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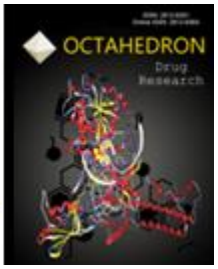

A potential therapy for rheumatoid arthritis: new drug discovery

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ABSTRACT

The most known disorder in inflammatory rheumatological classification is Rheumatoid Arthritis which is autoimmune in nature, starting when the inflammatory and immune systems interact with each other to lead to the destruction of self-cartilage and bone. Although the specific cause of rheumatoid arthritis is unknown, many studies and explanations involved in the generation of the disorder have been recognized and some of these have been identified as important sources for therapeutic studies and drug development. It has long been suggested that rheumatoid arthritis could be triggered by infectious agents mainly bacteria, the researchers found that 75% of people with new-onset, untreated rheumatoid arthritis had bacterium Prevotella copri in their intestinal microbiome, but proof of this is still lacking. According to clinical trials and research, rheumatoid arthritis patients respond effectively to chemotherapeutic drugs specifically that have antibiotic activity or are derived from antibiotics. The most therapeutic pathways were obtained by drug development are divided into three categories according to state of disease, for example in long-term aggressive disease two pathways are involved, disease- modifying anti-rheumatic drugs (DMARDs) such as methotrexate, hydroxychloroquine, sulfasalazine and called Janus kinases inhibitors (JAK Inhibitors) such as tofacitinib, baricitinib and upadacitinib. Although, the continuous development of drugs has led to the discovery of new agents with improved effective trials and safety profiles, but we still need more research and studies to reduce the seriousness of this disease and make it treatable.

1. Introduction

Rheumatology in the field of medicine can be defined as the science that deals with diagnosis of immune system problems and their therapies. They used to think of "Rheumatology" as like a fluid spreading across the body, causing symptoms in different organs with different conditions, so the disease is not flowing as a fluid, but the old name remains the same. When this word is divided, "Rheum" means flow of a current such as a thin fluid or something like that. Rheumatology is an "ology," which is an alternative word for science. The field of medicine known as rheumatology focuses on the diagnosis and management of rheumatic illnesses, including autoimmune disorders, autoinflammatory diseases, crystalline arthritis, metabolic bone diseases, pain syndromes, and vasculitides [1]. Rheumatism, on the other hand, is a general word that refers to any condition that causes pain and inflammation in the joints, muscles, or connective tissue. The majority of rheumatological conditions are autoimmune, including Systemic Lupus Erythematous (SLE), Sarcoidosis, and Rheumatoid Arthritis; autoinflammatory, including Familial Mediterranean Fever and Still's disease; crystalline, including gout and pseudogout; metabolic; pain syndromes, including fibromyalgia and rotator cuff tear; and vascular, including Kawasaki, Buerger's, In rheumatology, there are two main categories: non-inflammatory, commonly referred to as mechanical issues, such osteoporosis and osteoarthritis, and inflammatory issues like gout, seronegative spondylarthritis, and rheumatoid arthritis [2].In order to improve rheumatoid arthritis classification upon the 1987 criteria for identifying early illness, the American College of Rheumatology, (ACR), and the European League Against Rheumatism (EULAR) amended the rheumatoid arthritis classification criteria in 2010 [3].The updated standards benefit from a better comprehension of the role that antibodies to citrullinated proteins play in the etiology of rheumatoid arthritis [3].They are quantified as rheumatoid arthritis-specific anticyclic citrullinated peptide (CCP) antibodies[4]. Cader and colleagues compared the two classification criteria (n = 265) and found that the 2010 criteria lowered sensitivity by 15.8% while increasing specificity by 71.4% [3].To put it another way, fewer people with RA go undiagnosed, but a somewhat higher proportion of those without the condition are classified as having rheumatoid arthritis. According to research by van der Linden and colleagues, postponing rheumatologic screening might worsen illness remission rates and raise joint destruction rates, underscoring the significance of early identification. Early diagnosis and treatment are essential to getting the best outcomes for RA patients since there are medicines available that are efficient at reducing inflammation and preventing structural joint damage [3].

