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Immunomodulatory Potential of Stem Cells on Autoimmune Vesicullobullous Lesions: A Narrative Review

ABSTRACT:- *Vesicullobullous lesions represent a heterogeneous group of mucocutaneous disorders characterized by vesicle and bullae formation, often resulting from autoimmune, genetic, infectious, or drug-induced etiologies. Accurate diagnosis and effective management require a thorough understanding of the clinical presentation, histopathology, and underlying molecular mechanisms. This review provides a comprehensive overview of vesicullobullous lesions, including their classification, antigenic targets, and immunopathogenesis. Emphasis is placed on autoimmune disorders such as Pemphigus vulgaris, Bullous Pemphigoid, and dermatitis Herpetiformis, which involve distinct auto antibodies against structural proteins like Desmogleins, BP180, and type VII collagen. Diagnostic modalities including Nikolsky's sign, biopsy, Tzank smear, direct and indirect immunoflourosence, ELISA, and salt-split skin techniques are discussed in detail. Conventional treatment approaches involving corticosteroids, immunosuppressants, and Biologics such as Rituximab remain the mainstay of therapy. Furthermore, emerging regenerative therapies using Mesenchymal and Hematopoietic stem cells offer promising avenues for managing refractory cases, leveraging their immunomodulatory and tissue-repair capacities. This review aims to bridge current clinical practices with advances in molecular biology and regenerative medicine, offering a multidimensional approach to the diagnosis and management of vesicullobullous diseases.*

Key words:- *Vesicullobullous lesions, Autoantibody, Desmogleins, Pemphigus, Mesenchymal stem cells.*

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I. INTRODUCTION:

Vesiculobullous lesions represent a diverse group of mucocutaneous disorders characterized by the formation of fluid-filled vesicles and bullae. Vesicles measure less than 0.5 cm, while bullae are larger than 0.5 cm. These lesions arise from a wide range of etiologies, including autoimmune, genetic, infectious, inflammatory and drug-induced causes. Accurate clinical diagnosis is crucial, as the level of blister formation, histopathological features and immunological profile directly influence treatment planning and disease prognosis. A comprehensive understanding of clinical manifestations and microscopic findings therefore remains central to effective management of these conditions.

Among all types, autoimmune vesiculobullous lesions constitute the most clinically significant group. Conditions such as Pemphigus vulgaris, Pemphigus foliaceus, Bullous pemphigoid, Epidermolysis Bullosa Acquisita, Dermatitis Herpetiformis and Cicatricial pemphigoid are characterized by circulating autoantibodies directed against specific structural proteins. These include desmosomal components like Desmoglein-1 and Desmoglein-3, hemidesmosomal proteins such as BP180, BP230, and anchoring fibril proteins including type VII collagen. The binding of these autoantibodies leads to loss of cellular adhesion, complement activation, cytokine release and subsequent blister formation at different levels of the dermal-epidermal junction.

Diagnostic confirmation relies on a combination of clinical tests and laboratory investigations. Techniques such as Nikolsky's sign, histopathological examination, Tzanck smear, direct and indirect immunofluorescence, ELISA, and the salt-split skin technique play essential roles in differentiating various autoimmune vesiculobullous diseases based on their immunological targets and blister levels. These diagnostic tools not only establish the presence of disease but also help determine antigen specificity and guide treatment protocols.

Conventional therapy for autoimmune vesiculobullous lesions primarily includes systemic and topical corticosteroids, steroid-sparing immunosuppressants, antibiotics, intravenous immunoglobulins and biologic agents such as Rituximab. Although effective, these approaches are often limited by adverse drug reactions, long-term immunosuppression and refractory disease in some patients. This has led to increasing interest in regenerative and cellular therapies.

Stem-cell-based therapy, particularly using mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs), has emerged as a promising therapeutic approach due to their immunomodulatory, anti-inflammatory and tissue-repair properties. MSCs exert effects through paracrine signaling, cell-cell adhesion,

cytokine regulation, and immunosuppression, while HSC transplantation has shown success in selected refractory autoimmune vesiculobullous cases. Early-phase clinical trials indicate encouraging outcomes, improved wound healing and acceptable safety profiles, though standardized protocols and long-term data remain necessary.

