REVIEW ARTICLE

A Critical Study on the Synthetic Medication Pattern in the Management of Rheumatoid Arthritis

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Received: 02nd March, 2023; Revised: 10th April, 2023; Accepted: 15th June, 2023; Available Online: 25th June, 2023

ABSTRACT

An inflammatory condition known as arthritis affects one or more joints in the body. The pathophysiology of rheumatoid arthritis (RA), a diverse ailment with a complicated and still poorly known pathogenesis, involves many different cell types in the destruction of the joints. Due to this complexity, clinical course and severity vary widely amongst patients and genetic and/or environmental factors may also impact them. In addition to the conventional synthetic disease-modifying anti-rheumatic drugs, biologics have demonstrated efficacy and safety in symptomatic relief, reducing bone loss, and maintaining the function, which has considerably improved the treatment of rheumatoid arthritis. Since current drugs periodically fail, only substantially treat the ailment or have unfavorable side effects. There are still unmet treatment requirements in rheumatoid arthritis despite the availability of a wide range of therapeutic choices and their combinations. Unfortunately, the 'nonresponse' pathways are still not fully understood, although they most definitely have to do with the covert variability of the pathophysiology of the disease. In this research, we will narrate the current and upcoming biological treatments and their cellular aims.

Keywords: Cyclooxygenase, Natural products, Non-steroidal anti-inflammatory drugs, Rheumatoid arthritis, Methotrexate, Interleukin.

International Journal of Drug Delivery Technology (2023); DOI: 10.25258/ijddt.13.2.45

How to cite this article: Chauhan VS, Avijit M, Shobhini C. A Critical Study on the Synthetic Medication Pattern in the Management of Rheumatoid Arthritis. International Journal of Drug Delivery Technology. 2023;13(2):759-769.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

A joint ailment known as arthritis causes one or more joints in the body to become inflamed. There are more than 100 different types of arthritis. Osteoarthritis (OA), a chronic joint condition, is the most common kind of arthritis. Other types include psoriatic arthritis and rheumatoid arthritis-related inflammatory disorders, including lupus and gout. The most common joint condition is osteoarthritis. A significant section of people around the world has pain and impairment in body part as a result. The disease advances over years till it results in a reduction of joint function. Aging, genetics, and improper joint stress can all speed up the advancement of osteoarthritis.[1,2] Interleukin-6 (IL-6), tumor necrosis factor (TNF), Interleukin-1 (IL-1) local synthesis and release of proinflammatory cytokines, which are essential in the pathophysiology of OA, are interleukin-1, TNF-α, IL-6, and IL-1.[3]

The main target of rheumatoid arthritis is the joints. It is a systemic inflammatory condition that is persistent. The activation of the synovial membrane covering the joints, which leads to an invasion of the bone and cartilage and ultimately increases joint dysfunction, distinguishes RA from those other chronic inflammatory disorders.[4,5] Even though the molecular processes for osteoarthritis and rheumatoid arthritis are different, cartilage disintegration is a fundamental feature of both ailments that correlates to the inflammation and joint deformation that patients experience.

A new medicine must undergo a clinical trial process to prove both safety and effectiveness before being approved for broad usage. Osteoarthritis and rheumatoid arthritis have no known treatments as of now. The only existing treatments focus on minimizing symptoms, including pain and inflammation, keeping joints mobile, and preventing function loss. The primary objectives of the ideal osteoarthritis therapy are symptom modification, which involves lowering inflammation and pain and structural modification, which involves protecting joint structure and delaying joint deterioration to retain articular function.[6]

As we learn more about the fundamental processes of immune-mediated inflammation underlying the etiology and development of this chronic musculoskeletal ailment, disease-modifying anti-rheumatic medications (DMARDs) for rheumatoid arthritis have become more effective.

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In contrast, the majority of older medications used to treat osteoarthritis are NSAIDS. This fact emerges from what appears to be a discrepancy between the promising outcomes with novel experimental therapies in preclinical research and in animal studies of osteoarthritis and the somewhat underwhelming outcomes when these medications are subsequently tested for their action in osteoarthritis clinical trials.[7]

Causes

The cartilage is destroyed as a result of arthritis. A joint is often protected by cartilage, which allows easy movement. The procedure causes the synovium to enlarge as a result of joint cell hyperplasia, an accumulation of synovium, and the growth of synovial panes (sinusitis). Joint alkalosis and the disease's pathophysiology are responsible for articular cartilage degeneration.. In addition to pericardium, lungs, nodular lesions, pleura, and, sclera, disseminated inflammation from arthritis can also be found in subcutaneous tissue, pleura, pleura, and pericardium. Rheumatoid arthritis, despite its unknown etiology, is thought to be a disease with a systemic autoimmune component. It's chronicity and progression are significantly influenced by autoimmune disease.[8]

