

[Print](#) [Close](#)

## Musculoskeletal Disorders: Systemic Lupus Erythematosus

C. Douglas Smith, MD, FRCPC

Date of revision: March 2014

Systemic lupus erythematosus (SLE) is a prototype autoimmune disease affecting 1 in 1000–2000 individuals, predominantly young women in their reproductive years. For research purposes, the American College of Rheumatology (ACR) developed criteria for the diagnosis of SLE in 1982 (see [Table 1](#)).<sup>1</sup> In 2012, the classification criteria were revised and expanded to improve clinical relevance and incorporate new knowledge regarding the immunology of SLE.<sup>2</sup> However, the original classification criteria are sufficient for the needs of primary care practitioners.

**Table 1:** Criteria for the Diagnosis of SLE<sup>1</sup>

Criteria <sup>a</sup>	Comments
Malar “butterfly” rash	Rashes occur in 70%, often photosensitive
Photosensitivity	Rash on sun exposure
Discoid rash	Plaques
Mucosal ulcers	
Arthritis	Occurs in up to 80%
Serositis, pleuritis/pericarditis	Occurs in up to 50%
Kidney involvement	Proteinuria >0.5 g/day or cellular casts, occurs in up to 40%
Central nervous system	Seizures, psychosis (15%) in the absence of drugs or metabolic causes
Hematologic	Antibodies to white blood cells (leukopenia), platelets (thrombocytopenia) and/or red blood cells (hemolytic anemia)
Immunologic	Antibodies to double stranded DNA (dsDNA), phospholipids (anticardiolipin, lupus anticoagulant) and/or Smith nuclear antigen (anti-Sm)
Antinuclear antibodies (ANA)	Abnormal titers of ANA in the absence of drugs known to be associated with drug-induced lupus (see <a href="#">Drug-induced Lupus Erythematosus</a> , below)

<sup>a</sup> For diagnosis, at least 4 criteria of 11 criteria are required.

SLE is best viewed as a spectrum of diseases. Some individuals have mild disease with predominant involvement of the skin and/or joints, while others have more severe systemic disease. Loss of immunologic tolerance to nuclear antigens and the development of antibodies directed against self are key features of the disease.<sup>3</sup> These *autoantibodies* (produced by B cells and other immune cells) play a major role in the protean (widely variable) manifestations of the disease. Examples of autoantibodies include:

- antinuclear antibodies (ANA) in 90% of patients—highly sensitive but nonspecific
- antibodies to blood cells (red blood cells, white blood cells, platelets)
- antibodies to double stranded (native) DNA (dsDNA) in 60% of patients—highly specific, linked to disease activity (particularly to kidney involvement)
- antibodies to SSA/Ro and SSB/La in 33% of patients—linked to photosensitive rashes, dry eyes and neonatal complications
- antiphospholipid antibodies (anticardiolipin and lupus anticoagulant) in 33% of patients—linked to thrombosis and pregnancy complications

### Goals of Therapy

- Treat SLE symptoms and prevent damage
- Control inflammation and autoimmune activation
- In severe disease: induce remission, followed by maintenance
- Prevent complications

### Investigations

- History, physical examination
- Laboratory tests:
  - complete blood count (anemia, cytopenias)
  - kidneys: creatinine, albumin, urinalysis; if indicated, quantification of albumin/protein in urine, kidney biopsy
  - to confirm diagnosis: autoantibodies + tissue biopsy as indicated
  - to assess disease activity: anti-dsDNA antibodies (high in active disease) and levels of C3 and C4 complement (low in active disease)
  - if unexpected clots or pregnancy complications: antiphospholipid antibodies (anticardiolipin, lupus anticoagulant)

### Therapeutic Choices

For an approach to the treatment of SLE, see [Figure 1](#) - Treatment of Systemic Lupus Erythematosus<sup>4, 5, 6, 7, 8, 15</sup>.

### Nonpharmacologic Choices

- Patient education is a key component in supporting the goals of therapy
- Avoid prolonged sun exposure. Sun protection (both physical, e.g., protective hat and clothing, and use of **sunscreens with SPF  $\geq$ 30**) is important for all patients since sun-induced skin changes can trigger rashes and disease flares
- Lifestyle modifications including a heart-healthy diet and adequate exercise
- Smoking cessation is important as smoking adds to the already increased vascular risk associated with SLE, and decreases the effectiveness of antimalarial drugs.<sup>9</sup>
- Maintain immunizations including annual influenza vaccination (avoid live vaccines, particularly in individuals receiving corticosteroids or immunosuppressant drugs)

### Pharmacologic Choices

To reduce the risk of osteoporosis, encourage adequate **calcium** intake (elemental Ca<sup>++</sup> 1200 mg daily total from all sources) and a **vitamin D** supplement (at least 1000 IU daily).

For drugs used in the treatment of SLE, see [Table 2](#).

### Topical Therapies

Rashes (occurring in 70% of patients) may be treated locally with **topical corticosteroids** or **calcineurin inhibitors** (e.g., **tacrolimus**, **pimecrolimus**).<sup>10</sup>, <sup>11</sup> For more information on these agents, see [Skin Disorders: Atopic Dermatitis](#). More refractory skin disease may require systemic therapy, most often with antimalarial drugs.

### Systemic Therapies

**ASA** and other **NSAIDs** are often used to treat joint pain (arthritis occurs in 80% of patients), as well as pleuritic chest pain in patients with pleuritis or pericarditis (about 50% of patients). High doses of NSAIDs (e.g., ibuprofen and sulindac) have been associated with the development of aseptic meningitis in some patients with SLE.<sup>12</sup> For more information about NSAIDs, see [Musculoskeletal Disorders: Osteoarthritis](#).

