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Burden of Autoimmune Disorders; A Review

Kimberly Morton Cuthrell [a*], Nikolaos Tzenios [b] and Javeria Umber [c]

[a] Saint James School of Medicine, United States.
[b] Public Health and Medical Research, Charisma University, Grace Bay, Turks and Caicos Islands.
[c] Government College University Faisalabad (GCUF), Pakistan.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

When immunologic tolerance to auto-reactive immune cells is lost, autoimmune illness manifests as the immune system attacking self-molecules. Numerous autoimmune diseases are strongly predisposed by genetic, viral, and/or environmental factors. Autoimmune diseases include insulin-dependent diabetic mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, and multiple sclerosis. These autoimmune diseases are characterized by a variety of problems and symptoms that range from organ-specific to systemic. Autoimmune pathology may have a role in conditions like arteriosclerosis, inflammatory bowel disease, schizophrenia, and specific forms of infertility. This review consists of a brief explanation and analysis of the immune system and tolerance maintenance, a few autoimmune disorders, immune auto-reactivity mechanisms, and experimental autoimmune models.

Keywords: Autoimmune disease; systemic autoimmune diseases; B- cell tolerance; T- cell tolerance; immunosuppressive/immunocompromised disorders.

**Corresponding author: E-mail: researcher@kimberlymortoncuthrell.com;*

1. INTRODUCTION

When the immune system is unable to distinguish between healthy tissues and potentially dangerous antigens, it results in autoimmune diseases. The idea of molecular mimicry can be used to explain the immune system attacking its own host. The immune system typically fighting antigens and develops a reaction in response to the antigens. In autoimmune illnesses, the immune system is unable to tell its own host cells apart from foreign antigens. A mechanism called molecular mimicry is where a foreign antigen resembles a self-antigen structurally [1-4]. Molecular mimicry continues to be a significant mechanism that often is implicated in the atginning of autoimmunity despite its association with autoimmune disorders. Self-destructive attacks createdecular mimicry can result in a wide range of bodily reactions, from insignificant to potentially fatal. Different autoimmune diseases appear in various ways, and their onset ages vary [5-9]. Autoimmune disorders have a complicated origin, with genetic, hormonal, and environmental factors all contributing. Although autoimmune disorders are typically assumed to be relatively uncommon, their death and morbidity rates are high. In the United States of America, autoimmune illnesses rank among the top killers of young and middle-aged women (under 65 years of age) [10]. Numerous of these disorders are chronic, which has an impact on quality of life, use of medical services, and direct and indirect economic expenditures [11].

Autoimmune diseases significantly affect pathophysiological processes. The complexities of the immune system have a primary purpose of defending hosts against infectious pathogens. A pleiotropic immune system can cause pathology in two main ways: first, immune deficiency syndromes, in which one or more immune system cells are unable to react in a protective way to a pathogen; and second, autoimmune illnesses [12-14]. Previously thought to be uncommon, autoimmune diseases are now known to impact 3-5% of the population, with type I diabetes (T1D) and autoimmune thyroid disease (ATD) being the most prevalent of these ailments. The presence of almost 100 different autoimmune illnesses is more significant, some of which are organ-specific (like primary biliary cirrhosis, or Primary Biliary Cholangitis (PBC) and others of which are indicative of immunological dysfunction affecting several organs like systemic lupus erythematosus (SLE). The advent of innovative molecular immunology technologies and sophisticated evidence-based clinical laboratory testing have combined to produce considerable gains in prognosis, diagnosis, and illness classification over the past ten years [15].

The innate immune system and the more recently evolved adaptive immune system are the two components of the immune system. The innate immune system lacks memory and is non-specific to particular infections. The skin, saliva, tears, bacterial flora, and a variety of cells and proteins such as complement, lysozyme, white blood cells, red blood cells, and platelets make up the first line of defense. The adaptive immune system, on the other hand, may create targeted immune responses against pathogens that it has encountered since it has the ability to form memories. The adaptive immune system makes use of B-lymphocytes and T-lymphocytes and their byproducts, immunoglobulins, and cytokines to produce a highly specialized response that improves with each consecutive encounter with a particular disease [16-23].

Host receptors on lymphocytes go through substantial gene rearrangement and somatic mutation processes to develop a repertoire of receptors that can recognize a wide range of antigens to defend against a wide range of pathogens. The adaptive immune system responds to identification by sending a message of either immunity or tolerance. When "self" antigens present naturally in the body are tolerated, "non-self" antigens elicit the proper immune response but "self" antigens do not. Autoimmunity may arise when the tolerance process is unsuccessful. Tolerance at the central and peripheral levels is essential for preventing autoimmunity [24-28].

