J Young Pharm, 2017; 9(1): 14-22
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Review Article

Autoimmune Disorders–Immunopathogenesis and Potential Therapies

Sivadas Ganapathy[1*], Vaishnavi Vedam[2], Vini Rajeev[3], Rajeev Arunachalam[4]
[1]Department of Paedodontics and Preventive Dentistry, Asian Institute of Medicine, Science and Technology (AIMST) University, MALAYSIA.
[2]Department of Oral Pathology, Asian Institute of Medicine, Science and Technology (AIMST) University, MALAYSIA.
[3]Department of Prosthodontics, Asian Institute of Medicine, Science and Technology (AIMST) University, MALAYSIA.
[4]Department of Periodontics, Asian Institute of Medicine, Science and Technology (AIMST) University, MALAYSIA.

ABSTRACT
Autoimmune disorders are formed in the body as an outcome of inappropriate immune response against its own tissues. Failure of this immune system to recognize the body's normal constituents as "self" will result in inflammation and tissue damage. Several immune based mechanisms form the basis of autoimmune disorders in the body. Management of these lesions is based on the diagnostic criteria, evaluation of clinical and oral manifestation, and laboratory investigations of these lesions. There is currently no definitive cure for all autoimmune disorders, although in rare cases they may disappear on their own. As patients experience temporary remissions in symptoms or progressive worsening, our pharmacological management are targeted only for symptomatic relief and arrest the progression of the lesion. A detailed approach to titles and abstracts of importance in this field on the topic of interest via review and case reports was included. This review article highlights on various immune pathogenic mechanisms and treatment modalities of autoimmune disorders.

Key words: Autoimmune disorders, Autoimmunity, Molecular mimicry, Antigen, Auto antibody, Histocompatibility.

Correspondence:

Dr.Sivadas Ganapathy*,

Lecturer, Department of Paedodontics, Faculty of Dentistry, Asian Institute of Medicine, Science and Technology (AIMST) University, MALAYSIA.

Contact: +6017-6447241

E-mail: sivadasganapathy@gmail.com

DOI: 10.5530/jyp.2017.9.4

INTRODUCTION

Immune system of the human body acts as a '*double edged sword*' that can either heal or harm our physiological process. The integrity of this system is maintained with a balance played between various cells and tissues via soluble mediators. This immune system also shows a defensive role to prevent microbial infections in our body.

In a healthy person, the immune system can differentiate between the '*self*' and the '*non-self*' and destroys only those tissues that it recognizes as "non-self." Immune system is thus essential to eliminate the undesirable, non-self and possibly damaging substances entering the body without affecting the nearby tissues. Breakdown of this system as a result of destruction of body's own cells leads to *'Autoimmunity'*. Autoimmunity is therefore regarded as a disturbance in the process of antigenic recognition and elimination. These cells may undergo antigenic variation as a result of physical, chemical or biological influences. Such altered or 'neo-antigens' may elicit an immune response.

Autoimmune disorders are a group of conditions in which structural or functional damage to cells/tissues/organs/organ systems is produced by the correlation of immunologically competent cells or antibodies against the normal component of the body. This occurs as a result of interaction between several genetic, environmental and endocrine factors on our immune system by the following mechanisms[1] :- 1. Discharge of tissue specific auto antibodies via the initiation of complements lead to cytolysis of the target cells; 2. Auto antibody binding to soluble mediators resulting in immune complex deposition; 3.Auto antibody mediated attack on the natural immune system resulting in phagocytosis, cytotoxicity & antibody mediated cellular immunity; 4. Auto antibody directed against foreign antigen and epitopes of auto antigen that mimic the foreign antigen (cross reactive antigen) resulting in damage of the tissue[2] – *"Molecular mimicry"* and 5. Action of auto antibodies on cell surface structures resulting in either stimulation/ obstruction of the target structure.

Autoimmune diseases progresses from the stage of activation to chronic lesion via a rise in the number of neo-antigens targeted by lymphocytes and antibodies. This further triggers all the adjacent cells to exhibit more epitopes that propagate lesion resulting in tissue damage. Further discussion sheds light on the immune pathogenesis and various methods of pharmacological management targeted against these molecular mechanisms in several autoimmune disorders. This paper highlights the commonly occurring autoimmune disorders after a detailed approach to titles, abstracts, reviews and case reports of importance in this field by exclusion of duplicates, conference papers and posters.

MATERIALS AND METHODS

Pemphigus

Pemphigus vulgaris is an autoimmune intra-epidermal muco-cutaneous disorder of the skin and mouth resulting in blister formation.[3] Off late, lesions occur with an increased incidence of 0.5 to 3.2 cases per 100,000 population every year. These lesions predominantly occur in 4^{th}-6^{th} decades of life with equal gender predilection.

Immunologically, these patients present with circulating auto antibodies against pemphigus antigens (desmoglein 3. desmoglein 1, desmocollins, plakoglobin) on the epithelial keratinocytes. Disruption of this auto-antigen by the antigen-antibody reaction has a marked effect on the integrity of the epidermis resulting in cellular detachment (acantholysis), suprabasilar clefting and subsequent bullae formation.[4] Depending on the location of this antigen-antibody reaction, the level of cleft formation varies. Several cytokines like interleukins (IL-4, IL-10. IL-6), tumour necrosis factor (TNF alpha) and enzymes (phospholipase or proteinases)

are released by T-lymphocytes that propagate the tissue reaction and subsequent tissue injury.

Following trauma from physical or chemical agents, infectious agents, autoimmune or allergic processes, intercellular edema after breakdown of intercellular bridges, and subsequent loss of intercellular adhesion occurs within the epithelial layers producing intra epidermal bullae. Researchers have stated that binding of these auto antibodies to the keratinocyte cell surface also result in release of protease and plasminogen activator (converts plasminogen to plasmin) from the cells leading to acantholysis. Other factors like genetics (histocompatibility complex HLA-A13, HLA-DRw4n, HLA-A10), drugs (pencillamine, captopril). diet (garlic), viruses also act as triggering factors for pemphigus lesions.[5,6]

A combination of corticosteroids, immunosuppressive agents, pulse therapy, photophoresis and plasmaphoresis may reduce its progression.[7] Early lesions in the mouth can be best attended by appropriate periodontal therapy with maintenance of optimal oral hygiene. High grade lesions are treated by systemic glucocorticoids. Etiological drug must be removed in special cases of drug induced pemphigus.

Pemphigoid

Pemphigoid *refers to* 'pemphigus-like lesions' in the sub-epidermal regions of the skin and mucosa.[8] Depending on their clinical presentation, they can be further sub-divided into two types – *'Bullous Pemphigoid'* and *'Cicatricial Pemphigoid'*. Cicatricial Pemphigoid (CP) is a chronic blistering lesion of the mucous membrane and skin resulting in permanent scar formation.

Bullous Pemphigoid (BP) lesions commonly present elders above 40 years of age with no definite gender or racial predilection. However, CP occurs with slight female predominance (female: male ratio 1.5:1). Demographic data suggest that mucous membrane pemphigoid (MMP) occur 7 times less commonly than BP.[9-10]

In patients with Pemphigoid, autoanti bodies are directed against bulbous pemphigoid antigen (BP) (component of basement membrane) in the epithelium. Recent studies have shown that structurally, this bullous pemphigoid antigen to be an intracellular protein attached to the cytoplasmic plaque of the hemidesmosome. Studies indicate that pemphigoid antigen (transmembrane molecule) binds as an intracellular domain to the hemidesmosome on basement membrane and extracellular domain to the lower surface of epithelial basal cells.