Low-dose ASA may be used to reduce the risk of MI and stroke, and may be used to reduce the risk of complications related to the presence of antiphospholipid antibodies.<sup>13</sup>

### Antimalarials

**Hydroxychloroquine** or **chloroquine** is considered baseline therapy for the majority of patients with SLE.<sup>14</sup>, <sup>15</sup> They are particularly useful for the most common disease manifestations: photosensitive rashes, arthritis and fatigue. They are often used in combination with other agents, including corticosteroids and immunosuppressants. Early use of antimalarial drugs has been shown to reduce accrual of damage in patients with SLE.<sup>16</sup> Other relevant benefits ascribed to these agents include lipid- and glucose-lowering effects and reductions in blood clots.<sup>15</sup> In patients with stable disease, withdrawal of these agents has been associated with disease flares.<sup>17</sup>, <sup>18</sup>

Patients taking antimalarial drugs require regular ophthalmologic assessment.<sup>19</sup>, <sup>20</sup> Risk factors for ophthalmologic toxicity include a cumulative dose >1000 g of hydroxychloroquine or >460 g of chloroquine, doses >6.5 mg/kg or 400 mg/day of hydroxychloroquine or >3 mg/kg or 250 mg/day of chloroquine, treatment for greater than 5–7 years, liver or kidney disease, advanced age, obesity and pre-existing ophthalmologic disease.<sup>19</sup>, <sup>20</sup>, <sup>21</sup> Patients not at high risk require an ophthalmologic assessment at baseline then annually after 5 years of therapy; high-risk patients require an annual assessment without the initial 5-year delay.<sup>19</sup>, <sup>20</sup>, <sup>21</sup>

### Corticosteroids

Corticosteroids by a variety of routes (intra-articular, im, iv or oral) are generally used for more severe disease.

- Low doses (**prednisone** <15 mg/day or equivalent) are sometimes used for debilitating constitutional symptoms refractory to other agents (e.g., arthralgias/arthritis, myalgias, fatigue and low-grade fever). In these situations, corticosteroids are almost always combined with antimalarial drugs and are weaned to the lowest possible dose.
- Moderate (prednisone 0.5–1 mg/kg/day) or even high doses may be required for treatment of pleuritis/pericarditis.
- High doses (prednisone  $\geq$ 1 mg/kg/day, or equivalent) may be life- or organ-saving in patients with more severe disease (e.g., renal, hematologic or nervous system involvement, vasculitis and myositis). In urgent situations, iv “pulse” **methylprednisolone** (e.g., 500–1000 mg daily for 3 doses) may be used.

### Corticosteroid-sparing Agents

To reduce corticosteroid-associated adverse effects, they are almost always combined with corticosteroid-sparing (“steroid-sparing”) agents, e.g., immunosuppressants, immunomodulators or biologic agents.

**Azathioprine** is effective in moderate to severe lupus. In severe lupus affecting the kidneys, nervous system or in patients with vasculitis, azathioprine is generally used as maintenance therapy after induction with more potent agents (e.g., cyclophosphamide, mycophenolate).<sup>4</sup>, <sup>5</sup>, <sup>6</sup>, <sup>7</sup>, <sup>15</sup>

**Methotrexate** is likely effective and steroid-sparing in patients with refractory arthritis, skin disease, myositis, pleuritis or pericarditis.<sup>22</sup>

**Cyclophosphamide** is generally used as induction therapy and is combined with corticosteroids for treatment of severe lupus involving the kidneys or nervous system or in patients with vasculitis. It is usually given iv monthly for 6 doses, or a lower dose is given every 2 weeks for 3 months.<sup>4</sup>, <sup>5</sup>, <sup>6</sup>, <sup>8</sup>

Guidelines recommend the low-dose regimen for white patients with Western or Southern European backgrounds.<sup>15</sup> In this patient population, the low-dose regimen showed fewer adverse effects and equivalent efficacy compared to the high-dose regimen.

**Mycophenolate mofetil** is equivalent to cyclophosphamide for induction therapy in proliferative lupus nephritis. It is preferred to cyclophosphamide in patients who wish to preserve their fertility, as high-dose cyclophosphamide is associated with permanent infertility. Evidence also suggests that mycophenolate is more effective than cyclophosphamide in patients with African or Hispanic backgrounds.<sup>15</sup> Additionally, mycophenolate demonstrated greater efficacy and equivalent safety to azathioprine for maintenance therapy in patients with nephritis.<sup>23</sup>

**Leflunomide** is occasionally used for refractory arthritis.<sup>24</sup>

**Belimumab** is the first agent of a new class of **biologic response modifiers**, the B-lymphocyte stimulator (BLyS)-specific inhibitors.<sup>25</sup>, <sup>26</sup>, <sup>27</sup>, <sup>28</sup>, <sup>29</sup> Belimumab is approved for use in combination with standard therapies to treat mild to moderate active autoantibody-positive SLE.<sup>15</sup> It has not been studied in severe disease. It should be reserved for patients who cannot tolerate or have failed traditional therapies. Other biologic response modifiers are being studied but are not currently approved for use in lupus. Selected examples include targeting B cells with **rituximab** <sup>25</sup>, <sup>26</sup>, <sup>30</sup>, <sup>31</sup> (useful in patients with severe refractory hematologic involvement) and targeting costimulation (CTLA-4) with **abatacept**.<sup>32</sup>