Signs and symptoms

Figure 1 shows the representation of rheumatoid arthritis

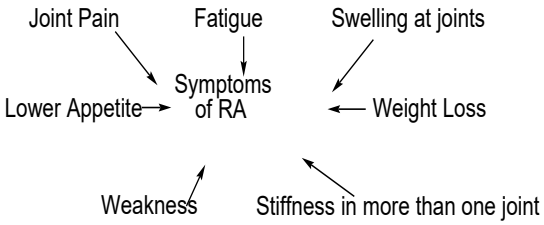


Figure 1: Pictorial representation of rheumatoid arthritis

Pathogenesis of Rheumatoid Arthritis

The causes of Rheumatoid arthritis's origin is still unknown, however, across the past 20 years, knowledge of its pathogenic pathways has increased. Through activated endothelial cells that express different adhesion molecules, a large number of cells are able to enter the synovium. Toll-like receptors are pattern-recognition molecules found on many different cell types, particularly dendritic cells. These molecules adhere to different self- and regional antigens as part of the innate immune system response function, become stimulated as a result, and then act on adaptive immune system cells. It's likely that antigen-presenting cells like macrophages, dendritic cells, or activated B cells expose T cells to arthritic antigens. The so-called similar epitope of the Human leukocyte antigen 04 cluster (HLADR), which is necessary for the interaction of specific antigens to MHC class II molecules, is present in more than 80% of patients with rheumatoid arthritis. These genotypes share an incredibly similar amino acid sequence in the third hypervariable region of the HLADR domain, which facilitates the binding of certain peptides and alters how antigens are presented to T-cell receptors.[9]

The peptide-MHC complexes rejuvenate the T-cell receptors, but for T cells to be fully active, they often require at least a second signal, delivered after an APC's co-stimulatory ligand binds to the appropriate T-cell receptor. The CD28 that is generated on T cells is connected to the CD80 and CD86 surface components of the APC, which furthers T-cell activation. T cells subsequently produce CTLA-4, which can send inhibitory signals and has a high affinity for CD80 and CD86 than CD28, to limit overshooting activation.[10,11]

Although its precise pathophysiology is uncertain, rheumatoid arthritis has documented the presence of different inflammatory mediators such tumor necrosis factor-Interleukins (IL-18 and IL20), monocyte chemoattractant protein-1 (MCP-1), C reactive protein (CRP), TNF-, CD40L, and receptor activator. Matrix metalloproteinase-9 (MMP-9), cell adhesion, and nuclear factor-B ligand (RANKL) fractalkine significantly impact how the illness develops (Table 1).[12]

Preclinical RA

The numerous IgM-Rheumatoid factors, RA33, and others specific to the illness autoantibodies, including Perinuclear factor, calpastatin, and rheumatism risk factor (RF) all play a significant role in the etiology of rheumatoid arthritis. To make the diagnosis as a sign of RA, the American Rheumatism Association states that serological criteria are used with arthritis risk factor.[13,14]

Genetic Factors

The relationship between genetic makeup and a number of environmental factors affected how RA developed. A molecular biology study has discovered that the MHC genes are significantly involved in the cause of the disease.[15] Given that several alleles in the DRB1*04 and *01 clusters encode specific "shared-epitope" regions within the DRB1 molecule, the HLA-DRB1 gene has been acknowledged as one of the most significant genetic correlations in MHC in RA.[16]

Additional genetic variables in the RA aetiology included CTLA4, CSF2, CD83, PTPN2, PDE2A-ARAP1, ANXA3, and PLD4.[17-21]

Environmental Factors

Recent research has confirmed that certain environmental factors enhance the incidence of RA. Smoking and drinking are the two risk factors that are most prevalent.[22] Other risk factors for arthritis include increased Na intake, contact dermatitis (AD), autoimmune thyroid dysfunction (AITD), schizophrenia, smoke, and endometriosis.[23,24]

Role of Interleukin-1

T cells were activated by IL-1, which also encouraged polymorphonuclear leukocyte, lymphocyte, and monocyte chemotaxis, stimulated tissue macrophages to release proteases, and increased the penetration of these particles into incited tissues. IL-1 increased fibroblast propagation, which resulted in pannus formation, and induced the growth of (PGE2). Synovial fluid samples from RA patients had shown

chemotactic activity in *in-vitro* tests, supporting the availability of IL-1 in the RA synovial sheath. IL-1 aided in the breakdown of osteoarthritis, bone, and periarticular tissues by stimulating synovial fibroblasts and chondrocytes. Increased proteoglycan breakdown and decreased proteoglycan synthesis are two of IL-1's impacts on cartilage. More proteoglycan breakdown was stimulated by producing neutral metalloproteinases such as collagenase and strome lysin, which are effective connective tissue-degrading enzymes. *In-vitro* testing has shown that IL-1 can selectively cause the release of Strome lysin. This research also showed that strome lysin expression was more effectively induced by IL-1 than by TNF, and that the two factors worked together to increase strome lysin expression.[25, 26]