The doctor-patient consultation

The patient is the most crucial individual, and gaining their trust is the most crucial aim if better medical results are to be achieved. The patient's history is the tale that the doctor crafts to assist him in diagnosing and treating the patient. Any doctor should have a method or approach when taking a patient's history, starting with the compliant, or what the main symptom is. This is also known as the history of the present illness followed by the past medical history, or how about surgical history, and then by general inquiries about the patient's health, including diet, exercise, sleep, and travel, as well as family and social history [5].

Anatomy

When defining Rheumatoid Arthritis, remember that "Arthro-" denotes a joint and "-itis" denotes inflammation. As a result, the major site of pathology for this ailment is a joint, particularly the knee joint. The name "Rheumatoid" derives from rheumatism, or musculoskeletal sickness. As previously said, rheumatoid arthritis is categorized as an autoimmune, inflammatory, programmed rheumatological illness that damages bone, cartilage, and joint components. The most intriguing aspect of rheumatoid arthritis is that patients may experience damage or aberrant operation in organs or systems that are not connected to the joints, such the skin and lungs. By considering the anatomical structure of healthy joints, particularly knee joints, also known as synovial joints, it was found that there are two bones covered in articular cartilage, the smooth, white connective tissue that covers the ends of bones and assists in their coming together to form joints. The periosteum, the sheath enclosing the bone and a source of blood supply, nerves, and cells that help in development and repair, is continuous with the "capsule" layer that surrounds the synovial joint [6]. A synovial membrane lines the inside of this capsule, producing synovial fluid that acts as lubrication. The synovial fluid, also known as synovia, is a viscous fluid that does not adhere to Newton's law of viscosity, or, to put it another way, fluids with continuous viscosity. Reduced friction between the articular cartilage of the synovial joint

during motion is the synovia's primary function (Figure 1) [7].

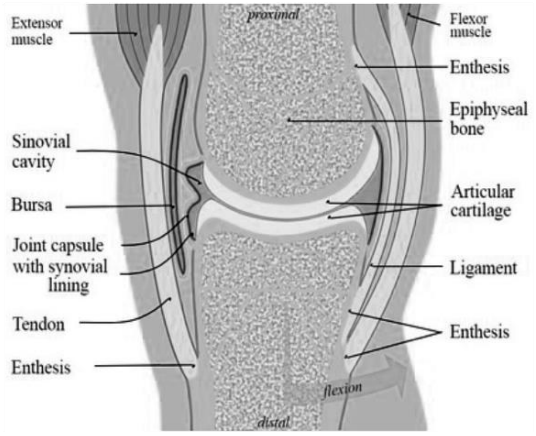

Figure 1. showing the simplified healthy knee joint [41].

Autoimmunity

Everybody's body normally experiences autoimmunity, but autoimmune disorders, which are brought on by antibodies that cross-react with self-antigens and cause pathology, are the problem. The immune system normally recognizes the self and only targets outside invaders when defending the self [8]. Every single individual possesses autoimmunity, but only a small percentage of people have autoimmune disorders similar to cancer cells. This is analogous to consuming food tainted with bacteria and owing to the presence of defensive mechanisms some people will become sick, but the majority will not. We all have DNA-mutated mutant cells in our bodies, however systems like tumor suppressor genes like p53 prevent cancer from spreading and eliminate these cancer cells. Autoimmunity is disproportionately prevalent in women, which may be due to sex-related genes and/or hormones. According to animal models and clinical research, endogenous estrogen and prolactin as well as exogenous endocrine disruptors may break tolerance and cause the onset of autoimmunity in various autoimmune illnesses including SLE. The etiology of other autoimmune illnesses including Myasthenia Gravis and RA does not appear to be significantly impacted by sex hormones [8,9].