This narrative review provides a comprehensive overview of autoimmune vesiculobullous lesions, their pathogenesis, molecular biology, diagnostic approaches, conventional treatments and the evolving role of stem-cell-based therapies, highlighting their potential in managing difficult and refractory cases.

BACKGROUNG & OVERVIEW OF VESICULLOBULLOUS LESION

Vesicullobullous lesions are diverse range of dermatological inflammatory diseases which are characterized by vesicles and bullae and clinical diagnosis of vesicullobullous lesion is a very important for inducing the targeted therapy and management[1]. A comprehensive understanding of the histopathology and clinical features is the key to diagnostic success and its treatment[2]. vesicullobullous lesions are generally fluid filled and which is less than 0.5 cm is termed as vesicles and more than 0.5 cm are termed as bullae.[3]. Vesicullobullous lesion may occur due to in Infective, genetic, Drug induced, viral, inflammatory conditions[4].

Classification of vesicullobullous lesion:-

SL.NO	ETIOLOGY	TYPES
1.	AUTOIMMUNE	PEMPHIGUS VULGARIS BULLOUS PEMPHIGOID DERMATITIS HERPETIFORMIS PEMPHIGOID GESTATIONS BULLOUS SYSTEMIC LUPUS ERYTHEMATOSUS LINEAR IGA DERMATOSIS EPIDERMOLYSIS BULLOSA ACQUISITA PARANEOPLASTIC PEMPHIGUS CICARTRICAL PEMPHIGUS BULLOUS LICHEN PLANUS
2.	FAMILIAL	HAILEY HAILEY DISEASE EPIDERMOLYSIS BULLOSA
3.	INFECTIOUS	VERICELLA HERPES ZOSTER HERPES SIMPLEX BULLOUS SCABIES BULLOUS IMPETIGO
4.	OTHERS	BURNS DIABETIC BLISTER TOXIC EPIDERMOLYSIS BULLOSA FIXED DRUG ERUPTION BULLOUS ERYTHEMA MULTIFORM

MOLECULAR BIOLOGY OF VESICULOBULLOUS LESIONS OVERVIEW.

Vesicullobullous lesion is characterized by blister formation in skin and mucous membranes.Histopathological features such as acantholysis [no specific always-for all vesicullobullous lesion] but it is seen in inherited conditions like Hailey Hailey disease &Darrier disease[5].Molecular techniques has been identified to create the best diagnostic criteria for vesicullobullous lesions like identifying Auto antibodies and Targeted proteins(eg.Desmogleins, Bullous Pemphigoid antigen).Methods like direct immunoflourosence and indirect immunoflourosence helps in classification according to antibody involvement and its location[6].

Pemphigus :-is a chronic autoimmune disease which leads to the formation of blister and erosion of skin and mucous membrane as it mainly happen due to the auto antibody against Desmosomal protein (Dsg) present in Desmosomes in cellular junction(it helps in cell -cell adhesion)[7]. In Pemphigus vulgaris Dsg3(130kDa) causes the oral blister formation Dsg1and Dsg3 target the skin and mouth blister formation[8].

Pemphigus folliaceous mainly affects the Dgs-1 (160Kda) which leads to the formation of superficial blister formation but there is no oral cavity involvement seen[9]. Auto-Antibody IgG1, IgG2 mainly binds to Desmogleins protein and disrupts the cellular adhesion which leads a pathological feature called acantholysis(Hallmark of Pemphigus vulgaris and Pemphigus folliaceous)[10].