Synthetic Treatment of Arthritis

Current treatment for rheumatoid arthritis

- NSAIDS- Aspirin, Indomethacin, Ibuprofen, Ketoprofen, Etodolac
- TNF inhibitor- Infliximab, Adalimumab
- IL-1 Antagonist – Anakinra
- Co-stimulation blockers – Abatacept
- Immunosuppressants- Methotrexate, Azathioprine, Cyclosporine
- Sulfasalazine
- Hydroxychloroquine sulphate
- Tofacitinib -Janus kinase inhibitor
- Leflunomide
- Glucocorticoids

NSAIDS

This well-respected group of drugs successfully reduces the pain, swelling, and stiffness brought on by rheumatoid arthritis. NSAIDs can be extremely helpful. However, there is no proof that NSAIDs can stop the clinical or radiographic development of RA; hence, they should not be administered alone in patients with the diagnosis.[27, 28]

Inhibiting cyclooxygenase is a factor in the effectiveness of NSAIDs (COX). The proinflammatory prostaglandins created by COX from arachidonic acid in cell membranes might result in local vasodilation and increased pain (Flowchart 1).[29]

Both the human COX-1 and COX-2 isoforms have undergone in-depth research. Continuous COX-1 production occurs in the stomach, platelets, kidneys, and intestines and is necessary for functions such as Gi defense against hydrochloric acid. COX-2, an isoform that is only constitutively synthesized in a select few tissues, produces prostaglandins E2 and I2 (such as the brain, and kidney). These prostaglandins are elevated during an inflammatory response. NSAIDs have been divided into subclasses based on their selectivity with regard to the blockage of these isoenzymes.[29,30] For short periods of time, NSAIDs are frequently well received; but chronic usage may cause GI problems; such as ulcer formation, bleeding, and perforations, which are anticipated to be the cause of 16,500 GI-related fatalities and more than 100,000 hospital admissions annually in the US.[31]

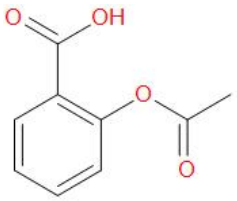


Figure 2: Aspirin

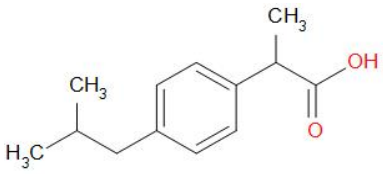


Figure 3: Ibuprofen

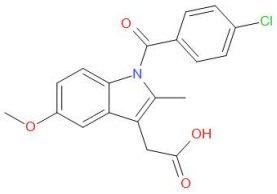
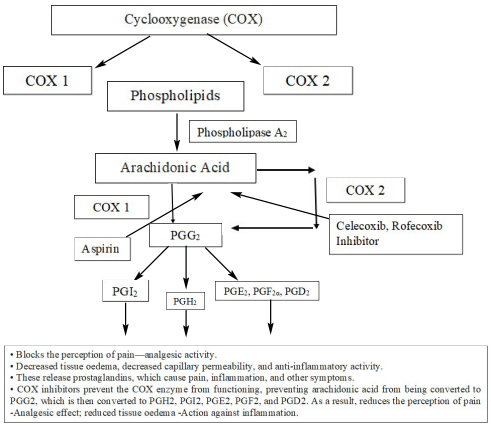


Figure 4: Indomethacin

Mechanism of NSAIDS



Flowchart 1: Mechanism of NSAIDS

TNF Inhibitor Agents

Infliximab

Infliximab was the first anti-TNF medication tested for the treatment of rheumatoid arthritis; nevertheless, it was initially accepted for treating Crohn's disease.

A recombinant protein called infliximab combines the Fc part of human immunoglobulin G1 with the variable portion of a rodent's anti-TNF antibody (IgG1).

It attaches to membrane and solvent-bound TNF, preventing it from adhering to its receptor and starting an immunological reaction toward TNF-expressing cells that is dependent on supplementation and antibodies (Figure 5).

Infliximab is infused i.v. over a two-hour period at a dose of 0.003 g/kg; however, the dose does need to be enlarged to 10 milligrams based on the patient's response. RA is normally

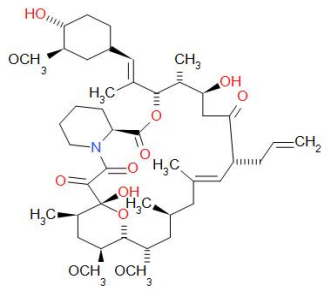


Figure 5: Infliximab

infused at weeks 0, 2, and 6; after that, a maintenance infusion is administered after 8 weeks Figure 6 shows structure of etanercept. [32]

Interleukin-1 Antagonist

Anakinra

After being extracted, processed, and duplicated as a cDNA, endogenous IL-1Ra has been expressed in *E. coli*. With a molecular mass of 17 kDa, anakinra binds to Interleukin-1 sites on chondrocytes and T lymphocytes with almost the same affinity as IL-1. The requirement for a secondary cellular membrane component known as IL-1 supplementary protein helps explain how anakinra works (IL-1AcP). The IL-1AcP joins the combination and starts cell stimulating when IL-1 attaches to the IL-1RI. There is no reaction when anakinra binds to the IL-1RI because the receptor cannot bind to it.[33]