Rheumatoid Arthritis Progression

An autoimmune disorder known as rheumatoid response and autoimmune disorder progression. [42]

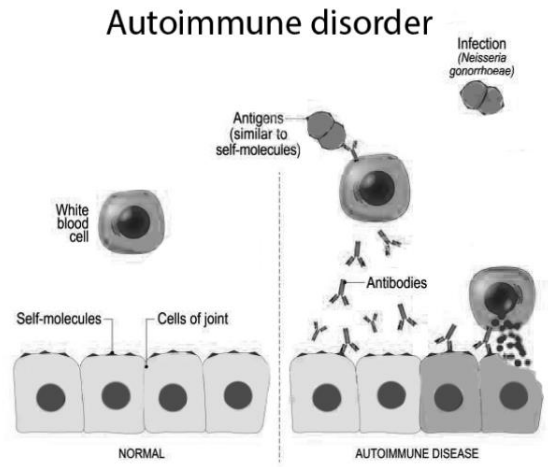

Figure 2. Comparison between the normal immune,

arthritis can be brought on by hormonal, environmental, or inherited reasons. Rheumatoid arthritis is most usually brought on by changes in or spontaneous mutations of a gene that encodes an immune protein, most notably human leukocyte antigen, also known as HLA-DR1 and HLA-DR4[10].These antigens may also change as a result of exposure to a virus or environmental contaminant, which might result in the onset of an autoimmune illness like rheumatoid arthritis. Periodontal diseases, which include the gut bacterium *Prevotella copri* in the intestinal microbiome, are the most notable example of pathogens that change such antigens. Rheumatoid arthritis sufferers are also tested for a range of hormonal abnormalities in addition to the aforementioned[11].The main hormonal abnormality that contributes to the onset and severity of rheumatoid arthritis may be the lack of steroid hormones produced by the adrenal glands, such as corticosteroids and dehydroepiandrosterone, or by the gonadal organs, such as estrogens and androgens (DHEA)[12].The targets that are altered or transformed most commonly in the process of delaying the development of disease are human antigens like IgG antibodies or other protein structures like type II collagen or vimentin. Articular cartilage and hyaline cartilage include the type III intermediate filament protein vimentin and type II collagen, respectively. The amino acid arginine, one of the 20 standard amino acids encoded in DNA, is changed into citrulline, an amino acid that is not one of the standard amino acids, during the citrullination process [10,13].Due to variations in the human leukocyte genes HLA-DR1 and HLA-DR4, the citrullination mechanism initiates and feeds the autoimmune response. Some human antigens are no longer recognized by immune cells [13,14].

Diagnosis depends on identifying the antigens that adhere to antigen-presenting cells and go to lymph nodes where they activate lymphocytes, in particular CD4+ T-helper cells. T-helper cells become activated when they recognize altered antigens. Cytokines that cause B cells to become activated B-cells multiplied, changed into plasma cells, and began producing autoantibodies against these self-antigens [15]. In rheumatoid arthritis, plasma cells' T-helper cells and antibodies go through the circulation to the joints. To attract more inflammatory monocytes, in particular macrophages, T cells enhance the production of cytokines like interferon-gamma and interleukin-17 in the synovial fluids around joints. Synovial membranous cells are encouraged to grow by the inflammatory cytokines TNF-alpha and interleukin-6 produced by macrophages. Pannus, a type of abnormal growth in the joints, can erode bone and cartilage and result in discomfort and swelling due to an overabundance of immune and synovial cells [14,16]. Over time, the pannus growth erodes the bones and damages the cartilage and adjacent soft tissues. The former causes the articular cartilage's synovial cells to release a particular enzyme called a protease that breaks big protein structures into smaller, more easily destroyed components. The afflicted bones might directly rub against one another because they lack lubricating cartilage. T-cells can bind to RANK protein, a 616 amino acid type I homotrimeric transmembrane protein that is on the surface of osteoclasts, and activate them to begin breaking down bone, when inflammatory cytokines start to increase RANKL, a type II membrane protein and a member of the tumor necrosis factor (TNF) superfamily[18,25].Rheumatoid factor (RF), an IgM antibody that attaches to the constant region, or Fc domain, of modified IgG antibodies, is one of the antibodies that penetrate the joint area. The anti-cyclic citrullinated peptide antibody is another antibody that binds citrullinated proteins (often abbreviated anti-CCP). These two elements come together to create immune complexes, which collect in the synovial fluid around the joint and bind to specially modified antibodies that are meant to be their target [17,19]. Inflammation and damage are caused by pathogens being opsonized by the complement system, a family of 9 tiny, specialized plasma proteins, after immune complexes have formed. Finally, persistent inflammation causes angiogenesis, or the growth of new, tiny blood vessels around the joint, which opens the way for additional inflammatory cells. Numerous joints on both sides of the body become inflamed and eventually degenerate as the disease progresses. However, these inflammatory cytokines escape from the restricted area and travel via the circulation to many organ systems, where they cause extra-articular problems—i.e., issues that extend beyond the joint region [19].

