Rheumatoid Arthritis: A New Challenge in Coming Era

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Abstract: Rheumatoid arthritis (RA) is mainly an auto-immune disease characterized by inflammation in joints. 1 in 50 people develop RA at some stage and at any age. This review summarizes the etiology, pathophysiology, risk factor, and treatment related to RA. The emphasis has been laid in particular on the new potential biological targets and the possible treatment as well as the current ongoing research status on RA.

Keywords: Arthritis, RA, DMARDs, Diagnosis, Pathophysiology, NSAIDs, TNF modifiers, Nutraceuticals.

INTRODUCTION

Arthritis is the oldest diseases known to human mankind. History records the evidence of individuals suffering from joint pain and inflammation or "fire in the joints". It is characterized by joint pain and inflammation affecting one or more synovial joints in the body. The most common types of arthritis include: Lupus arthritis, psoriatic arthritis, juvenile arthritis, spondylitis, gout, "**Rheumatoid arthritis (RA)"**, osteoarthritis (OA) [1].

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by immunopathology involving inflammation of multiple joints. About 1% of world population is associated with substantial premature mortality and morbidity. One in 50 people develop RA at some stage and at any age, but mostly in middle adult life (aged 40-60). It is 3 times more common in women than in men [2].

Risk factors for RA increase with age, from 5.4% among adults aged 18-24 to 63.5% among those aged 75 and over [3]. Certain genes are also known to be associated with a higher risk of some types of arthritis [6]. In adults OA and gout are associated with obesity [4]. Sports, occupational and repetitive motion joint injuries increase the risk of arthritis [5].

The main ***causes*** are, defective or weakened immunological system, genetic susceptibility to the antigens of a foreign protein which ascribed to micro-organisms [6]. Developed internal allergic response, external and food allergies, candidiasis [7], lack of appropriate nutrition, including vitamins and minerals [8], hormonal factors, stress may also results in RA [9, 10].

Symptoms include pain, stiffness, swelling, fatigue and inflammation around the affected joints [11]. Small painless lumps or 'nodules' develop on the skin. Inflammation around tendons, anemia, tiredness and sometimes fever, weight loss, muscle aches are observed [12].

Diagnosis is done by detecting the rheumatoid factor (RF) antibody in people with RA. Other diseases can also produced RF in the blood. Blood tests reveal an elevated erythrocyte sedimentation rate (ESR). People with RA may show a positive antinuclear antibody test (ANA). No single ***diagnostic test*** definitively confirms the diagnosis of RA thus a number of diagnostic tests carried out to confirm RA [13].

The exact *etiology* of RA is still not known, it was believed that factors like genetic susceptibility contained primarily in HLA-DR1 (Human lymphocyte antigen DR1) and HLA-DR4 (Human lymphocyte antigen DR4) loci, a primary exogenous arthnogen and sometimes hormonal factors [14]. Epstein-Barr virus (EBV) an associated antigen in RA patients. It is a polyclonal B-cell activator stimulating production of RF**.** Migration of immunocompetent cells is mediated by new vascularization of the synovium and increased expression of several adhesion molecules on synovial endothelial cells. Polymorphonuclear cells and macrophages release oxygen metabolites and proteases, contributing degradation of cartilage and CD4+ T-cells appear in the affected joints early in the disease onset [15, 16].

Pathophysiology: In normal joints the inner synovial membrane layer which is characterized by macrophage- and fibriblast-like cells, screening synovial fluid into the joint cavity to provide nutrition and lubrication. In inflamed joint the articular manifestation of RA is categorized into: Reversible signs, symptoms related to aseptic inflammatory synovitis and irreversible structural damage caused by synovitis [17]. After disease onset hypocellular synovial membrane becomes hyperplastic, comprising a superficial lining layer of synovial fibroblast and macrophages which overlines an interstitial zone with marked cellular infiltrates containing fibroblast, macrophages, dentric cells, mast cells, T cells and B cells [18]. Interaction between activated lym-

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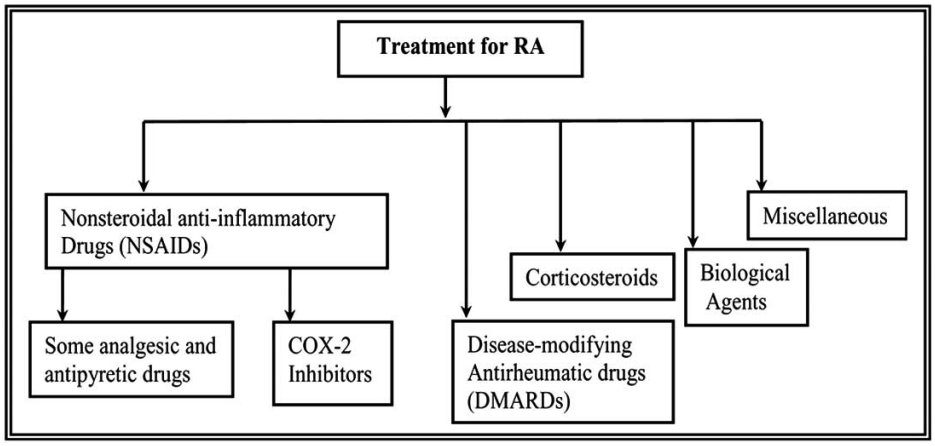


