Rheumatoid Arthritis New Approaches for Its Evaluation and Management

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Abstract: Rheumatoid arthritis (RA) is a chronic, inflammatory autoimmune disease that primarily affects the joints, but can also have systemic implications, leading to multi-organ involvement. It is characterized by progressive synovial inflammation that can cause cartilage and bone destruction, deformities, and significant functional impairment if left untreated. RA affects approximately 1% of the global population, with a higher prevalence in women and onset typically between the ages of 30 and 60. The exact etiology of RA remains unclear, though genetic factors such as the presence of specific human leukocyte antigen (HLA) alleles and environmental triggers, such as smoking and infections, are known to contribute to disease onset.

The pathogenesis of RA involves a combination of genetic susceptibility and environmental triggers that lead to the activation of the immune system, particularly the aberrant activation of T-cells and the subsequent production of pro-inflammatory cytokines like tumour necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). These cytokines drive the inflammatory cascade, leading to the recruitment of immune cells to the synovium, resulting in chronic inflammation, pannus formation, and joint destruction. Over time, this inflammation can extend beyond the joints, affecting other organs such as the lungs, heart, and vasculature, a phenomenon known as extra-articular disease.

Clinically, RA is characterized by symmetrical joint involvement, with the most commonly affected joints being the wrists, knees, and metacarpophalangeal joints. Early symptoms typically include pain, stiffness, and swelling, with morning stiffness lasting longer than 30 minutes. As the disease progresses, patients may experience joint deformities, functional limitations, and a decline in quality of life. If left untreated, RA can lead to significant disability due to joint destruction, muscle wasting, and decreased mobility.

The diagnosis of RA is based on clinical features, laboratory findings (including positive rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA)), and imaging studies. Early detection is critical in preventing irreversible joint damage, as RA progression can be rapid in some individuals. Advances in imaging techniques, such as ultrasound and MRI, have improved the ability to assess joint inflammation and damage.

Treatment for RA has evolved significantly over the past few decades, with the introduction of biologic disease-modifying anti-rheumatic drugs (DMARDs) and targeted synthetic DMARDs. Methotrexate remains the cornerstone of therapy, but biologics, such as TNF inhibitors, IL-6 receptor inhibitors, and Janus kinase (JAK) inhibitors, have revolutionized treatment by targeting specific immune pathways involved in disease activity. These therapies have shown to reduce inflammation, prevent joint damage, and improve quality of life in patients with moderate to severe RA. However, challenges persist, including treatment resistance, adverse effects, and the high cost of biologic therapies.

In addition to pharmacological treatment, multidisciplinary management involving physical therapy, occupational therapy, and psychosocial support is essential to optimize outcomes for RA patients. Long-term management requires continuous monitoring of disease activity, joint function, and the potential for extra-articular manifestations, such as rheumatoid lung disease, vasculitis, and cardiovascular risks.

1. NTRODUCTION

Rheumatoid arthritis (RA) is the most common autoimmune disease with an unknown ethology. The most common form of the disease is chronic inflammatory arthritis characterized by inflammation of synovial joints that become swollen and painful due to inflammation, thickening of the articular membrane and fluid accumulation. Over time, it typically leads to destruction of cartilage and bone, joint deformity, organ failure, and eventually leads to disability in patients. RA has a prevalence of about 1% and women are affected two to three times as often as men. Incidence is most frequent among people between 35 and 55 years old. While the exact and the main causes of RA are not clear, it is generally believed that a combination of genetic background of individuals, epigenetic markers, and environmental factors play a role as risk factors for this disease. As a hypothesis, it is generally accepted that RA originates from a high-risk genetic background that in combination with epigenetic markers and environmental factors causes new epitopes.

Clinical symptoms in the joints of patients with RA are caused by interactions between synovial membrane lining cells such as fibroblast-like cnidocytes (FLSs) with innate immune system cells (macrophages, dendritic cells (DCs), natural killer (NK) cells, mast cells, and neutrophils) and adaptive immune system cells (B and T lymphocytes; B- and T cells). These cells express Toll-like receptors (TLRs) on their surface which are involved in a variety of tissue injury responses It is assumed that FLSs, as cell participants in RA, are influenced by cytokines secreted from the immune system and in its specific microenvironment, transform from a quiescent state to a hyperplastic and invasive phenotype like those of tumour cells.

recent years, mesenchymal stromal cells (MSCs) have been considered regulators of the immune system. MSCs have been employed in several clinical studies, and the safety and efficacy of the cells have been verified in various disease states. MSCs can regulate the immune system rather than suppress it. The immunomodulatory properties of these cells on all major immune cell populations, including B cells and T cells, NK cells, neutrophils, macrophages, and DCs, have designated them for treating inflammatory diseases, especially autoimmune diseases, most important cells of the cellular immune system, in immune responses, is considerable

In this review, we characterize the RA disease from various aspects, discuss the immunomodulatory function of MSCs and explore their potential use in vivo

RA is a systemic condition, meaning it can affect other parts of the body, including the skin, eyes, lungs, heart, and blood vessels. The exact cause of RA remains unclear, but it is thought to involve a combination of genetic and environmental factors, including infections and smoking. Women are more likely than men to develop RA, and it typically begins between the ages of 30 and 60.

The symptoms of RA include joint pain, swelling, and stiffness, often worse in the morning or after prolonged periods of inactivity. If left untreated, RA can lead to joint deformities and loss of function. Early diagnosis and intervention are crucial in managing the disease and preventing long-term damage. Treatment options for RA include nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), biologics, and corticosteroids. Physical therapy and lifestyle changes are also important in managing the symptoms and improving quality of life.

Historical changes in assessments

Before 1990, there were multiple ways to assess RA. Approaches included recording the duration of morning stiffness, measuring finger sizes using jewellers' rings, and recording grip strength using modified sphygmomanometers. There was no sensitive or agreed way to assess the impact of RA on erosive joint damage, physical function, or quality of life. Finally, recording adverse events was difficult, and the toxicities of many early drugs including steroids were not fully understood when these treatments were introduced.

Historical changes in drug treatments

Until the 1980s, the treatment of RA involved treating symptoms with analgesics and non-steroidal anti-inflammatory drugs, giving non-responders disease-modifying drugs that were either toxic (such as gold) or relatively ineffective (such as hydroxychloroquine), and using steroids as needed to control inflammation, knowing that their toxicity would risk long-term problems. Since then, three main developments have occurred. Firstly, more effective and less toxic disease-modifying drugs including methotrexate, sulfasalazine, and leflunomide became available 4. Secondly, starting with tumour necrosis factor (TNF) inhibitors, a range of both highly effective and relatively safe biologic agents was developed 5. Finally, in recent years, new orally effective kinase inhibitors,

Common Symptoms and Complications in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory disease that primarily affects the joints but can also cause systemic complications due to its autoimmune nature. Understanding the common symptoms and potential complications is crucial for effective management and early intervention.