**Thalidomide** (initial dose 50–100 mg daily then reduced to the minimum effective dose) is highly effective for refractory skin disease<sup>33</sup> but its use is tightly restricted and long-term use remains problematic. A safer alternative for refractory skin disease may be **lenalidomide**.<sup>34</sup>

### Drug-induced Lupus Erythematosus

Many drugs are capable of inducing a lupus-like illness.<sup>35</sup>, <sup>36</sup> Those definitively associated with lupus include chlorpromazine, hydralazine, isoniazid, methylidopa, minocycline, procainamide and quinidine. Antinuclear antibodies are universally seen. Antibodies to histones are present in 75% of cases but are also seen in 75–80% of patients with idiopathic lupus. Patients with idiopathic SLE form a number of other autoantibodies, including those against DNA, while those with drug-induced lupus generally do not. Antitumor necrosis factor-alpha therapy and interferon-alfa have been implicated in the development of drug-induced lupus. Subacute cutaneous lupus, including induction of autoantibodies to SSA/Ro and SSB/La, has been associated with a growing list of drugs including calcium channel blockers, hydrochlorothiazide, leflunomide, ranitidine and terbinafine.

## Choices during Pregnancy and Breastfeeding

### SLE and Pregnancy/Postpartum Period

The effect of pregnancy on SLE is variable. While some women may experience increased disease activity during pregnancy, the overall risk of flares is not greater than in nonpregnant patients. However, flares of renal disease activity (renal lupus nephritis) may occur, and during the postpartum period disease activity may increase due in part to hormonal fluctuations (increased prolactin, changes in estrogen and progesterone levels).

### Pre-pregnancy Considerations

Pre-pregnancy assessment of disease activity, particularly renal function, is recommended at baseline and at least once per trimester during pregnancy. An active disease state prior to pregnancy is associated with high-activity lupus during pregnancy and negative outcomes (e.g., premature births, miscarriages).<sup>37</sup> Therefore, it is preferable that the patient be in remission for 6 months prior to conception.<sup>38</sup>

**Patients on methotrexate and mycophenolate are counselled to avoid pregnancy. These medications should be stopped 3 months (methotrexate) or 6 weeks (mycophenolate), prior to attempting conception [Evidence: SORT C].<sup>15,39</sup> However, recent small cohort studies showed no adverse pregnancy outcomes after preconceptional low-dose MTX exposure in males<sup>40</sup> or females<sup>41</sup>.** Useful Info?

**Leflunomide** is generally avoided in patients in whom future pregnancy is a possibility. If a pregnancy is desired, a “wash-out” regimen of **cholestyramine** 8 g TID or activated charcoal 50 g 4 times daily for 11 days (not necessarily on consecutive days) may be used to enhance leflunomide elimination following discontinuation.<sup>42</sup> For more information, see [Musculoskeletal Disorders: Rheumatoid Arthritis](#).

**Cyclophosphamide** may cause permanent infertility depending on the cumulative dose and the age of the patient.<sup>39</sup> A case-control study has shown that concomitant intake of synthetic gonadotropin releasing hormone (GnRH) may be effective in preserving fertility in women taking cyclophosphamide.<sup>43</sup>

### Management during Pregnancy and Postpartum Period

Pregnant women with SLE are often co-managed with a high-risk pregnancy team. The presence of antiphospholipid antibodies (anticardiolipin, lupus anticoagulant) is associated with an increased risk of thrombosis and pregnancy complications (e.g., pregnancy losses, preeclampsia). Antibodies to SSA/Ro and SSB/La are associated with an increased risk of neonatal lupus, including congenital complete heart block.

**ASA** and **NSAIDs** are considered safe in the first 2 trimesters.<sup>39</sup> Their use in the third trimester may be of concern, because of antiprostaglandin effects, NSAIDs can increase risks of fetal and maternal bleeding and premature closure of the ductus arteriosus, and can also interfere with labour onset or duration. ASA can affect hemostasis in both the mother and fetus, leading to higher risk of hemorrhage. **Ibuprofen** is favoured because of its safe use historically; data concerning chronic use of other NSAIDs (celecoxib) during pregnancy are lacking.<sup>44</sup>

**Hydroxychloroquine** is considered safe in pregnancy.<sup>14</sup>, <sup>45</sup>, <sup>46</sup> Its use likely reduces flares and the need for more aggressive (and toxic) therapies.

**Prednisone** is generally considered safe but has been associated with a small increase in the risk of cleft palate.<sup>47</sup> Higher doses in pregnancy are associated with complications such as hypertension, preeclampsia and prematurity. Therefore, the dose of prednisone should be kept as low as possible.

**Azathioprine** is considered safe in pregnancy at doses  $\leq 2$  mg/kg.<sup>15</sup>, <sup>48</sup>

**Methotrexate**, **mycophenolate** and **cyclophosphamide** are teratogenic.<sup>15</sup>, <sup>39</sup> Although mycophenolate appears more effective in preventing flares of

lupus nephritis, common practice would be to switch to azathioprine in those considering pregnancy and early data suggest this is safe.<sup>49</sup>

### SLE and Breastfeeding

Although most **NSAIDs** have been shown to be present in breast milk, amounts are generally small and they are consequently considered to be safe for use by breastfeeding women. Ibuprofen might be preferred due to its short half-life.<sup>44</sup>

**Hydroxychloroquine** is considered safe in breastfeeding.<sup>39</sup>, <sup>50</sup>

**Prednisone** at doses  $\geq 20$  mg/day will appear in breast milk with potential to affect the infant.

**Azathioprine** is considered safe in and breastfeeding at doses  $\leq 2$  mg/kg.<sup>51</sup>, <sup>52</sup>

**Methotrexate**, **mycophenolate** and **cyclophosphamide** are not compatible with breastfeeding.<sup>39</sup>

### General Considerations

Women on chronic corticosteroid therapy may be prescribed a bisphosphonate to prevent drug-induced osteoporosis. **Bisphosphonates** have demonstrated adverse effects (hypocalcemia, decreased fetal bone growth) in pregnancy.<sup>53</sup> While a small number of exposures reported in human pregnancies did not indicate skeletal or other abnormalities in the fetus,<sup>54</sup> the potential risks necessitate caution in prescribing bisphosphonates in women of childbearing age.

