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EVIDENCE FOR TREATING RHEUMATOID ARTHRITIS: A REVIEW WITH SPECIAL ATTENTION IN CLINICAL MANIFESTATIONS

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ABSTRACT

Rheumatoid Arthritis **(**RA) is an auto immune disease that affects in the clinical manifestations of arthritis in each patient. In addition to the development of medication, the clinical manifestations are to achieve the most effective role with less side effects by improving the pharmacokinetic and pharmacodynamic profiles. Multiple environmental factors including hormones, dietary factors, infections and exposure tobacco smoke as well as associated with increased risk for rheumatoid arthritis. Concurrently have proven in effective by retaining the therapeutic index at synovial cavity by virtue of its diagnostic medication. Current trends and future perspectives imply that definitive role in drug release are controlled by biological modifications in the anti-rheumatic drugs behaves the significant characteristic in achieving the disease remission without joint deformity.

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INTRODUCTION

Rheumatoid Arthritis is a systemic auto immune inflammatory disease that affects the multiple joints of the body. It is characterised by chronic inflammation of synovial membrane which often leads to destruction of articular cartilage, periarticular bone erosion and permanent deformities. RA can also have systemic effects such as sub cutaneous nodule development, pleural effusion and pericarditis. In India and china alone, about 19 million people are affected by RA. Although it affects persons of all age groups, it is particularly prevalent in middle age population of 30-50years as shown in Figure 1(a). This disease associated with progressive disability, systemic complications, early death and socio-economic costs[1-2]. RA is characterised by inflammation of the synovium and increased synovial exudate, which result in thickening of the synovium and joint swelling. These finding can be concluded that RA caused by factorial like gene and environment.

a) **b)**

Figure 1: a) chronic inflammation of Knee portion which often leads to destruction of cartilage. b) Thickening of the synovium and periarticular bone erosion and permanent deformities.

Now a days to deliver the drugs to the target site directly is still a problem. The drug delivery systems to individually design carriers like nano particles can make a cell specific targeting becomes achievable. The clinical manifestations of symmetrical joint involvement include, Arthralgia, swelling, redness, and even limiting the range of motion as represented in the Figure 1(b). Patients awareness of RA, the willing ness of patients to seek medical advice, the time for the patients from symptoms onset to receiving appropriate treatment and the diagnostic capability of the physician all the influence the treatment and outcome of RA.With poorly controlled or severe disease ,there is a risk that extra articular manifestations such as keratitis pulmonary granuloma(rheumatoid nodules), small vessel vasculitis and other non-specific extra articular symptoms will develop[3-5] . The treatment of RA is to relieve pain and inflammation and improve maintain joint function. The conventional drugs used in the treatment of RA are NSAIDS and steroids that control symptoms and DMARDS which prevent joint damage. Multiple environmental factors including hormones, dietary factors, infections and exposure tobacco smoke as well as associated with increased risk for rheumatoid arthritis (RA)[6].

ETIOLOGY

- RA has been elusive, but it finally seems to be explained by a combination of three factors.
- Relatively mild deficiency of cortisol.
- Deficiency of de hydro epi androsterone produced by the human adrenal cortex but which has been little studied.
- Infections by organisms such as mycoplasma, which have a relatively low virulence, are difficult to culture in the laboratory and cause inflammation and destruction of tissue in periarticular areas.

PATHOGENESIS

The inflammation of RA originates in the synovium; the synovial tissue shows synovial lining hyperplasia as a result of fibroblast-like synoviocytes and macrophage-like synoviocytes accumulation. These macrophages and fibroblast-like cells promote inflammation by producing chemical mediators such as pro-inflammatory cytokines such as TNF-a and IL-1b. Furthermore, both of them induce synovial cells to release tissue degrading matrix metalloproteases and TNF-a stimulates the development of osteoclasts, which are responsible for bone abrasion as shown in Figure2(a). Consequently, more macrophages, lymphocytes, and fibroblasts are activated and the RA inflammatory process remains. These inflammatory cytokines are abundant in the synovial fluid and synovium of RA patients which have a potent capacity to induce receptor activator. The main regulator of osteoclast genesis, on synovial fibroblasts and bone derived stromal cells and affect osteoclast signalling, therefore directly causing bone destruction process. Angiogenesis is of the initial hallmarks in the inflamed RA synovium as represented in Figure2(b)[7-10].

