IMPORTANCE OF BIOLOGICS IN RHEUMATOID ARTHRITIS MANAGEMENT- A REVIEW

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

Department of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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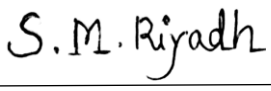

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Approval

The thesis titled “Importance of Biologics in Rheumatoid Arthritis Management” submitted by S. M. Riyadh (17146009) of Spring, 2017 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelors.

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Ethics Statement

This study does not involve any kind of animal or human trial.

Abstract

Rheumatoid arthritis (RA) is an autoimmune condition that causes chronic joint inflammation pain, eventually leading to significant bone and cartilage damage in the affected joint. Around the world, RA affects a large number of people in their later years. The most frequent joints affected by RA are the elbow, shoulder and metacarpophalangeal joints. Conventional medication previously only treated the symptoms of RA. To treat the etiology of RA, biological disease modifying anti-rheumatic medicines (bDMARDs) target biological receptors such as TNF-alpha, IL-1 and IL-6. This review article discusses the benefits of using biological disease modifiers.

Keywords: Rheumatoid arthritis; TNF-alpha; Interleukin; disease-modifying anti rheumatic drugs; biological disease-modifying anti rheumatic drugs

Dedication

Dedicated to my parents, grandparents and my project supervisor, Dr. Md.Aminul Haque.

Acknowledgement

First of all, our gratefulness goes to Almighty Allah who gave us strength and ability to complete the project and prepare this review; may your name be exalted, Honored and glorified now I wish to take this excellent opportunity to thank a lot of people who have assisted and inspired me in the completion of my project work.

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Last but not least, thanks go to my precious family for their never ending love and inspire at every stages of my life. Without their continuous I realize that I would not be a person I am right now.

Table of Contents

List of tables

List of figures

List of acronyms

RA	Rheumatoid arthritis
TNF-alpha	Tumor Narcosis Factor alpha
IL-1	Interleukin-1
IL-16	Interleukin-16
RF	Rheumatoid Factor
INF	Infliximab
ADA	Adalimumab
RANKL	Receptor activator of nuclear factor kappa-β ligand
Anti-CCPs	Anti-cyclic citrullinated
DMARDs	Disease-modifying anti-rheumatic drugs peptide
ACR	American College of Rheumatology
ASAS	Assessment of Spondyloarthritis International Society
RCT	Randomized controlled trial

Chapter 1

Introduction

1.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is indeed an acute condition that causes persistent inflammation in the joints, ultimately resulting in severe death and disability. Infections of both the synovial fluid of joints throughout time, articular cartilage deterioration and aggregation changes with time, as well as extra-articular infection, all contribute to bone loss (Kumar et al., 2016). People develop RA as they age. Men are less prone to it than women, and their odds of developing it are 2 to 3% higher. In Bangladesh, RA affects people of all ages, but the majority of those affected are between the ages of 30 and 50 (Alamgeer et al.., 2015). Large object connections, like the arms, shoulder, especially metacarpophalangeal joints, are particularly vulnerable to RA (Scott.., 2007). Infectious diseases perplex the human body, generating immune system malfunction that causes the immune system to target the joints. Although the true reason has yet to be discovered. The major causes of RA, according to specialists are tumor necrosis factor (TNF) but also interleukin-1. They induce RA by stimulating immune system-related microbes (Yung et al., 1995). Inflammation, stiffness, and soreness can affect any joint, including the knee. Knees, wrists, hands, shoulders, and feet can all be affected and the symptoms might appear gradually or suddenly (Greenwald et al., n.d.) because the symptoms of RA are so similar to those of other diseases, it is crucial to get the right diagnosis. Lab tests, x-rays, and clinical examinations are utilized to confirm the diagnosis as a consequence. It is critical to seek treatment as soon as possible to avoid twisting of the fibers that connect the joints, which can result in bone injury.

1.2 Several classes of Rheumatoid Arthritis

All diagnostic results of x-rays and laboratories examinations of the patient must be determined to define the kind of RA. The appearance of the rheumatoid factor distinguishes RA. More than 80% of persons with inflammatory arthritis have has screened positive for rheumatoid factor (RF), often known as affirmative (or seropositive) rheumatoid arthritis, according to a study. Some persons, however, came back negative for RF, meaning they do not have RA.

Rheumatoid Factor Positive (Seropositive):

If a patient's body generates a protein called raised serum, the physician must notice that the patient's condition is beginning an allergic response towards his or her healthy cells (Jo, 2017). Antibodies and RF can both be found in the same areas. When anti-CCPs as well as ACPAs are detected in a person's blood and physical symptoms persist, the patient has already been identified with Rheumatoid Arthritis (Yu et al., 2019). The citrullinated anti-cyclic peptide, as well as anti-citrullinated proteins antibodies (ACPAs), are anti-CCPs and anti-CCPAs, accordingly (Malaviya & Sawhney., 2014).

Anti-CCPs develop inside several joints when the chemical composition changes gradually (Hosein et al.., 2016). Antibodies to these proteins can be discovered in 60 to 80 percent of persons with RA and they can also be used to forecast when the disease will start (Jo, 2017). 5 to 10 years before symptoms develop, antibodies can be discovered in blood samples. RA occurs compliant when a person has an anti-RF antibody. When seropositive or anti-CCP positive people, a consistent sequencing of amino acids may be recognized within the HLA genetic area of the body.

Rheumatoid Factor Negative (Seronegative):

Even if blood testing suggests that a patient does not have RF or Rheumatology Factor Null (Seronegative) RA, the patient may still have it. In this scenario, just an x-ray analysis, medical symptoms, and additional analytical tests might be used to determine whether the patient has RA (Malaviya & Sawhney, 2014). Patients with RF-negative RA are less likely than those with seropositive RA to develop arthritis (Klein & Gay., 2013).

1.3 Importance of Rheumatoid Arthritis treatment:

Arthritis seems to be an inflammatory illness that mostly affects the patient's joints. The occurrence of persistent synovitis impacts joint impairment in almost all RA patients. Synovium is produced by inflammatory cells, which causes synovial fibroblasts and macrophages to grow. As bone and cartilage loss seems permanent, it's vital to start therapy as soon as possible after a diagnosis of rheumatoid arthritis (Kyburz & Finckh, 2013). Rheumatoid arthritis (RA) is defined as a persistent synovial inflammation. As a result, managing articular inflammation is critical for rheumatoid arthritis sufferers to avoid injury (Kyburz & Finckh, 2013).

1.4 Specific treatment for RA and their limitation:

Patients with rheumatoid arthritis use one of five types of medicines. The medicines in concern are DMARDs, NSAIDs, steroids, Janus kinase (JAK) inhibitors, biologics. Nonsteroidal anti-inflammatory drugs (NSAIDs) are medications that are used to treat inflammation (NSAIDs).

The etiology of RA can help with symptoms like chronic joint pain, persistent inflammation, and joint degradation. As a result, many more NSAID dosages are required to produce the optimal healing response, increasing the risk of gastrointestinal complications (Sofat et al., 2011). Prednisone as well as other short-acting steroids are particularly helpful in the early stages of RA treatment before other RA medications have had a chance to work (often 12 weeks or more). The ability to inject steroids into joints is one of its advantages. Injecting steroids into one or two troublesome joints can give targeted pain relief with few adverse effects. Steroids should be taken at the smallest amount and for the shortest time possible, according to experts. Steroid efficacy declines over time, As a result, the longer medication is used and the less likely it is that symptoms will be treated. Those who have performance-enhancing ring drugs should be made aware of the risks.

Disease-modifying anti-rheumatic drugs (DMARDs):

Disease-modifying anti-rheumatic medications (DMARDs) are being used to stop or slow the progression of rheumatoid arthritis by blocking the immune response. Methotrexate, azathioprine, sulfasalazine, and leflunomide are examples of Disease-modifying anti-rheumatic drugs with common names. When a patient is initially diagnosed with rheumatoid arthritis, methotrexate is generally the first drug administered. Patients with RA by using this medication once a week by itself or in combination with other medications. Some malignancies are occasionally treated with high-dose methotrexate. Patients with RA are given lesser doses than those with cancer. However, they come with a slew of negative side effects including fungal infection and other physiological issues if used for a lengthy period (Miwa et al., 2016).

Biologics:

The complexity of RA treatment therapy is increasing as a result of biological indications. Biological markers differentiate golimumab, etanercept, certolizumab, rituximab, infliximab, tocilizumab, anakinra, adalimumab and rituximab (Periplocae et al., n.d.). TNF inhibitors were added to the MTX combination in 60-70 percent of patients. Such are effective techniques, especially while the illness is still in its early stages (Atzeni et al., 2013). The FDA has

authorized TNF-alpha antagonists such as adalimumab, and infliximab monoclonal for use as a treatment (Rahman et al., 2017).

