Autoimmune disease: Mechanisms, Triggers, and Emerging Therapeutic Strategies

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ABSTRACT:

Autoimmune diseases are characterized by an abnormal immune response against self-antigens, resulting in chronic inflammation and tissue damage. These disorders arise due to the loss of immune tolerance, involving defects in central and peripheral tolerance as well as dysregulation of T and B lymphocytes. Environmental triggers and cytokine-mediated pathways further contribute to disease initiation and progression and also discusses the fundamental mechanisms underlying autoimmunity and highlights common autoimmune diseases, including rheumatoid arthritis, type 1 diabetes mellitus, Hashimoto's thyroiditis, psoriasis, inflammatory bowel disease, and systemic lupus erythematosus, with emphasis on their pathogenesis and available treatment strategies with some more additional information.

Recent advances in immunology have improved the understanding of disease mechanisms, enabling the development of targeted therapies such as biologics and immunomodulators. Despite these advancements, challenges remain in early diagnosis, disease heterogeneity, and long-term management. This review aims to provide a comprehensive overview of the etiology, pathophysiology, classification, diagnostic approaches, and current therapeutic strategies for autoimmune diseases, highlighting emerging trends and future directions in personalized medicine.

Keywords: Autoimmune diseases, immunological tolerance, autoantibodies, inflammation, biologics, immunotherapy, pathogenesis

INTRODUCTION:

Autoimmune illnesses arise when the immune system is unable to differentiate between potentially harmful antigens and healthy tissues (1**)**. As the immune system develops, immune cells that attack self-tissues are eradicated, making the immune system "tolerant" of itself (2**).** An autoimmune reaction, which is typically brought on by a triggering event, can be mainly

mediated by T cells, B cells, or both (3**) .** However, characterizing an autoimmune response as solely B-cell mediated may be oversimplified. In fact, CD4+ T lymphocytes assist whenever the synthesis of immunoglobulin (Ig) G antibodies is started. Certain autoimmune illnesses, such as insulin-dependent diabetes or Hashimoto thyroiditis, cause the targeted tissue to completely and irreversibly lose its ability to function. In others, such as Graves-Basedow disease or myasthenia gravis, the autoimmune reaction damages the tissue over time, causing either hyper stimulation or inhibition of its function. Lastly, in other circumstances, such as systemic lupus erythematosus (SLE), the pathogenic events are numerous and complex, resulting in the damage or destruction of multiple tissues simultaneously. (10) Typical epidemiology It has been demonstrated that 3–5% of people suffer from autoimmune illnesses, making them one of the most significant public health issues. Nearly every age group (0–95 years old) is susceptible to autoimmune disorders (4**)** Complex chronic inflammatory disorders caused by a lack of self-tolerance are known as autoimmune diseases.

In clinical practice, they are typically categorized as either non-organ-specific (the reaction targets systemic antigens) or organ-specific (the response targets antigens in a particular tissue (5**).** Although autoimmune disorders were thought to be uncommon, thorough epidemiological research has revealed that they affect 3–5% of the population, with type I diabetes (T1D) and autoimmune thyroid disease being the most prevalent (6**).** Women contribute for 78 to 85% of instances with autoimmune disorders, which have a global frequency of 3 to 8%. Organ-specific autoimmune illnesses and systemic autoimmune diseases are the two categories into which autoimmune disorders are often classified. Organ-specific autoimmune illnesses include psoriasis, Hashimoto's thyroiditis, multiple sclerosis, and type 1 diabetes, when the patient's immune system attacks a particular organ or tissue. Systemic autoimmune disorders, on the other hand, are conditions in which nearly every type of cell contains self-antigens that the immune system responds to. Systemic autoimmune illnesses include rheumatoid arthritis and systemic lupus erythematosus**. (8)** In addition to other related immune dysregulation, autoimmune disease arises from aberrant immune reactions against self-proteins and molecules, causing tissue damage and designated illness. Loss of self-tolerance, which is usually identified by the emergence of autoantibodies, happens years before the disease manifests itself in people who seem to be in good physical health and have no organ damage. Pre-clinical autoimmunity enables the implementation of primary and secondary prevention measures as well as the

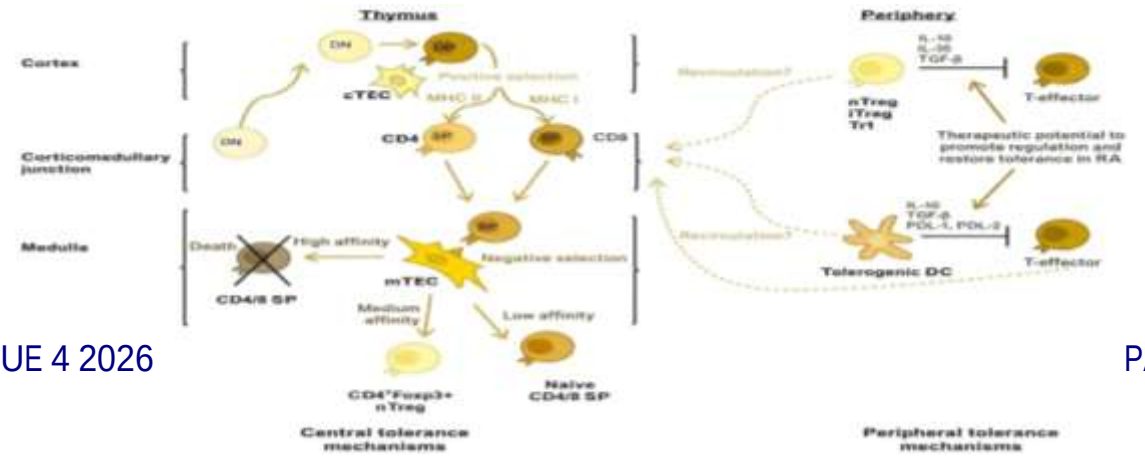
investigation of pathogenic pathways that cause disease. Using RA, SLE, and T1D as examples, this review explores recent developments in our understanding of aberrant immune responses at this pre-clinical stage. (9) A wide range of illnesses collectively referred to as autoimmune disorders are distinguished by abnormal B cell and T cell responses to normal host components. These illnesses are widespread and impact people of all ages, particularly women (7). In the past, autoimmunity or the immune system's reactivity to self-antigens was considered an abnormal reaction. More recently, scientists have shown that autoimmunity is a natural occurrence, with autoimmune cells and self-reactive antibodies found in every healthy person. Anti- self-responses are normally generated in the process of mounting an immune response to foreign antigens, but autoimmune illness arises only if autoimmunity is poorly regulated. Autoimmune diseases are caused by a confluence of environmental variables and genetic predisposition.

Despite the relative rarity of individual autoimmune disorders, they affect about 5–8% of the population in the United States and are the third most common category of disease in developed nations after cancer and cardiovascular disease. Environmental and genetic factors work together to cause autoimmune diseases. It is believed that the majority of autoimmune disorders are polygenic, involving many genes. Clinical observations that patients frequently describe a family history of autoimmune diseases gave rise to the theory that people are genetically susceptible to developing autoimmune diseases. The most accurate indicator of the development of an autoimmune disease is the human lymphocyte antigen, or HLA haplotype. (2)

MECHANISM:

LOSS OF TOLERANCE:

Self-antigens typically elicit no reaction from the immune system. The "**lower level**" of *peripheral tolerance* develops postnatally as a backup mechanism, while the "**upper level**" of *central tolerance* develops first during fetal life. Inadequate peripheral tolerance causes autoimmune illness to emerge, whereas inadequate central tolerance plants the seeds. (10)