The mode of action of indigenous IL-1Ra is similar to anakinra. Anakinra antagonizes IL-1- induced collagenase, (PGE) 2, and T-cell propagation generation in cultured synovial cells, demonstrating antagonistic effects on IL-1- induced proteoglycan disintegration, metalloproteinase production, and secretion of PGE2. Additionally, it stops the resorption of bone in produced mouse and rat bones. In a dose-dependent manner, Anakinra reduced the IL-l-induced activation of hyaluronic acid in animal synovial tissue and refined cartilage. Anakinra

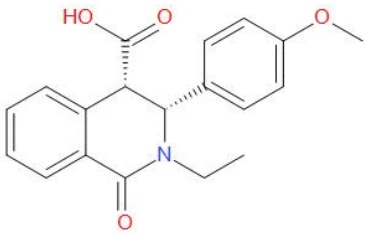


Figure 6: Etanercept

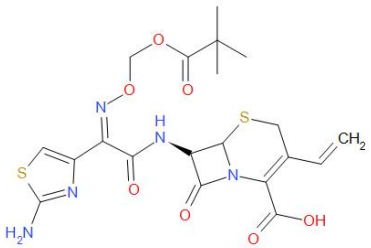


Figure 7: Anakinra

in the same trial corrected the reduction in proteoglycan compound brought on by IL-1. Anakinra prevented IL-1 from attaching to the articular chondrocytes of rabbits. Additionally, anakinra prevented matrix metalloproteinase and IL-l-activated rabbit osseous chondrocytes from synthesizing prostanoid (Figure 7).[34]

Pharmacokinetics of Anakinra

A - By subcutaneous route with 95% bioavailability
D- Plasma concentration 3 to 7 hours later, Half-life – 4 to 6 hours (S.C), 2 to 3 hours (i.v.)
M- By proteases throughout the body
E- By kidney

Immunosuppressant Agents

Methotrexate

Despite the latest emergence of numerous new aim management for rheumatoid arthritis (RA), methotrexate has continued to serve as the "anchor drug" for the majority of recipients since the late 1980s.[35] Despite this, the drug has been used to manage arthritis widely and for a long time, its precise mode of action is still unclear.

Methotrexate was shown to be helpful in rheumatoid arthritis patients at considerably lower levels (15–25 mg weekly) despite its initial use as a folate pathway blocker that inhibits dihydrofolate reductase (DHFR) when given at extremely high dosage for leukemia (as high as 1-gm in a single dose). Blocking purine synthesis causes cell cycle arrest in the S phase, which ultimately leads to apoptosis. This is how oncologic drugs work (Figure 8).

High doses of folinic acid and calcium can be utilized to combat the side effects and clinical ramifications of dosage methotrexate therapy for cancer. This implies that methotrexate's primary mechanism of action in RA is unlikely to be the reduction of purine metabolism, implying that other components must be underlying the drug's efficacy in RA patients.

Pharmacokinetics of Methotrexate

A-Orally absorbed at doses between 15 to 25 mg
D-Peak plasma concentration last for 1 to 2 hours
M-Metabolised by liver circulation
E-By renal glomerular filtration system and active secretion

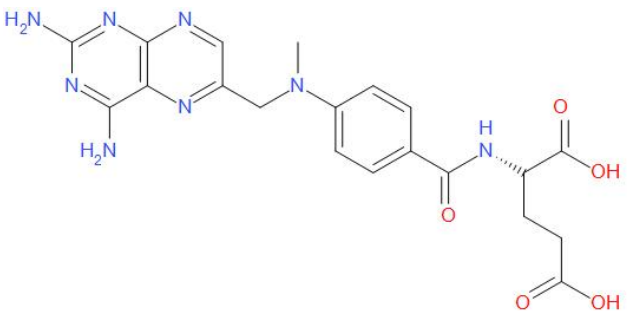
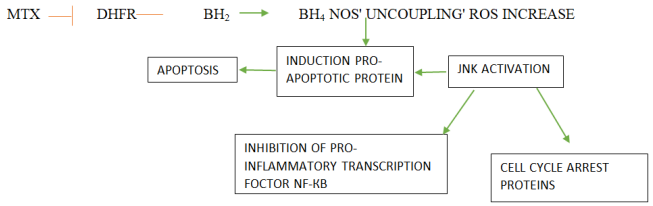


Figure 8: Methotrexate

Mechanism of Methotrexate in RA



Flowchart 2: Mechanism of Methotrexate in RA

Cyclosporine

In comparison with clinical trials, cyclosporine, a calcineurin antagonist frequently used to security measure to ensure organ transplant patients, approves effective treatment of RA. However, due to the availability of relatively safe DMARDs and biological agents, it acts as a third-line agent following the decline of first- and second-line medications. The majority of the initial trials were exclusively open to people with incurable RA.