Fig. (1). Treatments used for rheumatoid arthritis.

phocytes and monocytes leads to production of proinflammatory cytokines, immunoglobulins. Interlukin-1 (IL-1) and tumor necrosis factors (TNF) stimulate synoviocytes and osteoclasts with irreversible destruction of bone and cartilage [19]. Synoviocytes produce matrix metalloproteinases (MMPs), and inhibited by tissue inhibitors of MMPs [20]. It leads to the development of synovialitis [21]. Activity and differentiation are impaired by specific deletion of genes are important for osteoclast formation, or by targeting the cytokine receptor activator of nuclear factor-κB ligand (RANKL) known as osteoprotegerin ligand (OPGL), essential for differentiation and activation of osteoclast. Receptor activator of nuclear factor-κB (RANK) is a member of TNF family [22].

TREATMENT OF RA

Medications to prevent or minimize the progression of the disease (Fig. (**1**))[23].

I) NSAIDs

RA ranks pain as primary symptom and NSAIDs block prostaglandins by irreversible inactivation COX enzyme [24] (Fig. (**2**)).

Various studies indicated taking NSAID after the evening meal or on awakening are beneficial for therapy as RA symptoms increase gradually during the night, reaching their greatest severity at the time of awakening. Taking NSAIDs with food can reduce stomach discomfort, although it may slow down the pain− relieving effect [25]. Side effects includes ulcers and gastrointestinal (GI) bleeding [26]. High risk for bleeding are there with flurbiprofen, piroxicam, fenoprofen, indomethacin, meclofenamate and oxaprozin in elderly people having a history of ulcers of GI bleeding, patients with serious heart conditions, alcohol abusers, and those on certain medications, such anticoagulants, corticosteroids, or bisphosphonates. Lowest ulcer risks for NSAIDs are with nabumetone, etodolac, salsalate and sulindac. While medium ulcer risk are with the use of diclofenac, ibuprofen,

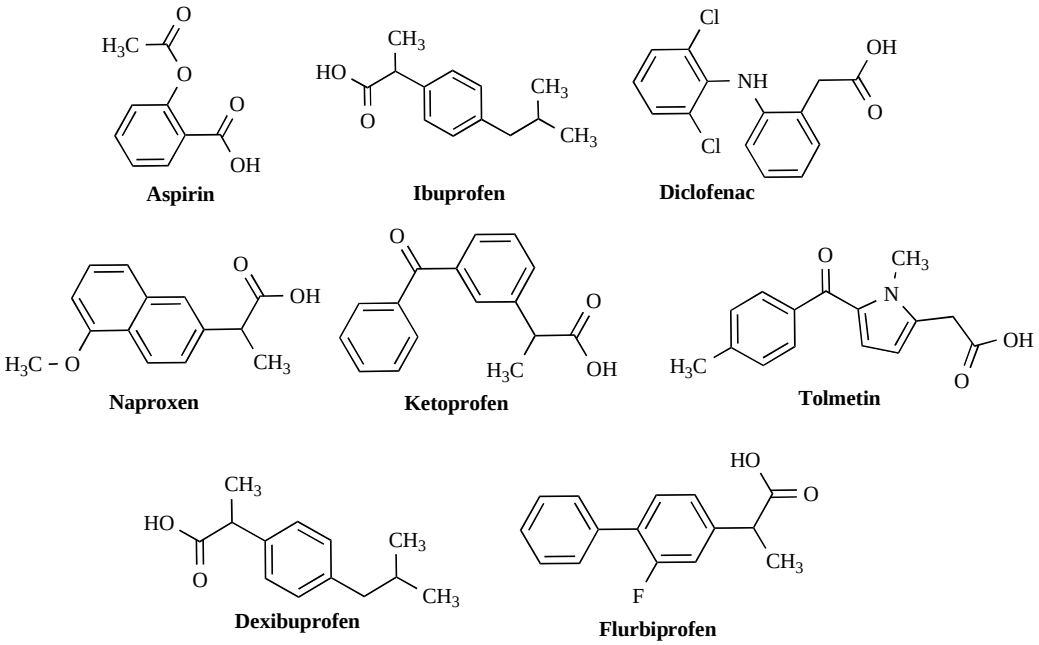


Fig. (2). Various NSAIDs used in RA.