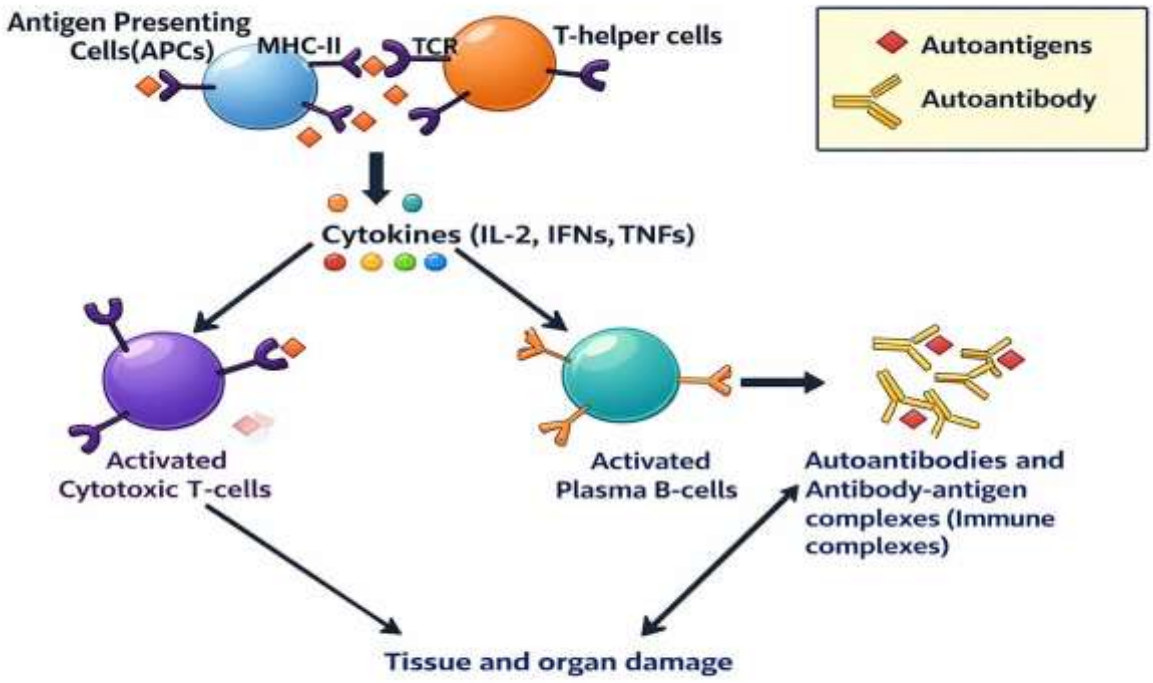


Central Tolerance:

During lymphopoiesis, developing lymphocytes undergo positive selection for low-affinity self-recognition and negative selection to eliminate strongly self-reactive cells. These processes, influenced by factors like HLA and self-antigen exposure, establish central tolerance. However, this tolerance is incomplete, allowing some self-reactive cells to enter the periphery, requiring lifelong regulation(11).

Peripheral Tolerance:

Peripheral tolerance prevents activation of self-reactive lymphocytes through mechanisms such as ignorance, anergy, and immune regulation. Ignorance occurs when autoantigens are sequestered or inaccessible, preventing immune recognition. Anergy arises when lymphocytes receive antigenic signals without proper co-stimulation, leading to functional inactivation or apoptosis. Regulatory mechanisms, including the action of CTLA-4 and regulatory T cells, suppress immune responses by inhibiting activation and cytokine signaling. Together, these processes maintain immune homeostasis and prevent autoimmunity**(11).**

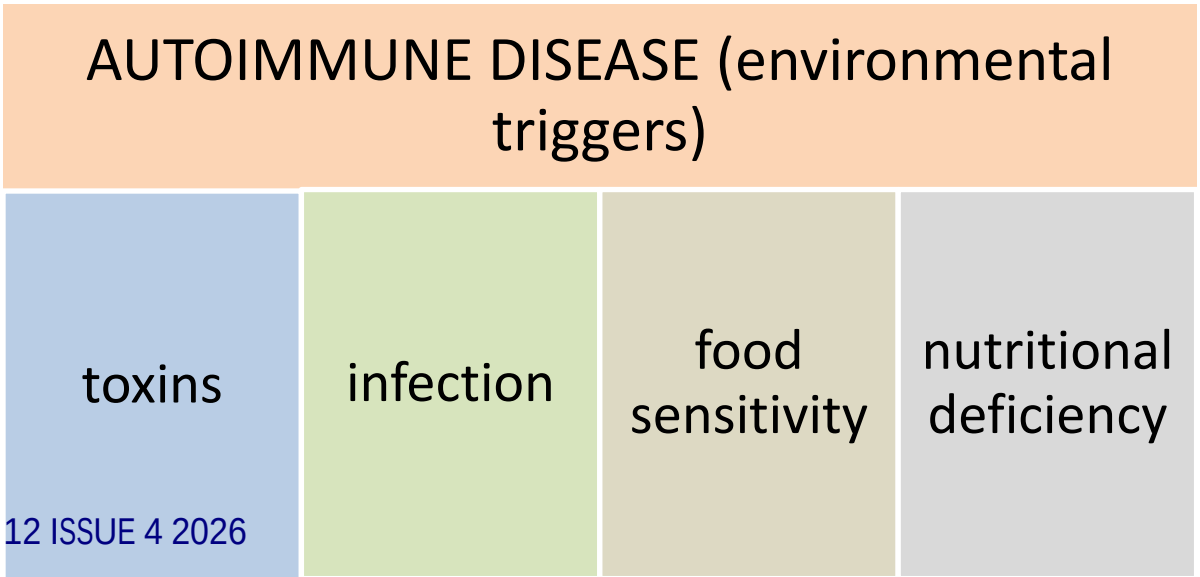


TOLERANCE IN T AND B LYMPHOCYTES:

Thymus-dependent (T) lymphocytes mediate cell-based immunity and support antibody production, whereas B lymphocytes are primarily responsible for antibody secretion. Antigen exposure plays a key role in immune tolerance, where intermediate doses induce immunity while high or repeated low doses lead to antigen-specific unresponsiveness rather than generalized immunosuppression. Studies have shown that T lymphocytes are more readily and durably tolerized compared to B cells, which may remain functional or only transiently unresponsive. In certain conditions, B cells can still be activated through cross-reacting antigens or adjuvant-mediated stimulation, leading to the production of autoantibodies despite T cell tolerance(12).