Cyclosporine was initially administered at a daily dose of 5 to 10 micrograms, which is currently regarded as high. In nine investigations, 283 individuals were treated with cyclosporine; 8% quit the medication early due to inefficacy, while 17% did so due to side effects. Clinical indicators are improved with cyclosporine but have no effect on how quickly erythrocytes sediment. Nephrotoxicity and gastrointestinal intolerance are the most significant adverse effects. With the current pharmaceutical schedule (beginning daily dose, 0.0025 g/kg), the former is only marginally relevant, and the increases should adhere to the adage "go slow, go low." Cyclosporine administration during the early stages of RA may be advantageous (Figure 9).[36-42]

T-lymphocyte proliferation and proliferation are suppressed by cyclosporine. It specifically suppresses the generation of interleukin-2 and other cytokines by CD+ (T helper) lymphocytes and their antigen-induced activation. Through successfully treating autoimmune illnesses, cyclosporine has demonstrated its ability to interfere with active immune responses, most likely by preventing lymphocytes from secreting cytokines. The drug inhibits the transcription of IL-2 receptors, whose induction is required for T-cell proliferation, and prevents the translation of IL-2 and interferon-y genes in vivo.[43,44] it is understood that cyclosporine reversibly blocks early, calcium-dependent T-lymphocyte stimulation processes and that its numerous, most likely molecular targets include the cellular membranes, cytoplasm, and nucleus. Cyclosporine absorbs and its quantities are regulated by the recently identified enzyme cyclophilin in systolic & nuclear cells that are targeted.[43, 44]

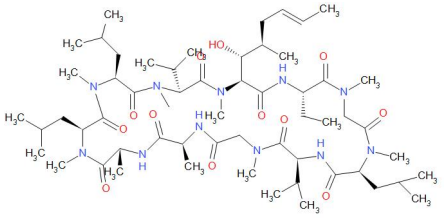


Figure 9: Cyclosporine

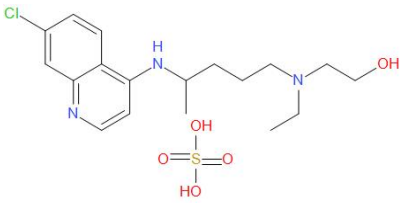


Figure 10: Hydro chloroquine sulphate

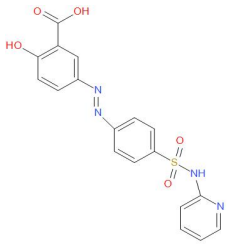


Figure 11: Sulfasalazine

Hydroxy Chloroquine and Sulfasalazine

In the 1950s, rheumatoid arthritis and chronic lupus were first treated with the antimalarial medication hydroxychloroquine. Its precise mode of action is uncertain; however, it seems to disrupt antigen presentation, protect the integrity of lysosomal membranes, and halt deoxyribonucleotide metabolism.[45, 46] Hydroxychloroquine taken orally is quickly absorbed, strongly adheres to cells, and has an elimination half-life of roughly 40 days. Due to the extremely unusual but potentially treatable disease known as retinopathy, which is almost never found at daily doses below 0.0065 g/kg, routine retinal exams are indicated. The most common side effects are GI-related (diarrhoea, cramps, and nausea).[47] A 400 mg oral dosage of HCQ sulphate is advised each day. At most, it seems to have modest effectiveness; frequently, action doesn't begin immediately. It is unusual to use the drug alone to treat arthritis; rather, its key therapeutic benefit comes from pairing it with other DMARDs (Figures 10 and 11).[48]

In the 1930s, sulfasalazine was created and produced on the unsubstantiated presumption that a pathogen was the cause of RA. Following absorption, microorganisms in the colon split the molecule into 5-aminosalicylic acid and sulphapyridine. The majority of sulfasalazine's therapeutic effects appear to be mediated by sulphapyridine.

Most adverse effects are GI-related (nausea, stomach discomfort and vomiting) hematologic in character, despite the fact that the medication is typically considered protected and well relevant (neutropenia, thrombocytopenia). DMARD sulfasalazine has long held a monopoly in Europe due to its efficiency and affordable price. According to RCTs, It is similar to other DMARDs such as leflunomide, penicillamine, and gold sodium thiomalate.[49, 50]

Janus Kinase Inhibitor (JAK Inhibitor)- Tofacitinib

An oral JAK antagonist called tofacitinib is used to treat RA. It is not a biologic, rather, it is a targeted synthesized small

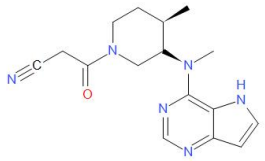


Figure 12: Tofacitinib

molecule with a M.W. of 312.4 Da (or 504.5 for the citrate salt). Tofacitinib acts intracellularly as opposed to targeted biological therapies that target extracellular targets such as specific soluble cytokines (like TNF), cytokine receptors (like IL-1R and IL-6R), or other cell membrane receptors (like CD20, CD80, and CD86). High passive *in-vitro* permeability characteristics of tofacitinib are compatible with transcellular diffusion-mediated intracellular entry. Tofacitinib, a competitive, reversible inhibitor, attaches to the ATP-binding domain in the JAK kinase domain's catalytic cleft. While ATP and tofacitinib have a structure, the latter does not contain a triphosphate group (Figures 12).