Common Symptoms

1. Joint Pain and Swelling: RA primarily presents as symmetrical joint pain, swelling, and tenderness, commonly affecting the small joints of the hands, wrists, and feet. As the disease progresses, larger joints may also be involved.

2. Morning Stiffness: A characteristic symptom of RA is morning stiffness lasting over an hour, which can also occur after periods of inactivity. This prolonged stiffness is a distinguishing feature of RA compared to other forms of arthritis, such as osteoarthritis (Rasch et al., 2015).

3. Fatigue and Generalized Weakness: Patients with RA often experience chronic fatigue, low-grade fever, and a feeling of malaise, attributed to systemic inflammation (Mestizos et al., 2015).

4. Loss of Joint Function and Deformities: If untreated, RA can lead to joint deformities, such as swan-neck or boutonnière deformities in the fingers, and reduced function, which may limit mobility and daily activities (van der Helm-van Mil & Huizinga, 2006).

Common Complications

1. Cardiovascular Disease (CVD): RA significantly increases the risk of cardiovascular complications, including heart attacks and strokes. Chronic inflammation accelerates atherosclerosis, which is a major cause of cardiovascular morbidity in RA patients (Turesson & Matteson, 2014).

2. Pulmonary Complications: Lung involvement is a common extra-articular manifestation, with complications ranging from interstitial lung disease (ILD) to pulmonary nodules and pleuritis, which can cause breathing difficulties (Brown, 2017)

3. Osteoporosis: Chronic inflammation, combined with corticosteroid use and reduced mobility, makes RA patients more susceptible to osteoporosis and fractures, particularly in the spine and hip (Gough et al., 2005).

4. Rheumatoid Nodules: Subcutaneous nodules, known as rheumatoid nodules, can form near affected joints or pressure points, often in advanced RA. While generally asymptomatic, they can occasionally become infected or ulcerated (Turesson, 2014).

5. Infections: RA and its treatments, particularly immunosuppressive drugs, increase the risk of infections. Opportunistic infections, such as bacterial, viral, and fungal infections, are more frequent in RA patients than in the general population (Doran et al., 2002).

6. Psychological Impact: Living with chronic pain, limited function, and fatigue can significantly impact mental health, leading to an increased prevalence of depression and anxiety in RA patients (Mitcham et al., 2014).

Classification:

Disease modifying anti- rheumatic drugs [DMADS]

1]non-biologics:

Eg: Methotrexate, azathioprine, cyclophosphamide, ciclafrine, chloroquine, gold salt.

2]Biologics:

A] TNF-ALPHA Antagonist: Etanercept, Infliximab, Adalimumab, Golimumab,

B]IL-Antagonist: Anakinra

C]T-Cell modulating agent: Abatacept

D]B-Lymphocyte Depletory: Rituximb, methylprednisolone

3]NSAIDS: Aspirin, Ibuprofen, Diclofenac, Napolcom,

4]Glucocorticoids: Prednisolone, triamcinolone, methyl prednisolone

2. Mechanisms Underlying Ra Pathogenesis Self-Reactivity Plays A Crucial Role In The Pathogenesis Of Ra Disease

A pathogenesis, involving immune dysregulation, genetic predisposition, environmental triggers, and the complex interplay of various cells and cytokines. Further research is needed to fully understand the mechanisms underlying RA and develop targeted therapies. The progression of RA disease is typically divided into three steps

Autoimmunity without symptoms: In the early stages of autoimmunity, genetic factors such as genes encoding major histocompatibility complex (MHC) class II, human leukocyte antigen (HLA) DR beta chain 1 (HLA-DRB1), epigenetic effects, and environmental factors (such as smoking, microbiota, female gender, etc.) can contribute to the susceptibility to RA. The role of environmental factors in predisposition to RA has not been well established yet, but it is shown that smoking affects mucosal cells and by induction of peptidyl arginine deaminase converts arginine to citrulline

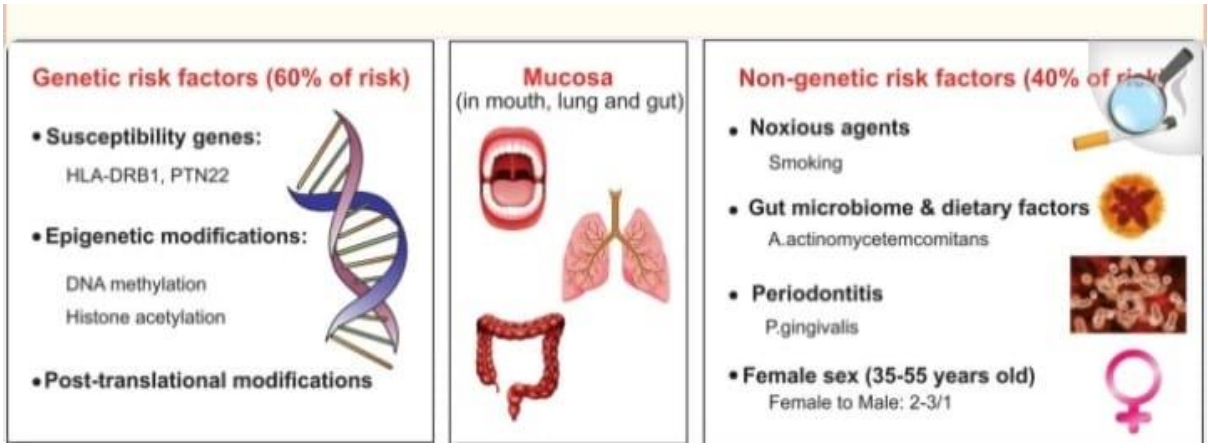

FIG: 1 Self Protein Citrullination

2.1 Initiation of autoimmunity

Gene-environment interactions can trigger RA at the potential trigger sites (lung, oral cavity, gut, etc.), causing self-protein citrullination, resulting in producing autoantibodies against citrullinated proteins. ACPA maturation may be induced by noxious agents, infectious agents (Prohormones gingival is, Aggregatibacter actinomycetemcomitans, and Epstein-Barr virus), gut microbiome, and dietary factors. RA Rheumatoid arthritis, HLA-DRB1 Human leukocyte antigen DR beta chain 1, PTN22 Protein Tyrosine Phosphatase Non-Receptor Type ACPA anti-citrullinated protein antibodies, P. gingival is Prohormones gingival is, A. actinomycetemcomitans Aggregatibacter actinomycetemcomitans

Such post-translational modifications (deamination and citrullination of proteins) occur in a wide range of intracellular proteins, such as histones and fibronectin, collagen, fibrinogen, enolase, and vimentin for example, prohormones gingival is, which causes gingivitis, produces the mentioned enzyme and leads to citrullination. Finally, the deformed peptides bind to the heterodimeric chains of MHC molecules, especially shared epitopes, and are presented as to T cells. Subsequently, B- antigens cells are activated, leading to the production

