agent that stops cancer cells from growing. It depletes both B and T cells, which reduces the production of pathogenic autoantibodies. Cyclophosphamide has been used for decades to treat severe manifestations of SLE, including renal involvement, which occurs in more than 60% of patients with SLE. Cyclophosphamide can be administered by oral or IV therapy. The IV therapy involves less cumulative exposure to the drug, less frequent cytopenias, fewer bladder-related complications, and fewer problems with patient adherence.[20]

Cyclophosphamide is typically used for 3 to 6 months to treat SLE; after remission, a less potent drug is typically used for disease maintenance. In oral form, cyclophosphamide dosing may be 1.5 mg/kg to 2.5 mg/kg of a patient's body

Why Not Anti-TNF Therapy in SLE?

In many rheumatic diseases, the use of anti-TNF agents has become a cornerstone of treatment over the last decade. Yet in SLE, their use has not been deemed promising enough to investigate in large clinical trials. Why is this so?

Between 2005-2010, a handful of small clinical trials examined the use of infliximab, among the more widely used anti-TNF agents in rheumatology, in patients with SLE. While the earliest, limited enrollment trials showed potential efficacy of infliximab to improve disease activity in patients with SLE with limited side effects, more robust, longer-duration trials identified more limited efficacy and more significant adverse effects.[58]

While the reasons for this are not entirely clear, the common hypothesis surrounds the impact that anti-TNF agents have on the production of autoantibodies such as antinuclear antibodies, antidouble-stranded DNA antibodies, and anticardiolipin antibodies. Small case series have shown that the use of anti-TNF agents for the treatment of rheumatoid or psoriatic arthritis will occasionally trigger drug-induced lupus and worsen autoimmunity.[59] Drug-induced lupus is a syndrome with symptoms, signs, and laboratory findings similar to SLE.

It is feared that the use of anti-TNF agents in patients who have already been diagnosed with SLE will further trigger the production of antinuclear antibodies, for which approximately 95% of lupus patients already test positive.[58,60] Although it is not clear why anti-TNF agents exacerbate underlying lupus or trigger SLE, there are no current trials that are exploring the use of these biologics in patients with SLE.

weight per day. The dose of the injectable form may be calculated based on a patient's height, weight, and kidney function, or can be given as a fixed dose of 1 g every 4 weeks. Patients with SLE who begin treatment with cyclophosphamide may not improve for several weeks, with the full effect not realized until several months or longer.[21] Because of its better efficacy-to-toxicity ratio, the intermittent IV pulse therapy of cyclophosphamide is usually preferred over the oral formulation in the United States.[7]

Significant side effects are associated with use of cyclophosphamide, including nausea and vomiting, reversible hair loss, and skin rashes. Ovarian failure is another side effect, occurring in up to 38% to 52% of women treated with cyclophosphamide; this is age and dose related. Use of cyclophosphamide is also associated with infertility among both men and women. The menstrual cycle may stop in women taking cyclophosphamide, but pregnancy remains a possibility; thus, women using cyclophosphamide should be advised to take birth control. Cyclophosphamide should not be used during pregnancy and for at least 3 months before a planned pregnancy. Men should stop the medication 3 months prior to planned conception to improve fertility.[7,21] There have been some reports of gonadal failure associated with use of cyclophosphamide in men, although this has mostly been shown in cancer patients.[22]

Azathioprine

Azathioprine is an anti-inflammatory immunosuppressive that has been used off-label in patients with SLE for approximately 50 years to decrease joint damage and disability in individuals with mild to moderate disease. Corticosteroid use can often be reduced when concomitant azathioprine is used. Azathioprine is commonly used to induce remission in patients with mild to moderate SLE, and is used as maintenance therapy in patients with more severe disease.[7]

Two large randomized controlled multicenter trials (ALMS and MAINTAIN) looked at the use of azathioprine as maintenance therapy in patients with lupus nephritis to compare the efficacy and safety of the drug in comparison to MMF. Both trials found that maintenance therapy with either MMF or azathioprine is well tolerated overall and leads to excellent results at 3 to 4 years of follow-up for the majority of patients. Both agents resulted in extremely low rates of doubling of serum creatinine, end-stage renal disease, and death. The ALMS trial suggests that MMF may be more effective and better tolerated than azathioprine in high-risk minority patients with SLE.[23]

A recent longitudinal nationwide study of Medicaid patients with SLE who were at high risk of infection found that rates of serious infection and mortality did not differ among new users of MMF, cyclophosphamide, or azathioprine.

Common side effects associated with azathioprine include toxicity to the GI tract, oral ulcers, nausea, vomiting, diarrhea, and epigastric pain. Dose-related toxicity to the bone marrow can lead to leukopenia and, although not as frequently, thrombocytopenia and anemia.[24] Azathioprine is one of the few medications commonly used to treat SLE that is considered relatively safe for use during pregnancy.[25] There is, however, an increased risk of having a small infant or of having pre-term premature membrane rupture with any immunosuppressive agent. The risk of fetal harm is small for pregnant women using azathioprine and is similar to those who use NSAIDs, aspirin, or prednisone.[8]

Methotrexate

Methotrexate (MTX) is another nonbiologic DMARD frequently used to treat the pain and swelling of arthritis associated with SLE. Its use can decrease long-term joint damage. Although effective for mild forms of SLE, it is less effective in patients with severe SLE. Improvement in symptoms often occurs within 3 to 6 weeks of starting MTX, but the full effect may not be felt for 3 months.[26]