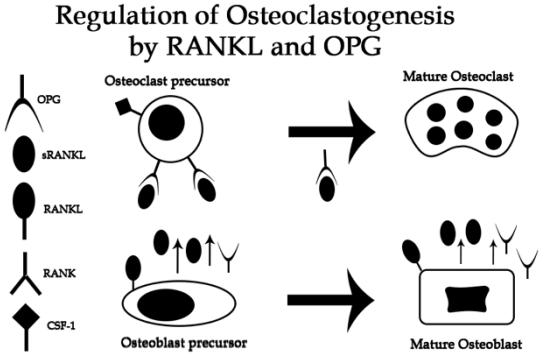

Figure 3. Regulation of osteoclastogenesis by RANKL and OPG [45]

Colony-stimulating factor 1 usually increases osteoclast recruitment, which is regulated by osteoprotegerin (OPG) and the receptor activator of NF-B ligand (RANKL) (CSF-1). To encourage osteoclast activation and recruitment, osteoblasts and osteoblast precursors release two different forms of RANKL. The membrane-bound form attracts osteoclast precursors nearby, which interact with it right away. The soluble form of RANK, which is discharged by osteoblasts or osteoblast precursors and diffuses through the intercellular space, contacts the membrane-bound RANK molecules on neighboring osteoclast precursors. As a fake receptor, OPG prevents RANKL or sRANKL from attaching to RANK. The ratio of RANKL to OPG produced by osteoblasts and osteoblast precursors determines how much osteoclastogenesis is brought about by RANKL.

For instance, when interleukin-1 or interleukin-6 enter the brain, they serve as pyrogens and increase body temperature. They affect and aid in the development of rheumatoid nodules, spherical clusters of macrophages and lymphocytes that are seen in the skin, skeletal muscle, and various internal organs and have a central zone of necrosis, or tissue death. Walls of blood vessels may also be impacted. They enlarge and more commonly form atheromatous or fibrofatty plaques. Vasculitis in a

