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Review on Rheumatoid Arthritis a Chronic Autoimmune Disorder

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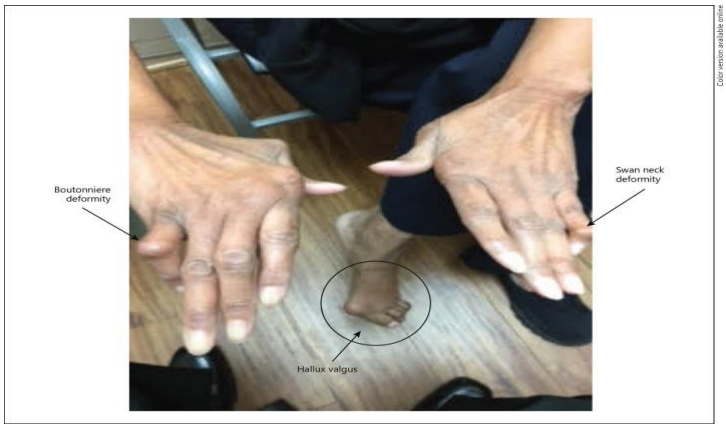
Abstract
Rheumatoid arthritisis a chronic autoimmune disorder featuring systemic inflammation and mainly affects joints. This condition leads to inflammation of the pilgrimage, causing joint damage, pain, and mobility. The pathogenesis of Rheumatoid arthritis involves a complex interplay of genetic predisposition, environmental factors and immune system dysregulation. Early diagnosis and intervention are key to managing symptoms and preventing permanent joint damage. Treatment strategies include pharmacological approaches such as disease-modifying antirheumatic drugs (DMARDs) and biologics, as well as nonpharmacological treatments including physical rehabilitation and lifestyle changes. Ongoing research aims to elucidate the underlying mechanisms of Rheumatoid arthritis and develop novel therapeutic targets, thereby improving patient outcomes and quality of life.

Index Terms: Rheumatoid Arthritis, Etiology, Epidemiology, Pathophysiology, dysregulation

INTRODUCTION

A symmetrical, inflammatory, chronic autoimmune disease, rheumatoid arthritis first affects tiny joints before moving on to larger joints and eventually the skin, eyes, heart, kidneys, and lungs. Joint bone and the cartilage are frequently damaged, & ligaments and tendons deteriorate [1]. Deformities and bone erosion result from all of this joint deterioration, which is typically extremely painful for the patient. Rheumatoid nodules beneath the skin, tiredness, fever, weight loss, and morning stiffness of the afflicted joints lasting more than thirty minutes are typical signs of RA. Additionally, it can affect young children before they turn 16 years old. Both in remission and worsening. Juvenile RA (JRA), which is comparable to RA but does not have the rheumatoid factor, can also affect young children before the age of 16 [2, 3, 4, 5]. It is estimated that the prevalence of RA is 1% globally [7] and 1-2% in the West [5, 6].Osteoarthritis (OA) usually affects the distal interphalangeal (DIP) joint; in contrast, Rheumatoid arthritis mostly affects the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints. This allows for a clinical differentiation between the two conditions. The most prevalent kind ofths arthritis, OA, is not an autoimmune disease but rather the result of the wear and tear. It doesn't affect the immune system, heart, or lungs.The immunological system or the heart. Furthermore, Rheumatoid arthritis is symmetrical, whereas OA usually affects only one side of the body. Patients with RA also differ in that they have morning stiffness that lasts for at least ≥1 hour Morning stiffness is common in OA patients, but it usually goes away or becomes better in 20 to 30 minutes [8, 9] This is a typical example of joint deformity associated with rheumatoid arthritis. There is a boutonniere deformity on the fifth finger of the right hand, a swan-neck deformity on the fifth finger of the left hand, and a hallux valgus deformity on the first toe.

The goals of RA treatment are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of a combination of pharmaceuticals, weight-bearing exercise, patient education, and rest.



Treatment is generally personalized according to the needs of the patient and depends on the overall health. This includes factors such as the progress of the disease, joints, joints, age, overall health, occupation, compatibility, and education education. This review provides a brief overview of the classical and modern treatment options available to manage the discomfort and complications of rheumatoid arthritis. A comprehensive review was recently published by Smolen et al. [11].

ETIOLOGY :

The etiology of RA has a significant genetic basis, which is thought to result from interactions between the patient's genotype and environmental factors. In a nationwide study of 91 monozygotic (MZ) and 112 dizygotic (DZ) twin pairs in the UK, the overall concordance rate for MZ was 15% and for dizygotic twins was 5%. The heritability of rheumatoid arthritis is approximately 40-65% in seropositive rheumatoid arthritis and 20% in seronegative rheumatoid arthritis. The risk of developing rheumatoid arthritis is associated with the HLA-DRB1 alleles, HLA-DRB1*04, HLA-DRB1*01, and HLA-DRB1*10. These HLA-DRB1 alleles contain a conserved five amino acid sequence called a "shared epitope" (SE) in the third hypervariable region of the DRB1 chain, which is associated with the risk of developing RA. 16][17]

Polymorphisms in other genes, such as PAD14, PTPN22, CTLA4, IL-2RA, STAT4, TRAF1, CCR6, and IRF5, have been associated with RA.[18][19][20] Single nucleotide polymorphisms (SNPs) in the PSORS1C1, PTPN22, and MIR146A genes have been associated with severe disease.[21] Several genetic polymorphisms have been associated with rheumatoid arthritis in different ethnic groups.[22][23]

The term epigenetics refers to heritable changes without modification of the"DNA sequence. These changes can be present in chromatin or in DNA. These include DNA methylation, histone modifications, and regulation via non-coding RNA.RA-FLS (fibroblast-like synoviocytes) overexpress the tyrosine phosphatase SHP-2, encoded by the gene PTPN11, compared with synoviocytes from osteoarthritis (OA) patients, promoting the invasiveness of RA-FLS. The enhancer region of the PTPN11 intron contained two hypermethylated sites, resulting in abnormal epigenetic regulation of the gene and altered RA-FLS function.[24]