The use of steroids can often be significantly reduced among patients using MTX.[27] Several randomized controlled trials have found the benefit of MTX on overall SLE activity, reduction in glucocorticoid doses, and effects on lupus arthritis and lupus skin manifestations.[28]

MTX was first developed as a chemotherapy agent to stop malignant cells from multiplying and spreading by blocking their access to folate. Depleting folate can, however, affect healthy cells, especially in the GI tract. Common side effects associated with use of MTX include nausea and vomiting, as well as the development of mouth ulcers and sores. A folic acid supplement of 1 mg daily or 5 mg once a week can help reduce these side effects. Splitting the methotrexate dose, with half taken in the morning and half 12 hours later, may also help prevent or relieve these side effects.[29]

Pregnant women should not use MTX as its use has been linked to high rates of miscarriage and birth defects. Based on evidence that MTX may disrupt sperm production, some experts recommend holding methotrexate for 3 months—long enough to wash out one spermatogenic cycle (74 days)—prior to planned conception.[30] MTX can cause sensitivity to the sun, prompting the need for caution and protective measures for patients with SLE who spend significant amounts of time outdoors. Patients taking MTX should avoid alcohol, particularly if they have a history of kidney disease.[8]

Nephrotoxicity has been noted in patients taking high doses of MTX; potentially life-threatening hepatoxicity, pulmonary damage, and myelosuppression have been reported with use of MTX as either high- or low-dose therapy.[31,32]

ACR Quality Indicators for SLE

In 2009, the American College of Rheumatology developed a quality indicator (QI) set for SLE, a document intended to represent a minimally acceptable standard of care for this patient population. The QI set covers diagnosis, preventive strategies, osteoporosis prevention and treatment, screening for cardiovascular disease, drug toxicity monitoring, renal disease, and reproductive health. Table 3 highlights several of the the quality indicators for drug monitoring and pharmacologic therapy recommended by the ACR for patients with SLE.[33]

EULAR Treatment Guidelines

In 2008, EULAR management guidelines for SLE were published that predate the introduction of newer therapies, limiting their current utility when it comes to medication options. These guidelines highlight 12 recommendations related to diagnosis, treatment, and monitoring of patients with SLE. There are statements directed at neuropsychiatric SLE, pregnancy, antiphospholipid syndrome, and lupus nephritis.[34]

Key recommendations include the following:

- Patients with SLE are at increased risk for several comorbidities: infections (urinary tract infections and others), atherosclerosis, hypertension, dyslipidemia, diabetes, osteoporosis, avascular necrosis, and malignancies (especially non-Hodgkin's lymphoma). Healthcare providers should minimize potential risk factors, have a high index of suspicion for their development, and perform prompt evaluation and diligent follow-up at signs of their emergence.
- Photo-protection is important for patients with skin manifestations of SLE. Lifestyle modifications such as smoking cessation, weight control, and exercise should be encouraged. Depending on a patient's individual medication and clinical situation, agents such as statins, calcium/vitamin D supplements, bisphosphonates, antihypertensives, and low-dose aspirin can be considered.
- Pregnancy may increase lupus disease activity, although flares are usually mild. Patients with lupus nephritis and antiphospholipid antibodies are at greater risk for preeclampsia and should be monitored closely. There is also increased risk of miscarriage, stillbirth, premature delivery, uterine growth restriction, and fetal congenital heart block in patients with SLE. In pregnant women, use of MMF, cyclophosphamide, and MTX should be avoided.

Table 3 *ACR Rheumatology Quality Indicators: General Preventive Strategies and Drug Monitoring*

PATIENT CATEGORY	STRATEGY
For every patient with SLE	Provide information about sun avoidance
If patient is on immunosuppressive therapy	Give annual inactivated influenza vaccination and pneumococcal vaccine
If patient is taking prednisone ≥7.5 mg/day for ≥3 months	Give supplemental calcium and vitamin D
If patient is prescribed new medication for SLE (eg, NSAIDs, DMARDs, glucocorticoids)	Discuss the risks vs benefits of the new drug; document the discussion
If patient is taking prednisone ≥10 mg (or other steroid equivalent) for ≥3 months	Make attempt to taper the prednisone, add a steroid-sparing agent, or escalate dose of an existing steroid-sparing agent
For every patient with SLE	Annually evaluate risk factors for cardiovascular disease, including smoking status, blood pressure, BMI, diabetes, and serum lipids

The Biologic Revolution in SLE

The development of new therapies for SLE has historically been a challenge due to the complexity of this heterogeneous disease that involves inflammatory processes in multiple organ systems, results in a broad range of clinical phenotypes, and has substantial patient-to-patient variation in clinical and serological manifestations.[35]

The mainstay therapies for SLE described in earlier pages of this issue have improved overall outcomes in patients over the past several decades, with 5-year survival rates improving from approximately 50–70% in the 1950s to more than 90% in the 1990s and beyond.

However, because of the adverse reactions related to therapies commonly used to treat SLE, patient adherence is often a challenge, which obviously affects therapeutic impact.[35,36] Consequently, the mortality rate associated with patients with SLE remains approximately 2.4 times greater than that of the general population; primary causes of death include cardiovascular disease, active lupus, renal failure, malignancy, and infection.[35]

Better understanding of the pathogenesis of SLE underlies the research on new therapeutic approaches targeting specific molecules: B-cell targets, T-cell downregulation and costimulatory blockade, cytokine inhibition, and modulation of complement.[37] A detailed description of the pathogenesis of SLE was included in Volume 3, Issue 6 of *Rheumatology Nurse Practice*.