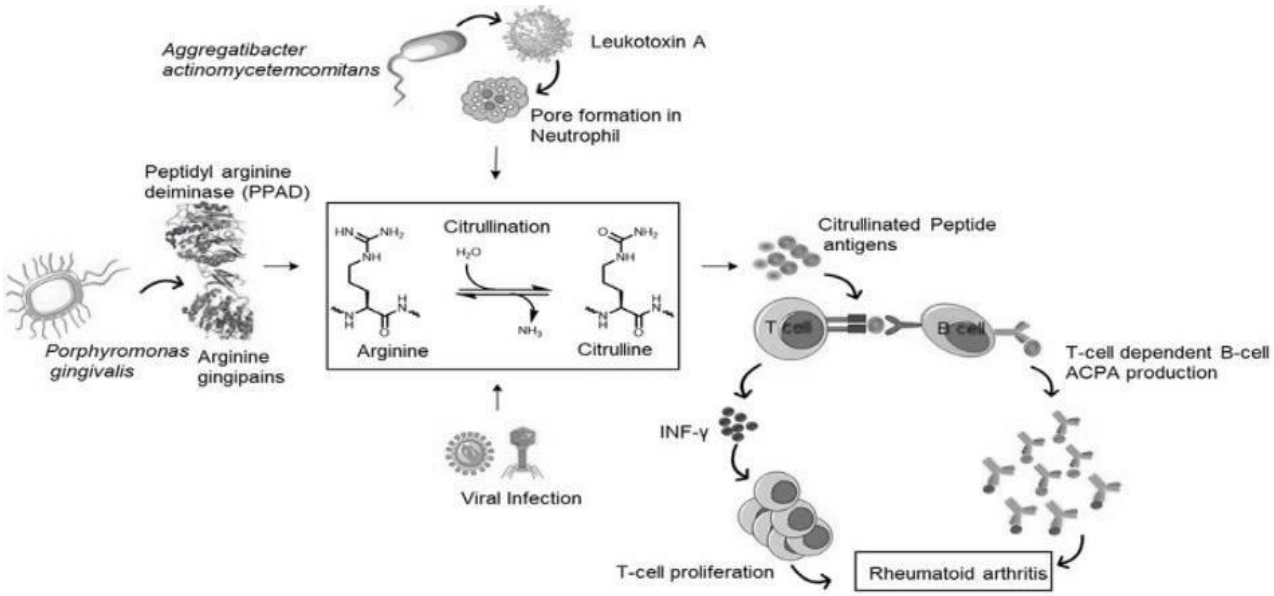

Figure 4. Schematic representation of citrullinated peptide in Rheumatoid Arthritis. [21]

Table 1 | showing the current armamentarium of DMARDs [45]

Table 1 | the current armamentarium of DMARDs

Agent	classification	Dosage	Risks
Sulfasalazine	Anti-inflammatory Anti-microbial	1,000 – 1,500 mg twice daily (oral)	Hepatotoxicity, myelotoxicity, hypersensitivity
Methotrexate	Anti-metabolite	10-25 mg weekly (oral or subcutaneous)	Myelosuppression (dose limiting toxicity) hepatotoxicity with long-term low dose therapy, stomatitis, renal damage
Ciclosporin A	T-cells activation inhibitor	2.5 – 5 mg / kg per day (oral)	Nephrotoxicity, hypertension
Azathioprine	Cytostatic	50 – 200 mg daily (oral)	Hepatotoxicity, myelotoxicity, gastrointestinal
Gold salts	Unknown	50 mg weekly (intramuscular)	Hypersensitivity reactions, nephritis
Leflunomide	Anti-metabolite	10 – 20 mg daily (oral)	Hepatotoxicity, myelotoxicity, hypertension
Hydroxychloroquine	Anti-malarial	200 - 400 mg daily (oral)	Retinopathy
Auranofin.	Unknown	3 – 6 mg daily (oral)	Diarrhea, hypersensitivity reaction

variety of types may occur from this. Hepcidin, a protein that lowers serum iron levels by preventing stomach absorption and holding it in macrophages or liver cells, is another inflammatory cytokine response that the liver generates in significant numbers [17,20]. Pleural effusion, an inflammation and fluid accumulation in the pleural cavities around the lungs, can occasionally prevent lung expansion. While this is happening, fibroblasts in the lung interstitial activate and multiply, resulting in fibrotic or scar tissues that hinder alveolar gas exchange. Most symmetrical instances of rheumatoid arthritis, or those that affect the same joint groups on both sides of the body, such both hands, typically involve numerous joints, usually five or more. Small joints that are frequently affected joints include the metacarpophalangeal and proximal interphalangeal joints of the hands, as

well as the metatarsophalangeal joints of the foot. Over time, they get stiff, especially in the morning or after spending a lot of time sitting still [21].

Clinical Picture

Ulnar deviation of the fingers, which most commonly occurs in the metacarpophalangeal joints of the hand, can occur in rheumatoid arthritis patients. Another type of malformation in the interphalangeal joint is called the boutonniere or buttonhole deformity. When a rupture occurs in the extensor tendon at the back of the finger, the proximal interphalangeal joint flexes and the distal interphalangeal joint hyperextends. The proximal interphalangeal joint hyperextends while the distal interphalangeal joint flexes, resulting in swan neck, another kind of finger deformity [22]. The knee joint may now develop a one-way value when the semi-membranous bursa is filled with fluid from the swelling knee. A Baker or popliteal cyst, which is filled with synovial fluid, may occur from the synovial sac enlarging to the point that it extends posteriorly into the popliteal fossa. Currently, organ-specific symptoms include rheumatoid nodules, or hard mounds of tissue, which are most frequently found in the skin close to pressure points like the elbows. Extra-articular indications of inflammation may manifest as generalized symptoms including fever, achiness, malaise, or weakness. Less frequently, in the heart, sclera of the eye, or the lungs. Additionally, there is a higher chance of developing atherosclerosis and experiencing a heart attack or stroke. Additionally, pleural effusions, anemia, and interstitial lung fibrosis can all cause increasing shortness of breath. The Felty syndrome, a trio of rheumatoid arthritis, splenomegaly, and granulocytopenia that can result in potentially fatal infections, is one extremely dangerous illness connected to rheumatoid arthritis [22,23].