Smoking is the most powerful environmental risk factor related to rheumatoid arthritis. Research has shown that positive and anti -dependent protein antibodies (anti -CCPs) have an interaction between general epitopes (SE) and smoking, increasing the risk of PR. [25] [26] [27][28] [30] [31]

Environmental triggers can play a role as a PR trigger. This is more closely related to HIV HIV. These include silica, asbestos, textile dust, P. This suggests that external influence of various antigens in parts of the host, far from joints, causes and then causes an autoimmune inflammatory response in joints. The other distant places include light, oropharynx and gastrointestinal tract. The sensation in the composition and function of the intestinal microbiome was also associated with rheumatoid arthritis. Composition of intestinal microorganisms depends on patients with rheumatoid arthritis. In this patient, in patients with rheumatoid arthritis, the type of intestinal microorganism decreases compared to healthy people. These families have an increase in actinobacteria, corinsela, Egager Sarah, and fecaribacterium. Collinsella alters intestinal mucosal permeability and is associated with increased severity of rheumatoid arthritis.

EPIDEMIOLOGY:

Rheumatoid arthritis in the Global Burden of Disease 2010 Study is about 0.24%.[30] The prevalence of Rheumatoid arthritis is higher in the Western & Northern Europe, North America, and other regions with people of European descent, such as Australia. prevalence is lower in Central and South America and even lower in East Asia & Africa.[30] The annual incidence of Rheumatoid arthritis in the United States and other western nations of northern Europe is about 40 per 100,000 persons.[31] According to epidemiologic data, Rheumatoid arthritis is more prevalent in women compared to men, with a lifetime risk of Rheumatoid arthritis of 3.6% in women compared to 1.7% in men.[32] RA risk also increases with age, with a peak incidence between age 65 to 80 years of age.[33][34][35] A systematic review of population-based studies (including 60 studies) showed a worldwide period prevalence of Rheumatoid arthritis of 0.51% (1955-2015).[36]

The ratio of the RA period was larger in urban areas (0.69 %) than in rural areas (0.54 %). The ratio of the RA period was higher in high -income countries (0.49 %), compared to low -income countries (0.35 %). [37] RA's illness was higher in North America and Europe, lower in Asia and South America (see the table below). [36] Data from Africa is limited, vary greatly from country to country, Rheumatoid arthritis is more common in North Africa, lower in Sahara Southern Africa. [37] RA is not very common in East Asia compared to other Asia. [30] Between 1980 and 2019, between 1980 and 2019, 67 research meta analysis [37]

As mentioned above, there is a genetic predisposition to RA, which a large study from Sweden in 2013 found was around 40%. This study also showed that seropositive RA and early RA are highly heritable. They reported that the risk of RA in RA positive first-degree relatives is three times higher than in RA in second-degree relatives with RA, resulting in a doubling of the risk [39]. Several different genetic predispositions have now been identified to explain this finding. The strongest genetic predisposition for Rheumatoid arthritis is from HLA-DRB1 region (shared epitope).

Among modifiable risk factors, smoking is most strongly associated with RA. Diet and nutrition have been shown to play an important role as environmental triggers for rheumatoid arthritis. A typical "Western" diet, high in calories and low in fiber, increases the risk of rheumatoid arthritis. Intake of long-chain omega-3 polyunsaturated fatty acids is associated with a lower risk of rheumatoid arthritis. [40]

Obesity is also recognized as a risk factor for rheumatoid arthritis. The risk of PR of 30 kg / m ^ 2 and 15 % or more body mass index (BMI) has increased the risk of 25-29.9 kg / m ^ 2 BMI patients by 30 %. [36]

There are important literature related to PR in patients with chronic mucous membranes or periodontal disease. However, established research does not reveal a clear and consistent connection. There is evidence that mucosal damage from occupational and environmental exposures may increase the risk of rheumatoid arthritis.[40]

PATHOPHYSIOLOGY OF RA

The pathophysiological mechanisms of RA are not fully understood, but several hypotheses have been proposed: It has been reported that immunological processes may occur several years before symptoms of joint inflammation appear, in the so-called pre-RA stage [42]. Interactions between epigenetic modifications in genome structure and environmental factors can result in modified autoantigens, as in the case of immunoglobulin G (IgG), type 2 collagen, and vimentin. These proteins, which contain arginine residues, are converted to citrulline by peptidylarginine deiminase in a post-translational modification called citrullination [42,43]. In addition, joint diseases such as synovial hyperplasia and synovial infection can lead to cytokine release that can cause joint inflammation and alterations of autoantigens [44]..

The HLA-DR1 and HLA-DR4 susceptibility genes prevent the immune system from recognizing citrullinated proteins (vimentin, type II collagen, histones, fibrin, fibronectin, Epstein-Barr nuclear antigen 1, α-enolase) with their unique structure.[45] The Anti Due genes are taken up by antigen-presenting cells (APCs), which are dendritic cells that are activated to trigger an immune response. The entire complex migrates to the lymph node, where activation of CD4+ helper T cells occurs. In addition, the germinal center of the lymph node contains B cells that are activated by reciprocal and sequential signals with T cells, an immunological process called costimulation.