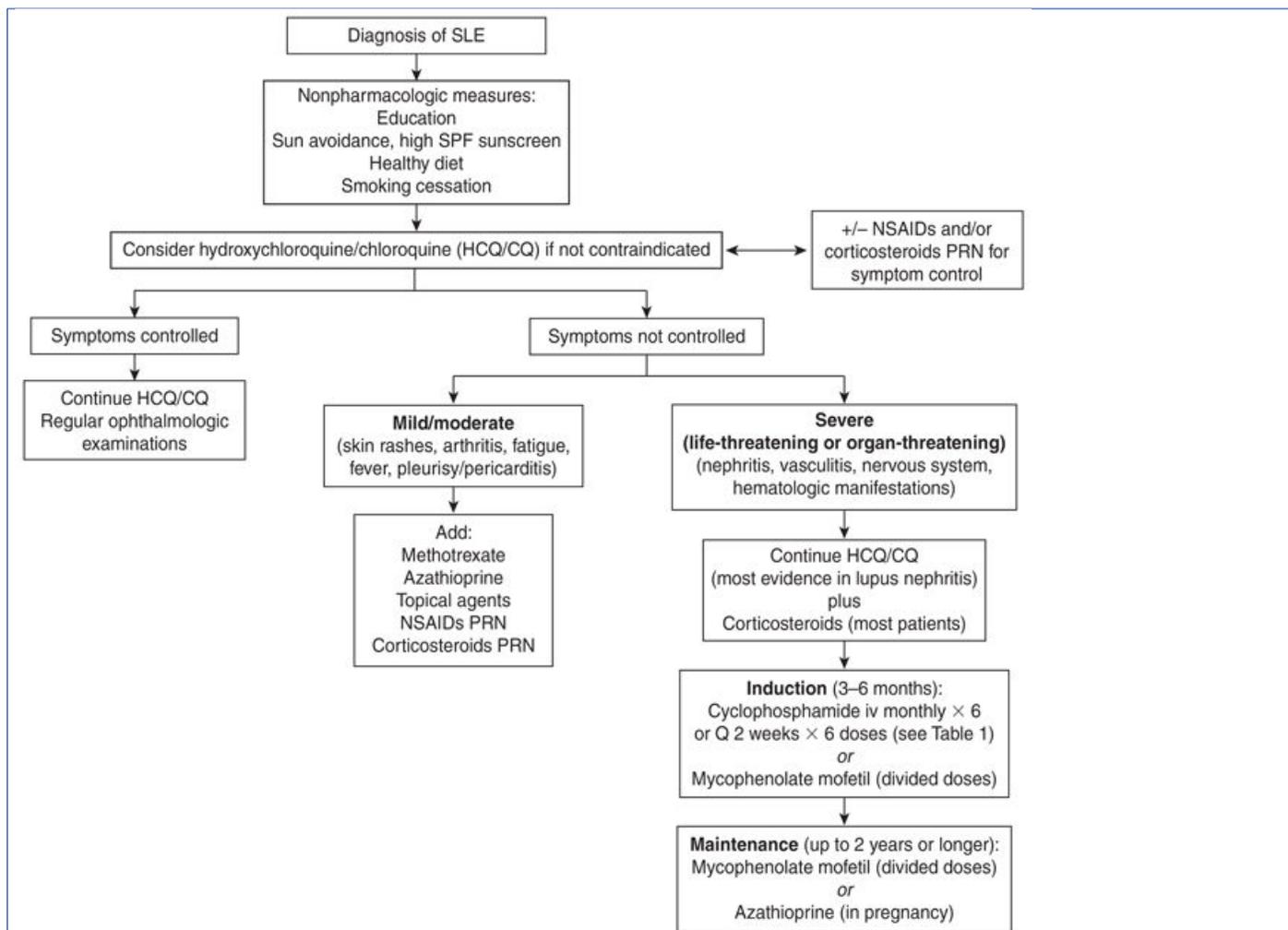
A discussion of general principles on the use of medications in these special populations can be found in [Drug Use During Pregnancy](#) and [Drug Use During Breastfeeding](#). Other specialized reference sources are also provided in these appendices.

