Importance of Biologically Active Agents over Other Therapies in Rheumatoid Arthritis- A Review

By

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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.
4. I have acknowledged all main sources of help.

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Approval

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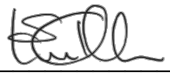

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Ethics Statement

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

Abstract

Rheumatoid arthritis (RA) is an autoimmune disease which causes chronic inflammation and joint pain and will eventually lead to serious damage in the bone and cartilage of the affected joint. Many people around the world develop RA in older age. RA usually affect the joints like- elbow, shoulder and metacarpophalangeal joints in the patient. Previously with conventional therapy only the symptoms of RA was treated. However, now-a-days with biological disease-modifying anti rheumatic drugs (bDMARDs) the reason for causing RA is treated by targeting the biological receptors like- TNF-alpha, IL-1 and IL-6 etc. In this review article we are reviewing the benefits of using biological disease-modifying anti rheumatic drugs over the conventional treatment of RA.

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

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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
ETN:	Etanercept
RANKL:	Receptor activator of nuclear factor kappa-β ligand
Anti-CCPs:	Anti-cyclic citrullinated peptides
DMARDs:	Disease-modifying anti-rheumatic drugs
ACR:	American College of Rheumatology
ASAS:	Assessment of Spondyloarthritis International Society
RCT:	Randomized controlled trial
GCs:	Glucocorticoids

Chapter 1

Introduction

1.1 Brief about rheumatoid arthritis:

Rheumatoid arthritis (RA) categorized as an autoimmune disorder which is characterized as prolonged inflammation in joint and eventually the root of serious incapacity and early mortality. Bone loss occurs because of the prolonged inflammation in synovial membrane of joints, damage of articular cartilage also long-lasting alterations in the aggregation along with extra-articular infection (Kumar et al., 2016). RA develop when people are getting older. Men are less vulnerable than women and they have 2 to 3 percent higher chance to grow it. In Bangladesh people of different age groups are affected by RA but most of them are between 30 to 50 years age range (Alamgeer et al., 2015). Huge joints in the body like the elbow, shoulder and metacarpophalangeal joints are more susceptible for growing RA (Scott, 2007). Human body gets confused by infectious condition which leads to immune system disorder and the immune system starts attacking the joints of the body. Although the real reasons are still unknown. According to the researchers, two chemicals- tumor necrosis factor (TNF) and interleukin-1 in the body are mostly responsible for RA. They activate organism responsible for immunity and cause RA (Yung et al., 1995). Symptoms like stiffness, swelling and pain can occur in multiple joints like knees, wrists, hands shoulders, feet which develop slowly or it can happen all on a sudden (Greenwald et al., n.d.). It is really important to identify the disease as the symptoms occurred in RA is very similar to other diseases. For this reason the identification is done through lab tests, x-rays and clinical examination. Early treatment is required so that it cannot distort fiber like connecting tissues of the joint and that will ultimately damages the bones (Abbasi et al., 2019).

1.2 Types of rheumatoid arthritis

To identify the type of RA medical results of x-rays and laboratory tests of the patients is required. RA can be distinguished by the presence or absence of rheumatoid factor (RF). RF is an antibody or a protein that is synthesized by the immune system of human body. Without the positive result of RF a human can have RA (Khaled et al., 2010). According to a statistical report, more than 80% of rheumatoid arthritis patient have been tested positive for rheumatoid factor (RF) which is called positive (or seropositive) rheumatoid arthritis. On the other hand,

some patient tested no presence of RF which is seronegative or negative rheumatoid arthritis (Klein & Gay, 2013).

- Seropositive or Rheumatoid Factor Positive

If the outcome of a patient's blood test reveals that they produce a particular protein known as rheumatoid factor, the doctor must recognize that the body of the patient produces an allergic reaction to his or her healthy tissues (Jo, 2017). RF is detected from the same sites where antibodies are present, RF is detected. If there are anti-CCPs or ACPAs in the blood of a patient and he or she still has physical signs, the patient is successfully diagnosed with RA (Yu et al., 2019). Anti-CCPs stand for citrullinated anti-cyclic peptides, and anti-citrullinated protein antibodies stand for ACPAs (Malaviya & Sawhney, 2014). Anti-CCPs are present in the human body as the molecular structure of the proteins in the body changes (Hosein et al., 2016). These antibodies are present in 60 to 80 percent of RA; they also act as an early RA predictor for patients (Jo, 2017). In blood samples, antibodies can be detected 5 to 10 years before any clinical signs occur. When there is an antibody for RF in person, RA is compliant. A common sequence of amino acids is found in seropositive or anti-CCP positive patients and is located inside the body's HLA genomic site.

- Seronegative or Rheumatoid Factor Negative

The patient may still have RA when the patient's blood test result demonstrates the absence of RF or Rheumatoid Factor Negative (Seronegative) RA (Malaviya & Sawhney, 2014). In this situation, only an x-ray report, clinical indications and other pathological tests can be used to diagnose RA (Malaviya & Sawhney, 2014). Compared to patients with Seropositive RA, patients with RF negative have a less chance of occurring RA (Klein & Gay, 2013).

1.3 Necessity of treating rheumatoid arthritis:

RA is an autoimmune disease that mostly affect the joints of the patient. Chronic synovitis condition in RA influence the joint damage almost in all patients. Cytokines are activated by the production of synovium in inflammatory cells that leads to that actuate multiplication of synovial fibroblasts and macrophages. The damage of bone and cartilage is not reversible, so it is very important to start treating the patient in the early stage of rheumatoid arthritis to minimize the damage (Kyburz & Finckh, 2013). Chronic synovial inflammation in rheumatoid arthritis (RA) leads to progressive damage to articular cartilage and bone, ultimately resulting in disability (Kyburz & Finckh, 2013). For this reason controlling the articular inflammation is

very important to prevent joint damage in rheumatoid arthritis patients (Kyburz & Finckh, 2013).

1.4 Types of treatments available for RA and their limitations:

Rheumatoid arthritis patients take some type of medications which is categorized in five classes. They are: Non-steroidal anti-inflammatory drugs (NSAIDs); steroids; disease-modifying anti-rheumatic drugs (DMARDs); biologics; and Janus kinase (JAK) inhibitors.

Non-steroidal anti-inflammatory drugs (NSAIDs)

The pathogenesis of RA helps to treat the symptoms like – chronic joint pain, chronic inflammation and destruction of joints. Because they have painkilling, non-pyretic, and non-inflammatory activities, NSAIDs were previously the first choice (Lee & Bae, 2016). NSAIDs have smaller half-life if taken through the oral route (Viljoen et al., 2012). For this reason, many and more doses of NSAIDs are required to receive the preferred healing reaction that increases the risk in the gastrointestinal tract (Sofat et al., 2011).

Steroids (Corticosteroids)

During initial care, acting steroids, such as prednisone, are especially useful before other RA drugs have had an opportunity to take effect (often 12 weeks or more). One benefit of steroids is that it's possible to inject them into joints. With minimal side effects, injected steroids may provide targeted pain relief for one or two sore joints. Experts recommend that steroids be taken at the lowest possible dose and warn against depending on them for longer than required. The efficacy of steroids also decreases with time, indicating that the longer a person takes a steroid, the less likely it is to alleviate symptoms. Furthermore, people who have been taking steroids regularly for several months or years may experience side effects such as weight gain, blood pressure rises, diabetes, and heart disease.

Disease-modifying anti-rheumatic drugs (DMARDs)

By suppression of the immune system, disease-modifying ant rheumatic drugs (DMARDs) are used to delay or stop rheumatoid arthritis. For widely used DMARDs, generic names include: hydroxychloroquine, methotrexate, sulfasalazine, azathioprine, leflunomide. Methotrexate is frequently the first medicine given to newly diagnosed persons with rheumatoid arthritis. This drug is taken weekly by RA patients, alone or in conjunction with other drugs. For the treatment of certain tumors, high-dose methotrexate is sometimes used. RA patients use slightly lower

doses than patients with cancer. However, they also have many side effects, such as fungal disease and other physiological disorders for extended use (Miwa et al., 2016).

Biologics

The increasing elegance of RA remedy therapy is being generated by biological markers-infliximab, etanercept, certolizumab, adalimumab, golimumab, tocilizumab, anakinra, abatacept, and rituximab are classified by different biological markers (Periplocae et al., n.d.). In 60-70 percent of patients, TNF inhibitors were used in the MTX mixture (Van Jaarsveld et al., 2000). These are powerful techniques, especially in the early sickness ranges (Atzeni et al., 2013). TNF-alpha-inhibitors such as etanercept, infliximab, and adalimumab monoclonal antibodies are approved as a remedy by the FDA (Rahman et al., 2017). Rituximab, a chimeric CD-20 monoclonal antibody, has been correctly developed by concentrating on B cells in the RA remedy (Atzeni et al., 2013). Various clinical studies have confirmed their effectiveness in patients with RA (Chrubasik et al., 2007).

