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AN OVERVIEW ON TREATMENT OF *RHEUMATOID ARTHRITIS*

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ABSTRACT: *Rheumatoid arthritis* (RA) is an autoimmune disease associated with chronic inflammation of the joints. If it is untreated then it leads to destruction of joints, erosion of cartilage and bone and eventually leads to loss of physical function. Since, RA is not complete curable disease, the treatment goals are to reduce the pain and stop/slow further damage. With advancement in the field of molecular biology, a better understanding of disease mechanisms is available which can help in the designing of more effective treatments. Old treatment modes have been optimized and new ones have been produced. Nowadays, different classes of drugs with different mechanism of action are available to control the inflammation and to achieve remission. The aim of this review is to discuss previous and present treatment options for treating RA and its complications.

INTRODUCTION: *Rheumatoid arthritis* (RA) is a chronic inflammatory disorder of autoimmune origin that may affect many tissues and organs but principally attacks the joints, producing a nonsuppurative proliferative and inflammatory synovitis [1, 2]. RA has a worldwide distribution with an estimated prevalence of 1-2%. Prevalence increases with age, including 5% in women over age 55. The average annual incidence in the US is about 70 per 100,000 annually. Both incidence and prevalence of RA are two to three times greater in women than in men. Although *Rheumatoid arthritis* may present at any age, patients most commonly are first affected between the ages of 30 and 60 years.

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RA is among the oldest diseases. Arthritis and osteoarthritis are the most prevalent conditions. RA affects all races. Older age and overweight are risk factors for arthritis. Patients with RA have shortened life span. For women over 45 years, arthritis is the leading cause of activity limitation [3, 4].

(RA) symptoms are different for each person who has this long-term disease. Some people have long periods with few or no symptoms. Others feel it for months at a time in an uptick of disease activity called flare [7]. Most people have lasting problems with episodes of more severe disease.

New and earlier treatment is changing the overall picture, though. More people are having low disease activity or even remission. RA almost always affects your joints. It may take a few weeks or months for the first signs to show. The inflammation it causes often leads to these three hallmark symptoms [8, 11]:

1. **Pain:** Inflammation inside a joint makes it hurt whether you're moving it or not. Over time, it causes damage and pain.
2. **Swelling:** Fluid in the joint makes it puffy and tender.
3. **Tenderness:** It hurts when you move or push on a joint.

The pathogenesis of *Rheumatoid arthritis* is complex and multifactorial, involving genetic, epigenetic and environmental factors. Central aspect of the pathogenesis is the activation of macrophages by autoreactive T cells resulting in the production of proinflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and interleukins 1, 6 and 17 [5]. Despite the drugs available present positive effects in disease control for most of the population, diseases of autoimmune nature continue to be a vast field of research to the elucidation of pathophysiology and search for alternative therapies for better control of the disease [6, 10].

Treatment: The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight bearing exercise, educating patients about the disease, and rest. Treatments are generally customized to a pain [9].

According to, therapeutic strategies and research has addressed the immunotherapies that targets the inflammatory cytokines and/or their receptors, the events that trigger the generation and recruitment of autoreactive T cells, the role of antigenic variants of autoreactive T cells against citrullinated antigens and the presence of citrullinated antibodies, which has been linked to the development and progression of autoimmune diseases [12].