### Therapeutic Tips

- Evaluate the immunization status of the patient before initiating immunosuppressive therapy. Once immunosuppressed, live vaccines (e.g., measles, mumps and rubella, varicella) are generally not recommended.<sup>55</sup> Encourage keeping vaccinations up to date while on therapy, including influenza and pneumococcal (both inactivated vaccines).
- The increased risk of cardiovascular disease and stroke in SLE patients requires aggressive evaluation and management of other risk factors, particularly smoking, lipids and blood pressure.
- Patients with SLE are at increased risk for osteoporosis due to sun avoidance (thus, possible vitamin D insufficiency) and long-term corticosteroid use (see [Musculoskeletal Disorders: Osteoporosis](#)). Assess and treat patients as needed; **bisphosphonates** are recommended to prevent corticosteroid-induced osteoporosis in those taking oral corticosteroids (prednisone equivalent  $\geq 7.5$  mg/day) for  $> 3$  months.<sup>56</sup>
- Use **sulfamethoxazole/trimethoprim** with caution as it may induce disease flares and photosensitive rashes.
- **Estrogen** should be avoided in patients with a history of thrombosis and those who have antiphospholipid antibodies. Oral contraceptives have not been associated with increased risk of disease flare.<sup>57</sup> Hormone replacement therapy has been associated with increased risk of mild to moderate disease flares.<sup>58</sup>
- Patients with mild or inactive disease should be followed with clinical and laboratory assessment at 3–4 month intervals.

### Algorithm

**Figure 1 - Treatment of Systemic Lupus Erythematosus**<sup>4</sup>, <sup>5</sup>, <sup>6</sup>, <sup>7</sup>, <sup>8</sup>, <sup>15</sup>



Abbreviations: CQ=chloroquine; HCQ=hydroxychloroquine; SLE=systemic lupus erythematosus; SPF=sun protection factor

### Drug Table

Table 2: Drugs Used in SLE

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost <sup>a</sup>
Antimalarials	<a href="#">chloroquine</a> generics	250 mg daily po Maximum: 3.5 mg/kg/day based on ideal body weight	Nausea, cramps, diarrhea, rash, headache, skin deposition (hyperpigmentation). Rare retinal deposition and ocular toxicity (dose-related), myopathy.		Ophthalmologic assessment required Q1-5 years, depending on risk factors. See <a href="#">Systemic Therapies</a> . To reduce the risk of retinal damage, do not exceed 3.5 mg/kg/day (based on ideal body weight).	\$
Antimalarials	<a href="#">hydroxychloroquine sulfate</a> Plaquenil, generics	200-400 mg daily po Maximum: 6.5 mg/kg/day based on ideal body weight	Nausea, cramps, diarrhea, rash, headache, skin deposition (hyperpigmentation). Rare retinal deposition and ocular toxicity (dose-related), myopathy.  Nightmares.	May increase digoxin levels, may increase effect of beta-blockers.	Ophthalmologic assessment required Q1-5 years, depending on risk factors. See <a href="#">Systemic Therapies</a> . To reduce the risk of retinal damage, do not exceed 6.5 mg/kg/day (based on ideal body weight).	\$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost <sup>a</sup>
B-Cell Depletors	<i>rituximab</i> <a href="#">Rituxan</a>	1 g iv × 2 doses, 2 weeks apart (with methylprednisolone 100 mg iv)	Mild to severe infusion reactions (very severe reactions resulting in death have been reported rarely). Rare: progressive multifocal leukoencephalopathy (PML).		Premedicate with acetaminophen and an antihistamine (e.g., diphenhydramine) before infusion. Monitor for hypersensitivity reactions.	\$9500
B-Lymphocyte Stimulator-Specific Inhibitors	<i>belimumab</i> <a href="#">Benlysta</a>	10 mg/kg infused over 1 h Q2 wk iv × 3 doses, then 10 mg/kg Q4 wk iv	Nausea, diarrhea, fever, anxiety, insomnia, depression, infusion reactions, hypersensitivity.		Premedicate with acetaminophen and an antihistamine (e.g., diphenhydramine) before infusion; monitor for hypersensitivity reactions. Safety and efficacy have not been evaluated in patients with severe active lupus nephritis or severe active central nervous system lupus.	~ \$1900 per dose <sup>b</sup>
Corticosteroids, oral	<a href="#">prednisone</a> Winpred, generics	Low: Up to 15 mg/day po Moderate: 0.5 mg/kg/day po  High: >1 mg/kg/day po	Acne, skin fragility, striae, GI upset, weight gain, glucose intolerance, mood swings, myopathy, glaucoma, cataracts, hypertension, osteoporosis, avascular necrosis, adrenal suppression, increased susceptibility to infections.	Increased risk of GI ulceration with NSAIDs.	Consider prophylaxis for drug-induced osteoporosis in patients taking ≥7.5 mg/day for >3 months (see <a href="#">Musculoskeletal Disorders: Osteoporosis</a> ).	\$
Corticosteroids, injectable	<a href="#">methylprednisolone sodium succinate</a> <a href="#">Solu-Medrol</a> , generics	100 mg iv (with rituximab). "Pulse" dosing: 500–1000 mg daily iv × 3	Acne, skin fragility, striae, GI upset, weight gain, glucose intolerance, mood swings, myopathy, glaucoma, cataracts, hypertension, osteoporosis, avascular necrosis, adrenal suppression, increased susceptibility to infections.			\$
Immunomodulators	<i>azathioprine</i>  <a href="#">Imuran</a> , generics	2 mg/kg daily po	Nausea, vomiting, diarrhea, fever, malaise, hepatotoxicity, increased LFTs, leukopenia, thrombocytopenia, infection, myalgia.	Allopurinol may increase azathioprine toxicity; dosage adjustment may be necessary. Increased risk of infection with other immunosuppressants (leflunomide, mercaptopurine, tacrolimus).	Monitor CBC weekly × 1 month, twice monthly for months 2–3, monthly thereafter. LFTs and creatinine monthly.	\$
Immunomodulators	<i>cyclophosphamide</i>  Procytox	First dose 500 mg/m <sup>2</sup> then 750–1000 mg/m <sup>2</sup> monthly iv × 6 doses; <b>or</b> 500 mg Q2 wk iv × 6 doses (in Caucasians) <sup>6</sup>	Nausea, vomiting, cytopenias, infertility, hemorrhagic cystitis, increased susceptibility to infections, malignancy potential.			\$\$
Immunomodulators	<i>leflunomide</i>  Arava, generics	10–20 mg daily po	Nausea, diarrhea, anorexia, weight loss, alopecia, rash, hypertension. May cause hepatotoxicity, cytopenias, pulmonary fibrosis, interstitial lung disease.	Decreased leflunomide levels with cholestyramine; increased risk of infection with live vaccines.	Avoid alcohol: possible increased risk of hepatotoxicity. Pregnancy is contraindicated while taking this medication. Wash-out procedure with cholestyramine 8 g TID × 11 days is	\$\$\$\$