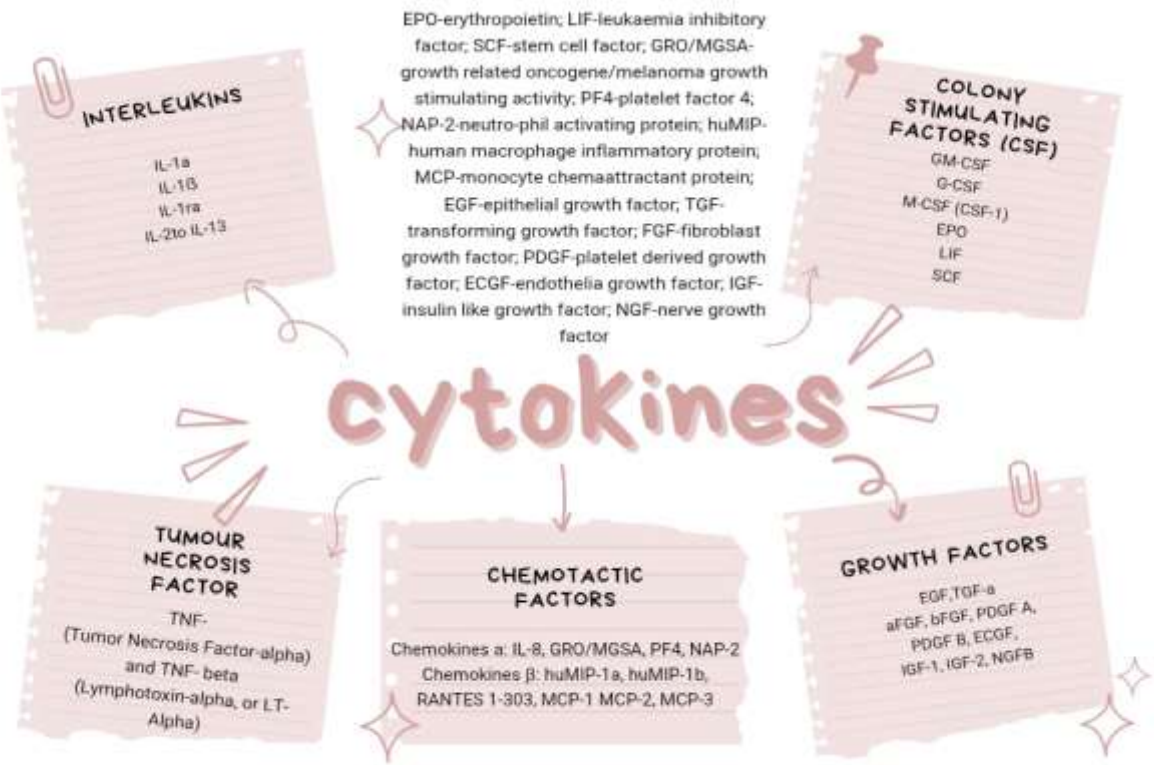
ENVIRONMENTAL TRIGERS

Environmental factors such as hormones, diet, drugs, chemicals, and infections significantly influence the risk of autoimmune diseases by disrupting immune tolerance and enhancing susceptibility. Agents like smoking, silica, pesticides, and heavy metals induce oxidative stress, promoting immune dysregulation through pathways such as NF-κB activation, neoantigen formation, and reduced regulatory T-cell function. These mechanisms contribute to diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and multiple sclerosis (MS), with effects including DNA demethylation, inflammation, and autoantibody production. Additionally, factors such as ultraviolet radiation and infections can trigger apoptosis and molecular mimicry, further impairing immune tolerance and leading to persistent autoimmune responses. (14)

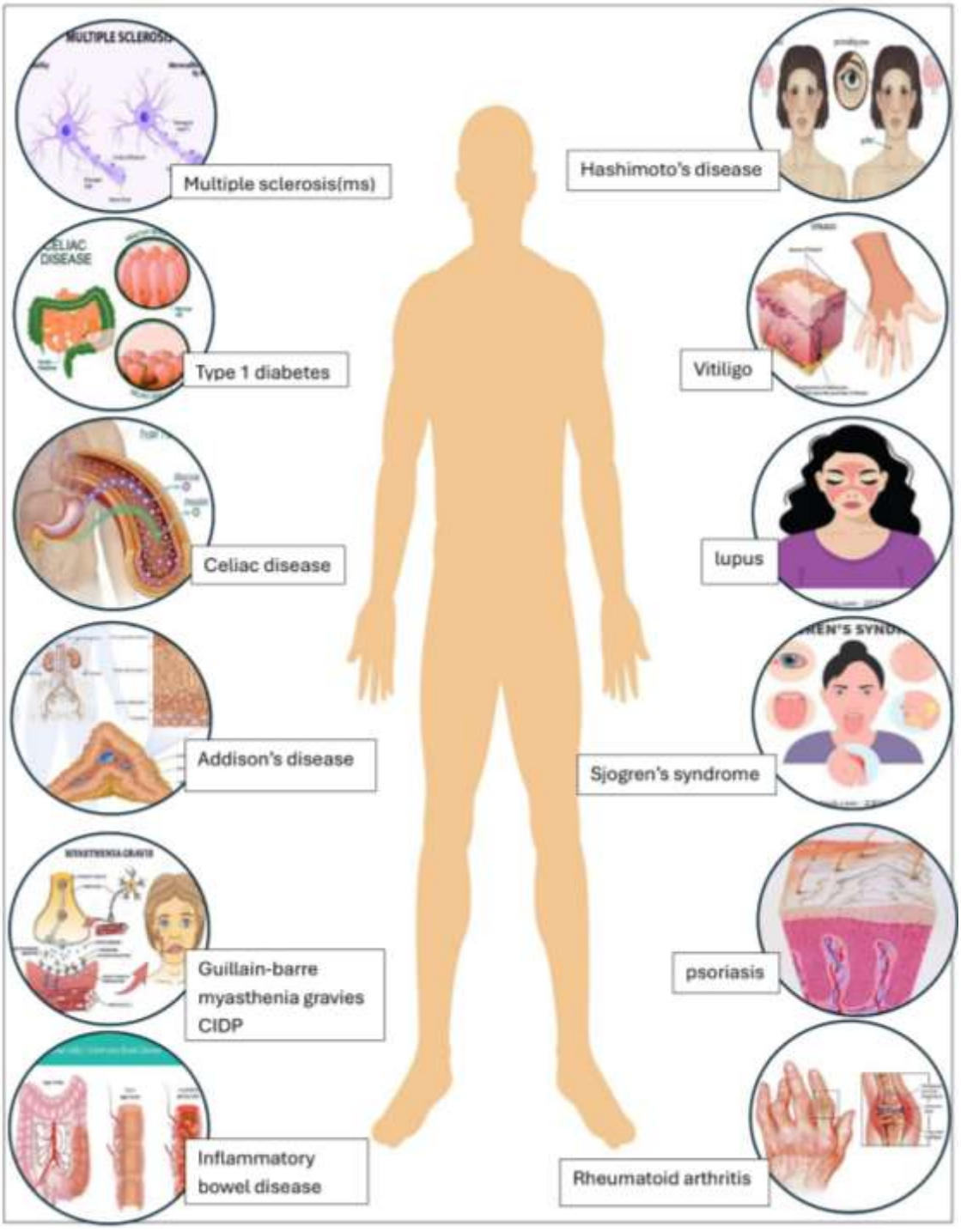


CYTOKINE PATHWAY:

Cytokines are low molecular weight protein mediators that regulate immunity, inflammation, cell growth, and differentiation, primarily acting locally as signaling molecules between immune cells. They play a crucial role in autoimmune diseases, where dysregulated production of proinflammatory cytokines such as TNF-α, IL-1, and IL-6 promotes activation and proliferation of autoreactive T and B cells, leading to tissue damage. Cytokines released by antigen-presenting cells (APCs) also direct T helper cell differentiation into Th1 or Th2 subsets, linking innate and adaptive immunity. Although the Th1/Th2 paradigm has long been used to explain autoimmune pathogenesis, conflicting evidence suggests a more complex role of cytokines, highlighting both pathogenic and protective effects and making them important yet challenging therapeutic targets (15–18).



COMMON AUTOIMMUNE DISEASES:



RHEUMATOID ARTHRITIS

INTRODUCTION:

A systemic autoimmune disease linked to a persistent inflammatory process, rheumatoid arthritis (RA) can harm not only joints but also extra-articular organs such as the heart, kidney, lung, digestive tract, eye, skin, and neurological system. (19)

The prognosis is uncertain, the clinical course of RA varies, and its natural history is not well defined. Deformity, loss of joint space, bone, and function, as well as gradual and irreversible destruction to the synovial-lined joints, are the hallmarks of RA. One of the hallmarks of RA is that it is symmetrical. Joint swelling and discomfort to the touch, morning stiffness, and significant motion limitation in the affected joints are examples of articular and peri-articular symptoms. (20)

SELF TOLERENCE BREAKDOWN MECHANISM:

In rheumatoid arthritis (RA), breakdown of immune tolerance occurs prior to clinical synovitis, with early presence of autoantibodies such as rheumatoid factors (RF) and anti-citrullinated protein antibodies (ACPA) against post-translationally modified proteins like citrullinated and carbamylated antigens. Genetic factors, particularly HLA-DRB1 alleles and PTPN22 variants, contribute to autoantibody production and impaired peripheral tolerance. Environmental triggers such as smoking and mucosal inflammation further enhance antigen modification and immune activation. T cells play a central role in sustaining autoimmunity through abnormal differentiation and support of B cell responses, including isotype switching and somatic hypermutation. These mechanisms collectively drive the progression from preclinical autoimmunity to overt disease (21).