Janus Kinase (JAK) inhibitors:

Inflammation is triggered when JAK enzymes link to X cells. JAK inhibitors bind to JAK enzymes and block them from attaching to X cells, therefore inhibiting the inflammatory process. In the inflammatory phase of the immune system, JAK enzymes are key mediators.

Chapter 2

The review's objectives and purpose

The review aims to:

- Assist in the identification of novel techniques as well as the identification of the most active anti-RF medicine is using in the therapies of Rheumatoid arthritis over worldwide.

The review's objectives are to:

- To emphasize the significance of the natural agents, it has been noticed to reduce the symptoms of Rheumatoid Arthritis.
- Another mission is to figure out how organisms work to treat RA.

Chapter 3

Rheumatoid arthritis (RA) pathogenesis and pathophysiology

3.1 Potential ability to produce RA:

It's still uncertain if RA causes disease. TNF, CRP, CD40L, IL-18 as well as IL20, MCP-1 or monocyte designed with the intent protein-1, nuclear factor-ka- receptor and attaching atoms are only a few of the inflammatory mediators involved in the healing process. These are some of the elements which play a role in the evolution of RA. Preclinical RA, genetic characteristics and environmental effects are examples of these causes. A group of researchers devised a novel solution to problems (Thakur et. Al. 2018).

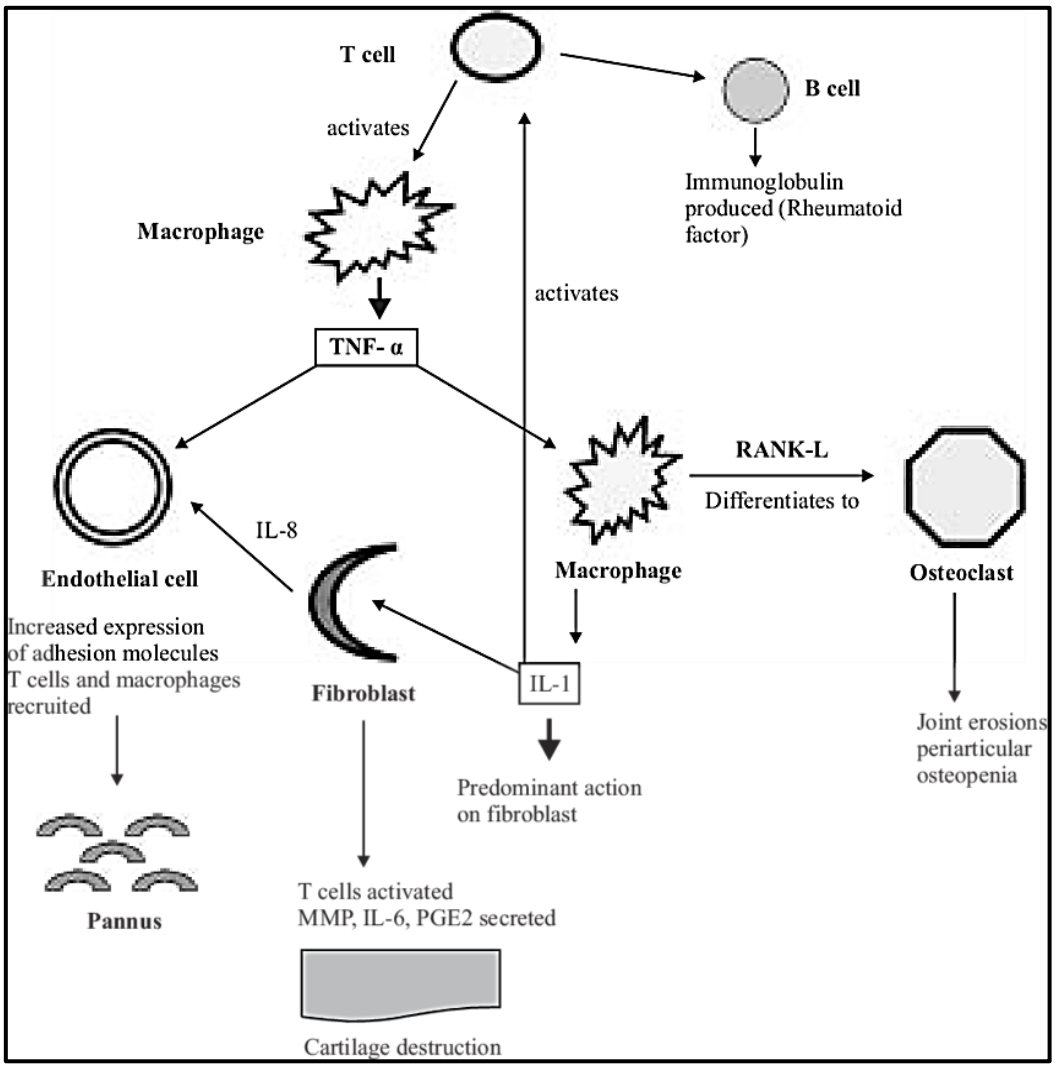

Figure 1: Factors that influence RA pathogenesis (Thakur et al., 2018)

Preclinical stage of RA:

The stage before the development of arthritis has referred to as preclinical RA. The level of illness indicators in the body, including antibodies, grows throughout this time (Kumar et al., 2016). RF plays a role in the development of RA (Thakur et al., 2018). The preclinical phases of RA are the first six stages of the disease's progression (Van Steenbergen et al, 2013). Rheumatoid Arthritis Genetic Risk Factors, Rheumatoid Arthritis Environmental Risk Factors, Rheumatoid Arthritis Systemic Autoimmunity, Symptoms without Clinical Arthritis, Unclassified Arthritis, and Rheumatoid Arthritis (Van Steenbergen et al., 2013).

Even though studies reveal that not all RA patients progress through all of the preclinical stages, the order where these phases manifest may differ from patient to patient. A patient may also be in two preclinical stages at the same time (Van Steenbergen et al., 2013). Suggested news regarding RA can be used only in retrospect. The recommendation was developed because so many people have hereditary features that lead to the development of RA, while others are exposed to natural factors that accelerate the advancement of RA.

Genetic factor:

The patient's genetics have a role in Rheumatoid Arthritis. MHC genes, according to molecular research, are expected to play a key role in pathogenesis (Thakur et al., 2018). The HLA-DRB1 gene has been identified as the most important genetic component in MHC in this disease, with patterns within the protein DRB1 characterized as the common epitope. They were discovered in DRB1*04 and DRB1*01 clusters (Thakur et al., 2018) other genetic origins for pathogen response should have been neglected (Kumar et al., 2016).

Environmental factors:

In 60% of cases, RA is assumed to be inherited, whereas 40% of cases are thought to be caused by natural conditions, such as smoking. As a result of long-term smoking, the risk of developing seropositive rheumatoid arthritis has risen. Anti-citrullinated proteins antibodies (ACPA) are 21 times more likely to develop in smokers with two HLA-DRB1 alleles. Even though the gene is not present in all smokers, it is present in a significant majority of them.

3.2 Pathophysiology:

Although the cause of RA is unknown, the early articular phase which starts from inflammatory cells in the bloodstream is an important stage in the disease's progression (Rahman et al., 2017). Synovial hyperplasia is the first sign of joint degeneration. Monocytes that have been attracted to a synovial membrane and its environs are known as macrophages. Leukocytes activate synovial from where cytokine is released.

A flow chart is illustrated below for a better understanding of the pathophysiology of RA:

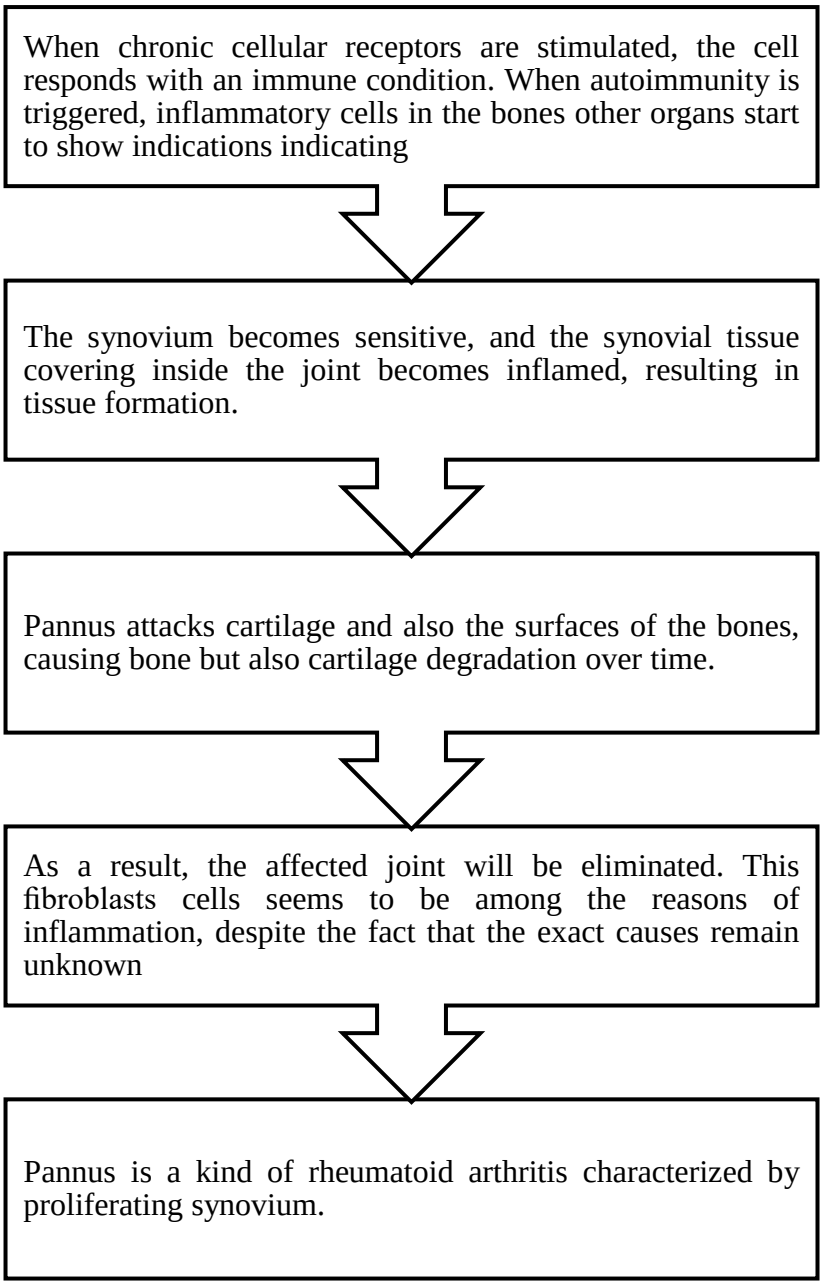

Figure 2: Pathophysiology of RA

The initiation, propagation and tissue damage phases of RA progression are as follows:

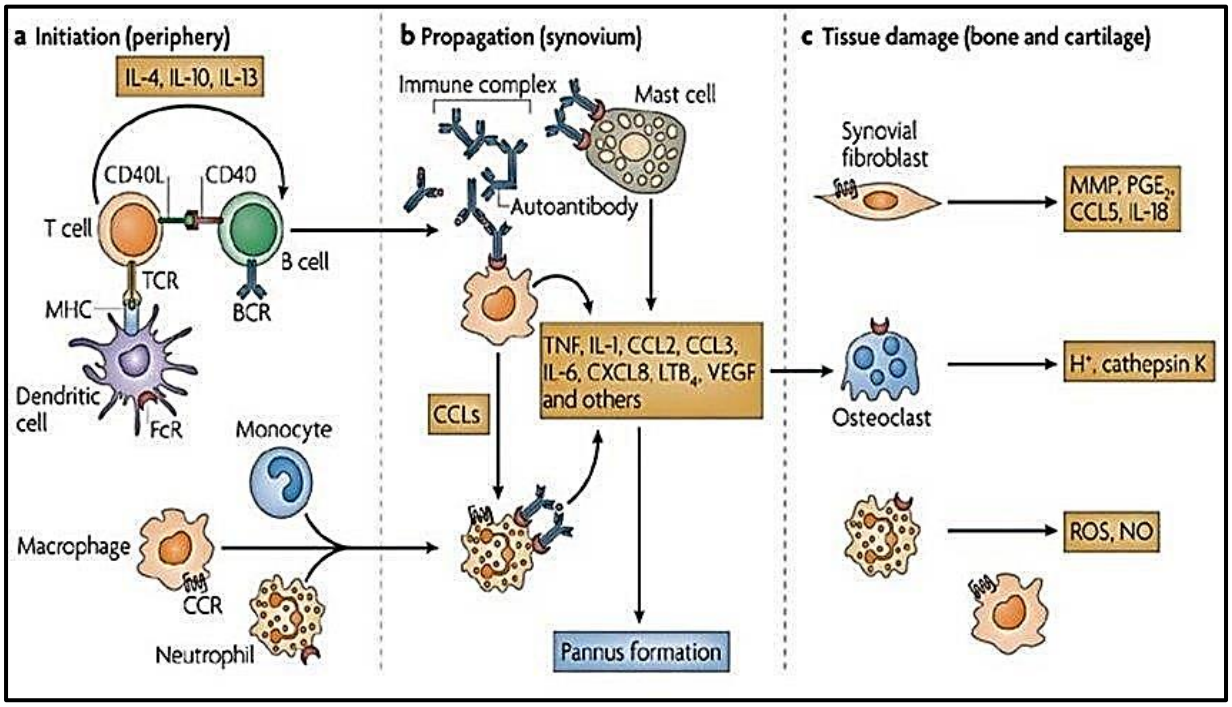

Figure 3: Rheumatoid arthritis has three stages of progression (Harrington et al., 2020)

Initiation phase:

Bone remodeling is aided by osteoclastic resorption and bone osteoblast cell production, both of which are common and continuous biological processes (Rahman et al., 2017). When RA patients get medication for bone growth, this process is disturbed (Rahman et al., 2016). CD4 helper T cells stimulate macrophages which produce inflammatory cytokines such as IL-1, Tumor necrosis factor and IL-6. Many multinucleated cells of osteoclast genesis and osteoclastic are activated by these cytokines, which are generated by merging cytoplasm for predecessor osteoclasts that govern their biological conditions in the human body as well re-establish cytoplasm for predecessor osteoclasts (Rahman et al., 2017). Furthermore, osteoblast cells help the human body recover from bone loss. The cytokines IL-1 and IL- 6TNF-a have also been linked to bone resorption.

All of these cytokines stimulate the connection of M-CSF to the RANK-associated receptor in osteoblastic cells during cell maturation as well as the production of M- CSF, an NF - kappa receptor activator that assists in the generation of synovial joint cells (Rahman et al., 2017). The conservation of general plant matter is also studied about osteoprotegerin (OPG), an osteoclastogenesis inhibitor that matches the lid RANKLL, which is transmitted from ameloblasts (Rahman et al., 2017). By inhibiting RANKL along the path of osteoclasts, that

cause blockage (Rahman et al., 2017). The osteoprotegerin ratio quickly declines whenever the nuclear factor kappa-ligand receptors activator differentiates osteoclasts under RA circumstances. An established osteoclast is a matrix that aids in the production of hydrochloric acid (HCl) and cathepsin k. Osteonectin and agglomeration are both impacted by severe joint damage (Boyce & Fuligni, 2007).

Propagation phase:

An endothelium and a few cells combine to generate articular cartilage. The three basic components of an ECM are collagens II, proteoglycans, as well as aggregation (Zhang et al., 2018a). Functioning macrophages release TNF alpha, Interleukins, and IL-6 cytokine which drives synovial fibroblast cells to create cartilage breakdown enzymes (Klein & Gay., 2013).To evaluate cartilage deterioration, RA enzymes are employed as a particular biological marker (Tanaka et al., 2012). Separate cells and essential parts of the tissue regeneration breakdown process can be found above the surface site joint. MMPs are inhibited and controlled by TIMPs (Lam & Bayer, 1983).

Tissue damage phase:

Synovium is a stretchy, perplexing substance located inside the joint layer that contains lubricating fluid in the articular protection chambers (Figure 2) and It is made up of three important components: a) Cartilage: soft, elastic headrest material that stays inside the joint surface. b) Joint capsule: intima plus chewy endothelium coating compressing. c) Atrium capsule: endothelium plus chewy endothelium coating compressing. The synovial membrane contains dual synoviocytes, comprising type A and type B intima cells (Figure 2). Types A cells, commonly called cells, eliminate undesired materials, and Type B cells, also known as FLS cells, create necessary lubrication polysaccharides such as hyaluronic acid and lubricating protein. (Kumar et al., 2016).

Fibers and macrophages are fibroblasts and macrophages found in the sub-intima layers that support the synovium membrane. It's the initial location of inflammation that might be causing the immunological problems that come with RA. GM-CSF, VEGF and IL17 are among the cytokines found in them. Synovial mononuclear lymphocytes, angiogenesis, and synovitis are all caused by this cytokine, which plays an important role in inflammatory processes (Kyburz & Finckh, 2013). This is important because it causes synovial inflammation.

