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Broad Concepts in Management of Systemic Lupus Erythematosus

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Abstract

Systemic lupus erythematosus is a multisystem autoimmune disease with protean manifestation. Although commonly seen in young women, it can affect men as well as elderly patients. Approach to treatment is multidisciplinary, involves defining the extent of organ involvement, and distinguishing between active manifestations and damage. The mainstay of therapy is judicious use of immunosuppressive medications. Long-term follow-up to address morbidity arising from treatment complications, disease damage, and increased cardiovascular risk is essential.

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Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease capable of affecting any organ system. Systemic lupus erythematosus is rare, with an incidence of 2.2 to 5.6 cases per 100,000 person-years and a prevalence of 24 to 207 cases per 100,000 person-years, and it is more common in women.[1] It presents earlier and in a more severe form in African Americans, Hispanics, Native Americans, and Asians. The diagnosis of SLE should be suspected in any patient with multiorgan symptoms, and after exclusion of infectious and other causes. The 1997 American College of Rheumatology (ACR) classification criteria can be helpful for diagnosis if 4 of 11 criteria are present; the sensitivity of these is 86% and specificity is 93%.[2] The criticism of ACR criteria is that they place emphasis on mucocutaneous manifestations and do not take into account important neurologic manifestations or isolated lupus nephritis. Furthermore, disease manifestations may accrue over time, making it difficult to make a diagnosis early. To address some of these deficiencies, the Systemic Lupus International Collaborating Clinics classification criteria[2] were proposed. A diagnosis of lupus can be made if patients meet 4 or more criteria, with at least 1 clinical and 1 laboratory criteria. Patients with biopsy-proven lupus nephritis with either positive antinuclear or anti-double stranded deoxyribonucleic acid (dsDNA) antibodies can now be classified as having lupus nephritis, which was not possible with the ACR criteria. The sensitivity of Systemic Lupus International Collaborating Clinics criteria is 94% and specificity 92%.

TREAT-TO-TARGET STRATEGY FOR SLE

A group of international experts proposed a "treat-to-target" strategy for lupus. Such a concept is already effective for the management of diabetes and hypertension, in which treatment is tailored to a goal level of glycosylated hemoglobin or target blood pressure, respectively. The international task force[3] put forth 4 overarching principles and 11 recommendations for management on the basis of extensive literature review. Broad goals include achieving remission or low disease activity, preventing flares, minimizing the use of corticosteroids, not treating patients who are serologically active (high anti—double-stranded DNA and hypocomplementemia) but clinically quiescent and addressing factors affecting health-related quality of life such as depression and pain. Early recognition of lupus nephritis and maintaining immunosuppressive therapy for at least 3 years is recommended. Hydroxychloroquine (HCQ) therapy is recommended for all patients with lupus because of its substantial benefits as discussed below.

There are, however, challenges in implementing such a strategy, including lack of a unified definition of remission and a paucity of effective immunosuppressive agents. Clinical heterogeneity of lupus makes a single disease activity assessment instrument difficult, and many available instruments are

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cumbersome to use in clinical practice. Nevertheless, the treat-to-target strategy is a promising concept. Many organizations[4-8] such as the ACR and European League against Rheumatism have published guidelines for the evaluation and management of patients with SLE and of lupus nephritis.

TREATMENT PRINCIPLES

Key Points

- Treatment decisions are often based on the type and severity of organ involvement.
- There is a paucity of clinical trials and evidence-based recommendations for the treatment of many of the lupus manifestations as well as doses of corticosteroids used.
- Distinction should be made between symptoms manifesting from active disease vs disease-related damage.
- Management of comorbidities, attention to bone health, increased cardiovascular risk, and immunization status should be part of general medical care.
- Active discussion about contraception and preconception planning should be undertaken with patients of childbearing potential.

The treatment approach can be summarized as follows.

General Medical Care

Patients with SLE are at an increased risk of several comorbidities secondary to active disease, damage, or treatment-related complications. The risk of cerebrovascular accidents and ischemic heart disease is increased 2.3-fold in patients with SLE.[9] We have reported a 2- to 3-fold increased risk of cerebrovascular accident and peripheral arterial disease in patients with cutaneous lupus as well.[9] There is an increased risk of infections, osteoporosis, and malignant tumors, especially non–Hodgkin lymphoma, lung, liver, vulvar/vaginal, and thyroid malignancies. Attention should be paid to immunization status, diet, physical activity, and management of fibromyalgia and fatigue. It is critical to take a look at the medication list to identify drugs that can either induce lupus or aggravate lupus skin rashes. The drugs we have commonly noted in our medical practice inducing systemic lupus are minocycline, nitrofurantoin, hydralazine, interferons, and tumor necrosis factor inhibitors. (For a comprehensive review of drug-induced systemic and cutaneous lupus, please refer to Chang and Gershwin.[10])

Table 1 summarizes general medical issues relevant to primary care in these patients.

Contraception

Many patients with lupus are young women taking teratogenic medications, and avoidance of pregnancy during active disease is desirable. The main concerns with hormonal methods of contraception are disease flares and risk of thromboembolism. Two large trials[17,18] have compared various methods of hormonal contraception in patients with SLE. Petri and coworkers conducted a double-blind, randomized, noninferiority trial comparing a triphasic combined oral contraceptive (COC) with a placebo in 183 women. The risk of total flares was not different between the groups. The trial by Sánchez-Guerrero et al compared a COC with a progestin-only pill and copper-containing intrauterine device. The disease activity remained stable and was comparable among the 3 groups. Thrombotic events were seen in 4 patients, 2 in each hormonal group; all patients had low-titer antiphospholipid antibodies. Severe infections were seen in 3 patients in the COC group, 2 in the group receiving the progestin-only pill, and 5 (including 2 cases of meningitis) in the intrauterine device group. Both trials excluded patients with severe disease, smokers, history of thrombosis, history of gynecologic cancers, myocardial infarction, and liver disease. Patients with positive antiphospholipid antibodies and lupus anticoagulant were excluded in the trial by Petri and coworkers but not by Sánchez-Guerrero et al. Barrier methods of contraception, hormonal intrauterine device, injectable progestin are other options.