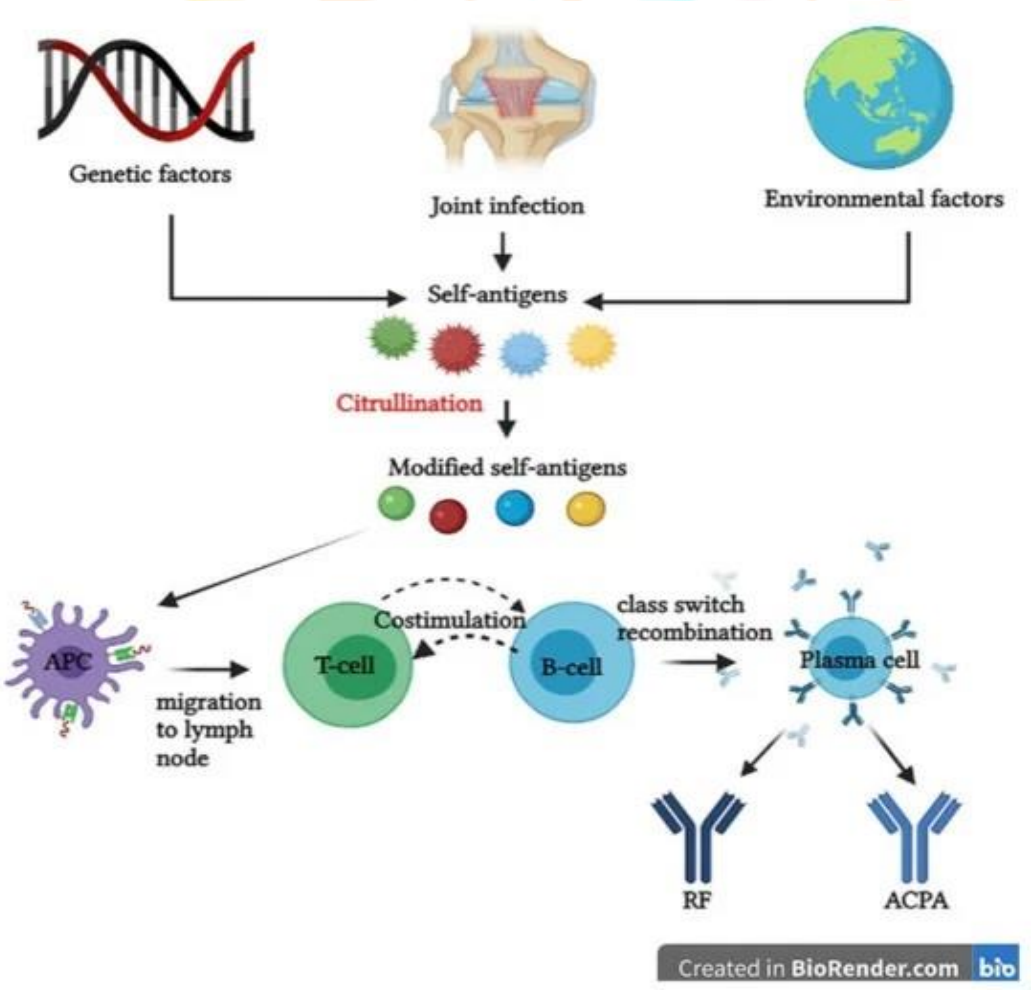


Figure 2 . Immunological process in the Do-RA phase. ACPA, anticularized protein antibody; APC, antigen presentation cells. RF, rheumatism factor.

In the RA field, the air pollution, which consists of various sizes and gas (nitrate, ozone, sulfur dioxide, coche, pm), has not recently attracted attention. Pollutants are released into the air by various natural and man-made sources including agriculture, fossil fuel combustion, chemical industries, solvent use, volcanic eruptions, wind-blown dust, plant emissions, etc. The clinical impact of air pollution is mainly considered in relation to respiratory diseases. The alveoli, a vital part of the respiratory system that filters oxygen and carbon dioxide, can be damaged by ozone. The pollutant can react with various enzymes to cause secondary damage to lung tissue and can also lead to lung inflammation and infection. Three large epidemiological studies

conducted in the United States, Canada, and Sweden demonstrated that air pollutants may be associated with the development of rheumatoid arthritis [46].

Alsaber et al. (2020), we conducted research to study the correlation between air pollutants and PR activities using a regression model. Nitrates and sulfur dioxide have been discovered as significant risk factors for the development of PR [47].

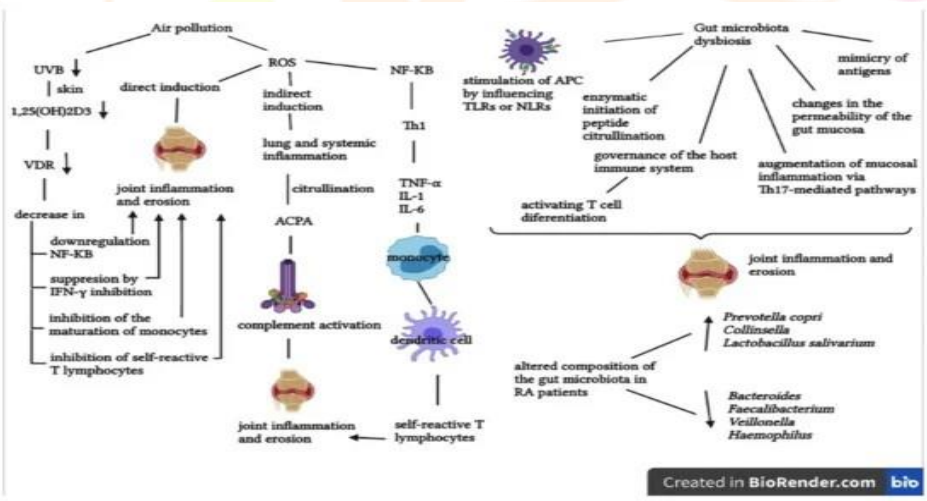
One of the latest research studies that has been published is a crossing study (which assessed a potential association between air pollutants in the Verona region and the evolution of PR) in 888 PR patients, showed that air pollution is linked to high proteins in C reactive C Levels (CRP), the severity of PR disease and its reactivations due to poor response to biological therapies [48].

The involvement of air pollutants in RA's pathology may be based on several mechanical processes. A free-reaction oxygen (AFC) obtained during the inhalation of PM can activate kappa B (NF-KB) nuclear factors. This activates the T-shelper cell type 1 (Th1) to obtain the alpha factor of the tumor necrosis (TNF-α). Inter Lykin -1 (IL -1) and Interroikin -6 (IL -6). These cytokines promote the maturation of resting monocytes into mature dendritic cells, which then deliver self-antigens to autoreactive T cells, leading to their migration to target tissues and promoting joint inflammation and erosion. Additionally, ROS also induce citrullination of arginine amino acid residues into citrullinated peptides, contributing to chronic lung disease and systemic inflammation. ACPAs, generated by biochemical reactions, trigger an immunological response by binding to cellular Fc receptors and activating complement, leading to joint inflammation and bone erosion [49].