Janus Kinase (JAK) inhibitors

In the inflammatory phase of the immune system, JAK enzymes are necessary messengers. They cause inflammation when the JAK enzymes bind with other cells, called X cells. JAK inhibitors bind to JAK enzymes, stopping them from binding to X cells and preventing the process of inflammation.

Chapter 2

Aim and objective of the review:

The aim of the review is to –

- Aid the search for discovering new methods and find out the most effective anti-Rheumatoid arthritis drug that is used in the treatment of Rheumatoid arthritis throughout the world.

The objectives of the review is to -

- To highlight the importance of the biological agent which has been reported to reduce the sufferings of RA.
- The other objective is to understand the mechanism of biological agents to control RA.

Chapter 3

Pathogenesis and pathophysiology of RA

3.1 The pathogenicity for RA:

Pathogenicity for RA remains obscure. Numerous inflammatory mediators like- TNF-α (tumor necrosis factor-α), CRP or C receptor protein, CD40L, IL-18 and IL20, MCP-1 or monocyte chemoattractant protein-1, receptor activator of nuclear factor kappa-β ligand or receptor activator of nuclear factor-κB ligand fractalkine, MMP-9 and attachment atoms perform a crucial part in improvement of the illness. These are some responsible factors that causes the pathogenesis of RA. These factors are preclinical RA, genetic factors, and environmental factors(Thakur et al., 2018).

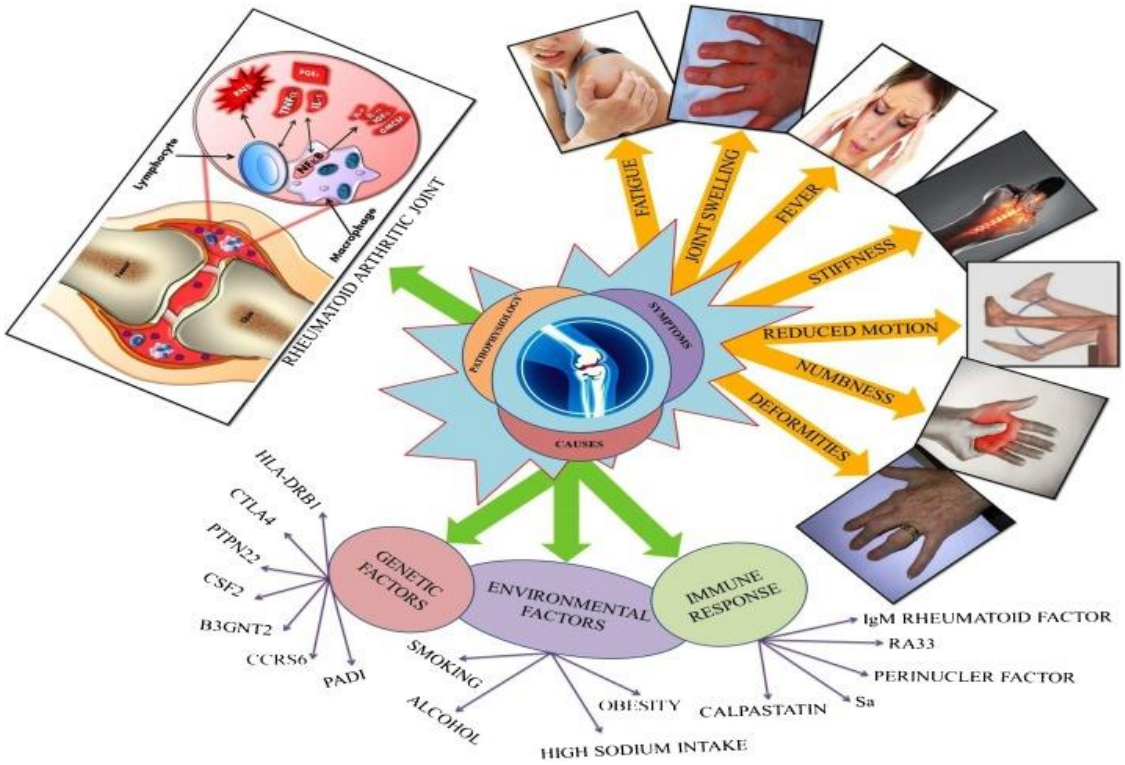


Figure 1: Factors that affect the pathophysiology of RA (Thakur et al., 2018).

Preclinical stage of RA:

The stage before arthritis development occurs is also known as preclinical RA. During this time, the level of pathological markers, including the auto-antibodies of the body, is increased (Kumar et al., 2016). In the pathogenesis of RA where RF is an important part (Thakur et al., 2018).There are six phases of RA development and this phases are also knows as the preclinical

stages (Van Steenbergen et al., 2013). These phase are- 1.Genetic risk factors for RA;2. Environmental risk factors for RA; 3.Systemic autoimmunity associated with RA; 4.Symptoms without clinical arthritis; 5.Unclassified arthritis; and 6. Rheumatoid Arteritis (Van Steenbergen et al., 2013). Although researches shows that, all the RA patient does not go through all the pre-clinical phases and the order of development of this stages can be different for each patient. Furthermore one patient can be in two preclinical stages parallel (Van Steenbergen et al., 2013). Significantly, it was also suggested RA only be used retrospectively. This suggestion was made because many people carry genetic factors that causes RA and some people are exposed in the environment that cause the growth of RA (Van Steenbergen et al., 2013).

Genetic factor:

The development of rheumatoid arthritis is also influenced by the patient's inheritance. Molecular biology studies indicate that histocompatibility complex (MHC) genes play a major role in pathogenesis (Thakur et al., 2018). The most important genetic component in MHC has been established in this disease as the HLA-DRB1 gene, where the sequences inside the molecule DRB1 are recognized as the shared epitope. They were encoded within the clusters of DRB1*04 and *01 (Thakur et al., 2018). Bare the other suppliers of genetics for RA pathogenesis (Kumar et al., 2016).

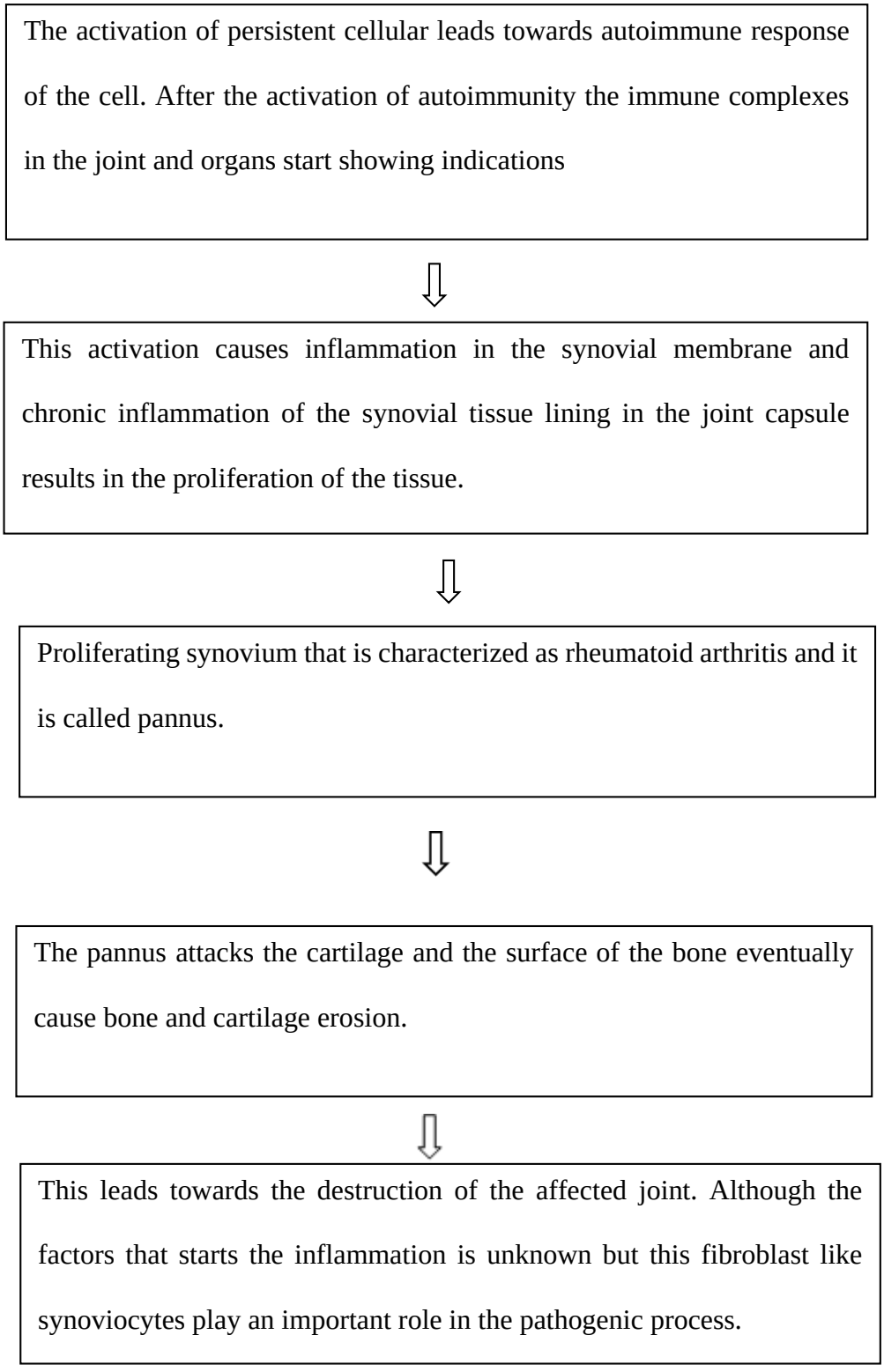
Environmental factors:

It is estimated that RA can be inherited in 60% of cases, but 40 percent cases occur due to environmental factors particularly smoking. Via long-term smoking, the risk of developing seropositive rheumatoid arthritis has increased. Smokers have two HLA-DRB1 alleles that are 21 times more likely to produce anti-citrullinated protein antibody (ACPA) in RA. Although it is not universal among all smokers, this gene does not appear in a wide group of smokers.