Supportive Therapy

Patients with lupus are photosensitive, and UV light is associated with flares. It is important for all patients to practice sun protection methods and avoid peak UV-B hours from 10 AM to 4 PM. Sunscreens blocking both UV-A and UV-B with a sun protection factor of 50 or more should be applied liberally and at least 20 minutes before sun exposure. Wide-brimmed

TABLE 1. General Medical Care: What the Primary Care Physician Needs to Know

Medical issues	Comments
1. Infection prevention	
A. Review immunization per CDC guidelines a. Annual influenza vaccination and TDap every 10 y b. Pneumococcal vaccination c. HPV vaccination (young patients aged <26 y)	Anecdotal reports of SLE flares in patients receiving immunization; however, multiple studies have shown vaccines to be safe and should not be withheld[11]
B. Screen for hepatitis B, hepatitis C, and HIV before immunosuppression	
C. Consider PJP prophylaxis	Low incidence of 1% of PJP in patients with SLE Number needed to treat is 112 and number needed to harm is 32 owing to adverse reactions to TMP-SMX[12] Recommended for those taking ≥16 mg prednisone or equivalent for ≥8 wk, especially those receiving cyclophosphamide
D. Antibiotic usage	Some antibiotics have sun-sensitizing property and potential to flare cutaneous rashes and occasionally systemic disease (tetracyclines, sulfonamides, and fluoroquinolones) Cutaneous reactions to sulfa antibiotics is higher; use sparingly and with caution, but use not contraindicated[13]
2A. Toxicity of immunosuppressive medication	Familiarity with common toxicities and frequency of laboratory monitoring of rheumatic medications reviewed in reference[14]
2B. Screening for antimalarial eye toxicity	American Academy of Ophthalmology recommendations, revised in 2016 and summarized in reference[15]
3. Bone health: Assess for fracture risk using clinical data, steroid dose, and calculation of FRAX score	Calcium (1200-1500 mg/d) and vitamin D supplements to achieve therapeutic levels (generally 800-1000 units/d) ACR guidelines for prevention and treatment of glucocorticoid-induced osteoporosis.[16] Treatment should be individualized. Generally if ≥7.5 mg of prednisone is used, treatment with bisphosphonates or teriparatide for high-risk individual is recommended
4. Cancer screening	Increased risk of malignant tumors with SLE especially of non–Hodgkin lymphoma, lung, liver, vulvar/vaginal, and thyroid Bladder cancer (especially in smokers) and secondary malignancy with cyclophosphamide use
5. Cardiovascular risk assessment and counseling: Increased risk of cardiovascular disease	Risk increased because of the high prevalence of conventional risk factors such as hypertension, sedentary lifestyle, dyslipidemia, as well as those related to disease activity Counseling to address traditional risk factors is recommended Routine statin therapy to prevent atherosclerosis in low-risk patients is not recommended at this time

ACR = American College of Rheumatology; CDC = Center for Disease Control; FRAX = Fracture Risk Assessment Tool; HIV = human immunodeficiency virus; HPV = human papillomavirus; PJP = *Pneumocystis jiroveci* pneumonia; SLE = systemic lupus erythematosus; TDap = tetanus, diphtheria, pertussis; TMP-SMX = trimethoprim/sulfamethoxazole.

hats and tightly woven clothing should be worn. Specialized sun protection clothing is made by several companies dealing in outdoor gear, and a UV protection factor ranging from 40 to greater than 50 is associated with excellent protection. With such diligent sun avoidance and protection, patients should be given vitamin D supplements. Low levels of vitamin D have been associated with higher lupus activity. Aerobic exercises along with strength training are helpful in the management of fatigue, and fibromyalgia.

Immunosuppressive Therapy

Table 2 lists common drugs used in the treatment of lupus.

Treatment of Mild Disease. Manifestations such as inflammatory arthritis, serositis, and cutaneous rashes are treated with antimalarial

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agents, judicious use of nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids (empirical doses used at 0.25-0.5 mg/kg). Mild cutaneous rashes can be treated with topical steroids as discussed below. Persistent disease usually requires addition of agents such as leflunomide, methotrexate, and mycophenolate mofetil (MMF).

Treatment of Severe Life- or Organ-Threatening Manifestations. Myocarditis, lupus nephritis, severe thrombocytopenia or hemolytic anemia, mesenteric vasculitis, myositis, and central nervous system lupus are a few examples of this. The treatment approach is usually multidisciplinary and involves a team of subspecialists such as nephrologists, hematologists, and neurologists. Although high-dose corticosteroids form the mainstay of management, there are no clinical trials regarding the effective dose. Prednisone (40-60 mg or 1 mg/kg per day) and parenteral steroids such as intravenous (IV) methylprednisolone, with most regimens using 1 g for 3 days, are used. Steroids are associated with considerable adverse effects, and regimens to minimize their use are being evaluated. Ezeonyeji and Isenberg[19] found the efficacy of combination of cyclophosphamide (Cy) and rituximab in patients with newly diagnosed SLE for considerable reduction in steroid dose. Steroid-free regimen of rituximab followed by MMF was also found to be effective in an open-label trial in patients with lupus nephritis.[20] The impressive results have led to this regimen being tested in the RITUXILUP Trial (clinicaltrials.gov identifier: NCT01773616).

The choice of a second-line immunosuppressive agent depends on the clinical manifestation and is noted in Table 2. Refractory disease is often treated with Cy or rituximab therapy. Intravenous immunoglobulin is helpful for the management of immune thrombocytopenia, lupus-associated Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, and congenital heart block. Benefit has also been observed in small reports for autoimmune hemolytic anemia, pregnancy, lupus nephritis, refractory disease, and severe cutaneous rashes.[21] Therapeutic plasma exchange or plasmapheresis has been used in the treatment of neuropsychiatric (NP) manifestations such as myelitis, thrombotic thrombocytopenic purpura, and cytopenias.[22]

Antimalarial Therapy

The beneficial effects of antimalarial agents, namely, HCQ and chloroquine (CQ), in lupus extend beyond their immunomodulatory property, and unless contraindicated, all patients should be receiving antimalarial therapy. Antimalarial agents prevent lupus flares, organ damage, and thrombosis and increase long-term survival. There are beneficial metabolic effects on lipid levels, prevention of diabetes, and improved bone mass.[23] Hydroxychloroquine use during pregnancy is associated with a lower risk of flare. The risk of eye toxicity with HCQ is 1% at 5 years but increases to 20% at 20 years. Risk factors include dosage (HCQ dose, >5 mg/kg of real body weight; CQ dose, >2.3 mg/kg), longer duration of use, tamoxifen, retinal disease, older age, and renal and liver disease. The American Academy of Ophthalmology has recently published revised guidelines for screening for eye toxicity.[15] Baseline screening should include a fundus examination, visual fields, and spectral-domain optical coherence tomography. Annual screening is performed in those at high risk but can be deferred to 5 years in low-risk patients. Screening tests should include automated visual fields and also objective tests such as multifocal electroretinogram and fundus autofluorescence. Color testing, Amsler grid testing, and so on, are not recommended for screening.