Research revealed the presence of two types of principal antigen BP1 (230 kd protein associated with hemidesmosome related to desmoplakins) and BP-2 (180 kd protein in BP – transmembrane collagen associated with hemisesmosome anchoring filament complexes). Although the pathogenesis of both types of Pemphigoid remains the same, immunological methods prove it to be difficult to identify the circulating immunoglobulins in MMP than BP. Further reports suggest the presence of antigens like epiligrin complex, pemphigoidgestationis, collagen type 7 and integrin to be involved in its pathogenesis. Circulatingauto antibodies - complement activating (IgG3) and non-complement activating (IgG4) antibodies, complement system (C1q, C4, C3, C5, factor B, C5-9 and Properdin) and leukocyte activation play an important role in the immunopathogenesis.[11]

At the lesional site immunoglobulin IgG4 antibodies combine with the pemphygoid antigen, and subsequently activate the complement cascade. Inflammatory mediators like complements (C3a, C5a anaphylotoxins), interleukins, TNF alpha and beta are activated that recruit the mast cells. Mast cells degranulate releasing the eosinophil and neutrophil chemotactic factors, histamine, leukotreine (LTB4) and proteolytic enzymes (neutrophil elastases). Activated neutrophils and lymphocytes produce proteolytic enzymes (matrix metalloproteinase) at the basement membrane leading to dermal-epidermal junction split and sub epidermal blister formation.[12]

The treatment of pemphigoid is relatively complex due to extreme unpredictability of steroid receptiveness. Superficial lesions can be treated by use of intra-lesional corticosteroids, plasmaphoresis therapy and dapsone (25-150 mg/day depending on the severity of the lesion). Extreme cases are treated by systemic corticosteroids and immunosuppressive drugs like azathioprine (1-2 mg/kg/day) or cyclophosphamide (0.5-2 mg/kg/day).[10] Usage of antibiotics like tetracycline (500 mg - 2.5 g/day), erythromycin and niacinamide inhibit neutrophil chemotaxis, complement induced inflammatory responses to basement membrane, alters antigen-antibody complexes thus maintaining the cohesion of epithelial connective tissue junction. Ocular cases are treated by cryosurgery while laryngeal or esophageal stenosis is treated by surgical resection.

Sjögren's syndrome

Primary Sjögren's syndrome is a long-lasting systemic autoimmune disorder characterized by focal infiltration of lymphocytes into the exocrine glands and lacrimal glands ensuing in dry mouth (xerostomia) and dry eyes (kerato conjunctivitis sicca) respectively. Secondary Sjögren's syndrome is characterized by a triplet of kerato conjuctivitis sicca, xerostomia and autoimmune systemic disorder like rheumatoid arthritis.[13]

In Sjögren's syndrome, the presence of lesions are associated with the activation of chronic inflammatory infiltrate (lymphocytes, monocytes & plasma cells) with release of antibodies against the salivary glandular epithelial cells. Destruction of acinar tissue in Sjögren's syndrome is associated with two factors. First factor includes glandular infiltration by lymphoid cells surrounding the interlobular ducts and second factor includes the presence of anti salivary duct antibodies that coat the ductal antigens thereby protecting all the antigenic sites and preventing further lymphocytic infiltration.[14] Hence, anti salivary duct antibody and the periductal cellular distribution of salivary gland suggest the presence of sensitizing antigen on the salivary ducts only. Sensitized lymphocytes release the soluble factors that result in the glandular destruction.

Presence of histocompatibility complexes HLA-A, B and C antigens with inappropriate expression of HLA-DR antigenson salivary epithelial cells and release of cytokines interleukins IL-2, IL-4, IL-6 and tumour necrosis factor (TNF-α/ TNF-ý) by the inflamed tissues underlie the initiation of immunogenesis of this disease.[15] Leukocyte-endothelial interactions ICAM-1/LFA-1, Interferon ý (apoptosis of salivary gland epithelial cells) and tumour necrosis factor TNF-α(enhances the stimulation of antigen presenting glandular epithelial cells) and vascular cell adhesion molecule (VCAM 1)are critical for homing and release of the cell sat the lesion site. Progressive loss of salivary acini and ducts with gradual increase in the foci of lymphocytes result in tissue injury.

Researchers have also elucidated the role of B- lymphocytes in the salivary gland infiltrates and release of auto antibodies via cytokines like B-cell activating factor (BAFF) or B-lymphocyte stimulator (BLýS) member of the TNF super family in primary Sjögren's syndrome.[16] Auto antibodies are directed against this nuclear La antigen of cytoplasm and the membrane of the epithelial cells. These cells express the adhesion molecules on their surface that helps in the recruitment of lymphocytes to the lesion site and subsequent release of auto antibodies. BAFF and gamma interferon result in B-cell activation perpetuating autoimmune response in Sjögren's syndrome.

Other autoantigen targets in Sjögren's syndromeinclude ribo nucleo protein autoantigens Ro/SS-A and La/SS-B, coiled-coil-containing molecules, members of golgin family, poly (ADP)ribose polymerase (PARP) and type 3 muscaranic receptor etc. These cytokines aid in the B-lymphocyte maturation, plasma cell survival and autoantibody production (Anti SSA/Ro and anti SSB/La antibodies) are correlated

with the disease onset, duration, recurrent salivary gland enlargement and extraglandular manifestations.

Few cases present with viral infecting salivary tropic agents [Epstein Barr virus (EBV) and Hepatitis-C virus] resulting in apoptosis of the glandular epithelial cells (increased expression of classical Fas-FasL interaction, granzyme A and apoptotic proteins like Bax and Bad proteins)and surrounding tissue. Proteolysis occurs with increased caspase activation resulting in altered autoantigen for immune target and release of antinuclear antibodies, rheumatoid factor, Anti-Ro and Anti-La antibodies in the exocrine tissue. Increase in cytokines transforming growth factor (TGF-ß) and platelet derived growth factor (PDGF)leads to progressive glandular destruction and functional disability.[17]

Activation and binding of acetylcholine with muscarinic 3 receptors triggers an increased calcium mobilization, activation of potassium and chloride channels that drive the fluid secretion into the cells. Autoantibodies directed against the muscarinic receptors on the salivary epithelial cells (M3R) inhibit the calcium mobilization resulting in the hypofunction of the salivary glands. Progressive invasion of inflammatory cellsinto the glandular epithelium lead to the glandular dysfunction.

Treatment of such lesions include replacement of saliva by salivary substitutes, saliva stimulating drugs (pilocarpine / cevimeline), adjuvant systemic therapy with anti-inflammatory drugs corticosteroids (prednisolone 5-10 mg/day), immunomodulatory drugs (hydroxychloroquine 6-7 mg/kg/day) and cytotoxic drugs (cyclophosphamide 2.5-5 mg/day).[18]

Mikulicz disease

Mikulicz disease is a chronic lesion associated with irregular enlargement of lacrimal and salivary glands. Mikulicz disease and Mikulicz syndrome were always considered as a solitary entity due to the similar clinical features. Mikulicz syndrome presents with diseases like tuberculosis, sarcoidosis, leukemia, syphilis, hodgkin disease, mumps, or lymphoma whereas Mikulicz disease occurs primarily as an autoimmune disease in the glands with plenty of lymphocytes replacing the normal glandular tissue.[19] Mikulicz disease (MD) is most likely to occur in adults around 50-60 years of age with an increased predilection among the females (60-80%) (3:1). Parotid gland is the most frequent site of lesion in 80-85% of the individuals.

Several theories like lymphatic hyperplasia, autoimmunity associated chronic enlargement of salivary glands and lacrimal glands, parasitic infections, inflammation, neoplasm or a primary defect of the ductal system are proposed. Immunologically, these patients present with elevated serum immunonoglobulin IgG4 and lymphocytic infiltration of glandular tissue leading to replacement of normal acini. Damaged cells of the acini and ducts of the gland release excessive serotonin which, increases further capillary permeability within the lacrimal gland only.[20-22]

Mi kulicz disease is treated either by administration of steroids, surgical therapy or radiotherapy. Prednisolone (30-40 mg) per day improved the status on glandular secretion and reduced the lacrimal/salivary swelling. Surgical excision is the main treatment of choice in advanced cases. Radiotherapy approach is not used anymore due to the risk of radiation induced malignancy.