Decreased ultraviolet B (UVB) radiation reduces the production of 1,25-dihydroxyvitamin D3 in the skin, which acts as an immunomodulator by activating the vitamin D receptor (VDR), resulting in suboptimal immune regulation and potentially contributing to rheumatoid arthritis.[50]

Another important element with major implications in the pathogenesis of RA is the gut microbiota, the most densely colonized bacterial population within the human body [51].

Immunological, metabolic, and neurobehavioral properties have been shown to be influenced by the gut microbiome: compared to healthy controls, patients with rheumatoid arthritis had significant differences in the composition of their gut microbiota, associated with an increase or decrease in specific bacterial populations (52). The gastrointestinal microbiota can affect the development of PR by proximal intestinal immunomodulation cells found in specific places inside the intestine. Several studies on the case-testimous witness have shown quantitative changes in specific bacteria in patients with RRNC 16S of PR sequencing and sequencing a metagenomic hunting rifle. According to the results of the studies, Prevotella copri, Collinsella and Lactobacillus salivarius were found in higher amounts in patients with RA, while Bacteroides, Faecalibacterium, Veillonella and Haemophilus were found in lower amounts [53].



The mechanisms underlying the involvement of air pollutants and gut microbiota in the pathogenesis of RA are shown in Figure3. [54].

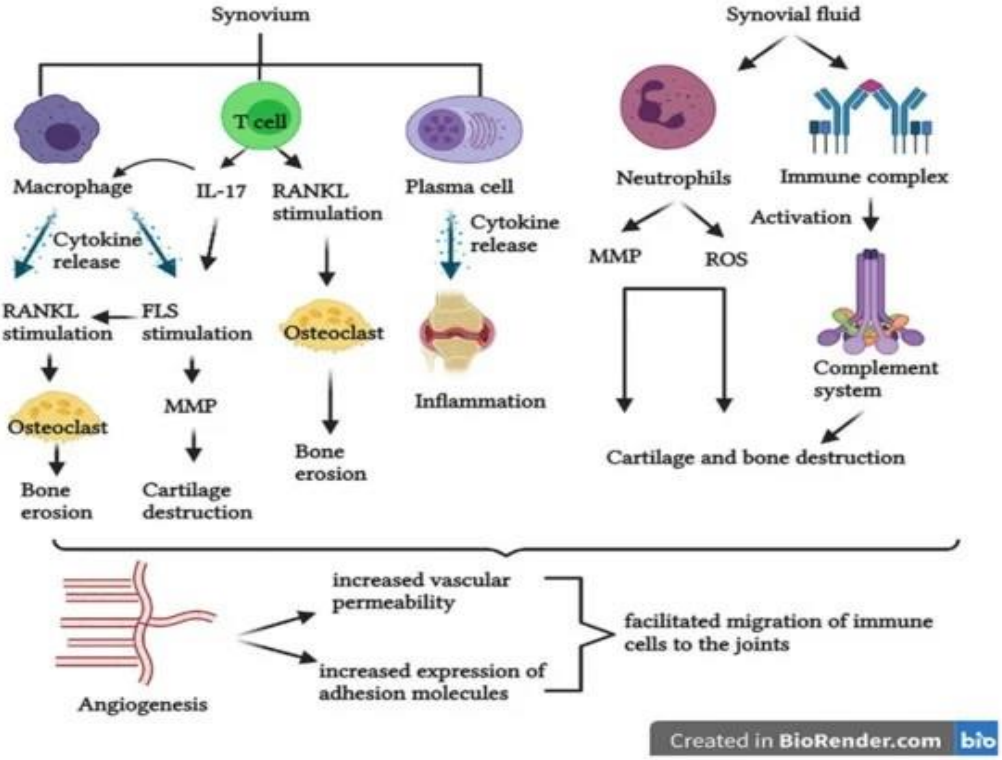
The involvement of air pollution &microbiota inpathogenesis of RA.anti-citrullinated protein antibody; antigen-presenting cell; interferon gamma; IL, interleukin; NF-KB, nuclear factor kappa light chain enhancer of activated B cells; NLR, nod-like receptor; RA, rheumatoid arthritis; ROS, reactive oxygen species; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; UVB, ultraviolet B radiation; VDR, vitamin D receptor.

Rheumatoid arthritis is usually characterized by a silent onset of symptoms, but over time the disease gradually progresses and worsens. The trigger for the onset of RA symptoms is unknown, although immunological processes occurring in the synovial membrane and synovial fluid have been described [55]. Synovial macrophages release cytokines such as tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are associated with the inflammatory process, stimulation of fibroblast-like synoviocytes (FLS) and stimulation of osteoclast activity [56]. MMPs can lead to cartilage degradation and cartilage also secretes proteases in a feedback mechanism [57,58]. FLS migrate from joint to joint, forming a symmetrical picture of rheumatoid arthritis. Additionally, FLS stimulates the expression of receptor activator of nuclear factor kappa B ligand (RANKL), allowing T cells to bind to the protein.CD4+ T cells bind to osteoclast proteins, which also enhance osteoclast activity, leading to bone erosion [59].

CD4+ T cells

Promote inflammation, bone erosion, and cartilage degradation by stimulating RANKL expression and producing interleukin-17 (IL-17), which plays an important role in stimulating synovial macrophages and FLS [60, 61]. Plasma cells also promote inflammation through cytokines and autoantibodies [62].