Bullous Pemphigoid :-is autoimmune skin condition present with tense blister (bullae)with erythema and it is distributed in all over the body[11]. pathologically there is sub-epithelial blistering with immense neutrophill accumulation[12]. Autoimmunity in Bullous Pemphigoid results from IgG class of antibodies and it mainly attacks the Hemidesmosomes ,it mainly targets hemidesmosomal protein like BP230,BP180,BPAG2 and another proteinacous domain NC16A[12]. Immunoglobulins like IGg,IgG4,IgE and memory B cells maily responsible for autoimmine dermal reaction [13]. Complement system activation(C3a,C5a) and release of cytokines like IL-

6,IL-8,TNF-α, TNF-β, IFN-γ ,Eotaxin causes cascades if enzymatic reaction which leads to the accumulation polymorphonucleocytes and cause blistering[14]. Sub-epithelial is the hallmark of Bullous Pemphigoid[15].

Dermatitis Herpetiformis (DH):- it is a chronic autoimmune disease with blistering and intense pruritus which is commonly seen in Elbows, Axilla, Face, very rare oral cavity involvement[16].Pathologically there is an involvement of Granular IgA deposits in dermal papillae and is associated with complement activation[17]. The main action is on microfibrillar bundles on elastic fibres beneath the basal lamina with intense neutrophill accumulation causing dermal microabsess formation which sometimes coalesce to form unilocular sub-epidermal bullae within 24 hours[18].

Linear IgA Bullous Dermatosis :- A rare mucocutaneous autoimmune dermatological condition due to the immune reaction against the BP180, BP230, Type VII collagen, laminin 332 by IgA auto-antibodies, also protein LABD-97 and LAD-1 is targeted in this condition. By immunoflourosence assay the IgA antibodies are seen in BMZ(Basement membrane zone) mainly by Direct immunoflourosence (DIF)[19].

Epidermolysis Bullosa Acquisita(EBA):- It is a condition which mimics Bullous Pemphigoid which shows multiple blister formation in all over body, clinically it has two variants classical(non infective)and infective type.In molecular pathogenesis autoimmunity is seen against Type VII collagen and by immunological florescence studies there is a intense deposition of antibody lamina densa and sub lamina densa[20].

Para-neoplastic Pemphigus (PNP):- It is characterized by the production of Auto antibodies predominantly IgG targeting Desmosomes plakins,clinically painful blisters and erosive mucosal ulceration is the hallmark of PNP . The common neoplasms associated with PNP is Non hodgkins lymphoma, Castle-man disease,chronic, lymphocytic leukemia[48].

Cicartrical Pemphigoid(CP):- It is also known as mucous membrane Pemphigoid and these condition has atypical ocular involvement and also have oral lesion (Desquamative gingivitis).The circulating auto antibody mainly IgG class is involved in production of immune reaction , the target molecule are Laminin332, BP180(CollagenXVII), Aplha-6 Beta-6 integrins are present in cellular junction and destruction of transmenbrane component of Hemidesmosomes is involved in this disease[49].

SL.NO	Histopathological dermal layers involved in vesicullobullos lesion	Types
1.	Spinous layer	Pemphigus Vulgaris
2.	Granular cell layer	Pemphigus Foliaceos Pemphigus erythematosus
3.	Basal cell layer	Epidermolysis Bullosa Simplex
4.	Lamina Lucida	Bullous pemphigoid Cicartical pemphigoid Epidermolysis Bullosa Acquisita Dermatitis Herpetiformis
5.	Sublaminar connective tissue	Erytema multiforme Epidermolysis Bullosa Dystrophica

(Histopathological areas involved in Vesicullobullous lesions).

Autoimmune Vesiculobullous Lesion	ANTIGENS
Pemphigus Vulgaris	Desmoglein 1,3
Paraneoplstic pemphigus	Desmoglein 1,3,& plains
Pemphigus foliaceous	Desmoglein 1
IgA Pemphigus	Desmoglein -3, Desmocolin 1,2
Pemphigus Herpetiformes	Desmoglein1
Cicartricl Pemphigoid	Bullous pemphigoid 180 ,laminin V
Bullous Pemphigoid	Bulous pemphigoid 180,230
Epidermolysis Bullosa Acquisita	Type VII collagen
Erythema Multiforme	Desmoplakins
Dermatistis Herpetiformes	Tissue glutaminases

(Table showing Antigen being attacked by the circulating antibody which consider them as antigens).

