Antibody Cures

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Pemphigus

Pemphigus vulgaris (PV) is a potentially fatal autoimmune blistering disease that affects the skin, oral cavity and other mucosal surfaces. There are intraepithelial vesicles with acantholysis and an intact basal layer. The pathogenesis involves an autoimmune reaction against desmoglein-3 (Dsg3) that is one of the cell-cell adhesion molecules of the desmosome (a major intercellular adhesive junction).

Conventional therapy of PV consists of high-dose corticosteroids, immunosuppressive agents, and intravenous immune globulin (IVIG). Ahmed et al,[1] studied 11 patients with refractory PV involving 30% body-surface area (BSA) who had inadequate responses to conventional therapy. They treated the patients with rituximab, a humanized monoclonal antibody against B-cell antigen CD20 that depletes the antibody producing B-cells. IVIG was also given with the rationale to provide protection from reduced immunoglobulin levels which rituximab causes. The regimen was two cycles of rituximab (375 mg/ m2 of BSA) once weekly for 3 weeks and IVIG (2 g per kilogram of body weight) in the fourth week. This was followed by a monthly infusion of rituximab and IVIG for 4 consecutive months. The regimen of two cycles of induction therapy followed by consolidation was designed to eliminate pathogenic antibody-producing B-cells and then to destroy memory B cells.[1]

Of 11 patients, 9 had rapid resolution of lesions and a clinical remission lasting 2-3 years. All immunosuppressive therapy, including prednisone, could be discontinued before ending rituximab treatment in all patients. Two patients were treated with rituximab only during recurrences and had sustained remissions. Titers of IgG4 antikeratinocyte antibodies correlated with disease activity. Peripheral-blood B cells became undetectable shortly after initiating rituximab therapy but subsequently returned to normal values. Side effects that have been associated with rituximab were not observed, nor were infections. This study shows that combination of rituximab and IVIG is effective in patients with refractory pemphigus vulgaris.[1]

Exfoliative toxins produced by Staphylococcal aureus, which causes Staphylococcal Scalded Skin Syndrome (SSSS) and bullous impetigo, specifically digest Dsg1.[2] A subset of patients with SSSS develop a low titer of anti-Dsg1 IgG autoantibodies.[2] A mutation in DSG1 gene causes striate palmoplantar keratoderma and a mutation in DSG4 gene causes inherited hypotrichosis. It is interesting to note that quite varied pathology results from destruction or dysfunction of Dsg(s) and the desmosome.

1. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med. 2006;355:1772-9.
2. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. N Engl J Med. 2006;355:1800-10.

Paroxysmal nocturnal hemoglobinuria (PNH)

PNH is an uncommon form of hemolytic anemia and results from the clonal expansion of hematopoietic stem cells that have somatic mutations in the X-linked gene PIG-A (phosphatidylinositol glycan anchor biosynthesis, class A). PIG-A mutations cause an early block in the synthesis of glycosylphosphatidylinositol (GPI) anchors, which tether many proteins to the cell surface. Intravascular hemolysis is a prominent feature of PNH and is the consequence of the absence of the GPI-linked complement regulatory protein CD59, which normally blocks the formation of the membrane-attack complex (complement cascade). Free plasma hemoglobin released, scavenges nitric oxide resulting in clinical manifestations such as thrombosis, abdominal pain, dysphagia, erectile dysfunction, and pulmonary hypertension.

In a preliminary study Hillmen et al showed that eculizumab, a humanized monoclonal antibody against terminal complement protein C5 that inhibits terminal complement activation, reduced intravascular hemolysis and the patients' transfusion requirements.[1] Here they conducted a double-blind, randomized, placebo-controlled, multicenter, phase 3 trial of eculizumab in PNH.[2] Patients received IV eculizumab 600 mg weekly for 4 weeks, followed 1 week later by a 900-mg dose and then 900 mg every other week through week 26. Eighty-seven patients underwent randomization.[2]