In the synovial fluid the presence of neutrophils has been reported, which produce proteases and reactive oxygen species (ROS) that may cause bone erosion and cartilage degradation [63,64]. Immune complexes, including antibodies, have also been found in synovial fluid and can bind to each other, promoting inflammation and overactivating the complement system (65).
Angiogenesis is the process of formation of new blood vessels from existing vessels, which also occurs in RA. In contrast to its beneficial role in many physiological processes, in RA it plays a critical role as immune cells can migrate into joints due to



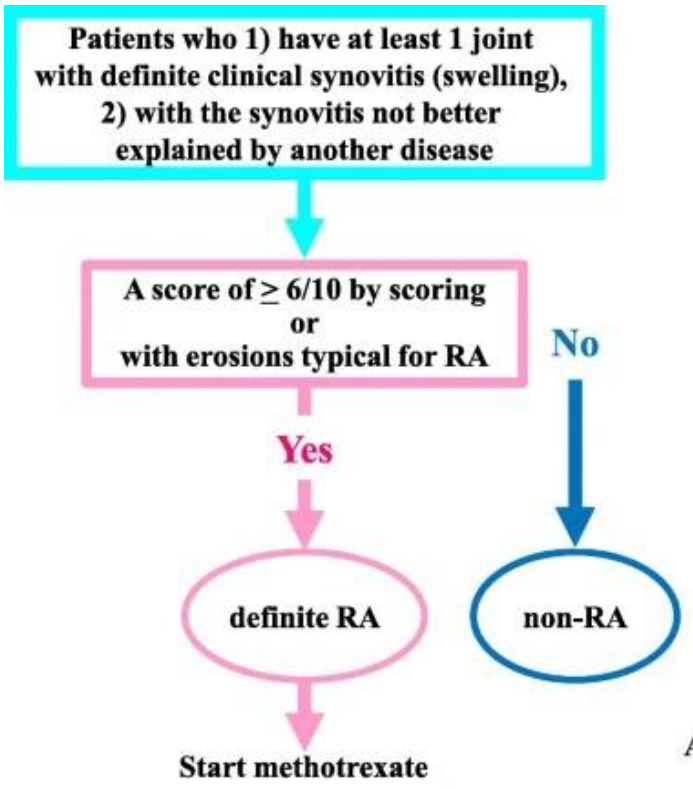
increased vascular permeability and expression of adhesion molecules (vascular adhesion molecule 1) [66,67] Furthermore, vascular endothelial growth factor (VEGF) is a proangiogenic factor present in the synovium of RA patients, which plays an important role in bone destruction as a stimulator of osteoclast genesis [68].

The pathophysiological processes that lead to RA symptoms are summarized in Figure 4.

Pathological mechanisms of rheumatoid arthritis. IL, Interloykin; FLS, fibrous and positive cells; MMP, matrix metalo protein; Rankl, nuclear KB factor ligand receptor activation factor. Ros, oxygen reaction species.
The complexity of this pathology is also based on many signal transmission molecules that play a specific role in the inflammatory process. Janus kinases (JAKs) are small signaling proteins with pathophysiological significance as they may represent molecular targets for many therapeutic agents [69]. Thus, further studies are needed to elucidate all pathological mechanisms and optimize future treatments with high safety and efficacy profiles.

Diagnosis

The classification criteria for rheumatoid arthritis published by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR) in 2010 are widely used for diagnosis (Fig. 1) [70]. These criteria, which define RA as a persistent and potentially destructive arthritis, were developed with the aim of distinguishing RA from other forms of arthritis soon after onset and allowing rapid initiation of DMARD treatment. Initially, various diseases such as connective tissue diseases with arthritis of one or more joints, osteoarthritis, spondyloarthritis, and microcrystalline arthritis are excluded. Then, the score ratios of four elements are weighted and added: arthritis (swelling of small or medium-large joints), serological test results (rheumatoid factor and anti-CCP antibodies), duration of disease (≥6 weeks), and acute phase reaction (erythrocyte sedimentation rate and CRP). Conditions with a score of 6 or more out of 10 are classified as persistent rheumatoid arthritis. In addition, arthritis affecting one or more joints and typically accompanied by bone erosions is also classified as rheumatoid arthritis, regardless of its grade. With a complete diagnosis of rheumatoid arthritis based on classification criteria, DMARD treatment begins. This diagnostic process potentially allows therapeutic intervention before joint destruction. Classification criteria for rheumatoid arthritis published by ACR/EULAR in 2010. Modified from link [70]



	score
Joint involvement	
=1 large joint	0
>1 large joint	1
1-3 small joints	2
4-10 small joints	3
>10 joints (small joint≧1)	5
Serology	
Negative RF and ACPA	0
Low positive RF or ACPA	2
High-positive RF or ACPA	3
Duration of symptoms	
<6 weeks	0
≧6 weeks	1
acute-phase reactants	
Normal CRP and ESR	0
Abnormal CRP or ESR	1

A score of ≥ 6/10 is needed for classification of a patient as having definite RA