CONVENTIONAL TREATMENT OF VESICULLOBULLOUS LESIONS:-

Systemic steroid including Prednisolone ,dexamethsone are being used commonly in various autoimmune Vesicullobullous lesion and also topical steroid formulations are used[47].Azathioprine, mycophenolate mofetil,Cyclosporin , Methotrexate are used as a aadjuvent therapy with existing Steroidal Treatment for better results[44]. Dapsone is exclusively for Dermatitis Herpetiformis and also for some other vesicullobullous lesions[43]. Intravenous Immunoglobulin is used in various vesicullobullous lesion as immunosuppression therapy and Antimicrobial treatment with tetracycline and Doxycyline is also used for super

infections due to immunosuppression[47].Biologics Such as Rituximab Is extensively used in vesicullobullous lesion therapy when the steroidal treatment is fail[46].

DRUG SIDE EFFECTS WITH CONVENTIONAL TREATMENT FOR VESICULLOBULLOUS LESIONS:-

Biologics(Rituximab)	Multi-focal leukoencephalopathy, increased risk of infections, infusion reactions.
Tetracyclins	GI upset, photo-sensitivity,Esophagitis.
Intavenous immunglobulin	Thromboembolic events, Renal Dysfunction,Headache ,Fever, Chills.
Dapsone	Haemolysis(especially in G6PD deficiency),Methhaemoglobinaemia,renal dysfunction.
Azathioprine	Hepatotoxicity, Bone marrow suppression
Mycophenolate Mofetil	GI upset, Leukopenia
Methotrexate	Bone Marrow suppression, pulmonary toxicity.
Cyclosporin	Gingival hyperplasia, nephrotixicity, Hypertension.
Systemic Streoid	Cushingoid Features, Immunosuppression , Leukopenia.

DIAGNOSTIC CRITERIA OF VESICULLOBULLOUS LESIONS:-

Nikolsky's sign:- This is clinical diagnostic criteria of various vesicullobullous lesions[]. application with firm sliding pressure by finger causes separation of erosive surfaces in skin due to unstable inter-cellular anchorages.[57]. Nikolsky,s sign is commonly seen with steves jhonson syndrome, toxic Epidermolysis necrosis, Staphylococcal scalded skin syndrome, Pemphigus vulgaris, Pemphigus folliaceous, mucous membrane Pemphigoid, Bullous Pemphigus, Graft versus host disease, erythema multiforme[58].

Biopsy:- This is a very crucial step for the diagnosis of vesicullobullous lesion in which the per lesion tissue is taken without involving the affected region , pre-biopsy procedure is required to contraindicate use of topical steroid to avoid false positive results[]. 3-4mm punch biopsy is done from the non affected region of the skin.A 10% buffered formalin is used for H&E staining by the help of Micheal's medium(to preserve the immune reactants) for immunoflourosence studies[59].

Tzank smear :- This helps mainly in differentiating from viral or acantholytic type . In Autoimmune vesicullobullous lesion no inclusion bodies are seen only acantholytic epithelial remnants are seen[59].

ELISA (ENZYME LINKED IMMUNOSORBENT ASSAY):- ELISA is emerged has a wide choice for the detection of antigen and antibody from sample. This procedure helps to avoid radioactive labelled procedures. The enzyme such as Horse reddish peroxide Alkaline phosphatase is used in the identification of Antigen and Antibody. ELISA is widely used for the diagnosis of Pemphigus Vulgaris and Pemphigus Folliaceous[59].

SALT SPLIT TECHNIQUE:- It is a specialized immunoflourosence technique used mainly to differentiate between Bullous Pemphigoid and Epidermolysis Bullosa Aquistisia . the separation of lamina densa and basement membrane zone is done to identify the disease pathogenesis , IgG and C3 fluorescent labelled antibody is used . For Bullous Pemphigoid a typical roof pattern in seen which shows he epidermal side and in case of Epidermolysis Bullosa Aquistisia a typical floor pattern is seen which demonstrate the dermal side and is seen targeting type VII collagen in sub densa lamina is being observed[60].

