Current Therapeutic Modalities of Immunobullous Lesions

Immunobullous mucosal disorders manifest in the skin and mucous membranes and are clinically characterized by the appearance of vesicle or bulla and secondary erosions. Both vesicles and bullae are fluid-filled lesions, and they are distinguished by size, with vesicles being <1 cm and bulla being >1 cm in diameter. Immunobullous disorders have a common mechanism involving binding of autoantibodies to specific adhesion molecules in epidermal desmosomes or in dermo–epidermal basement membrane zone. The binding of circulating autoantibodies and the induction of an inflammatory reaction in the area of target structures lead to loss of adhesion.[1]

Pemphigus vulgaris (PV) is a chronic, mucocutaneous, autoimmune bullous disease with an incidence of 0.5–3.2/100,000 population. The word "pemphigus" has its roots in the Greek "pemphix," which means blister; Hippocrates first used it in 460–370 BC.[2] The clinical features include superficial, ragged erosions and ulcerations on the oral mucosal surface, which is preceded by thin, friable vesicles. The gold standard diagnosis of PV is direct immunofluorescence microscopy, which can detect tissue-bound autoantibodies. Corticosteroids have been the mainstay for the treatment. Intravenous immunoglobulin (IVIG) and pulse therapy (suprapharmacologic doses of drugs in an intermittent manner) have been used recently in the treatment of pemphigus.[3] The drugs commonly used in the pulse therapy are dexamethasone-cyclophosphamide, dexamethasone-azathioprine, and dexamethasone-methotrexate. Rituximab, a B-cell depleting agent, is one of the promising new therapies, demonstrating steroid-sparing effects and early induction of remission.[4] FcRn, a neonatal Fc receptor which protects circulating immunoglobulin G (IgG) from degradation, is used in the treatment of pemphigus.[5] Bruton tyrosine kinase (BTK) is a signalling molecule necessary in the mechanism of B cell activation and BAFF (B cell Activating Factor) an immune regulatory cytokine and its inhibitors can be proposed for the treatment of pemphigus.[3] Dsg3 peptide could specifically bind to human leukocyte antigen-DR4 molecule and specifically to the DRB1*0404 allele, which is also used in treating PV.[3] Chimeric autoantibody receptors (CAAR-T cells) consisting of Dsg-3 fused to CD137-CD3ζ signalling domains exhibit specific cytotoxicity against Pemphigus autoantigen and hence can be used as a treatment of pemphigus.[6]

Bullous pemphigoid (BP) is a subepidermal blistering skin disease that usually occurs in the elderly population with a prevalence of 2.4/million and is characterized by large tense blisters with immunopathological findings of linear deposits of C3 and IgG at the basement membrane zone, hallmarked by the production of autoantibodies directed against the hemidesmosomal anchoring proteins BP180 and BP230.[1,7] The most well-established immunosuppressive medication is azathioprine, a purine analog, followed by mycophenolate mofetil, a DNA-synthesis inhibitor, and methotrexate, a folate antagonist.[8] Rituximab, a humanized chimeric monoclonal antibody that targets CD20+ B cells, and omalizumab, a humanized monoclonal antibody that inhibits the binding of immunoglobulin E to its receptors, are used as treatment modality.[9] High-potency corticosteroids combined with dapsone, doxycycline, methotrexate, or azathioprine are also used in the treatment of BP.[10]

Mucous membrane pemphigoid (MMP) is a chronic blistering or vesiculo-bullous disease that affects predominantly oral and ocular mucous membranes with a prevalence of two cases per million. Deposits of immunoglobulin and complement components along the basement zone are characteristic. The antigenic targets include laminin 5 (epiligrin) and a 180-kd protein or bullous pemphigoid antigen 180 (BP180).[1] It is also known as cicatrical pemphigoid, benign MMP, ocular pemphigus, and mucosal pemphigoid; when it affects the gingiva exclusively, it is referred to clinically as gingivosis or desquamative gingivitis.[11] The common drugs used in the treatment of cicatricial pemphigoid are corticosteroids, azathioprine, methotrexate, cyclophosphamide, and mycophenolate mofetil. Rituximab, daclizumab, and IVIG can be used in the recalcitrant cases of cicatrical pemphigoid.[12]

Paraneoplastic pemphigus is a rare immunobullous disorder that affects patients who have a neoplasm, usually lymphoma or chronic lymphocytic leukemia. It is thought that cross-reactivity develops between antibodies produced in response to the tumor and antigens associated with the desmosomal complex and the basement membrane zone of the epithelium.[1,13] Several nonsurgical treatments have proven effective in reducing symptoms in patients with PNP. Initially, glucocorticoid therapy – prednisone – should be implemented.[14] Immunosuppressants such as cyclosporin, cyclophosphamide, azathioprine, and mycophenolate mofetil are often used in combination with prednisone.[15] The concomitant use of rituximab with IVIG has proven successful in those patients who do not respond to conventional therapy.[16,17]

The term lichen planus (LP) is derived from the Greek word "lichen" meaning tree moss/green algae and

the Latin "planus" meaning flat. Erasmus Wilson first described the condition of LP in 1869. Bullous LP is one of the rare variants of LP, which is characterized by vesicles or multiple tense bullae and usually develops from the preexisting lesions with a worldwide prevalence of 1%. The diagnosis of oral lichen planus is usually made by clinical and histological examinations.[18,19] The main modality of treatment of LP is corticosteroids. A new treatment used is the topical form application of 0.2% hyaluronic acid.[20] Hydroxychloroquine sulfate is suggested to be effective in oral erosive LP which has a malignant transformation rate of 0.5%–2%.[21] The newer drugs used for treatment are cyclosporine, tacrolimus, tretinoin, fenretinide, dapsone, mycophenolate mofetil, enoxaparin, efalizumab, psoralen and ultraviolet A, photodynamic therapy, and low-level laser therapy.[15,22] Alefacept fully human LFA-3/IgG1 fusion protein which preferentially targets memory T cells (CD45RO+), interrupts activation of T cells and hence can be used in the treatment of lichen planus.[23,24] Efalizumab humanized monoclonal antibody that binds to the CD11 blocking T-cell activation and migration can be used to treat erosive lichen planus.[24] Basiliximab, rituximab, etanercept, infliximab and adalimumab are other drugs currently used in treatment for lichen planus.[24]

Immunobullous disorders include a wide range of lesions with a variety of pathogenesis. The researches in the recent past have led to a better knowledge of pathogenesis, diagnosis, and treatment. Prompt referral and multidisciplinary approach toward the diseases will aid in the proper diagnosis and better treatment planning, which will improve the quality of life. Significant advances and new researches in the treatment aid in the better prognosis of the disease, and the use of biologic agents has led to the better control of the disease.

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