ADAMS13. Plasma exchange or extensive plasmapheresis is usually life-saving; most authorities recommend concomitant glucocorticoid therapy; there is no evidence that cytotoxic drugs are effective.

Lupus Dermatitis Patients with any form of lupus dermatitis should minimize exposure to ultraviolet light, using appropriate clothing and sunscreens with a sun protection factor of at least 30. Topical glucocorticoids and antimalarials (such as hydroxychloroquine) are effective in reducing lesion severity in most patients and are relatively safe. Systemic treatment with retinoic acid is a useful strategy in patients with inadequate improvement on topical glucocorticoids and antimalarials; adverse effects are potentially severe (particularly fetal abnormalities), and there are stringent reporting requirements for its use in the United States. Extensive, pruritic, bullous, or ulcerating dermatitides usually improve promptly after institution of systemic glucocorticoids; tapering may be accompanied by flare of lesions, thus necessitating use of a second medication such as hydroxychloroquine, retinoids, or cytotoxic medications such as methotrexate, azathioprine, or mycophenolate mofetil. In therapy-resistant lupus dermatitis there are reports of success with topical tacrolimus (caution must be exerted because of the possible increased risk for malignancies) or with systemic dapsone or thalidomide (the extreme danger of fetal deformities from thalidomide requires permission from and supervision by the supplier).

PREVENTIVE THERAPIES

Prevention of complications of SLE and its therapy include providing appropriate vaccinations (the administration of influenza and pneumococcal vaccines has been studied in patients with SLE; flare rates are similar to those receiving placebo) and suppressing recurrent urinary tract infections. Vaccination with attenuated live viruses is generally discouraged in patients who are immunosuppressed. Strategies to prevent osteoporosis should be initiated in most patients likely to require long-term glucocorticoid therapy and/or with other predisposing factors. Postmenopausal women can be protected from steroid-induced osteoporosis with either bisphosphonates or denosumab. Safety of long-term use of these strategies in premenopausal women is not well established. Control of hypertension and appropriate prevention strategies for atherosclerosis, including monitoring and treatment of dyslipidemias, management of hyperglycemia, and management of obesity, are recommended.

EXPERIMENTAL THERAPIES

Studies of highly targeted experimental therapies for SLE are in progress. They include targeting (1) activated B lymphocytes with anti-CD22 or TACI-Ig, (2) inhibition of IFN-α, (3) inhibition of B/T cell second signal coactivation with CTLA-Ig, (4) inhibition of innate immune activation via TLR7 or TLR7 and 9, (5) induction of regulatory T cells with peptides from immunoglobulins or autoantigens; (6) suppression of T cells, B cells, and monocyte/macrophages with laquinimod; and (7) inhibition of lymphocyte activation by blockade of Jak/Stat. A few studies have used vigorous untargeted immunosuppression with high-dose cyclophosphamide plus anti-T cell strategies, with rescue by transplantation of autologous hematopoietic stem cells for the treatment of severe and refractory SLE. One U.S. report showed an estimated mortality rate over 5 years of 15% and sustained remission in 50%. It is hoped that in the next edition of this text, we will be able to recommend more effective and less toxic approaches to treatment of SLE based on some of these strategies.

PATIENT OUTCOMES, PROGNOSIS, AND SURVIVAL

Survival in patients with SLE in the United States, Canada, Europe, and China is approximately 95% at 5 years, 90% at 10 years, and 78% at 20 years. In the United States, African Americans and Hispanic Americans with a mestizo heritage have a worse prognosis than whites, whereas Africans in Africa and Hispanic Americans with a Puerto Rican origin do not. The relative importance of gene mixtures and environmental differences accounting for ethnic differences is not known. Poor prognosis (~50% mortality in 10 years) in most series is associated with (at the time of diagnosis) high serum creatinine levels (>124 μmol/L [>1.4 mg/dL]), hypertension, nephrotic syndrome (24-h urine protein excretion >2.6 g), anemia (hemoglobin <124 g/L [<12.4 g/dL]), hypoalbuminemia, hypocomplementemia, antiphospholipid antibodies, male sex, ethnicity (African American, Hispanic with mestizo heritage), and low socioeconomic status. Data regarding outcomes in SLE patients with renal transplants show mixed results: some series show a twofold increase in graft rejection compared to patients with other causes of ESRD, whereas others show no differences. Overall patient survival is comparable (85% at 2 years). Lupus nephritis occurs in approximately 10% of transplanted kidneys. Disability in patients with SLE is common due primarily to chronic fatigue, arthritis, and pain, as well as renal disease. As many as 25% of patients may experience remissions, sometimes for a few years, but these are rarely permanent. The leading causes of death in the first decade of disease are systemic disease activity, renal failure, and infections; subsequently, thromboembolic events become increasingly frequent causes of mortality.

DRUG-INDUCED LUPUS

This is a syndrome of positive ANA associated with symptoms such as fever, malaise, arthritis or intense arthralgias/myalgias, serositis, and/or rash. The syndrome appears during therapy with certain medications and biologic agents, is predominant in whites, has less female predilection than SLE, rarely involves kidneys or brain, is rarely associated with anti-dsDNA, is commonly associated with antibodies to histones, and usually resolves over several weeks after discontinuation of the offending medication. The list of substances that can induce lupus-like disease is long. Among the most frequent are the antiarrhythmics procainamide, disopyramide, and propafenone; the antihypertensive hydralazine; several angiotensin-converting enzyme inhibitors and beta blockers; the antithyroid propylthiouracil; the antipsychotics chlorpromazine and lithium; the anticonvulsants carbamazepine and phenytoin; the antibiotics isoniazid, minocycline, and nitrofurantoin (Macrodantin); the antirheumatic sulfasalazine; the diuretic hydrochlorothiazide; the antihyperlipidemics lovastatin and simvastatin; and IFNs and TNF inhibitors. ANA usually appears before symptoms; however, many of the medications mentioned above induce ANA in patients who never develop symptoms of drug-induced lupus. It is appropriate to test for ANA at the first hint of relevant symptoms and to use test results to help decide whether to withdraw the suspect agent.

379 Antiphospholipid Syndrome

Haralampos M. Moutsopoulos, Panayiotis G. Vlachoyiannopoulos

DEFINITIONS

Antiphospholipid syndrome (APS) is an autoantibody-mediated acquired thrombophilia characterized by recurrent arterial or venous thrombosis and/or pregnancy morbidity. The major autoantibodies detected in the patient's sera are directed against phospholipid (PL)-binding plasma proteins, mainly against a 43-kDa plasma apolipoprotein known as β2 glycoprotein I (β2GPI) and prothrombin. The plasma concentration of β2GPI is 50–200 μg/mL. β2GPI consists of 326 amino acids arranged in five domains (I through V). Domain V forms a positively charged patch, suitable to interact with negatively charged PL. In plasma, β2GPI has a circular conformation with domain V binding to and concealing the B cell epitopes lying on domain I. Another group of antibodies termed *lupus anticoagulant* (LA) elongate clotting times in vitro; this elongation is not corrected by adding normal plasma to the detection system (Table 379-1). Patients with APS often possess antibodies recognizing *Treponema pallidum* PL/cholesterol complexes, which are detected as biologic false-positive serologic tests for syphilis