Clinical test	**Nikolsky's Test**
Histopathological test	**Biopsy** **Tzank Test**
Molecular techniques	**Immunoflourosence test** **Salt Split test** **ELISA & Western blotting**

(Different diagnostic Criteria of Vesicullobullous lesion)

Direct Immunoflourosence:- It is done after a small skin fragment is taken from the perilesional area , the floroscienated antibodies specific to Human immunoglobulin(IgG,IgA, IgM), Complement(C3) or fibrin is applied and molecular evaluation is done[59]

Indirect immunoflourosence:- The detection of circulating antibody is done with this technique the floroscienated Antibodies mainly IgG, IgA is used for the detection [59].

Pemphigus vulgaris	Intercellular IgG
Paraneoplastic pemphigus	Intracellular dermoepidermal and intradermal antibody deposition is seen
Pemphigus Herpetiformes	IgG in epidermal cells
Cicartrical pemphigoid	Circulating IgG in besement membrane zone,laminin 5
Bullous Pemphigoid	Circulating IgG in Basement membrane zones.
Epidermolysis Bullosa acquisita	Circulating IgG In type VII collagen

Linear IgA Dermatosis	Antibody Against Basement membrane zones

(Immunoflourosence studies showing Circulating Antibody against various areas of dermal epithelium of vesicullobullous lesions).

Pemphigus Vulgaris	Fisnet pattern
Pemphigus Foliaceous	IgG /C3in upper epidermis (Roof pattern)
Bullous Pemphigoid	Linear IgG /C3 in basement membrane zones

(Direct Immunofluoresence aessement of molecular pathogenesis of Vesicullobullous lesion)

STEM CELL BIOLOGY

Stem cells are specialized cells in the body with remarkable elf renewal capacity have intense capability of differentiation into specialized types of cells[21]. It is classified into major three categories,

Totipotent:- Capacity to develop into entire organism

Pluripotent:- Develop mainly in lab conditions(In Vitro) intp different multiple types of cells.

Multi potent :- These have special capacity to develop into multiple lineages [22].

TYPES OF STEM CELLS

According to the origin of stem cells there are different types of stem cell and used for multiple therapeutic purpose.

EMBRYONIC STEM CELL**:-** Embryonic stem cells pluripotent form of germ cells obtained from inner cell mass of pre implantation blastocysts[23]. Embryonic stem cells are isolated from several mammalian species including rodents (Murine Embryonic stem cells), primates,Human[24].

ADULT STEM CELL**:-** These are mainly of two broad categories like multi potent which can differentiate into several different types of stem cell types including blood, nerve,cartilages (Hematopoietic stem cells, neuronal stem cells, intestinal stem cells, Mesenchymal stem cells) And another type is uni-potent stem cells which can differentiate into only one type of cell type(eg:- Skeletal,or renal etc.)[25].

MESENCHYMAL STEM CELLS**:-** Stem cells obtained from different types of tissue which includes, Endometrial polyp, Fallopian tube, Endometrial menstruation, cruciate ligament.Mesenchymal stem cells have immunomodulatory effects which have a ability for inhibition of T cell, B-cell, Natural killer cells proliferation and this property ids highly used for tissue regeneration and other therapeutic areas[26].

HEMATOPOIETIC STEM CELLS**:-** These are rare cells found on bone marrow which have unique ability to regerate and maintain lymphoid and myeloid lineages and have high proliferative and self renewal capacity [27].

MECHANISM OF ACTION OF MESENCHYMAL STEM CELL:- Mesenchymal stem cell works with multiple cytological pathways which include paracrine signaling, cell-cell Adhesion , immunmodulation, Migration(Homing), Enhancement Administration[28]. paracrine signaling is the main driver of Mesenchymal stem cells which helps in tissue repair, angiogenesis and Immune modulation. Cell-cell adhesion helps in mitochondrial transfer and enhances the survival of cell with cellular injury. In terms of immunmodulation it suppresses the inflammatory cytokines and reduces the inflammation which acts as a therapeutic agent for Autoimmune disorders[28]. The delivery (Homing) of Mesenchymal stem cells are administered systematically , Mesenchymal stem cells express CD44(HCAM) and interacts with Endothelial selectins(P-selectins,VCAM-1,ICAM-1), Galectin-1, CD24, FGFK also play an important role in homing.The main mechanism of homing initially occurs with adhesion with blood vessels with CD44 and selectins, then chemokine receptor (CXCR4)which activates integrins, THE VCA-4 and VCAM-1 helps in the entrapment of Integrins.The diapedesis of Mesenchymal stem cells in bloodvessels are finally guided by MMPs followed by migration of Mesenchymal stem cell into the injury site guided by chemokines [29,33,34].