Behcet's disease

Behcet's disease is a systemic inflammatory disorder with unknown cause manifesting as recurrent, multiple lesions in the mouth (recurrent aphthous stomatitis), eyes (uveitis), genital regions and skin.[23] Current concepts suggest that Behcet's disease affects 2-5% of the population with increased prevalence in the middle east region with an onset typically in the 3rd-4th decade of life. Current prevalence is estimated to range from 0.3 per 100,000 cases in Europe to a peak of 80 to 370 per 100,000 in Turkey. In the Middle East, Europe, and the United States, young men are most often affected, however, in Japan and Korea there appears to be a slight female predominance.[24]

Research currently postulated the interaction of T-lymphocytes with multiple antigens as a crucial step in the pathogenesis. T-lymphoctes activated monocytes occur via cluster of differentiation (CD40-CD154) cytokines (interferon IFN-delta and tumour necrosis factor TNF-α) and several interleukins (IL-1, IL-8, IL-17). Abnormal T-cell with neutrophil activation and subsequently cytokine mediated reaction results in tissue injury.[25-26]

Another mechanism with neutrophil activation, increased superoxide production, chemotaxis and excessive production of lysosomal enzymes, increased adhesion molecules with neutrophil hyper responsiveness lead to tissue injury. Multiple factors like paracrine and/or autocrinepro inflammatory cytokines, interaction with activated endothelial cells, genetic studies are involved in the neutrophil hyperfunction in Behcet's disease.

On activation of macrophages during a cell mediated immune response in Bechets disease, lysosomal enzymes are released by stimulation. Types of macrophages include - Type 1 macrophages in the prickle cell layer phagocytose the cellular components and process them to phagosomes, *Type II Macrophages* transfer the immunological information from the degenerated cells to the lymphocytes, which then undergo blastoid transformation, immunoglobulins and cytotoxic factors and *Type III* macrophages (Langerhan cells) have an important role in regulating the ulceration. Molecular mimicry occurs wherein the lymphocyte specific for the heat shock protein HSP60 is expressed with highly homologous bacterial heat shock protein HSP65 (cross reactivity between the bacterial HSP with human mitochondrial HSP) in Behcet's disease. Reports suggested the presence of circulating anti-cardiolipin, anti-endothelial cell antibodies and auto antibodies to protein-S, von-Willebrand factor and anti-neutrophil cytoplasmic antibodies.[27]

Behcet's disease is also associated with systemic vasculitisdue to immune complex formation affecting all types and sizes of blood vessels. Activation of both coagulation system and fibrinolytic system occurs in reflecting the endothelial activation and injury. There is no specific treatment for this lesion. Only supportive measures like topical/systemic corticosteroids for muco-cutaneous lesions, and topical mydriatic agents / corticosteroid therapy, cytotoxic agents and immunosuppressive drugs for ocular lesions can be given.

Psoriasis

Psoriasis is a chronic, reverting, papulo-squamous dermatitis characterized by scaliness of the eyes and scrotum by abnormal hyper proliferation of the epidermis.[28] Psoriasis commonly affects 1-3% of the entire population with equal racial predilection. They occur predominantly in male population with a mean age of about 20-30 years.

Initially, psoriasis was associated with a defect in the epidermal keratinocyte leading to keratinocyte hyper proliferation. Later, studies suggests that both immune system and keratinocytes played a major role in pathogenesis of Psoriasis. Psoriasis occurred primarily due to the presence of super antigens of microbial origin (Streptococcal antigens/ Staphylococcus) in the keratinocytes. Antigen presenting cells like dendritic cells present these antigens to the T cell receptor (TCR) on the T lymphocytes leading to activation of the cells by the Lymphocyte function associated antigen (LFA-3)/Intercellular adhesion molecule (ICAM) interactions (signal 1) and cluster of differentiation CD28-CD80/86 interactions (signal 2). Secondly, CD4 and CD8 T cells from the Psoriatic dermis and epidermis are activated upon the contact with specific MHC class I (intracellular antigens) or MHC class II (extracellular antigens) on the antigen presenting cells. Although, activated T lymphocytes elicit both type 1 (cell mediated) immune reaction and Type 2 (humoral) immune reaction,

Psoriasis produces a type 1 dominant reaction in response to IL-12, IL-23 and IFN-ý release and subsequent tissue injury.[29]

Etiological factors like HLA Cw6 / HLA B8 & HLA A13 & A17, B13 & B16 have a several fold risk of developing Psoriasis than with normal individuals. Various triggering factors include infections (Streptococcal infections), alcohol consumption & smoking, diet, hormones (dehydroepistandrosterone, aldosterone and somatotrophic hormone), stress and drugs (lithium, ß blockers, antimalarials, systemic corticosteroids and NSAIDS).Other cytokines involved are Matrix metalloproteinases 2 and 9; skin derived anti leukoproteinases (SKALP), Heat shock proteins and Phospholipase C/ Protein kinase C signal transduction pathway. The lymphocytes also express specific cell surface markers that allow them to transmigrate from the blood circulation to the lesion site. Increased E-selectin and P-selectin expression with cutaneous lymphocyte antigen (CFA) on T lymphocytes facilitates transmigration of immune cells across the vasculature. Increased interaction of LFA-1 and VLA-4 with ICAM and VCAM, cause the T lymphocytes to stick to the blood vessel. Other molecules like TNF-α (recruitment of lymphocytes to the lesion site), calmodulin, epidermal growth factor receptor, IL-A, IL-ß, IL-6 AND IL-8, cytokeratin 16 & 17, psoriasis associated fatty acid binding protein, psoriasin and fibronectin in smaller quantities are involved in the pathogenesis of this lesion. Chronicity of this lesion may be attributed due to the expression of selectin, CD31 and CD34, lymphoid organizing chemokines (CCL19 & CCL21), aggregates of T cells and mature dendritic cells.

Topical emollients, corticosteroids or calcitriol for keratinocyte proliferation and differentiation, psoralen and ultraviolet therapy (PUVA) for itching by reduction of substance P, retinoids (etretinate) reduces tissue inflammation and arrest keratinocyte proliferation, immunosuppressive agents (cyclosporine) acts on keratinocyte adhesion molecules and pulsed dye on dilated vessels in papillary dermis are normally administered. Other drugs -biological immunomodulators like efalizumab, alefacept, tumor necrosis factor inhibitorslikeetanercept, infliximab, daclizumab and CD11a (subunit of leukocyte function associated antigen (LFA-1) can also be considered in advanced cases.

The current approach includes drugs that act on potential targets like T cell trafficking, T-cell activation, cytokine inhibitors and counteroffensives. They have transformed from arsenic drugs to immunosuppressive drugs (methotrexate) and vitamin analogues. Recently, certain biologic agents, predominantly alefacept and efalizumab act on few potential pathologic targets.[30]

Scleroderma

Scleroderma is an autoimmune connective tissue disease associated with basic features of skin indurations and thickening due to excessive collagen deposition, vascular abnormalities and fibrotic degenerative changes in the muscles, joints and other internal organs.[31] The prevalence of Systemic Sclerosis is reported as 105-140 per million in North America, Australia and Europe respectively. Systemic Scleroderma is known to occur four times more commonly in women than men. Localized Scleroderma is common in children.[32]

Scleroderma maybe conceptualized as a multilateral disease by immunological abnormalities like disease specific chronic inflammatory immune cells (T-lymphocytes/B-lymphocytes), fibroblasts dysfunction leading to fibrosis of the skin and internal organs, endothelial dysfunction resulting in deposition of extracellular matrix by Raynaud's phenomenon. Systemic Sclerosis is observed as an autoimmune disease by the presence of antinuclear antibodies (speckled or nucleolar type), anti centromere antibodies, anti-endothelial cell, anti-fibroblast, anti-matrix metalloproteinase and anti-fibrillin 1 antibodies against auto antigens in the endothelium and extracellular matrix resulting in immune mediated tissue injury.[33]

Basement membrane antigens, type 1 collagen, lymphocyte endothelial adhesion molecules, extracellular matrix by fibroblasts auto epitopes react with T lymphocytes, macrophages and mast cells via MHC class II complexes. This reaction aids in release of IL-4, IL-10, IL-13 and IL-17, TGF-ß that propagates the activation of fibroblasts, collagens, proteoglycans and fibronectin synthesis, inhibit the matrix metalloproteinase (involved in the degradation of collagen), produces IL-6 and PDGF and endothelial cell adhesion molecules like ICAM-1 and VCAM-1 in scleroderma. Detailed studies on fibroblasts results in over expression of collagen 1, 2, 3, fibronectin and proteoglycan, fibrillin 1 genesmutations (COL1A1, COL1A2) and matrix metalloproteinases alterations.[34] This causes a release of TGF ß that promotes fibrosis and unmasks the cryptic epitopes that become the targets of autoimmune response in the host with impaired immune tolerance.