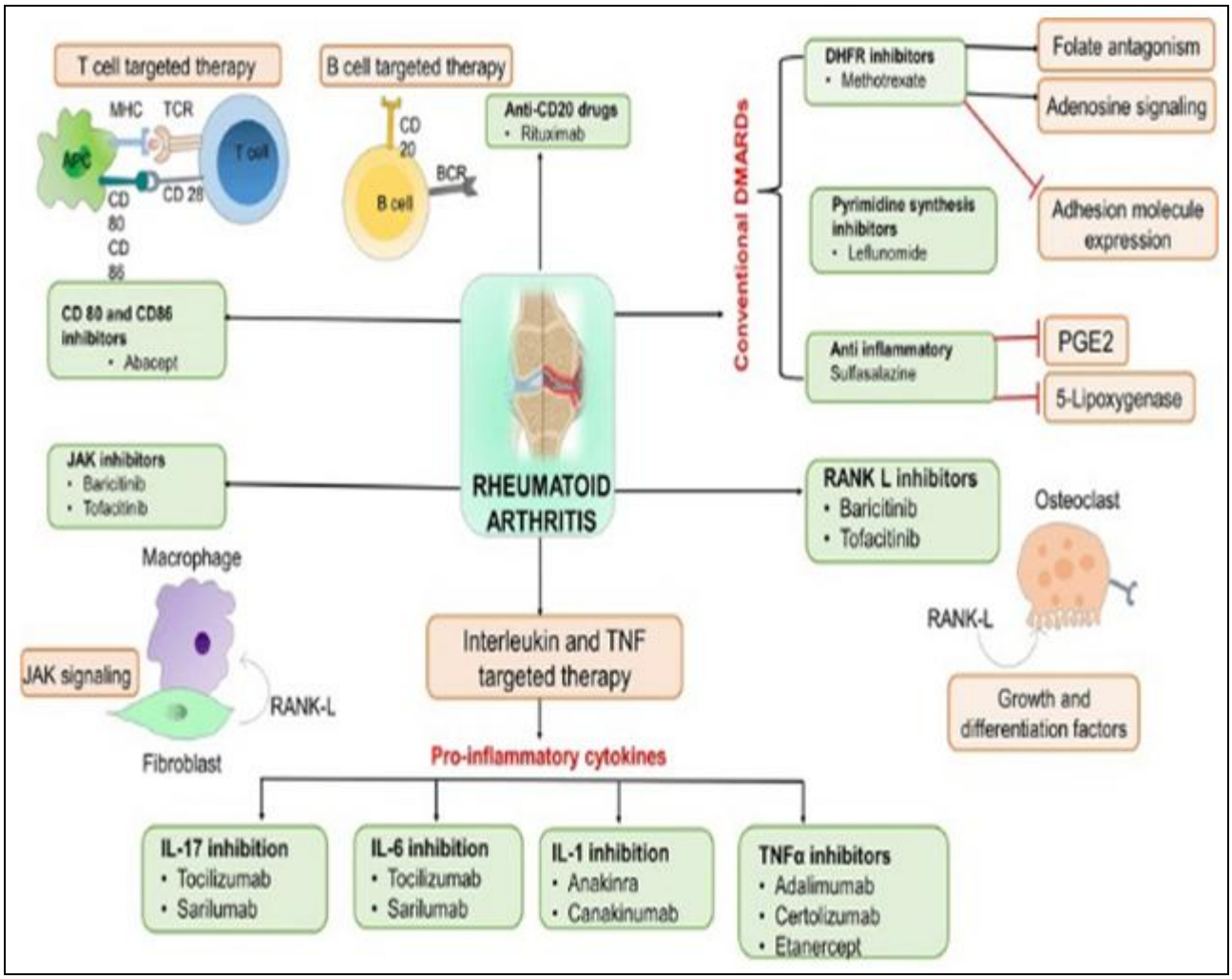

FIG. 1: TARGETS OF RHEUMATOID ARTHRITIS

First-Line Management: NSAIDS and Corticosteroids: The overall goal of first-line treatment is to relieve pain and decrease inflammation. Medications, considered to be fast-acting, are nonsteroidal anti-inflammatory drugs (NSAIDs) including Aspirin, naproxen, ibuprofen, and etodolac.

NSAIDs work by inhibiting cyclo-oxygenase to prevent the synthesis of prostaglandins, prostacyclin and thromboxane. Common side effects are nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleeding.

These symptoms can be reduced if taken with food, antacids, proton pump inhibitors, or misoprostol. An even newer NSAID called celecoxib is a selective Cox-2 inhibitor that has less risk of GI side effects.

Aspirin is an effective anti-inflammatory for RA when used at high doses, due to the inhibition of prostaglandins. It is one of the oldest NSAIDs used for joint pain. Side effects of aspirin at high doses include tinnitus, hearing loss, and gastric intolerance. There are other NSAIDs that are newer on the market than aspirin and just as effective. In addition, these drugs require fewer doses per day [14].

Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses, during exacerbations or flares of RA. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation.

They work by preventing the release of phospholipids and decreasing the actions of eosinophils, thereby decreasing inflammation. Their side effects include bone-thinning, weight gain, diabetes, and immunosuppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of the bone. Side effects can be reduced by gradually tapering doses as a patient's condition improves.

It is important to not abruptly discontinue injected or oral corticosteroids as this can lead to suppression of the hypothalamic-pituitary-adrenal axis (HPA) or flares of RA [20].

Conventional Synthetic DMARD (csDMARD): As soon as the diagnosis of *Rheumatoid arthritis* is made, a treatment with a csDMARD should be started.

A controlled comparison between csDMARDs for the first-line therapy does not exist; however, within this group, methotrexate should be the first choice because, for this drug, most clinical experience exists in monotherapy and as a combination partner with other DMARDs [17].

Methotrexate is usually started at a dose of 15 mg/week and can be stepwise increased up to 25 mg/week. The combination with glucocorticoids is recommended.

Due to the decreased bioavailability, a subcutaneous way of administration is recommended. The induction of remission with a combination of conventional synthetic DMARDs at this stage is not superior to methotrexate monotherapy; however, these combinations are associated with more adverse events and a higher rate of drug discontinuation.

Patients with a higher baseline disease activity and Rheumatoid factor (RF)-positive patients have an increased risk of methotrexate (MTX) failure due to inefficacy. If methotrexate cannot be used, e.g., due to intolerance or contraindications, leflunomide (20 mg/week) or sulfasalazine (2 g/day) should be started. In a placebo-controlled randomized controlled trial (RCT), both substances showed a similar efficacy.