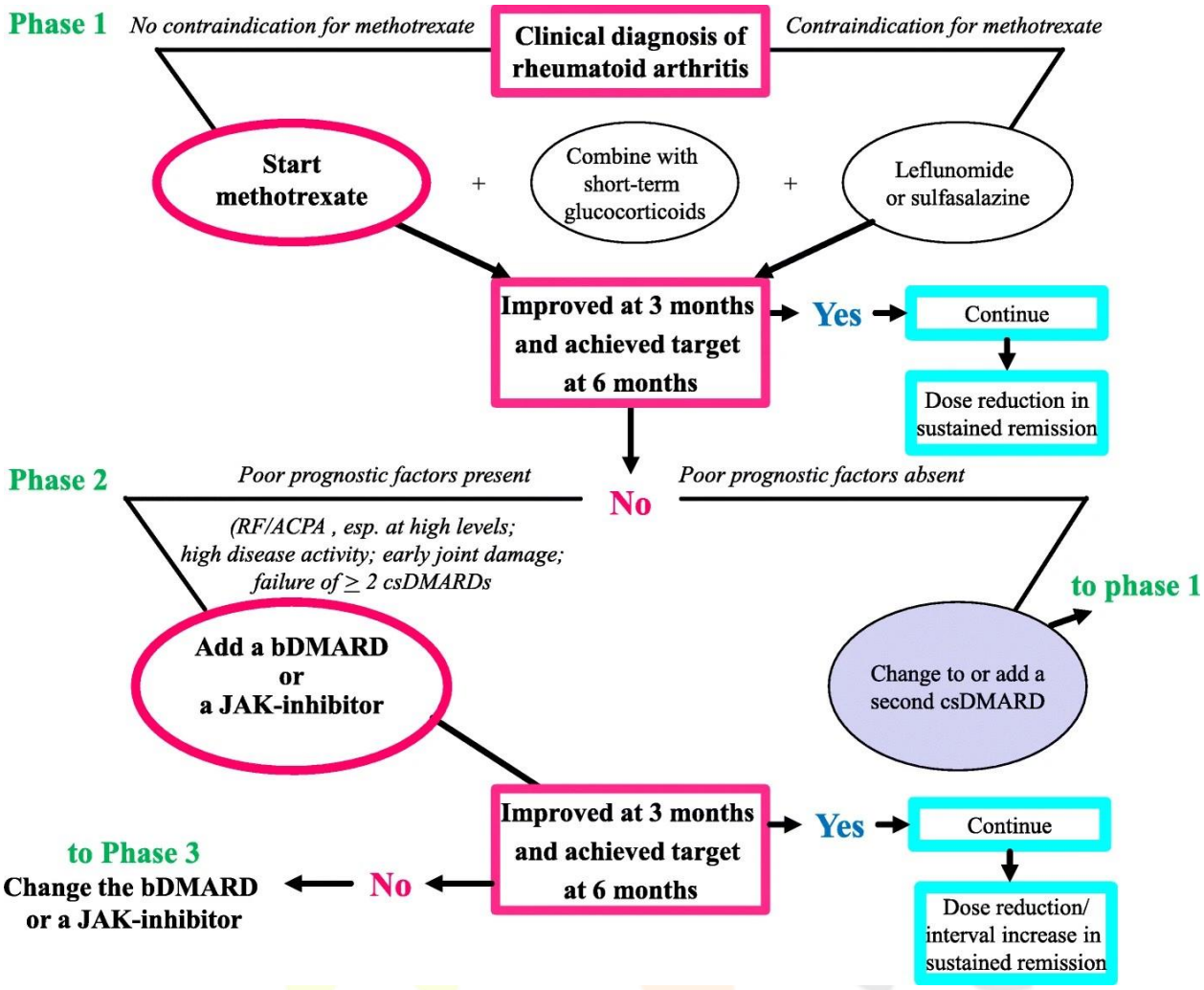
Assessment of disease activity is important for planning therapeutic strategies. The activity score of 28 seals (DAS28) is calculated based on the number of soft or swollen joints between 28 specified joints, and the overall evaluation of patients, and patients This disease is widely used in the objective evaluation of disease activity, accompanied by dedicated prescriptions. The DAS28 score is interpreted as follows. > 5.1, high disease activity. 3.2 –5.1, medium -sized disease activities;

As mentioned above, rheumatoid arthritis is often complicated by extra-articular involvement of the eyes, mouth, blood, lungs, heart, skin, nerves, kidneys, lymph nodes, etc. Pulmonary disease is a significant organ disorder that affects prognosis. Computed tomography (CT) of the chest is used to detect lung disease in about 70% of patients. Of these patients, about 50% have nonspecific changes, about 30% have interstitial pneumonia, and about 20% have chronic infection or chronic obstructive pulmonary disease. Other pathological conditions that may occur include pleuritis, alveolar hemorrhage, and bronchiectasis [63,64,65]. In rheumatic vasculitis, progressive arthritis occurs with systemic vasculitis of the skin, gastrointestinal tract, heart, lungs, spleen, and pleura, in addition to interstitial pneumonia. In addition, as the activity of the disease of rheumatoid arthritis increases, lymphopoliferative diseases can occur. Patients can also simultaneously develop various autoimmune diseases, including Hashimoto disease, other thyroid diseases and the secondary Schegren syndrome. In all cases, it is necessary to distinguish between conditions such as organ dysfunction associated with the rheumatoid arthritis pathology, other concomitant diseases, concomitant bacterial or viral infections, and adverse events caused by drugs.

Treatment

The basic policy of treatment of rheumatoid arthritis involves immediate intervention after diagnosis, before the onset of joint destruction, to suppress arthritis and induce remission. Therapeutic strategies should be determined based on the comprehensive assessment of disease activity, imaging findings , complications, and comorbidities. Objective composite indices such as the SDAI, CDAI, and DAS28 are widely used to assess disease activity. The treatment goal is remission, defined as a clinical state in which no future progression of joint destruction or functional disability is predicted. Boolean remission and numerical targets such as SDAI score 3.3 and CDAI score ≤2.8 have been statistically established as remission criteria [7 1].

Standard initial treatment after diagnosis of rheumatoid arthritis should use methotrexate, a common synthetic DMARD, unless contraindicated [72,73]. However, if there is no improvement within 3 months or if remission cannot be obtained within six months, despite the increase in the dose of the methotrexate We recommend that you add. If the treatment has not been achieved yet, DMARD or JAK biological inhibitors must be changed in about 3-6 months. On the other hand EULAR recommendations for the treatment of rheumatoid arthritis with synthetic and biologic DMARDs: 2019 update Adapted from ref [74]



Glucocorticoids are recommended for temporary use for up to 3 months as adjunctive treatment to reduce pain and swelling during initial onset or relapse of arthritis (Figure 5)

Although more than 10 conventional synthetic DMARDs are approved, methotrexate is recommended as the first-line standard drug therapy given after the diagnosis of rheumatoid arthritis, unless its use is contraindicated. Methotrexat is mainly effective by controlling the growth of lymphocytes and slap cells during the split phase of folic acid. It is more effective than any other conventional synthetic DMARD. Side effects of methotrexate include liver dysfunction and gastrointestinal dysfunction. Elderly patients should be aware of bone marrow suppression, interstitial pneumonia, opportunistic infections, and lymphoproliferative disorders. Taking folic acid along with it helps reduce side effects. Sulfasalazine and leflunomide are recommended when methotrexate is contraindicated.

