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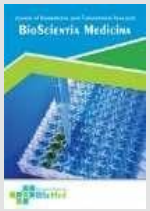

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Pathophysiology and Management of Refractory Rheumatoid Arthritis: A Narrative Literature Review

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A B S T R A C T

Refractory rheumatoid arthritis is rheumatoid arthritis that fails to achieve low levels of disease activity using 2-3 DMARDS treatment and at least one other first-line bDMARD. The definition of refractory action is based on the number of failed DMARDs, the scale of the problem, and risk factors for a refractory disease course. Until now, there has been no further research discussing the pathophysiology of refractory RA, but it is known that TNF-α, IL-6, and IL-1 are the most important mediators that enable cell migration and inflammation in RA. IL-6 in particular, acts directly on neutrophils, which then contribute to inflammation and joint destruction by secreting proteolytic enzymes. The main goal to be achieved in RA is remission, low disease activity and an alternative goal for those who fail to achieve therapy targets. Currently, there are several bDMARD agents that can be used as therapy for refractory RA, namely TNF alfa inhibitors, B cell depletion agents, T cell activity inhibitors, and cytokine inhibitors.

1. Introduction

Rheumatoid arthritis (RA) is a systemic chronic inflammatory autoimmune disease that attacks various tissues, especially the joints. This is caused by the proliferation of nonsuppurative synovitis, which develops and can destroy the articular cartilage and other underlying bones, resulting in inflammation of the joint. Apart from causing inflammation of the joints, RA can also attack other body organs, such as blood vessels, skin, eyes, and lungs. Based on data from the 2013 Basic Health Research (Riskesdas), the prevalence of RA increases with age and attacks more women, especially those over 40 years. More women (24.7%) suffer from RA than men (11.9%). Almost 75% of RA sufferers are women aged 40-60 years, and this is because the prevalence of RA is related to a decrease in the amount of estrogen, especially after menopause. RA is related to the amount of estrogen because apart from working as a hormone, estrogen also has immunomodulatory properties by influencing interleukin-17 from Th cells and the sialylation process of G antibodies (IgG). Refractory rheumatoid arthritis is rheumatoid arthritis that fails to achieve a low level of disease activity using 2-3 DMARDS treatment and/or at least one other first-line bDMARD. This disease often causes joint damage and disability and affects many people of productive age, thus having a large social and economic impact. RA

disease activity assessment is carried out based on the disease activity score 28 (DAS28) value by calculating painful joints, swollen joints, erythrocyte sedimentation rate (ESR), and global health score measured on the visual analog scale (VAS).[1,2]

The typical clinical manifestation of AR is symmetrical polyarthritis with the distribution of the joints involved based on frequency, namely the wrist and finger joints (75-95%), sternoclavicular, and manubriosternal (70%). Early diagnosis and therapy are the most important steps to optimally control disease progression and influence the prognosis of RA. Good therapeutic results in the first 6 months from disease onset can be predictive of therapeutic response over the next 5 years. Administration of RA therapy drugs can be done by administering a single drug or a combination of two to three drugs. The combination of methotrexate and hydroxychloroquine is equivalent in effectiveness to leflunomide in reducing disease activity during the initial treatment of severe RA. Choosing the type of RA drug requires various considerations in terms of quality, affordability, side effects, and the success of therapy.[3]

The csDMARD therapy recommended as the first choice is MTX as an anchor drug, which is used in RA both as monotherapy and combination therapy because of its good efficacy/toxicity ratio. If the target is not achieved within 3-6 months with the first csDMARD, then a second csDMARD can be added as combination therapy, or bDMARD can be started as a combination therapy or replacement for csDMARD, especially in patients with poor prognostic factors. Patients who fail with the first bDMARD can be given another bDMARD from a different anti-TNF- or anti-IL-6 group or can be given an alternative bDMARD from another group.