aspirin, naproxen and tolmetin. Another drawback of NSAIDs in RA is increased blood pressure generally with piroxicam, naproxen and indomethacin [27]. Dizziness, tinnitus, headache, skin rash, depression, confusion or bizarre sensation are also seen. Acetaminophen is associated with an increased risk of kidney failure. Kidney abnormalities have been reported in people taking other NSAIDs as well, which resolve when the drugs are withdrawn. Diabetics taking oral hypoglycemics may need to adjust the dosage to avoid harmful interactions between the drugs [28].

Ia) Analgesic and Antipyretic Drugs

Simple analgesics often are used to treat musculoskeletal pain when an anti-inflammatory analgesic may be more effective for the painful condition. Paracetamol (Fig. (**3**)) and salicylate are weak inhibitors of both isolated cyclooxygenase-1 (COX-1) and COX-2 but are potent inhibitors of prostaglandin (PG) synthesis if low concentrations of arachidonic acid [29]. The effects of both drugs are overcome by increased levels of hydroperoxides. At low concentrations of arachidonic acid, COX-2 is the major isoenzyme involved in PG synthesis when both COX-1 and COX-2 are present in cells. Paracetamol and salicylate selectively inhibit PG synthesis involving COX-2 because lower flux through this pathway produces lesser levels of the hydroperoxide, PGG_2, than the pathway involving COX-1. A splice variant of COX-1, termed COX-3, may be a site of action. Thus paracetamol, salicylate and possibly, the pyrazolone drugs like dipyrone, represent a distinct class of atypical NSAIDs termed as peroxide sensitive analgesic and antipyretic drugs (PSAADs) [30]. The mechanism of action of codeine phosphate (Fig. (**3**)) in relieving pain has not been established [31].

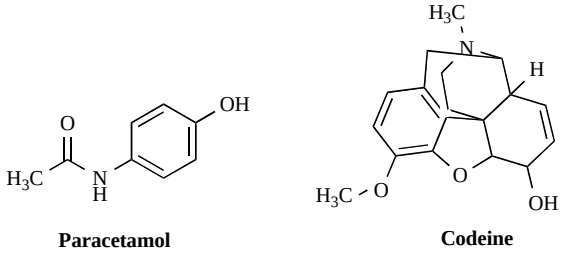


Fig. (3). Analgesic and antipyretic drugs.

Drawback of analgesic and antipyretic drugs in RA are associated with the people taking paracetamol at recommended doses do not have side effects. But sometimes stomach pains and nausea have been rarely reported. Allergy to paracetamol can occur very rarely. It causes constipation if prescribed as an anti-diarrheal. Patients suffering from bronchial asthma, chronic heart failure, kidney disease, or liver disease should discuss whether taking a drug containing codeine is safe with their physicians. It is passed to infants through breast milk. It is dangerous in combination with alcohol or antihistamines [32].

Ib) Selective Cyclooxygenase-2 (COX-2) Inhibitors (Coxibs)

Celecoxib, rofecoxib and valdecoxib (Fig. (**4**)) are known as COX-2 inhibitors or coxibs. They inhibit an inflammation-promoting enzyme called COX−2. Meloxicam (Fig. (**4**)) is a related drug known as a COX−2 preferential. They are equally effective to each other and NSAIDs with respect to arthritic pain. Serious cardiovascular hepatotoxic side effects and life threatening reactions have been reported for valdecoxib and are contraindicated in patients taking anticoagulants, lithium, methotrexate [33].

Side effects of RA treatment with Selective COX-2 inhibitors compared to the conventional non-steroidal NSAIDs, selective COX-2 inhibitors are GI related. Compared to these above-mentioned renal side effects of COX-2 inhibitors in normal kidney, it was found that increased renal COX-2 expression in remnant kidney, renovascular hypertension and diabetes mellitus while COX-2 has been implicated in the progression of renal failure and may be renoprotective in renal diseases by COX-2 inhibitor [34].