Diagnosis

Antibodies to citrullinated peptide and rheumatoid factor are frequently found in confirmatory blood testing for rheumatoid arthritis. Decreased bone patient with numerous rheumatoid nodules.[43] density, swollen soft tissues, and bony erosions

Rheumatoid Arthritis Treatment Overview

Treatment recommendations include using nonbiologic and, or biologic disease-modifying antirheumatic medications DMARDs within three months of diagnosis to avoid joint deterioration preserve functional status and reduce discomfort[26].when biologic and non-biologic DMARDS are used properly the illness can be in

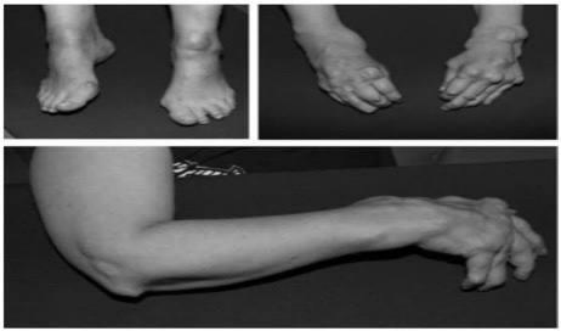

Figure 5. Clinical observation of rheumatoid arthritis seen on imaging tests including X-rays.

Early and aggressive diagnosis, symptom control, careful monitoring of disease status and drug toxicity, and early and robust therapy, including disease-modifying antirheumatic medicines or biologics, are all required for successful rheumatoid arthritis management [7,24].

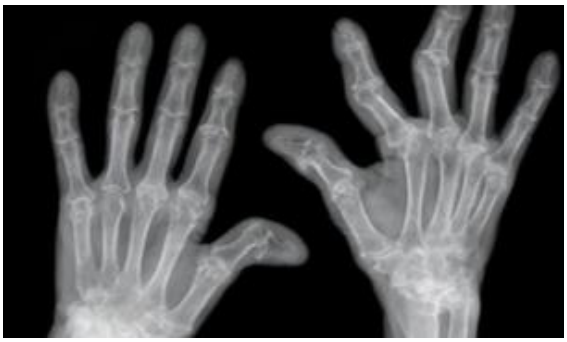

Figure 6. X-ray showing image of rheumatoid arthritis progression in hand joints and complications on nearby tissues such as decreased bone density around affected joints, soft tissues swelling, narrowing of joint space, and bony erosions. [43]

remission as shown by the absence of joint pain and swelling normal inflammasome testing and a lack of erosive radiographic progression. A cost-effectiveness ratio of 4849 per quality-adjusted life-year's figure that accounts for the quality and quantity of life by changing the number of life-years via quality is produced by the early commencement of biologic and nonbiologic DMARDs. Significant improvements have been achieved in the drugs used to treat moderate-to-severe RA during the past 24 years. An international workforce recommended utilizing medications that target. The treat-to-target recommendations promote the core objective of treating RA until low disease activity or disease remission. The recommendations state that until this objective is accomplished, disease activity measures should be utilized, and medication

modifications should be done every three months. After being revised in May 2012, recommendations for the use of biological and non-biologic DMARDS were first made in 2008 [14,15]. Non biologic DMARDs can be administered as monotherapy for mild, moderate, and high disease activity in accordance with the 2012 guidelines if the patient doesn't exhibit signs of a bad prognosis. The possibility for a patient's poor prognosis was assessed using radiographic erosions, functional restrictions, positive rheumatoid factor/anti-CCP antibodies, and extra-articular illness. Combinations of nonbiologic DMARDs should be utilized in patients with moderate disease activity who have poor prognostic characteristics, or in individuals with high disease activity who do not have these symptoms [27]. Rheumatoid arthritis has no known cure, although there are a variety of effective treatments that can aid with symptom relief and decrease the disease's development. Based on the stage of the illness, the three most effective therapy modalities discovered through medication research are split into. For instance, DMARDs (disease-modifying anti-rheumatic drugs) including prednisone and methotrexate, as well as hydroxychloroquine, sulfasalazine, and leflunomide, are two treatment modalities used for long-term aggressive illness. Acute flare-ups of illness may be related to the third major therapy route when NSAIDs are combined with brief glucocorticoid usage. Tofacitinib, baricitinib, and upadacitinib are examples of the relatively new family of medications known as Janus kinases inhibitors (JAK Inhibitors) [28].