If by week 12 after the start of methotrexate therapy no adequate response is achieved or no remission is reached with optimum doses after 24 weeks, the therapy should be adjusted. To find the best individual treatment strategy, patients should be categorized using prognostic markers.

Poor prognostic markers such as the presence of autoantibodies, early joint damage, and high disease activity are associated with rapid disease progression; therefore, a biologic DMARD or a targeted synthetic DMARD should be added at this stage. In the absence of poor prognostic markers and with moderate disease activity, a second csDMARD should be added to the therapy [20].

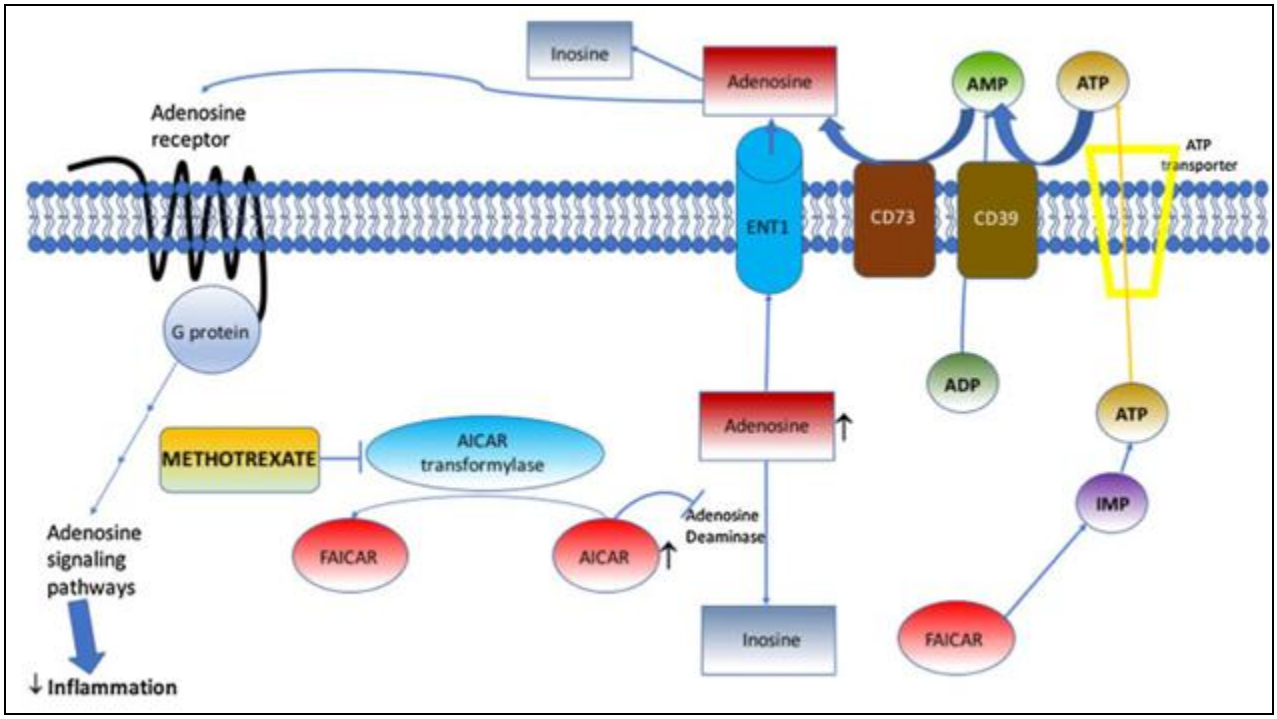

FIG. 2: MODE OF ACTION OF METHOTREXATE IN RHEUMATOID ARTHRITIS

The mode of action of high-dose methotrexate *via* the depletion of thymidine and purine residues and cell-cycle arrest at S1 are well-known. However, this mechanism does not seem to play a major role in the clinical effect of low-dose methotrexate, as folate co-therapy does not result in a loss of clinical benefit. Methotrexate has pleiotropic therapeutic effects on various immune cells and mediators, resulting in an overall reducing of the inflammatory response. The main mode of action of low-dose methotrexate in *Rheumatoid arthritis* is thought to be via the potentiation of adenosine signaling. Adenosine acts as a paracrine signaling agent via four distinct purinergic G-protein-coupled receptors, which in *Rheumatoid arthritis* are overexpressed. In addition to downregulating the production of tumor necrosis factor (TNF) and NF-kB, adenosine might be one of the main mediators of the downregulation of the activation and proliferation of T-lymphocytes, creating an immunotolerant environment [14, 15].

Side effects of methotrexate are usually dependent on dose, mode of application, and duration of methotrexate therapy. Unlike high-dose methotrexate, the side effects of low-dose methotrexate are rarely life-threatening and can often be relieved by substituting folate. Common side effects of low-dose methotrexate are hematologic abnormalities (thrombocytopenia and leucopenia), stomatitis, gastrointestinal problems (e.g., anorexia, loose stools, nausea, or stomach upset), elevation of liver enzymes, or central system symptoms like fatigue or headache. The substitution of folate significantly lowers the risk for side effects like hepatotoxicity (relative risk reduction of 77%) and decreases the number of serious adverse events (by 61%). If side effects occur, substituting folate acid regularly and gradually increasing the dose up to 5 mg daily can help to control the symptoms.