3.2 Pathophysiology:

Pathophysiology for RA is not discovered yet but primary event in this pathogenesis will initiate with complexes of immunity on stream of blood acknowledged as premature articular stage (Rahman et al., 2017). Damaging of the joint starts in synovial hyperplasia. Monocytes that are recruited inside the synovium and nearby distinguish into macrophages. Synovial cells are activated by the leukocytes which produce cytokines and causes the proliferation of synovial fibroblasts (Kyburz & Finckh, 2013).

A diagram is illustrated below for better understanding of pathophysiology of RA.



There are three phases of progression of RA them are- i) initiation phase, ii) propagation phase, and iii) tissue damage phase.

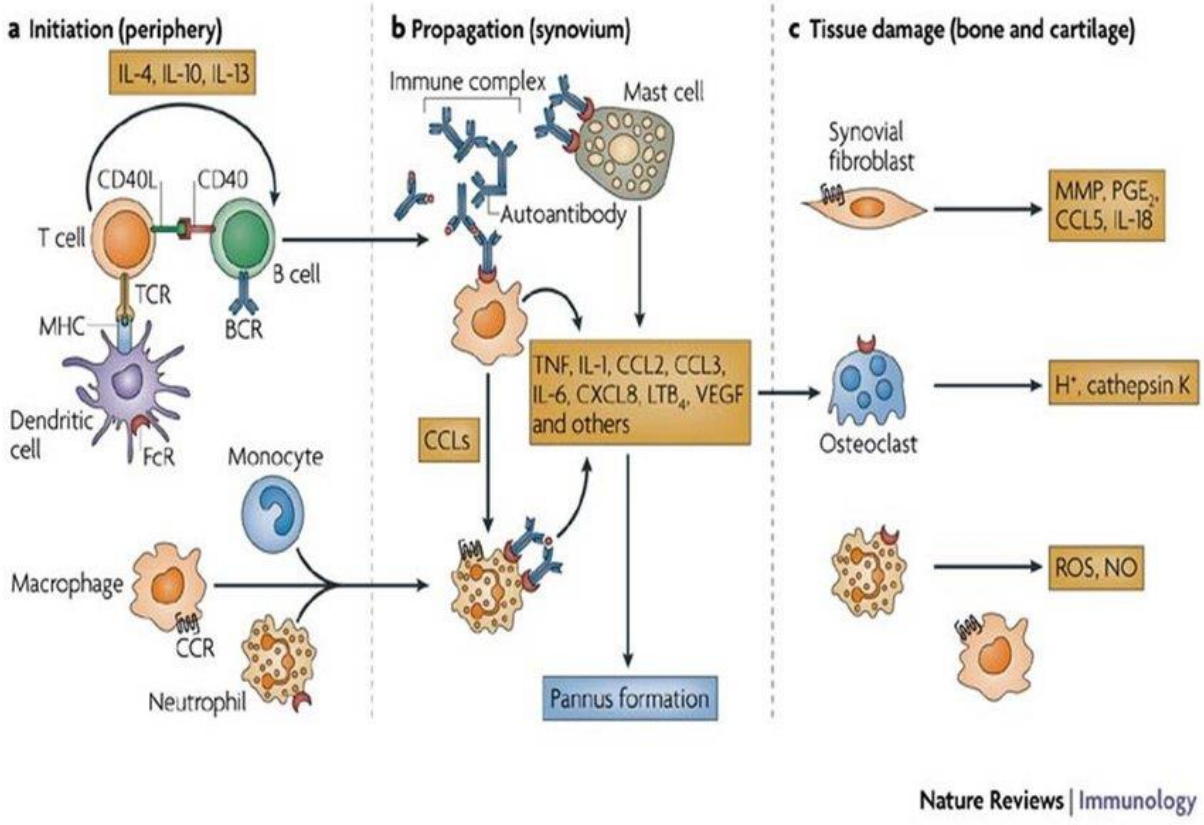


Figure. 2: Three phases of progression of Rheumatoid Arthritis (Harrington et al., 2020).

Initiation phase:

Osteoblastic resorption and bone osteoblast cell formation are typical and ongoing biological methods that contribute to bone remodeling (Rahman et al., 2017). In RA disease, this mechanism is disrupted by intervention in bone formation (Rahman et al., 2016). Macrophages are another donor antigen cells that are activated by CD4 helper T cells and discharge inflammatory cytokinesIL-1, TNF-alpha and IL-6 that are responsible for triggering multiple nucleated cells of osteoclastogenesis and osteoclastis that are formed by fusion of cytoplasm for predecessor osteoclast that control their own biological condition in the human body and re-establish cytoplasm for predecessor osteoclast (Rahman et al., 2017). Moreover, the bone loss in the human body is recovered through osteoblast cells. The resorption of bone is triggered also through the cytokines IL-1 & IL-6TNF-a. All of these cytokines initiate fabrication of M-CSF, receptor activator of nuclear factor kappa-β ligand and make synovial joint cells and also trigger receptor activator of nuclear factor kappa-β ligand for osteoblastic cells to attach with associated receptor of RANK for maturating the cell (Rahman et al., 2017). In addition, general

organic material maintenance is also scrutinized in proportion to osteoprotegerin (OPG) transmitted from osteoblasts, which is an inhibitory component of osteoclastogenesis corresponding to the ligand RANKLL (Rahman et al., 2017). This can build blocks by deactivating RANKL in the route of osteoclasts (Rahman et al., 2017). After the nuclear factor kappa-β ligand receptor activator begins to separate osteoclasts under RA conditions, the osteoprotegerin ratio is reduced rapidly. Established osteoclast, which is a matrix that helps to secrete hydrochloric acid (HCl) along with cathepsin k. As a result of sustained joint injury, osteonectin and aggregation are damaged.(Boyce & Fuligni, 2007)

Propagation phase:

Articular cartilage is produced by an extracellular matrix and a couple of cells. Collagen type II, proteoglycans and aggregation are the primary ECM constituents (Zhang et al., 2018a). Activated macrophages generate pro-inflammatory TNF alpha, IL-1 & IL-6 cytokines that motivate synovial fibroblast cells to produce cartilage degradation enzymes (Klein & Gay, 2013). RA enzymes are used as a specific biological measure to classify cartilage degradation (Tanaka et al., 2012). There are separate cells located above the superficial site joint and important elements of the course of cartilage tissue devastation. TIMPs control and inhibit MMPs (Lam & Bayer, 1983). Therefore, their level of well-adjusted metabolizing cartilage to maintain physiological condition cartilage deprivation contributes to the impression of bone joints that cause bone sharpening, appendage or bone spur formation on the nodes of bouchard’s and heberden's (Zhang et al., 2018a).

Tissue damage phase:

Synovium is lenient elusive and resides within the joint layer in which lubricating synovial is found in the articular protective cavity (Figure 2) comprising three key components, such as a) cartilage: lenient, elastic headrest material remaining within the joint surface, (b) joint capsule: it contains intima coating plus chewy intima coating compressing and (c) atrium capsule: Dual synoviocytes such as type A and type B intima cells are present in the synovial membrane (Figure 2). Form A cells or macrophage cells that extract undesirable void elements, but Type B is FLS that produces essential items such as lubricating polysaccharides, i.e. hyaluronic acid and lubricating (Kumar et al., 2016). Fibrous sub-intima layers that support synovium layers include fibroblasts and macrophages. It is the initial position intended for inflammation that can lead to RA unique disruption of immune acceptance. They contain cytokines such as—GM-CSF, VEGF, IL-1, 6, and 17. This cytokine plays a significant role in synovial

inflammation and triggers synovial mononuclear cells, angiogenesis, and synovitis (Kyburz & Finckh, 2013). For synovial inflammation, this plays an essential and critical substantial role (Bayer et al., 1985).