Belimumab

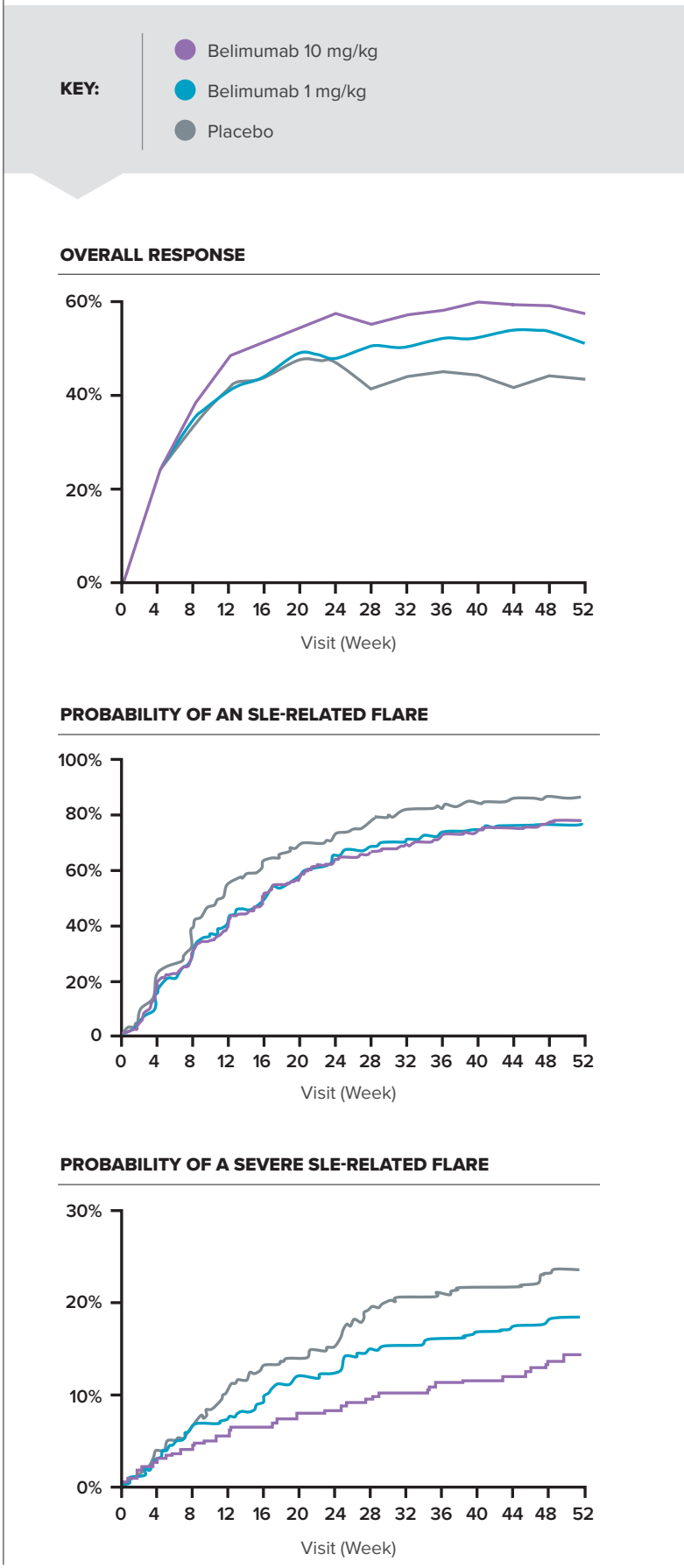
Many investigational biologic agents that showed initial promise in the treatment of SLE have later demonstrated insufficient efficacy or inadequate safety in clinical trials, illustrating the difficulty of new drug development for the treatment of SLE.

The one recent success came in 2011, when belimumab received FDA approval for the treatment of adult patients with active, autoantibody-positive SLE who are receiving standard therapy. Belimumab's approval made it the first new drug for lupus approved in the past 50 years.

Belimumab is a fully human monoclonal antibody that binds to and inhibits action of the soluble form of B lymphocyte stimulator (BLyS), also known as B-cell activating factor (BAFF). The IV formulation was the first to be approved; a subcutaneous self-injectable version was approved in July 2017.

Adherence to the IV formulation of belimumab may be challenging for some patients, as they need to

Figure 1 *BLISS-52 Primary Endpoints*[39]



visit a clinic or infusion center every 2 weeks for the first 3 doses, followed by once every 4 weeks thereafter. The subcutaneous, self-injectable formulation is hoped to be more convenient for patients.[38,39]

Belimumab was approved by the FDA based on results from two Phase 3 trials—BLISS-52 and BLISS-76. Results from both trials showed that use of belimumab results in a reduction in dosage of concomitant prednisolone and improvement in the physical component score of the SF-36 health survey.[40,41] In both studies, belimumab also improved time to first flare and physician global assessment (PGA). The greatest benefit was seen in patients with high baseline disease activity, defined either by low C3 or C4 levels plus anti-dsDNA positivity or by a SELENA-SLEDAI (Safety of Estrogens in Lupus Erythematosus National Assessment/SLE Disease Activity Index) score ≥10.[35]

BLISS-52 was a double-blind, placebo-controlled study that randomized 867 patients with SLE to one of two doses of IV belimumab (1 mg/kg or 10 mg/kg) or IV placebo at weeks 0, 2, and 4, and then every 4 weeks thereafter for a total of 52 weeks. The majority of patients were treated with one or more of the following throughout the study in addition to a study drug: prednisone, an immunosuppressive drug such as MMF, and an antimalarial.[40]