MANAGEMENT OF SPECIFIC ORGAN SYSTEMS

We discuss below the treatment approach to manifestation that general internists will commonly encounter. Detailed treatment of all manifestations of lupus is beyond the scope of this review.

Musculoskeletal Manifestations

Musculoskeletal manifestations of lupus include inflammatory arthritis, inflammatory myopathy, and soft tissue rheumatism. Secondary fibromyalgia can be seen in 22% to 25% of patients and can be a source of significant disability.[24] Inflammatory arthritis is symmetric and commonly starts

TABLE 2. Drugs Commonly Used in the Management of Lupus[a]

Medication	Dose	Pregnancy category	Adverse effects	Comments
Glucocorticoids				
1. Prednisone	Mild disease: 0.25-0.50 mg/kg per day Severe disease: 0.5-1 mg/kg per day	C	Weight gain, edema, hypertension, dyslipidemia, cataract, hyperglycemia, infections, skin fragility, mood changes, osteoporosis, delayed healing, steroid myopathy, and osteonecrosis	Life- or organ-threatening lupus, use IVMP
2. Methylprednisolone	IV, 500-1000 mg for 3 days			
Antimalarial agents				
1. Hydroxychloroquine	400 mg/d (or <5 mg/kg of real body weight)	—	Nausea, diarrhea, skin rashes, eye toxicity, neuromyotoxicity, potential for hemolysis in G6PD-positive individuals, cardiomyopathy, heart block, and skin pigmentation	
2. Chloroquine	250 mg (<2.3 mg/kg)	C[b]		
Methotrexate	Oral or subcutaneous 15-25 mg once a week	X	Gastrointestinal adverse effects, hepatotoxicity, hematologic toxicity, infections, lung infiltrates, and malignancy	Avoid use in renal insufficiency, use folic acid 1 mg/d to reduce toxicity, and discontinue 3-6 mo before pregnancy
Leflunomide	20 mg/d, maintenance 10 mg/d	X	Diarrhea, infection, hematologic toxicity, hepatotoxicity, and rare risk of cutaneous lupus exacerbation	Avoid pregnancy until plasma levels are <0.02 mg/L and administer cholestyramine to hasten removal from the body
Mycophenolate mofetil (MMF) mycophenolic acid	Oral 2000-3000 mg/d 720 mg MPA = 1000 mg MMF	X REMS program for prescribers	Diarrhea, infection, neutropenia, infection, and lymphoproliferative disorder	Therapeutic drug level monitoring recommended Discontinue drug at least 6 wk before pregnancy is contemplated
Azathioprine	Oral 1-2.5 mg/kg per day	D	Nausea, abdominal pain, diarrhea, myelotoxicity, elevated levels of liver enzymes, and malignancy	Consider thiopurine S-methyltransferase testing before therapy. Generally safe to use in pregnancy
Cyclophosphamide	500-1000 mg/m^2 IV monthly for 6 mo as induction therapy for LN. 500 mg IV every 2 wk × 3 mo as the Euro-Lupus regimen	X	Nausea, vomiting, cytopenias, infections, hemorrhagic cystitis, gonadal failure malignancy, and bladder cancer	IV dose titrated to achieve a nadir WBC count between 2000 and 4000 cells/m^2 between days 10 and 14. IV Mesna administered to prevent hemorrhagic cystitis. Consider leuprolide therapy for ovarian protection
Rituximab	1000 mg IV for 2 doses separated by 2 wk or 375 mg/m^2 weekly × 4 wk	C	Infusion reaction, anemia, neutropenia, hepatitis B reactivation, and PML	Hepatitis B and tuberculosis screening before infusion and complete immunization before administration

Continued on next page

TABLE 2. Continued

Medication	Dose	Pregnancy category	Adverse effects	Comments
Belimumab	10 mg/kg IV every 2 wk × 3 doses and then every 4 wk	C	Infusion reaction, fever, depression, infection, nausea, and diarrhea	Used for the treatment of arthritis, cutaneous lupus, and hematologic disease. Trials ongoing for LN
Intravenous immunoglobulin	400 mg/kg per day × 5 d	C	Renal dysfunction, thrombosis, aseptic meningitis, and transfusion-associated acute lung injury. Adequate hydration before infusion	Use in patients with concomitant infection, pregnancy, neurologic manifestation, and ITP. Contraindicated in patients with IgA deficiency (use IgA poor preparations).

[a]G6PD = glucose-6-phosphate dehydrogenase; IgA = immunoglobulin A; ITP = immune thrombocytopenia; IV = intravenous; LN = lupus nephritis; MMF = mycophenolic acid; PML = progressive multifocal leukoencephalopathy; REMS = risk evaluation and mitigation strategy; WBC = white blood cell.
[b]Hydroxychloroquine can be safely used in pregnancy with no reports of fetal.

with the involvement of the small joints of hands. Unlike rheumatoid arthritis, many of these deformities are reducible and not associated with bony destruction or erosions. Rheumatoid factor can be positive in 20% of patients with SLE. Rarely, destructive arthritis or overlap with rheumatoid arthritis can be seen and is termed *rhupus*. Many of these patients have positive anti-cyclic citrullinated peptide antibodies.[25] Jaccoud arthropathy, classically described in rheumatic fever, can also be seen in SLE. It refers to deformities of the hands such as swan-neck and "boutonniere" resulting from laxity of ligaments or capsular fibrosis. Inflammatory arthritis is treated with judicious use of NSAIDs or prednisone (dose, 0.25-0.5 mg/kg) and HCQ. Inability to taper prednisone or persistent disease requires the addition of second-line immunosuppressive therapy such as methotrexate and MMF.[26,27] Azathioprine, leflunomide, and cyclosporine are effective as well. The new biological agent belimumab was tested in 2 double-blind randomized controlled trials, namely, BLISS-52 (a study of Belimumab in Subjects with Systemic Lupus Erythematosus) and BLISS-76.[28,29] Pooled data from both trials suggested that belimumab (in doses of 1 mg/kg or 10 mg/kg) considerably improved musculoskeletal signs in comparison to placebo.[30] Although the Exploratory Phase II/III SLE Evaluation of Rituximab trial did not meet its primary end point, registry data from the French AutoImmunity and Rituximab registry[31] revealed that 26 of 50 patients (52%) displayed a complete response and 10 (20%) displayed a partial response in terms of the severity of joint symptoms to treatment with rituximab combined with steroids. In a phase II, double-blind, randomized controlled trial,[32] patients treated with abatacept (10 mg/kg IV) had lower flare rates than did the placebo-treated group. We use abatacept only in patients with refractory disease or those who have failed conventional treatment.