Intravascular hemolysis was monitored with serum LDH levels which decreased 10-fold to within normal limits. Stabilization of hemoglobin levels in the absence of transfusions was achieved in 49% of the patients assigned to eculizumab and none (0 of 44) of those assigned to placebo ($P<0.001$). In the 6-month period before the study, the mean number of units of packed red cells transfused (PRBC) were 9.6±0.6 and 9.7±0.7 in the eculizumab and placebo cohorts respectively. After 26 weeks of therapy the mean numbers of PRBC units transfused were 3.0±0.7 and 11.0±0.8 respectively.[2]

Clinically significant improvements were also found in the quality of life, as measured by scores on the Functional Assessment of Chronic Illness Therapy-Fatigue instrument ($P<0.001$) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.[2]

1. Hillmen P, Hall C, Marsh JC. Effect of eculizumab on hemolysis and transfusion requirements in patients with paroxysmal nocturnal hemoglobinuria. N Engl J Med 2004;350:552-59.
2. Hillmen P, Young NS, Schubert J. The complement inhibitor eculizumab in paroxysmal nocturnal hemoglobinuria. N Engl J Med. 2006;355:1233-43.

Multiple sclerosis

Fingolimod (FTY720) is a new oral immunomodulating agent preventing lymphocytes from moving out of the secondary lymphoid tissue into circulation, thereby reducing their numbers in the CNS. Kappos et al, evaluated FTY720 for the treatment of relapsing multiple sclerosis.[1] They randomized 281 patients to receive two different doses of oral fingolimod or a placebo once daily. These patients were followed for 6 months with MRI and clinical evaluations. A total of 255 patients completed the core study. The median total number of gadolinium-enhanced lesions on MRI was lower with low-dose FTY720 (1.25 mg) than high dose FTY720 or placebo, which was inferior to both ($P<0.001$). The relapse rate in the treated groups was half that of the placebo group ($P<0.01$). Several adverse events were noted in the treated groups including nasopharyngitis, dyspnea, decreased FEV1, bradycardia, headache, asymptomatic elevation of LFTs, and a case of the posterior reversible encephalopathy syndrome. The study concluded that fingolimod may be a valuable treatment option in relapsing MS though its correct dose and adverse events need to be evaluated further.

1. Kappos L, Antel J, Comi G. for FTY720 D2201 Study Group. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med. 2006;355:1124-40.

DVT anticoagulation monitoring

The optimal duration of oral anticoagulation in patients with idiopathic venous thromboembolism is uncertain. Testing of D-dimer levels may play a role in the assessment of the need for prolonged anticoagulation. Palareti et al. performed D-dimer testing 1 month after the discontinuation of anticoagulation in patients with a first episode of proximal deep-vein thrombosis (DVT) or pulmonary embolism (PE) who had received warfarin for at least 3 months. Patients with a normal D-dimer level did not resume anticoagulation, whereas those with an abnormal D-dimer level were randomly assigned either to resume or to discontinue treatment. Since the risk of recurrence is greatest in the first 6 to 12 months after the initial episode of thromboembolism, protracted anticoagulation may carry increased risk of bleeding. After a 1.4-year follow up thromboembolism vs bleeding was assessed as outcome measures.

A total of 18 events (15.0%) occurred among the 120 patients who stopped anticoagulation as compared with 3 events (2.9%) among the 103 patients who resumed anticoagulation ($P=0.02$). Thromboembolism recurred in 24 (6.2%) of 385 patients with a normal D-dimer level. The study concluded that patients with an abnormal D-dimer level 1 month after the discontinuation of anticoagulation have a significant incidence of recurrent venous thromboembolism, which is reduced by the resumption of anticoagulation. The optimal course of anticoagulation in patients with a normal D-dimer level has not been clearly established.

1. Palareti G, Cosmi B, Legnani C, Tosetto A, Brusi C, Iorio A, Pengo V, Ghirarduzzi A, Pattacini C, Testa S, Lensing AW, Tripodi A; PROLONG Investigators. D-dimer testing to determine the duration of anticoagulation therapy. N Engl J Med. 2006;355:1780-9.