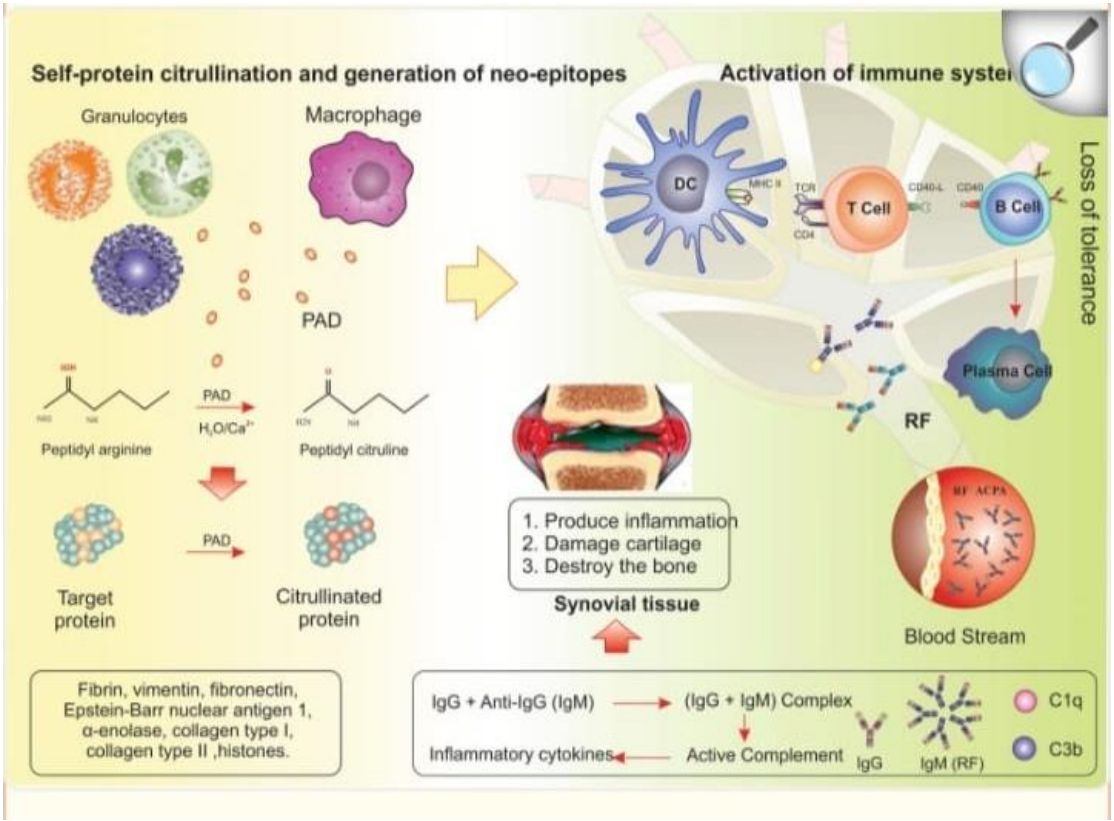

FIG: 2 Pre-Clinic stage in RA

RA, both macrophages and granulocytes can secrete PAD. The calcium-dependent enzyme PAD catalyses the post-translational change known as citrullination, which converts a positively charged arginine into a polar but neutral citrulline. ACPA is caused by an aberrant immune response to a variety of citrullinated proteins, including type II collagen, histones, fibrin, vimentin, fibronectin, Epstein-Barr Nuclear Antigen 1, -enolase, and Epstein-Barr Nuclear Antigen 1. Numerous citrullination neoantigens would trigger MHC class II-dependent T cells, which in turn would encourage B lymphocytes to produce more ACPA antibodies against a variety of native citrullinated proteins in secondary lymph tissue. The phase is additionally known as loss of tolerance. If this stage continues, the disease will progress, and the cartilage and bone tissue in the joints will be destroyed. RA rheumatoid arthritis, PAD peptidyl-arginine-deiminase, ACPA anti-citrullinated protein antibodies, RF rheumatoid

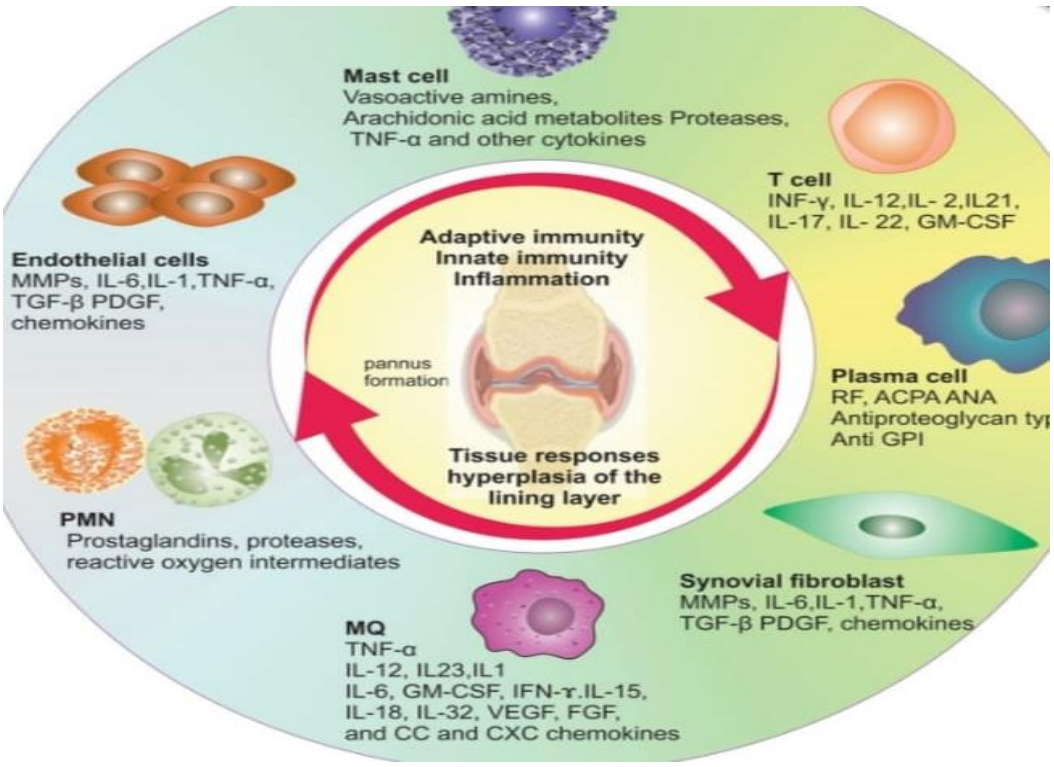

FIG: 3

RA joints. In the establishment of RA, several cells and their cytokines play key roles. Leukocytes infiltrate the synovial compartment, and pro-inflammatory mediators are produced in the synovial fluid to cause an inflammatory cascade. This cascade is characterized by interactions between fibroblast-like cnidocytes and cells of the both innate (mast cells, macrophages, dendritic cells) and adaptive (T cells and B cells) immune system. These interactions contribute to the hyperplastic synovium, pannus formation, cartilage degradation, bone erosion, and systemic effects that are characteristic of the severe clinical stage of RA. IL interleukin, TNF tumour necrosis factor, MMP matrix metalloproteinase, TGF transforming growth factor, PDGF platelet-derived growth factor, IFN interferon, GM-CSF granulocyte–macrophage colony-stimulating factor, VEGF vascular endothelial growth factor, FGF fibroblast growth factor