Class	Drug	Dose	Adverse Effects	Drug Interactions	Comments	Cost <sup>a</sup>
					recommended for serious toxicity or imminently planned pregnancy (see <a href="#">Musculoskeletal Disorders: Rheumatoid Arthritis</a> ).	
Immunomodulators	<a href="#">methotrexate</a>  <a href="#">Methotrexate</a> <a href="#">Methotrexate Injection USP</a> , <a href="#">Methotrexate Tablets USP</a> , Metoject, other generics	10–25 mg weekly po or sc	Nausea, malaise, headache, oral ulcers, alopecia, diarrhea, cytopenias, hepatotoxicity, pneumonitis.	Alcohol restriction may minimize hepatotoxicity. NSAIDs or ASA may increase MTX serum concentrations minimally but this is not clinically significant; these can be combined at low doses. Penicillins (e.g., amoxicillin, cloxacillin, piperacillin) and sulfonamides (e.g., sulfamethoxazole/trimethoprim) may decrease MTX clearance.	MTX is abortogenic/teratogenic.	\$\$
Immunomodulators	<a href="#">mycophenolate mofetil</a> <a href="#">Cellcept</a> , <a href="#">Apo-Mycophenolate</a> , other generics	Induction: 2–3 g daily po for 6 months; Maintenance: 1–2 g daily po	Anemia, leukopenia, thrombocytopenia, hyper/hypotension, edema, hyperglycemia, hypercholesteremia, hypokalemia, nausea, vomiting, diarrhea, abdominal pain, headache, dizziness, rash.	Antacids, iron, magnesium and cholestyramine decrease absorption. Decreased efficacy of oral contraceptives. Increased mycophenolate concentrations with probenecid.	Monitor CBC weekly × 1 month, twice monthly for months 2–3, monthly thereafter. LFTs and creatinine monthly. Mycophenolic acid is likely equivalent in efficacy in SLE to mycophenolate mofetil. Mycophenolic acid 1440–2160 mg = mycophenolate mofetil 2000–3000 mg.	\$\$\$\$

<sup>a</sup>. Cost of 30-day supply, includes drug cost only.

<sup>b</sup>. Based on 70 kg body weight.



Dosage adjustment may be required in renal impairment; see [Appendices: Dosage Adjustment in Renal Impairment](#)

Abbreviations: GI=gastrointestinal; LFT=liver function test; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug

Legend: \$ <\$20    \$\$ \$20–40    \$\$\$ \$40–60    \$\$\$\$ \$60–80

## Suggested Readings

[Bomback AS, Appel GB. Updates on the treatment of lupus nephritis. \*J Am Soc Nephrol\* 2010;21\(12\):2028-35.](#)

[Duru N, van der Goes MC, Jacobs JW et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. \*Ann Rheum Dis\* 2013;72\(12\):1905-13.](#)

[Hahn BH, McMahon MA, Wilkinson A et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. \*Arthritis Care Res \(Hoboken\)\* 2012;64\(6\):797-808.](#)

[Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update on therapeutic options part I. \*J Am Acad Dermatol\* 2011;65\(6\):e179-93.](#)

[Petri M, Orbai AM, Alarcon GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. \*Arthritis Rheum\* 2012;64\(8\):2577-86.](#)

## References

- [Tan EM, Cohen AS, Fries JF et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. \*Arthritis Rheum\* 1982;25\(11\):1271-7.](#)
- [Petri M, Orbai AM, Alarcon GS et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. \*Arthritis Rheum\* 2012;64\(8\):2577-86.](#)
- [Rahman A, Isenberg DA. Systemic lupus erythematosus. \*N Engl J Med\* 2008;358\(9\):929-39.](#)
- [Chan TM, Li FK, Tang CS et al. Efficacy of mycophenolate mofetil in patients with diffuse proliferative lupus nephritis. Hong Kong-Guangzhou Nephrology Study Group. \*N Engl J Med\* 2000;343\(16\):1156-62.](#)
- [Contreras G, Pardo V, Leclercq B et al. Sequential therapies for proliferative lupus nephritis. \*N Engl J Med\* 2004;350\(10\):971-80.](#)