By attaching to the ATP site, tofacitinib antagonizes the phosphorylation and stimulation of JAK. This stops STATs from being phosphorylated and stimulated, which in turn stops gene transcription from being activated. The cytokine production is consequently decreased and the immune system reaction is altered. Tofacitinib is an effective antagonist of the JAK class of kinases and exhibits excellent selectivity against other mammalian kinases. *In-vitro* kinase assays show that tofacitinib suppresses JAK1, JAK2, JAK3, and, to a lesser extent, TYK2. Tofacitinib as a choice antagonizes cytokine receptors' signaling linked to JAK3 and/or JAK1 in biological conditions where JAKs signal in pairs with functional differentiation over channels that signal via pairs of JAK2.

Tofacitinib specifically inhibits IL-15-induced activation of STAT5 with a half maximum growth inhibition (IC_{50}) of 56 nm and IL-6-convicted activation of STAT1 and STAT3 with IC_{50}s of 54 and 367 nm, respectively, in human whole blood cellular tests (15). JAK1 is required for both IL-15 and IL-6, and JAK3 is required for IL-15. Conversely, Tofacitinib has a lower potency and an IC_{50} of 1377 nm, inhibiting GM-CSF-induced phosphorylation of STAT5, a JAK2-mediated signaling event.[51,52]

Glucocorticoids

Glucocorticoid therapy benefits were first recognized 65 years ago. Philip Hench 1949 was the first to note the remarkable impact of component E on rheumatoid arthritis. Today, glucocorticoids are required for the treatment of a variety of inflammatory rheumatic diseases (Figures 13 and 14). [53]

Despite the development of complementary therapies, such as treatment approaches suitable for many rheumatic illnesses, glucocorticoids continue to be the most often prescribed class of anti-inflammatory drugs, with use increasing recently. The data from community surveys showed that 0.5% of the overall community and 1.4% of women over the age of 55 take glucocorticoids. Globally, between 14.6 and 90% of RA patients are receiving glucocorticoid therapy.[54]

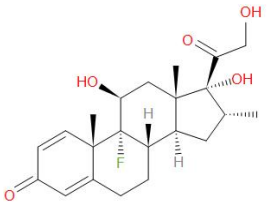


Figure 13: Dexamethasone

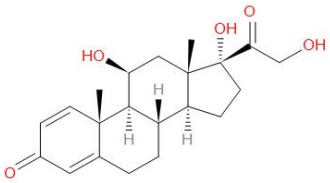


Figure 14: Prednisolone

The usage of glucocorticoids, which are powerful anti-inflammatory and immunosuppressive medications, is constrained due to concern over potential side effects. Cortisol-cytosolic glucocorticoid receptor subunit clusters inhibit the trans regulation of two (proinflammatory) transcription factors, nuclear factor B and activator protein 1. This prevents the creation of (proinflammatory) proteins.

However, cell, tissue, or organ adjustments typically take hours to days.[55,56]

Typically, it takes at least 30 minutes for genomic events to affect the production of regulatory proteins.[57] Until recently, it was believed that the majority of the glucocorticoid therapy's anti-inflammatory and repressive effects were based on trans-repression, while its negative effects, with the exception of a higher risk of illness, and metabolic impacts were based on transactivation. This viewpoint has been slightly modified in light of the theory that some of the main anti-inflammatory effects of glucocorticoids are caused through gene activation.[55,58]

In extremely high therapy levels, nongenomic events also take place with immediate repercussions.[56] These non-genomic pathways are mediated by the cell's glucocorticoid receptor, cytoplasmic glucocorticoid receptor, and non-specific interactions with the membranes of cells and organelles, including the membranes of mitochondria. The extent of glucocorticoid preparations› genomic effects determines their dose equivalence. Specific glucocorticoid preparation dosages are typically stated in terms of the potency of prednisone, the most widely used preparation.[59-61]

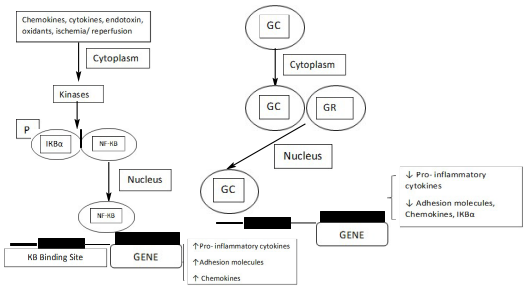


Table 1: Important cytokines and signal mediators associated with RA pathogenesis therapeutic aims for the present and future.