Biologic DMARDs are chosen when response to synthetic DMARDs is inadequate. In Japan, TNF-targeting agents (i.e., infliximab, etanercept, adalimumab, golimumab, and certolizumab), IL-6-targeting agents (i.e., tocilizumab and sarilumab), and abatacept, a selective T-cell costimulatory regulator, can be administered by injection or infusion. All of these drugs have quick and powerful clinical effects. By using it in combination with a metotole xyt, remission can be guided in about half of the case. Biological DMARDs can also prevent progression of joint destruction &dysfunction for long periods of time [76].

In the Contrast, inhibitors against JAKs, which are intracellular signaling molecules such as cytokines, classified as targeted synthetic DMARDs. Tofacitinib, baricitinib, peficitinib, upadacitinib, & filgotinib all are used for treatment of rheumatoid arthritis and differ in their selectivity for different JAK isoforms [77,78,79,80,81]. Everything is verbally injected, but it has a high versatility effect and has a clinical effect as it is as an organic DMARD. JAK it after necessary to confirm the safety of the market [82]. In a 6-month all- inhibitors can be used individually or combined with the metotrexate.

In Japan, when the organic DMARD was used to treat rheumatoid arthritis, it was necessary to observe case surveillance study of infliximab administered to 5,000 patients, 1,401 patients experienced adverse events, with 108 patients developing bacterial pneumonia, 25 developing interstitial pneumonia, and Risk factors for pneumonia with biologic DMARD use include older age, a history of respiratory disease, and concomitant use of glucocorticoids. From these factors, the use of biological DMARD requires medical treatment and treatment of serious side effects, such as pneumonia, tuberculosis, and other date -see -infectious diseases, and has established a guideline for preventing and treating side effects. I did it.

effects such as pneumonia, tuberculosis, and other divergent infectious diseases, and instructions for preventing and treating unwanted effects. For example, isoniazid vaccination is recommended for patients with risk factors for tuberculosis, and pneumococcal vaccination is recommended for patients with risk factors for pneumonia.

Furthermore, because JAK inhibitors are oral drugs with multitarget effects based on the inhibition of intracellular signaling, they should not be used without special caution and require rigorous screening before use and monitoring during treatment. It must be

controlled by a doctor who can perform the system check when a side effect occurs. JAK inhibitors should not be used for severe infections, liver disorders, kidney disorders, or hematopathic disorders, but need to establish long -term safety evidence of infections such as herpesozosts and malignant tumors. There is. Lymphoma tumor, etc. In our department, approximately 4000 patients have been treated with biological DMARDs that were included in the FIRST registry or replaced by other drugs since 2003. According to the clinical pathway, these patients were admitted to hospital to be evaluated for contraindications and precautions and then carefully screened for indications for the use of these drugs. In addition, the safety and efficacy of the drug in these patients was closely monitored through outpatient visits over a period of more than a year.Specifically, CT scans from the head to the abdomen detected early-stage lung cancer in 11 of the approximately 2,500 patients, and nontuberculous mycobacterial disease before symptoms appeared in 13 patients. This shows importance

Developments

New therapeutic systems and the strategies for the rheumatoid arthritis are being applied to other connective tissue and rheumatic diseases. While the indications are expanding, these systems and strategies have also led to therapeutic advances in all fields. The infliximab, a drug targeting TNF, was initially indicated for rheumatoid arthritis, but this indication was extended to the treatment of more than 10 immunas, HCET disease, Kawasaki disease, psoriasis, 'PSORIASIC arthritis, ankyland spondylist, Crohn's disease, and ulcerian psorias colitis. Similar trends have been observed for other drugs for TNF, such as Adalimumab. Treatment with drugs that target TNF has prevented vision loss due to uveitis in most patients with Behçet's disease and significantly reduced the incidence of fistulas in patients with Crohn's disease and inflammatory bowel disease. Additionally, tocilizumab, a drug that targets IL-6, has been shown to have significant benefits in juvenile idiopathic arthritis. Its indication has been expanded to include Castleman's disease and cytokine-release syndrome associated with chimeric antigen receptor T cell therapy, in addition to adult-onset Still's disease, Takayasu's arteritis, and giant cell arteritis.

Since various molecular drugs are used for many autoimmune diseases, it is necessary to develop new therapeutic strategies, including the differential use of drugs. This is particularly important for very diverse autoimmune diseases. Biologics targeting TNF, IL-17,[83] and IL-12/IL-23 are approved for the treatment of psoriatic arthritis with destructive spondyloarthritis, but there is no way to differentiate between the use of these agents.In our department, we use eight-color flow cytometry to analyze lymphocyte phenotypes in peripheral blood from patients with psoriatic arthritis enrolled in the FLOW registry . Patients were classified into four groups according to the expression of chemokine receptors: auxiliary T lymphocytes (TH) 17 dominance, TH1 tumor, hybrid and normal. TH17 home-type patients are treated with IL-17 antibodies, Type to Dominant Th1 patients were treated with P40 antibodies, and hybrids or normal patients were treated with TNF targeted drugs. The percentage of patients who did not improve was reduced to less than 10% in these patients compared to those traditionally treated with biological agents. Thus, the differentiated use of organic products has proven to be highly effective. This result suggested that for diseases in which characteristic cytokines are involved in the pathology, the use of molecular-targeted drugs can be optimized according to the pathology by stratification based on lymphocyte analysis. It is expected that these findings will contribute to the development of new treatment systems and strategies.

Treatment of rheumatoid arthritis requires long-term safe and supportive care after induction of remission with methotrexate and biological DMARDs. However, the burden of medical expenses and medical economic issues due to long-term continued use are urgent issues both in Japan and overseas, and the safety of long-term target inhibitors such as TNF is currently unknown. Although reduction in the dose and extension of the administration interval of biological DMARDs are associated with a lower relapse rate than discontinuation of the drug, there is concern that drug antibodies are more likely to develop in these situations. If biologic disease-modifying therapies can be withdrawn, adverse effects should be avoided. The RRR study and the HONOR study reported the possibility of withdrawal of biologic disease-modifying therapies after induction of remission in patients with rheumatoid arthritis [84].