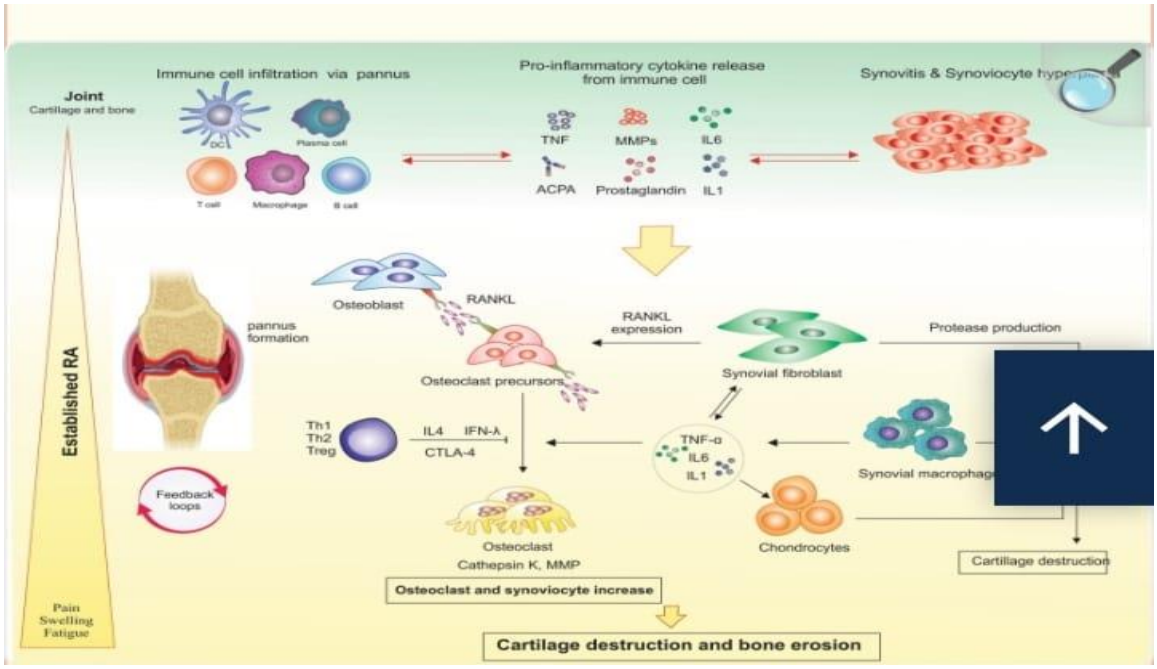

FIG: 4 Pro Inflammatory Cytokine

fibroblasts, and synovial macrophages secrete Matrix metalloproteinase (MMP), a disintegrant and metalloproteinase with thrombospondin motifs (ADAMTS), respectively, which are responsible for cartilage degradation. CD40L denote CD40 ligand, RANKL RANK receptor activator of nuclear factor-κB ligand, Fin interferon-γ, TNF tumour-necrosis factor, CTLA] The synovial membrane lining cells proliferate at this step, increasing the number and activation of macrophage-like cnidocytes (producing inflammatory cytokines like IL1, IL6, and TNF) and fibroblast-like cnidocytes (producing IL6, MMP, and various prostaglandins and leukotrienes). CD4 + lymphocytes' production of RANKL ligand activates Osteoclasts, which together with cytokines like IL6, IL1, and TNF secreted by macrophages and FLSs of the synovial layer, activates the RANKR receptor on the surface of osteoclasts.

which are secreted by chondrocytes, synovial -4 cytotoxic T-lymphocyte–associated antigen 4 MMPs

Cytokines in pathogenesis of RA:

Cytokines play a key role in the pathogenesis of RA by effecting cellular receptors and activating inflammatory signalling pathways, inducing phenotype alterations, migration, differentiation and proliferation of cells. TNF-α, IL-6, IL-7, IL-17, IL-21, IL-23, IL-1β, IL-18IL-33, granulocyte macrophage colony-stimulating factor (GM-CSF), and IL-2 are known to be active Cytokines play a key role in the pathogenesis of RA, by affecting cellular receptors and from the acute to the chronic stages of RA major roles in the pathogenesis of RA. These cytokines stimulate the proliferation of synovial membrane cells, which ultimately leads to thickening of the synovial membrane and a reduction in synovial fluid volume. This typically manifests with signs of painful and stiff joints limiting their movement TNF-α also stimulates the secretion of angiogenic factors such as transforming growth factor beta (TGFβ), which causes the pannus formation and the invasion of immune cells into the articular cavity. Subsequently, inflammatory macrophages induce cartilage injury and destruction by producing neutral collagenases, proteases and proteolytic cartilage enzymes. On the other hand, TNF-α and IL-1 trigger osteoclasts activation, which induces demineralization and decomposition of the bones in the joint.

In addition, TNF-α has effects on the central nervous system and causes cognitive change, depression and fatigue and also by affecting metabolism, results in an alternation of cholesterol synthesis homeostasis and insulin resistance. Another important cytokine in RA is IL-6 which has a notable effect on the proliferation and differentiation of macrophages, B cells and T cells, osteoclasts, chondrocytes and endothelial cells. IL-6 worsens inflammatory conditions by invoking immune cells from the bone marrow T cells differentiate into CD4+/Th17 cells. Th17 cells are self-reactive and inflammatory cells that exacerbate inflammation by the production of IL-17. Increased serum IL-17 levels are directly associated with the

severity of clinical symptoms. The role of other cytokines such as IL-21 and IL-23 in the pathogenesis of RA has been well-established. In our recent study, we evaluated the therapeutic effects of three types of MSCs

This confirms the ability of these cells to modulate the immune system and alleviate inflammation. Our study revealed a significant decrease in specific IgG levels autoantibodies across all three MSC treatment groups compared to the sham group. This provides strong evidence for the ability of MSCs to reduce serum levels of autoreactive antibodies against CII, specifically CII-specific IgG, and to modulate humoral-specific immune responses.