Biologics

In the previous five years, the FDA has already authorized four of the nine genetically generated biologic drugs for the treatment of rheumatoid arthritis. The TNF alpha family of drugs also includes the IL-6 inhibitor tocilizumab and the B-cell inhibitor rituximab in addition to certolizumab and golimumab [29]. RA is effectively treated with Biologic agents as shown by multiple measures of disease activity as American College of Rheumatology ACR response rates, which range from 85% to 48%, 50% [30]. (50% improvement in multiple measures of disease activity), which range from 21% to 69%, and 70% (70% improvement in multiple measures of disease activity), which range from 11% to 47%. (With the exception of anakinra, which is discussed below). Despite being effective in treating illness, many medications are costly. Finckh and colleagues recently investigated the cost-effectiveness of RA therapy (as opposed to clinical efficacy), and they discovered conflicting financial evidence to support the short-term usage of biologic medications (less than three months) [31].

Anti-TNF alpha agents

Three anti-TNF alpha have been used for over 10 years in the management of RA. The proinflammatory cytokine TNF alpha has a significant role in the synovial inflammation seen in rheumatoid arthritis. One of the first anti-TNF alpha drugs, infliximab, got FDA clearance for treatment of RA patients in 1999. Infliximab is a chimeric IgG1 monoclonal antibody that targets human TNF alpha. Recombinant human antibody adalimumab was approved by the FDA in 2002 for use in the treatment of rheumatoid arthritis. Monoclonal immunoglobulin G antibody specific for human TNF-alpha. The distinction between these two drugs—adalimumab provides a humanized monoclonal antibody while infliximab supplies a chimeric monoclonal antibody—is clear[29,32].Etanercept, a third early anti-TNF alpha drug, reduces TNF alpha in a different method. Etanercept is a medication that requires a prescription. A dimeric fusion protein made up of the human 75 kDa (p75) TNF receptor's extracellular ligand binding domain and the Fc component of human immunoglobulin G1[32].Two novel anti-TNF alpha medicines for the treatment of RA were authorized by the FDA in 2009. A humanized antibody Fab fragment with specificity for human TNF alpha attached to a polyethylene glycol (PEG) of around 40 kDa is called certolizumab pegol. Due to pegylation, this medication's half-life is 14 days longer than that of other anti-TNF alpha medications. The structure of this substance may provide protection against complement, antibody-dependent cytotoxicity, or another distinctive property, cell death. A human IgG1 monoclonal antibody called golimumab, the second anti-TNF alpha drug recently approved, targets human TNF alpha. Golimumab can neutralize TNF alpha with lower doses than infliximab [33].

Anti-T-cell Co-stimulation

In 2005, the FDA authorized abatacept as a treatment for RA. This substance is a soluble fusion protein made up of the human immunoglobulin G1's modified Fc region and the cytotoxic T lymphocyte-associated antigen 4 (CTLAA4) (CTLA4). The inhibitory molecule CTLA4 has a

greater affinity for CD28 compared to CD80 or CD86. The T-cell is activated as part of its normal physiological process when CD28 on the T-cell contacts with CD80 or CD86 on the antigen-presenting cell. Abatacept selectively alters T-cell activation by outbidding CD80 and CD86 for CD28 binding [34].

IL-6 receptor inhibitors

Tocilizumab is a humanized monoclonal antibody that works by attaching to the IL-6 receptor. IL-6 is a proinflammatory cytokine that is overexpressed in RA patients. On cell surfaces, there are two IL-6 receptors (CD126 and IL6R alpha) that mediate IL-6 actions. Tocilizumab, which acts on both receptors, was licensed by the FDA for the treatment of RA in 2010[35].