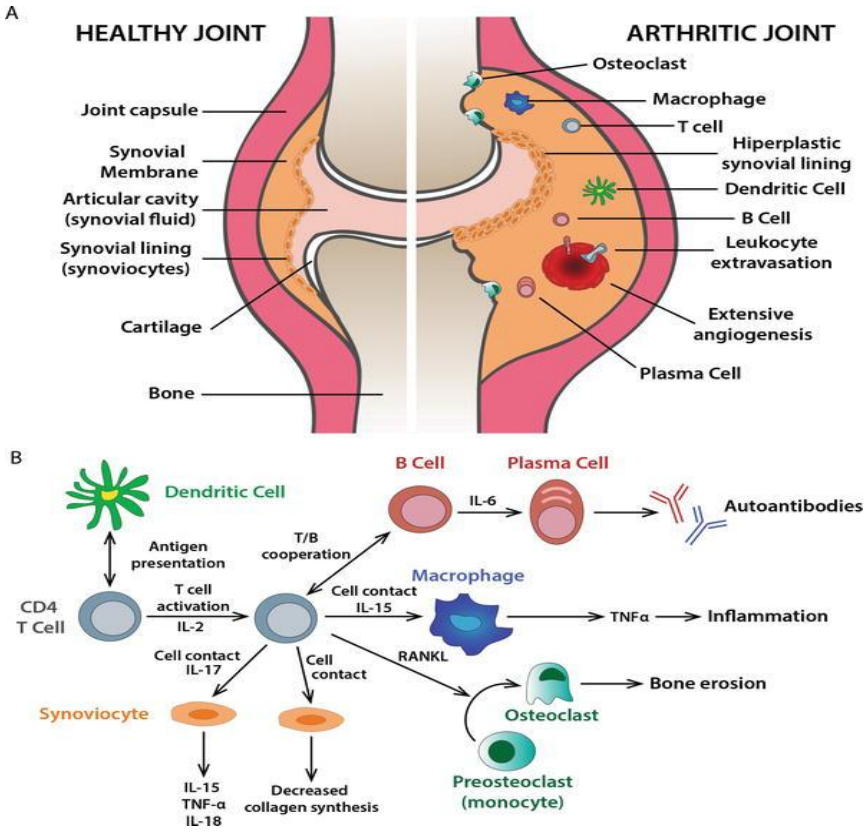

Figure 2: Role of CD4 T cells in rheumatoid synovitis in healthy and arthritic joint.

(A) In a healthy synovial joint (left), a thin layer of synoviocytes delimits the joint capsule. By contrast, in RA (right), synoviocytes form an invasive synovial lining and leukocytes infiltrate the synovial membrane.
(B) Activated CD4 T cells play a central role in inflammatory responses in the synovial membrane, including autoantibody production by plasma cells, secretion of inflammatory cytokines by macrophages and synoviocytes, bone erosion by osteoclasts and inhibition of collagen secretion by synoviocytes

BEHAVIOUR ASPECTS OF RA INFLUENCE OF STIMULI

Sleep disturbance is thought to contribute to pain, fatigue, and depressed mood in patients with RA and a number of studies show that subjective sleep complaints correlate with fatigue, functional disability, greater joint pain, and more depressive symptoms in these patients. Sleep difficulties, pain, depressed mood, and fatigue appear to cluster in RA. Alternatively, both sleep disturbance and depression may be manifestations of an underlying biological disturbance[11-13]. Prospective or experimental studies that simultaneously asses multiple symptoms using state of the art measurement techniques are needed to advance our understanding of sleep and its association with other RA symptoms. Temporally associated with an overnight increase in tenderness in the peripheral joints in patients with RA. On the other hand, noxious stimuli and pain are thought to interfere with sleep[14].

Reciprocal Influence of Inflammation

Although there is exert much speculation about the role of biological factors in RA related sleep complaints and associated sickness symptoms of fatigue, pain, and affective disturbance. Basic research on neural immune signalling has shown that peripheral pro inflammatory cytokines exert potent effects on neural processes that lead to a constellation of behaviour changes including abnormal sleep, depressed mood and social withdrawal. Experimentally induced immune activation is associated with depressed mood, fatigue, and difficulty concentrating[15]. Acute administration leads to fatigue and early night decreases of delta sleep as shown in Figure 3. Although some data show that endotoxin challenge and release of cytokines enhances non-REM sleep. In other words, stress, sleep and proinflammatory cytokines show a bi directional relationship that develops into a feed forward, vicious circles in patients with RA and contributes to a progressive deterioration in clinical outcomes as measured by disease severity and associated psychiatric comorbidities[16].

Figure 3: Inflammation and speculation of sickness in fatigue, pain and affective disturbances.

CONTRIBUTION OF GENERAL PROSPECTIVE LEADS TO PSYCHIATRIC COMORBIDITIES

Smoking

Multiple case-control and prospective cohort studies have demonstrated that cigarette smoking is the strongest environmental factor linked with RA, and it can increase the risk of rheumatoid arthritis until 25%. Furthermore, several studies demonstrate a dose-response between heavier smoking and RA, some studies show that people who have the habit of smoking more than 20 years led to persistent RA. However, the specific mechanism of how smoking can induce autoimmunity is still unknown.