S.no.	*Inflammatory mediators*	*RA related effects*	*Treatment target*
1.	IL-6	Activates osteoclasts and leukocytes and draws in neutrophils. controls the differentiation, growth, and production of B and T cells as well as antibodies. encourages VEGF synthesis and aids in pannus development. causes anaemia and the synthesis of acute-phase proteins.	**Tocilizumab:(**IL-6 receptor inhibiting recombinant humanised monoclonal antibody, inhibits signalling and B cell activation)
2.	IL-1	Releases cytokines, chemokines, MMPs, and PG from synovial fibroblasts, endothelial cells, and leukocytes after activating these cells. increases the release of reactive oxygen intermediates and monocyte cytokines. activates osteoclasts and causes chondrocytes to produce matrix enzymes. controls the expression of endothelial cell adhesion molecules.	**Anakinra:** (IL-1 receptor antagonist)
3.	TNF-alpha	Produces cytokines, chemokines, adhesion molecules, PG release, and matrix enzymes by activating polymorphonuclear leukocytes, endothelial cells, monocytes, and synovial fibroblasts. By causing T-cell death, clonal regulation, and TCR malfunction, it inhibits regulatory T-cell function. reduces the production of collagen and the proliferation of synovial fibroblasts. activates osteoclasts and causes cartilage to be resorbed. causes the creation of acute-phase proteins.	**Infliximab:**(TNF-alpha chimeric monoclonal antibody that prevents TNF-alpha from interacting with its receptors). **Adalimumab:**(Humanized monoclonal-anti-TNF-alpha antibody; prevents TNF-alpha from interacting with its receptors). **Etanercept:**(Human TNF-alpha receptor 2 and human IgG1 Fc region fusion protein; prevents TNF-alpha from attaching to its receptors). **Golimumab:**(Human TNF-alpha monoclonal antibody that prevents TNF-alpha from attaching to its receptors).
4.	IL-17A and 17F	Operate in concert with IL-1beta, TNF-alpha, and IFN-gamma to promote chondrocyte, osteoclast, and synovial fibroblast activation. Increase the synthesis of the chemokine IL-6 to boost the immunological response and to attract monocytes and neutrophils. encourage the invasion and activation of T cells.	**Secukinumab:** Phase III trials for (anti-IL-17A monoclonal antibody) are being conducted in patients who did not respond well to prior TNF-blocker therapy. **Brodalumab:**(monoclonal anti-IL-17 receptor subunit A antibody) in phase II trials with successful outcomes.
5.	JAK (Janus kinase)	Tyrosine kinase that controls the synthesis of cytokines, immunoglobulins, and leukocyte maturation and activation.	**Tofacitinib:** (Combined JAK1/2/3 Inhibitor): This medication is currently approved by the FDA (the EMA rejected the initial application due to concerns about the safety profile) and is indicated for the treatment of moderately to highly active RA with an insufficient response to one or more DMARDs.

Newer Agents For Rheumatoid Arthritis

Rituximab

Rituximab is a monoclonal antibody created from recombinant human and rat proteins only directed at mature and pre-B cells showing the CD20 antigen.[62, 63] Numerous methods are used to precisely decrease CD20+ B cells.[59, 60] The ability of rituximab to manage CD20+ non-Hodgkin lymphoma is well documented.[60, 61] In the USA and Europe, it is now approved for the management of RA in patients who have failed to respond to TNF-inhibitor therapy. B lymphocytes perform a wide range of tasks in the aetiology and progression of disease, including the presentation of antigens, the synthesis of antibodies, and cytokine production. This result backed up the usage of rituximab to treat this ailment. The precise method through which rituximab works for the treatment of arthritis is uncertain, despite the fact that it greatly lowers rheumatoid factor concentrations. In spite of receiving weekly dosages of 10 mg of methotrexate, patients in a six-month phase II trial with active chronic autoimmune rheumatoid arthritis discovered that rituximab in conjunction with methotrexate was much more effective than methotrexate advancement alone. This comes after brief open-label research among people with rheumatoid arthritis. Then, 465 people who had active rheumatoid arthritis taking 10–25 mg of MTX weekly participated in the DANCER 24-week phase IIb amount of the drug study. The impact of glucocorticoids on effectiveness and negative effects was also evaluated in this experiment. Patients were randomly assigned to nine treatment arms that either consisted of placebo infusions on days 1 and 15 or rituximab injections at 0.5 or 1 g. The primary efficacy study was only performed on patients who had rheumatoid factor positivity. Inducing ACR20 and 50 responders at mid-fifty percentile points and 30% levels, respectively, rituximab substantially outperformed placebo. However, these ACR reactions were comparable when the two rituximab groups were compared, with the 1000 mg dosage showing a little higher level of response. From 8 weeks on, rituximab efficacy (in comparison to placebo) was obvious. In this trial, a small subset of patients who tested negative for the rheumatoid factor had an ACR20

response to rituximab that was considerably (p0001) higher than the response to placebo (12%).[62]