Table 1: Cytokine, autoantibody and other mediators associated with RA (Kumar et al., 2016):

Mediators in cells	Explanation
COX-2	Prostaglandins (inflammation mediators) are transferred to arachidonic acid by the isoenzyme Cyclooxygenase-2. (Rahman et al., 2017).
TNF-alpha	Tumor necrosis factor-alpha inhibits GM-CSFF and inflammatory cytokines.
IL-1	At first, this modulates the inflammatory cytokines (Rahman et al., 2017).
IL-2	After stimulation, T cells are removed.
IL-6	This regulates the inflammatory cytokine at first (Rahman et al., 2017)
IL-15	T-cell proliferation activation.
IL-16	Re-energized CD4-expressing cells.
IL-17	Promotes macrophage expression of pro-inflammatory cytokines.
IL-18	IFN-ɣ circulation (Rahman et al., 2017).
IFN-ɣ	Facilitate the creation that promotes pannus and synoviocyte-like fibroblasts (FLS).
OPG	Osteoprotegerin is a RANK decoy receptor that suppresses Osteoclastogenesis in the body (Rahman et al., 2017).
GM-CSF	Granulocyte myocyte protein that stimulates granulocyte or Macrophages development (Rahman et al., 2017).
VEGF	A cytokine that also functions as a steroid hormone is found in the cell membrane.

Chapter 4

Rheumatoid arthritis (RA) treatments from the previous generation

4.1 Non-steroidal anti-inflammatory drug:

The most popular therapy for early-stage RA is nonsteroidal anti-inflammatory medications (NSAIDs). Based on their structure, they are divided into eight categories. Salicylate, naproxen, and ibuprofen are the most often given NSAIDs for RA therapy. They're recommended because they swiftly reduce pain and inflammation. They function by preventing the formation of prostaglandin (PG) by blocking the cyclooxygenases COX-1 and COX-2 (Bulletin, 2006). Inflammation and discomfort in the afflicted joints are caused by the enzymes Cox-1.

COX-2 is the enzyme that makes PGs, which have been the irritants' intermediates. COX-1 produces prostaglandins after COX-2 produces PGs, which affect the gut's biological process by maintaining the mucosal barrier and GI fluids (Khaled et al., 2010). The digestive system, blood platelet, the extraction portion, and arterial endothelium cells are all regulated by COX-1. COX-2 mobility, which also affects COX-1, is associated with the therapeutic efficacy of NSAIDs (Agha, 2016).

As proven by Celecoxib as well as other COX-2 inhibitors, particular NSAIDs are superior, and COX-2 is preferable to COX-1. Even though several COX-2 blockers have been demonstrated to put COPD patients at risk (Agha, 2016). Figure 3 shows how NSAIDs inhibit the formation of arachidonic acid, which is the precursor to COX-1 and COX-2. COX-1 and COX-2 have been regarded to be the most effective in the development of inflammation for a long time.

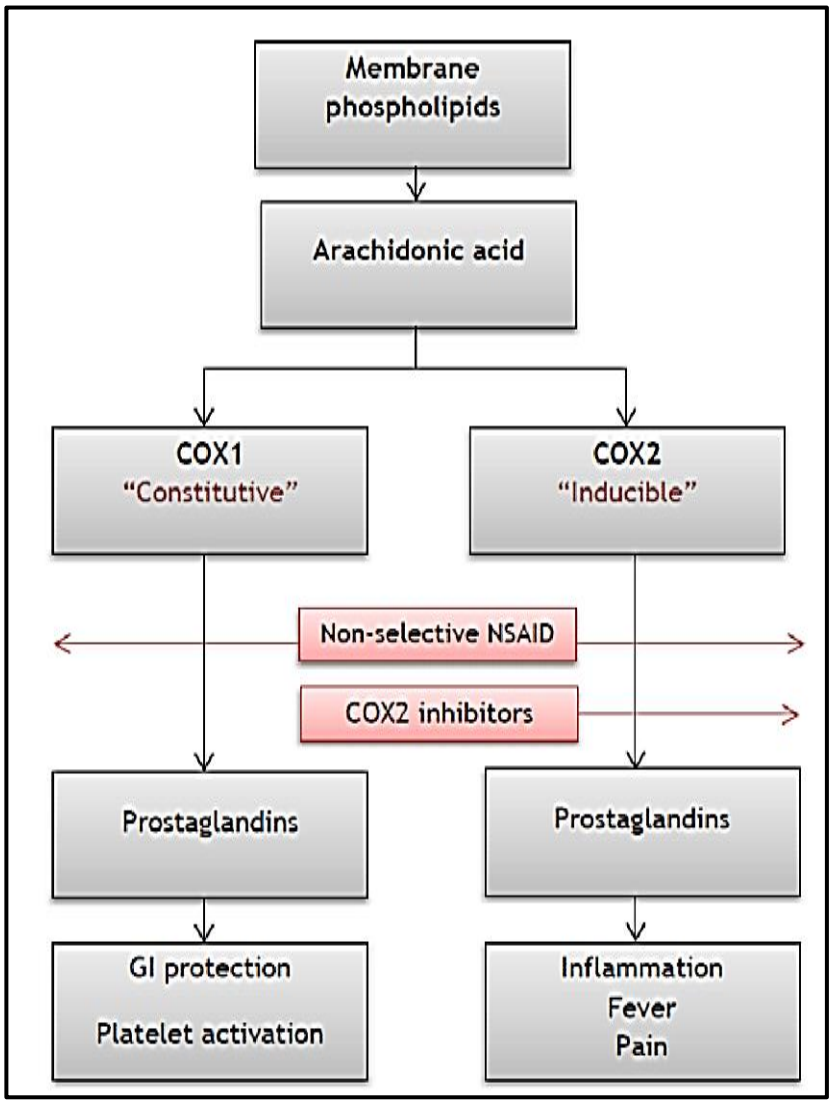

Figure 4: The mode of action of NSAIDs (Agha, 2016)

4.2 Glucocorticoids (GCs):

The use of glucocorticoids (GC) to reduce inflammation has the potential to be beneficial because of this property, GCs are frequently used to treat rheumatoid arthritis. It is usually administered in tiny dosages to minimize toxicity (Kapoor et al., 2014). Inflammation is combated by GCs by reducing the inflammatory expression of genes in all kinds of inflammation. Interfere with the body's immune system's ability to reduce chronic inflammation by fibroblastic and endothelial cells (Gouveia et al., 2015). They can participate in two sorts of activities: genomic and non-genomic. Through the genetic mechanism, GCs act as an anti-inflammatory and immune system suppressor. Although GCs can treat RA, they also have a slew of negative side effects, as seen in Figure 4. As a result, GCs are given out regularly.

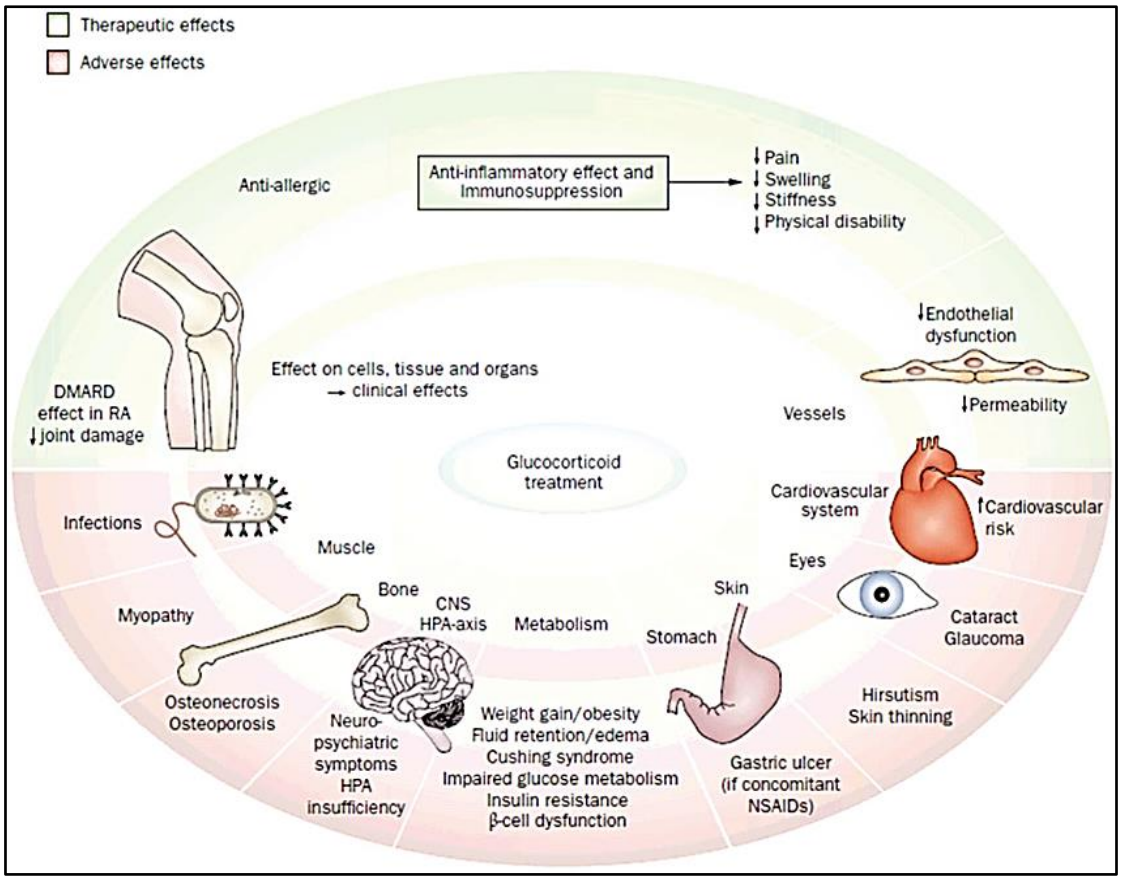

Figure 5: GCs-related side effects (Reviews, 2006)

4.3 Disease-modifying anti-rheumatic drugs or DMARDs:

DMARDs are quite effective in treating RA and they take a long time to work and can take months. Various strategies are used by different types of DMARDs to demonstrate that they are effective (Kapoor et al., 2014). Physiological DMARDs target a biological component generated during an immune response. TNF-alpha blockers are routinely used in combination with this kind of DMARD (Manjanna et al., 2010). Although methotrexate resistance affects 40% of patients, modified DMARDs like it operate within the cell (Rahman and colleagues, 2016). Each DMARD has its own set of side effects on various organs, such as the gastrointestinal system, kidneys, and liver.