Overall, fewer than 5% of patients have to stop using methotrexate because of adverse events. methotrexate therapy can, in many cases, be safely continued perioperatively; however, a potentially decreased kidney function in this setting should be taken into account. In addition, to decrease the risk of pneumonia, the treatment should be paused if pulmonary comorbidities exist. At high doses (25 mg/week), a temporary dose reduction should be considered. methotrexate exposure during pregnancy can induce multiple congenital deformities. Therefore, methotrexate therapy during pregnancy is not recommended. methotrexate should be withdrawn prophylactically 3 months before conception. Daily folate supplementation should be continued antenatal and throughout pregnancy [21, 22].

Leflunomide: The primary mechanism of action of leflunomide (LEF) is the reversible inhibition of the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), the rate limiting step in the de novo synthesis of pyrimidines. Activated lymphocytes expand their pyrimidine pool by approximately eightfold during proliferation. Therefore, the inhibition of DHODH prevents activated lymphocytes from moving from G1 to the S phase, hence triggering apoptosis. The leflunomide effect seems to be rather lymphocyte-specific on other cells, can reuptake pyrimidines, and can thereby overcome the DHODH blockade. The rate of discontinuation due to side effects is similar with methotrexate. Potential side effects include diarrhea and nausea as well as the elevation of liver enzymes. The changes in liver function are generally reversible with dose reduction or a discontinuation of the drug, but in rare cases, hepatotoxicity can be severe. However, transaminase elevation mainly occurs if other comorbidities contributing to hepatotoxicity, e.g., concomitant non-steroidal anti-inflammatory drugs (NSAID) or methotrexate therapy, previous or concurrent alcohol abuse, or viral or autoimmune hepatitis, are present. A small percentage of patients with RA develop hypertension when taking LEF; therefore, blood pressure monitoring is recommended during treatment. The active metabolite of leflunomide is detectable in plasma until 2 years after the discontinuation of the drug; therefore, a discontinuation of leflunomide perioperatively is generally not recommended [18].

Only at a high risk of infection or if a greater intervention is planned, a wash out with cholestyramine should be initiated as recommended. Leflunomide is contraindicated during pregnancy. Safe contraception during therapy in both women and men is recommended. Before conception, leflunomide must be withdrawn and a washout should be carried out until the drug is undetectable in the blood.

Hydroxychloroquine (Plaquenil) [19] is an antimalarial drug and can be used for long-term treatment of RA. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the GI tract, skin, and central nervous system. The eyes, in particular, can be affected when this drug is taken at high doses. Patients on this medication require routine consultation with an ophthalmologist. Gold salts, such asaurothioglucose**,** auranofin, gold sodium thiomalate, and D-penicillamine have been used frequently in the treatment of RA. These DMARDs require frequent blood and urine tests due to damage to the bone marrow and kidneys. They have not been used recently due to the more effective treatments, particularly methotrexate. Other immunosuppressive medications like azathioprine, cyclophsphamide, chlorambucil, and cyclosporine can be employed but are typically reserved for patients with very aggressive RA or complications of the disease.[18]

Sulfasalazine: Sulfasalazine SSZ was specifically designed in 1938 for the treatment of rheumatoid arthritis. The idea behind the drug was to combine an antibacterial and an anti-inflammatory agent. Sulfasalazine is effective in the treatment of rheumatoid arthritis; however, the mode of action is incompletely understood. The main pharmacological effects of SSZ include effects on the gut bacterial flora, on inflammatory cell functions, and on immunological processes. Several plausible mechanisms of action have been observed *in-vitro*, such as the inhibition of NF-kB and osteoclast formation *via* modulatory effects on the receptor activators of NF-kB (RANK), osteoprotegerin (OPG), and RANK-ligand. In addition, SASP can inhibit tumor necrosis factor (TNF)-alpha expression and may reduce the secretion of inflammatory cytokines such as interleukin (IL)-8 as well as suppress B-cell function. An additional mechanism that has been suggested is the increased production of adenosine at sites of inflammation similar to the mode of action of methotrexate [16, 17].

Adverse reactions, including idiosyncratic (e.g., hypersensitivity-/immune-related) and dose-related effects which are common with sulfasalazine, especially gastrointestinal, central nervous system, cutaneous, and hematologic adverse effects. The withdrawal rate for adverse events is about 25%, two thirds of which are due to gastrointestinal and central nervous system toxicity. If dose-related side effects occur, treatment can be paused for a week and after a resolution of the symptoms, the treatment can be restarted at a lower dose. However, if idiosyncratic effects like skin

reactions, hepatitis, pneumonitis, or hematologic side effects like agranulocytosis and hemolytic anemia occur, immediate discontinuation of the drug is necessary; patients with this type of adverse effect should not be rechallenged with the drug.