II) DMARDs

DMARDs are the standard second line drugs, slow down the progression of RA [35]. They include methotrexate, hydroxychloroquine, cyclosporine and leflunomide. Unfortunately, they loose effectiveness over time. Combining DMARDs with each other or with drugs in other categories offers best approach for treatment of RA. They may produce

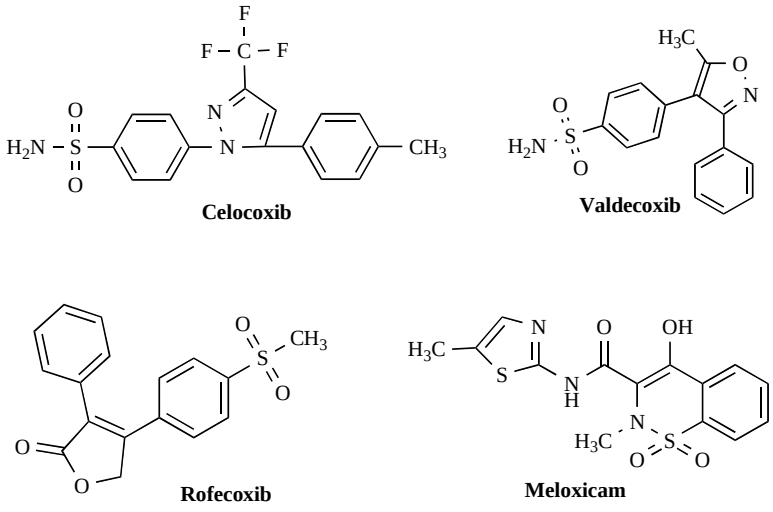


Fig. (4). Selective Cox-2 inhibitors.

stomach and intestinal side effects, and over the long term, some risk for rare but serious reactions [36].

Methotrexate (Fig. (**5**)) is the most frequently used DMARD. It's lower doses is effective for the management of RA [37]. Inhibition of dihydrofolate reductase (DHFR) is not thought to be the main mechanism, but rather the inhibition of enzymes involved in purine metabolism, leading to accumulation of adenosine, or the inhibition of T cell activation and suppression of intercellular adhesion molecule expression by T cells [38]. It has faster mode of action than other DMARDs, the best record to date for long-term use and reduction in mortality rates from heart disease by 70% compared to other DMARDs [39]. Using it with cyclosporine and corticosteroid may be effective and allow lower doses of methotrexate, thereby minimizing side effects. The combination of methotrexate and leflunomide is effective compared to methotrexate alone, while combinations with the newer agents, TNF modifiers and the IL-1 antagonist anakinra are very promising. Patient taking methotrexate may suffer from nausea and vomiting, rash, mild hair loss, headache, mouth sores, and muscle aches [40]. People at particular risk for liver damage from methotrexate include diabetics with existing liver or kidney problems. Possibly osteoporosis at high doses. Increased risk for infections, particularly herpes zoster and pneumonia. Lung disease can occurs in up to 5% of people who take methotrexate. The drug increases the risk for birth defects when taken by pregnant women. Sometimes the disease appears to go into remission when the drug is stopped [41].

Leflunomide (Fig. (**5**)) blocks autoimmune antibodies reducing inflammation. It inhibits MMPs involved in cartilage destruction. It is the first oral treatment approved for RA slows disease progression as early as 6 months into treatment. Comparison studies with methotrexate report a better quality of life with leflunomide, including more energy, greater vitality and fewer side effects [42]. Nausea, diarrhea, hair loss, and rash are the common symptoms but sometimes with serious infections and liver injury [43].

Hydroxychloroquine (Fig. (**5**)) originally used for preventing malaria and is now also used for mild, slowly progressive arthritis. They reduce T-lymphocyte transformation and chemotaxis. It is speculated that this drug alters the lysosomal pH in antigen presenting cells, further helping curb inflammation [44]. It relieves pain, improves mobility with one of the least toxic profiles of the DMARDs but does not appear to slow disease progression. GI complaints, mild headaches, eye problems, damage to the retina, aggravation of psoriasis birth defects may be observed [45].

Cyclosporine is actually an immunosuppressant that started out as a third-line drug and proven to be effective and safe agent when used in combination with methotrexate or as a sole agent for RA. Side effects like gum disease, hair growth, flare-ups in the joints is seen [46].

Immunosuppressants are used for the treatment of severe RA as a third-line drugs that suppress the body's immune system [47]. They include azathioprine, cyclophosphamide and chlorambucil. They shows stomach, GI distress, skin rash, mouth sores and anemia. All are potentially toxic and should not be used unless other drugs are ineffective [48].

III) Corticosteroids

It controls inflammation, pain and effective as aspirin. Oral corticosteroids, such as prednisolone and prednisone, are most often used in combination with DMARDs, which significantly enhance the benefits of DMARDs. Steroid injections in the joints may be a safe and effective treatment for RA [49]. Treatment shows the Side effects like osteoporosis, cataracts, glaucoma, diabetes, fluid retention, susceptibility to infections, weight gain, hypertension, capillary fragility, acne, excess hair growth, wasting of the muscles, menstrual irregularities, irritability, insomnia, and rarely psychosis [50].