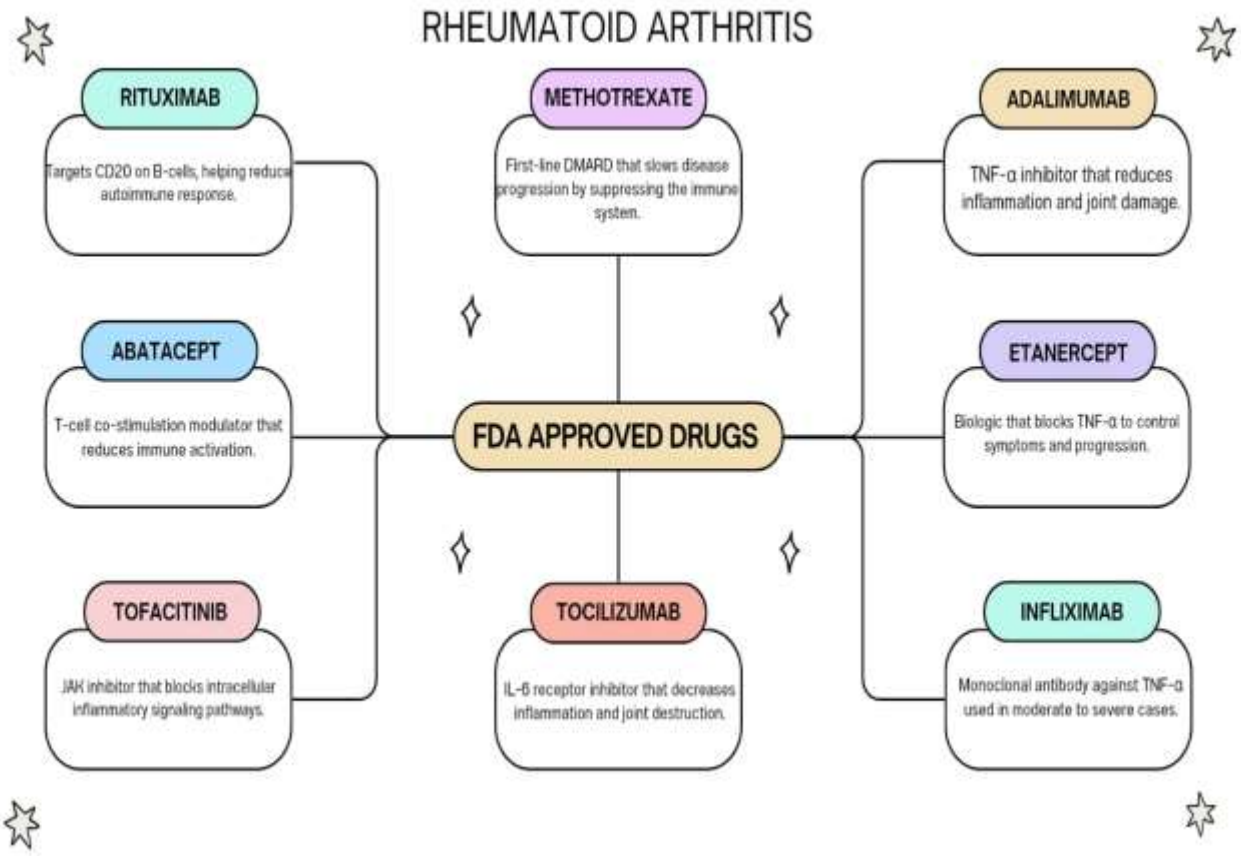
TREATMENT:

Rheumatoid arthritis (RA) management primarily involves anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids for rapid relief of pain and inflammation. Disease-modifying antirheumatic drugs (DMARDs), including methotrexate, leflunomide, hydroxychloroquine, and sulfasalazine, are used to slow disease progression and prevent joint damage, often with NSAIDs or glucocorticoids as bridging therapy due to their delayed onset. Biologic agents such as infliximab, etanercept, adalimumab, abatacept, and rituximab specifically target inflammatory mediators and have advanced RA treatment.

Therapeutic efficacy is commonly assessed using standardized criteria like ACR20, ACR50, and ACR70, indicating 20%, 50%, and 70% clinical improvement, respectively (22).

FDA APPROVED DRUGS FOR RHEUMATOID ARTHRITIS:

Traditional synthetic disease-modifying antirheumatic drugs (DMARDs) remain the cornerstone of rheumatoid arthritis (RA) management. Methotrexate is FDA-approved and strongly recommended as first-line therapy for DMARD-naïve patients with moderate-to-high disease activity. Hydroxychloroquine, also FDA-approved, is preferred for patients with mild disease due to its favorable safety and tolerability profile. Sulfasalazine is indicated for patients who show inadequate response to NSAIDs and is often used in mild disease owing to its relatively lower immunosuppressive effects. These agents are recommended based on American College of Rheumatology (ACR) guidelines to tailor therapy according to disease severity (62).Leflunomide: Adults with active RA can be treated with leflunomide, which has FDA approval. (61)



TYPE 1 DIABETES MELLITUS:

INTRODUCTION:

Hyperglycemia, or elevated blood glucose, is a hallmark of type 1 diabetes mellitus (T1DM), a chronic autoimmune disease caused by an insulin shortage brought on by the death of pancreatic islet β-cells. One of the most prevalent metabolic and endocrine disorders affecting children is type 1 diabetes. The majority of individuals (70–90%) who have autoimmune type 1 diabetes mellitus (T1DM) experience the loss of β-cells as a result of T1DM-related autoimmunity, which occurs concurrently with the development of T1DM-associated autoantibodies.

The source of β-cell death is unknown in a smaller subset of patients (idiopathic T1DM or type 1b diabetes mellitus), which has a significant hereditary component. No immune responses or autoantibodies are seen in these patients. In this primer, "T1DM" refers to autoimmune T1DM unless otherwise noted. (23) Since the 20th century, the prevalence of type 1 diabetes has increased. In the first half of the century, the incidence was consistent and modest, but in the second half, there was a noticeable increase, as Gale (2002b) showed. According to Onkamo et al. (1999), type 1 diabetes is becoming more common worldwide by 3% year. According to the Diamondd Project Group (2006), the prevalence increased by 2.8% annually worldwide between 1990 and 1999. Numerous arguments and opposing theories have been put out in the literature to explain this sharp rise in the prevalence of type 1 diabetes. Numerous theories attempt to explain this immune system weakness, which results in pancreatic b-cell autoimmunity. The goal of this review is to examine and compile the most recent data available in the literature. (24)

GENETIC SUSPECTIBILITY OF TYPE 1 DIABETES:

Although the exact origin of T1D is still unknown, it is recognized that environmental and genetic factors work together to predispose people to the condition. 50% of people have monozygotic concordance, and if a sibling has the condition, there is a 6% chance of getting it yourself. In contrast, the overall population has a 0.4% risk. The idea that T1D is immune-mediated is strongly supported by the genetic loci linked to an elevated risk of the disease. The HLA locus, which controls the specificity of alpha beta T lymphocytes, is the genetic area most closely linked to the illness. The areas coding for the genes interleukin-2 receptor a, cytotoxic T lymphocyte antigen 4, protein tyrosine phosphatase, and non-receptor type 22, which are all

mostly expressed in immune cells, also exhibit a weaker but substantial correlation with illness. However, due to the identification of correlations with insulin and other b cell chemicals, not all genetic variables are associated with the immune system. (25)

PATHOPHYSIOLOGY:

T1DM arises as a result of proinflammatory reactions and immune system elicitation against beta-cell antigens. Following the immune system's exposure to beta-cell antigens by antigen presentation cells (APCs), ineffective control of immunological responses results in persistent immunological responses and beta-cell death. These antigens are often taken up by dendritic cells (DCs) and presented to T cells. Only when autoreactive T cells have managed to evade thymic negative selection may an auto-immune reaction occur.

Autoreactive cytotoxic T and B cells are stimulated by autoreactive T cells that have been activated by DCs. Lastly, the effector mechanism of beta-cell death necessitates the collaboration of natural killer (NK) cells, T, B, macrophages, and DCs. (26)

AUTOIMMUNE MECHANISM AND ENVIRONMENTAL FACTORS OF TID:

Environmental factors play a significant role in the pathophysiology of type 1 diabetes (T1D), as evidenced by incomplete concordance in monozygotic twins. Key triggers include viral infections, dietary factors, and toxins, which may initiate or accelerate autoimmune destruction of pancreatic β-cells. Viruses such as enteroviruses, rubella, and coxsackievirus B are strongly implicated, with molecular mimicry proposed as a major mechanism, where viral antigens resemble β-cell autoantigens (e.g., GAD65, IA-2), leading to cross-reactive immune responses. Although molecular mimicry is widely suggested, its exact role remains unclear, and other immune pathways may also contribute to disease initiation and progression (27,28).