Rheumatoid arthritis

Rheumatoid arthritis is an autoimmune disease that involves multisystems and is chronic inflammatory. Although there are various systemic manifestations, the characteristic of RA is persistent inflammatory synovitis that causes destruction of cartilage and erosion of bone, as well as changes in joint integrity. The word arthritis comes from the Greek, "arthon" meaning joint, and "itis" meaning inflammation. Literally, arthritis means inflammation of the joints. Rheumatoid arthritis is an autoimmune disease in which the joints (usually hands and feet) experience inflammation, resulting in swelling and pain and often causing damage to the inside of the joint.

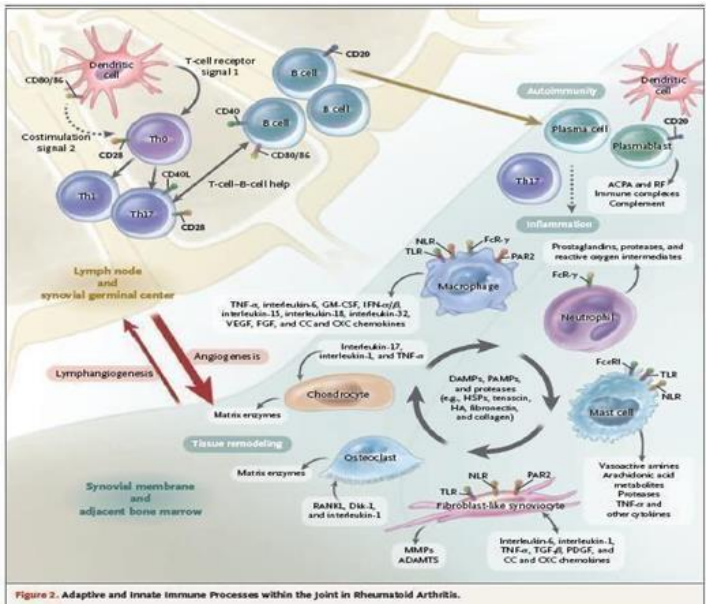

Figure 1. Pathophysiology of rheumatoid arthritis.

The prevalence and incidence of this disease vary from one population to another. In the United States and several regions in Europe, the prevalence of AR is around 1% in adult Caucasians, France is around 0.3%, The UK and Finland are around 0.8%, and the United States is 1.1 %. In Indonesia, from the results of an epidemiological survey in Bandungan, Central Java, the prevalence of RA was 0.3%, while in Malang, among residents aged over 40 years, the prevalence of AR was 0.5% in the Municipal area and 0.6% in the Regency area. At the rheumatology polyclinic, Cipto Mangunkusumo General Hospital Jakarta, in 2000, new RA cases constituted 4.1% of all new cases. In the rheumatology polyclinic at Dr. Hasan Sadikin General Hospital, 9% of all new rheumatism cases were found in 2000-2002. Rheumatoid arthritis is an autoimmune disease of unknown etiology and is characterized by symmetrical erosive synovitis and, in some cases, accompanied by extra-articular tissue involvement. Several factors are thought to cause RA, including genetic factors, inflammatory reactions in the joints and tendon sheaths, rheumatoid factors, chronic synovitis, and destruction. Joints, Gender and Infections. There is a hypothesis that RA is a manifestation that occurs due to a response to an infectious agent in a susceptible host. Several infectious agents that are suspected of causing RA include EBV, mycoplasma, CMV, parvovirus, and rubella. However, there is still no data that supports definitively that these agents are the cause of DA.[4,5]