Studies on endothelium in scleroderma patients exhibited the presence of endothelial cytotoxic factor in the granules (granzyme A) in activated T- lymphocytes for arterial intimal proliferation, capillary dilatation, destruction and endothelial injury.Abnormalities in molecules of endothelin family (ETA and ETB), renin-angiotensin converting enzyme (ACE) and nitric oxide synthases (NOS) alter the vascular tone in Scleroderma patients and result in Raynaud's phenomenon. Other cytokines like TGF, TNF, IL-4 and connective tissue factor (CTF) promotes fibroblast proliferation and extracellular matrix deposition in Scleroderma patients.[35]

Current therapies aim at halting or limiting further progression of the disease.Skin lesions can be best treated by administration of D-pencillamine, interferon gamma and cyclophosphamide and photophoresis.[36] Flexion contractures can be completely eliminated by surgical management. Regular physical therapy and bilateral commissurotomy surgery suffices this lesion.

Epidermolysis bullosa aquisita

Epidermolysis bullosa aquisita (EBA) is an acquired mechano bullous lesion of the skin and mucosal membranes with IgG antibodies targeted against non-collagenous component of collagen 7.[37] Blister is formed by the separation of the skin at the zone of the basement membrane between the epidermis and dermis.EBA occurs commonly between the 4th- 5th decades of life with no evidence of racial and gender predilection.

Recent reports stated that auto antibodies are secreted against laminin 5, laminin 6, Bullous pemphigoid antigen and NC2/NC1 domain type VII collagen. Polymorphism of the gene (chromosome 6 that encode for class I/class II HLA proteins - HLA-DR1, HLA-DR5 and HLA-DR8), altered collagen VII (EBA antigen), increased collagenase activity, result in the damage to sub basal fibrous components leading to autoimmunity.[38-39]

Collagen type VII is the primary target of autoimmune response that contributes to dermal-lamina densa dysadherence. IgG auto antibodies interact with NC1 domain of type VII collagen in patients with EBA either by complement dependent inflammation and auto antibody mediated interference with the adherence function of Collagen VII. Complement 5 (chemotactic and leukocyte activating complement peptide) induced the recruitment of leukocytes along with the Collagen VII auto antibodies to the basement membrane. Migration and attachment of leukocytes to the basement membrane causes further activation of leukocytes and separation of basement membrane resulting in skin fragility and blisters without inflammation.[40]

Patients with this lesion may respond to various drugs like prednisone, dapsone, or colchicine, phenytoin, gold and vitamin E, while others may respond to mixture of anti-inflammatory and immunosuppressive therapy (azathioprine and cyclophosphamide) or sometimes the patients may not respond to any medical therapy.[41]

Systemic lupus erythematosus

Systemic lupus erythematous (SLE) is a chronic autoimmune disease affecting heart, lungs, blood vessels, skin, joints, blood and kidneys. This lesion produces characteristic butterfly-like rashes on the face and skin of the body. Appearance may be attributed to the immune complex formed due to hyperactivity of the body's immune system with the formation of auto antibodies and immune-mediated tissue injury.[42]

The annual incidence of SLE is estimated to be 6.4-7.6 cases per 100,000, whereas, approximately one case per 2,000 Caucasians are reported. SLE occurs more commonly in females (15-45 yrs) than males in the ratio of 9-10:1. This is a rare disease affecting about 5 in a million children per year (males are predominantly affected in children before puberty). The etiopathogenesis of SLE is associated with several genetic factors (HLA-DR2 and HLA-DR3; C4a and C4b, C1q, C1r/s and C2 (complement consumption and immune complex deposition), non-MHC genes that encode mannose binding protein (MBP), tumour necrosis factor-α, T cell receptor (TCR), interleukin 6 (IL-6), CR1, immunoglobulin G (both IgG Fc receptors) and heat shock protein 70, hormonal imbalance (estrogen and androgens), autoimmunity and environmental influence with SLE.[43]

SLE is characterized by a myriad of immune system aberrations that involve B cells, T cells, and cells of the monocyte lineage, resulting in polyclonal B cell activation, increased numbers of antibody-producing cells, hyper gammaglobulinaemia, autoantibody production, and immune complex formation. As a result, auto antigen-antibody reaction cause inflammation of various organs like blood vessels, joints, skin and kidneys. Both professional antigen presenting cells and B cells process the antigens into peptides and present them to T-cells through their surface HLA molecules.[44] The activated T cells in turn stimulate the B cells to produce pathogenic auto antibodies. In addition to contact stimulation, the interaction of B and T-cells is facilitated by several cytokines (IL-10, IL-12,CD40/CD40L and B7/CD28/CTLA-4 systems).In humoral immunity increased levels ofendogenous factors B lymphocyte stimulator (BLyS) (B-cell activation factor from TNF family – BAFF) exhibit a co-stimulatory function for B-cell activation causingB-cell hyperplasia. This produces auto antibodies against nuclear antigens and results in the formation of immune complex deposition.

SLE is an autoimmune disease characterized by the production of antibodies against a variety of cellular macromolecules like DNA, nuclear proteins, histones, and various RNA proteins.Anti-DNA (DNA) antibodies, antinuclear ribonucleic acid protein (anti nRNP), anti smith(Anti-Sm) antibodies, anti SS-B and Ha antibodies, anti La antibodies, anti Ro antibodiesanti-neutrophil cytoplasmic antibodies (ANCA) are a group of auto antibodies directed against several components leading to various clinical manifestation in SLE. Impairment in *Fas-FasL* pathway (apoptosis activation), inactivated C2, C4 and C1q and increased Bcl-2 can result in defective apoptosis. Clearance of apoptotic cells by macrophages is also impaired in SLE patients. Various environmental factors like sun exposure, viral infections (increased loads of Epstein Barr virus/ Hepatitis C virus), diet, stress and certain medications may predispose to SLE.[45]

Treatment is fundamentally intended at the avoidance of complications and reduction of inflammation during the course of the disease. Various drugs include immunosuppressive agents (cyclosporine), systemic corticosteroids, anti-malarial, other biological drugs like non-steroidal anti-inflammatory drugs, acetaminophen (anti-inflammatory) and anti-coagulants.[46] Adjuvant agents include sun-protection using sunscreen lotions, vitamin D supplements and cosmetic camouflage.

Ehlers-danlos syndrome

Ehlers-Danlos syndrome (EDS) refers to hereditary connective tissue disorder characterized by the defects of the major structural protein in the body (collagen). Primary disorder include articular hypermobility, "stretchy" (elastic) skin and excessive fragility of the skin, bodily tissues, blood vessels and membranes.[47]

The molecular basis of EDS is heterogeneous with 3 fundamental mechanisms: a deficiency of collagen-processing enzymes, dominant negative effects of mutant collagen chains, and haploinsufficiency.[48] Treatment of Ehlers Danlos syndrome is done using physical therapy (myofacial exercises), assistive devices (orthopedic braces, wheelchairs, air mattresses), pain medications (non-steroidal anti-inflammatory drugs, tricyclic antidepressants, serotonin inhibitors, skeletal muscle relaxants, and opioids), genetic counseling, ongoing therapies like vitamin C and losartan. At later stages of the disease, treatment is based on the organ affected subsequently. Dental abnormalities are corrected by orthodontic and palatal corrections (retainer), temporomandibular joint dysfunction (intra oral devices), local myofacial release, and muscle relaxant medications. Surgical intervention should be considered only as a final option.