As sulfasalazine only has a short half-life of about 4–5 h and only a minimal immunosuppressive effect, it can usually be continued perioperatively. If there is a risk of interaction or a potential additive hepatotoxic effect with medication used preoperatively, sulfasalazine can be paused on the day of the operation.

If treatment of *Rheumatoid arthritis* is required during pregnancy, SSZ is an acceptable therapeutic option, as the continuation of SSZ during pregnancy is very unlikely to cause fetal harm. To increase safety, a concomitant folate supplementation before and throughout pregnancy is advised and the dose of SSZ should not exceed 2 g per day to prevent neutropenia in the newborns. SSZ can cause reduced male fertility; however, spermatogenesis recovers at about 2–3 months after a withdrawal of the drug.

Biologic DMARDs (bDMARD) [18, 19, 21]: According the EULAR (European League Against Rheumatism) guidelines, a bDMARD should be considered if remission or LDA (Low Disease Activity) is not achieved with the first DMARD strategy, if poor prognostic factors (i.e., high acute phase reactant levels, high swollen joint counts, or the presence of early erosions) exist, or if the patient responds inadequately to methotrexate and/or other csDMARD strategies.

Before starting a therapy with bDMARD, active or latent infections with hepatitis or tuberculosis must be ruled out. Patients, if possible, should be brought up to date with all immunizations before initiating therapy. Blood cell counts and liver and kidney function also need to be evaluated prior to treatment.

Tumor Necrosis Factor-Alpha Inhibitors (TNF-αi): Until now, five TNF-αi were available. Although all anti-TNF drugs bind TNF-α, there are differences in their molecular structures, their administration regimens, and their modes of action. The first preclinical studies using antibodies against TNF- α were performed in animal models of sepsis in 1985. About 6 years later, Keffer *et al.* provided the first evidence that TNF plays a role in developing arthritis. In 1994, it has been found that the blockade of a specific cytokine can be an effective treatment in patients with rheumatoid arthritis. Since then, antibodies against TNF-α have gotten an important keystone in the treatment of RA and changed the lives of our patients [23].

The first TNF-α-inhibitor, approved in 2000 for the therapy of RA, was the chimeric murine/human IgG1 monoclonal antibody *Infliximab* (IFX) that binds to both soluble and membrane-bound TNF-α. The administration is intravenous every 8 weeks at a dosage between 3–5 mg/kg. Another TNF-inhibitor also approved in 2000 is *Etanercept* (ETN), a recombinant fusion protein compound of the soluble TNF-alpha receptor linked to the Fc portion of human IgG.

ETN binds to the TNF receptor, preventing TNF-mediated cellular responses. ETN is administered subcutaneously at a dose of 25 mg twice a week or 50 mg weekly. The third inhibitor approved in 2003 by the European Medicines Agency (EMA) is *Adalimumab* (ADA).

It is a recombinant human IgG1 monoclonal antibody that binds to soluble and membrane-bound TNF-α with a high affinity. It is administered by subcutaneous injection once every 2 weeks. *Golimumab* (GOL) is a human IgG1 monoclonal antibody neutralizing both soluble and membrane-bound TNF-α. GOL was approved in 2010 and is administered as a subcutaneous injection at an initial dose of 50 mg every 4 weeks that can be increased to 100 mg if there is no response after 4 doses (in patients with a body weight > 100 kg).

Certolizumab Pegol (CZP) was approved by the EMA in 2007. CZP is a recombinant humanized Fab' fragment of a TNF antibody coupled to polyethylene glycol (PEG) that prolongs its plasma half-life to approximately 2 weeks.

It has an initial loading dose of 400 mg every 2 weeks for 6 weeks, followed by 200 mg every 2 weeks. Only certolizumab, adalimumab, and etanercept are approved as monotherapy as well as in combination with methotrexate.

