It is important to realize the potential risks of these immunosuppressive monoclonal antibodies. Natalizumab is a humanized IgG antibody against an α4 integrin that inhibits leukocyte migration into tissues and has been approved for treatment of multiple sclerosis in the United States. Both it and anti-CD20 (rituximab) have been associated with the onset of progressive multifocal leukoencephalopathy (PML)—a serious and usually fatal CNS infection caused by JC polyomavirus. Efalizumab, a humanized IgG monoclonal antibody previously approved for treatment of plaque psoriasis, has now been taken off the market due to reactivation of JC virus leading to fatal PML. Thus, use of any currently approved immunosuppressant immunotherapies should be undertaken with caution and with careful monitoring of patients according to FDA guidelines.

Tolerance Induction Specific immunotherapy has moved into a new era with the introduction of soluble CTLA-4 protein into clinical trials. Use of this molecule to block T cell activation via TCR/CD28 ligation during organ or bone marrow transplantation has showed promising results in animals and in early human clinical trials. Specifically, treatment of bone marrow with CTLA-4 protein reduces rejection of the graft in HLA-mismatched bone marrow transplantation. In addition, promising results with soluble CTLA-4 have been reported in the downmodulation of autoimmune T cell responses in the treatment of psoriasis; and it is being studied for treatment of systemic lupus erythematosus (Chap. 378).

Intravenous Immunoglobulin (IVIg) IVIg has been used successfully to block reticuloendothelial cell function and immune complex clearance in various immune cytopenias such as immune thrombocytopenia (Chap. 140). In addition, IVIg is useful for prevention of tissue damage in certain inflammatory syndromes such as Kawasaki disease (Chap. 385) and as Ig replacement therapy for certain types of immunoglobulin deficiencies (Chap. 374). In addition, controlled clinical trials support the use of IVIg in selected patients with graft-versus-host disease, multiple sclerosis, myasthenia gravis, Guillain-Barré syndrome, and chronic demyelinating polyneuropathy.

Stem Cell Transplantation Hematopoietic stem cell transplantation (SCT) is now being comprehensively studied to treat several autoimmune diseases, including systemic lupus erythematosus, multiple sclerosis, and scleroderma. The goal of immune reconstitution in autoimmune disease syndromes is to replace a dysfunctional immune system with a normally reactive immune cell repertoire. Preliminary results in patients with scleroderma and lupus have showed encouraging results. Controlled clinical trials in these three diseases are now being launched in the United States and Europe to compare the toxicity and efficacy of conventional immunosuppression therapy with that of myeloablative autologous SCT. Recently, SCT was used in the setting of HIV-1 infection. HIV-1 infection of CD4+ T cells requires the presence of surface CD4 receptor and the chemokine receptor 5 (CCR5) co-receptor. Studies have demonstrated that patients who are homozygous for a 32-bp deletion in the CCR5 allele do not express CD4+ T cell CCR5 and thus are resistant to HIV-1 infection with HIV-1 strains that use this co-receptor. Stem cells from a homozygous CCR5 delta32 donor were transplanted to an HIV-infected patient following standard conditioning for such transplants, and the patient has maintained long-term control of the virus without antiretrovirals. Thus, a number of recent insights into immune system function have spawned a new field of interventional immunotherapy and have enhanced the prospect for development of more specific and nontoxic therapies for immune and inflammatory diseases.