The autoimmune process in the pathogenesis of RA is still incompletely understood, and the theory is still developing. It is said that there are various interrelated roles, including the role of genetics, infection, and autoantibodies, as well as the role of cellular and humoral immunity, the role of cytokines, and various inflammatory mediators. All of these roles are interrelated and ultimately cause inflammation of the synovium and damage to surrounding joints or possibly other organs. Cytokines are local protein mediators that can cause growth, differentiation, and cell activity in the inflammatory process. Various cytokines play a role in the inflammatory process, namely TNF α and IL-1, which are mainly produced by monocytes or macrophages that cause stimulation of mesenchymal cells such as synovium fibroblast cells, osteoclasts, chondrocytes and stimulate the release of tissue destroying enzymes, namely matrix metalloproteases enzymes. The inflammatory process due to the autoimmune process in RA is indicated by laboratory examination by the presence of RF (rheumatoid factor) and anti-CCP in the blood. RF is an antibody against the Fc component of IgG. So, there is the formation of antibodies against one's own antibodies due to exposure to external antigens, possibly viruses or bacteria. RF is found in 75 to 80% of RA sufferers who are said to be seropositive. Anti-CCP is found in almost 2/3 of cases with high specificity (95%) and is mainly present in the early stages of the disease. At present, RF and anti-CCP are important diagnostic tools for RA and reflect disease progression.[6,7]

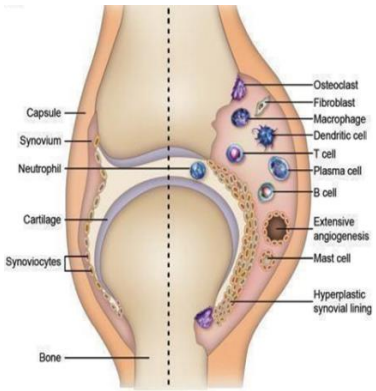

Figure 2. Comparison of healthy joints with AR patient joints.

B cells, T cells, and proinflammatory cytokines play an important role in the pathophysiology of RA. This occurs because the results of differentiation of T cells stimulate the formation of IL-17, a cytokine that stimulates synovitis. Synovitis is inflammation of the synovial membrane, the tissue that lines and protects joints, while B cells play a role by forming antibodies, binding to pathogens, and then destroying them. Joint damage begins with an inflammatory reaction and the formation of new blood vessels in the synovial membrane. This event causes the formation of pannus, namely granulation tissue consisting of proliferating fibroblast cells, microvasculature, and various types of inflammatory cells. The pannus can destroy bone through enzymes formed by synoviocytes and chondrocytes that attack cartilage. Apart from these local processes, systemic processes can also occur. One of the systemic reactions that occurs is the formation of acute phase protein (CRP), anemia due to chronic disease, heart disease, and osteoporosis, and can affect the hypothalamic-pituitary-adrenal axis, thus causing fatigue and depression. In the initial state, there is microvascular damage, edema in the tissue under the synovium, mild synovial proliferation, PMN infiltration, and blockage of blood vessels by inflammatory cells and thrombus. In RA that is clinically clear, macroscopically, the synovium will be seen to be very edematous and protruding into the joint space with the formation of villi. Microscopically, hyperplasia and hypertrophy of synovial cells are visible, and a collection of residual bodies is visible. Focal or segmental blood vessel changes can be seen in the form of venous distension, capillary blockage, areas of thrombosis, and perivascular bleeding. In chronic RA, there is complete damage to the cartilage, ligaments, tendons, and bones. This damage is due to two effects, namely destruction by joint fluid, which contains destructive substances, and due to granulation tissue, which is accelerated due to the presence of pannus.[8]