Cutaneous Lupus

The Gilliam classification[33] divides skin lesions in lupus as lupus erythematosus (LE) specific (seen only in lupus) or LE nonspecific (can be seen in other diseases, eg, urticaria). Lupus erythematosus—specific lesions include acute LE with localized (malar) erythema or

generalized erythema, subacute cutaneous lupus with papulosquamous or annular and chronic cutaneous lupus such as discoid lesions.[33] Medications with a potential to flare lupus rashes such as diuretics (hydrochlorothiazide, chlorthiazide, and spironolactone), antihypertensive drugs (diltiazem, verapamil, and nifedipine), NSAIDs (naproxen and piroxicam), antifungal agents (terbinafine, etc), and antirheumatic drugs such as tumor necrosis factor inhibitors should be reviewed.

Topical Therapy. Topical steroids are useful for mild cutaneous rashes. High-potency corticosteroid fluocinonide 0.05% is more effective than hydrocortisone 1%.[34] Treatment with steroids should be time-limited and intermittent. Discoid lesions can be treated with intralesional steroids. Topical tacrolimus 0.1% and pimecrolimus 1%, calcineurin inhibitors, result in improvement of lesions of lupus erythematosus tumidus, subacute cutaneous lupus, and acute cutaneous lupus.[35,36] Tazarotene and tretinoin (Retin A 0.025% and Retin A 0.05% creams) and imiquimod 5% are useful in resistant lesions.

Systemic Therapy. Antimalarial agents are the first-line therapy for all types of cutaneous lupus erythematosus. A clinical effect may be seen as early 2 weeks; if there is no change in 12 weeks, therapy should be escalated. Combination therapy of 2 antimalarial agents (HCQ + CQ) or quinacrine can be tried first. Smokers tend to have more resistant cutaneous lesions, and nicotine may interfere with metabolism of HCQ.[37] Smoking cessation should be actively encouraged. Patients with resistant skin lesions require additional immunosuppressive therapy with weekly methotrexate (dose, 10-25 mg), azathioprine (1-2.5 mg/kg per day), or MMF (2-3 g/d).[38] Dapsone therapy (25-150 mg) is useful for patients with urticarial vasculitis, oral ulcerations, and bullous rash of SLE. Dapsone therapy can result in hemolysis and methemoglobinemia, and a glucose-6-phosphate dehydrogenase level should be checked before therapy.

For refractory disease, lenalidomide and thalidomide have been used because of their immunomodulatory and anti-inflammatory characteristics.[39] In patients with discoid lupus and other types of cutaneous lupus, a complete or marked response was noted in 80% to 90%; however, the lesions relapse after cessation of therapy. Both thalidomide and lenalidomide have thrombotic risk, and this may be an issue in patients with high-titer antiphospholipid antibodies. Acitretin may be helpful in hypertrophic forms of discoid lupus erythematosus. Intravenous immunoglobulin or cyclosporine may be beneficial. In severe cases, biological therapy with belimumab or rituximab is advised. We have occasionally used Cy in patients with disseminated active skin rashes that are often coupled with disease activity elsewhere.

Cardiopulmonary Manifestations

Pericarditis and pleurisy are the most frequent cardiopulmonary manifestations in patients with SLE. Clinical presentation is similar to other causes of serositis. Effusions may occur and are exudative with lymphocytic or neutrophilic predominance. A negative pleural fluid ANA test has a high negative predictive value, and secondary causes such as malignancy or infections (such as TB) need to be excluded.[40] It is important to think of and exclude pulmonary embolism in patients with chest pain, especially those with positive antiphospholipid antibodies.

Serositic manifestations usually respond to antimalarial agents; NSAIDs or prednisone 5 to 15 mg can be used for symptomatic relief. Inability to fully control disease or taper steroids requires addition of second-line agents such as azathioprine, methotrexate, or MMF. Serious manifestations that require aggressive immunosuppressive treatment include myocarditis, lupus pneumonitis, diffuse alveolar hemorrhage, and pulmonary hypertension.

Lupus Nephritis

Forty-five percent of patients will have some degree of renal involvement over their lifetime, and renal involvement is 3 times more common in men, African Americans, Hispanics, and nonwhites.[8] The presence of nephritis is associated with a 2.38-fold increased risk of overall mortality and a 2.37 increased risk of SLE-related mortality.[41] Treatment decisions are guided by clinical presentation, laboratory abnormalities, and histologic subtype on kidney biopsy. The International Society of Nephrology and the Renal Pathology Society

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classification[42] divide lupus nephritis into 6 histologic subtypes.

Therapy for diffuse proliferative glomerulonephritis is usually divided into a period of intense immunosuppression to achieve a clinically meaningful and sustained response and is termed *induction therapy*. Duration usually lasts 3 months but can be extended to 6 months in persistent disease. Induction is followed by a period of less-intensive *maintenance immunosuppression* for a period of 2 to 3 years, with the aim of keeping the patient free of disease activity.

Induction Regimen. The drugs commonly used for initial induction therapy are Cy and MMF. Other agents used for treatment include calcineurin inhibitors, azathioprine, and most recently rituximab. The induction regimen also includes oral prednisone (starting at 1 mg/kg and tapered by 5 mg every 2 weeks) and/or IV methylprednisolone (IVMP; 1 g ×3 days) followed by oral prednisone therapy. Table 3 summarizes the various induction regimens.

Cyclophosphamide. There are 2 regimens for the administration of IVCy: the high-dose National Institutes of Health regimen and the lower-dose Euro-Lupus Nephritis Trial (ELNT) regimen.[43,44] The original high-dose National Institutes of Health regimen, although effective, is associated with considerable adverse effects and the practice of quarterly IVCy pulses for 2 years is obsolete (Table 2). The Euro-Lupus regimen was developed to combat these adverse effects and decrease the cumulative dose of Cy. Although oral Cy is effective in induction treatment of lupus nephritis, we do not use it in clinical practice because of the high incidence of toxicity.