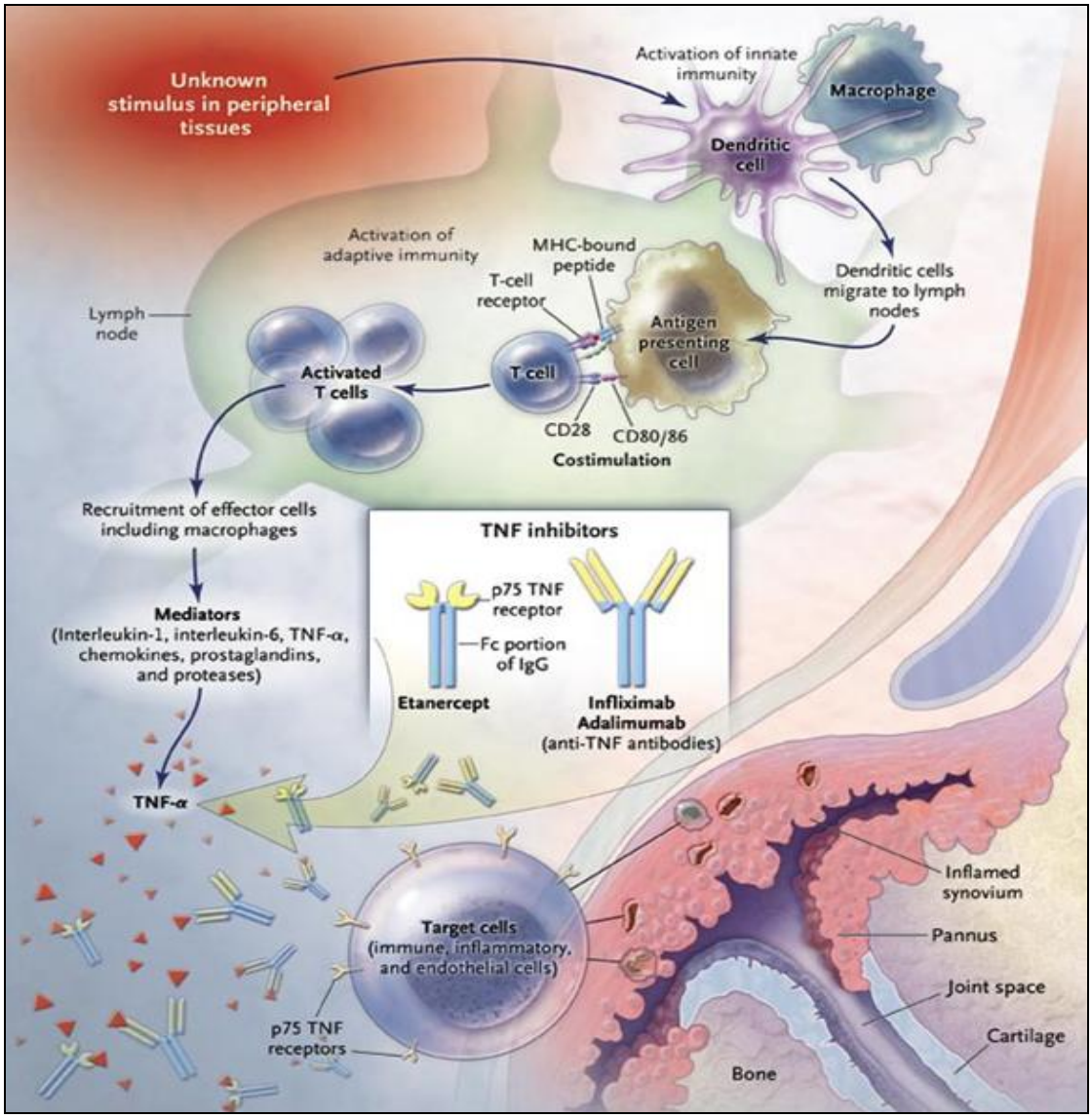

FIG. 3: MODE OF ACTION OF TNF-A IN RHEUMATOID ARTHRITIS

Adverse effects include skin reactions characterized by itching, pain, and redness at the site of medication injection. Such injection site reactions characteristically occur during the first weeks of treatment. For intravenously administered agents, acute infusion reactions can occur with hypotension, bronchospasm, wheezing, and/or urticaria. The majority of acute infusion reactions that occur are anaphylactoid reactions and not immunoglobulin E mediated. These reactions can be managed by just reducing the rate of infusion. However, delayed infusion reactions can also occur, and they are associated with skin rash, diffuse joint pains, myalgia, and fatigue and sometimes accompanied by fever. Delayed reactions may represent mild type III (immune complex-mediated) reactions. It has been shown that the formation of Anti-monoclonal antibodies may lead to a greater risk of infusion reactions and also may limit the long-term efficacy of the drug. It has also been shown that the use of concomitant immunomodulators prior to starting a TNF-α-inhibitor is effective in reducing antibody production and therefore decreasing immunogenicity [21, 22]. As TNF-alpha is a key player of the immune system during infections, this treatment has been associated with an increased risk of serious infections. These include bacterial infections (particularly pneumonia), herpes zoster, tuberculosis, and opportunistic infections. As mentioned above, screening for latent tuberculosis infections should be performed before the initiation of TNF-alpha inhibitor therapy. If there is an indication of latent tuberculosis, a treatment for latent tuberculosis should be initiated before starting therapy with a TNF-alpha inhibitor.

Another side effect occurring in a few cases is neutropenia. However, anti-TNF-alpha agents should generally be avoided in patients with established diseases that are associated with demyelination and should be discontinued directly in any patient with suspected demyelination.

Interleukin 1 Inhibitor [21, 22]: Anakinra was first approved in the US in 2001 and in Europe in March 2002. It is a recombinant human IL-1 receptor antagonist with a short half-life (4–6 h), administered subcutaneously at a dose of 100 mg once a day. It was first developed for use in RA and showed some effects in early trials. A big systematic review of the literature in 2009 showed only a moderate effectiveness. Anakinra plays not a very great role in RA therapy; today, it is much more effective in the therapy of auto-inflammatory diseases, gout, or polyserositis. Adverse effects include injection site reactions characterized by itching, pain, and redness at the site of medication injection and lasting days to weeks. Between one and ten percent of people have severe infections, decreased white blood cells, or decreased platelets.