DIAGNOSIS AND THERAPY:

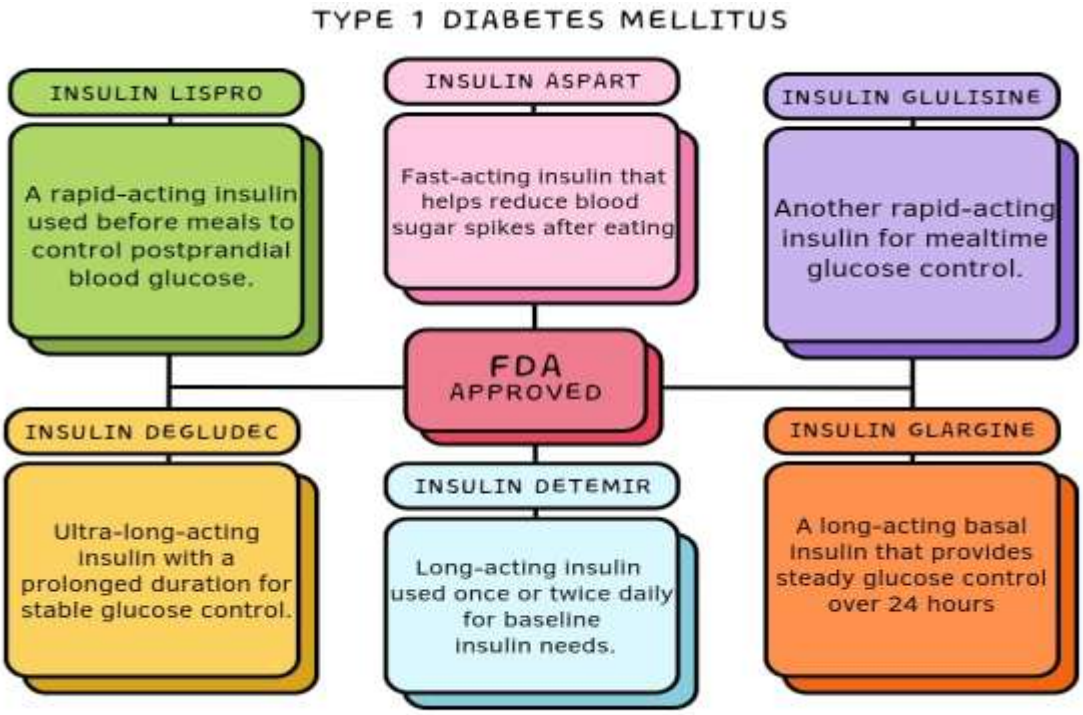
Type 1 diabetes (T1D) is diagnosed based on criteria such as fasting blood glucose ≥126 mg/dL, random glucose ≥200 mg/dL with symptoms, abnormal oral glucose tolerance test, or HbA1c ≥6.5% as per established guidelines. Despite standardized diagnostic criteria, distinguishing T1D from type 2 diabetes remains challenging, particularly in adults, leading to potential misdiagnosis, especially in cases with islet autoantibodies. Early recognition of diabetic ketoacidosis is critical for appropriate management and prevention of complications.

Genetic predisposition plays a major role in T1D, making gene therapy a promising future approach. Strategies include gene replacement, gene silencing, and introduction of functional

genes to prevent disease onset, enhance β-cell survival, or induce insulin production in non-β cells. Although still largely experimental, these approaches aim to modify disease progression at the molecular level.

Currently, insulin therapy remains the cornerstone of T1D management, with strict glycemic control essential to delay complications, as demonstrated by the DCCT study. However, the risk of hypoglycemia continues to limit optimal control. Advances such as rapid-acting insulin analogs and long-acting basal insulins like insulin glargine have improved glucose regulation and patient convenience. Combination regimens and insulin pump-like strategies further enhance treatment outcomes and quality of life (29–31).

FDA APPROVED DRUGS FOR TYPE 1 DIABETES MELLITUS:



Type 1 diabetes mellitus (T1D) is an autoimmune disorder characterized by destruction of pancreatic β-cells, leading to impaired insulin production. Since the approval of human insulin (Humulin) in 1982, numerous antihyperglycemic agents have been developed, including 36 novel molecular entities and multiple combination therapies. A major proportion of approved treatments consists of insulin and its analogues, with over 14 formulations designed to optimize glycemic control.

Insulin remains the cornerstone of T1D therapy, with recombinant analogs offering improved pharmacokinetic profiles. In contrast, type 2 diabetes management includes oral agents such as metformin, a biguanide approved in 1995, which reduces hepatic glucose production and activates AMPK. Metformin is recommended as first-line therapy by major guidelines. Additionally, α-glucosidase inhibitors such as acarbose and miglitol help control postprandial glucose levels. These advancements highlight the evolving therapeutic landscape of diabetes management (63).

HASHIMOTO'S THYROIDITIS:

INTRODUCTION:

The most common autoimmune thyroid disease (AITD) is Hashimoto's thyroiditis (HT). About 20–30% of patients develop hypothyroidism as a result of the persistent inflammation of the thyroid tissue.(32) Up until the late 1950s, HT was thought to be rare. Today, it is the most common autoimmune illness, with an annual incidence of roughly 1 case per 1000 people. HT is more common in Whites and Asians than in African-Americans, and it affects women at least eight times more frequently than in men. (33) Thyroid autoantibodies (TAbs) against two primary thyroid antigens, thyroglobulin (Tg) and thyroid peroxidase (TPO), are the main biochemical feature of the condition. Thyroid hormone synthesis, iodine oxidation catalysis, iodination of tyrosine residues in Tg, and coupling of iodothyrosines into thyroxine (T4) and triiodothyronine (T3) all depend on the TPO antigen, which is found at the apical membrane of the thyrocyte. Tg, a big glycoprotein found in thyroid follicles, is where the thyroid hormones are made and stored. A tiny quantity of Tg is released into the bloodstream, where its half-life is thought to be around three days. (34)

MECHANISM:

Autoimmune thyroid diseases arise from a complex interplay of genetic, environmental, and epigenetic factors that disrupt immune tolerance. Key genetic contributors include HLA, CTLA-4, PTPN22, IL2R, and genes related to apoptosis, cytokines, and hormone receptors. Environmental triggers such as infections, smoking, chemicals, and maternal-fetal microchimerism can initiate disease in genetically susceptible individuals. Alterations in gut microbiota, including increased *Bacteroides fragilis* and decreased *Bifidobacterium* and *Lactobacillus*, are also associated with thyroid autoimmunity.

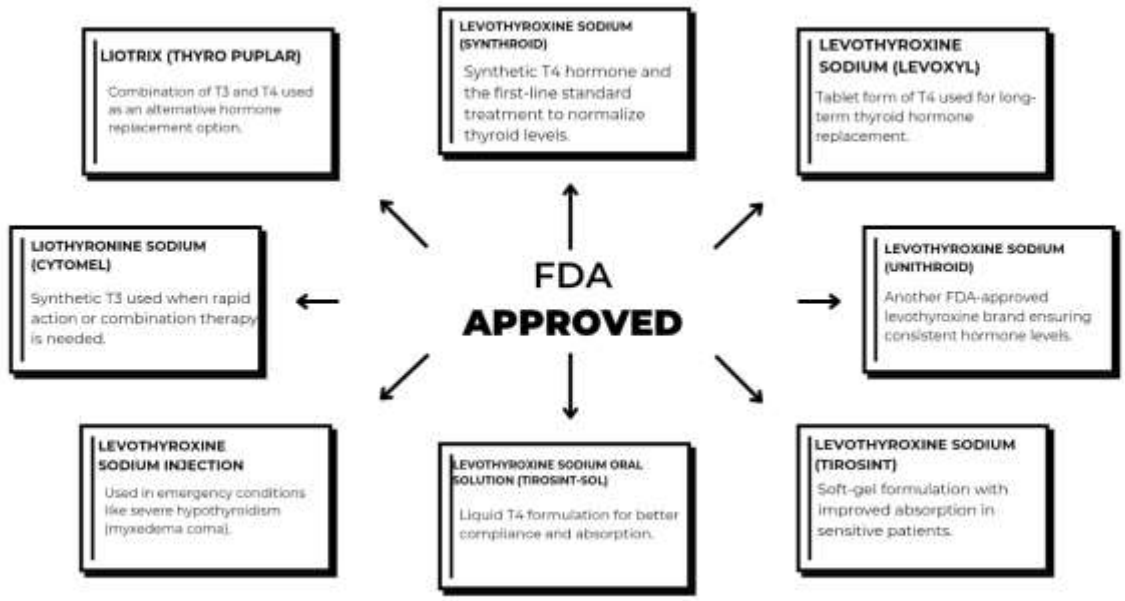
Immune dysregulation involves both B cell dysfunction with autoantibody production and abnormal T cell responses. Epigenetic mechanisms such as DNA methylation, histone modification, and non-coding RNAs further influence gene expression and disease susceptibility. X chromosome inactivation contributes to the higher prevalence of autoimmune thyroid disease in females. Overall, epigenetic modifications act alongside genetic and environmental factors to drive the development of autoimmune thyroid disorders (35,36).