3.Common Medications For Ra:

Over the past two decades, the treatment of RA has improved substantially. First, the treatments aim to reduce pain and decrease inflammation, by using non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids However, these treatments were not efficient in preventing the progression of the disease or the destruction of cartilage and bone. Subsequently, a new generation of RA drugs were introduced to the market, namely the Disease-Modifying Anti-Rheumatic Drugs (DMARDs). In addition to alleviating pain and inflammation and reducing the acute phase proteins, DMARDs can be used to slow down the progression of the disease Methotrexate as an anti-metabolite and folic acid analogue, is one of the most important and useful DMARDs. This drug acts by binding to dihydrofolate reductase and preventing the reduction of dihydrofolate to tetrahydrofolate. Thereby inhibits the production of DNA and RNA, thymidylate and protein. Since the cause of pathologic and clinical manifestations of RA is mainly due to local production of cytokines. Inhibition of cytokines is one of the new biological therapies for RA. Accordingly, a new generation of biological drugs has been introduced to the market that are effective inhibitors of known inflammatory cytokines.

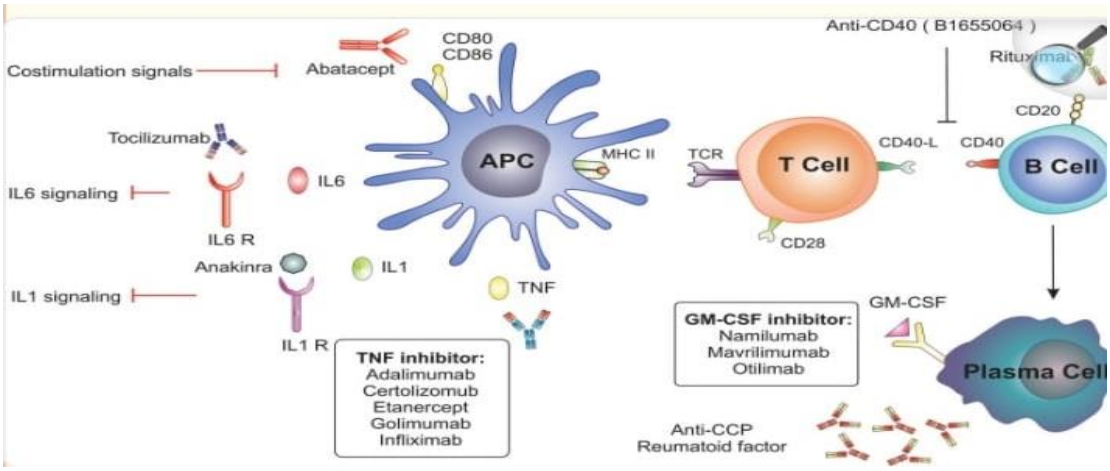

FIG: 5 Inflammatory cytokines

Biologic DMARDs function as antibodies that bind to external targets like circulating cytokines or cell surface receptors: TNF is a key player in the pathogenesis of RA and is the target of five biologic medications: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. Recombinant human IL-1Ra, also known as anakinra, inhibits the biological effects of IL-1. Tocilizumab, a humanized anti-IL-6 receptor monoclonal antibody, binds to the membrane-bound and soluble forms of the IL-6 receptor and inhibits IL-6 for binding to its receptor. Rituximab is a chimeric monoclonal anti-CD20 antibody that decreases the number of B—lymphocytes T-lymphocyte antigen 4 (CTLA-4), a natural inhibitor of T-cell activation. Abatacept prevents T-cell co-stimulation by blocking the interaction between CD28 on a T cell and B7 on an antigen presenting cell. Granulocyte macrophage colony-stimulating factor (GM-CSF), which signals via the JAK-STAT pathway and induces the production of interleukin-6 and other proinflammatory cytokines, has been approached as a therapeutic target in chronic autoimmune disease trials such as rheumatoid arthritis. DMARDs Disease-modifying antirheumatic drugs, TNF tumour-necrosis factor, RA rheumatoid arthritis, IL-1Ra interleukin-1 receptor antagonist, IgG immunoglobulin G considering the limitations of currently available DMARDs, the development of new DMARDs, small-molecule inhibitors (SMIs), has recently emerged. The

mechanism of action of SMIs is to block signalling pathways involved in cytokines production, important role in the treatment of RA. Tofacitinib is a small molecule that inhibits the Jak/Stat pathway and exerts its therapeutic benefit combinatorial regimen of a biological drug with methotrexate may be used to treat patients who have shown an inadequate response to synthetic drugs or were intolerant to them. Nonetheless, approximately 20–40% of RA patients do not respond appropriately to any of the available treatment

5. Stem cell therapy for RA:

Due to the immunomodulatory effects of MSCs, extensive in vitro and in vivo studies have been conducted in RA. MSCs are multipotent stem cells that can differentiate into various cell types, including cartilage, bone and fat. They are easily reproducible in culture and express low levels of MHC-I on their surface, while not expressing MHC-II and costimulatory molecules CD80, CD86, or CD40. This results in their low immunogenicity, allowing for allogeneic transplantation. MSCs can be harvested from various adult tissues such as bone marrow, adipose tissue, and peripheral blood, as well as neonatal tissues like the umbilical cord, placenta, and amniotic membrane. MSCs have multiple functions and can be used in the treatment of a wide range of diseases.

They secrete large quantities of cytokines, chemokines, growth factors, and exosomes, which stimulate angiogenesis, prevent cell death, inhibit oxidative stress reactions, and promote the regeneration of extracellular matrix (ECM). Various preclinical studies have extensively investigated the use of MSCs in tissue repair, yielding encouraging results. In addition to their capability for tissue regeneration, the immunomodulatory effects of MSCs have been proven in various studies. These properties of MSCs have led to their use in the treatment of autoimmune diseases and graft versus host disease (GvHD) in recent decades with promising results in autoimmune diseases, MSCs can regulate the secretion of immunomodulatory factors such as shola (soluble human leukocyte antigen)-G5, PGE2 (prostaglandin E2), IDO (Indole 2,3-dioxygenase). IL-10, and TGF-β (transforming growth factor-β). Through this mechanism, MSCs can control the functions of T cells, B cells, macrophages and DCs, as well as the secretion of inflammatory cytokines Results from experimental models of RA Demonstrate that MSCs, through secretion of different soluble factors and cell–cell interactions, can reduce inflammation and potentially play a role in tissue repair, angiogenesis, bone marrow development, haematopoiesis and immune system modulation

6. Immunomodulatory functions of MSCs in immune diseases:

One of the key functions of MSCs is their suppressive effects on immune system. MSCs were described to be able to inhibit production of inflammatory cytokines from activated lymphocytes and mature DCs in vitro. These effects are dose-dependent, MHC-independent, non-antigen-specific, and do not involve Tregs. The therapeutic effects of MSCs have been investigated in RA ulcerative colitis, autoimmune encephalitis, and other inflammatory and autoimmune diseases. In our study, we compared the therapeutic effects of bone marrow clonal-MSCs (BM-CMSs) to BM- and Wharton jelly (WJ)-MSCs on a rat model of collagen-induced arthritis. The results showed that MSCs significantly reversed adverse changes in body weight, paw swelling, and arthritis score in all MSC-treated groups,