Sarcoidosis

Sarcoidosis is a chronic multisystem disorder exhibiting granulomatous inflammation of lungs, lymph nodes, muscles, eyes, liver, spleen, joints, bone marrow and skin in the body.[49] This lesion occurs commonly in African-Americans, German, Irish, Scandinavian, Asian and Puerto Rican origin. It appears most often in young women (1.3%) and men (1%) between 25-40 years of age. Etiological agents-viral or bacterial infections (mycobacterium, Epstein–Barr virus (EBV), and human herpes virus-8 (HHV-8),; abnormalities in the body's immune system; environmental factors such as toxins or chemical(wood dust, pollen, clay, mold, and silica), occupational exposure (farmers, fire fighters, military)and genetic factors (HLA-A1, HLA-B8, HLA-DRB1 and HLA-DR3) play a major role in its pathogenesis. Most accepted theory suggests infectious or environmental trigger asan exaggerated immune response in genetically susceptible individuals.[50]

At the immune level, T-lymphocytes play an important role in the presentation of antigenic material in the tissue. Macrophages and dendritic cells present the processed antigen to the T-lymphocytes via MHC class II interaction and co-stimulatory molecules (B7 to CD28, CD40 to CD40L). Mononuclear macrophages and lymphocytes migrate to the site of the lesion under the effect of cytokines (interferon gamma (IFN-γ) and, TNF-α, IL-12 and IL-18) resulting in the granuloma formation. Immunological features include depression of cutaneous delayed-type hypersensitivity and increased CD4/CD8 ratio at the site of involvement. Circulating immune complexes along with signs of B-cell hyperactivity may also be detectable.[51]

Granulomas usually form in response to a foreign substance, chronic infection or inflammation. Treatment is rendered to reduce inflammation and arrest the progression of the granuloma. Management with corticosteroids, methotrexate, non-steroidal anti-inflammatory drugs immunosuppressive drugs (azathioprine, hydroxychloroquine, chlorambucil, cyclophosphamide and pentoxifylline), anti-malarial drugs, anti TNF-α and infliximab (latest drug) is aimed systemically in maintaining good lung function, reducing symptoms and preventing further organ damage.[52] Oral lesions of sarcoidosis are treated medically using topical corticosteroids and surgical excision. Gingival hyperplasia and gingivitis is reduced using scaling, polishing and good oral hygiene procedures. Jaw lesions are curetted and the tooth splinting is done in other essential cases

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy

Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED) is aninfrequent autosomal recessive disorder considered by the presence of chronic mucocutaneous candidiasis, multiple endocrinopathies (Addison's disease) and ectodermal manifestations.[53] Studies

described its presence in more isolated populations such as Finns (1/25,000), Sardinians(1/14,400) and Iranian Jews (1/9000).

APECED is the first autoimmune disease associated with mutation in a single gene autoimmune regulator gene (AIRE) and other enzymes (cytochrome P450 and hydrolases). AIRE gene is expressed in the epithelial cells of thymus. Negative selection occurs in the central tolerance while anergy, homeostatic control and regulation of T cells in peripheral tolerance. These patients present with auto antibodies directed against organ specific antigens, hydrolases, tyrosine and tryptophan.[54-55]

Chronic mucocutaneous candidiasis (CMC) is frequently associated with deficiencies of certain hormones that predispose to the emergence of oral candidasis(Diabetes mellitus, Hypothyroidism, Hypoparathyroidism, Hypoadrenalism and Addison's disease) and T cell immune deficiencies. Pro inflammatory IL-17A producing Th17 subset is implicated in protection against fungi at epithelial surfaces. Anti-IL-17A antibody against Th17 cells result in the tissue injury.

Candidiasis is treated symptomatically by topical and systemic antifungal therapy (polyene, imidazole and triazole agents) and immunomodulatory drugs. Recent studies indicate the transfer factor – cell free protein extracted from the T-lymphocytes of candida donor species to be effective in treating this disease.[56]

Wegener's granulomatosis

Wegener's granulomatosis (WG) is a systemic necrotizing granulomatous inflammation of the respiratory tract, renal system and vasculature.[57] Estimated incidence of 3/100,000 in USA and 5 /100,000 populations in Europe affects all gender groups (40-60 years) equally with slight increase in caucasians.[58]

Anti-neutrophil cytoplasmic auto antibody (c-ANCA) (Auto antibodies secreted against neutrophil 29 kd protein – serine proteinase PR-3), nuclear or perinuclear pattern antibodies (Antibodies to myeloperoxidase-MPO) have been observed. The presence of these antibodies results in the activation of neutrophils and subsequent tissue injury.[59]

The proposed mechanism involved the presence of auto antibodies secreted against the cross reacting auto antigen (proteinase PR3 and myeloperoxidase MPO) on the blood vessels. Antigen-antibody reaction releases IFN-ý, TNF-α, IL-1, IL-4, IL-5 and IL-10 through a Th-1 mediated response. This results in increased expression of ICAM-1 and VCAM-1 that produces a granulomatous vasculitis. The released cytokines have the ability to accelerate the reaction by inducing the surface expression of the proteinase-3 on the neutrophils and endothelial cells. The final event is inflammation-induced tissue breakdown with the release of intracellular materials from infiltrating cells (proteinase-3), causing autoimmune responses that amplify the primary lesion. PR3 is presented through the macrophages to the T cells. Antibodies against the neutrophil cytoplasmic Ag proteinase-3 (c-ANCA) are potent inducers of endothelial cell signaling response and uniquely associated with WG and elevated during disease activity.

Interaction between PR3-ANCA and TNF-α primed mononuclear cells by FcýR receptors leads to secretion of IL-8 and monocyte chemoattractant protein 1. Factors like TNF-α, IL-1α and thrombaxane A_2 (TxA 2) play an important role in an autocrine and paracrine manner resulting in the tissue injury.

Various risk factors include infectious agents like staphylococcus aureus (enterotoxins), genetic factors protein tyrosine phosphatase (PTPN22) and alpha antitrypsin 1 deficiency and environmental factors (silica, lead and mercury). Three types of exotoxins (staphylococcal enterotoxins, exfoliative toxins, and the toxic-shock-syndrome-toxin-1 (TSST-1) and rarely the presence of staphylococcal acid phosphatase is associated with the recruitment of T cells in a non-specific manner (super antigens) to the inflammatory site.

Cytotoxic therapy of cyclophosphamide (2mg/kg/day), prednisolone (1 mg/day 3-4 weeks), azathioprine (2-3 mg/kg/day) and methotrexate (0.3 mg/kg/weekly) are commonly administered. Sino-nasal manifestations may be treated medically with saline and topical nasal/ systemic steroids. Antibiotics are prescribed for superadded bacterial infections. Induction treatment is usually given as combined treatment with cyclophosphamide and corticosteroids.[60] Use of corticosteroids alone is associated with a higher relapse rate. The roles of anti-T-cell or anti-cytokine therapy in this situation are presently being tested. More recent treatment options include cyclosporin, mycophenolatemofetil, deoxyspergualine, intravenous pooled immunoglobulin, anti-CD20 monoclonal antibodies (Rituximab), plasma exchanges and anti-tumour necrosis factor- alpha. Special emphasis on dental management includes the use of antibacterial mouth rinses and treatment of all existing mouth lesion in addition to the routine mentioned systemic therapy.

Crohn's disease

Crohn's disease (CD) is an idiopathic chronic inflammatory disease of the gastrointestinal tractdefined by transmural inflammation of the bowel involving the terminal ileum and colon preferentially. Other extra intestinal sites like mouth, skin, eyes and joints have been identified.[61] In India, Crohn's disease occurs with with a peak incidence in adolescence and young adults with equal gender predilection. The proportion of patients with CD below the age of 20 years varies between 25-40% with around 10% being less than 10 years of age. Autoimmune theory, immune deficiency theory and mycobacterial theory are involved in its pathogenesis.

CD is an autoimmune disorder with circulating antibodies directed against self-antigens (mutated NOD2/ CARD 15 (Caspase activation and recruitment domain). Imbalance of T-regulatory cells function incited by normal gut flora results in autoimmune disease. Others suggest the dysregulated immune response as result of inappropriate activation of the mucosal immune system driven by the presence of normal luminal flora.

Three main hypotheses regarding the NOD2 protein have been proposed. The first hypotheses states that absence of NOD2 leads to defective activation of macrophages and persistent infection owing to a marked NOD2 independent effector T-cell response. The second hypothesis, state that in the absence of NOD2 expression by epithelial cells, leading to first, the proliferation of bacteria in crypts and second, loss of barrier function allowing marked stimulation of mucosal cells by antigens. The third hypothesis, suggest that recognition of microbial peptides by NOD2 normally conditions antigen presenting cells to their induction of regulatory and effector T-cell responses, failure of this mechanism disrupts mucosal homeostasis.[62-63]

Recent concept that dysfunctional neutrophils also play an important role in inflammatory immune response in Crohn's disease. This neutrophil dysfunction is hypothesized to result from interplay of genetic factors, environmental factors, or possibly exotoxins associated with subsets of the gut flora.NOD2 is a cytosolic protein whose expression is restricted to monocytes, intestinal epithelial cells, dendritic cells, macrophages and other immune processing cells. A deficit in sensing bacteria in monocytes/macrophages might result in an exaggerated inflammatory response by the adaptive immune system. Normally, NOD2 may mediate the induction of interleukin-10 that down regulate the inflammatory response. A failure to recognize the intracellular pathogen and mobilize a coordinated cytokine response results in failure to clear the pathogen resulting in chronic infection.[64]

Mycobacterial species (Mycobacterium Avium Paratuberculosis) are involved in the causation of the Crohn's disease. The presence of lipid laden cell walls and virulence factors, ability of evasion of the M.TB

phagosome-lysosome fusion (enhancement survival of the bacteria), interference with the cytokine signaling pathway and chronic persistent antigenic stimulation leads to destructive disease. Of all these mechanisms, it is the impaired phagosome-lysosome fusion in MAP kinase infected phagocytes in Crohn's disease patients.