At 52 weeks, the rates of serious and severe adverse events were similar across all 3 groups, with slightly more adverse events in the belimumab 1 mg/kg cohort than the other groups. The most common adverse events were infections, infusion reactions, renal and urinary disorders, and nervous system disorders. Only 5-7% of patients in all study groups required discontinuation of therapy due to adverse events.[40]

The BLISS-76 trial shared a similar design to BLISS-52, with 819 patients with SLE randomized to one of two doses of IV belimumab (1 mg/kg or 10 mg/kg) or IV placebo at weeks 0, 2, and 4, and then every 4 weeks thereafter. This trial included an extra 24 weeks of treatment for a total of 76 weeks. Again, a huge percentage of patients were treated with one or more mainstay SLE treatments during the course of the study.[41]

After 76 weeks, patients treated with belimumab 10 mg/kg were significantly more likely to generate an SRI response than placebo; improvements in patients treated with belimumab 1 mg/kg did not achieve statistical significance. Patients treated with both doses of belimumab had reduced risk of severe flares through 76 weeks, though this reduction did not reach statistical significance in the 10 mg/kg group. The most common adverse events and rates of study discontinuation were similar to the BLISS-52 trial.[41]

Data are limited on use of belimumab in pregnant women and are insufficient to determine whether a drug-associated risk for major birth defects or miscarriage exists. Women of childbearing age should be advised to use effective contraception during treatment with belimumab and for 4 months after final treatment.[39]

Live vaccines should not be given for 30 days before or concurrently with belimumab. The drug's mechanism of action may interfere with a patient's response to immunization.[42]

A 7-year open-label continuation study of a phase 2 study that included 3 doses of belimumab—1 mg/kg, 4 mg/kg, and 10 mg/kg—showed that rates of adverse events were stable throughout 7 years of belimumab treatment. Adverse event rates tended to decrease over time, and the rate of serious infections peaked during the first year. Infections that affected ≥5 patients in any year included cellulitis, transient ischemic attack, and pneumonia. There were 7 deaths reported during the span of the trial, with an incidence rate of 0.4/100 patient-years.[43,44]

More recent results from the BLISS-SC trial demonstrated the efficacy and safety of the subcutaneous (SC) formulation of belimumab. In that trial, 836 patients

Table 4 *BLISS-SC Phase 3 Trial Results at Week 52*[37]

	Belimumab 200 mg subQ (n=463)	Placebo (n=214)	P Value
SRI4 responders	61.4%	48.4%	0.0006
Median time to severe flares	171 days	118 days	0.0004
Increase in corticosteroid use through week 52	8.1%	13.2%	0.0117
Reduction in steroid use ≥25%, weeks 40-52	18.2%	11.9%	0.0732
Serious adverse events	10.8%	15.7%	

with moderate-to-severe SLE were randomized on a 2:1 basis to receive either weekly belimumab SC 200 mg or placebo for 52 weeks. At the end of trial, patients in the belimumab group were significantly more likely to generate an SRI response than placebo, had improved time to and reduced risk of severe flare, and were more likely to be able to reduce their corticosteroid dosage by ≥25% compared to placebo.[38]

Rituximab

Rituximab is a B-cell depleting therapy that was first approved by the FDA for the treatment of relapsed or refractory B-cell lymphoma in 1997. It is a chimeric mouse/human monoclonal antibody against the B-cell-specific antigen CD20 that has been found effective for the treatment of RA, multiple sclerosis, and other diseases. It is commonly used off-label for the treatment of SLE as overall clinical experience has been generally positive.[36]

While retrospective analyses and open label phase 1/2 trials were promising with the use of rituximab for the treatment of both childhood-onset and adult-onset active and refractory SLE, large randomized controlled trials evaluating rituximab for treatment of SLE did not yield conclusive definitive results.[24]

The phase 3 LUNAR study randomized 144 patients with class III/IV lupus nephritis to treatment with either rituximab or placebo on a background of MMF and corticosteroids. At week 52, there was no significant difference in complete and partial responses between the two groups.[45] One potential reason offered for this result is that that the trial was not long enough to show a significant difference.[24,35]

A second phase 3 trial called EXPLORER tested the safety and efficacy of rituximab vs. placebo in patients with moderately to severely active extra-renal SLE. In this trial, neither the primary nor secondary endpoints were met, with an overall response rate of 28.4% in placebo group vs. 29.6% in the rituximab group. Reasons for the trial failure are still being debated, with potential problems attributed to study design, including steroid use, trial size, and endpoints.[7,24,36]

What's in the Pipeline for the Treatment of SLE?

The success of belimumab and increasing interest in the value of biologic agents that act on specific immunologic targets continue to fuel research efforts in SLE. Several novel agents have been developed, with some yielding promising results in clinical trials for SLE and lupus nephritis (LN), while others have followed the often-seen pattern of disappointing outcomes in this difficult-to-treat condition.