2. THE EMERGENCE OF IMMUNOLOGICAL TOLERANCE

In 1948, Macfarlane Burnet of the Walter and Eliza Hall Institute for Medical Research in Melbourne, Australia, claimed that immunological tolerance to oneself is a trait learned throughout development as opposed to an innate trait. In 1953, Peter Medawar and his associates experimentally proved that inbred mice could be trained to develop immunological tolerance. Immune tolerance was finally explained as the capacity of the immune system to refrain from attacking self-molecules, cells, or tissues [29].

Intriguingly, Paul Ehrlich's groundbreaking work at the beginning of the 20th century had already established the concept of "horror autotoxicus" (horror of self-toxicity) in which many researchers did not believe in the concept of autoimmunity. The earliest murine model of autoimmunity, the New Zealand black (NZB) mouse, was initially published in 1959. Thyroid autoantibodies were later discovered, and autoimmune thyroiditis was established as the archetypal autoimmune disease [30,31]. To comprehend immunological tolerance, many fundamental ideas should be introduced, such as central tolerance, peripheral energy, T regulatory cells (Tregs), and the homeostasis brought on by cytokines and chemokines and their corresponding receptors. Immune system homeostasis is mainly shaped by central tolerance, which is found in the thymus and bone marrow. Before growing and leaving the thymus, developing lymphocytes go through positive selection in the brain. Notably, the thymic medulla of an otherwise healthy host undergoes negative selection and deletion of cells with potential self-peptide sensitivity. Importantly, mature T cells undergo secondary selection (peripheral tolerance) after leaving the thymus, during which the majority of self-reactive T cells are eliminated or became anergic. Additionally, immature B cells are destroyed through a process known as clonal deletion or clonal anergy if they express surface IgM that detects common self cell-surface antigens. Receptor editing is a technique that allows deletion-resistant auto-reactive B cells to survive. Peripheral tolerance also has an impact on mature B cells [32,33] in which an illustration is depicted in Fig. 1.

2.1 Central Tolerance

The thymus and bone marrow, respectively, are the primary sites of T-lymphocyte and B-lymphocyte maturation. As a result, central tolerance refers to the processes of tolerance found in these places.

2.1.1 T- cell tolerance

When immature T-cells enter the thymus from the bone marrow and come into contact with proteins attached to major histo-compatibility complexes, the process begins major histocompatibility complex (MHC). MHC molecules are cell-surface antigens found in vertebrates that \ are also known as human leukocyte antigens in humans (HLA). MHC Class I is made up of three subtypes HLA-A, HLA-B, and HLA-C. Almost all cell types in the body express MHC I antigens. HLA-DP, HLA-DQ, and HLA-DR are additional subtypes that fall under MHC Class II. Less frequently, MHC II molecules are seen in reticuloendothelial system cells such as macrophages and B-lymphocytes. The type of T-lymphocytes that each MHC molecule interacts with determines its relevance. When MHC I molecules bind to CD8+-T lymphocytes, a

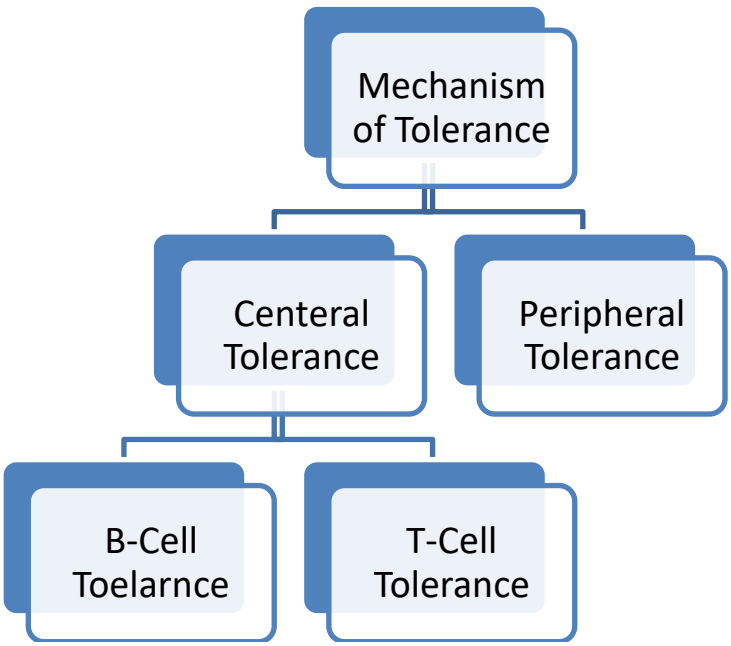

Fig. 1. Emergence of immunological tolerance

cytotoxic response is triggered, and when MHC II molecules connect to CD4+-T cells, a helper T-cell response is triggered [34,35].