These results confirm the therapeutic effects and immunomodulatory properties of these cells. MSC exert their immunomodulatory effects through both cell–cell contact and the secretion of soluble factors in response to active immune cells. Studies have shown that MSCs interact with different subgroups of leukocytes, inhibiting immune responses. Paracrine secretion of mesenchymal stem cells. Mesenchymal stem cells' paracrine secretion is crucial to their ability to modulate the immune response. In this regard, a variety of soluble factors have been discovered that act on innate and adaptive immune system cells to substantially modulate inflammatory reactions. TGF-β1 including growth factor-β1, PGE2 conversion, prostaglandin E2, HGF hepatocyte growth factor, IDO indolamine-pyrrole-2,3-dioxygenase, NO nitric oxide, HLA-G5 human leukocyte antigen G5 and IL-10 interleukin-10

7. Clinical translation of MSC-based therapies in RA:

MSCs have been shown to modulate autoimmune diseases by applying regulatory effects on the activity and proliferation of T cells. In most clinical studies of RA, MSC therapy induced tolerance in T cells, along with decreased Th17/Th1 cells, decreased immune response to B cells, increased IL-10 secretion, and increased production of Treg cells. The great

beneficial potency of MSCs in tissue regeneration and modulation of immune-related diseases has been demonstrated in clinical trials and experimental studies in animal models. Most studies have been conducted with MSC-derived bone marrow as the first known source of MSCs However, aspiration of bone marrow is invasive and painful to donors, and only a small volume (about 20 ml) of bone marrow can be harvested during each sampling procedure.

In addition, the amount of MSCs in individuals decreases with age and there is a requirement for younger donors. MSCs is essential in cell therapy. In recent years, embryonic-related tissues such as umbilical cord, placenta, and WJ have been studied as appealing sources of stem cells, and their curative and inhibitory effects on the immune system have been demonstrated. Rheumatoid arthritis, BM bone marrow, MSC mesenchymal stromal cell, UC umbilical cord, sad adipose derived, IV intravenous, IP intra intraperitoneal, as an advantage, although WJ-derived MSCs have substantial proliferation capacity, they do not cause teratoma-like embryonic stem cells. This may be due to the overexpression of tumour suppressor genes. Recent in vitro studies have found that culture medium supplemented with lysates WJ or culture medium of WJ-MSCs prevents the proliferation of different tutor cells

8. Pharmacological treatment

The initial drug treatment for RA involves the use of salicylates, nonsteroidal anti-inflammatory drugs, or selective cyclooxygenase-2 inhibitors to reduce pain and improve motion. Low-dose oral glucocorticoids and local injections of glucocorticoids are highly effective for relieving symptoms in patients with active RA, and prolonged treatment appears to have disease-modifying properties [9]. However, because these agents do not affect disease progression, they should not be used as monotherapy in RA. All RA patients are therefore candidates for DMARD therapy to prevent structural joint damage and maintain function. Furthermore, referral from a primary care physician to a rheumatologist is recommended in the event of clinical suspicion. Early initiation of DMARD therapy is advocated to prevent irreversible structural joint damage. van der Heijde reported that approximately 75% of RA patients with early disease have joint erosions or develop erosions within the first 2 years after the onset of symptoms . Three studies have compared the use of early single-DMARD treatment with the delayed approach and reported that early introduction of DMARD therapy is associated with a better outcome after 1 or 2 years of treatment. Furthermore, a recent evaluation of primary data from 14 randomized clinical trials in RA patients indicates that patients with a longer disease history do not respond to DMARD therapy as well as patients treated at earlier stages of the disease importantly, major side effects of early DMARD treatment are manageable, which supports the conclusion that all early RA patients should be treated with DMARDs. The large majority of RA patients are eventually subjected to the potential side effect of DMARD therapy; it is thus pointless to delay early treatment that may improve long-term outcome. Early DMARD treatment may also result in reduced total health care costs.

The DMARDs most frequently used include methotrexate (MTX), sulfasalazine, hydroxychloroquine, and leflunomide. The choice of a DMARD for an individual patient is based on many factors, including the efficacy/toxicity spectrum of a drug, monitoring requirements, costs, and patient variables such as prognosis, comorbidity, and preferences.

The most recently approved DMARD is leflunomide (Arava™; Aventis Pharmaceuticals, Kansas City, MO, USA), a pyrimidine synthesis inhibitor that has both immunosuppressive and immunomodulatory effects. Leflunomide inhibits T-cell proliferation, autophosphorylation of epidermal growth factor receptors, and activation of nuclear factor-κB. The efficacy of leflunomide was investigated in three large, phase II clinical trials. Leflunomide significantly increased the proportion of patients who experienced an ACR20 score and significantly improved tender joint counts, swollen joint counts, and physician and patient global assessments compared with placebo. However, MTX and sulfasalazine were found to be as effective as leflunomide. Common adverse events associated with leflunomide included gastrointestinal disorders, alopecia, skin rash, and elevated liver enzymes.

Many rheumatologists already prescribe combination therapy even though evidence to support combination therapy was limited until recently three main strategies are often used in combining DMARDs, and include parallel, step-up, and step-down regimens. Data from an increasing number of trials that support combination therapy have recently been completed. Step-down bridge therapies that include corticosteroids have been shown to provideenhanced

efficacy with low toxicity improved a suboptimal response to MTX, and the triple combination of MTX, sulfasalazine, and hydroxychloroquine appears to be clinically superior compared with the agents used in monotherapy, Because of the immunosuppressive properties of DMARDs, the combination of leflunomidewith MTX or any other immunosuppressive agent needs to be closely monitored. Indeed, most of the rare reports of pancytopenia in patients receiving leflunomide occurred in patients who had recently discontinued or were receiving concomitant immunosuppressive agents.

9. Non-pharmacological management

Patients should have access to a multidisciplinary team (MDT) to address both the pharmacological and non-pharmacological aspects of disease management. Patients with RA require access to specialist physiotherapy, with regular, periodic review to assess function and design a programme to aid pain relief and rehabilitation. The programme should aim to improve general fitness, enhance joint flexibility and muscle strength, and overcome other functional impairments through regular and individually tailored exercises. Physiotherapists may also provide education about use of transcutaneous electrical nerve stimulators and wax baths to provide short-term symptom relief.

Occupational therapy aims to provide support and aid patients in improving function, and limit disability in their activities of daily living (e.g. using devices to alleviate tasks that are difficult for those with restricted manual dexterity, such as twisting lids to open bottles). Some patients may benefit from a tailored strengthening and stretching hand exercise program to reduce pain and dysfunction of the hands or wrists if they have been on a stable drug regimen for RA for at least three months (or if they are not on drug treatment).