Reproductive and hormone

The abundant study of evidence shows there is a relation between hormone and incident of RA. In Women are 2 to 4 times more prone than men to develop may increase the risk of RA.

Infection

The body's immune system consists of cellular and humoral. When there is an infection, the immune system raises inflammatory substances to eliminate infectious agents, this inflammation can occur in the joints. The best example to explain this concept is an infection of porphyromonas gingivalis. The causal direction remains uncertain, but recent discoveries suggest that inflammation and in particular infection by Porphyromonas gingivalis may be important in the pathophysiology of RA development. The current hypothesis is that Porphyromonas gingivalis mediated citrullination of human peptides might responsible for the initial breakdown in self-tolerance that leads to the development of RA-related autoimmunity.

Dietary intake

The type of food or nutrient which is having relation with RA are vitamin D and protein. Study show that vitamin D has pleotropic effects on the immune system, inhibiting pro-inflammatory cytokines, upregulating anti-inflammatory cytokines, and regulating the innate and adaptive immune system through the vitamin D receptor. In addition, Vitamin D prevents the development of inflammatory arthritis in collagen-induced mouse models. Foods contain high protein and Fe is red meat[17-18].

POTENTIAL AGENTS CAUSING AFFINITY TOWARDS RHEUMATOID ARTHRITIS

The diagnosis and early therapy of RA are very crucial because 30% patients with newly diagnosed RA are unable to work within 3 years of diagnosis. At present, there is no cure of RA and it is most commonly treated with a combination of nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying antirheumatic drugs (DMARDs), and biological agents. The treatment also involves the use of unconventional therapies such as enzymes like superoxide dismutase, antisense oligodeoxynucleotides, boron neutron capture therapy, and radioisotopes.

Gene therapy

Gene therapy is another approach by which nucleic acids deliver into the cell to suppress expression of disease promoting proteins. In RA, gene therapy is local and joint-specific targeted approach to both silence expression of proinflammatory cytokines genes or high-expression anti-inflammatory cytokines genes. So is hopefulness for that long-term expression of these anti-arthritic agents will result in persistent anti-inflammatory effects whereas preventing systemic adversative reactions. Viral vectors, including retroviral, adenoviral, and adeno-associated virus vectors has been explored for gene therapy in RA both in animal models and a few clinical trials. However, nonviral, nanotechnology-based vectors for gene therapy show many advantages to viral-based vectors, such as low immunogenicity, no insertional mutagenesis, and no risk of infection[19-20].

CLINICAL MODIFICATIONS IN LONG TERM DELIVERY IN THE TREATMENT OF NON-STEROIDAL ANTI INFLAMATORY DRUGS

Till date, oral administration of antirheumatics for treatment of arthritis has been a consistent challenge for the clinicians, as there are severe clinical complications attached to their long-term oral use. The long-term administration of NSAIDs [Non-steroidal anti-inflammatory drugs] for the treatment of RA is associated with gastro destructive effects that may be manifested as ulcers and intra-abdominal bleeding. Oral or intramuscular administration of steroidal drugs is generally associated with irreversible suppression of the immune system. DMARDs [Disease modifying anti rheumatic drugs] given by oral or intravenous or intramuscular route are known to be toxic to the immune system as shown in Table no 1. In order to overcome the systemic effects of these drugs, they can be directly targeted to the synovial capsule of the affected joint through intravenous route, especially when the disease manifests only in limited number of joints. However, the rapid clearance of drugs from the synovial cavity into the blood stream defeats the purpose of their intra-articular administration. The clearance of intrasynovially administered drugs can be overcome through liposomes by virtue of the size of multilamellar vesicles. This facilitates the uptake of drug by the target synovial cells and reduces the exposure to nontarget sites, eliminating the undesirable side effects[21-22].

Table No:1 DMARDs [Disease modifying anti rheumatic drugs] given by oral or intravenous or intramuscular route by its own mechanism and adverse effects.

DMARDS		
Agent	**Mechanism**	**Adverse effects**
MTX	Purine antimetabolite	-Hepatotoxicity -Stomatitis -Cytopenias
Leflunomide	Pyrimidine synthesis inhibitor	-Hepatotoxicity -Cytopenias
Hydroxychloroquine	TNF + IL-1 suppressor	-Retinopathy
Sulfasalazine	TNF + IL-1 suppressor	-Hepatotoxic -Stomatitis -Hemolytic anemia
-Adalimumab **-Certolizumab** **-Etanercept** **-Golimumab** **-Infliximab**	Inhibit TNF	-Infection --(Get PPD) -CHF -Malignancy

A new trend of targeted drug delivery systems is developing in nanomedicine. Numerous researchers are discovering new targeting moieties and respective receptors to achieve successful formulations. The basic principle behind ligand-targeted therapeutics is the association of molecules such as antibodies to the nano system. From this time, these ligands shall bind to target cells. There are some examples of conjugation of NPs with antibodies, along with the outstanding properties of NPs such as their ability of working as drug carriers or intrinsic magnetic characteristics, with the targeting capacity[23].