The cortical epithelial area of the thymus is where the central tolerance process starts. To interact with immature double-positive T cells that express both CD4+ and CD8+, endogenous proteins are linked to either MHC I or MHC II molecules. T-lymphocytes that bind with a medium affinity are indicated to continue living and develop into single-positive lymphocytes, producing either CD4+ or CD8+ lymphocytesin which this process is called the positive selection. Each CD4+ or CD8+ T-lymphocyte is then exposed to MHC molecules that are coupled to self-peptides as these cells travel to the corticomedullary junction region. If there is strong binding at this point, the corresponding T-cell will die through apoptosis which is the negative selection process [36-40].

The first line of defense against autoreactive T-cell spread into the systemic circulation is central tolerance. The medullary epithelial cells of the thymus play a significant role in the effectiveness of this process. These cells produce autoimmune regulator transcription factors (AIRE), which lead to enhanced production of tissue-specific antigens prevalent in other parts of the body, to display a comprehensive array of self-peptides found in all organs of the body. Effective negative selection is aided by the expression of tissue-specific antigens. When AIRE mutations occur and less tissue-restricted antigen expression occurs, autoimmune disease may result. An illustration of this is the illness known as autoimmune poly-glandular syndrome type I (APECED), which is defined by Addison disease, hypoparathyroidism, and at least two of the following three disorders [41-44].

2.1.2 B-Cell tolerance

In the bone marrow, the immature B-cell central tolerance process takes place. B-cells produce antibodies, also known as immune globulins, which are crucial for the immune response to a variety of infections. These antibodies are heavyand lightchained glycoprotein molecules that attach to antigens, including those of microbial origin, and aid in their destruction. Immunoglobulins come in five classes: IgG, IgM, IgA, IgE, and IgD. Each class has a different purpose in defending the body against both acute and chronic infections as well as different sorts of pathogens, such as bacteria, viruses, parasites, and fungi. Recurrent infections are more likely to happen when people are unable to manufacture some or all antibodies [45]. The membrane-bound version of the B-antibody cells interacts with the antigen on the antigen-presenting cell to activate it. In response to this encounter, B-cell transforms into a plasma cell and secretes significant amounts of certain immunoglobulins that are intended to attack the antigen. This procedure is essential for defense against foreign antigens. However, autoimmunity develops when B-cells identify and eliminate self-antigens. There are tolerance mechanisms in place to stop this from happening, just like T-cells do [46].

2.2 Peripheral Tolerance

T-lymphocytes and B-lymphocytes penetrate peripheral immunological organs and tissues, such as the spleen and lymph nodes, after leaving the thymus and bone marrow. In these areas, peripheral tolerance mechanisms guard against the development of autoimmunity in the event that autoreactive cells get past all central tolerance checks. Peripheral tolerance can take many different forms [47]. The first primary peripheral tolerance mechanism is energy. A lack of immunological response brought on by the lack of costimulatory signals is referred to as energy which is the process that T-lymphocytes undergo. . In addition to the MHC: T-cell receptor connection, mounting an immune response necessitates the delivery of a second signal via costimulatory molecules. There are other costimulatory pathways, but the CD28:B7 axis is a significant one. T-lymphocytes have a receptor called CD28 that interacts to B7, a ligand found on antigen-presenting cells. The interaction between the MHC: TCR and CD28:B7 helpthe T-lymphocyte develop and survive by causing the cytokine interleukin-2 to be produced. The immunological response will not continue if the second costimulatory signal is not supplied [48-51].

Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 are two proteins that help to maintain energy. T-lymphocytes have the CTLA4 receptor that has a stronger affinity for B7 than CD28. When a T-lymphocyte detects a self-antigen, CTLA4 binds to B7 and triggers its clearance by clathrin, blocking the costimulatory signal. The Programmed death-1 PD-1 operates similarly. PD-1 detects the ligands PD-L1, and PD-L2 located on antigen-presenting cells and is

expressed on different kinds of T-cells. The phosphorylation of PD-1's tyrosine motifs upon interaction with either of its ligands has the downstream impact of downregulating TCR signaling. Autoimmunity can be brought on by any anomaly in the peripheral tolerance pathway [52-55]. Clonal ignorance is another mechanism of peripheral tolerance. Through a variety of methods, autoreactive T-lymphocytes disregard self-antigen during this process. The inability of lymphocytes to access self-antigens may be the result of a physical barrier, such as the blood-brain barrier, which can also be because lymphocytes were not exposed to enough self-antigen to trigger an autoimmune reaction. In other instances, apoptosis leads to peripheral tolerance. The Fas-Fas ligand system becomes activated when autoreactive T-cells bind to self-antigen complexes. T-lymphocytes contain both Fas and its ligand, and their interaction causes the T-lymphocyte to die by inducing the caspase cascade. Therefore, a mutation in the Fas gene can cause both lymphoproliferative diseases and autoimmunity which is i how the disease autoimmune lymphoproliferative syndrome develops (ALPS) [56].

3. EPIDEMIOLOGY OF DIFFERENT AUTOIMMUNE DISEASES

The prevalence and incidence of autoimmune disorders differ. When variations in age, gender, ethnicity, and other demographic variables are taken into account, the geo-epidemiology becomes more complexas shown in Table 1 and Fig. 2.

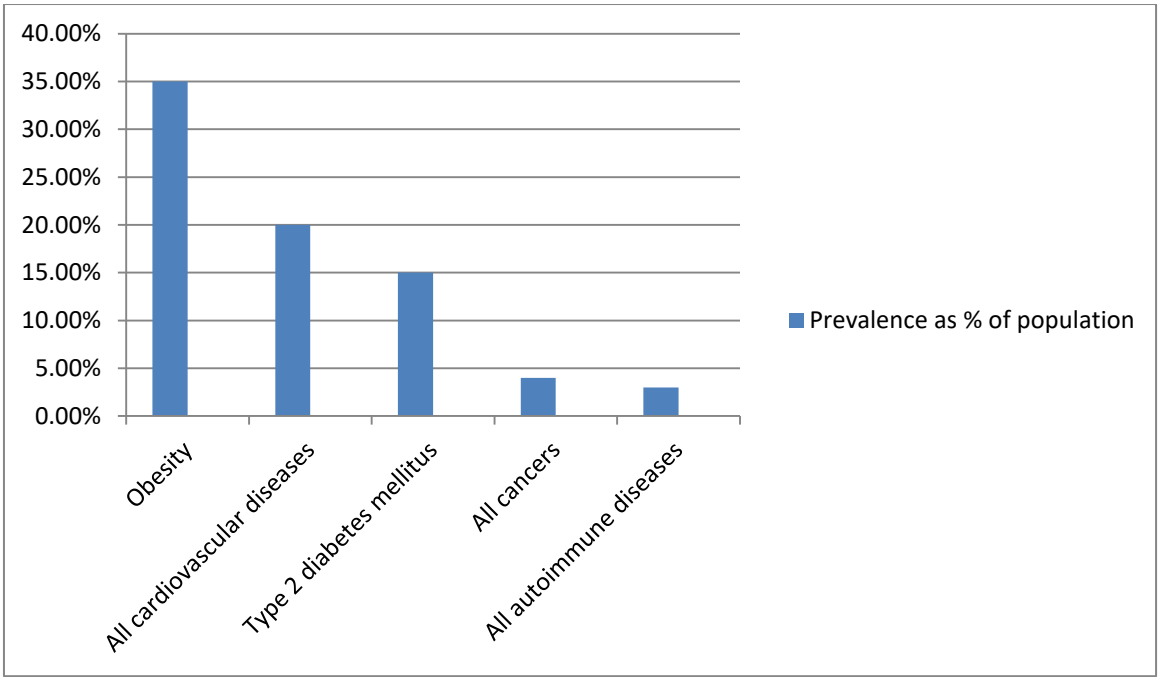

Fig. 2. Prevalence of some autoimmune diseases [58]