TREATMENT FOR HASHIMOTOS THYROIDITIS:

Management of Hashimoto's thyroiditis (HT) primarily focuses on thyroid hormone replacement to restore function and prevent disease progression. Levothyroxine (LT4) remains the standard lifelong therapy for patients with hypothyroidism, effectively improving symptoms and correcting metabolic dysfunctions. However, some patients continue to experience residual symptoms, leading to consideration of combination therapy with LT4 and T3.

Adjunctive therapies such as selenium supplementation have shown benefits in reducing thyroid autoantibody levels and may help restore thyroid function in subclinical cases. Similarly, vitamin D supplementation has been associated with decreased antibody titres, although it does not directly improve thyroid function. These approaches highlight the importance of both hormonal and supportive therapies in comprehensive HT management (37,38).

FDA APPROVED DRUGS:



PSORIASIS

INTRODUCTION:

Psoriasis is a skin condition where skin cells multiply ten times faster than normal. As a result, red, bumpy patches with white scales occur on the scalp, lower back, elbows, and knees, though they can also appear on other areas. Although psoriasis cannot be passed from one person to another, it can occasionally run in families. Young adults are usually the first to develop psoriasis. Psoriasis often affects a small number of body parts. (39)

The ratio of proliferating to nonproliferating keratinocytes is approximately 60% in normal skin, but it is nearly 100% in psoriasis, and the mean cell cycle time in psoriatic lesions is shortened from 311 to 36 hours. It has been proposed that this hyperproliferation of keratinocytes may affect suprabasal cells in addition to the basal cell compartment that contains the stem cells. In addition to the increased keratinocyte proliferation seen in psoriasis, there are clear alterations in the expression of different keratins, primarily type I keratins K16 and K17, which are not expressed in normal epidermis with the exception of K17, which is present in normal hair follicles at a low level.(40)

MECHANISM:

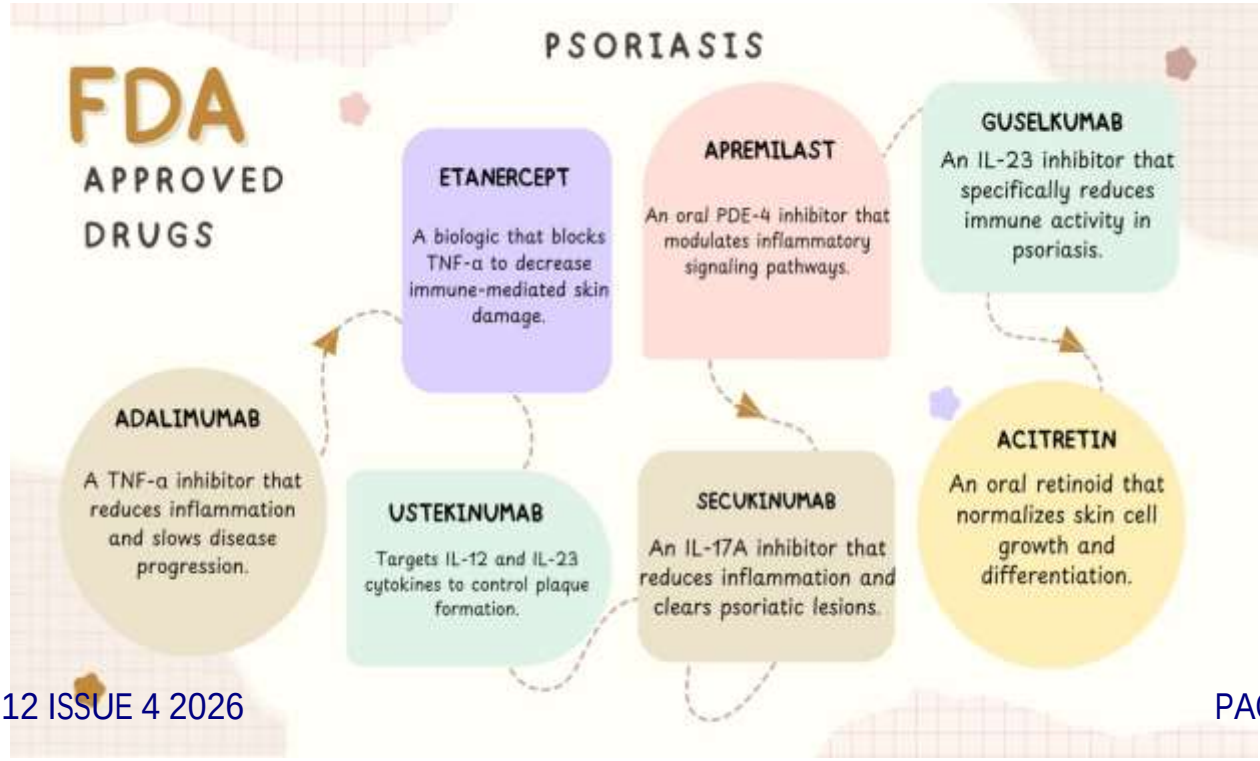
Psoriasis is driven by a complex cytokine network dominated by Th1-mediated immune responses, with key cytokines including TNF-α, IFN-γ, and IL-12. Both CD4+ and CD8+ T cells produce IFN-γ, which plays a central role in lesion formation, while dendritic cells (DCs) and keratinocytes release additional pro-inflammatory cytokines and chemokines. IL-12 and IL-18 synergistically enhance IFN-γ production, and IL-17 from activated T cells further amplifies inflammation by stimulating keratinocytes to produce cytokines such as IL-6 and IL-8.

This creates a self-sustaining inflammatory loop, promoting T-cell recruitment and persistence in the skin. Cytokines such as TGF-α, IL-20, and IFN-γ contribute to keratinocyte hyperproliferation, while IFN-γ and IL-15 increase resistance to apoptosis. TNF-α plays a critical pathogenic role, as evidenced by the effectiveness of anti-TNF therapies. Additionally, chemokines regulate leukocyte recruitment and trafficking, contributing to inflammation, neovascularization, and epidermal hyperplasia. Overall, the intricate cytokine network underlies the key clinical features of psoriasis and represents an important target for therapeutic intervention (39–42).