CD-80/86- CD-28 Inhibitor: Abatacept is a fusion protein constituted by an immunoglobulin fused to the extracellular domain of cytotoxic T-lymphocyte antigen 4 (CTLA-4). This is a molecule that binds with a high affinity to the CD80/86 ligand on antigen-presenting cells. Therefore, abatacept is able to block the interaction between the antigen-presenting cell's CD80/86 ligand and the CD28 ligand on the T cell. This results in decreased T cell proliferation and cytokine production. Abatacept is administered intravenously once every 4 weeks or subcutaneously once a week. Adverse effects including cases of hypersensitivity and anaphylaxis or anaphylactoid reactions have been reported with iv administration. As in other bDMARDs, serious infections (including tuberculosis and sepsis) have been reported, particularly in patients receiving concomitant immunosuppressive therapy. The use of CTLA-4 Inhibitors due to its T cell inhibition affect defenses against malignancies. As compared to the general population, an increased risk of lymphoma has been noted in clinical trials; however, *Rheumatoid arthritis* has been previously associated with an increased rate of lymphoma. Abatacept itself seems not to further increase this risk [22, 23].

Anti-CD 20 Antibody [22]: Rituximab (RTX) was initially developed for the treatment of hematologic malignancies. Since 2006, RTX is approved for the therapy of RA refractory to a combination therapy of anti-TNF-alpha and methotrexate. RTX is a chimeric murine-human monoclonal antibody that binds to the CD20 membrane receptor, leading to the depletion of circulating B cells. It is also able to inhibit the activation of T cells that produce proinflammatory cytokines. A cycle of RTX consists in 1000 mg by intravenous infusion, followed by a second 1000-mg intravenous infusion two weeks later. This is then repeated every 6 months. One of the common side effects is an infusion reaction especially during the first infusion, occurring in up to 30 to 45 percent of patients. Symptoms include headache, fever, skin rash, dyspnea, hypotension, nausea, rhinitis, pruritus, and mild angioedema. Repeated courses of RTX are associated with an increasing risk of hypogammaglobinemia. A meta-analysis in 2009 found no increase in serious infections associated with the use of rituximab with or without methotrexate compared with methotrexate plus a placebo, but other studies have found that repeated courses may be associated with a higher rate of serious infections. The risk of serious infections seems to increase with age.

Interleukin 6 and Interleukin 6 Receptor Inhibitors [16, 18, 22]: Interleukin-6 (IL-6) was identified in 1986 as a key cytokine in the pathogenesis of RA with proinflammatory activity. It is able to enhance the production of acute-phase proteins involved in the systemic inflammation process. Tocilizumab (TCZ) is the first humanized recombinant IgG1 monoclonal antibody that binds to both the soluble and membrane-bound IL-6 receptor, blocking its action and leading to the decrease of the inflammatory response cascade. Its half-life (10–13 days) allows its administration intravenously (8 mg/kg) every 4 weeks. A subcutaneous formulation of TCZ (162 mg/week) has been approved, with an efficacy and safety profile comparable to intravenous administration.

A second agent, Sarilumab is a human immunoglobulin G1 anti-interleukin-6 (IL-6) receptor monoclonal antibody that blocks IL-6 from binding to membrane-bound and soluble IL-6 receptor alpha. Events of gastrointestinal (GI)

perforations have been reported in Phase III clinical trials, primarily as complications of diverticulitis, including generalized purulent peritonitis, lower GI perforation, fistula, and abscess. Tocilizumab or Sarilumab should be used with caution in patients who may be at increased risk for GI perforation.

Patients presenting with new-onset abdominal symptoms should be evaluated promptly for the early identification of GI perforation. It is important to keep in mind that, during IL-6 blockade, C-reactive protein or other acute phase reactants will increase slowly and less pronounced. Other side effects are neutropenia or thrombocytopenia as well as hyperlipidemia. Also, serious infections and liver enzyme elevations were observed and can require dose adjustments or drug discontinuation [20, 22].

Targeted Synthetic DMARDS: JAK-Inhibitors: Recently, with the Janus–Kinase (JAK) Inhibitors, a new group of drugs for the treatment of *Rheumatoid arthritis* was introduced. These targeted, synthetic DMARDS (tsDMARDS) are effective in inflammatory diseases by intracellularly blocking tyrosine kinase. The JAK are cytoplasmic protein tyrosine kinases that are critical for signal transduction to the nucleus from the common gamma chain of the plasma membrane receptors for interleukin (IL)-2, -4, -7, -9, -15, and -21. JAK are receptor-associated intracellular proteins, with a tyrosine-kinase component. They are important downstream mediators of many pro-inflammatory cytokines, e.g., interferons or interleukin 6. Once a ligand binds to its receptor, the intracellular kinase is phosphorylated, which further leads to the phosphorylation and activation of the signal transducer and activator of transcription (STAT)-pathway. Accordingly, blocking these enzymes with a targeted molecule affects multiple inflammatory pathways [13].