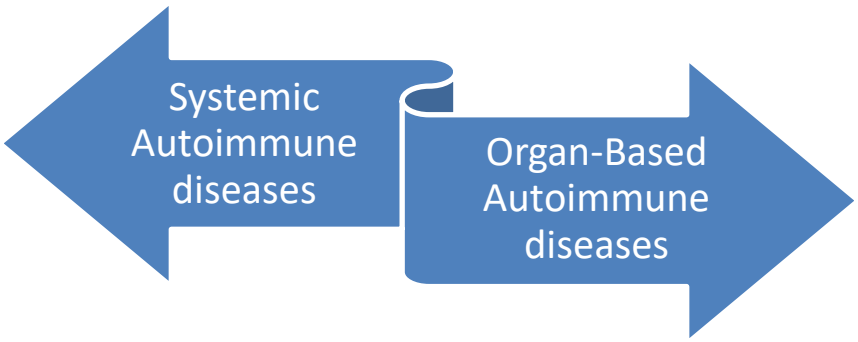

Fig. 3. Catagories of autoimmune disorders

Table 1. Data from [57]

Types	Age Onset	Female/Male	Incidence inUSA and Europe	Incidence inMiddle east and Asia
Multiple sclerosis	20–40	2/1	2.7–7.5	0.7–3.6
Type 1 diabetes	6–13	1/1	10–20	<1
Primary biliary cirrhosis	50–60	10/1	2.7 (USA)	0.34–0.42
Autoimmune hepatitis	<40 (T1) 2–14 (T2)	4/1 (T1) 10/1 (T2)	0.5 (USA)	0.08–0.15 (Japan)
Graves' disease	50–60	5/1	38	120
Crohn's disease	15–30, 60–80	1/1.2	6.9–20.2	0.24–1.34
Ulcerative colitis	15–30, 60–80	1/1	8.3–19.2	0.36–6.02
Coeliac disease	Childhood	1/1	0.9–9.1 (all ages)	Unclear
Addison's disease	15–45	0.8–2.4/1	1 (USA)	Unclear
Sjogren's syndrome	40–50	9/1	3–5 (USA)	6.57
Systemic lupus erythematosus	30–50	9/1	1.2–8.7	0.9–3.1
Rheumatoid arthritis	44–55	2/1	31–45	8–42

Table 1. Symptoms, diagnoses, and treatment of selected systemic autoimmune diseases

Types	Symptoms	Diagnosis	Possible treatments	Reference
Systemic Lupus Erythematosus:	Malar rash, discoid rash, photosensitivity, mouth ulcers, arthritis, serositis, kidney disease, hematologic disorder, neurologic disorder, immunologic disorder, and antinuclear antibody positive.	By assessment of different symptoms, physical examination, X-rays, and lab tests.	Hydroxychloroquine, corticosteroids	[64-67]
Sjogren Syndrome	xerophthalmia, xerostomia, and numerous manifestations affecting the neurological system, lungs, kidneys, and skin.	antibodies , pattern of inflammation, found most often on the salivary glands lips,	Hydroxychloroquine (Plaquenil), certain immunosuppressors	[68-71]
Scleroderma	excessive buildup of collagen in the skin and internal organs, which can manifest locally or systemically (limited cutaneous systemic and diffuse cutaneous systemic). The CREST syndrome of calcinosis, Raynaud's phenomenon, esophageal involvement, scleroderma, and telangiectasia are all linked to the limited cutaneous systemic variant.	physical exam and biopsy	Using corticosteroids or non-steroidal anti-inflammatory drugs to relieve pain	[72, 73]
Sarcoidosis	Noncaseating granulomas can develop in any organ of the body, including the eyes, skin, heart, gastrointestinal tract, nervous system, and endocrine system. Sarcoidosis most frequently manifests as bilateral hilar lymphadenopathy in the lungs.	biopsy	Corticosteroids	[74]
Rheumatoid Arthritis	Symmetric synovial inflammation, morning stiffness lasting more than 30 minutes, and numerous extra-articular symptoms such as rheumatoid nodules, amyloidosis, and systemic vasculitis	Magnetic resonance imaging (MRI) and ultrasound	Methotrexate	[75]

Table 3. Symptoms, diagnoses, and treatment of selected Autoimmune Disorder/Organ-based