6. [Houssiau FA, Vasconcelos C, D'Cruz D et al. The 10-year follow-up data of the Euro-Lupus Nephritis Trial comparing low-dose and high-dose intravenous cyclophosphamide. \*Ann Rheum Dis\* 2010;69\(1\):61-4.](#)
7. [Ginzler EM, Appel GB, Dooley MA et al. Apreva Lupus Management Study \(ALMS\): maintenance results \[abstract\]. \*Arthritis Rheum\* 2010;62\(Suppl 10\):2085.](#)
8. [Appel GB, Contreras G, Dooley MA et al. Mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis. \*J Am Soc Nephrol\* 2009;20\(5\):1103-12.](#)
9. [Turchin I, Bernatsky S, Clarke AE et al. Cigarette smoking and cutaneous damage in systemic lupus erythematosus. \*J Rheumatol\* 2009;36\(12\):2691-3.](#)
10. [Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update on therapeutic options part I. \*J Am Acad Dermatol\* 2011;65\(6\):e179-93.](#)
11. [Kuhn A, Ruland V, Bonsmann G. Cutaneous lupus erythematosus: update on therapeutic options part II. \*J Am Acad Dermatol\* 2011;65\(6\):e195-213.](#)
12. [Rodríguez SC, Olguín AM, Miralles CP et al. Characteristics of meningitis caused by Ibuprofen: report of 2 cases with recurrent episodes and review of the literature. \*Medicine \(Baltimore\)\* 2006;85\(4\):214-20.](#)
13. [Wahl DG, Bounameaux H, de Moerloose P et al. Prophylactic antithrombotic therapy for patients with systemic lupus erythematosus with or without antiphospholipid antibodies: do the benefits outweigh the risks? A decision analysis. \*Arch Intern Med\* 2000;160\(13\):2042-8.](#)
14. [Ruiz-Irastorza G, Ramos-Casals M, Brito-Zeron P et al. Clinical efficacy and side effects of antimalarials in systemic lupus erythematosus: a systematic review. \*Ann Rheum Dis\* 2010;69\(1\):20-8.](#)
15. [Hahn BH, McMahon MA, Wilkinson A et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. \*Arthritis Care Res \(Hoboken\)\* 2012;64\(6\):797-808.](#)
16. [Akhavan PS, Su J, Lou W et al. The early protective effect of hydroxychloroquine on the risk of cumulative damage in patients with systemic lupus erythematosus. \*J Rheumatol\* 2013;40\(6\):831-41.](#)
17. [A randomized study of the effect of withdrawing hydroxychloroquine sulfate in systemic lupus erythematosus. Canadian Hydroxychloroquine Study Group. \*N Engl J Med\* 1991;324\(3\):150-4.](#)
18. [Tsakonas E, Joseph L, Esdaile JM et al. A long-term study of hydroxychloroquine withdrawal on exacerbations in systemic lupus erythematosus. The Canadian Hydroxychloroquine Study Group. \*Lupus\* 1998;7\(2\):80-5.](#)
19. [Marmor MF, Kellner U, Lai TY et al. Revised recommendations on screening for chloroquine and hydroxychloroquine retinopathy. \*Ophthalmology\* 2011;188\(2\):415-22.](#)
20. [American College of Rheumatology. Position Statement. \*Screening for hydroxychloroquine retinopathy\*. August 2011. Available from: \[www.rheumatology.org/practice/clinical/position/hydroxyp2.pdf\]\(http://www.rheumatology.org/practice/clinical/position/hydroxyp2.pdf\). Accessed October 12, 2012.](#)
21. [Wolfe F, Marmor MF. Rate and predictors of hydroxychloroquine retinal toxicity in patients with rheumatoid arthritis and systemic lupus erythematosus. \*Arthritis Care Res \(Hoboken\)\* 2010;62\(6\):775-84.](#)
22. [Fortin PR, Abrahamowicz M, Ferland D et al. Steroid-sparing effects of methotrexate in systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. \*Arthritis Rheum\* 2008;59\(12\):1796-804.](#)
23. [Dooley MA, Jayne D, Ginzler EM et al. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. \*N Engl J Med\* 2011;365\(20\):1886-95.](#)
24. [Tam LS, Li EK, Wong CK et al. Double-blind, randomized, placebo-controlled pilot study of leflunomide in systemic lupus erythematosus. \*Lupus\* 2004;13\(8\):601-4.](#)
25. [Calero I, Sanz I. Targeting B cells for the treatment of SLE: the beginning of the end or the end of the beginning? \*Discov Med\* 2010;10\(54\):416-24.](#)
26. [Wallace DJ. Advances in drug therapy for systemic lupus erythematosus. \*BMC Med\* 2010;8:77.](#)
27. [Wallace DJ, Stohl W, Furie RA et al. A phase II, randomized, double-blind, placebo-controlled, dose-ranging study of belimumab in patients with active systemic lupus erythematosus. \*Arthritis Rheum\* 2009;61\(9\):1168-78.](#)
28. [Navarra SV, Guzman RM, Gallacher AE et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. \*Lancet\* 2011;377\(9767\):721-31.](#)
29. [Furie R, Petri M, Zamani O et al. A phase III, randomized placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. \*Arthritis Rheum\* 2011;63\(12\):3918-30.](#)
30. [Merrill JT, Neuwelt CM, Wallace DJ et al. Efficacy and safety of rituximab in moderately-to-severely active systemic lupus erythematosus: the randomized, double-blind, phase II/III systemic lupus erythematosus evaluation of rituximab trial. \*Arthritis Rheum\* 2010;62\(1\):222-33.](#)
31. [Terrier B, Amoura Z, Ravaud P et al. Safety and efficacy of rituximab in systemic lupus erythematosus: results from 136 patients from the French AutoImmunity and Rituximab registry. \*Arthritis Rheum\* 2010;62\(8\):2458-66.](#)
32. [Merrill JT, Burgos-Vargas R, Westhovens R et al. The efficacy and safety of abatacept in patients with non-life-threatening manifestations of systemic lupus erythematosus: results of a twelve-month, multicenter, exploratory, phase IIb, randomized, double-blind, placebo-controlled trial. \*Arthritis Rheum\* 2010;62\(10\):3077-87.](#)
33. [Duong DJ, Spigel GT, Moxley RT et al. American experience with low-dose thalidomide therapy for severe cutaneous lupus erythematosus. \*Arch Dermatol\* 1999;135\(9\):1079-87.](#)
34. [Cortes-Hernandez J, Avila G, Vilardell-Tarres M et al. Efficacy and safety of lenalidomide for refractory cutaneous lupus erythematosus. \*Arthritis Res Ther\* 2012;14\(6\):R265.](#)
35. [Katz U, Zandman-Goddard G. Drug-induced lupus: an update. \*Autoimmun Rev\* 2010;10\(1\):46-50.](#)
36. [Lowe G, Henderson CL, Grau RH et al. A systematic review of drug-induced subacute cutaneous lupus erythematosus. \*Br J Dermatol\* 2011;164\(3\):465-72.](#)
37. [Clowse ME, Magder LS, Witter F et al. The impact of increased lupus activity on obstetric outcomes. \*Arthritis Rheum\*. 2005 Feb;52\(2\):514-21](#)
38. [Mitchell K, Kaul M, Clowse ME. The management of rheumatic diseases in pregnancy. \*Scand J Rheumatol\* 2010;39\(2\):99-108.](#)
39. [Østensen M, Khamashta M, Lockshin M et al. Anti-inflammatory and immunosuppressive drugs and reproduction. \*Arthritis Res Ther\* 2006;8\(3\):209.](#)
40. [Weber-Schoendorfer C, Hoeltzenbein M, Wacker E et al. No evidence for an increased risk of adverse pregnancy outcome after paternal low-dose methotrexate: an observational cohort study. \*Rheumatology \(Oxford\)\* 2014;53\(4\):757-63.](#)
41. [Weber-Schoendorfer C, Chambers C, Wacker E et al. Pregnancy outcome after methotrexate treatment for rheumatic disease prior to or during early pregnancy: a prospective multicenter cohort study. \*Arthritis Rheumatol\* 2014;66\(5\):1101-10.](#)
42. [e-CPS. Ottawa \(ON\): Canadian Pharmacists Association; 2012. \*Arava\* \[product monograph\]. Available from: \[www.e-therapeutics.ca\]\(http://www.e-therapeutics.ca\). Subscription required.](#)
43. [Somers EC, Marder W, Christman GM et al. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. \*Arthritis Rheum\* 2005;52\(9\):2761-7.](#)
44. [Clouvers M, Schaefer C. Analgesics and anti-inflammatory drugs. In: Schaefer C, Peters P, Miller, RK, eds. \*Drugs during pregnancy and lactation: treatment options and risk assessment\*. 2nd ed. London \(GB\): Elsevier; 2007. p. 29-49.](#)
45. [Clowse ME, Magder L, Witter F et al. Hydroxychloroquine in lupus pregnancy. \*Arthritis Rheum\* 2006;54\(11\):3640-7.](#)
46. [Buchanan NM, Toubi E, Khamashta MA et al. Hydroxychloroquine and lupus pregnancy: review of a series of 36 cases. \*Ann Rheum Dis\* 1996;55\(7\):486-8.](#)