IV) Biological Agents

Tumor-necrosis factor modifiers (TNF modifiers) are biologic response modifiers and a major breakthrough in the treatment of RA. They are the activated macrophages and have important role in autoimmune diseases [51]. Currently, there are three approved TNF-α inhibitors for the treatment

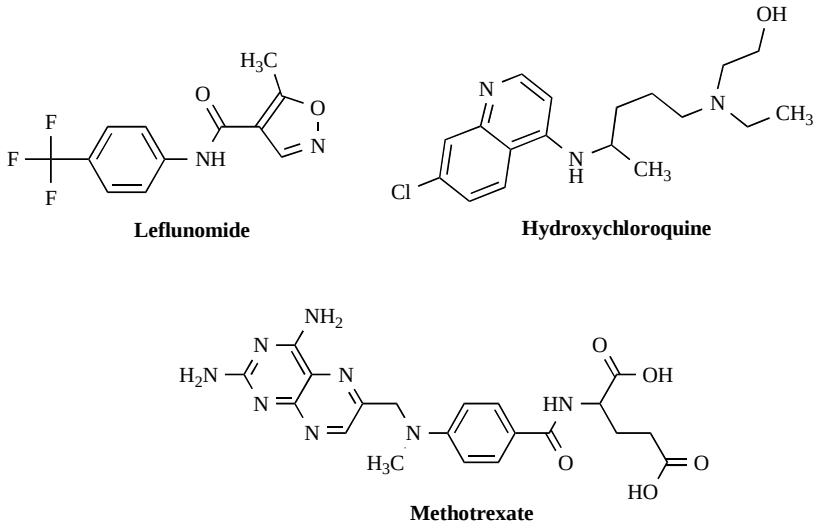


Fig. (5). Various DMARDs in RA.

of RA: infliximab, etanercept and adalimumab. They are genetically engineered to interfere with specific components of TNF. These drugs have some differences: Etanercept is a protein made from the fusion of two TNF receptors whereas infliximab and adalimumab are both monoclonal antibodies (MAbs), targeting TNF. TNF-α plays an important role in the pathogenesis of autoimmune diseases and in normal immune homeostasis [52, 53]. ***Infliximab*** acts by binding with both soluble and transmembrane TNF-α and inhibits the binding of TNF-α to TNF receptor. In the treatment of RA, infliximab is used in combination with methotrexate enhancing efficacy and decrease the incidence of immunogenicity [54]. Infliximab also improves signs and symptoms of RA. Most impressively, patients receiving infliximab had an arrest in radiographic progression, unlike those who received traditional DMARDs. Interestingly inhibition of this radiographic progression of disease seemed to be dissociated from clinical efficacy [55]. ***Etanercept*** is a human soluble TNF receptor fusion protein, which interferes with binding of TNF-α to its cell bound receptor, by mimicking the actions of naturally occurring soluble TNF receptors. Clinically it is effective in RA, used for monotherapy and in combination therapy with methotrexate. This therapy shows the progression of radiographic damage and maintenance of physical function [56]. The mechanism of action of ***Adalimumab*** is same as that of infliximab. It has also slowed progression of radiographic damage and maintenance of physical function and effective as a single agent and in combination therapy with methotrexate. The major side effect with infliximab is tuberculosis reactivation, reactions at the injection site, aplastic anemia, nerve damage, confusion, numbness, demyelinating disease, cytopenias, and changes invision risk for severe infections, difficulty in walking and increased risk of lymphomas [57]. ***Interleukin−1 antagonists*** (IL-l) is a pleiotropic and highly proinflammatory mediator for inflammation and tissue destruction in RA and other diseases. Agents that are able to reduce the production or effects of IL-1 may prove efficacious in the treatment of chronic inflammatory diseases like RA. It is an important pro-inflammatory cytokine. Drugs that inhibit the interleukin cytokines are also under development. Anakinra is an intravenous agent that blocks IL-1. It is showing good results when used in combination with DMARDs, such as methotrexate [58]. There are two isoforms of IL-1, IL-lα and IL-1β, that share 26% amino acid homology. Both forms are produced as 31-kDa precursor peptides, which then are cleaved to generate either a 17.5-kDa protein for mature IL-Iα or a 17.3-kDa protein for mature IL-1β. IL-1β is primarily produced by monocytes and macrophages and is secreted after the cleavage of its proform by IL-1β-convertase enzyme (ICE). In contrast, IL-1α is not secreted and plays roles either as an intracellular cytokine or a membrane-bound protein. An important distinction between these two isoforms is that pro-IL-1β is not biologically active, whereas both the pro- and mature forms of IL-lα exhibit full activity. The systemic effects of IL-1α mainly include neuroendocrine, hematopoietic [59]. IL-1 induces the chemotaxis of neutrophils, lymphocytes and monocytes by increasing the expression of both chemokines and adhesion molecules, enhances pannus formation and stimulates the production of prostaglandin E2 (PGE2). IL-1 also contributes to the destruction of cartilage, bone and periarticular tissues through effects on both synovial fibroblasts and chondrocytes. Release of collagenase and stromelysin by fibroblasts and chondrocytes cause inhibition of collagen type II and proteoglycan production. Pain at the injection site and leucopenia are observed [60].