4.3.1 Methotrexate or MTX:

In the year 1988, the FDA (Food and Drug Administration) approved it as a RA treatment drug because of its minimal toxicity, consistency, efficacy and long-term therapeutic value, it is a cost-effective treatment option. MTX is regarded as an excellent pharmacological treatment for RA (Abbasi et al., 2019). In the therapy of RA, all four actin pathways for MTX are

effective. To begin with, it is an anti-folate chemical that may hinder the proliferation of immune cells as well as lymphocytic cells which are an alternative to inflammatory tissue. Immunosuppressants are employed because extracellular altitude nucleosides, which generate anti-inflammation, are enhanced (Abbasi et al., 2019). Methotrexate is administered to several persons with RA who have not responded to NSAIDs (Bulletin, 2006). Although it is a useful therapy for a small percentage of patients, it has substantial side effects in others, including damage to the liver and bone marrow. Patients with RA are given 15– 25 mg of MTX orally once a week (Chan & Gladman, 2018). Because 80 percent of MTX is excreted through the kidneys, it might produce long-term adverse effects include recurrent oral infections, liver illness and renal disease if used regularly. When compared to other DMARDs, it is highly recommended since it is less expensive, less hazardous, and more effective. As a result, it is regarded as the gold standard in the treatment of RA.

4.3.2 Sulfasalazine or SSZ:

SSZ is cleaved to 5- aminosalicylic acid or sulfapyridine by bacteria in the colon. A 500 mg dose of SSZ is taken orally once a day. The dose can be increased to 1500 mg twice daily if tolerance has been established. Nausea, vomiting, diarrhea, stomach discomfort, neutropenia and thrombocytopenia are all common adverse effects of this medication (Reviews, 2006).

When SSZ is digested in the colon, it produces 5- aminosalicylic acid which inhibits COX-1, COX-2, LOX, PAF, mediators, as well as IL-1 and TNF-alpha, reducing inflammation and discomfort (Guo et al., 2018).

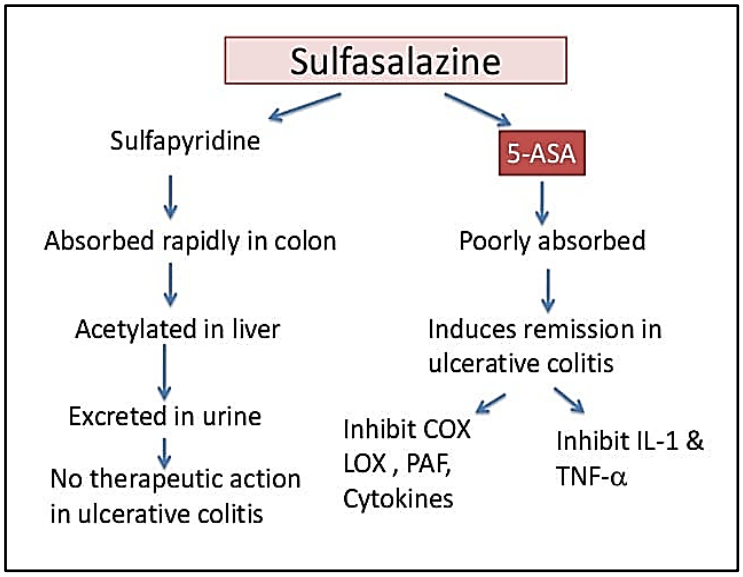

Figure 6: Sulfasalazine's mode of action (Abbasi et al., 2019)

4.4 Natural treatment for rheumatoid arthritis:

However, there are a variety of old and new generation medications available to treat RA, they all have bioavailability, effectiveness, and toxicity concerns. As a result, researchers have developed several plant extracts with anti-RA effects. Patients who have not seen any improvement while using traditional or biological medications are more likely to seek CAM treatment (Wadekar et al., 2015). In the treatment of RA symptoms such as inflammation, joint discomfort and joint degradation, 60–70% of RA patients choose complementary and alternative medicine (CAM) over conventional medication. Herbal RA treatments, on the other hand, now are widely utilized worldwide (Wadekar et al., 2015). For the treatment of RA, homeopathic medicines that interact with inflammatory receptors are routinely recommended (Wadekar et al., 2015). Several herbal therapies are used to treat RA according to the researchers, but the effects are inconsistent and vary from person to person (Curtis et al., 2004). Plant-based medications differ from conventional and biological therapies in several ways. Shen and his associates (Shen et al., 2019). Although they may cause diarrhea, difficulty breathing, and anxiety in certain people, Moringaceae, Clusiaceae and Verbenaceae have a lesser impact on RA therapy than NSAIDs.

However, when they are given a mixture of Oleaceae and Liliaceous, they have fewer side effects (Hosein et al., 2016). The anti-RF impact of Rhaphidophora glauca plants was assessed using a heat-induced approach, with the anti-arthritic activity of 53.16 percent, 69.62 percent, and 62.03 percent in their highest concentrations, respectively, when compared to NSAIDs (Hajja & Bahlouli, 2018). In comparison to Diclofenac–Na, they also demonstrate 49.05 percent, 71.9 percent, and 60.22 percent membrane-stabilizing action (Hajja & Bahlouli, 2018). Glycyrrhizin glabra aqueous extract has anti-oxidant properties that protect proteins, lipids, DNA, cartilage, and extracellular collagen, all of which are damaged in RA patients. In radiographic imaging of RA, it is less effective than MTX medications (Assunçomiranda et al., 2013). Depending on the patient's needs and historical experience, different combinations of plants are utilized for different methods (Moussaieff & Mechoulam, 2009). According to several data, plant-based extracts are occasionally utilized as a key component in the creation of dependable drugs (Price et al., 2009).

Chapter 5

Newer RA treatments Biological Agents

By decreasing the production of cytokines that cause additional inflammation in RA patients' joints, genome editing develops biological agents. In the therapy of RA, biological agents are employed. IL-1 inhibitors, TNF-receptor antagonists, IL-17 inhibitors, co-stimulant blockers, anti-B cell medicines, and JAK inhibitors are only a few examples (Thakur et al., 2018). Patients with severe RA who have not improved while on DMARD therapy are given biological medicines (Firth, 2011). The biological medicines used to treat RA target all of the receptors and pathways are shown in Figure 6.