Crohn's disease are treated either medically using sulfa drugs (sulfasalazine 2mg/day), steroids (prednisolone 1-2 mg/day), mesalazine, immunomodulatory drugs (mercaptopurine 1-1.5mg/kg/day & azathioprine 2-2.5 mg/kg/day), antibiotics (ciprofloxacin and metronidazole), biological therapy (natalizumab, infliximab, Interleukin 10 and anti-tumor necrosis factor), nutritional therapy (calcium supplements), psychological therapy, surgical procedures-strictureplasty, abscess drainage, and diversion byplasty (intractability, uncontrolled hemorrhage, perforation, obstruction, fistulae, growth retardation, and carcinoma).[65] Oral lesions can be treated using topical and intra lesional corticosteroids, oral sulfasalazine and antimicrobial mouth washes. Systemic thalidomide can is administered for obstinate cases of Crohn's disease.

Autoimmune haematological disorders

Idiopathic thrombocytopenic purpura, Pernicious anemia and Autoimmune hemolytic anemia are autoimmune hematological diseases associated with auto antibodies against platelets, gastric mucosal cells and intrinsic factor, and red blood cells respectively.[66]

Enhanced circulating platelet-specific auto antibodies (anti-platelet factor) occur resulting in Fc-mediated destruction of platelets by the mononuclear phagocytosing system. GP IIbIIIa-specific monoclonal antibodies have been suggested to activate platelets via the platelet Fc RIIA receptors thereby affecting the megakaryocytes in the bone marrow. Genotype (HPA-5a5b), molecular mimicry, determinant spreading, imbalance in Th1/Th2 cells and cytokine production result in thrombocytopenic purpura.[67]

Idiopathic thrombocytopenic purpurais treated by glucocorticoids, splenectomy, administration of immunoglobulin and finally platelet transfusion. Intractable cases are treated with immunosuppressive agents and H. Pylori eradication therapy. Autoimmune hemolytic anemia is treated by administration of glucocorticoids, folic acid, and immunosuppressive agents. Treatment of pernicious anemia disorder depends on the red blood cell count and severity of the disease. Standard treatment includes the administration of vitamin B12 (i.m 1000ug/day hydroxocobalamin/ methylcobalamin) for two weeks.[68]

Rheumatoid arthritis

Rheumatoid arthritis is anchronic autoimmune inflammatory disease that affects the joints. Temporomandibular joint is affected in 70% of all rheumatoid arthritis patients during the progression of the disease. It may be associated with the presence of rheumatoid factor in the affected patients.

Certain triggering agents (Epstein-Barr virus, parvo virus, super antigens of heat shock proteins obtained from M. Tuberculosis, E.colI/ streptococci bacterial cell wall or cross reaction antibodies against streptococci/ other microorganisms cause an antigen-antibody reaction in immunologically predisposed individuals. Bacterial, viral infections, surgical interventions, trauma, childbirth, stress, may act as triggering factors.

In rheumatoid arthritis, inflammatory response result in severe joint destruction. Immune reaction causes the thinning of synovial capsule, thickens several folds, and becomes edematous with ingrowths of new blood vessels, infiltration of mononuclear cells and proliferation of the synovial membrane, Formation of granulation tissue results in panus (reactive macrophage laden fibroblastic proliferation), which gradually erodes the bone and cartilage from the periphery, creating irreversible changes in the joint morphology. As a consequence, instability of the joint occurs, leading to progressive development of deformations typical for rheumatoid arthritis.[69]

Temporomandibular joint disorders are treated medically using analgesics, non-steroidal anti-inflammatory drugs and anti-rheumatic drugs, nutrition, physical and electromagnetic procedures like modulated currents, short frequency wave, interference currents, ice packs on hot and painful joints, hot baths (reduce pain and joint stiffness especially in the morning).[70] In addition, local surgical and prosthetic treatment is given using occlusal aids like splints (correction of occlusion, reduced loading of the TMJ joint, adaptation of inter-jaw relations, and enabling the return of the shifted meniscus to the normal position). Finally check of the joint is necessary by evading any non-functional movements. In addition, dietary changes and psychiatric counseling is also done. Few patients of rheumatoid arthritis with sicca syndrome should be treated by artificial devices.

CONCLUSION

This paper provides an overview on the possible immune pathogenesis mechanism and treatment options for all the lesions of autoimmune origin that are of paramount importance to a clinician to enable prevention, aid in definitive diagnosis, and successfully manage autoimmune diseases. Treatment of autoimmune disorders depends on the individual and may change over time. The objective is to get rid of symptoms, diminish tissue damage, and conserve organ function. New treatments with a better understanding of autoimmune disorders is essential to be investigated for enhanced care to immune mediated disorders in patients and expansion of novel vaccines for the betterment of our future.

CONFLICT OF INTEREST

No conflict of interest are declared.

ABBREVIATIONS USED

IL: Interleukin; **TNF:** Tumour necrosis factor; **HLA:** Human leukocyte antigen; **MHC:** Major histocompatibility complex; **CP:** Cicatricial pemphigoid; **BP:** Bullous pemphigoid; **MMP:** Mucous membrane pemphigoid; **IgG:** Immunoglobulin; **C:** Complement; **LTB:** Leukotriene; **VCAM:** Vascular cell adhesion molecule; **ICAM:** Intercellular adhesion molecule; **LFA:** Lymphocyte function associated antigen; **VLA:** Very late antigen; **BAFF:** B-cell activating factor; **BLyS:** B-lymphocyte stimulator; **PARP:** Poly (ADP)ribose polymerase; **EBV:** Epstein Barr virus; **TGF:** Transforming growth factor; **PDGF:** Platelet derived growth factor; **M3R:** Muscarinic receptors; **MD:** Mikulicz disease; **CD:** Cluster of differentiation/Crohn disease; **HSP:** Heat shock protein; **TCR:** T cell receptor; **IFN:** Interferon; **SKALP:** Skin derived anti leukoproteinases; **CLA:** Cutaneous lymphocyte antigen; **CC:** Chemokine; **PUVA:** Psoralen and ultraviolet therapy; **COL:** Collagen; **ET:** Endothelin; **ACE:** Angiotensin converting enzyme; **NOS:** Nitric oxide synthases; **CTF:** Connective tissue factor; **EBA:** Epidermolysis bullosa aquisita; **NC:** Non collagenous; **SLE:** Systemic lupus erythematous; **MBP:** Mannose binding protein; **CTLA:** Cytotoxic T-lymphocyte-associated protein; **nRNP:** Nuclear ribonucleic acid protein; **Sm:** Smith; **ANCA:** Anti-neutrophil cytoplasmic antibodies; **Bcl:** B cell lymphoma; **TMJ:** Temporomandibular joint; **EDS:** Ehlers-Danlos syndrome; **HHV:** Human Herpes Virus; **APCED:** Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; **AIRE:** Autoimmune regulator gene; **CMC:** Chronic mucocutaneous candidiasis; **Th:** Thymus; **WG:** Wegener's granulomatosis; **PR:** Proteinase; **MPO:** Myeloperoxidase; **Tx:** Thrombaxane; **PTPN:** Protein tyrosine phosphatase; **TSST:** Toxic shock-syndrome-toxin.