Cytokines bind to the receptors, which then undergo a change in their configuration into a dimeric structure, thereby activating their ability to work as a kinase. Consequently, they phosphorylate the STAT molecules (Signal Transducer and Activator of Transcription). Phosphorylated STATs also form dimers that travel to the cell core, where they activate transcription processes, which further fuel inflammatory processes [10].

Pharmacological Aspects: JAK-inhibitors are referred to as small molecules, meaning that these compounds carry a low molecular weight and bind to a macromolecular target, altering their activity and function. Till now, two JAK-inhibitors are approved for therapeutic use in rheumatoid arthritis: Tofacitinib and Baricitinib.

Tofacitinib was approved by the FDA (Food and Drug Administration) in the US in 2012. In 2017, the European Medicines Agency (EMA) approved the drug for use in the European Union. Tofacitinib is an inhibitor of JAK 1 and 3, with only little affinity to JAK 2 and Tyrosine-Kinase 2. It has been shown effective in moderate and severe *Rheumatoid arthritis* in monotherapy or in combination with methotrexate. Tofacitinib is taken orally twice daily with a dosage of 5 mg. The elimination is mostly hepatic; therefore, an adaption to impaired kidney function is not necessary up to a GFR > 30 mL/min. Consequently, the treatment of patients with end-stage renal failure with a GFR < 30 mL/min with Tofacitinib is possible with reduced dosage. Side effects of Tofacitinib are headaches, hypertension, nausea, and diarrhea. Elevated levels of low-density lipoprotein (LDL), high-density lipoprotein (HDL), total cholesterol, and liver enzymes, increased risk of deep vein thrombosis and pulmonary embolism have also been reported [8].

The second JAK-inhibitor currently approved is Baricitinib which is an inhibitor of JAK 1 and 2. It was approved by the FDA as well as the EMA in 2017. Baricitinib can be administered as monotherapy or in combination with methotrexate. Baricitinib is taken orally once daily. There are two dosages available: 4 mg or 2 mg. The elimination for Baricitinib is mostly renal, which makes it necessary to reduce the dosage for patients with impaired kidney function (estimated GFR 30–60 mL/min) from 4 mg to 2 mg daily. For patients with an estimated GFR < 30 mL/min, the use of Baricitinib is not recommended. The most common side effect of Baricitinib is an increase of cholesterol levels. Other side effects include upper respiratory tract infections and nausea [22, 23].

According to the EULAR Guidelines, both JAK-Inhibitors can be used in *Rheumatoid arthritis* once a therapy with csDMARDs has been insufficient or

had to be discontinued due to adverse events. JAK-inhibitors should not be prescribed for patients with neutropenia (<1/nL), active tuberculosis or severe infections, or severe liver impairment and during pregnancy. Both Tofacitinib and Baricitinib have been shown to be more efficient than a placebo in the treatment of rheumatoid arthritis; both could show non-inferiority compared with the TNF-inhibitor Adalimumab. Two selective JAK-1-Inhibitors are currently undergoing Phase 3 trials for clinical approval: Upadacitinib and Filgotinib.

Non Pharmacological Therapy [14, 16, 22]: If medications fail to prevent or slow joint damage, you and your doctor may consider surgery to repair damaged joints. Surgery may help restore your ability to use your joint. It can also reduce pain and improve function.

Rheumatoid arthritis surgery may involve one or more of the following procedures:

- **Synovectomy:** Surgery to remove the inflamed lining of the joint (synovium) can help reduce pain and improve the joint's flexibility.
- **Tendon repair:** Inflammation and joint damage may cause tendons around your joint to loosen or rupture. Your surgeon may be able to repair the tendons around your joint.
- **Joint fusion:** Surgically fusing a joint may be recommended to stabilize or realign a joint and for pain relief when a joint replacement isn't an option.
- **Total joint replacement:** During joint replacement surgery, your surgeon removes the damaged parts of your joint and inserts a prosthesis made of metal and plastic.

CONCLUSION: Early treatment is important to control disease activity and to prevent joint destruction. With the treat to target (T2T) strategy and the possibility to choose from different mode of actions, the aim of stable remission can be reached and joint destruction can be prevented. T2T further improves the prognosis of RA. Gene array analysis is proving beneficial in finding out which patients will be more responsive to specific medications. This customization will allow for more rapid treatment as well as decrease the likelihood of disease progression during the experimental phase to seek an appropriate treatment for a particular patient. Gene array analysis is also being used to determine which patients are at greater risk for more aggressive forms of RA. Many complications lead to permanent joint damage requiring arthroplasty, rheumatoid vasculitis, and Felty syndrome requiring splenectomy if it remains unaddressed. Nowadays, it has been seen that treatment options lead to tremendous improvements in the management of RA.

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