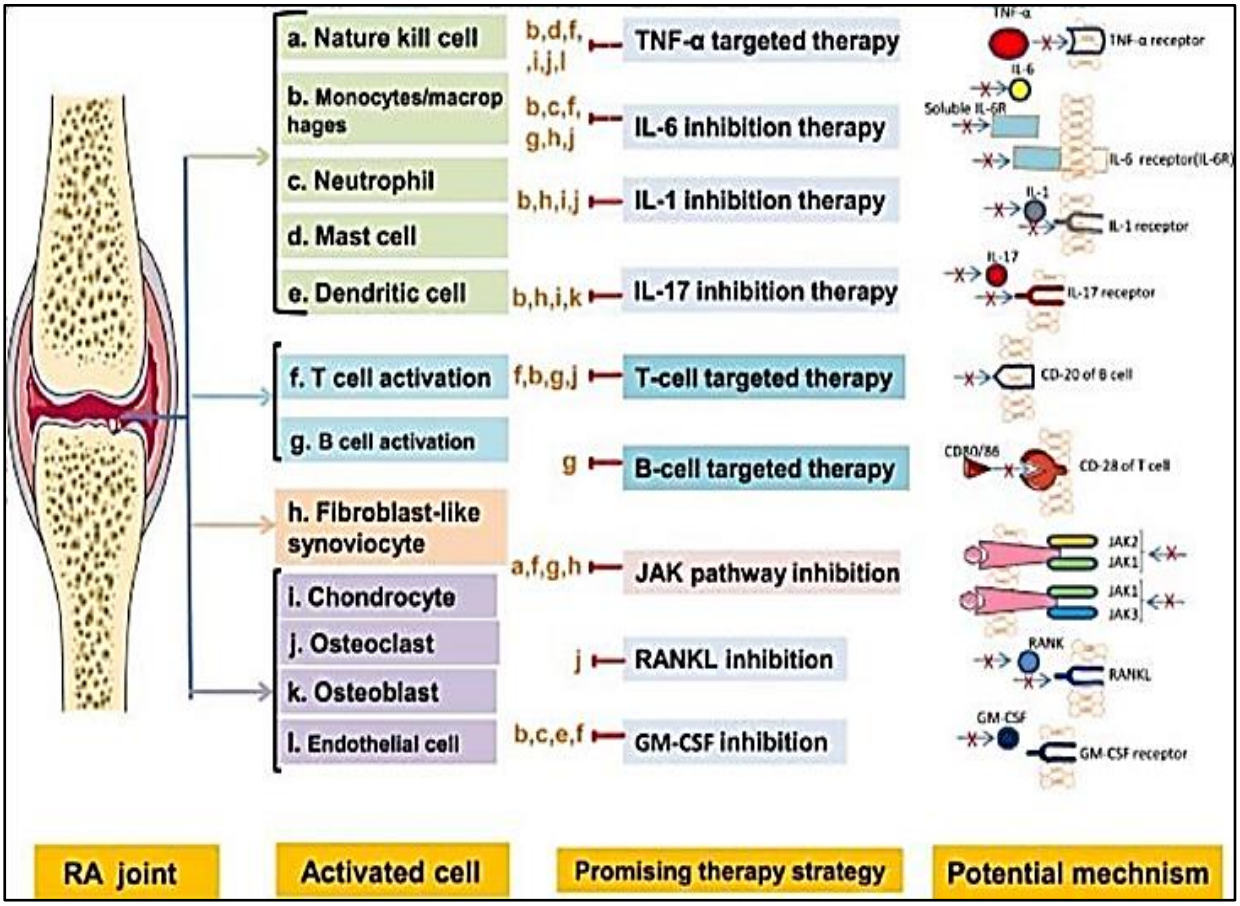

Figure 7: Biological agents' targeted receptors and pathways (Guo et al., 2018)

5.1 Inhibitors of tumor necrosis factor (TNF):

TNF-, or tumor necrosis factor-alpha, is indeed a cytokine that has been linked to the onset of RA. This stimulates macrophages cells which activate T cells. TNF- stimulates the growth of fibroblastic and osteoplastic cells in articular cartilage and bone, as well as the differentiation

and proliferation of osteoclast cells (the main cells involved in bone disintegration) (Atzeni et al 2013). Tissue necrosis factor is made up of pro-TNF which becomes active when the TNF-converting protein cleaves its pro-domain (Atzeni et al., 2013). The TNF receptors TNFR-1 and TNFR-2 are two different types of TNF receptors. On TNFR-2, there are 5 times as many attractions as on TNFR-1 (Atzeni et al., 2013). Rituximab, golimumab, etanercept and certolizumab (CTZ) are the three drugs (Atzeni et al., 2013).

5.1.1. Infliximab:

By connecting to the TNF-alpha receptor, infliximab binds to soluble IgG1k and blocks pro-inflammatory factor cascade signaling. TNF-alpha cannot bind to the TNF-alpha receptor because the antibody binds to it (Figure 7). It takes an hour or two for the body to respond when a 3mg/kg anti-TNF chemical is injected into the veins (Abbasi et al., 2019). Patients who were administered infliximab exhibited four times as efficacy of those who were given MTX, according to the revised health assessment survey and Hamilton Depression Rating Scale (Miwa et al., 2016). Despite having fewer adverse medication responses and side effects, 16 percent of patients acquired anti dsDNA after using infliximab for 30 weeks, according to research published in the journals.

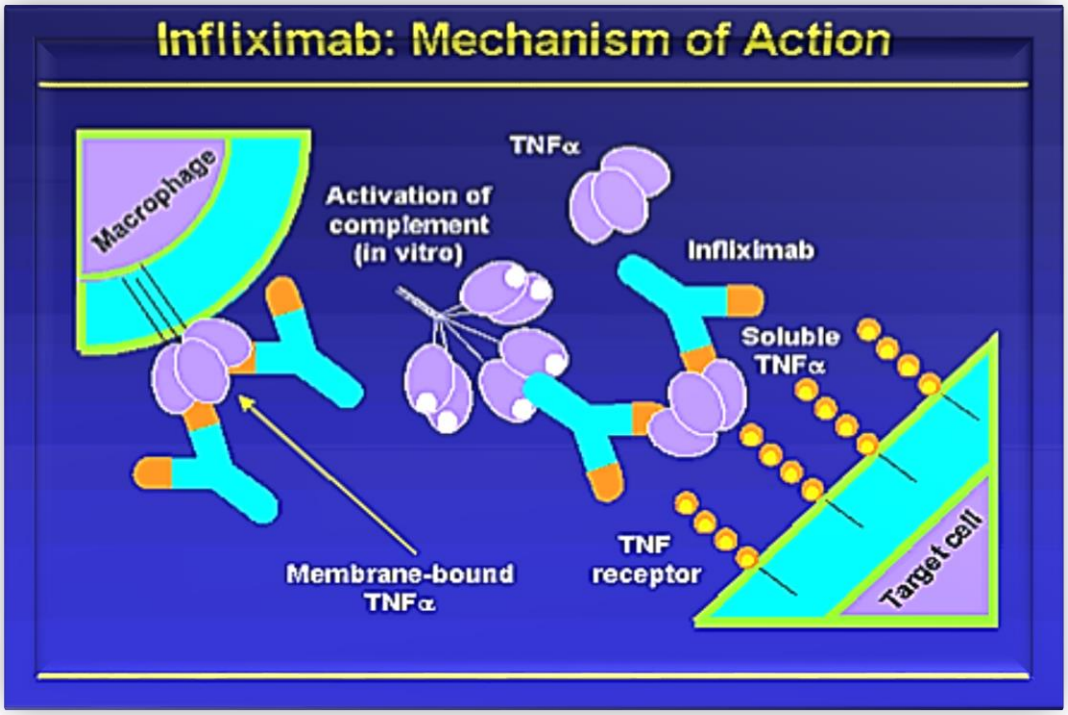

Figure 8: Infliximab's Action mechanism (Abbasi et al., 2019)

5.1.2. Adalimumab:

The FDA approved adalimumab, a genetically modified antibody that targets TNF as a RA treatment in 2003. Whenever injected into the subcutaneous layer of skin, adalimumab binds to TNF-alpha. TNF-biological alpha's function is inhibited and tumor necrosis factor leukocyte cells die (Figure 8) (Miyata et al., 2005). It appears to have a lengthy active shelf-life (10–20 hours) and could be administered twice a month in this layer of the skin for a maximum of forty milligrams by the patient. According to an algorithm comparing adalimumab therapy to MTX therapy, adalimumab therapy is preferable to MTX therapy because it has a lower risk profile and a reaction that is free of side effects. According to a Bayesian structured analysis including 1796 people.

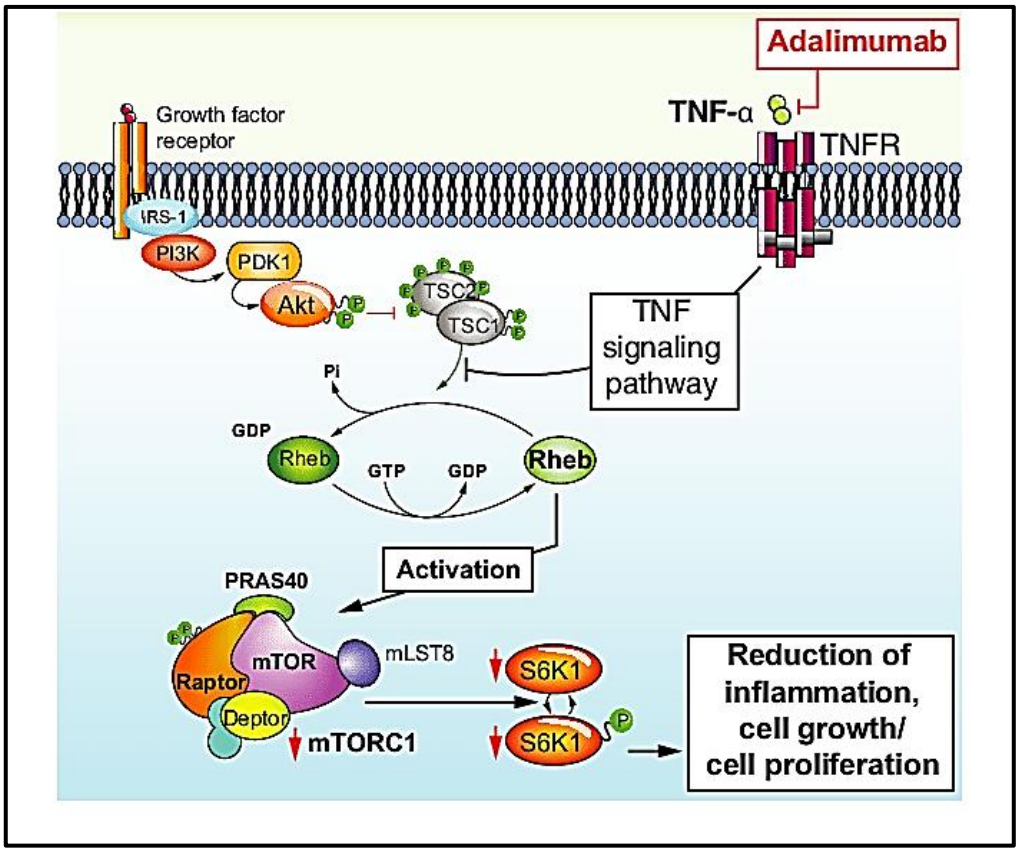

Figure 9: Adalimumab's mode of action (Abbasi et al., 2019)