RA may need psychological support and counselling to help them adjust to living with their condition. They may benefit from sessions with a clinical psychologist, ideally one specialising in rheumatology or the management of chronic conditions. Other psychological interventions include relaxation, stress management and cognitive coping skills.There is no strong evidence that diet modification and complementary therapies benefit management of RA. However, patients could be encouraged to follow the principles of a Mediterranean diet owing to its focus on anti-inflammatory foods

10. Bespoke management

RA is a variable disease. In some patients it is mild, and in others it is severe. Not all patients need identical treatment. It therefore seems self-evident that we should move on from standard care, aimed at all patients, towards individualised care: in other words, from “one size fits all” into the realm of bespoke care There are several examples of known factors that predict the need for more intensive management. Firstly, almost all drug trials enrol patients with active RA who have high DAS28 scores and many tender and swollen joints. The exact dividing line between active and inactive RA is not well defined. However, it usually involves patients having at least three swollen and tender joints and some evidence of an elevated ESR or C-reactive protein level. Patients with inactive disease do not usually have their treatment changed unless they have adverse events with one drug.

There is some evidence that patients who are seropositive for anti-citrullinated protein antibody (ACPA) are more likely to benefit from intensive treatment. Secondary analysis of early RA trial data has shown that intensive treatment is only beneficial in ACPA-positive patients. The impact of ACPA status on remissions with intensive treatment is shown in Figure It is likely that other markers of severe disease also help identify those patients most likely to benefit from higher treatment intensities. However, there is also evidence that low-risk early arthritis patients benefit from bridging therapy with glucocorticoids given together with methotrexate This more recent research implies current assessments of prognostic risk are incomplete, and for the present every patient with early RA could benefit from some form of initial intensive treatment. To inter-related developments changed this historic scenario. The end results were greatly improved clinical outcomes. The first improvement was identifying new drugs and new treatment strategies. The second change was developing new and better ways to assess RA and define the benefits of treatment. Whilst therapeutic innovations are widely recognised, the importance of assessments has received less emphasis. However, without better assessment methods, the ability to identify new drugs would have been greatly reduced.

11. Rheumatoid arthritis pathogenesis

The pathogenesis of rheumatoid arthritis has been extensively reviewed1–3 and will be summarised only briefly in this Review. The genetic architecture of the disease has been well characterised through

conventional and genome-wide approaches. More than 100 loci are associated with disease risk and progression, most of which implicate immune effector or regulatory gene products.4 Prominent among these loci are genes encoding MHC class II molecules, especially HLADR01/04, which is implicated in T-cell recognition of autoreactive peptide, as well as co-stimulatory pathways (CD28, CD40, chemokines, and cytokine receptors such as the interleukin-6 receptor), post-translational modification enzymes (e.g., PADI, which catalyses the post-translational modification of peptidyl arginine to citrulline), and intracellular regulatory pathways (eg, PTPN22, TNFAIP3, STAT3), all of which might alter the threshold for immune activation or failed regulation.

Strong environmental effects operate on this genetic background to promote disease. Pro-disease factors include smoking (especially in individuals with HLADR01/04) and other pulmonary exposures such as silica dust, vitamin D deficiency, and obesity.1,5 A perturbed microbiome in the gastrointestinal tract could also cause long-term effects on immune regulation and maintenance of host tolerance, and prohormones gingival is or Aggregatibacter actinomycetemcomitans in the oral mucosa have been proposed to promote disease, in part, by affecting tissue citrullination.6,7 The earliest events in the pre-rheumatoid arthritis stage thus include altered innate immune reactivity and aberrant T-cell and B-cell cross-regulation, most probably in mucosal tissues, culminating in the production of autoantibodies that recognise a range of post-translationally modified proteins with citrulline residues.

Due to the susceptibility genes HLA-DR1 and HLA-DR4, the immune system is no longer able to recognize citrullinated proteins (vimentin, type II collagen, histones, fibrin, fibronectin, Epstein-Barr nuclear antigen 1, α-enolase) as self-structures . Antigens are taken up by antigen-presenting cells (APC), which are dendritic cells that are activated to initiate an immune response. The whole complex migrates to the lymph node, where the activation of CD4+ helper T cells takes place. Furthermore, the germinal center of the lymph node contains B cells that get activated by reciprocal and sequential signals with T cells, an immunological process called costimulation.

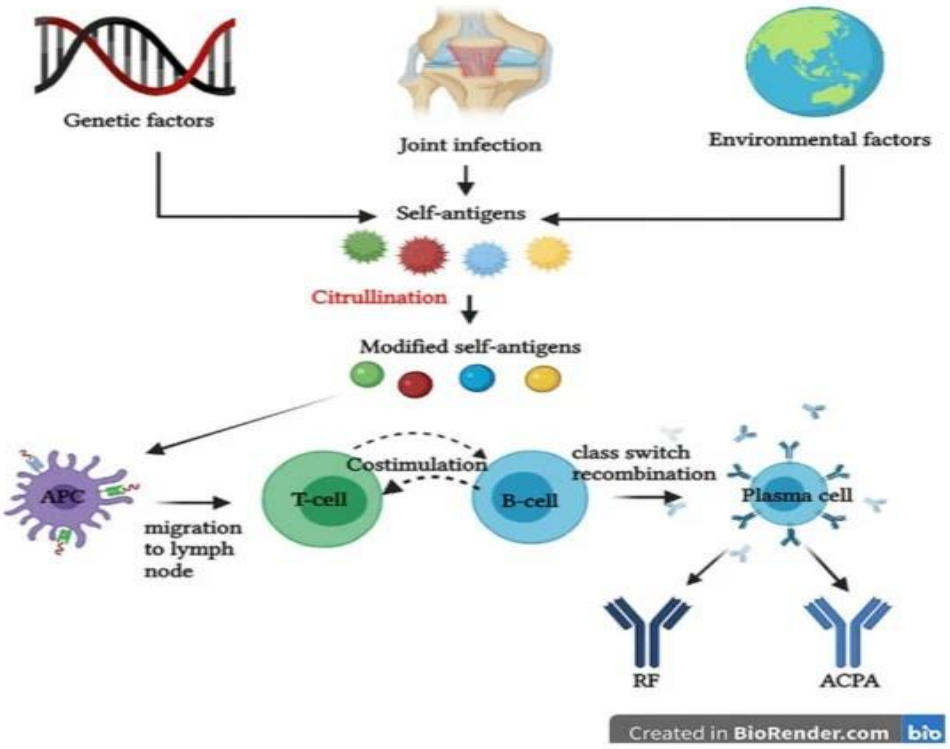

FIG:6 Pathogenesis RA

Emerging therapy

Dynamic and fast-growing insights into cell biology and the understanding of inflammation have resulted in a new appreciation of the pathophysiology of RA. It is now believed that RA is mediated by a vast array of cells and soluble factors that recruit immune cells and perpetuate inflammation Although the primary