V) Miscellaneous

Sulfasalazine (SLZ) (Fig. (**6**)) was developed in the 1930s for treating RA, but fell into disfavor when gold treatment emerged. It is now beneficial for both adult and juvenile RA. It causes stomach and intestinal distress, skin rash, sensitivity to sunlight and in rare cases lung problems. People with intestinal or urinary obstructions or who have allergies to sulfa drugs or salicylates should not take SLZ [61]. ***Gold*** has been a long-standing DMARD for RA. Rather than suppressing immune factors that cause inflammation, it may stimulate specific *protective* factors. Auranofin, the oral form has fewer side effects but is less effective than the injected form and, injected form known as chrysotherapy uses either gold sodium thiomalate (Myochrysine) or aurothioglucose. Although injected gold used to be the favorite second-line drug, it is generally used for mild, slowly progressive cases [62]. Side effects differ according to the method of administration. Mostly skin rash, mouth sores, stomach irritation and diarrhea is observed. Most toxic, causes skin problems, sores in the mucous membranes, kidney damage and decreased white blood cell count. Women who are pregnant or people with major medical conditions of the heart, kidney, liver, skin and blood should be very cautious about using this therapy [63]. ***Penicillamine*** may take up a year for penicillamine (Fig. (**6**)) to be effective in reducing the effects of RA and its use is declining. Causes stomach and intestinal side effects, metallic taste in the mouth or, even no taste at all, inflamed muscle skin blisters, fever, liver kidney damage and problems in the lungs [64].

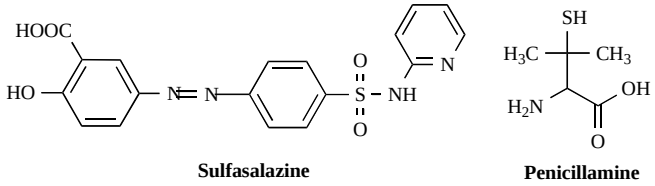
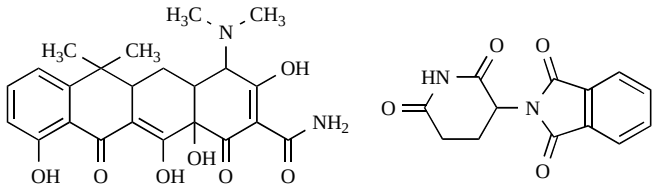


Fig. (6). Miscellaneous agents in RA.

INVESTIGATIVE TREATMENTS

Tetracyclines antibiotics (Fig. (**7**)) are of interest because they have anti-inflammatory actions and because some cases of RA may be triggered initially by an infection. Minocycline, one of the tetracyclines being studied, has achieved mixed results [65]. ***Thalidomide*** (Fig. (**7**)) inhibits TNF and other cytokines. It also reduces the formation of new blood vessels that allow the disease to progress. It was notorious in the past for causing birth defects, it is now being investigated for many diseases, including RA. Severe adverse effects, however, may outweigh any benefits [66].

Oral collagen therapy is based on the theory, by consuming a foreign substance orally, the body will slowly become tolerant to it and will not launch an immune attack against it [67]. Compounds derived from ***Statins*** are highly



Tetracycline **Thalidomide**

Fig. (7). Investigative treatment for RA

regarded. Cholesterol-lowering drugs, may suppress inflammation responsible for RA damage. Statins are used for lipid modulation, have anti-inflammatory and immunomodulatory actions that is useful in the management of RA patients e.g. ezetimibe and simvastatin [68]. ***Hormonal treatments*** research is investigating the use of dehydroepiandrosterone (DHEA), a mild male hormone, which has anti-inflammatory effects and which is reduced in RA. Although estrogen is associated with heightened immune factors, some autoimmune diseases, including RA, improve during pregnancy when levels of estriol, a form of estrogen, are high. Investigators are testing estriol on patients with autoimmune diseases [69]. ***Nitric oxide (NO) releasing NSAIDS i.e. NO-NSAIDs*** agents are being developed that combine nitric oxide (NO) releasing with NSAIDs (NO-NSAIDs). Combining NO releasing with NSAIDs may prevent GI problems and provide benefits similar to the COX−2 inhibitors. ***Licofelone*** is drug that inhibits both the COX enzyme plus an inflammatory substance called Lipoxygenase. Early trials indicate they may be effective and safer than either NSAIDs or COX−2 inhibitors [70]. ***Kappa Opioids*** are powerful pain relievers but are not regularly used in RA. However some are specific agents known as kappa opioids, such as asimadoline, that work in the peripheral nervous system. Some evidence suggests that they are powerful anti-inflammatory agents [71].