The first thing that occurs in pathogenesis is the activation of the innate immune response, namely the activation of dendritic cells by exogenous materials or autologous antigens. Antigen-presenting cells (APC), namely activated dendritic cells, macrophages, and B cells, present antigens to T cells. Then, CD4+ T cells, which secrete IL-2 and IFN-γ, infiltrate the synovial membrane. B cells contribute to RA pathogenesis not only by presenting antigens but also through the production of antibodies, autoantibodies, and cytokines. RF and anti-CCP autoantibodies are common in patients with RA. Autoantibodies can form larger immune complexes, which can then stimulate pro-inflammatory cytokines such as TNF-α. Activation of T cells and B cells increases the production of cytokines and chemokines, which will then increase the number of T cells, macrophages, and B cells. In the synovial membrane itself, there is an increase in synovitis, such as activated fibroblasts, which also produce pro-inflammatory cytokines, PGs, and MMPs. Synovysite cells contribute to cartilage and bone damage by secreting MMPs into the SF and also by direct invasion of these tissues. It is well known that proinflammatory cytokines (IL-6 and TNF-α) are involved in the pathogenesis of RA. TNF-α and IL-6 have a dominant role in the pathogenesis of RA, but IL-1, VEGF, and IL-17 also have a significant role in the process of RA. Through a complex pathway of pathogenesis, these cytokines activate genes related to the inflammatory response, including the addition of cytokines and MMPs involved in tissue degradation. Apart from cardiovascular disease, a disease that is often encountered in AR patients is anemia. In RA patients, higher IL-6 levels were found, and IL-6 levels were inversely correlated with hemoglobin levels. High levels of IL-6 induce the formation of hepcidin. Hepcidin inhibits iron release from macrophages and also inhibits iron absorption in the duodenum. Iron is one of the main components in the formation of hemoglobin. Apart from cardiovascular disease and anemia, RA patients are also more susceptible to osteoporosis, fatigue, and depression. This occurs because pro-inflammatory cytokines are released systemically, causing disruption of osteoclast function and also disruption of the HPA axis.[9,10]

Refractory rheumatoid arthritis

Refractory rheumatoid arthritis is rheumatoid arthritis that fails to achieve low levels of disease activity using 2-3 DMARDS treatment and at least one other first-line bDMARD. However, to date, there is no universally accepted definition of refractory rheumatoid arthritis, but various working definitions are based on the number of failed DMARDs, the scale of the problem, and risk factors for a refractory disease course. Only a few studies have described the prevalence of refractory rheumatoid arthritis. Based on data from the British Society of Rheumatology, it was reported that around 17% of 412 patients experienced refractory RA. According to Andrew 2020, it is estimated that around 2 out of 5 patients experience therapy failure using first-line therapy and require biologic therapy or targeted therapy with synthetic DMARDs. There are several risk factors that influence a person to experience RA, such as gender, genetics, age, socio-economic status, education, stress factors, etc. Of the many factors that play a significant role are gender factors and also genetic factors. According to Sargeant et al., there are several factors that influence the lack of response to treatment, such as high BMI, smoking, alcohol consumption, old age, serious comorbid illnesses, psychosocial factors, and medication compliance. Treatment of RA patients requires good monitoring of disease activity through clinical and laboratory evaluation using scores such as DAS28 or the remission criteria from ACR 1987. LED or CRP measurements are key to disease monitoring. This monitoring is necessary to increase treatment so that the disease is better controlled or to carefully reduce the dose of medication if the patient is under control and then continuously. It is recommended that in newly treated patients, control be carried out every month until the disease is under control. The patient needs to be explained so that he can immediately obtain a consultation with a rheumatologist.[11]

Refractory rheumatoid arthritis therapy

After the concept of refractory is established, the therapeutic target must be prepared. More than 60 experts from various parts of the world developed recommendations to achieve optimal therapeutic results in the face of refractory RA. This recommendation assumes that the primary goal to be achieved in RA is remission and low disease activity and is an alternative goal for those who fail to achieve therapy targets. Regular follow-ups are carried out every 1-3 months in patients with disease activity above the target and 3-6 months in patients who reach the therapy target. Based on this initiation, refractory disease can be interpreted as a failure to achieve the expected targets. Until now, there has been no biological marker that can support the meaning of refractory AR because the concept itself has not been defined in a clinical sense. Nevertheless, recent EULAR recommendations on the management of RA state the importance of prognostic markers in their impact on treatment. Several factors appear to independently predict poor outcomes, such as high levels of rheumatoid factor (RF) and/or anti-citrullinated peptide antibodies (ACPA), high disease activity as measured by indices, and early appearance of erosions. Other factors may play a role in refractory AR in individual patients, such as genetic variability that influences the metabolism of DMARDs and the relevance of pathogenic pathways that are not targeted by available DMARDs.[12] To date, there are several biological agents used in the therapy of refractory RA and approved by the FDA and EMEA, namely:

TNF alfa inhibitor

TNF is a pro-inflammatory cytokine produced by activated monocytes that is upregulated in the synovium in active RA. Inhibition of TNF has been associated with improved clinical symptoms and also reduced radiological progression. To date, there are five biological agents whose action is to inhibit TNF that have been used in RA therapy, namely: Infliximab (INF), Etanercept (ETN), Adalimumab (ADA), Golimumab (GLM) and Certolizumab (CMZ). INF is a TNF inhibitor class of drugs that was first available.

INF is a chimeric monoclonal antibody against TNF and is given by intravenous infusion at a dose of 3-10 mg/KgBW, then in the sixth week after the first administration and continued in the eighth week. ETN, which is a soluble dimer of the p75 TNF receptor, binds to the Fc IgG1 component, whose function is to prevent TNF from binding to cells. ETN also has the ability to neutralize lymphotoxin (a pro-inflammatory cytokine that binds to the TNF receptors p55 and p75). This is what differentiates ETN from other TNF inhibitors. A clinical trial of etanercept 25 mg subcutaneously twice a week (dose 50 mg a week) for 52 weeks in active AR patients compared with the MTX alone group showed a significant reduction in disease activity (measured by the health assessment questionnaire (HAQ) disability index). ADA is a fully-humanized monoclonal antibody against TNF, which is given by subcutaneous injection at a dose of 40 mg every 2 weeks. GLM is also a fully-humanized monoclonal antibody against TNF, which is used in RA therapy and is given by subcutaneous injection at a dose of 100 mg every 4 weeks. CMZ is a fully humanized monoclonal antibody against TNF, which binds to 2 polyethylene glycol (PEG) molecules. This PEG molecule functions to increase the half-life of CMZ and increases the distribution of CMZ into inflammatory tissue. Although it is different from other TNF inhibitors because it does not have an Fc component, which results in the inability to form immune complexes with TNF, therefore CMZ does not activate the cell lysis process through complement-dependent cell processes or antibody-dependent toxicity. CMZ also cannot kill cells by binding to TNF. CMZ is given by subcutaneous injection at a maintenance dose of 200 mg every 2 weeks or 400 mg every 4 weeks after the loading dose.[13]

TNF inhibitors have been shown to be highly effective in the treatment of RA. Currently, there is no data to suggest that there is different efficacy between the TNF inhibitor class of drugs. However, one TNF inhibitor may be more beneficial than another TNF inhibitor in certain patients. For example, in patients at high risk of TB, ETN is more appropriate to administer due to the low reported incidence of TB. On the other hand, monoclonal antibodies may be an appropriate choice in patients suffering from scleritis. Apart from that, the patient's choice of how to administer drugs also plays an important role in the selection of the TNF inhibitor class of drugs. Drugs in the TNF inhibitor class have not shown teratogenic effects in animal studies and are category B for pregnancy. Contraindications for therapy with TNF inhibitor drugs are in patients with acute hepatitis B and NYHA class III and IV congestive heart failure.[14]

B cell depletion

The precise role of B cells in the pathogenesis of RA is still not clearly understood, although there is evidence that B cells play a role in the manifestation of RA symptoms. Both mature B cells and pre-B cells express surface antigens on CD-20 cells. Rituximab (RTX) has been used effectively in the treatment of non-Hodgkin's lymphoma since the late 1990s. The advantage of using RTX in RA therapy in 2006 is that RTX reduces clinical symptoms effectively. RTX is given as two separate infusions at a dose of 500-1000 mg every 2 weeks. Based on the consensus, when you want to re-treat a patient who previously did not attend a second treatment, RTX should be given less than 6 months after the first infusion. The appropriate approach to retreatment is still not clearly understood. Should RTX be given according to schedule (every 6-12 months) even if there are no symptoms, or should RTX be given again when disease activity becomes more severe? RTX has demonstrated good safety when used as a therapy for RA. Side effects usually occur during the first administration, and the risk of infection is almost the same in the placebo group and those receiving RTX therapy, namely at weeks 24 and 28. Another complication of RTX therapy is progressive multifocal leukoencephalopathy (PML). Although it is very rare, it can be a serious complication. fatal. Contraindications to RTX therapy are acute viral hepatitis, chronic hepatitis B or C (Child-Pugh B or C), or active infection.[15]