antigen is unknown, the initial autoimmune response is associated with an infiltration of T lymphocytes that secrete chemotactic agents, particularly TNF-α and IL-1. These chemotactic agents recruit lymphocytes, macrophages, and B cells to the synovial interstitium of the joint. Extracellular signals also activate complex intracellular signaling pathways, alter messenger RNA synthesis, and increase the production of pro-inflammatory cytokines. Increases in pro-inflammatory cytokines lead to further cell recruitment of macrophages and the activation of synovial fibroblasts, chondrocytes, and endothelial cells in a synovial capsule Activation of these cell types further increases cell migration to the area, and leads to more inflammation, cartilage degradation, and increased bone resorption. Anakinra (Kineret™; Amgen, Thousand Oaks, CA, USA), a recombinant nonglycosylated form of IL-1 receptor antagonist, is an approved therapy for RA patients. The efficacy and safety of anakinra was demonstrated in three double-blind trials. In those studies, patients treated with anakinra experienced significant improvements in tender and swollen joint counts, pain scores, morning stiffness, and radiographic progression [36–39]. Anakinra treatment was associated with injection-site reactions, a higher incidence of neutropenia compared with placebo, and an increased risk of infection. Interestingly, neutralizing concentrations of IL-1 receptor antagonist reduced the production of IL-6 and IL-8, but not TNF-α, in rheumatoid synovial membrane cultures [40]. In contrast, anti-TNF-α antibodies neutralized not only TNF-α levels, but also IL-6, IL-8, and IL-1 levels, anti-TNF therapy provides significant benefit to patients with RA. However, because TNF is a normal component of the immune system, some investigators have questioned whether blockade of TNF could lead to an elevated risk of infection. Although infections are more common in the RA population relative to the general public, there is a concern that anti-TNF therapy may increase serious infections. Indeed, serious infections and sepsis have been reported in postmarketing reports in patients treated with etanercept and infliximab. Furthermore, rare cases of tuberculosis have been reported in patients treated with TNF antagonists.

Monitoring of RA

Accurate monitoring of disease progression is mandatory to assess therapeutic efficacy of agents that slow or inhibit structural joint damage and limit long-term disability. Because of Gene therapy was investigated initially as a means of treating inherited monogenic diseases such as cystic fibrosis and hemophilia. The first striking success was obtained in 2000 by Alain Fischer and coworkers in a group of children with X-linked severe combined immune deficiency (X-SCID) [1]. In X-SCID, the immune system is virtually non-existent, as a result of a mutation in the γ chain shared by receptors for several cytokines. The patients must be confined to sterile bubbles. Administration of the normal gene in a retroviral vector restores normal immune function. However, insertion of the retroviral vector within the host genome caused leukemia in three children 3 years after gene administration Because this serious side effect occurred in patients with a life-threatening disease that was corrected by gene administration, it should not be interpreted as an insurmountable obstacle to gene therapy. Instead, additional preclinical work should be conducted to better define the risk/benefit ratio. Gene therapy remains fully warranted in X-SCID.

In addition to monogenic diseases, polygenic multifactorial diseases such as cancer or autoimmunity are good candidates for gene therapy. In these diseases, instead of a gene, a protein with known or suspected therapeutic effects is delivered by gene therapy.

Most of the proteins used to treat autoimmune diseases have short half-lives (e.g. cytokines) and therefore need to be injected several times a day. In addition, production costs are extremely high. Gene therapy side-steps these limitations by ensuring efficient long-lasting delivery of therapeutic proteins. Ideally, protein delivery should be controlled. Gene therapy can also be used to influence intracellular regulatory events.

Pharmacologic treatment heterogeneity in disease progression between individual patients, a composite evaluation of a variety of clinical parameters is needed. The selection of an evaluation index should governed by parameters sensitive to changes that are easy to obtain, are not redundant, and have high predictive attributes for long-term disease outcome, Both the European League Against Rheumatism and the ACR have defined core sets of disease activity measures for RA with the goal of providing uniformity in the assessment of outcome in clinical trials These measures include tender and swollen joint counts, patient and physician global assessments of disease activity, acute-phase reactants, and pain and physical disability assessments. Each core set has proven viability and reliability, and has a high level of

agreementTo avoid these limitations, Smolen et al. recently proposed a simplified disease activity score (DAS). Using the sum score of the tender and swollen joint counts (28 joints), patient and physician global assessments of disease activity, and the Creative protein level, high correlations are obtained with validated measures. This simplifiedindex may be a viable supplement to the core sets and can be implemented in dailyclinical practice. In addition, when used in clinical trials, this index would have anintuitive familiarity, thereby allowing the practitioner to compare the results of clinical trials with familiar clinical observations.

12. GENE TH ERAPY IN RHEUMATOID ARTHRITIS

Gene therapy was investigated initially as a means of treating inherited monogenic diseases such as cystic fibrosis and hemophilia. The first striking success was obtained in 2000 by Alain Fischer and coworkers in a group of children with X-linked severe combined immune deficiency (X-SCID) . In X-SCID, the immune system is virtually nonexistent, as a result of a mutation in the γ chain shared by receptors for several cytokines. The patients must be confined to sterile bubbles. Administration of the normal gene in a retroviral vector restores normal immune function. However, insertion of the retroviral vector within the host genome caused leukaemi in three children 3 years after gene administration [2]. Because this serious side effect occurred in patients with a life-threatening disease that was corrected by gene administration, it should not be interpreted as an insurmountable obstacle to gene therapy. Instead, additional preclinical work should be conducted to better define the risk/benefit ratio. Gene therapy remains fully warranted in X-SCID.

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JAK INHIBITORS IN RHEUMATOID:

inhibitor developed and brought to market for the treatment of RA. Its development was undertaken in the mid-1990s by a joint public–private partnership between the National Institute of Health (NIH) and Pfizer.13 It was approved by the Food and Drug Administration (FDA) in November 2012 at 5mg BD dose and brought to market under the brand name Xeljanz. The original target cohort was intended to be adults with moderately to severely active RA who have had an inadequate response to, or who are intolerant of methotrexate.14 Tofacitinib was finally approved by the EuropeanMedicines Agency (EMA) in March 2017 after over 4 years of post-marketing safety surveillance in North America.

JAK pathway within the pharmaceutical industry resulted in the development of Baricitinib (Oluminant) by Eli Lilly and Upadacitinib (Rinvoq) by AbbVie, receiving FDA approval in May 2018 and August 2019, respectively. There are a few key differences in the therapeutic targets of each of JAK inhibitor. Tofacitinib is a pan JAK inhibitor with greater selectivity for JAK1/JAK3 with minor activity on JAK2 and TYK2. Baricitinib is a JAK1/JAK2 inhibitor with moderate activity against TYK2 and minimal activity against JAK3.15,16 Upadacitinib aims to solely target the JAK1 pathway. The rationale here being that more specific selectivity of JAK inhibition may reduce dose-related toxicity and side effects without a significant loss of efficacy.

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