REFERENCES

1. Wucherpfennig KW. Mechanisms for the induction of autoimmunity by infectious agents. J Clin Invest. 2001;108(8):1097-104. http://dx.doi.org/10.1172/JCI200114235 ; PMid:11602615 PMCid:PMC209539.
2. Davies JM. Molecular mimicry: Can epitope mimicry induce autoimmune disease?. Immunology and cell Biology. 1997;75(2):113-26. http://dx.doi.org/10.1038/icb.1997.16 ; PMid:9107563.
3. Kalish RS. Pemphigus vulgaris: the other half of the story. The Journal of Clinical Investigation. 2000;106(12):1433-5. http://dx.doi.org/10.1172/JCI11828; PMid:11120748 PMCid:PMC387261.
4. Eversole LR. Immunopathology of oral mucosal ulcerative, desquamative and bullous diseases. Oral Surg Oral Med Oral Path. 1994;77(6):555-71. http://dx.doi.org/10.1016/0030-4220(94)90312-3.
5. Toto P, Feliciani C, Amerio P. Immune Modulation in Pemphigus Vulgaris: Role of CD28 and IL-10. J Immunol. 2000;164:522-9. http://dx.doi.org/10.4049/jimmunol.164.1.522.
6. Stanley JR. Pemphigus and Pemphigoid as paradigms of Organ-specific, Autoantibody-mediated diseases. The Journal of Clinical Investigation. 1989;83(5):1443-8. http://dx.doi.org/10.1172/JCI114036 ; PMid:2651476 PMCid:PMC303845.
7. Scully C, Challacombe SJ. Pemphigus vulgaris: Update on etiopathogenesis, oral manifestations and management. Critical Reviews in Oral Biology & Medicine. 2002;13(5):397-402. http://dx.doi.org/10.1177/154411130201300504.
8. Sciubba J. Autoimmune Aspects of Pemphigus Vulgaris and Mucosal Pemphigoid. Adv Dent Res. 1996;10(1):52-6. http://dx.doi.org/10.1177/08959374960100011001 ; PMid:8934925.
9. Mutasim FD, Pelc NJ, Anhalt GJ. Cicatricial Pemphigoid. Dermatologic Clinics. 1993;11(3):499-509.
10. Scully C, Carrozzo M. Sergio G, *et al*. Update on mucous membrane pemphigoid. Oral Surg Oral Med Oral Path. 1999;88(1):56-68. http://dx.doi.org/10.1016/S1079-2104(99)70194-0.
11. Korman NJ. Bullous Pemphigoid. Dermatologic Clinics. 1993;11(3):483-95. PMid:8365034.
12. Kim YB. The pathophysiology of autoimmune blistering diseases. The Journal of Clinical Investigation. 2005;115(4):825-8. http://dx.doi.org/10.1172/JCI200524855; PMid:15841169 PMCid:PMC1070439.
13. Coll J, Rives A, Grino MC. Prevalence of Sjögren's syndrome in autoimmune diseases. Annals of the Rheumatic Diseases. 1987;46(4):286-9. http://dx.doi.org/10.1136/ard.46.4.286 ; PMid:3592784 PMCid:PMC1002121.
14. Fox PC, Speight PM. Current Concepts of Autoimmune Exocrinopathy: Immunologic Mechanisms in the Salivary Pathology of Sjögren's Syndrome. Critical Reviews in Oral Biology and Medicine. 1996;7(2):144-58. http://dx.doi.org/10.1177/10454411960070020301 ; PMid:8875029.
15. Isine A, Bolstad, Jonsson R. Genetic aspects of Sjögren syndrome. Arthritis Res. 2002;4(6):353-9. http://dx.doi.org/10.1186/ar599; PMid:12453311 PMCid:PMC153844.
16. Ittah M, Richard MC, Gottenberg JE. B cell-activating factor of the tumor necrosis factor family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. Arthritis Research and Therapy. 2006;8(2):1-9. http://dx.doi.org/10.1186/ar1912 ; PMid:16507175 PMCid:PMC1526588.
17. Beher HMG, Peck AB, Dang H, Talal N. The role of apoptosis in the initiation of the autoimmune response in Sjögren's syndrome. Clin Exp Immunol. 1999;116:383-7. http://dx.doi.org/10.1046/j.1365-2249.1999.00888.x; PMid:10361223 PMCid:PMC1905316.
18. Maggie LJ. A Short review of the pathogenesis of Sjögren's syndrome. Autoimmunity Reviews. 2006;5:132-5. http://dx.doi.org/10.1016/j.autrev.2005.08.005; PMid:16431344.
19. Shearn M. The Sjögren-Mikulicz Syndrome - Its Relationship to Connective Tissue Disorders. California Medicine. 1961;95(3):159-62. PMid:18732436 PMCid:PMC1574499.
20. Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, *et al*. Clinical and pathological differences between Mikulicz's disease and Sjögren's syndrome. Rheumatology. 2005;44:227-34. http://dx.doi.org/10.1093/rheumatology/keh447 ; PMid:15509627.
21. Yamamoto M, Takahashi H, Ohara M, *et al*. A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease. Mod Rheumatol. 2006;16(6):335-40. http://dx.doi.org/10.3109/s10165-006-0518-Y; PMid:17164992 PMCid:PMC2785894.
22. Alvin GF. Experimental Mikulicz-Like Disease of the Lacrimal Gland, Induced by Repeated Subcutaneous Injections of 5-Hydroxytryptamine. J Dent Res. 1968;47(2):286-9. http://dx.doi.org/10.1177/00220345680470021501.
23. Sakane T, Hiroko NSN. Etiopathology of Behcet's Disease: Immunological Aspects. Yonsei Medical Journal. 1997;38(6):350-8. http://dx.doi.org/10.3349/ymj.1997.38.6.350 ; PMid:9509903.
24. Sakane T, Mitsuhiro T, Suzuki N , Inaba G. Behcet's Disease. The New England Journal of Medicine. 1999; 341(17):1284-91. http://dx.doi.org/10.1056/NEJM199910213411707; PMid:10528040.
25. Lehner T. Behcet's Syndrome and Autoimmunity. British Medical Journal. 1967;1:465-7. http://dx.doi.org/10.1136/bmj.1.5538.465; PMid:6017524 PMCid:PMC1840831.
26. Gul A. Behcet's disease: An update on the pathogenesis. Clinical and Experimental Rheumatology. 2001;19(Suppl. 24):6-12.
27. Fietta P. Behcet's disease: Familial clustering and Immunogenetics. Clin Exp Rheumatol. 2005;23(Suppl 38):96-105.
28. Brian NJ. Skin innate immune system in psoriasis: friend or foe?. The Journal of Clinical Investigation. 1999;104(9):1161-4. http://dx.doi.org/10.1172/JCI8633; PMid:10545511 PMCid:PMC409832.
29. Nickoloff BJ, Frank NO. Recent insights into the immunopathogenesis of Psoriasis provide new therapeutic opportunities. The Journal of Clinical Investigation. 2004;113(12):1664-75. http://dx.doi.org/10.1172/JCI200422147; PMid:15199399 PMCid:PMC420513.
30. Prignano F, Ricceri F, Pescitelli L, Lotti T. Itch in psoriasis: epidemiology, clinical aspects and treatment options. Clinical, Cosmetic and Investigative Dermatology. 2009;2:9-13. http://dx.doi.org/10.2147/CCID.S4465.
31. Frank AC. Is scleroderma an autoantibody mediated disease?. Curr Opin Rheumatol. 2006;18(6):579-81. http://dx.doi.org/10.1097/01.bor.0000245726.33006.c3 ; PMid:17053501.
32. Roy CLE. A brief overview of the pathogenesis of scleroderma (systemic sclerosis). Annals of the Rheumatic Diseases. 1992;51(2):286-8. http://dx.doi.org/10.1136/ard.51.2.286.
33. Chung L, Paul J. Antibodies in Scleroderma: Direct Pathogenecity and Phenotypic Associations. Current Rheumatology Reports. 2004;6(2):156-63. http://dx.doi.org/10.1007/s11926-004-0061-9 ; PMid:15016347.
34. Takehara K, Sato S. Localized scleroderma is an autoimmune disorder. Rheumatology. 2005;44(3):274-9. http://dx.doi.org/10.1093/rheumatology/keh487; PMid:15561734.
35. Zuper JP, Spertini F. Immunological basis of systemic sclerosis. Rheumatology. 2006;45(3):23-5. http://dx.doi.org/10.1093/rheumatology/kel285.
36. Albilia JB, Lam DK, Nick B, Clokie CML. Small Mouth. Big Problems?. A Review of Scleroderma and its Oral Health Implications. JCDA. 2007;73(9):831-6.
37. Gammon WR, Briggaman RA. Epidermolysis Bullosa Acquisita and Bullous Systemic Lupus Erythematosus. Dermatologic Clinics. 1993;11(3):535-47. PMid:8365038.
38. Raab B, Fretzin DF, Bronson DM. Epidermolysis Bullosa Aquisita and Inflammatory Bowel Disease. JAMA. 1983;250(13):1746-8. http://dx.doi.org/10.1001/jama.1983.03340130064034 : http://dx.doi.org/10.1001/jama.250.13.1746; PMid:6887488.
39. John RS, Nurit R, Vera KK. Epidermolysis Bullosa Acquisita Antigen is synthesized by both Human keratinocytes and Human dermal fibroblasts. The Journal of Investigative Dermatology. 1985;85(6):542-5. http://dx.doi.org/10.1111/1523-1747.ep12277377.
40. David TW, Keefe EJ, Reese MJ. Epidermolysis Bullosa Aquisita Antigen, a New Major Component of Cutaneous Basement Membrane, Is a Glycoprotein with Collagenous Domains. J Invest Dermatol. 1986;86(6):668-72. http://dx.doi.org/10.1111/1523-1747.ep12275978.
41. Ngan V. Epidermolysis Bullosa acquisita. Derm Net. 2003;1-4.
42. Dimitrios TB, Howard AA, Barri JF. Systemic Lupus Erythematosus: Emerging Concepts. Ann Intern Med. 1995;122(12):940-50. http://dx.doi.org/10.7326/0003-4819-122-12-199506150-00009.
43. Mok CC, Lau CS. Pathogenesis of Systemic lupus erythematosus. J Clin Pathol. 2003;56:481-90. http://dx.doi.org/10.1136/jcp.56.7.481.
44. Caraba A, Savoiu G, Crisan V. Endothelial dysfunction in Systemic Lupus Erythematosus. Romanian J Biophys. 2008;18(3):237-44.
45. Jessica JM, Anisur R. Systemic lupus erythematosus. Orphanet Journal of Rare Diseases. 2006;1-9. PMCid:PMC1435995.
46. Feng PH. Management plan of Systemic Lupus Erythematosus – A flow chart. Singapore Medical Journal. 1980;21(4):634-8. PMid:7221573.
47. Dominique PG. Ehlers-Danlos syndrome type IV. Orphanet Journal of Rare Diseases. 2007;2(32):1-9. http://dx.doi.org/10.1186/1750-1172-2-32.
48. Konrad Pesudo vs. Orbscan mapping in Ehlers-Danlos syndrome. J Cataract Refract Surg. 2004;30(8):1795-8. http://dx.doi.org/10.1016/j.jcrs.2004.05.002; PMid:15313310.
49. Michael LC, Benjamin RA, Alvin TS. Sarcoidosis. N Engl J Med. 2007;357:2153-65. http://dx.doi.org/10.1056/NEJMra071714 ; PMid:18032765.
50. Hilario N, Diane B, Dominique SPV. Sarcoidosis. Orphanet Journal of Rare Diseases. 2007;2(46):1-8. PMid:17204147 PMCid:PMC1774562.
51. Grutters JC, Dent M, van den Bosch JMM. Sarcoidosis. Eur Respir Mon. 2009;46:126-54. http://dx.doi.org/10.1183/1025448x.00046008.
52. Suresh L, Radfar L. Oral sarcoidosis: a review of literature. Oral Diseases. 2005;11:138-45. http://dx.doi.org/10.1111/j.1601-0825.2005.01014.x; PMid:15888103.
53. Jaakko P. Autoimmune Polyendocrinopathy- Candidiasis- Ectodermal Dystrophy. The Journal of Clinical Endocrinology and Metabolism. 2006;91(8):2843-50. http://dx.doi.org/10.1210/jc.2005-2611 ; PMid:16684821.
54. Meriluoto T, Halonen M, Pelto-Huikko M. The autoimmune regulator: a key toward understanding the molecular pathogenesis of autoimmune polyendocrinopathy-candidiasis- ectodermal dystrophy. Keio J Med. 2001;50(4):225-39. http://dx.doi.org/10.2302/kjm.50.225.
55. Halonen M, Eskelin P, Myhre AG. AIRE Mutations and Human Leukocyte Antigen Genotypes as Determinants of the Autoimmune Polyendocrinopa-