Table 5 *Biologics in SLE Pipeline*

Drug Name	Drug Category	Lupus Subset Being Studied	Current Clinical Trial Status	Expected Phase 3 Trial Completion Date
Anifrolumab	Human IgG1 mAb	SLE or LN	Phase 3 trial evaluating efficacy, safety of 2 doses vs. placebo	September 2018
Blisibimod	Peptibody targeting the BLyS pathway	SLE	Phase 3 trial did not meet its primary endpoint; development will continue only for treatment of IgA nephropathy	Trials in lupus discontinued after disappointing phase 3 results
Lupuzor	Immunomodulatory, tolerogenic agent	SLE	Phase 3 trial evaluating efficacy, safety of drug vs. placebo	Early 2018
Voclosporin	Calcineurin inhibitor	LN	Phase 2 results positive; now in phase 3 trial	March 2020
Abatacept	T-cell inhibitor	LN	Phase 2 results positive; now in phase 3 trial evaluating renal response of drug vs. placebo	May 2018

Anifrolumab

Development and clinical testing of cytokine/innate immunity targeting agents is ongoing. One example of this type of agent is anifrolumab, a human immunoglobulin 1 (IgG1) monoclonal antibody (mAb). A phase 2b clinical trial of anifrolumab in patients with moderate-to-severe SLE met its primary endpoint of SLE4 score achievement at 24 weeks.[46] A pair of phase 3 multicenter, randomized, double blind, placebo-controlled trials are now underway with an estimated completion date for both trials in the second half of 2018.[47,48]

Blisibimod

Like belimumab, blisibimod is a B-cell targeting agent. A peptibody made of 4 BAFF-binding domains, blisibimod binds to both membrane-bound and soluble BAFF. While a phase 1 trial demonstrated that blisibimod was well tolerated, the primary endpoint—the achievement of SRI5 at week 24—was not met in a phase 2 randomized controlled trial. In addition, there were injection site reactions in 12.9% of treated patients vs. 0.8% among the control group.[35,49]

The phase 3 international CHABLIS-SC1 trial that included 442 patients with SLE also did not meet its primary endpoint —SRI6 improvement at 52 weeks. Even though 47% of patients treated with blisibimod achieved the endpoint compared with 42% of patients treated with placebo, the difference was not statistically significant.[50] Another phase 3 trial studying the efficacy and safety of subcutaneous blisibimod in patients with severe lupus with or without nephritis was terminated early.[51] While blisibimod will continue to be developed for the treatment of IgA nephropathy, further development for the treatment of SLE is not expected.[50]

Lupuzor

Lupuzor is an immunomodulatory and tolerogenic agent, a phosphopeptide intended to induce tolerogenic dendritic cells. Dendritic cells induce and regulate T cell response, and tolerogenic dendritic cells can promote development of regulatory T cells with suppressive activity.[52,53] A phase 2b trial showed that, after 12 weeks of therapy, 67.6% of patients with severe SLE who were treated with Lupuzor 200 µg SC every 4 weeks achieved an SLE1 response compared to just 41.5% of patients in the placebo group. This increased to 84.2% vs. 45.8% after 24 weeks of treatment. In the trial, Lupuzor was well tolerated; the side effect profile was nonproblematic.[54] The FDA granted fast track status to Lupuzor based on these trial results.

In 2016, a phase 3 randomized, double-blind, placebo-controlled study was initiated comparing the 200 µg SC dose of Lupuzor vs. placebo in patients with active SLE.[55] Final trial results are expected in early 2018.[56]

Voclosporin

Voclosporin is a calcineurin inhibitor (CNI) with a chemical structure similar to that of cyclosporine A. It is an immunomodulatory agent being studied, in conjunction with MMF, for the treatment of lupus nephritis. It has also been granted fast track status by the FDA. After success with a phase 2B trial—the AURORA trial—a phase 3 randomized controlled double-blind study was initiated in May 2017 that is testing the efficacy and safety of voclosporin vs. placebo in more than 300 patients with active lupus nephritis. The primary endpoint of the trial is achievement of renal response at 52 weeks. The estimated completion date for the study is March 2020.[57]

Summary

Mainstay therapies for SLE have improved the overall prognosis for patients with SLE in the past several decades. However, their side effects can limit adherence to therapy and some patients remain unresponsive to trials of multiple agents.

With the approval of belimumab—the first new drug for SLE in 50 years—and promising results for other novel agents in late-stage clinical trials, the biologic revolution is underway. Given the increasing understanding regarding the pathogenesis of SLE, the recognized value of biologic agents that can act on specific immunologic targets is driving research into new targets for therapy.

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What to Do with a Patient Who Won't Listen

by Monica Richey, NP, MSN, ANP-CP/GNP

HL was 19 years old when she was transferred from a pediatric rheumatology practice into our adult practice. Her medical and social history was messy. In the foster care system since the age of 12 years old, HL had been diagnosed with systemic lupus erythematosus (SLE) at age 10. She had serious trust issues, tended to often miss scheduled appointments, and would then only receive a check on her SLE when she showed up in the emergency room with a disease flare.

Given her history, HL's social worker set up a meeting with her pediatric and adult rheumatology teams, as well as HL, prior to her transfer to our practice. Unfortunately, HL did not show up to the meeting.

I first met HL 6 months after this unsuccessful meeting when she came to our office for the first time after calling for an "urgent" appointment. It was an inauspicious beginning. For starters, HL wasn't interested in waiting to see a rheumatologist—she just wanted to have bloodwork done quickly so she could be in and out of our office. I tried talking to her about her current medications, but she shrugged me off, telling me, "I'm not taking any." I asked HL why and was told that she had been homeless for the last 3 months and had run out of insurance anyway. I put in a call to our social work team to see if there was anything they could do that might help.

HL's attitude was a challenge. She was equal parts demanding and despondent with an "I don't care" attitude about her disease and life in general. I knew that this was not the first time HL had been homeless, and she seemed resigned to this being her long-term fate.

HL's blood work showed large amounts of proteinuria, severe anemia, and extremely active SLE. Fortunately, our social work team was able to get her re-instated on Medicaid so that she could again begin to receive treatment.

Not surprisingly, we didn't hear anything from HL for the next 2 months. She popped back onto our radar after coming to the ER with a severe hypertension headache. HL told the ER team that she wasn't taking her medications because there were just too many of them. I received a call to perform a medication review and to try to assist HL with her issues.