STEPS OF HOMING	KEY MOLECULES INVOLVED	PURPOSE
Adhesion	CD44,SELECTINS	Initial attachment to Endothelium
Activation	CHEMOKINE RECEPTOR(CXCR4)	Increases integrins affinity
Entrapment	VLA-4,VCAM-1	Firm adhesion to vessel wall
Diapedesis	MMPs, CXCL-9	Transmigration through vascular Endothelium.
Migration	PDGF,IGF-1,SDF-1	Chemotaxis to injury site.

MECHANISM OF ACTION OF HEMATOPOEITIC STEM CELLS:-

Hematopoietic stem cells are mainly found in bone marrow, peripheral blood, umbilical cord blood.It has a very self renewal capacity which has ability to divide and produce identical daughter cell. Mostly it exists in its quintessence stage-for long term preservation and it can be activated on demand.Hematopoietic stem cells are regulated by cytokine, Growth factors, Transcription factors, in terms of homing of Hematopoietic stem cells it is

between bone marrow and blood which later helps for clinical harvestation and transplantation, CD34,CD133, are the common surface marker of Hematopoietic stem cells.[36,37,38].

TREATMENT TECHNIQUES FOR VESICULLOBULLOUS LESION WITH STEM CELLS

1. Hematopoietic stem cell Transplantation (ALLOGENIC HSCT):- The most common use of this stem cells therapy is for patient with resistant conventional treatment of Pemphigus vulgaris. Allogenic Hematopoietic stem cells are generally infused with cytokine stimulant and injected in bone marrow , thymus, peripheral blood , recovery of new lesion has been observed within 24 hours and a6 to 8 month clinical followup is required and no graft versus host disease is observed[].
2. MESENCHYMAL STEM CELL THERAPY:- Allogenic bone marrow derived Mesenchymal stem is seen to effective in Dystrophic Epidermolysis Bullosa , use of stem cell intravenously helps helps in wound healing and reduces the erythema and Dermal infection helps in healing of blister formation[39].
3. STEM CELL DERICED EXTRAVASCULAR VESICLES:- Exosomes and microvesicles promote tissue repair which aids in immunomodulatory immune response and also proote neo vascularisation and contain neuroregerative properties[40].

Adverse Effect of Treatment based with Mesenchymal stem cell s for Autoimmune Disorder:-

Mesenchymal stem cells are described as the potent immunomodulatory effect due the low expression of major histocompatibility class II factor, but repeated allogenic infusion could result host immune responses which may lead to immune rejection and potentially affecting the future transplants. Mesenchymal stem cells tumorigenic potential which is exactly not oncogenic although angiogenesis , cytokine production , immune suppression can create an pro oncogenic micro environment, therefore it is avoided in patient with existing neoplastic lesions.Another risk in using MSC based treatment is development of ectopic tissue or fibrotic scarring has been observed in various models in Vivo therefore systemic infusion has been creating a concern with MSC based treatment.Prolonged in vitro expansion of MSCs, necessary for therapeutic doses, may lead to chromosomal aberrations, cellular senescence, or epigenetic alterations. These changes can affect the safety and efficacy of the transplanted cells, possibly resulting in unpredictable biological behavior. Strict monitoring of cell batches for genomic stability and limiting the number of passages during cell culture is recommended.The therapeutic effects of MSCs depend on their interaction with the host immune micro environment. Chronic autoimmune conditions may alter this niche, reducing the immunosuppressive functionality of MSCs or leading to phenotype drift. This variability introduces uncertainty in the durability and reproducibility of treatment outcomes over time.By suppressing immune cell activity, MSC therapy may increase susceptibility to opportunistic infections, especially in patients already on concurrent immunosuppression. Long-term immune suppression can lead to latent viral reactivation (e.g., CMV, EBV) or increased risk of bacterial/fungal infections[50-53].