Mycophenolate Mofetil. Recently MMF in doses of 2 to 3 g has been tested as an induction therapy for lupus nephritis and is equivalent to IVCy in inducing remission with fewer adverse effects.[46,54-59] Table 3 summarizes results of the large international trial.[46] The Aspreva Lupus Management Study[46,60] has found better response to MMF than to IVCy in African American and Hispanic patients.

Pharmacokinetic properties vary widely among individuals, and Asians are particularly susceptible to drug toxicity.[60] Studies have found that a trough mycophenolic acid level of greater than 3 to 3.5 μg/L (to convert to μmol/L, multiply by 3.12) or mycophenolic acid area under the curve greater than 35 mg/h per liter is associated with lower disease activity and flares; however, more studies are needed in this field.[61]

We choose MMF as initial therapy and, for reserve, the use of IVCy in patients with rapidly progressive kidney failure, with severe lupus nephritis (creatinine clearance level <30 mL/min; serum creatinine level >3 mg/dl [to convert to μmol/L, multiply by 88.42]), or with widespread (>50%) segmental glomerular necrosis or crescents on biopsy or in those in whom drug compliance may be an issue.

Tacrolimus. Tacrolimus is a calcineurin inhibitor that binds FK506-binding protein 12 and inhibits the phosphatase activity of calcineurin. Most studies on its effectiveness are in Asians, and longer-term follow-up and studies in other racial groups are needed.

Other Agents. Rituximab. Although the Lupus Nephritis Assessment with Rituximab trial,[62] a phase III randomized controlled trial involving anti-CD20 antibody, rituximab plus MMF, and glucocorticoids, did not meet its primary and secondary efficacy end points, the response rate was numerically higher in the rituximab arm than in the MMF arm (57% vs 46%) and highest in African American patients. The negative results were surprising and in contrast to those of several open-label trials and registry studies[63,64] that have found efficacy of resistant SLE treatment with rituximab. The criticism of the Lupus Nephritis Assessment with Rituximab trial is that it was underpowered and that the placebo arm (which was glucocorticoid, MMF 2 g, and placebo infusion) was an effective therapy. An observation period longer than 12 months is sometimes required to see benefit of therapy, and the study did not include patients with refractory lupus nephritis.

Both Cy and MMF are teratogenic, and tacrolimus or azathioprine can be considered during pregnancy. An induction treatment regimen with azathioprine 2 mg/kg plus IVMP 1 g × 3 days at weeks 0, 2, and 6 and

TABLE 3. Treatment of LN[a]

Treatment	Regimen	Comment
Induction therapy for class III[b] and IV[c] LN		
1. IVCy A. High-dose NIH regimen	0.5-1 g/m^2 monthly × 6 doses and then quarterly × 2 y plus IV methylprednisolone (1 g/m^2 BSA) × 3 d followed by 12 consecutive monthly infusions[43]	Combination therapy achieved remission in 85% In follow-up (11 y), Cy therapy superior to methylprednisolone alone in preventing treatment failures and decreasing risk of SCr doubling Cy group: infections (32%-45%), herpes zoster (21%-25%), amenorrhea (55%-57%), and avascular necrosis 18%-33%
2. Low-dose Euro-Lupus Cy regimen	500 mg IV every 2 weeks × 6 doses[44]	Renal remission in 71% vs 54% in those on conventional Cy regimen Amenorrhea (2%), zoster (2%), avascular necrosis (0%), and severe infections (11%) Long-term follow-up, death, doubling of SCr, and ESRD were similar[45]
3. MMF	IVCy monthly pulses (0.5-1 g/m^2 monthly) vs oral MMF 3 g[46]	Response rates with MMF (56.2%) was similar to those in the IVCy group (53%) No differences with respect to improvement in renal function, nonrenal parameters, rates of adverse events, infection, or mortality[45]
4. TAC	Maintenance therapy: 150 Chinese patients, TAC (0.06-0.1 mg/kg per day) or MMF (2-3 g/d) in combination with prednisone for 6 mo followed by AZA × 5 y[46] Combination therapy: TAC (4 mg/d) + MMF (1 g/d) vs IVCy 0.75 (adjusted to 0.5-1.0 g/m^2 monthly × 6 mo)[47]	At 6 mo, CR similar in the TAC (62%) and MMF (59%) groups A nonsignificant trend of higher incidence of renal flares and renal function decline in the TAC group More remissions in the combination group (45.9%) than in the IVCy group (25.6%) at the end of 24 wk Overall response incidence was higher in the multitarget group than in the IVCy group (83.5% vs 63.0%)
Maintenance therapy for class III and IV LN		
1. Cy	IVCy monthly followed by IVCy quarterly (0.5-1 g/m^2; n=20), or AZA (1-3 mg/kg; n=19) or MMF (0.5-3 g; n=20)[48]	72-mo event-free survival rate for the composite end point of death or chronic renal failure higher in the MMF and AZA groups than in the CYC group (P=.05 and P=.009, respectively) Rate of relapse-free survival higher in the MMF group than in the Cy group (P=.02) Cy associated with an increased incidence of hospitalization, amenorrhea, infections, nausea, and vomiting Practice of quarterly IVCy pulses for 2 years is obsolete

Continued on next page

TABLE 3. Continued

Treatment	Regimen	Comment
Maintenance therapy for class III and IV LN, continued		
MMF vs AZA		
1. Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis study	MMF 2 g/d or AZA 2 mg/kg after receiving the low-dose Euro-Lupus Cy regimen[49]	Long-term follow-up of up to 10 y did not show any difference in rates of renal and extrarenal flares or doubling of SCr in this predominantly white cohort[50] Trial was underpowered to show the difference
2. ALMS, maintenance phase	MMF (2 g/d) or AZA (2 mg/kg) as maintenance showed superiority of MMF over AZA in preventing renal flare, doubling of SCr, or death[51]	The ALMS patient group was racially more diverse Nonwhites respond better to MMF; unlike MAINTAIN, only patients who achieved remission were entered into the maintenance phase
Treatment of class V[d] LN		
1. IVCy vs CsA	IVCy (0.5-1 g/m^2 every 2 mo × 6 doses) + prednisone (1 mg/kg per day × 8 wk and then tapered to 0.25 mg/kg per day) or CsA (5 mg/kg per day; duration 11 mo) + prednisone	Higher probability of renal CR + PR: 60% with CYC, 83% with CsA vs 27% with prednisone alone[52] Adverse effects were similar; relapses were more common after discontinuation of cyclosporine
2. IVCy vs MMF	Pooled data from 2 trials (n=84)[53]	Similar rates of remission, relapses, and overall response
Treatment of class VI[e] LN		Renal replacement and supportive therapy, no immunosuppression

[a]ALMS = Aspreva Lupus Management Study; AZA = azathioprine; BSA = body surface area; CR = complete remission; CsA = cyclosporine A; Cy = cyclophosphamide; ESRD = end-stage renal disease; IV = intravenous; IVCy = intravenous cyclophosphamide; LN = lupus nephritis; MAINTAIN = Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis; MMF = mycophenolate mofetil; NIH = National Institutes of Health; PR = partial remission; SCr = serum creatinine; TAC = tacrolimus.