Table 1: *Cytokine, autoantibody and other mediator associated with rheumatoid arthritis are described below* (Kumar et al., 2016)*:*

Mediators inside the cell	Explanation
COX-2	Isoenzyme Cyclooxygenase-2 is known to transmit prostaglandins (inflammation mediator) from arachidonic acid through the process (Rahman et al., 2017)
TNF-alpha	Tumor necrosis factor alpha is an inhibitor of GM-CSFF and inflammatory cytokines (Rahman et al., 2017)
IL-1	The inflammation cytokine is initially regulated by this (Rahman et al., 2017)
IL-2	Activation of T cell separation (Rahman et al., 2017)
IL-6	For the development of RF and ACPA autoantibodies by plasma cells that stimulate B cells (Rahman et al., 2017)
IL-15	Stimulation for the proliferation of T cells (Rahman et al., 2017)
IL-16	Energized CD4 expressing cells (Rahman et al., 2017)
IL-17	Increases the production of inflammatory cytokines by macrophages (Rahman et al., 2017)
IL-18	Regulates the IFN-ɣ (Rahman et al., 2017)
IFN-ɣ	Assist in the development and promotion of pannus and fibroblast like synoviocytes (FLS) (Rahman et al., 2017)
OPG	Osteoprotogerin is a biologically occurring decoy receptor of RANK which inhibits the osteoclastogenesis(Rahman et al., 2017)

GM-CSF	Granulocyte macrophage-Colony stimulating factor which stimulates the proliferation of granulocytes and macrophages(Rahman et al., 2017)
VEGF	Vascular endothelial is a growth factor and pro-antigenic cytokine(Rahman et al., 2017)
CRP C	Reactive protein active inflammatory mediator induces receptor activator of nuclear factor kappa-β ligand expression and directs precursor osteoclasts differentiation(Rahman et al., 2017)
RF	Rheumatoid factor (IgM) is an autoantibody most found in patients with RA, it targets the Fc region of IgG(Rahman et al., 2017)
ACPA	In 80% of RA patients anti citrullinated peptide antibody is found which is an another autoantibody responsible for RA(Rahman et al., 2017)

Chapter 4

Available old generation therapies for RA

4.1 NSAIDs (Non-steroidal anti-inflammatory drug):

NSAIDs are the most commonly used drug treatment for the early stage of RA. They are classified into eight classes based on their structure. Among them most commonly used NSAIDs for RA treatments are – aspirin, naproxen and ibuprofen. They are preferred for their fast action towards removing pain and inflammation. They works by inhibiting cyclooxygenase COX-1 and COX-2 (Bulletin, 2006) that plays an significant part for the production of PG also known as prostaglandin. Figure 3, shows all kind of cyclooxygenase enzymes (COX) and its parts inside each biological and disease condition instances are mentioned in the figure. COX-1 and COX-2 is responsible for causing irritation and inflammatory actions in the affected joints. COX-2 manufactures PGs which is the intermediaries of irritation. After the PGs produced by COX-2, COX-1 also produces prostaglandins which alter the biological system of intestine such as protecting the mucus membrane and GI secretion (Khaled et al., 2010). COX-1 performs vital function in the regulation of biological characteristic for GI tract, blood platelet, extraction part and vascular endothelium cells. Therapeutic effectiveness of NSAIDs are associated with the movement of COX-2 but it also effect the COX-1 (Agha, 2016). Target specific NSAIDs are more suitable and COX-2 is more acceptable than COX-1 for example- Celecoxib etc. Though it's been mentioned that specific COX-2 blocker can be a threat for the COPD (Chronic obstructive pulmonary disease) patients (Agha, 2016). In figure 3, NSAIDs acts as a blocker for the production of arachidonic acid that is primarily responsible for the production of COX-1 and COX-2. COX-1 and COX-2 has been considered as the most appropriate for the production of inflammation. NSAIDs show shorter half-life which requires frequent doses to perform the healing of RA after consuming it through oral route. Some common side effects of NSAIDs are- peripheral edema, renal necrosis, nephritic syndrome and hepatic injury amongst others (Rahman et al., 2017).

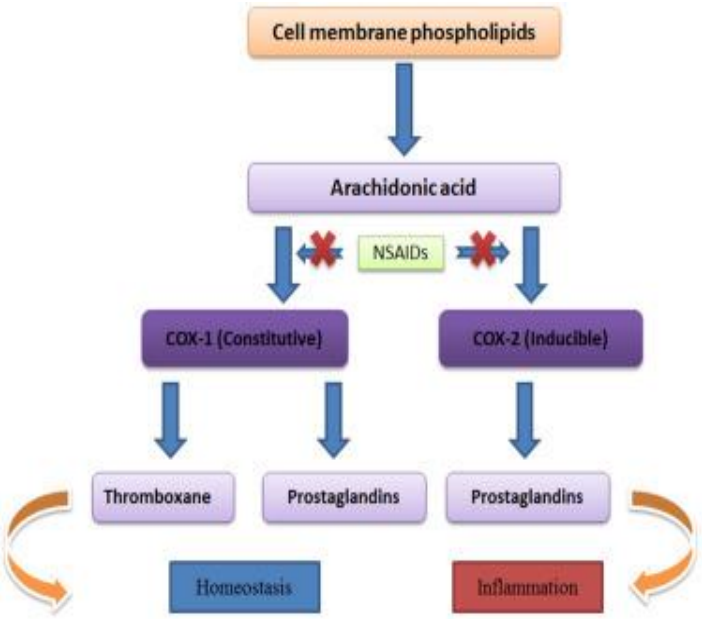


Figure 3: Illustration of the mechanism of action of NSAIDs (Agha, 2016).

4.2 Glucocorticoids (GCs)

Glucocorticoids (GC) contains potential characteristics for treating inflammation. For this characteristic GCs are broadly prescribed to control rheumatoid arthritis. It is usually prescribed as a small dose for reduce toxicity (Kapoor et al., 2014). GCs shows their action against inflammation by repressing the inflammatory gene expression in all kinds of inflammation. Also interfere with fibroblastic and endothelial cells capacities lessen the inflammation reaction on the humor (Gouveia et al., 2015). Genomic and non-genomic are the two ways for their action pathway. GCs acts as anti-inflammatory and immune system suppressor through genomic pathway. It is usually prescribed as small or medium dose (7.5–30 mg). Through this it is inferred that lower dosage and higher dosage of GC has distinctive instruments of activity and distinctive unfavorable impact outline (Mercieca, 2014). Though GCs have the potency to treat RA but it also associated with lots of side effects which is illustrated in Figure 4. For this reason GCs are usually prescribed for those patients who does not shows any response towards NSAIDs and DMARDs or other immunity or inflammatory path blocker. (Kapoor et al., 2014).

Onset early in therapy, essentially unavoidable
Emotional lability
Enhanced appetite, weight gain, or both
Insomnia
Enhanced in patients with underlying risk factors or concomitant use of other drugs
Acne vulgaris
Diabetes mellitus
Hypertension
Peptic ulcer disease
When supraphysiologic glucocorticoid treatment is sustained
Cushingoid appearance
Hypothalamic–pituitary–adrenal suppression
Impaired wound healing
Myopathy
Osteonecrosis
Susceptibility to infections
Delayed and insidious, probably dependent on cumulative doses
Atherosclerosis
Cataracts
Fatty liver
Growth retardation
Osteoporosis
Skin atrophy
Rare and unpredictable
Glaucoma
Pancreatitis
Pseudotumor cerebri

Figure 4: Side effects related with GCs (Reviews, 2006)

4.3 Disease-modifying anti-rheumatic drugs or DMARDs:

DMARDs are referred as disease modifying anti rheumatic drugs which are very preferable in the treatment of RA but it gives therapeutic affect very slowly and required up to few months. Different types of DMARDs shows different type of mechanism to show proper action (Kapoor et al., 2014). Physiological DMARDs such as- adalimumab, infliximab attacks the biological matters produced as a response of immunity. This type of DMARDs are mostly used with the combination of TNF-alpha blockers (Manjanna et al., 2010). However, modified DMARDs like- methotrexate works inside the cell although 40% patients are immune to this therapy (Rahman et al., 2016). Every kinds of DMARDs have different kinds of adverse effects on different organs like – GI tract, kidney and liver etc.