Regulatory clinical trials on Stem cells based treatment for vesicullobullous lesions:-Stem cell-based therapies are increasingly being investigated in clinical trials as potential treatment options for refractory vesicullobullous diseases. While Mesenchymal stem cells (MSCs) and Hematopoietic stem cells (HSCs) have shown promising pre clinical and early-phase results, their incorporation into mainstream dermatological practice remains under regulatory evaluation.

Registered Clinical trial	Phases of trial ongoing	Types of Mesenchymal stem cell used	Reactions/status	Country registered
NCT03529877	Phase I/II completed	Allogenic MSC	Mild adverse reaction, good tolerabilty, reduction of scarring	US/Europe
NCT04153630	Phase I/II	Haploidentical MSC	unknown	Spain
NCT04520022	Phase I/II	Umbilical cord	Well-tolerated	Korea
NCT02579369	Phase I/II, Unknown	Adipose MSC Hydrogel	Unknown	Korea
NCT02582775	Phase II, Active	BM-HSC with MSC infusions	Improved safety, restoration of anchoring fibrils	US
NCT02323789	Phase I/II, Unknown	Allogeneic BM-MSCs	No serious adverse events, transient benefits	UK
2012-00894-87	Phase I/II, Completed	Allogeneic BM-MSCs	Good tolerance, clinical improvements	UK
NCT05111600	Phase II/III, Recruiting	RV-LAMB3 Stem Cell Grafts	Promising safety profile,permanent restoration of DEJ	Italy, France

Most trials are well tolerated with absence of adverse reaction which indicates favorable reliability of the Mesenchymal stem cells. Clinical improvements such as reduced scarring, improved safety, transient benefits, and restoration of tissue structures (anchoring fibrils, dermal–epidermal junction) have been observed in various

studies.Trials are active in the US, Europe, UK, Korea, Spain, Italy, and France, reflecting international momentum[54-56].

Ethical and Legal consideration:- In India National Guidelines for Stem Cell Research (ICMR-DBT, 2017) ,Draft New Drugs, Medical Devices & Cosmetics Bill 2022, Drugs and Cosmetics Rules, 1945. Only Hematopoietic stem cell transplantation (for specific conditions) is an approved therapy All other stem cell therapies must be conducted as regulated clinical trials Commercial use and advertisement of stem cell therapies not allowed Banking of umbilical cord blood only permitted currently Germ-line engineering, reproductive cloning, and xenotransplantation with stem cells are not permitted.

Conclusion:- Autoimmune vesicullobullous lesions represent a complex group of dermatological disorders characterized by diverse immunopathogenesis mechanisms, histopathological features, and clinical presentations. Despite advancements in conventional therapies—including corticosteroids, immunosuppressants, and Biologics—treatment resistance, adverse effects, and long-term immunosuppression remain critical challenges. Recent insights into molecular biology have improved diagnostic precision, particularly through immunoflourosence techniques and antigen-specific assays such as ELISA and salt-split skin tests. Stem cell-based therapies, particularly involving Mesenchymal stem cells (MSCs) and Hematopoietic stem cells (HSCs), have emerged as promising alternatives due to their immunomodulatory, potential, and anti-inflammatory properties. These therapies have shown encouraging early clinical outcomes in managing cases, especially in Pemphigus vulgaris and Epidermolysis Bullosa. However, safety concerns including immune rejection, tumorigenic potential, and variability in efficacy remain significant.Detailed clinical trials, strict regulatory protocol , and long-term follow-up are essential to translate these innovative therapies into safe, standardized, and effective clinical practice. Future research must focus on optimizing delivery systems, minimizing risks, and understanding patient-specific responses to stem cell therapy.

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