TREATMENT OR PSORIASIS:

The size and location of the rash, age, past medical history, and other factors all influence the duration of treatment. Steroidal creams, dry skin moisturizers, coal tar (a well-known active ingredient found in lotions, shampoos, foams, and bath solutions for psoriasis of the scalp), vitamin D only in cream or ointment because it has no effect when added to pills, and foods high in vitamin D. Common treatments include retinoid creams. To stop skin cells from proliferating, a dermatologist will expose the skin to UV radiation. Psoralen is mixed with a particular kind of UV light in a compound called PUVA. Because methotrexate causes issues with the bone marrow, liver, and lungs, dermatologists only recommend it for patients with severe disease progression. Apremilast, also known as Otezla, is an enzyme inhibitor used to treat long-term inflammatory conditions such psoriasis and psoriatic arthritis. It slows down the inflammatory process by blocking a certain enzyme. (39) may be used when psoriasis is more severe or does not improve with topical treatments. These drugs work systemically to lower inflammation and decrease the immune response. They can be injected or taken orally.For the treatment of moderate to severe psoriasis, highly effective biological treatments have been developed. These biologic medications target particular chemicals and cells that contribute to psoriasis-related inflammation and cell growth. Biologic treatments for psoriasis include interleukin inhibitors (IL) and tumor necrosis factor-alpha (TNF-α) inhibitors. It has been demonstrated that these drugs are quite successful in reducing symptoms and enhancing patients' quality of life. (43)

FDA APPROVED DRUGS



INFLAMATORY BOWL SYNDROME:

INTRODUCTION:

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory disorders of the gastrointestinal tract with multifactorial etiology involving genetic susceptibility, immune dysregulation, dysbiosis, and environmental factors. While UC is confined to the colon and rectum, CD can affect any part of the gastrointestinal tract and is characterized by transmural inflammation. Common symptoms include abdominal pain, diarrhea, rectal bleeding, weight loss, and anemia, with complications such as fistulas, strictures, and increased risk of colorectal cancer, particularly in UC.

Conventional therapy includes aminosalicylates, corticosteroids, and immunomodulators; however, limitations such as adverse effects and treatment resistance have driven the development of advanced therapies. Biologic agents, particularly monoclonal antibodies targeting TNF-α, integrins, and interleukins, have significantly improved disease outcomes. Additionally, Janus kinase (JAK) inhibitors such as tofacitinib, upadacitinib, and filgotinib offer effective oral alternatives for patients unresponsive to conventional or biologic therapies. These evolving treatment strategies highlight ongoing advancements in achieving remission and improving quality of life in IBD patients (44–47).

MECHANISM OF IBD:

Inflammatory bowel disease (IBD) is associated with disruption of the intestinal barrier, which normally maintains homeostasis between luminal contents and the mucosa through intestinal epithelial cells (IECs) and innate immune cells. Increased intestinal permeability, reduced expression of junctional proteins such as E-cadherin, and altered epithelial regeneration contribute to disease susceptibility. Specialized IECs, including goblet cells and Paneth cells, play critical roles in mucosal defense; defects in mucin production (e.g., MUC2) or antimicrobial activity increase the risk of inflammation.

Genetic factors such as NOD2 and ATG16L1 mutations impair Paneth cell function and autophagy, leading to reduced antimicrobial defense and enhanced microbial translocation. Innate immune dysfunction, including altered macrophage and dendritic cell activity, further promotes chronic inflammation through increased proinflammatory cytokine production and impaired immune regulation. These combined defects in epithelial integrity, microbial handling, and immune responses drive the pathogenesis of IBD (48–50).

TREATMENT OF INFLAMMATORY BOWEL SYNDROME:

Aminosalicylates, particularly mesalamine (5-ASA), are first-line agents for inducing and maintaining remission in mild to moderate ulcerative colitis (UC), often used alone or with corticosteroids. Sulfasalazine, a prodrug of 5-ASA linked to sulfapyridine, is metabolized in the colon to release the active component, mesalamine, which exerts anti-inflammatory effects. Its mechanisms include inhibition of proinflammatory cytokines (TNF-α, IL-1), suppression of NF-κB, and scavenging of free radicals.

Oral sulfasalazine demonstrates efficacy in 60–80% of patients, while other 5-ASA formulations such as olsalazine and balsalazide are also used. However, the role of 5-ASA in Crohn's disease remains limited. Common adverse effects include headache, dyspepsia, and rash, while diarrhea is more frequent with olsalazine. Rare but serious complications such as nephrotoxicity may occur, highlighting the need for monitoring during therapy (51–53).

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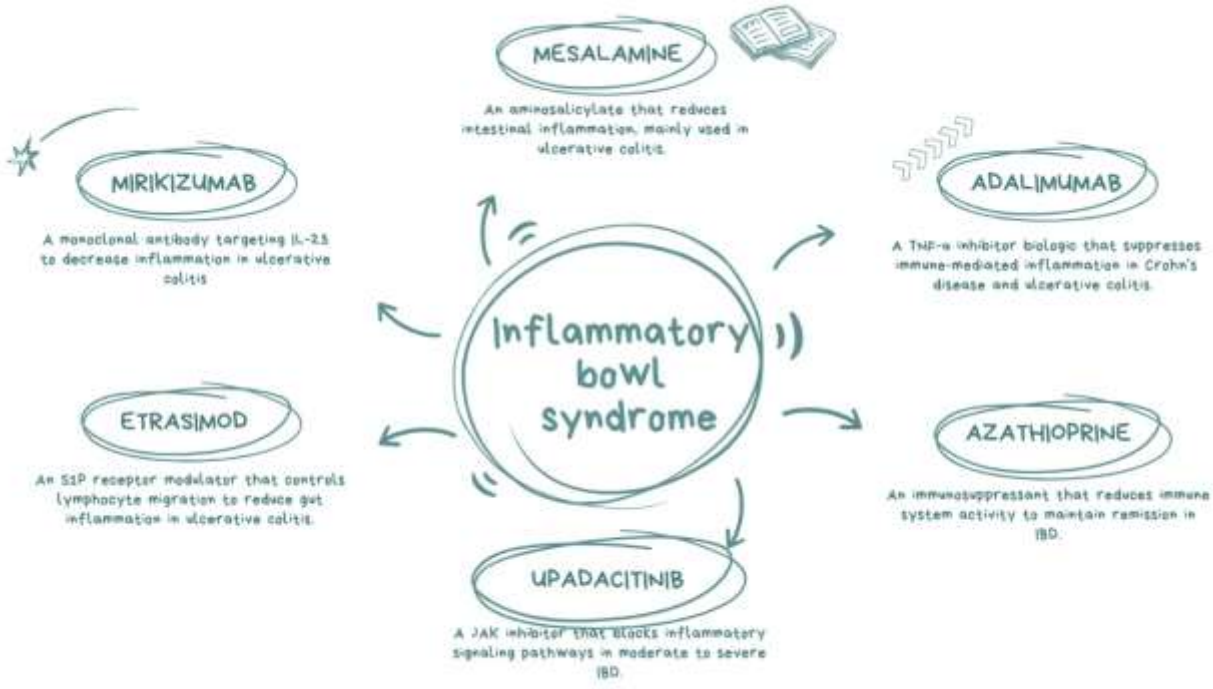


SYSTEMIC LUPUS ERYTHEMATOSUS:

INTRODUCTION:

The majority of medical professionals were taught in medical school that the classic multisystem autoimmune illness is systemic lupus erythematosus, also known as lupus. Lupus can show in numerous medical specialties because patients with systemic lupus erythematosus exhibit immune-mediated inflammatory damage in almost every organ system. Numerous challenges arise from this well-known clinical heterogeneity, such as how to diagnose patients or standardize treatment methods. Additionally, we now know that a variety of distinct molecular diseases that may account for these varied phenotypes are present in patients who are clinically diagnosed with systemic lupus erythematosus. (54)

There have been few significant advancements in the treatment of systemic lupus erythematosus due to the difficulties presented by the combination of clinical and biochemical heterogeneity. Despite the introduction of three novel medications for lupus nephritis and systemic lupus erythematosus in recent years, most patients' long-term results are still marked by substantial morbidity and death. The most recent methods for treating systemic lupus erythematosus are summarized in this review, which focuses on evidence that has been independently verified, such as in independent clinical or laboratory investigations. There are still significant knowledge gaps even though some topics are supported by solid data

There are significant regional differences in the incidence and frequency of systemic lupus erythematosus. Different regions' access to care, environmental exposures and socioeconomic status, genetic risk factors, and heterogeneity in systemic lupus erythematosus features are probably the main causes of the variations in epidemiological estimates in global populations, though methodological variations between studies may also play a role. (55)

MECHANISM:

Autoantibody production in systemic lupus erythematous:

A B-cell's activation, deletion, or anergic state are determined by positive and negative signals from the B-cell receptor (BCR) and co-receptors as well as competition for survival factors such B-cell activating factor (BAFF, also known as BLyS). The result of both positive and negative signals is also determined by regulatory T cells. Increased levels of circulating autoreactive B lymphocytes can result from genetic disorders impacting BCR signaling.