4.3.1 Methotrexate or MTX:

Sixty years ago Seeger et al. first produced methotrexate or MTX also known as, 4-diamino-N10-methyl propyl glutamic acid (Abolmaali et al., 2013). Later in 1988 it was approved by

FDA (Food and Drug Administration) as a RA treatment agent. MTX considered as an advantageous drug therapy for RA for it cost effectiveness, consistency, efficacy, low toxicity and prolonged therapeutic effect (Abbasi et al., 2019). All four actin pathway for MTX works in the positive way for RA treatment. Firstly, it's an anti-folate compound and may inhibit the propagation for the cells of the immunity along with lymphocytic cells which are the alternative for inflammation tissues. Secondly, tissue damage during RA is because of increasing toxic components is desiccated with immunosuppressant which are assisted with tetra-hydro-folate. Thirdly, MTX reduces animate thing intensities for glutathione which is important for tissue harm because of toxicant compound-8 metabolism. Fourthly, immunosuppressant because of the promotion of extracellular altitudes nucleoside, that cause anti-inflammation (Abbasi et al., 2019). Methotrexate is the drug choice for several patients who have RA and do not show any response with NSAIDs (Bulletin, 2006). Although it is an effective treatment for few patients but produce toxic effect like- liver and bone marrow toxicity in many patients. For patients with RA, MTX administrated orally and the dosage is 15–25 mg just once per week (Chan & Gladman, 2018). If MTX is administrated regularly for a longer period of time it causes side effects like- chronic mouth infection, liver diseases, kidney disease as 80% of the MTX is eliminate through kidneys. However if it is compared with the other DMARDs it is highly recommended because they are budget friendly, less toxic and more effective. For this reason it has become the primary medicinal therapy for RA (Zhang et al., 2018b).

4.3.2 Sulfasalazine or SSZ:

SSZ is used as a pro-drug and it is activated by cleaving in the bowel through microorganism and produce 5-aminosalicylic acid and sulfa pyridine. The standard dose is 500 mg oral SSZ every day. When tolerance occurs then dosage might increasingly inflated to 1500 mg twice a day. The common side effects are- nausea, vomiting, diarrhea, abdominal pain and neutropenia, thrombocytopenia (Reviews, 2006). In figure 5 shows that after the cleave of SSZ in the colon, 5-aminosalicylic acid is produce which reduce the inflammation by inhibiting the COX-1, COX-2, LOX, PAF, cytokines and also inhibit the IL-1 and TNF-alpha and reduce the inflammation and pain (Guo et al., 2018).

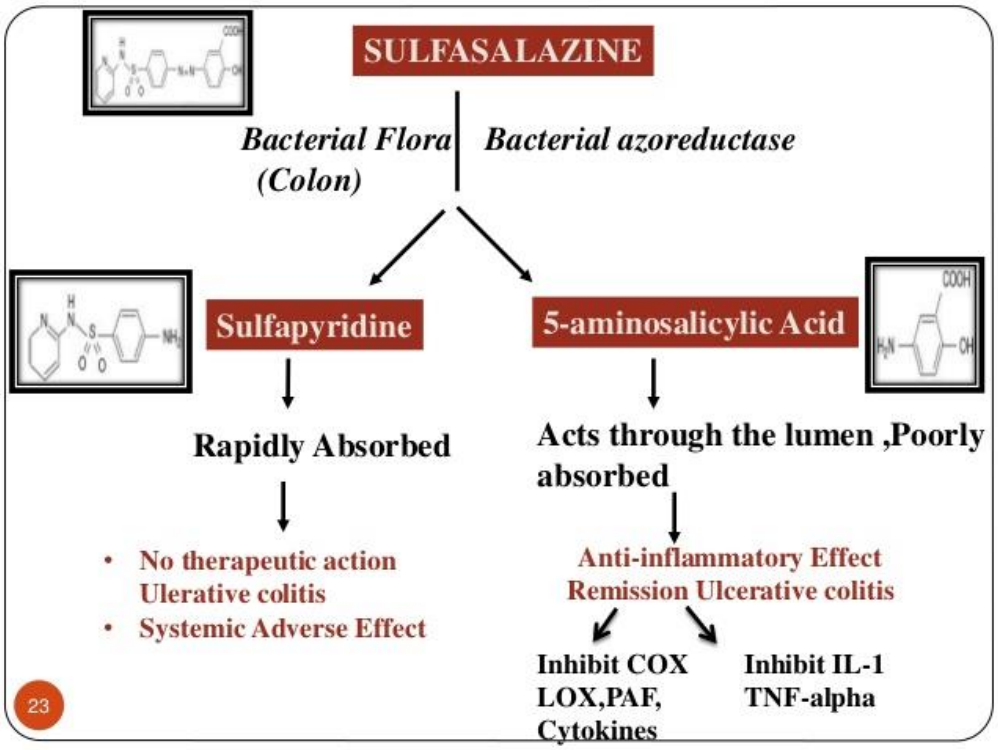


Figure 5: The mechanism of action of sulfasalazine (Abbasi et al., 2019).

4.4 Herbal approach for RA therapy:

Although there are lots of old and new generation drugs are available for the treatment of RA, but they have lots of limitations related to their bioavailibity, efficacy and toxicity profile. For this reason researchers come with lots of plant extract which have therapeutic properties for RA in some extend. Patients who don't have shown any progress by taking conventional or biological drugs are usually look for a Complementary and Alternative Medicine (CAM) (Wadekar et al., 2015). Worldwide almost 60% to 70% RA patient choose CAM as an alternative for conventional treatment (Wadekar et al., 2015) for treating the symptoms like inflammation, joint pain and joint damage in RA. However, herbal treatments for RA are now famous in the whole world (Wadekar et al., 2015). Homeopathic drugs that have the property for interact with the inflammatory receptors are mostly prescribed for RA management (Wadekar et al., 2015). According to the researchers many herbal approaches are taken for the treatment of RA but the effect of this medicine are inconsistent and vary from patient to patients (Curtis et al., 2004). When this plant based medication are used there are many difference are found between them and conventional and biological treatments (Shen et al., 2019). Moringaceae, Clusiaceae and Verbenaceae shows less effect on the RA therapy than NSAIDs and they also cause diarrhea, shortness of breath and anxiety in some patients. However, when

they are treated with the combination of Oleaceae, Asteraceae and Liliaceous they shows less side effects (Hosein et al., 2016). In a study of three medicinal plants in Bangladesh *Rhaphidophora glauca, Phrynium imbricatum, Steudneracolocasiifolia,* have been examined for their arthritic and membrane stabilizing activity in vitro. In heat induced method the inhabitation of proteinase actions were assessed to examine the anti-arthritic effect of *Rhaphidophora glauca, Phrynium imbricatum, Steudneracolocasiifolia* plant which show 53.16%, 69.62%, and 62.03% of anti-arthritic activity significantly in their maximum concentration compared to NSAIDs (Hajja & Bahlouli, 2018). They also shows 49.05%, 71.9% and 60.22% of membrane stabilizing activity compared to Diclofenac–Na (Hajja & Bahlouli, 2018). Aqueous extract of *Glycyrrhiza glabra* shows anti-oxidant effects which damage to proteins, lipids, DNA, cartilage, and extracellular collagen responsible for RA in patients. Compared to MTX drugs it shows less effectiveness in RA radio graphical image (Assunção-miranda et al., 2013). Further in depth studies on this plant can result in an eco–friendly cost effective anti-arthritic herbal drug with anti– inflammatory potential contributing towards the better healthcare of human society For different strategies different combination of plants are used based on the need of the patients and his or her past history (Moussaieff & Mechoulam, 2009). In different clinical trial for RA therapy result shows that some herbal drugs like-*Tripterygium wilfordii* are more effective than methotrexate, leflunomide (Wang et al., 2016). Many statistics shows that the plant based extract are sometime used as a lead component for the discovery of a constant drug (Price et al., 2009). Homeopathic drugs are potential to treat RA but they are not very specific they sometimes attacks healthy tissues associated with the damaged tissues (Chen, 2012).

Chapter 5

Available new generation therapies for RA

Biological Agents:

Biological agents are made by genomic modification which constrain the manufacture of cytokines that cause inflammation that is produced excessively on the joints of RA patients. Different types of biological agents are used as RA therapy. IL-1 inhibitors, TNFα-receptor antagonist, Il-17 inhibitors, co-stimulant blockers, anti-B cell agents, JAK inhibitors etc. (Thakur et al., 2018). Patients who are severely affected by RA and do not show any improvement while using DMARDs therapy are prescribed with biological agents (Firth, 2011). Figure 6, shows all the targeted receptors and paths of the biological agents that are used for the treatment of RA.