thy- Candidiasis-Ectodermal Dystrophy Phenotype. The Journal of Clinical Endocrinology and Metabolism. 2002;87(6):2568-74. http://dx.doi.org/10.1210/jcem.87.6.8564; PMid:12050215.

56. Buzi F, Badolato R, Mazza C. Autoimmune Polyendocrinopathy- Candidiasis-Ectodermal Dystrophy Syndrome: Time to Review Diagnostic Criteria?. J Clin Endocrinol Metab. 2003;88(7):3146-48. http://dx.doi.org/10.1210/jc.2002-021495; PMid:12843157.
57. Guillevin L. Wegeners granulomatosis. Orphanet. 2004:1-5.
58. Rookard P, Hechtman J, Baluch AR, Kaye AD, Manmohansingh V. Wegener's granulomatosis. MEJ Anesth. 2009;20(1):21-30.
59. Hattar K, Bickenbach A, Csernok E *et al*. Wegener's granulomatosis: antiproteinase 3 antibodies induce monocyte cytokine and prostanoid release—role of autocrine cell activation. Journal of Leukocyte Biology. 2002;71(6):996-1004.; PMid:12050185.
60. Ponniah, Ahmed, Shaheen K, Shankar A, Kumaran MG. Wegener's granulomatosis: The current understanding. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100(3):265-70. http://dx.doi.org/10.1016/j.tripleo.2005.04.018; PMid:16122651.
61. Malathi S, Shivbalan S. Crohn's Disease. Indian Journal of Pediatrics. 2006;73(8):723-9. http://dx.doi.org/10.1007/BF02898453.
62. Ogura Y, Bonen DK, Inohara N, *et al*. A frame shift mutation in NOD2 associated with susceptibility to Crohn's disease. Nature. 2001;411(6837):603-6. http://dx.doi.org/10.1038/35079114 ; PMid:11385577.
63. Vavricka SR, Rogler G. New insights into the pathogenesis of Crohn's disease: are they relevant for therapeutic options?. Swiss Med Weekly. 2009;139(37-38):527-34.
64. William M. Chamberlin, Saleh A. Naser. Integrating theories of the etiology of Crohn's Disease on the etiology of Crohn's Disease: Questioning the Hypotheses. Med Sci Monit. 2006;12(2):27-33.
65. Antoine. Crohn's disease. Orphanet Encyclopedia 2003;1-5.
66. Kenji Y, Yasuo I. Autoimmune Hematological Diseases. Journal of the Japan Medical Association. 2004;129(7):907-11.
67. Semple JW. Immune pathophysiology of aurtoimmune thrombocytopenic purpura. Blood Reviews. 2002;22:1-4.
68. Vanamala A, Devi S, Sitalakshmi S, Karuna RK. Clinical patterns and Hematological Spectrum in Autoimmune Hemolytic Anemia. Journal of Laboratory Physicians. 2010;2(1):17-20. http://dx.doi.org/10.4103/0974-2727.66703; PMid:21814401 PMCid:PMC3147080.
69. Oliver S, Ryan S. Rheumatoid arthritis. Nursing standard. 2002;16(20):45-52. http://dx.doi.org/10.7748/ns.16.20.45.s47: http://dx.doi.org/10.7748/ns2002.01.16.20.45.c3147.
70. Peric P, Peric B. Temporomandibular Arthritis in Association with Rheumatoid Arthritis - a Differential Diagnostic Approach to Temporomandibular Pain in Dental Practice. Acta Stomat. 2002;36(1):113-8.

Article History: Submission Date: 08-08-16; Revision Date: 09-09-16; Accepted Date: 01-10-16.
Cite this article: Ganapathy S, Vedam V, Rajeev V, Arunachalam R. Autoimmune Disorders–Immunopathogenesis and Potential Therapies. J Young Pharm. 2017;9(1):14-22.