When we went through her prescriptions—and remember that this was a 19-year-old—it was stunning. We figured out that HL was supposed to take 23 pills a day—6 tablets of mycophenolate mofetil, 2 tablets of hydroxychloroquine, 3 tablets of prednisone, 6 tablets of methotrexate, 1 folic acid tablet, several blood pressure medications, 2 calcium tablets, an osteoporosis prevention pill, and a birth control pill. Personally, I sometimes forget to take my daily multivitamin so I can't imagine how HL, with all of the issues in her life, could realistically be expected to take 23 pills on a daily basis.

My first step was to get HL 2 pill boxes and see if I could at least make it a little easier to manage her medications. I met with HL's rheumatologist to go over her medication regimens. We went on a cutting spree, switching the calcium and folic acid supplements into a single prenatal vitamin. We referred HL to a gynecologist so that she could receive an implantable intrauterine device and discontinue her use of daily birth control pills. We found combination therapies for her blood pressure medications. We exchanged the 6 daily mycophenolate pills for the liquid form. At this first pass, we managed to take HL from 23 daily pills down to 13, which seemed far more palatable.

Our social work team and I set up weekly appointments with HL over the course of the next month, which she fortunately actually showed up for. We taught her what each of her medications were for, when they should be taken, what side effects were possible, and

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what she should do if she forgot to take any. We found a simple application for her phone where we uploaded the full medication list and set reminders to cue HL to take each medication.

Little by little, our team was able to build mutual trust with HL. I think she enjoyed the personal attention and genuine concern we all had for her. She became a model patient, showing up with her pill boxes every 4 weeks and telling us about any troubles she was having with her medications. She even took her struggles to social media, posting pictures of her pill box and recording videos where she talked about the struggles of a young woman with SLE.

HL's turnaround has been remarkable. SLE is a very challenging disease to treat—even after the best of our efforts, HL still needs to take 13 pills a day to keep her disease at bay. There are some options for patients like HL with a long list of medications, including injectables, infusions, liquids, and combination pills that can help cut down on the daily requirements, but it can still be somewhat overwhelming. Medication nonadherence is a common problem in patients with SLE, and providers need to be vigilant in checking in with patients to make sure they are not letting their disease bubble untreated. Building trust with SLE patients like HL doesn't happen overnight, but by being open and assessing our patients' social as well as physical well-being, we can help to tame this difficult disease.

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Coming Up with Our Own Recipes

by Iris Zink, MSN, NP, RN-BC

Every healthcare provider knows that lupus is the great imposter. One day, it can affect one organ; the next, a whole different system can be targeted.

One lupus patient I have been treating for more than a year has traversed a difficult path since the day I saw her, swallowed up by the unpredictability of her disease.

NS is a 31-year-old woman who drove more than an hour to my office for her first visit in October 2016. She came to me with severe joint and chest pain, as well as a full body rash, which tested positive on biopsy for systemic lupus erythematosus (SLE).

During our initial conversations, NS told me that she had been sick since the birth of her daughter in 2014, but since she had no health insurance for the last 2 years, she could not afford a visit to a healthcare provider or any medication to treat her condition until she got on Medicaid.

An initial lab workup showed that NS was producing an overabundance of antibodies. She had high anti-nuclear antibodies (ANA) titers (1:1280) and tested positive for both anti-SSA and anti-SSB antibodies. NS also tested positive for rheumatoid factor (RF) with a high titer. Her anti-double stranded DNA test was negative, as was her anti-cyclic citrullinated peptide.

After her first visit, I knew we had to do something quickly. NS had recently been hospitalized for bronchitis, and I was concerned about organ damage if her SLE continued to progress.

NS was started on hydroxychloroquine 200 mg twice daily, along with 10 mg of daily prednisone. After four doses of this combination, she returned to my office complaining of uncontrolled, irregular tremors. NS was convinced they were being caused by her new medications, yet even when we stopped the hydroxychloroquine and prednisone, the tremors continued. While NS waited for an appointment with a neurologist to get more clarity on the source of her tremors, we started her on daily azathioprine 50 mg (increased to 100 mg after the first week).

After a full workup, the neurologist concluded that NS's tremors were of unknown origin. The irregularity of the tremors was deemed "suspicious." Along with azathioprine; she also reported to me that she was taking medical marijuana to help suppress her symptoms and sleep at night.

Several weeks later, NS's rash had not improved and her lab results remained concerning. Her azathioprine was increased to 150 mg daily and prednisone 10 mg daily was restarted. Unfortunately, that regimen also proved ineffective as NS's symptoms persisted and her cognition continued to decline. Even more worrisome, NS began reporting chest pain and shortness of breath. An echocardiogram and chest X-ray failed to reveal any organ damage.

We were starting to run out of options.

Our next step was a trial of IV belimumab. NS tolerated the treatments well and finally began showing some improvement over the next 4 months. Her cognition and depression both improved significantly; it was like she was a new person. Although her joint pain persisted, she was able to stop using medicinal marijuana and sleep more normally. Unfortunately, NS continued to suffer sequelae of SLE, including hair loss, oral and nasal sores, night sweats, and oral dryness. Her labs showed little improvement, her neutropenia persisted, and urinary casts began appearing. Because of the positive momentum we were able to gain with belimumab, we decided to keep trying, adding leflunomide to her regimen. Unfortunately, three months later, NS continued to have debilitating joint pain and stiffness, and she reported that she was struggling to care for her young daughter.