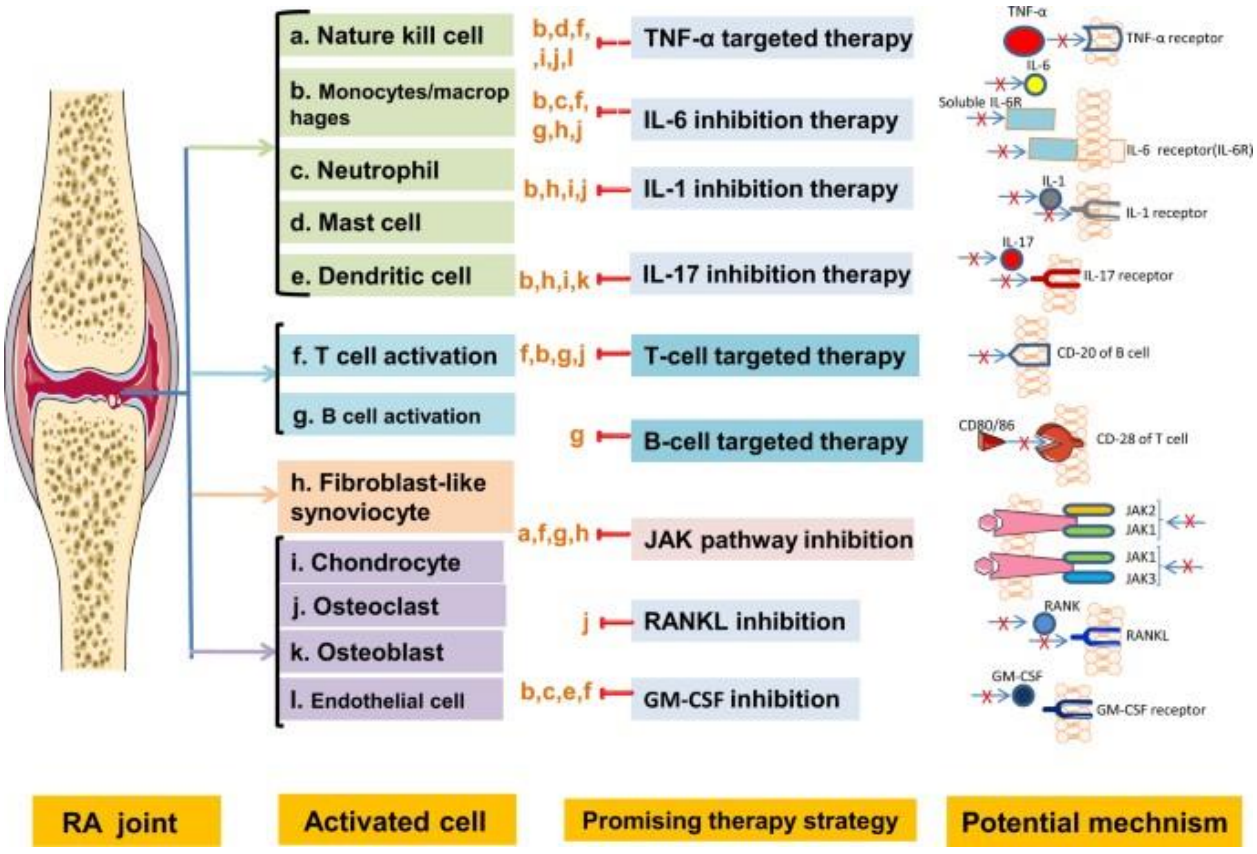


Figure 6: Targeted receptors and paths of biological agents in RA (Guo et al., 2018).

5.1 TNF-α inhibitors

Tumor necrosis factor alpha or TNF- α may be a main cytokine for the pathological process for RA. This encourages macrophagic cells and different cells to produce proinflammatory cytokines like- lymphocytes (IL) IL-1, IL-6 and IL-8 ends up in T-cell stimulation because of this epithelium cells. TNF-α are concerned within the distinction and growth for cells of osteoclast (major cells concerned for bone damage) and excites fibroblastic, osteoplastic of articular cartilage and bone (Atzeni et al., 2013). TNF-α is produced pro-TNF (26 kDa) that is activated after the cleavage of its pro-domain by the TNF-converting protein (Atzeni et al., 2013). The TNF-α acts through two separate receptors such as- TNFR-1 and TNFR-2. Though attractions for TNFR-2 are 5 times more than TNFR-1 (Atzeni et al., 2013). Four kinds of Tumor necrosis factor alpha inhibitors are accepted in European countries to treat RA. They are- infliximab [IFN], adalimumab [ADA], etanercept [ETR] also certolizumab [CTZ] (Atzeni et al., 2013). However, there pharmacological, structural and morphological actions differ from each other.

5.1.1 Infliximab

Infliximab works as a monoclonal antibody which binds with soluble IgG1k and interfere in the cascade signaling of pro-inflammatory factors by binding with TNF-alpha receptor. As the antibody binds with the TNF-alpha receptor it prevents the binding of TNF-alpha to bind with the receptor (Figure 7) (Abbasi et al., 2019). Anti-TNF compound is run in veins at a dosage of 3mg/kg requires an hour or two to respond (Abbasi et al., 2019). The modified health assessment questionnaire and Hamilton Depression Rating Scale shows that when patients treated with infliximab they shows four times more effectiveness then the patients who has been treated with MTX (Miwa et al., 2016). American College of Rheumatology studies with infliximab, approximately 9% of patients developed anti-double stranded DNA (anti-dsDNA) antibodies. In American College of Rheumatology study shows, 16% of patients developed anti dsDNA during the 30 weeks after treating with infliximab where they shows less adverse drug reactions and side effects (Harriman et al., 1999). Drug induced lupus occurred in less than 0.5% of patients treated with infliximab compared with other conventional drugs and all of them were successfully treated medically. None of these patients developed renal complications or other major organ damage (Harriman et al., 1999).

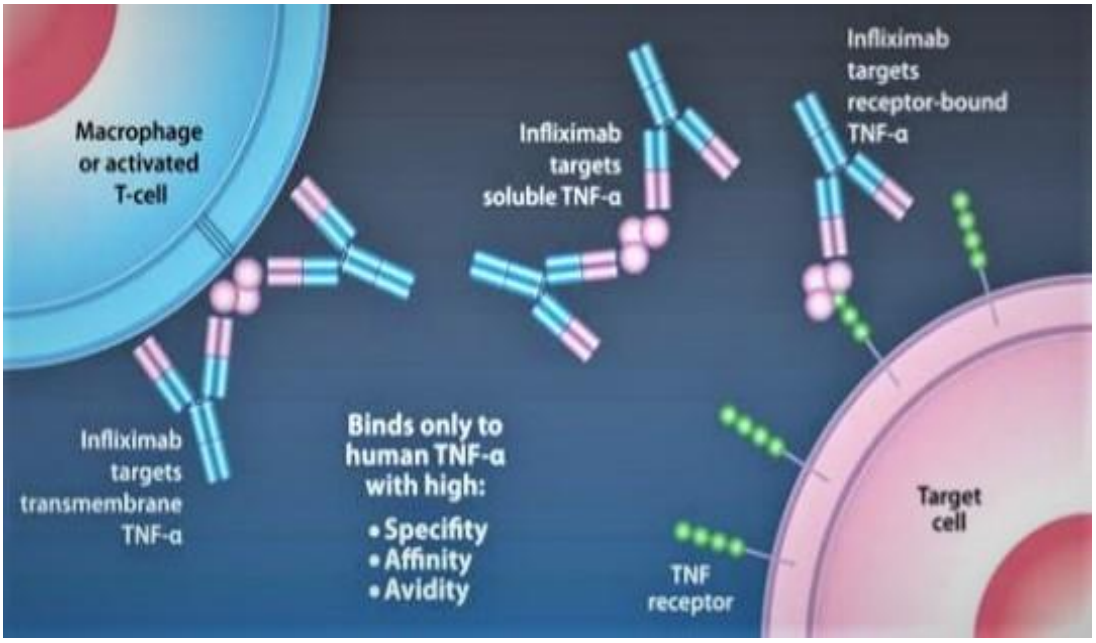


Figure 7: Mechanism of action of infliximab (Abbasi et al., 2019).

5.1.2 Adalimumab

Adalimumab genetic engineering-IgG1 antibody for TNF-α permitted by FDA as RA therapy in 2003. Adalimumab binds with the TNF-alpha when it is given through the subcutaneous layer of the skin. It neutralizes the biological activity of TNF-alpha and the induction of apoptosis of TNF-expressing mononuclear cells (Figure 8) (Miyata et al., 2005). It's a protracted current half-life (10–20 hours) and might be taken by the patient in a subcutaneous layer each twice in a month forty mg per dosage. An analytical report demonstrated that adalimumab treatment was more superior to MTX treatment as it has less risk profile and have adverse effect free response compared with MTX treatment (Reich et al., 2010). Bayesian organize meta-analysis including 1796 patients, found that adalimumab 8 mg was the second-line TNF biologic with the highest execution with respect to an early great response based on ACR20 reaction and satisfactory security profile (Lee & Bae, 2016).