47. [Park-Wyllie L, Mazzotta P, Pastuszak A et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. \*Teratology\* 2000;62\(6\):385-92.](#)
48. [Polifka JE, Friendman JM. Teratogen update: azathioprine and 6-mercaptopurine. \*Teratology\* 2002;65\(5\):240-61.](#)
49. [Fischer-Betz R, Specker C, Brinks R et al. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. \*Rheumatology \(Oxford\)\* 2013;52\(6\):1070-6.](#)
50. [American Academy of Pediatrics Committee on Drugs. Transfer of drugs and other chemicals into human milk. \*Pediatrics\* 2001;108\(3\):776-89.](#)
51. [Sau A, Clarke S, Bass J et al. Azathioprine and breastfeeding: is it safe? \*BJOG\* 2007;114\(4\):498-501.](#)
52. [Christensen LA, Dahlerup JF, Nielsen MJ et al. Azathioprine treatment during lactation. \*Aliment Pharmacol Ther\* 2008;28\(10\):1209-13.](#)
53. [Briggs GG, Freeman RK, Yaffe SJ, eds. \*Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk\*. 9th ed. Philadelphia \(PA\): Lippincott Williams & Wilkins; 2011.](#)
54. [Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? \*J Obstet Gynaecol Can\* 2008;30\(12\):1146-8.](#)
55. [Public Health Agency of Canada. \*Canadian immunization guide. Part 3: Vaccination of specific populations\*. Available from: \[www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php\]\(http://www.phac-aspc.gc.ca/publicat/cig-gci/p03-07-eng.php\). Accessed January 17, 2014.](#)
56. [Papaioannou A, Morin S, Cheung AM et al. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. \*CMAJ\* 2010;182\(17\):1864-73.](#)
57. [Culwell KR, Curtis KM, del Carmen Cravioto M. Safety of contraceptive method use among women with systemic lupus erythematosus: a systematic review. \*Obstet Gynecol\* 2009;114\(2 Pt 1\):341-53.](#)
58. [Buyon JP, Petri MA, Kim MY et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. \*Ann Intern Med\* 2005;142\(12 Pt 1\):953-62.](#)

*Therapeutic Choices*. © Canadian Pharmacists Association, 2014. All rights reserved.