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"We all probably know a patient who runs through the gamut of ups and downs on various treatment regimens"

While not approved by the U.S. Food and Drug Administration for the treatment of SLE, I knew that there were some positive results of abatacept in patients with severe lupus nephritis.[1,2] Not being able to bear seeing NS suffering through another belimumab infusion by rocking herself back and forth to ward off her joint pain, I decided to venture into the unknown territory (at least for me) of abatacept in SLE. Using her positive RF as justification, I was able to get NS's insurance company to approve the drug; a few days later, NS received her first infusion.

NS tolerated the abatacept infusion just fine, but reported to me a few days later that her rash had worsened. We bumped up her prednisone from 5 to 10 mg daily prior to her second infusion. NS's reaction to the second abatacept infusion was worse than the first—her whole body broke out in an angry, red, pruritic rash. A dermatology consultation resulted in a biopsy that showed a drug-induced rash due to the abatacept.

So now what? I consulted with our in-house team and NS, and we jointly decided that, since there were at least some cognitive and psychological improvements with belimumab, we would give that another try. If only to attempt to mix things up, we also introduced subcutaneous weekly methotrexate (MTX) 17.5 mg to NS's regimen.

After only a month, we started seeing dramatic improvements in NS's lab results. Her ANA titers—previously sky-high at 1:1280—dipped to 1:80. Her neutropenia resolved. Her compliments improved. The urinary cases disappeared. NS's rash slowly began to disappear and she was left with only four spots on her skin. Even her joint pain, which had previously been resistant to every other regimen we tried, began to slightly improve.

It's hard to imagine that these improvements were due to the MTX after such a short period of use, so we were left with more questions than answers. Did the use of the T-cell inhibitor (abatacept) modify NS's immune system for the better? Was this a rare case where use of MTX actually did result in a more rapid improvement than expected? It's one of those cases where the medical literature isn't helpful, so we can only guess.

SLE patients are complicated. We all probably know a patient like NS who runs through the gamut of ups and downs on various treatment regimens. It would be great if there was a reliable recipe to follow that showed us which medications we should try first and which have the best chance to work in various SLE patients. But since there is so much that remains mysterious about this disease, we are often left to experiment, trying a little of this and a little of that if only to see incremental gains. Yet we need to keep trying, no matter how frustrating it gets, for that glimmer of hope before the breakthrough finally comes.

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Putting the Puzzle Pieces Together

by Linda Grinnell-Merrick, MS, NP-BC

New patient referrals are always exciting (at least to me). It's like putting a jigsaw puzzle together. Sometimes, you find all of the pieces right away and are able to figure out the whole picture pretty easily. Other times, you realize that you are missing a few pieces, and it takes time and patience to figure out what you are really looking at.

DL was one of those more complicated patients, a 48-year-old female referred to us for evaluation with an elevated rheumatoid factor (RF) of 55.8 u/ml and pain in her hands and neck that had been responsive to prednisone. She was referred by her primary care provider for evaluation after a preliminary diagnosis of rheumatoid arthritis (RA).

At her first visit, DL reported having pain in her hands and wrists for several months. She told us that her hands felt "puffy," but she was uncertain if they were swollen. DL told us that she usually felt awful in the mornings, with stiffness in her hands that would last for hours. She also reported swelling in her feet and ankles with periorbital edema, which again was worst in the mornings, as well as general fatigue. The remainder of our review of symptoms was normal.

On physical exam, we found mild periorbital swelling that was worse in the right eye. No joint swelling or synovitis was noted. She had tenderness of the 2nd thru 4th proximal interphalangeal joints over the right hand and over the bilateral trapezius muscles. No other abnormalities were noted.

As we listened to DL's description of her symptoms and began assembling the pieces of her diagnostic puzzle, it became more and more obvious that this was not likely a case of RA. While DL had some characteristics consistent with RA (such as arthralgias and elevated RF), several of her other complaints (such as neck pain, lower extremity edema, and periorbital edema) are not typically associated with RA.

Clearly, additional testing was needed to help fill in some of the gaps. We ordered anti-citric citrullinated peptide and anti-nuclear antibody tests, along with other serologies, to evaluate for possible connective tissue disease. Full lab results are included in Table 1 (values in yellow fields are considered abnormal).

Sure enough, DL's CCP results were negative, confirming our suspicion that we were not looking at an RA patient. Her serologies were notable for high-titer ANA, positive

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Table 1

TEST	RESULTS	NORMAL VALUES
ANA Screen	Positive	Negative
ANA Titer	2560	<40
ANA Pattern	Mixed	Mixed
dsDNA Ab	76	(0-4 IU)
Anti-RO/SS-A	>8.0	(0.0-0.9 AI)
Anti-LA/SS-B	<0.2	(0.0-0.9 AI)
Anti-RNP	0.7	(0.0-0.9 AI)
Anti-Smith	1.1	(0.0-0.9 AI)
Cyclic Citrullinated Peptide Ab	12	(0-19 U)

anti-Smith antibodies, positive anti-double stranded DNA (dsDNA), and positive anti-Sjögren's-syndrome-related antigen A antibodies. The positive dsDNA and anti-Smith antibody results are very specific for lupus. These results, coupled with DL's arthritic symptoms, led us to a diagnosis of systemic lupus erythematosus (SLE).

When we brought DL back to our office and told her the news, she was naturally surprised. She came to our office expecting to have her initial diagnosis of RA confirmed and to begin on a treatment regimen. Now, she was being given a completely different diagnosis with very different consequences. This was a difficult conversation for all of us, and I took considerable time explaining to DL the natural history of SLE and the possible courses it might take in the future.