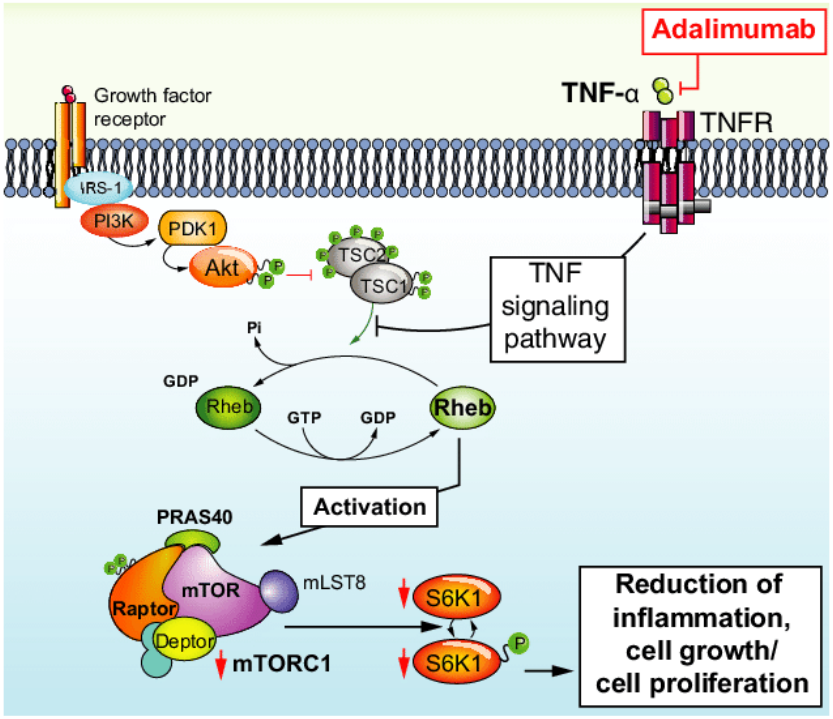


Figure 8: Mechanism of action of Adalimumab (Abbasi et al., 2019).

5.1.3 Etanercept

Etanercept act as a soluble form of the p75 receptor that inhibits TNF-α, and to some extent TNF-β, by blocking its interaction with cell-surface TNF receptors. It is a complex of two p75 TNF and Fc-IgG1 and it is bind with TNF-alpha receptors and give an extended half-life (Figure 9) (Atzeni et al., 2019). This mixture of macromolecule can easily bind with TNF-α and TNF-β receptor and inhibit the activity of TNF-alpha. Anti-TNF compound can be taken by the patient and dosage will be 25 mg twice a week or 50 mg once a week. Half-life of etanercept is four days also more effective than other anti-TNF compound (Atzeni et al., 2013). RA the average frequency of remissions with active treatment of etanercept was 19% in only one trial did 50% or more active patients achieved remission 65% with etanercept trial compared with DMARDs (Hughes et al., 2018).

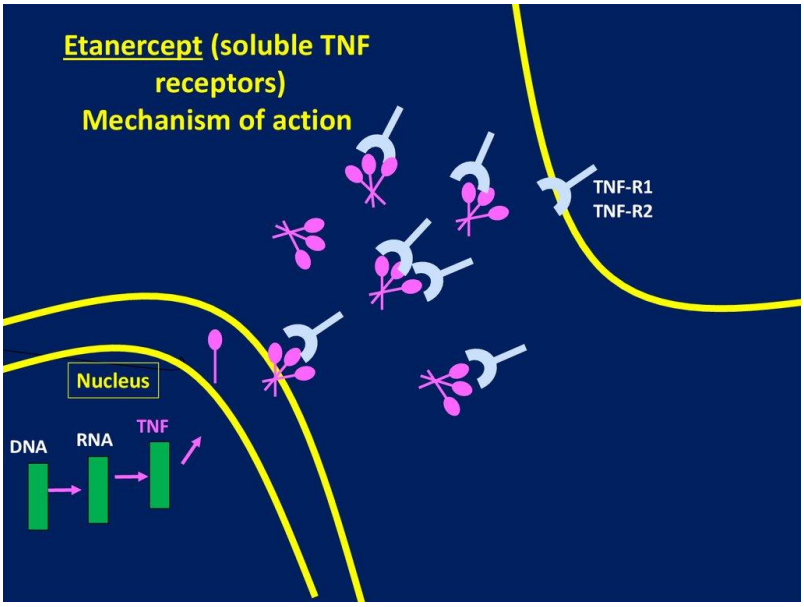


Figure 9: Mechanism of action of etanercept (Abbasi et al., 2019).

5.1.4 Certolizumab

When the soluble and membrane-bounded TNF-alpha binds with certolizumab pegol, they inhibit the cytokine activity. Through this interference, it minimizes the activity of TNF-alpha and inhibits inflammation (Figure 10) (Rhim et al., 2013) CTZ are taken twice a month through injection. Certolizumab is still in the clinical trial phase (Guo et al., 2018).

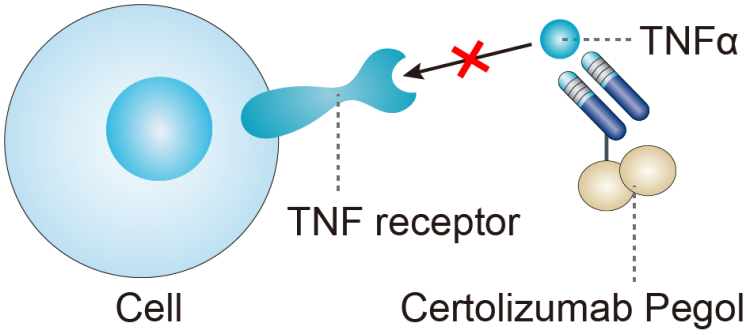


Figure 10: Mechanism of action of certolizumab (Abbasi et al., 2019).

5.2 Interleukin inhibitors

5.2.1 IL-1 inhibitors:

In RA patients the synovial membrane produces pro-inflammatory protein also known as IL-1. In high concentration, it will trigger the macrophagic and fibroblastic action. IL-1 is responsible for the stimulation of immunologic response which causes inflammation in disease

condition similar to TNF- alpha. IL-1 inhibitors target those receptors and block the therapeutic response (Walsh & Gravallese, 2004). To show a therapeutic response almost 95% of IL-1R1 receptors must be bonded with IL-1Ra. RA patients IL-1 are superior to IL-1Ra expression in RA patients which increases IL-1 signals and cause inflammation (Walsh & Gravallese, 2004). Interfering with IL-1signals through the target to inhibit of IL-1R1 receptor leads toward suppressing the disease indications of RA and therefore the bone erosion and tissue damaged are controlled. Like as TNF-alpha, IL-1 will ultimately control the osteoclast by regulating receptor activator of nuclear factor kappa-B ligand (RANKL). Available agents are a combination of IL-1Ra (Anakinra). It blocks more than 95% of IL-1Ra receptors which reduces the production of IL-1 on bone cells to decrease bone and tissue damage. In a randomized clinical trial (RCT) 472 patient was divided into two groups (J. R. Curtis & Singh, 2011). They received treatment with placebo and IL-1 inhibitors for six months (J. R. Curtis & Singh, 2011). Their radiographic report of week 24 and week 48 showed that the IL-1 inhibitor group reduced 38% of joint erosion progression and joint space narrowing was 58% compared to placebo treatment (J. R. Curtis & Singh, 2011). IL-1 inhibitors drugs are usually prescribed as monotherapy for RA in 20% of patients who have an intolerance for TNF-alpha (Abbasi et al., 2019).

5.2.2 IL-6 inhibitors:

IL-6 is an inflammatory and hematopoiesis protein. The pathological mechanism for RA, IL-6 invigorate pannus arrangement through vasodilation of endothelial growing factors and boost bone resorption that causes osteoclasts along with oxidation in leukocytes (Guo et al., 2018). Tocilizumab which is an anti-IL-6 drug and the dosage available for it is subcutaneous and intravenous form. In SAMURAI (the study of active-controlled monotherapy used for RA, an IL-6 inhibitor) clinical trial 306 patients were divided into two groups one was treated with TCZ and another was treated with conventional DMARDs (Kim et al., 2015). The radiographic response was examined after 52 weeks where the TCZ group shows lower TSS (total modified Sharp score) approximately 2.3 then the DMARDs group approximately 6.1 (Kim et al., 2015). TCZ groups also show more improvement in the signs and symptoms than the DMARDs group (Kim et al., 2015). Sirukumab, a monoclonal counter-acting agent for IL-6 and have high effectiveness and now it is in the third phase of medical assessment. It gives another profitable chance to investigate the effect of cytokine hindrance in RA instead of cytokine receptor restraint (Guo et al., 2018).