5.1.3. Etanercept:

Etanercept is a fluid of the gene that encodes rea receptor that inhibits TNF- as well as to a lesser extent, TNF- by preventing TNF receptors from being activated at the cell surface. This is a 2 TNF and Fc-IgG1 combination with a long half-life that binds to TNF-alpha receptors (Figure 9) (Atzeni et al., 2019). TNF and TNF receptors may be easily bound by this mixture

of substances, limiting TNF-alpha function. Anti-TNF medication can be taken in doses of 25 mg twice a week or 50 mg once a week by the patient. Etanercept is significantly more effective than other anti-TNF medications due to its four-day half-life (Hughes et al., 2018).

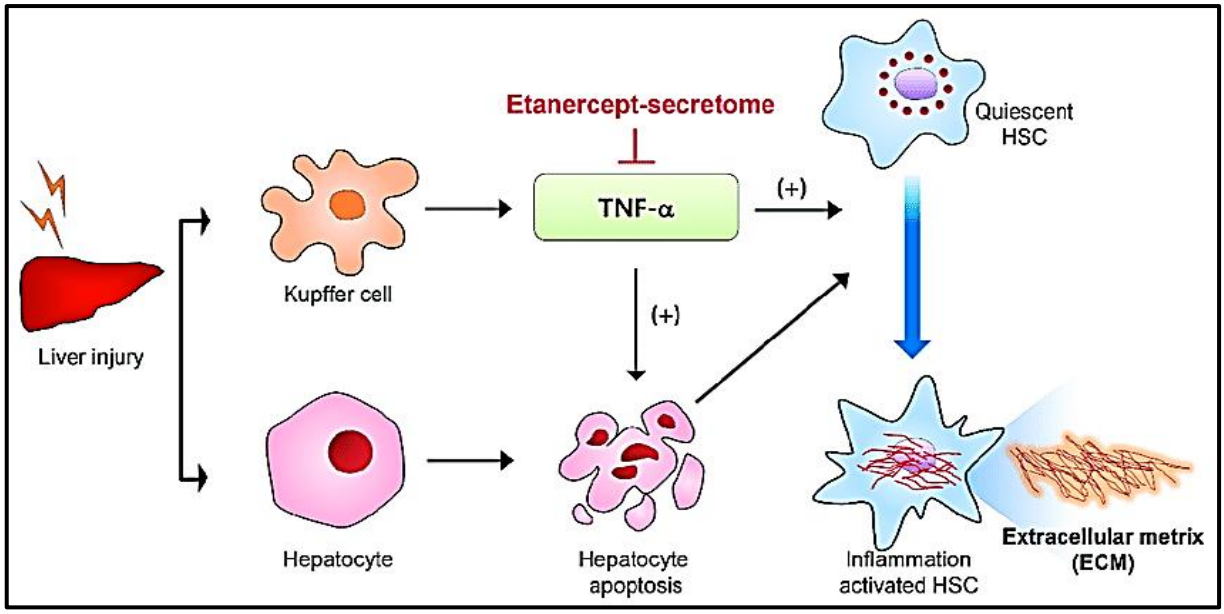

Figure 10: Etanercept's mode of action (Abbasi et al., 2019)

5.1.4. Certolizumab:

When membrane-bound TNF-alpha interacts with certolizumab pegol, the cytokine movement is reduced. As a result of this interference, TNF-alpha activity is lowered, as well as inflammation (Figure 10). Every two months, the patient receives CTZ injections. Certolizumab is still in its infancy (Guo et al., 2018).

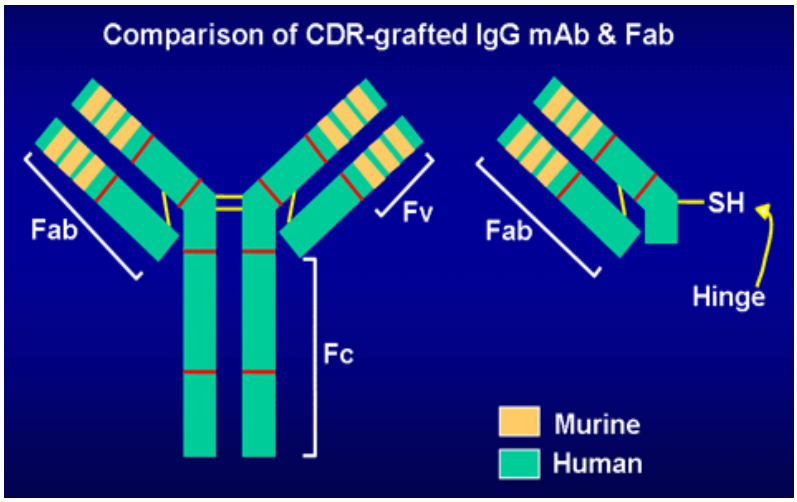

Figure 11: Certolizumab's mode of action (Abbasi et al., 2019)

5.1.5. Interleukin inhibitors:

IL-1 inhibitors:

A pro-inflammatory enzyme called IL1 is produced in the synovium of RA patients. At high doses, it will trigger fibroblastic and substantially exhibited activity. TNF-alpha and IL-1 both have a role in immune system activation, which contributes to inflammation during illness. Targeting specific receptors, IL-1 inhibitors reduce the therapeutic effect. IL-1 expression is greater in RA patients than in IL-1Ra individuals, which amplifies signals and causes pain. Inhibiting the IL-1R1 receptor lowers bone deterioration and tissue damage in RA patients by interrupting the IL-1 signal. TNF-alpha and IL-1 both regulate the activity of osteoclasts through modulating the nuclear factor kappa-B ligand-receptor activator (RANKL). A drug that combines IL-1Ra and other drugs is available (Anakinra). It inhibits approximately 95% of IL-1Ra receptors, lowering IL-1 production and preventing bone and tissue damage. 472 people were randomly allocated to one of two groups (RCT) in a randomized clinical trial (J. R. Curtis & Singh, 2011). By collecting data from weeks 24 and 48, the IL-1 inhibitors group showed a 38% reduction in joint erosion progression and a 58% reduction in joint space narrowing when compared to the placebo group.

IL-6 inhibitors:

IL-6 is a protein that has a function in cell regeneration and inflammation. The pathogenic mechanism for RA is that IL-6 increases pannus production by increasing bone resorption and vasodilating endothelial growth factors, which promotes osteoclasts and leukocyte oxidation. Tocilizumab seems to be a local or intravenous anti-IL-6 medication. In the Japanese study, 306 people were split into two groups clinical trial, with one group getting TCZ and the other receiving conventional DMARDs (Kim et al., 2015). The TCZ group had a TSS (total modified Sharp score) of about 2.3 after 52 weeks, compared to the DMARDs group, which had a TSS of around 6.1 (Kim and colleagues, 2015). A monoclonal anti-IL-6 antibody that has shown to be effective in clinical studies and is currently in the third phase. It opens up new avenues for research into the function of cytokine hindrance rather than cytokine receptor limitation in RA (Guo et al., 2018).

IL-17 inhibitors:

Interleukin-6 is a T-cell-derived hormone that circulates in the synovium of RA patients and is produced by activated T cells (Lubberts et al., 2005). The ability of numerous cell types to

release various cytokines and chemokines is enhanced by IL-17, which plays a role in cell-induced irritation. Furthermore, when IL-17 is coupled with IL-1 and TNF In terms of cytokine expression and joint disease, it appears to have additive or even synergistic effects. T-cell IL-17 may also be a potent inducer of nuclear factor kappa-ligand receptor activator, a key cytokine involved in skeletal disintegration and osteoclastogenesis. IL17 appears to have an activity that is independent of IL-1 in inducing synovial hypersensitivity and inflammation.