We started DL on hydroxychloroquine (HCQ) since it has been shown to help control pain in patients with SLE as well as to help reduce the frequency of disease flares. Before writing the prescription, I emphasized to DL some of the potential adverse effects of HCQ, including retinal toxicity, and reinforced the need for regular field vision testing.

DL returned to our office 3 months later, reporting some general improvement, include a reduction in fatigue and joint pain. She had discontinued prednisone, which was also a positive sign. None of the classic symptoms of SLE, such as malar rash, photosensitivity, alopecia, fevers, and pleuritic chest pain, were yet apparent.

DL's case isn't one of those classic presentations of SLE that many of us are used to seeing. By listening closely to her story and identifying outlying results from her physical exam and lab tests, we were able to figure out how her jigsaw puzzle of symptoms fit together. We're hopeful that she's on the right track to a more stable future, though we'll obviously have to watch carefully for any further bumps in her path.

JUST SAY No

by Jacqueline Fritz, RN, MSN, CNS, RN-BC

Hopefully, you are familiar with the patient Bill of Rights that was drafted by the federal government's Advisory Commission on Consumer Protection and Quality in the Health Care Industry in the late 1990s. It was created with the following three overarching goals:[1]

- To ensure that the healthcare system is fair and works to meet patients' needs
- To give patients a way to address any problems that they may have
- To encourage patients to take an active role in staying or getting healthy

As part of these rights, patients are urged to learn about their treatment options and take part in decisions about their care. Knowledge is power, and empowering patients with knowledge can help guide them make the best decisions for their safe and effective care.

Sounds great, right?

Unfortunately, the reality of the healthcare environment is that some patients refuse to make the best decisions for their care even when armed with reams of high-quality information. Take, for instance, a patient of mine who I will call Ms. No (or MN, for short). MN was diagnosed with systemic lupus erythematosus (SLE) in 2009. She initially presented with joint pain and fatigue. She had 4 tender and 2 swollen joints. Her labs were off the charts, with results that were positive for anti-Smith antibodies, anti-nuclear ribonucleoprotein, and anti-Sjögren's-syndrome-related antigens A and B. Despite all this, MN continued to work full time on an assembly line screwing lids onto vitamin bottles 8 hours a day.

After making our diagnosis of SLE, we started MN on twice-daily hydroxychloroquine (HCQ) 200 mg and daily prednisone 2 mg. She was also taking high doses of daily NSAIDs to help manage her pain. Accompanied by her daughter at every follow-up visit to ensure that MN understood every component of her treatment plan (MN's English was spotty), I initially felt confident that we were all on the same page.

And for three years, things went reasonably well. We were able to wean MN off of daily prednisone, and her disease remained relatively stable, with minimal joint pain. Things didn't start going sideways until 2012, when MN arrived for a routine follow-up with mild malar rash, increasing knee and shoulder

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pain, mild elevation in liver enzymes, skin greying, and increasing fatigue.

We reduced the HCQ 200 mg from twice a day to once a day in an effort to reduce the skin discoloration and told MN to stop taking NSAIDs. Knowing that this would likely cause her pain to spike, we encouraged MN to try to reduce her work schedule or ask her employer for accommodations that would let her sit down during her shift. She adamantly refused to consider our recommendations. Even as her daughter pleaded with her to consider that her job was not as important as her health, all we heard was "No, no, no!"

Fast forward a few months later, and MN landed in the hospital with thrombocytopenia, which required a high dose of prednisone, intravenous immunoglobulin, cyclophosphamide, and several transfusions. Despite this episode, MN was as stubborn as ever when she returned to our office. We suggested to her that she might want to try belimumab and again pushed for her to consider stopping work. "No, no, no," was all we heard.

More than three years went by. MN continued to work despite recurrent infections, alopecia, increasing fatigue, and persistent joint pain. We added mycophenolate mofetil to her regimen and brought back daily prednisone as well. Despite our frustrations, we kept at MN regarding a trial of belimumab and the need to cut back on her work responsibilities. Alas, MN was still extremely prideful and would accept decisions made only on her terms. Her daughter, who had quit school to care for her mother full-time, was as frustrated as we were.

Over the next 2 years, MN's health continued to deteriorate. She was diagnosed with interstitial lung disease in early 2016 and continued to suffer from severe greying of the skin and alopecia. Later that same year, she was admitted to the hospital with cardiac palpitations, shortness of breath, and oral candida. A pericardial effusion was diagnosed and successfully treated.

Shortly after her discharge, MN was due for another visit to our office. I was again ready for a fight. This time, though, there was another combatant who came along with MN—her son.

MN's son was initially furious with me—"Don't you see my mother is dying right before your eyes? What is wrong with you?!?!" He even started to cry out of fear for his mother's future. It was a powerful moment. And finally, it gave us the breakthrough we needed. MN could no longer ignore the impact her stubborn refusals had on those around her and agreed to (finally!) truly listen to the recommendations we had been making for years.

She defended me to her son, explaining to him that her declining health was due to her obstinance and not to any mismanaged care on my part. I told her the best thing she could do for me is to listen to her son and allow me to become a partner in her care. MN agreed, and soon after quit her job and began a regular schedule of belimumab infusions. It's a tragedy that so many negative health impacts had to happen before MN finally agreed to a treatment plan that aligned with her symptoms, but better late than never.

As rheumatology nurses, there are sometimes limits to the help we can give our patients. It is within their rights to seek out information and participate actively in decisions surrounding their care, which means that it is also within their rights to tell us "no" over and over and over. It can be frustrating, especially when we see the impact their refusals have on their care, but we nonetheless need to remain respectful and professional, hoping one day for that breakthrough to come.

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