5.2.3 IL-17 inhibitors:

IL-17 could be a T cell-derived cytokine created by enacted T cells and is communicated within the synovium of patients with RA (Lubberts et al., 2005). IL-17 contains work in T cell-triggered irritation by fortifying distinctive cell sorts to discharge different types of cytokines and chemokine. In expansion, IL-17 appears added substance or even synergistic impacts with IL-1 and TNF in actuating cytokine expression and joint pathology. Besides, T cell IL-17 may be a powerful inducer of receptor activator of nuclear factor kappa-β ligand which is a pivotal cytokine that is responsible for osteoclastogenesis and bone resorption. It has appeared that IL-17 has IL-1-independent exercises in actuating synovial aggravation and joint devastation in exploratory joint pain. Moreover, IL-17 features work in prolongation of the joint pain preparation and can be considered as a vital target for the treatment of dangerous joint pain. The disclosure of IL-17 family individuals may assist expand the part of this cytokine family in joint pain (Lubberts et al., 2005). Six randomized, double-blind, placebo-controlled phase III studies were involved, including 1733 patients (1153 patients received IL-17 inhibitors compared with 580 patients receiving placebo) (Koenders & Joosten, 2006). There was a substantial improvement in the ASAS20 response rate (Risk Ratio = 1.63, 95 percent Confidence Interval 1.45 to 1.84) and secondary endpoint ASAS40 response rate (Risk Ratio = 2.12, 95 percent Confidence Interval 1.75 to 2.56) relative to placebo at week 16 of the IL-17 inhibitor regimen (C. L. Curtis et al., 2004). With regard to the safety profile, after treatment with IL-17 inhibitors, more treatment-emergent adverse effects (Risk Ratio = 1.11, 95% Confidence Interval 1.01 to 1.22) and non-severe infections (Risk Ratio = 1.82, 95% Confidence Interval 1.40 to 2.37) were recorded than after treatment with placebo, and no increased risk of other adverse events, including death, was reported after IL-17 inhibitor therapy (J. R. Curtis & Singh, 2011).

5.3 Co-stimulation blockers:

Abatacept which is the primary member in the newest discussion for biological mediators for stifling aggravation they are called co-stimulation blockers. In comparison with former organic specialists, co-stimulation blockers apply their action by inflammation cascades cause interference for co-stimulatory signals which is required for the enactment of T cells (Abbasi et al., 2019). The adequacy of Abatacept is expanded by combining it with Methotrexate (Abbasi et al., 2019). 500–1000 mg of Abatacept is taken by intravenous route within half an hour. In a randomized clinical trial (RCT) 568 patient was divided into two groups

(Westhovens & Verschueren, 2008). They received treatment with placebo and abatacept for four weeks (Westhovens & Verschueren, 2008). Their radiographic report showed that the abatacept group reduced 45% of joint erosion progression and joint space narrowing was 78% compared to placebo treatment (Westhovens & Verschueren, 2008).

5.4 B-cell inhibitors:

Rituximab is an anti-CD20 mAb or B-cell inhibitor that works by reducing selected B cells. FDA approved rituximab as a treatment of RA but it must be combined with methotrexate (Abbasi et al., 2019). 1000-mg of rituximab must be administrated through infusion twice a month. Scientific reports show that rituximab has fewer side effects and more potent for RA treatment with the combination of MTX (Abbasi et al., 2019). However, it shows an allergic reaction-infused site (Abbasi et al., 2019). Consortium of Rheumatology Researchers of North America Rheumatoid Arthritis Registry clinical trial included two groups of patients one was given placebo another one was given rituximab for six weeks (Harrold et al., 2015). The radiographic report indicates that patients who were treated with rituximab show a 56% reduction in joint erosion than the placebo-controlled group (Pappas et al., 2020).

5.5 JAK inhibitors:

JAK inhibitors are small molecules of DMARDs that are modernizing for RA management. Many cytokines utilize the Janus kinase (JAK) and signal transducer and activator of translation (STAT) path for showing their pathogenesis on RA and create beneficial blockade with JAK inhibitors which have demonstrated viability for the management of RA. JAK-inhibitors are modified to target STATs and other intracellular signaling paths for the management of RA (Guo et al., 2018). Tofacitinib is made in a way so that it can restraint JAK in RA. Tofacitinib particularly suppresses JAK-3 and JAK-1 rather than JAK-2 (Guo et al., 2018). 74% of Tofacitinib is orally bioavailable and the half-life is 3h. Metabolism occurs through cytochrome P450 3A4 (CYP3A4) and 30% excreted through the renal route. FDA approved 5mg of Tofacitinib for RA management in early-stage (Guo et al., 2018). Common side effects were related to contamination, hematologic and hepatic disarranges, and affiliation of Tofacitinib, with carcinogenicity and contaminations debatable (Guo et al., 2018). Baricitinib is another inhibitor of JAK-1 and JAK-2 which is taken through the oral route. All 7 Phase III randomized control trials (RCTs) of tofacitinib demonstrated the efficacy of JAK1 or JAK3 inhibition in RA during the FDA approval process. ORAL-START demonstrated substantially higher ACR20, ACR50, and ACR70 response rates with tofacitinib 5 mg and 10 mg BD at 6 and 24

months compared to MTX monotherapy (Harrington et al., 2020). The ORAL-SCAN posthoc analysis demonstrated the efficacy of tofacitinib versus placebo regardless of the background dose of methotrexate (Harrington et al., 2020). In ORAL-STRATEGY, tofacitinib + MTX was not inferior to adalimumab + MTX. Tofacitinib monotherapy, however, was not as favorable as the combination of adalimumab +MTX (Harrington et al., 2020). This means that the synergistic effect of tofacitinib+ MTX is superior in terms of disease control to tofacitinib monotherapy in mild to extreme RA if the combination is combined (Harrington et al., 2020). Progression of structural joint frameworks using the amended van der Heijde Total Sharp Ratings, harm was also measured (Harrington et al., 2020). Tofacitinib in ORAL-START, monotherapy has been shown to be superior to MTX monotherapy in minimizing structural damage progression.

5.6 Osteoclast differentiation factor:

One of the most commonly used osteoclast differentiation factors is Denosumab (DMab) which is an IgG2 antibody that is responsible for the inhabitation of the bone resorting process. It acts through bonding and inhibit NF-kB substance (RANKL), an important cytokine for osteoclast and bone destruction. Receptor activator of nuclear factor kappa-β ligand is associated important existence issue for DCs. RANK because Th17 cells to facilitate bone resorption (Zhang et al., 2018b). Additionally receptor activator of nuclear factor kappa-β ligand synthesized by B cells that cause bone destruction in RA. Finally, receptor activator of nuclear factor kappa-β ligand is better-known as an inducer of immunity acceptance through endorsing the difference between target cells. It's possible for receptor activator of nuclear factor kappa-β ligand antagonist to stimulate immunity. The interaction synovial cell dysplasia, associated protein raises an osteoclast triggered by TNF-α and RANKL. An experimental trial shows that DMab prevents focal and general bone loss in RA. A clinical test is needed to distinguish the amount of inhabitation result on bone losses. The side effects embrace lower Ca2+ level and phosphate level within the blood, muscle spasms, cellulitis. (Zhang et al., 2018b).

Chapter 6

Conclusion

RA is an exceptionally severe condition that influences a wide portion of the world population (Quan et al., 2008). There are lots of researches done just to find out a stable treatment of RA that will fully treat this condition without any side effects. The present management alternatives like NSAIDs, corticosteroids, DMARDs are good options for treatment but they are related to a few side effects and drawbacks (Santos & Morand, 2006). NSAIDs cause a gastric disturbance, corticosteroids cause disabled wound healing, and peptic ulcers on long-term utilization. DMARDs after taking for a prolonged period they will show their side effects like-liver and kidney dysfunctions, (Thakur et al., 2018). The field of RA treatment has changed significantly after the presentation of biologic DMARDs. Biologics have had a groundbreaking impact on the treatment of RA. These compounds can have a stable and pronounced therapeutic effect with a unique ability to inhibit signal transmission supplied by a wide branch of inflammatory cytokines. Apart from conventional treatment, there are two currently approved JAK inhibitors (tofacitinib and baricitinib) for clinical use. According to different studies it is claimed that JAK inhibitors might have the potentiality over classical biologics. These drugs have the potentiality to blockade a broad range of cytokines which cover several established cytokines inflammatory mechanisms and proven to be beneficial for RA treatment. However, it is too early to speculate if these compounds will replace the biologics currently in use. Despite the benefits of biologics, they have fewer side effects like immune suppression and thus make the patient more vulnerable towards bacterial and parasitic contaminations (Thakur et al., 2018). As biologics are highly expensive mostly NSAIDs, corticosteroids, DMARDs are preferred in Bangladesh for the treatment of RA despite their poor efficacy and side effects (Alamgeer et al., 2015). For these reasons, more clinical trials and researches are required to find out its efficacy and minimize side effects and price to use it for RA treatment.

Chapter 7

Future studies

For now only a few biologics are available for the treatment of RA. Almost all of them are given through intravenous and intramuscular route, for this reason, it has less patient acceptability. In the future, there is scope for research about the route of administration of the biological drugs which will increase their acceptability towards the patients. Moreover, there is plenty of opportunities to decrease the side effects and increase the potentialities of the biologics. TNF-alpha receptor, Interleukin receptor, and other biological receptors that are responsible for RA can be targeted and their inhibitors can be used to treat the RA condition in the early stage of RA which will eventually help to cure the condition before severe symptoms shows to a patient.

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