Exploratory joint discomfort causes joint deterioration. Furthermore, it helps to delay the onset of joint pain, IL-17 can be regarded as an important target for the treatment of serious joint pain. Individuals from the IL-17 family have been discovered, which may help to increase the role of this cytokine family in the treatment of back pain (Lubberts et al., 2005). There were 1733 persons in six randomized, double-blind, placebo-controlled phase III studies (1153 patients were administered IL-17 inhibitors vs. 580 placebo patients) (Koenders & Joosten, 2006). The ASAS20 responses were received (Rate Ratio = 1.63, 95 % Confidence Interval 1.45 to 1.84) and supplementary endpoint ASAS40 number of responses (Vulnerability Ratio = 2.12, 95 percent Confidence Interval 1.75 to 2.56) were significantly improved relative to placebo during week 16 of the IL17 inhibitor combination (C. L. Curtis et al., 2004). In terms of safety, IL- 17 antagonists were associated with higher treatment-emergent side events (Risk Ratio = 1.11, 95 percent Ci 1.01 to 1.22) and non-severe infections (Risk Ratio = 1.82, 95 percent Ci 1.40 to 2.37) than placebo therapies. After taking an IL-17 inhibitor, no increased risk of any negative outcomes, including mortality, was discovered (Singh, and J. R. Curtis, 2011).

5.2 Blockers of interleukin:

Abatacept is the newest addition to the co-stimulation inhibitor family with biological regulators for suffocation aggravation. Unlike former organic specialists, co-stimulation blockers function by interfering with co-stimulatory signals, which are essential for T cell activation (Abbasi et al., 2019). When Abatacept is used with Methotrexate, its efficacy is increased (Abbasi et al., 2019). Abatacept is administered intravenously every half hour in 500–1000 mg dosages. 568 participants were allocated into two groups in a randomized clinical trial (RCT) (Westhovens & Verschueren, 2008). For four weeks, they were given a placebo and abatacept (Westhovens & Verschueren, 2008). When compared to the placebo group, the abatacept group demonstrated a 45 percent reduction in joint erosion advancement and a 78 percent reduction in joint space narrowing (Westhovens & Verschueren, 2008).

5.3 Blockers of co-stimulation:

Abatacept is now the most recent member of a group of biological mediators for suffocating aggravation known as co-stimulation blockers. In contrast to former organic specialists, co-stimulation blockers work by interfering with co-stimulatory signals, which are essential for T cell activation (Abbasi et al., 2019). Combining Abatacept with Methotrexate improves Abatacept's efficacy (Abbasi et al., 2019). Abatacept is administered intravenously in doses of 500–1000 mg every half hour. A total of 568 patients were allocated into two groups in a randomized clinical trial (RCT) (Westhovens & Verschueren, 2008). For four weeks, they were given a placebo and abatacept (Westhovens & Verschueren, 2008). When compared to placebo therapy, the abatacept group demonstrated a 45 percent reduction in joint erosion advancement and a 78 percent reduction in joint space narrowing (Westhovens & Verschueren, 2008).

5.4 Inhibitors of B-cells:

Rituximab, also known as an anti-CD20 monoclonal antibody, is a B-cell inhibitor that works by lowering the number of B cells in the body. Rituximab has been authorized by the FDA as a therapy for RA, methotrexate is used (Abbasi et al., 2019). Rituximab infusions of 1000 mg are required twice a month. Rituximab has fewer adverse effects and is more effective than MTX alone in treating RA, according to studies (Abbasi et al., 2019). However, reveal a part of the body that is impacted by reaction (Abbasi et al., 2019). North American Consortium of Rheumatology researchers. Two groups of patients participated in the Rheumatoid Arthritis Registry clinical research.

5.5 Inhibitors of JAK:

DMARDs are JAK inhibitors that are being updated for therapeutic options. Several cytokines in RA use the Janus kinase (JAK) and signals transducers and activators of translation (STAT) pathways to express their pathogenicity, which can be inhibited by JAK inhibitors, which have proven to be beneficial in the treatment of RA. In the therapy of RA (Guo et al., 2018). Tofacitinib is a medication used to treat rheumatoid arthritis patients who have JAK inhibitors. Tofacitinib inhibits JAK-3 and JAK-1 rather than JAK-2 (Guo et al., 2018). Tofacitinib has a three-hour half-life and is used orally by 74% of patients. The drug metabolic enzyme cytochrome P450 3A4 (CYP3A4) is involved, and the kidneys eliminate 30% of the medicine. Tofacitinib 5 mg has been authorized by the FDA for the treatment of early-stage RA (Guo et al., 2018). Contamination, hematologic and hepatic problems, and Tofacitinib association were

the most prevalent adverse events, with toxic effects and pollutants being questioned (Guo et al., 2018). JAK-1 and JAK-2 inhibitor baricitinib is another oral JAK-1 and JAK-2 inhibitor. During the FDA approval process, all 7 Phase III randomized control trials (RCTs) of tofacitinib established the effectiveness of JAK1 or JAK3 inhibition in RA. ORAL-START had substantially higher ACR20, ACR50, and ACR70 response rates with tofacitinib 5 mg and 10 mg BD at 6 and 24 months when compared to MTX monotherapy (Harrington et al., 2020). In the ORAL-SCAN analysis, tofacitinib was shown to be more effective than placebo, despite the baseline dosage of methotrexate (Harrington et al., 2020). Tofacitinib with MTX did not outperform adalimumab plus MTX in ORAL-STRATEGY. Tofacitinib treatment, on the other hand, did not work as effectively as adalimumab combined with MTX (Harrington et al., 2020). This shows that the synergism of tofacitinib and MTX is superior to tofacitinib monotherapy in terms of disease control in patients with moderate than severe RA (Harrington et al., 2020).

The modified van der Heijde Total Sharp Ratings were employed to assess damages and track the advancement of structural joint frameworks (Harrington et al., 2020). The ORAL-START research found that tofacitinib monotherapy was more efficacious than MTX treatment at preventing structural progress. Osteoclast differentiation factor (ODF) is a protein that regulates the development of DMab, an Autoantibodies antibody essential for the inhabitation of a bone remodeling cycle, is among the most widely utilized osteoclast differentiation medicines. It binds to the NF-kB substance (RANKL), a cytokine that has a role in the production of osteoclasts and bone disintegration. Associated to a major problem with DC survival. Th17 cells because of bone loss, which is why RANK was developed (Zhang et al., 2018b).

In RA, B cells also produce a nuclear factor kappa-ligand receptor activator, which accelerates bone deterioration. Finally, the nuclear factor kappa-ligand receptor activator is well-known for aiding in the differentiation of target cells, which increases immune acceptance. This NF-kappa ligand antagonist receptor stimulator may help to boost immunity. TNF and RANKL interact due to synovial cell dysplasia-related protein, resulting in an osteoclast. In an experimental study, DMab was shown to reduce both localized and overall bone loss in people with RA. To determine the amount of inhabitation that causes bone loss, a clinical test is required. Lower blood Ca^{2+} and phosphate levels, muscle spasms and cellulitis.

Chapter 6

Conclusion

RA is a serious disease that affects a large percentage of the world's population (Quan et al., 2008). There have been several studies conducted to discover a stable RA therapy that can treat this illness without causing any adverse effects. The current management choices, such as NSAIDs, corticosteroids and DMARDs are effective therapeutic options but they are associated with several side effects and disadvantages (Santos & Morand, 2006). In long-term usage, NSAIDs induce stomach disturbances, corticosteroids because of impaired wound healing and peptic ulcers. After using DMARDs for a long time, people develop adverse effects such as liver and renal problems (Thakur et al., 2018). After the introduction of biologic DMARDs, the area of RA therapy has altered dramatically. The advent of biologics in the treatment of RA has changed the game completely. These compounds provide a long-lasting and potent therapeutic effect. Two JAK inhibitors (tofacitinib and baricitinib) have recently been approved for clinical use in addition to standard treatment. According to various studies, JAK inhibitors have the potential to outperform standard biologics. It's too soon to tell if these compounds will eventually take the place of biological drugs. Regarding their benefits, biologics have fewer adverse effects, including immunological suppression, making patients more susceptible to bacterial and parasite infections (Thakur et al., 2018). DMARDs, despite their poor effectiveness and adverse effects, are favored in Bangladesh for the treatment of RA due to the high cost of biologics (mainly NSAIDs and corticosteroids) (Alamgeer et al., 2015). As a result, further clinical studies and research are needed to determine its efficacy while also minimizing adverse effects and costs when used to treat RA.

Chapter 7

Future Studies

A group of monoclonal antibodies is currently available to treat RA. Patient acceptability is minimal because the vast majority of them are delivered via intravenous and intramuscular methods. More research into the method of administration of biological medicines is made in the future that will increase patient acceptance. Moreover, there are numerous options for reducing side effects and improving the potential of biologics. Other biological receptors linked to Arthritis might all be targeted and inhibitors of these receptors could be used to treat the disease.

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