T-cell costimulatory blocking

Abatacept (ABT) is a new T cell activity inhibitor drug. Its function is through inhibition of the second signal needed for T cell activation. ABT is a fully humanized soluble fusion protein that works directly against cytotoxic T-lymphocyte-associated antigen-4 (CTLA4) cells. ABT has been approved for use as RA therapy and is administered intravenously at a dose of 100 mg (based on body weight) after a loading dose at weeks 0, 2, and 4. ABT has a good durability effect with efficacy that can be maintained for up to 5 years in open-label extension clinical trials. In RA patients who failed one of the TNF inhibitor therapies and then received ABT therapy, it turns out that ABT can improve the quality of life of these patients. Although there are no specific contraindications to the use of ABT, ABT must be used with caution in patients with chronic obstructive pulmonary disease because it can worsen the condition of COPD. Initial ABT therapy is not recommended in patients with acute hepatitis B or C, chronic hepatitis B or C (Child-Pugh B or C), or in patients with signs of active infection. Screening for latent TB is recommended before starting ABT therapy, although there have been no cases of hepatitis B reactivation in patients receiving ABT therapy.[16]

Cytokine inhibitors

Tocilizumab (TCZ) is a fully-humanized monoclonal antibody that works directly on the IL-6 receptor. IL-6 is a pleiotropic cytokine produced by several cells and has been shown to play a role in the inflammatory process that occurs in RA. IL-6 is involved in the process of differentiation of B cells into plasma cells and T cells into cytotoxic T cells, induction of osteoclast differentiation, osteoclast activation, and production of acute phase reactants, especially C-reactive protein (CRP). All of these processes play a role in the occurrence of synovitis and bone destruction in RA. The chronic inflammatory process in RA is associated with increased production of IL-6 and IL-6 receptors. TCZ provides a remission rate of 35.1% in RA therapy, with a continuation rate for 3 years of 68.2%. The recommended dose is 4 mg/kg body weight every 4 weeks by intravenous injection or 162 mg every 2 weeks by subcutaneous injection. TCZ is the only bDMARD that can be given as monotherapy based on the results of several studies. TCZ is especially effective in AR patients with high systemic inflammatory response, anemia, AA amyloidosis, and other IL-6-mediated diseases. TCZ has different side effects from other biological agents, namely neutropenia. Neutropenia occurs within days of TCZ therapy and is postulated to result from IL-6 inhibition of neutrophils. Data from a long-term study found that serious infections occurred in 17.5% of RA patients who received TCZ therapy, with an incidence rate of 5.7 per 100 patient-years. Pneumonia is the most common finding, followed by herpes zoster, bronchitis, and pyelonephritis. Other side effects are increased liver function tests (transaminase and bilirubin) and increased total cholesterol, triglycerides, and HDL.[17-19]

2. Conclusion

Refractory rheumatoid arthritis is rheumatoid arthritis that fails to achieve low levels of disease activity using 2-3 DMARDS treatment and at least one first-line bDMARD. The prognosis for RA will worsen if diagnosis and therapy are delayed. Giving DMARD therapy in the early phase of RA (less than 12 weeks from the appearance of symptoms) provides the best chance of achieving remission. RA patients who fail cDMARD therapy should be started immediately on bDMARD therapy. Currently, there are several bDMARD agents that can be used as therapy for refractory RA, namely TNF alfa inhibitors, B cell depletion agents, T cell activity inhibitors, and cytokine inhibitors.

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