NUTRACEUTICAL INTERVENTIONS IN ARTHRITIS

These are the specific nutrients that address the various aspects of arthritis. ***Glucosamine*** is an amino sugar component of chitin, heparin sulphate, chondroitin sulphate and many complex glycosaminoglycans. Glucosamine sulfate provides building block for cartilage matrix. Proteoglycans are hydrophilic and provide resiliency, load distribution, shock absorption and compressive resistance functions [72]. Glucosamine sulfate have the ability to rebuild and restore thickness to joint cartilage with an anti-inflammatory effect but in clinical trials it appears to failed. Individuals taking NSAIDs and glucosamine concurrently have found less benefit than with glucosamine alone. It absorbed intact with one study indicating greater than 88% absorption. It was believed that glucosamine HCl is equally effective [73]. ***Chondroitin sulfate*** is a glycosaminoglycan a major component of the extracellular matrix and connective tissue of animals, found outside of the cell membranes of some animal cells. They are repeating polymers of glucuronic acid and sulphated N-acetyl- glucosamine residues that are highly hydrophilic and anionic. Initially chondroitin sulfate would not be absorbed intact and therefore accounted for some of the failure in treatment also absorption and availability in the disaccharide form is not well absorbed as glucosamine but have similar anti-inflammatory effect to glucosamine [74]. It protect existing cartilage by decreasing water loss from the matrix and inhibiting the breakdown of cartilage by enzymatic reactions. Many recent studies demonstrated that combined glucosamine/chondroitin therapy seems to be more effective for certain individuals suffering from several types of arthritis [75]. Although glucosamine is a precursor for chondroitin synthesis and logic would seem to indicate that administration of glucosamine would address all cartilage maintenance and repair issues. Sometimes the metabolic energy for this is limited or unavailable; therefore administration of chondroitin may spare this metabolic pathway and helps to protect cartilage better than glucosamine sulfate. ***Methylsulfonylmethane (MSM)*** is a source of organic sulfur found naturally in the human body and in many foods. It is the major metabolite of dimethyl sulfoxide (DMSO), and is 34% elemental sulfur. While sulfur supports many functions, maintaining connective tissue health and therefore supports those tissues with significant amounts of collagen and keratin such as ligaments, tendons, arteries and cartilage. It helps in regulating insulin production, improving skin smoothness and elasticity [76]. Sulfur is a key element necessary in the detoxification processes, thus MSM is very useful in the treatment of most types of arthritis [77]. ***Hyaluronic acid (HA)*** is a component of the cartilage matrix valuable in the treatment for arthritis. Various studies indicated that inflammation within joints will cause fragmentation of HA and degradation of the cartilage matrix. The vast majority of HA administration by intra-articular injection was found to be effective in long-term studies. Implantation of surgical films and gels can also be applicable. HA administration in osteoarthritis will reduce inflammation and promote fibrinolysis [78]. Glucosamine and chondroitin sulfate have both been demonstrated to increase HA production within joints with long term administration. It is directed towards ligament and tendon repair, and connective tissue support. The exact dosages orally to provide the best benefit are still unclear [79]. ***Type II collagen*** is a component of connective tissues and cartilage. Conditions that generate long term inflammatory processes such as RA seem to cause a biochemical change whereby these collagen fibers are replaced with less hydrophilic and flexible material. It was found that type II and V collagen are most commonly affected in arthritis and may even be the focus of the auto-antigens of RA. Administration of purified type II undenatured collagen will act almost like an “allergy shot” to reduce inflammation in joints of RA patients. This response appears to be dose dependent giving greater imuno-responsiveness at slightly higher doses. Thus there may be a double benefit by decreasing inflammation through immune modulation and providing raw materials for connective tissue repair and maintenance [80].

RA is usually an aggressive disease that needs to be treated forcefully if subsequent deformity and disability are to be reduced. Referring patients to a specialist rheumatology unit that can implement new treatment regimens at an early stage is therefore important. The various drugs which are under clinical trials, to overcome the problems associated with the RA (Table **1**) targeting the various sites for better efficacy and less toxicity.