[b]Class III = subendothelial immune deposits and proliferative changes in <50% of glomeruli.

[c]Class IV = subendothelial deposits and proliferative glomerular changes involving ≥50% of glomeruli.

[d]Class V = subepithelial immune deposits and membranous thickening of glomerular capillaries.

[e]Class VI = advanced sclerosis of >90% glomeruli.

oral prednisone exhibited comparable efficacy with IVCy at 2 years. However, the azathioprine arm exhibited significant relapses, sustained doubling of creatinine, and worsening chronicity scores on kidney biopsy on long-term follow-up.[65]

Maintenance Therapy for Class III and IV Lupus Nephritis. Maintenance therapy is recommended to consolidate renal response and prevent flares. There are no data to guide duration of immunosuppressive therapy beyond 3 years, and continuing treatment should be individualized. Agents that have been used for maintenance include Cy (Table 2); however, this is not a favored agent because of cumulative toxicity. Mycophenolate mofetil and azathioprine have been compared head to head in the Mycophenolate Mofetil Versus Azathioprine for Maintenance Therapy of Lupus Nephritis study and the Aspreva Lupus Management Study[50,51] (Table 2), and MMF is found to be equivalent or superior to azathioprine, respectively.[50,51] Small studies[66] have used cyclosporine (2.5-3 mg/kg) or tacrolimus as maintenance regimen; however, more long-term data are needed.

Supportive Therapy. The use of HCQ is associated with lower nephritis flare rates, and a reduced risk of developing renal disease and thrombotic complications.[5,67] Renal failure is associated with an increased risk of HCQ toxicity, and dose adjustments may need to be made. The use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers is recommended in nonpregnant patients with hypertension or proteinuria levels of 0.5 g/24 h or more for their renoprotective effect. Target blood pressure of 130/80 mm Hg or lower is recommended to delay progression of renal disease. Attention to cardiovascular risk factors and appropriate management is recommended. Statin therapy for low-density lipoprotein level greater than 100 mg/dL (to convert to mmol/L, multiply by 0.0259) is recommended, although its benefit in patients with SLE has not been proven.

Neuropsychiatric Lupus

Neuropsychiatric manifestations constitute severe complications of SLE, contributing substantially to increased morbidity and mortality in these patients. In most patients, NPSLE presents early in disease course in the first 2 years, and in 39% to 50%, it can be the first manifestation of disease. The ACR[68] has published a set of case definitions for 19 NPSLE syndromes that include central nervous system manifestation, psychiatric manifestation, and peripheral nervous system manifestation of SLE. Patients presenting with longitudinal transverse myelitis, involving at least 3 vertebral segments, and optic neuritis commonly have antineuromyelitis optica antibodies directed against aquaporin-4.[69] Coexistent Sjögren syndrome may be present. Identification of antineuromyelitis optica antibodies has important prognostic significance and portends a severe disease course with frequent relapses.

The diagnostic and therapeutic approach consists of determining whether the event is a manifestation of SLE (primary NPLE), a complication of disease or therapy, a coincidental association, or secondary to other causes such as drugs, infections, and metabolic. Treatment is often directed by whether the manifestations are inflammatory or thrombotic or mixed (Figure 1). Patients with a predominantly inflammatory process (acute confusional state, aseptic meningitis, and optic neuritis) are often treated with immunosuppressive therapy, whereas predominantly thrombotic manifestations (eg, stroke due to antiphospholipid antibody syndrome) require antiplatelet and/or anticoagulation therapy.

There is a paucity of evidence-based guidelines, and most recommendations are based on small cohorts or case series. Steroids including IV methylprednisolone (1 g × 3 days) form first-line treatment. Several case series[70-74] have found good improvement in NP manifestation with Cy. The dose and route used have been variable; Mok et al[73] used a combination of prednisone and oral Cy (1-2 mg/kg for 6 months) followed by azathioprine maintenance and reported complete response in all 13 patients. A retrospective review[71] of use of IVCy monthly (dose, 250-1000 mg/m^2) in 31 patients reported response in 61% of patients. In patients with mild manifestations, improvement was seen as early as 4 days but on average 4 monthly IVCy infusions (range, 2-9 months) were required for response.