Types	Symptoms	Diagnosis	Possible Treatments	References
Type 1 Diabetes	Autoantibodies to pancreatic islet cells in type 1 diabetes prevent the pancreas from producing insulin, which causes hyperglycemia, polyuria, and polydipsia.	blood sample	Intensive insulin therapy	[76-78]
Crohn Disease	patchy, transmural lesions that can affect the entire gastrointestinal tract.	Colonoscopy, Biopsy	Steroid medicines	[79]
Bullous Pemphigoid	symmetric, tense bullae on the trunk, inner thighs, and flexures as well as urticaria, pruritus, and eczema.	skin biopsy and immunofluorescence testing of skin and serum	Topical corticosteroids, systemic corticosteroids, and doxycycline	[80]
Ankylosing Spondylitis	Sacroiliac joint soreness, lower back pain, peripheral arthritis, and dactylitis	X-Ray	Nonsteroidal anti-inflammatory drugs (NSAIDs) — such as naproxen (Aleve, Naprosyn, others) and ibuprofen (Advil, Motrin IB, others)	[81]
Multiple Sclerosis	demyelination resulting in spinal cord syndromes, ocular neuritis, brainstem, and cerebellar syndromes, and cognitive impairment as a result of persistent central nervous system inflammation	a thorough neurological examination and medical history of the patient. The neuroaxis using magnetic resonance imaging. testing for evoked potentials. a spinal fluid analysis	injectable, oral, and infusions medications.	[82]

4. CLINICAL SIGNIFICANCE

In 2009, between 7.6 and 9.5% of Americans reported having one of 29 common autoimmune disorders [59]. There is a possibility that the prevalence now maybe significantly higher. In addition, autoimmune illnesses affect women more frequently than men. Numerous clinical symptoms, many of which are disabling and significantly affect the quality of life, resultingfrom an aberrant cellular response to self-antigen recognition. Systemic and localized consequences are also possible with autoimmune diseasesin which Fig. 3 is reflective of the categories..he following list includes the key clinical features of several significant autoimmune disorders from both categories. Significantly to note, this is not a comprehensive list, and even organ-based autoimmune disorders can proceed to different systemic symptoms [60-63].

4.1 Systemic Autoimmune Diseases

Numerous systemic autoimmune diseases contribute to significant affects within the body. The effects range from minor to chronic complexities and symptoms with minimal to vast treatment options as illustrated in Table 2.

4.2 Autoimmune Disorders/Organ-Based

There is significant complication assocated with autoimmune disorders that adversely affect the body. Symptoms may primarily consist of chronic effects with ranging treatment availabilities as specified in Table 3.

5. NEW INSIGHTS INTO THE TREATMENT OF AUTOIMMUNE DISORDERS

Type 1 diabetes, multiple sclerosis, and rheumatoid arthritis are examples of autoimmune diseases caused by immune system dysfunction. In these illnesses, the body's own cells are attacked rather than protected by T lymphocytes, which normally coordinate the immune response against viruses and bacteria and harm the target organ. Current medications lack the mechanisms to distinguish between defective and normal cells, making it difficult to eradicate the disease's defective cells. The medications used to treat certain autoimmune diseases also lower healthy immunity, making the patient more prone to infection. The use of a novel class of nanoparticles coated with protein targets targeted at the T-cells responsible for autoimmune illnesses allows for their reprogramming into regulatory T cells and the selective removal of the disease, according to a study, which is A new biological mechanism that controls the immune response is responsible for this [21].

Multifactorial treatments are being tried to treat pathologic conditions and restore immunological tolerance in affected people as the pathogenetic processes of autoimmune disorders are revealed. Immune-regulatory cell populations are used in cell therapies, which are promising approaches that can help researchers in the domains of immunology and rheumatology reach their long-term objectives. There is a high possibility that the aggressively continuous development of biotechnologies for producing and controlling in vitro expanded cell therapies will hasten the use of these drugs in clinical trials for a variety of autoimmune illnesses. Future clinical studies may offer uniform efficacies and safety contributive to to protocols for each cell therapy that have received international attention regarding the best manufacturing techniques and regimens, including sources, doses, and intervals. Though there are still a lot of difficulties to overcome, significant efforts being made all over the world will improve the standing of the present cell therapies used to treat autoimmune illnesses [83-91].

6. CONCLUSION

From diagnosis to treatment, the identification and management of immunosuppressive/immunocompromised disorders remaina challenge. More than 100 different syndromes are being studied actively to better define the pharmacologic medicines that particularly target the illness pathways of many of these syndromes. The medical community's capacity to properly handle autoimmune disorders continues to be complicated by knowledge gaps. Providers may not significantly inquire about the presence of a family history of autoimmune illnesses, and patients may avoid discussing it it, and as a result of this, a lack of awareness of certain autoimmune disorders may remain in the public and the medical community. Biologic drugs that alter particular inflammatory effector pathways are still a popular and effective pharmacologic strategy. Hope exists for potential modification of the host immune system to return balance and immune tolerance to the human

body through research to further create medication s that will entirely reverse, if not cure, autoimmune disorders.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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