JAK Inhibitor

A JAK inhibitor, also known as a Janus kinase inhibitor or jakinib, works by competitively binding to the adenosine triphosphate-binding site of JAK and reducing JAK enzyme activity, hence preventing cytokine signal transmission and action [36].

Acute Flares

A Rheumatoid Arthritis flare can involve any symptom of the condition, although it is most typically characterized by acute pain and stiffness in the joints. The duration of a flare might range from a few hours to several days or weeks. If a flare does not improve after 7 days, you should consult a doctor. The doctor may advise the patient to change their medication. One or more factors, such as food, stress, sickness, weather changes, smoking, and overexertion, induce RA flare-ups[37]. The most frequent symptoms of RA are joint pain and swelling, weariness, and joint stiffness, particularly in the morning and after prolonged sitting. Nonsteroidal anti-inflammatory medicines (NSAIDs), which are used to treat acute pain and inflammation, can be used to manage flare-ups. Usually, these are the initial medicines given to RA patients [38].

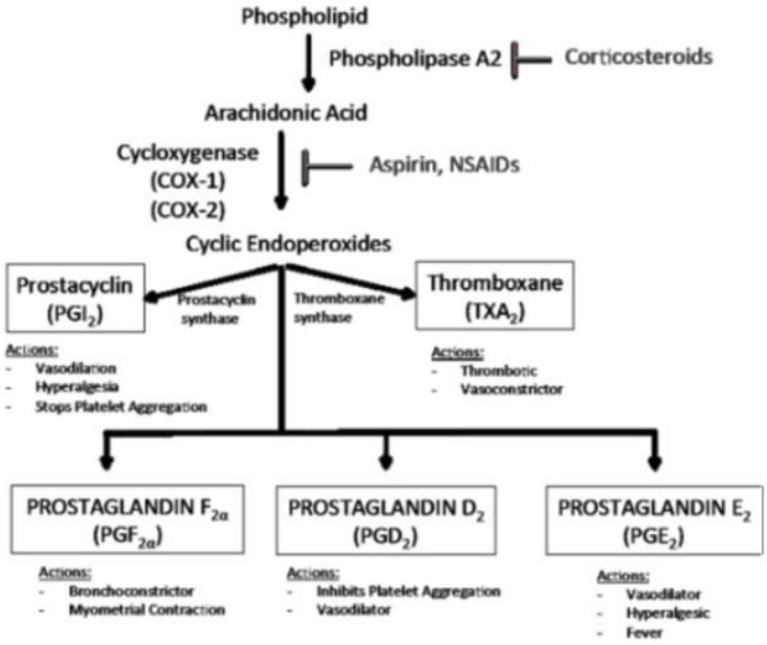

Figure 7. Schematic representation of mechanism of action of NSAIDs and Corticosteroids in treatment of Rheumatoid Arthritis. [44]

Ibuprofen and naproxen are two NSAIDs that are available over the counter, even though physicians can prescribe them at larger dosages. In rare circumstances, dehydroepiandrosterone (DHEA) and short-term glucocorticoid usage may also be employed [12,38].

Investigation Of Biologics

Thirteen Phase III trials including seven different types of medicines are being conducted to investigate. new biologic drugs for rheumatoid arthritis therapy [39,40].

Conclusion

The number of painful joints, the number of swollen joints, and the overall ratings from the doctor and the patient all showed significant improvement (p 0.001). In > 65% of the patients, the joint pain and swelling indices showed a 50% improvement. Prednisone dosage was significantly decreased.

Sixteen participants left the study. Three study participants had to stop taking the drugs due to toxicity (alopecia 1; pneumonitis 2). 10 patients (38%) had finished the study at 132 months, and 3 patients (11%) had stopped due to MTX toxicity. MTX was an effective treatment for RA in the most diagnostic studies. Despite all these drug development studies and research, rheumatoid arthritis remains an extremely deadly disease with no cure. This field is still being studied in the hopes of finding a cure for this disease. But I hope, with the development of research methods and treatments, that a complete cure for this disease will be found.

Conflicts of Interest: The authors declare no conflict of interest.

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