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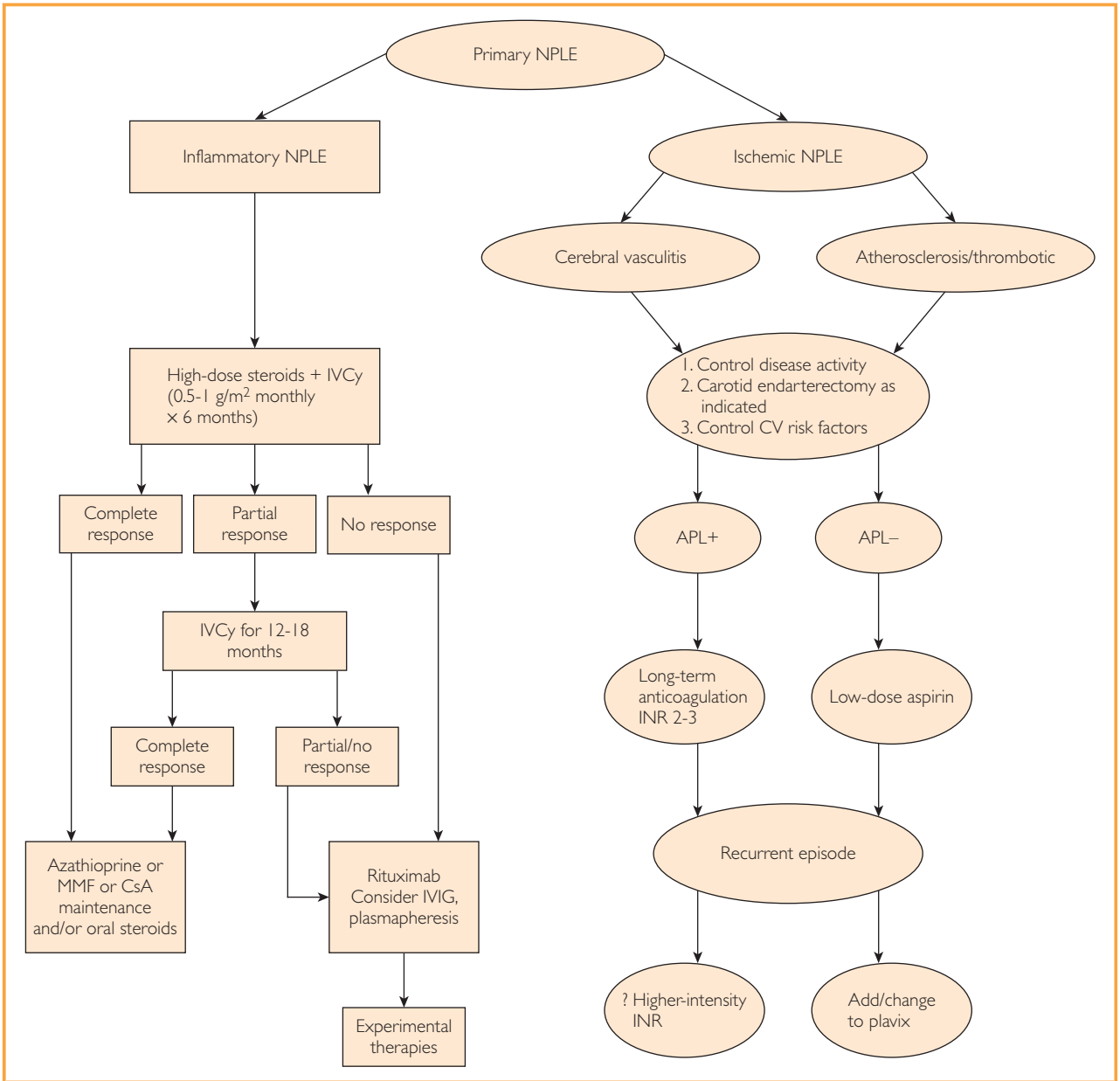

FIGURE 1. Treatment of primary NPLE. APL = antiphospholipid antibody; CsA = cyclosporine A; CV = cardiovascular; INR = international normalized ratio; IVCy = intravenous cyclophosphamide; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; NPLE = neuropsychiatric lupus erythematosus; ? = indicates unclear efficiency.

Cyclophosphamide is the only therapy that has been tested in a small controlled clinical trial that compared IVCy and IV methylprednisolone in patients with severe NP manifestations.[75] Patients received either IVCy (0.75 g/m^2 body surface area, monthly × 1 year and then quarterly for additional year, plus oral prednisone) or IVMP (1 g × 3 days, monthly × 4 month, bimonthly × 6 months and then every 3 months × 1 year). There was a lesser number of treatment failures in the Cy group (1 of 19) than in the IVMP group (7 of 13). Cyclophosphamide was more effective than MP in the management of seizures, optic neuritis, brainstem lesions, and peripheral neuropathy, but a clear benefit over MP was not apparent for transverse

myelitis and coma; however, the numbers were extremely small.

Isolated case reports or series[76-79] have found good response of MMF (combined with IV dexamethasone) in a patient with myelitis and cerebral vasculitis or for psychotic manifestation (with IV immunoglobulin). Others[80,81] have reported only modest results of mycophenolate in NP lupus. Rituximab was used as an initial therapy in 6 patients with myelopathy, with complete response seen in 4 patients[82]; most published reports have been in patients with refractory disease. In a systematic review,[83] complete remission or partial remission was seen in 85% of patients after 1 cycle of treatment; however, relapses were noted in 45% (median, 9.5 months; range, 4-22 months) despite a maintenance regimen. Intravenous immunoglobulin has been used as adjunctive therapy, and the response is usually rapid.[84,85] Plasmapheresis has also been used in patients with manifestations such as acute confusional state, seizure disorder, cerebrovascular disease, cognitive dysfunction, demyelinating syndrome, intractable headache, myelopathy, aseptic meningitis, and psychosis.[86] Improvement occurred in 54% to 74% and usually in the first week of treatment.[86,87] A daily or every other day course, 3 to 6 times, is sufficient to see response in lupus.[88] It is commonly combined with immunosuppressive therapy, with published series on cyclosporine and Cy.[89] Azathioprine was not found to be useful in short-term treatment, but may be useful as a maintenance agent in NPLE.[73,90] Further studies are needed to define the differences among various second-line drugs.

Supportive Therapy. Symptomatic therapy such as anticonvulsants (for seizures), antidepressants/anxiolytic agents (for mood disorders) or antipsychotic agents (for psychosis), and antihypertensive drugs should be used, as indicated. Hydroxychloroquine should be considered for primary prevention of thrombosis in patients with SLE and persistently high-titer positive antiphospholipid antibodies.[91] Some studies[92] have also reported benefits of low-dose aspirin as primary prophylaxis in patients with SLE. Antiplatelet therapy and/or anticoagulation was beneficial for secondary prevention of thrombotic manifestations.[93,94] These adjunct therapies may be effective for some patients with chorea, transverse myelitis, and ischemic optic neuropathy.[95-98]

Hematologic Issues

Hematologic abnormalities constitute an important manifestation of lupus often paralleling activity of disease. Figure 2 depicts the management of autoimmune hemolytic anemia and cytopenia.[99-105]

Reproductive Issues

Pregnancy. Active discussion with patients about pregnancy planning should be held. Although most women have successful pregnancy, we discourage pregnancy in patients with active lupus nephritis, severe or symptomatic pulmonary hypertension (estimated systolic pulmonary artery pressure >50 mm Hg), renal failure, heart failure, stroke in past 6 months, and severe restrictive lung disease (forced vital capacity <1 L). Disease flares can be seen in 30% to 50% of patients, with rates being considerably lower when the disease is in remission. Most of these are minor flares. Several studies have found that active disease 6 months before pregnancy, lupus nephritis, and discontinuation of antimalarial agents are a risk factor for adverse maternal outcomes. Medical complications such as sepsis, postpartum bleeding, pulmonary embolism, and deep venous thrombosis are more common in SLE. There is increased incidence of preterm labor, intrauterine growth retardation, premature rupture of membranes, and preeclampsia.[106] The postpartum period may be characterized by disease flares, failure of lactation, thrombotic complications, and postpartum bleeding.[107]