Table 1. Drugs under Clinical Trials for Treatment of Rheumatoid Arthritis

Sr. No.	Name	Developed By	Mechanism of Action
1.	Rituximab [81]	Biogen Idec/Hoffmann-La Roche/Genentech	Rituxan binds to the CD20 antigen, which is predominantly expressed on mature B cells and on >90% of B-cell non-Hodgkin's lympohomas. The antibody leads to selective killing of B-cells.
2.	Abatacept [82]	Bristol-Myers Squibb	It has activity as a selective costimulation modulator with inhibitory activity on T lymphocytes.
3.	Golimumab [83]	Centocor, Inc./Schering-Plough/Janssen Pharmaceutical K.K./Mitsubishi Tanabe Pharma Corporation	Targets tumor necrosis factor alpha (TNF-alpha), a pro-inflammatory molecule.
4.	MRA/ Tocilizumab [84]	Chugai Pharmaceutical/Hoffmann-La Roche	Anti-interleukin-6 (IL-6) receptor antibody
5.	Ocrelizumab [85]	Genentech/Hoffmann-La Roche/ Chugai Pharmaceutical	Targets mature B lymphocytes
6.	Ofatumumab [86]	Genmab/GlaxoSmithKline	Inhibit early-stage B lymphocyte activation
7.	Rebamipide [87]	Korea Otsuka Pharmaceutical Co.,Ltd	Works by enhancing mucosal defense, scavenging free radicals, and temporarily activating genes encoding cyclooxygenase-2
8.	CDP870 [88]	Celltech Group plc /Pfize	A polyethylene glycol (PEG)ylated anti-TNF antibody fragment
9.	CP-690,550 [89]	Pfizer	Hitting a target that is exclusively expressed in the immune system, a more specific mode of action should be possible, and one that is being investigated is Janus kinase 3, or JAK-3, one of the many cytokines that is required for immune cell development and homeostasis.

SUMMARY AND CONCLUSION

Conventional treatment for RA presents a number of problems in terms of safety and efficacy. Frequent intake of higher doses of NSAIDs over longer duration which poses the risk of Gastro-intestinal tract (GIT) hemorrhage and ulcers. COX-2 inhibitors have significant renal and cardiovascular toxicities. Prolonged use of steroids and immunosuppressants present risk of many serious side effects. Over the past several decades this expanded RA has caused permanent joint damage early in the course of disease, the current therapeutic model encourages prompt and appropriately aggressive step-up approaches with agents that can effectively alter the outcome of disease. Gluco-corticoids are reserved mainly for adjunctive or bridge therapy while waiting for DMARDs to take effect. Lastly, with a better understanding of the pathogenesis of RA, a new class of drugs called biologicals has opened up many new therapeutic options for both patients and physicians. Their quick onset of action and the ability to radiographic progression offer new hope for patients with RA. This marks a new therapeutic era where future agents will be targeting molecular pathogenesis and not only the symptoms of RA.

ABBREVIATIONS

RA = Rheumatoid arthritis

OA = Osteoarthritis

DMARDs = Disease-modifying anti-rheumatic drugs

ESR = Elevated erythrocyte sedimentation rate

ANA = Antinuclear antibody test

ACRSRA = American College of Rheumatology Subcommittee on Rheumatoid Arthritis

ESR = Erythrocyte sedimentation rate

CRP = C-reactive protein

HLA-DR1 = Human lymphocyte antigen DR1

HLA-DR4 = Human lymphocyte antigen DR4

EBV = Epstein-Barr virus

TNF = Tumor necrosis factor

IL = Interleukin

INF = Interferon

MMP = Metalloproteinase

RANK = Receptor activator of nuclear factor- B

RANKL = Receptor activator of nuclear factor- B ligand

RF = Rheumatoid factor

DCs = Dendritic cells

APC = Antigen containing cell

MHC class II = Class II major histocompatibility complex

NSAIDs = Non-steroidal anti-inflammatory drugs

COX = Cyclooxygenase

PPI = proton−pump inhibitor

SLZ = Sulfasalazine

MAb	=	Monoclonal antibody
DHEA	=	Dehydroepiandrosterone
T_H	=	Helper T-cells
GIT	=	Gastro- intestinal tract
SA	=	Salicylic acid
SP	=	Sulphapyridine
OSZ	=	Olsalazine
FDA	=	Food & Drug Administration
MAOIs	=	Monoamino oxidase inhibitors
CSM	=	Committee on Safety of Medicines
5-ASA	=	5-aminosalicylic acid
BPAA	=	Biphenlyacetic acid
6-MNA	=	6-methoxynaphthyl acetic acid
NAP-PP	=	Naproxen–propyphenazone

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