In 2016, an international roundtable conference reviewed studies from Japan and other countries and reached a consensus on drug withdrawal procedures. Drug therapy should be discontinued in the following order: glucocorticoids, anti-inflammatory drugs, biological DMARDs, and finally synthetic DMARDs. In addition, four requirements for DMARD discontinuation were identified: meeting standard criteria for remission, maintaining remission for at least 6 months, continuing treatment with the same drug and dose for at least 6 months, and not using glucocorticoids. Furthermore, it has been stated that negative anti-CCP antibody results, deep remission, and the absence of ultrasound signs of synovitis are associated with the likelihood of remission after DMARD cessation, suggesting that if remission can be maintained after cessation of biologic DMARDs, drug-free remission can be achieved thereafter (Figure 2). Also, if the pathological process is controlled, it is assumed that the drug can be obtained by pouring immune disorders, but the cause will continue. The establishment of a new treatment system that involves recuperation is expected to contribute to reducing medical costs and resolving medical economic issues.

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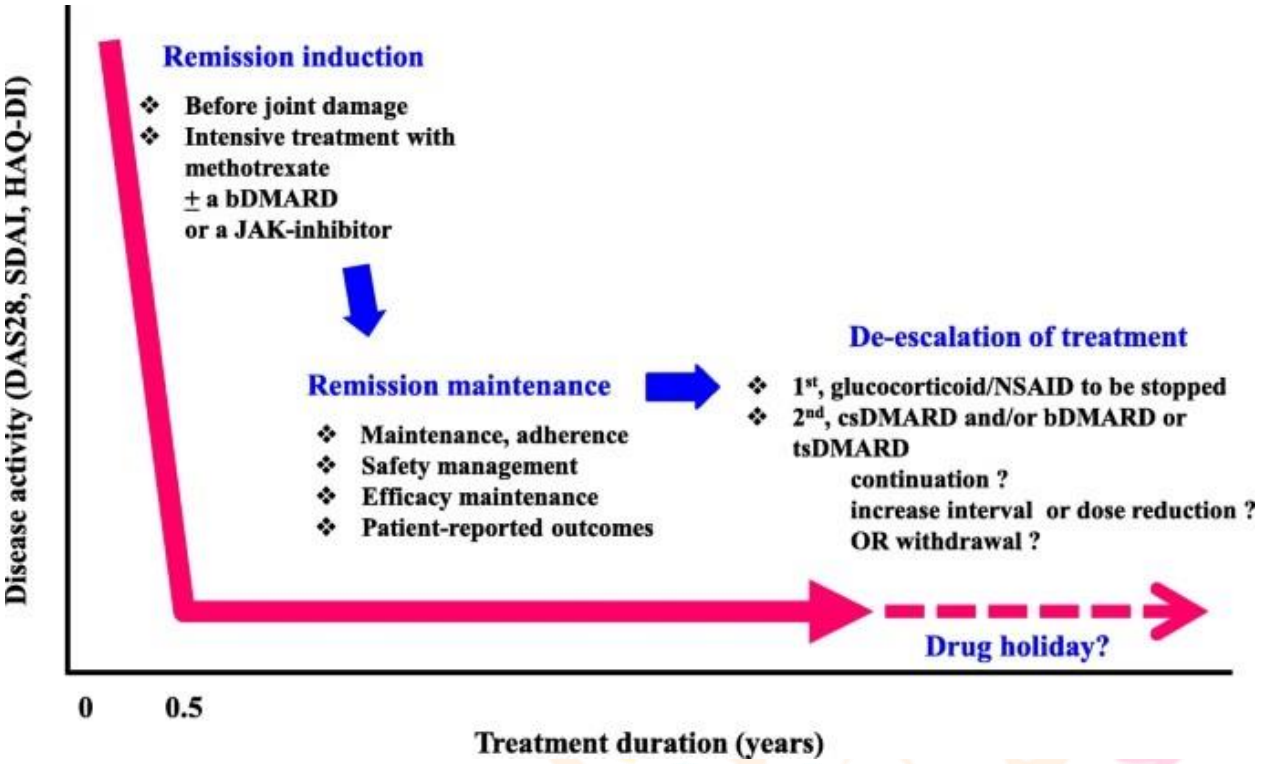

Treatment strategies for rheumatoid arthritis. Inducing remission in rheumatoid arthritis requires intensive treatment, but maintaining remission thereafter with high compliance and safety are prerequisites for a good long-term outcome. De-escalation and discontinuation of DMARDs is continued maintenance of remission

CONCLUSIONS

Rheumatoid arthritis is the autoimmune inflammatory disease pathologically characterized by primarily by synovitis. Joint destruction, which is associated with the prolonged arthritis, progresses soon after the onset of disease. The deformation of the affected joints is irreversible and leads to physical disability, therefore proper diagnosis and treatment at an early stage are necessary. The classified criteria published by the ACR and EULAR in 2010, which define rheumatoid arthritis as arthritis that is persistent and can be destructive in the future, were formulated with the aim of differentiating it from other types of arthritis soon after onset and to allow for therapeutic interventions prior to joint destruction.

For the treatment, DMARDs are used to suppress immune abnormalities &control disease activity. DMARDs are classified into the conventional synthetic DMARDs (e.g., methotrexate), targeted synthetic DMARDs (e.g., JAK inhibitors), and biologic DMARDs. Appropriate treatment with these drugs has allowed physicians to achieve remission in patients with rheumatoid arthritis. These classes of drugs have been shown to prevent structural damage to joints and prevent progression of physical dysfunction. The advent of biologics and targeted drugs such as JAK inhibitors represents a revolutionary advancement, enabling the use of disease mechanism-based targeted therapies and management of autoimmune inflammatory diseases that were previously considered incurable. In the future, safer and more effective treatments, therapeutic strategies aiming at a cure, and the introduction of precision medicine are expected. Translational research aimed at developing new treatments and preventive measures can motivate young clinicians and researchers.

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