Neonatal Lupus and Congenital Heart Block. Anti-Ro and anti-La antibodies can be cardiotoxic to the fetus, and varying degrees of congenital heart block can be seen in 1% to 3% of children born to women who are seropositive.[108] The risk of recurrence increases to 18% in subsequent pregnancies. The heart block can be transient or complete, leading to heart failure in utero and hydrops fetalis. There is no known effective therapy for complete heart block. Corticosteroids, particularly fluorinated steroids such as

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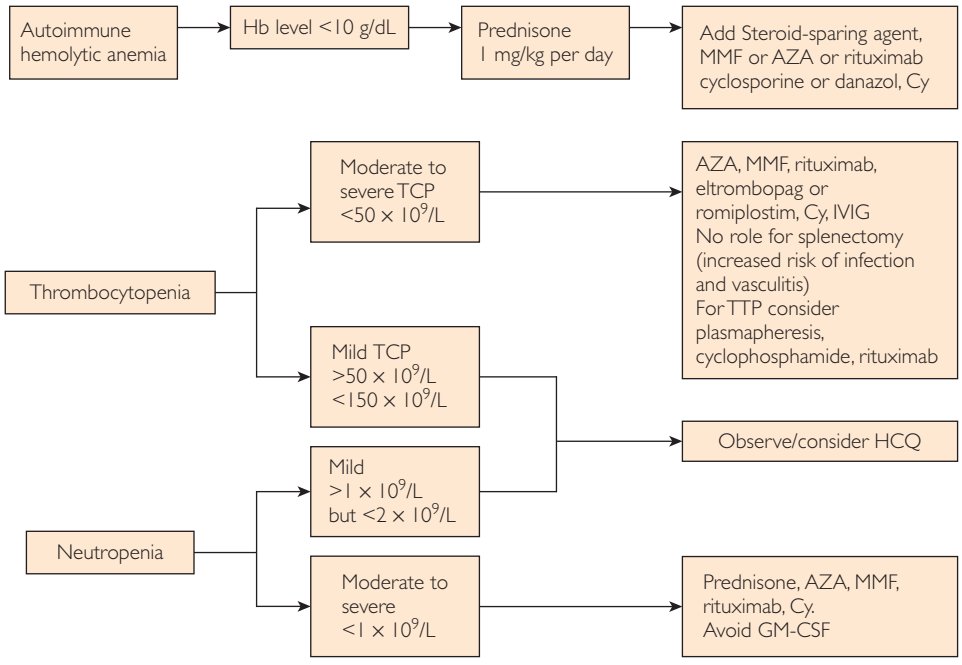

FIGURE 2. Management of hematologic lupus manifestations. AZA = azathioprine; Cy = cyclophosphamide; Cy = cyclophosphamide; GM-CSF = granulocyte-macrophage colony-stimulating factor; Hb = hemoglobin; HCQ = hydroxychloroquine; IVIG = intravenous immunoglobulin; MMF = mycophenolate mofetil; TCP = thrombocytopenia; TTP = thrombotic thrombocytopenic purpura. SI conversion factor: To convert hemoglobin value to mmol/L, multiply by 0.0626.

dexamethasone or betamethasone that can cross the transplacental barrier, are administered. Intravenous immunoglobulin has been used for treatment; however, a recent trial to prevent congenital heart block was negative.[109] Hydroxychloroquine use during pregnancy is associated with a reduced risk of fetal development of neonatal lupus.[110] Seropositive women without a previous child born with congenital heart block should undergo serial fetal echocardiograms at 16, 18, 20, 22, and 24 weeks of pregnancy.

Antiphospholipid Antibody–Positive Mother. Antiphospholipid antibodies are well-known risk factors for thromboembolism and pregnancy loss. In a large multiethnic cohort,[111] the presence of lupus anticoagulant was associated with adverse pregnancy outcomes. The presence of antiphospholipid antibody also increases risk of preeclampsia, hypertension, intrauterine growth restriction, and fetal death. Management goals are to reduce the risk of thromboembolic events and prevent fetal loss. Low-dose aspirin can reduce the risk of preeclampsia, but some studies[111,112] have not found a reduction in adverse obstetrical outcome in asymptomatic patients and decision to use aspirin should be individualized. The antiphospholipid antibody–positive patient with history of thrombotic episodes should be warned about its embryotoxicity before conception and switched to low-molecular-weight heparin (LMWH) as soon as pregnancy is confirmed. Although unfractionated heparin and LMWH are equal in efficacy, LMWH is preferred because of lower risk of thrombocytopenia and osteoporosis. Treatment is with low-dose aspirin plus therapeutic dose of LMWH (eg, enoxaparin 1 mg/kg subcutaneously [SC] or dalteparin 100 units/kg SC every 12 hours or enoxaparin 1.5 mg/kg per day or dalteparin 200 units/kg SC every day). Anticoagulation should be continued for 6 weeks after delivery. Women with a positive obstetric history

(recurrent early miscarriages, fetal death [>10 weeks], or prior early delivery [<34 weeks] due to severe preeclampsia or placental insufficiency) but no thrombotic episodes are treated with low-dose aspirin and prophylactic LMWH (enoxaparin 40 mg/d or dalteparin 5000 units/d SC).[107]

RECOMMENDATIONS

Management of SLE is exceedingly complex and associated with significant morbidity from disease and medication complications. Development of new effective therapeutics is greatly needed. Current research is focused on targeting the B and long-lived plasma cells, the interferon pathway and receptors, signaling molecules in T and B cells, and epigenetic targets.

Abbreviations and Acronyms: **ACR** = American College of Rheumatology; **COC** = combined oral contraceptive; **CQ** = chloroquine; **Cy** = cyclophosphamide; **HCQ** = hydroxychloroquine; **IV** = intravenous; **IVMP** = intravenous methyl prednisone; **LE** = lupus erythematosus; **LMWH** = low-molecular-weight heparin; **MMF** = mycophenolate mofetil; **NP** = neuropsychiatric; **NSAID** = nonsteroidal anti-inflammatory drug; **SC** = subcutaneously; **SLE** = systemic lupus erythematosus

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