Numerous BCRs with affinity for self-antigens, like DNA, make up the early B-cell repertoire in the bone marrow (BM). Before they may leave the BM, B cells that express receptors with a strong affinity for self-antigens produced in the BM are usually eliminated or undergo receptor editing to produce a receptor devoid of self-reactivity. However, B cells that detect self-antigens not present in the BM or bind self-antigens weakly may leave the BM and be suppressed by energy-induction or deletion. (56)

Somatic hypermutation of the immunoglobulin heavy and light chain variable areas results in the peripheral generation of a second wave of autoreactive B lymphocytes in germinal centers (GC). A single mutation in one of these areas can change a BCR that is specific for phosphorylcholine, a bacterial antigen, into a receptor that is specific for DNA.

According to HEp-2 cell lysate ELISA, about 40% of immature, recently emigrated peripheral blood B cells from healthy individuals are autoreactive. Nevertheless, these cells do not secrete immunoglobulin unless they go through additional maturation and final differentiation into plasma cells, and they are prone to censorship between the immature and naïve B-cell phases of development.

Therefore, control of terminal B-cell differentiation may restrict the generation of serum autoantibodies in addition to the censorship (central and peripheral) of autoreactive B cells. (57)

TREATMENT AND DIAGNOSIS:

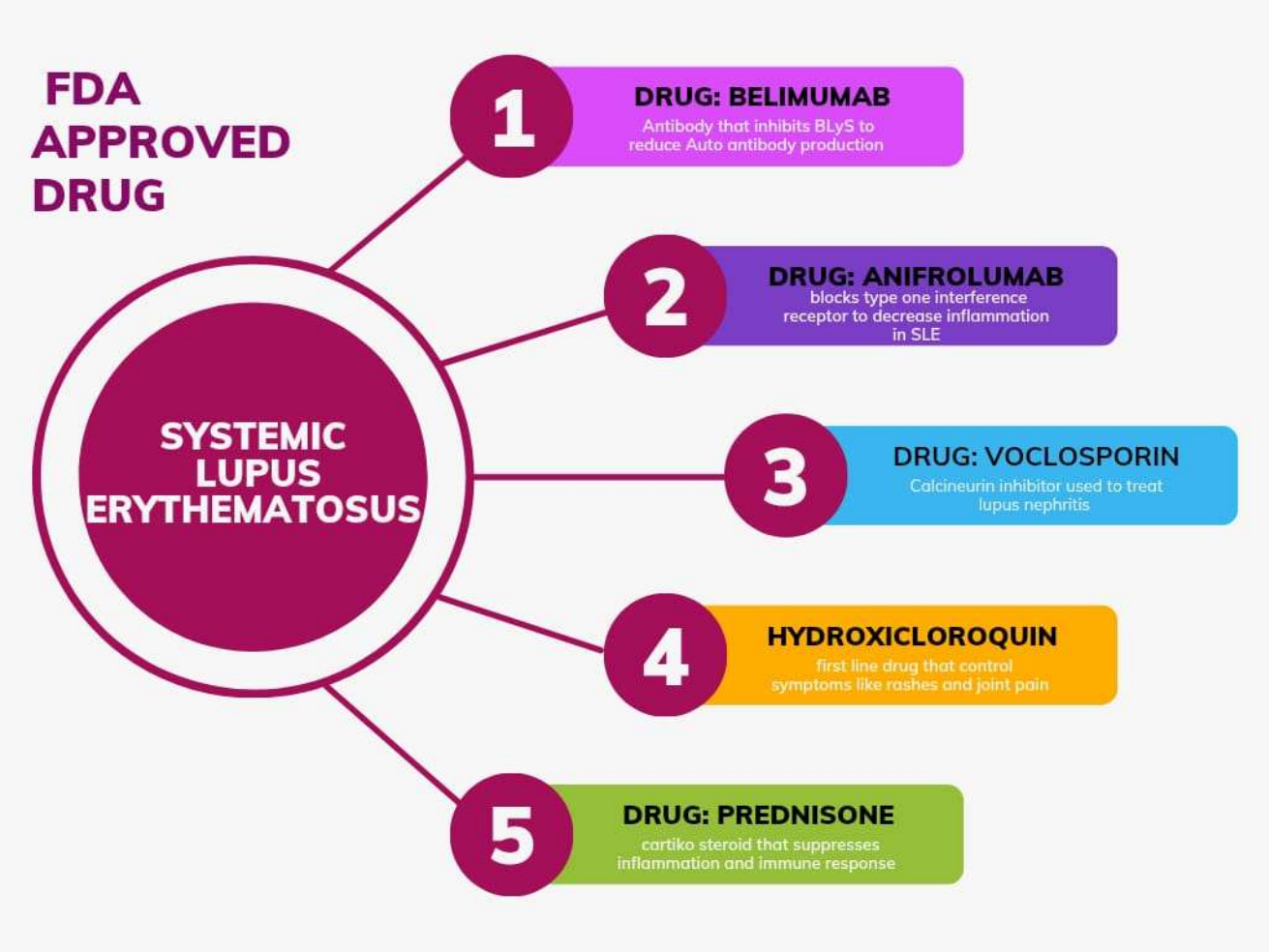
SLE is diagnosed by laboratory testing, patient-specific diagnostic testing, and observable signs and symptoms. A useful tool for evaluating patients when SLE is suspected is the 1997 Update of the 1982 American College of Rheumatology (ACR) Revised Criteria for Classification of Systemic Lupus Erythematosus. SLE can be diagnosed with 95% specificity and 85% sensitivity if a patient exhibit four or more of the 11 criteria, either concurrently or at various times. However, a 2003 study that contrasted modified weighted criteria with ACR criteria showed that the weighted criteria had a greater sensitivity (sensitivity, 90.3% vs. 86.5%; specificity, 60.4% vs. 71.9%). (58)

ANA testing is crucial for the diagnosis of SLE because nearly all SLE patients are ANA-positive. Although lower titers are typically seen with rheumatoid arthritis than with SLE, a positive ANA result is occasionally recorded in conditions other than SLE, such as rheumatoid arthritis. Two particular autoantibodies that are highly diagnostic for SLE are anti-dsDNA and anti-Smith (Sm). A complete blood count (CBC) with differential, a full metabolic profile, and a

urinalysis to ascertain the creatinine clearance and the presence of proteinuria or active sediment are additional often performed diagnostic laboratory procedures in addition to autoantibody testing. (59)

Further research is being done on the usefulness of testing complement levels (C3 and C4) as potential markers during SLE flare-ups. Individualized diagnostic tests may be used to address each patient's unique signs and symptoms. Joint involvement can be evaluated with radiography, kidney size and impairment with renal ultrasound, pulmonary involvement with chest radiography, and chest discomfort with electrocardiography. (60)

FDA APPROVED DRUG:



CONCLUSION:

Autoimmune diseases represent a complex interplay between genetic susceptibility, environmental triggers, and dysregulation of immune tolerance mechanisms. The breakdown of central and peripheral tolerance in both T and B lymphocytes leads to the activation of autoreactive immune responses, further amplified by pro-inflammatory cytokine pathways. This results in chronic inflammation and progressive tissue damage, as observed in conditions such as rheumatoid arthritis, type 1 diabetes mellitus, Hashimoto's thyroiditis, psoriasis, inflammatory bowel disease, and systemic lupus erythematosus.

Despite significant advancements in understanding their pathogenesis and the development of targeted therapies, autoimmune diseases remain a major clinical challenge due to their heterogeneity and unpredictable course. Current treatments primarily focus on controlling immune responses and alleviating symptoms rather than providing a definitive cure. Therefore, continued research into immune regulation, early diagnosis, and personalized therapeutic approaches is essential to improve patient outcomes and quality of life.

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