Abatacept

The presentation of information by APC and stimulated molecules like CD80 or CD86 are required for T-cell stimulation. These two molecules bind with CD28 on T lymphocytes, although CTLA 4—a molecule generated on activated T cells that regulated T-cell dysregulation—had a greater selectivity for these two substances. The extramural component of human CTLA 4 and a portion of the Fc region of the human IgG1 are combined to form the recombinant fusion protein known as abatacept.[63] This CTLA 4 immunoglobulin molecule competes with CD28 for the binding of CD80 and CD86 and has a high affinity for CD28, preventing T-cell activation. An arthritic murine model that uses CTLA 4 antibody has demonstrated success. In a different phase III study (ATTAIN), 393 participants with active rheumatoid who had a poor response to TNF antagonists were examined. Until day 141, these patients received either abatacept (10 mg/kg) or a placebo.[64]

The safety and effectiveness of abatacept were evaluated to infliximab (at the least tolerable dose of 3 mg every 8 weeks) and a control medicine in a one-year study. Similar results were shown at six months, and at one year, 46% of patients who took abatacept had an ACR50 result compared to 36% of those who received infliximab; radiography data were not published. Compared to infliximab, abatacept was accompanied with less side effects.

Tocilizumab

A pluripotent cytokine that stimulates macrophages, osteoclasts, T cells, and B cells, interleukin 6 is a crucial regulator of the hepato acute-phase response. The potential for IL-6 as a pharmacological treatment was looked into in a small open trial using a mouse anti-IL-6 that decreased clinical disease activity since IL-6's pathogenetic involvement in RA is linked to these actions. The next trials investigated tocilizumab, a humanized anti-IL-6 receptor, with rheumatoid arthritis. These molecules cannot bind interleukin 6 on their own, but instead dimerize to create a trimolecular receptor complex on the membrane. Tocilizumab specifically targets the beta chain to stop the homodimerization of the transmitting gp130 moieties and the ligation of IL-6. Anti-interleukin-6 receptor blocks interleukin-6-induced osteoclast formation in vitro and reduces chronic collagen arthritis in rats and monkeys. A Japanese orphan drug licence has been granted for this substance, which has been studied as a potential therapy for an area of ailments, including Castleman's syndrome. A Japanese phase II trial of three injections every four weeks of either 0.004 or 0.008 g/kg tocilizumab or placebo was conducted after phase I studies showed the efficacy of one injectable of tocilizumab at 0.004-0.01 g/kg. Twelve weeks were selected as the endpoint (i.e., four weeks after the 3rd infusion). In comparison to the placebo group, the ACR20 response in the 4 and 8 mg/kg groups was 57 and 78%, respectively, whereas the ACR50 and 70 responses in the control, 0.004, and 0.008 g/kg groups were 2, 0, 26, and 40%, respectively. Within three months of receiving tocilizumab, over 80% of patients in the 0.008 g/kg group had their C-reactive total protein return to baseline and their rheumatoid component concentration decline by about 30%. It will be interesting to examine how tocilizumab affects the auto-antibody component of RA, specifically anti-citrullinated peptide, given that TNF inhibition appears to have significant effects on rheumatoid variable titre but not quantities of auto-antibodies vs. citrullinated peptide.[65-68]

Despite the ineffectiveness of tocilizumab at a dose of 2 mg/kg, 8 mg/kg led to the best monotherapy results (16% ACR70, 41% ACR50, and 63% ACR20 participation rates). Contrarily, ACR20 responses for tocilizumab were substantially different from those for placebo + continued MTX. ACR20 responses for methotrexate dose of 0.008 g/kg were 74% (ACR50 and 70 were 53 and 37%, respectively), about two to three times higher than the control's. As has been seen with all other biological agents, mixing methotrexate with other biological agents increased this medication's efficacy.[69]

CONCLUSION

One of the most prevalent diseases in the world, arthritis affects a large number of people. One of the main reasons of arthritis in the modern world is that individuals do not lead a healthy lifestyle that includes a balanced diet, regular exercise, and a lot of time spent in front of laptops. Therefore, this disease also affects the younger generations. Therefore, there are various treatments for arthritis, including NSAIDs, steroids, and others. Although these medications have serious side effects, they can relieve pain and help somewhat control the condition. For the traditional Indian medical system, quality control and uniformity must be strengthened. After reading this article, scholars can use it as directed for additional research because so many other papers have been utilized as references. As a result, a variety of medications, including NSAIDs, steroids, and others, are available to treat arthritis. Although these medications have serious adverse effects, they can reduce pain and help to some extent, control the illness. The traditional Indian medical system needs more quality assurance and standardization.

ACKNOWLEDGEMENT

Authors acknowledge expressing our sincere gratitude to the management of the Noida Institute of Engineering and Technology (Pharmacy Institute) for continuous support, motivation, enthusiasm, and immense knowledge.

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