TECHNOLOGICAL AND INNOVATIVE SURFACE ADSORBED MATRIX IN MONOLITHIC BASED MEMBRANE SPECIFIED POLYMERS

Nanoparticles delivery system has been describing as particles formulation which been disperse in the scale of nanometre. National Nanotechnology Imitative defined nanoparticles as structures of sizes ranging from 1 to 100 nm. There are 2 types of nanoparticles based upon their preparation, such as nanospheres and nano capsules. Nanospheres has a monolithic type structure, where the active compound is dispersing actively in the surface or adsorbed into the surface of its carrier matrix. Nano capsules form a membrane-like structure with the active compound trapped in to the “heart” of its structure or adsorbed on the membrane surface. One of the simplest preparation methods of polymeric nanoparticles is via ionic gelation method. Ionic gelation concept makes the usage of two biopolymers in one formulation system becomes possible. The two biopolymers should have a different charge, so they can form a flexible matrix to entrap various kind of drugs with different characteristics. Some of the advantages of using nanoparticles are their small size enable them to penetrate intercellular spaces, cell walls compared to bigger particles, and flexibility to combine with other technologies. Nanoparticles can be used to encapsulate, protect drugs from degradation, and improve targeted drug delivery. Nanoparticles can modify the drug release, and can be produce in large, reproducible scale. Nanoparticles’ wide variety of physical and chemical properties affect the encapsulated drug biomedical potential such as bioavailability and biodistribution. Surface modification of nanoparticles particularly with PEG, could prolong its residence time in the circulation, reduce in vitro toxicity, prevents agglomeration that lead to destabilization of nanoparticle suspension. The other advantage is that the drugs in the form of nanoparticles possess good storage stability[24].

POLYSACCHARIDE FOR BIODEGRADABLE POLYMER ACTING TOWARDS IMMUNOGENICITY

Naturally occurring polymers, principally of the polysaccharide type, have been used pharmaceutically for the delivery of a wide variety of therapeutic agents. Chitosan, the second abundant naturally occurring polysaccharide next to cellulose, is a biocompatible and biodegradable mucoadhesive polymer that has been broadly used in the preparation of micro as well as nanoparticles. Chitosan is a non-toxic biodegradable polycationic polymer with low immunogenicity. Chitosan, a natural copolymer of N- Acetylglucosamine and D-glucosamine, is attractive for encapsulating quantum dots because it enables properties such as chelation of metal ions, water solubility and ease of processing. Chitosan and dextran are two promising biodegradable polymers for targeted drug and gene delivery via conjugation with folic acid, galactose and transferrin. Chitosan nanotherapeutics have received great attention in the field of oncology because of enhanced tumour targeting, ability to load different hydrophobic anticancer drugs, and the ability to control the anticancer drug release rate.

CONTROLLED AND LOCALIZED DRUG DELIVERY APPROACHES CONSERVE EFFECTIVELY RETENTION TIME

Intra-articular (IA) injection is a method that physicians may use to treat inflammation of joints. It has the advantage of increase local drug concentration at site of action, decreasing drug dose and minimize typical side effects of these drugs. In addition, IA administration would also facilitate the highly efficient delivery of drugs with low oral bioavailability, including the delivery of recombinant proteins, therapeutic genes and inhibitory RNAs. Various glucocorticoid and HA (Hyaluronic acid) formulations are currently available on the market for IA treatment options for RA. The main problems with this method are rapid clearance of injected agent from joints region, which decrease drug concentration at site of action so that frequent injections are required leading to infection, inflammatory events, joint disability and post-injection flare. The IA [Intra-articular] mean elimination half-lives of anti-inflammatory drugs after oral administration is about 1-5hrs. To increase drug retention time, reduction of drug clearance from joints and also increase patient compliance, different kind of controlled release delivery systems including microspheres, liposomes, NPs and hydrogels were developed. These sustained release systems for IA injection conserved effectively within the joint cavity, uptake or kidnapped by synovial cells in the synovium. Solid lipid nanoparticles by a hot melt homogenization technique shows faster clearance of drug from the joints and higher distribution of drug in liver, spleen, and kidney was seen after IA injection. Rapid equilibration between the synovial fluid and plasma was the main reason for faster clearance of the drug solution from the joint and release of appreciable levels of drug into the systemic circulation[25].

SYMPTOMATIC TRANSFORMATION IN THE MANAGEMENT OF VASCULAR HAEMOSTASIS

Nonsteroidal anti-inflammatory drugs are commonly prescribed in the management of osteoarthritis, RA, and musculoskeletal pain. They only provide symptomatic relief and do not alter the course of the disease or prevent joint damage. Mostly NSAIDs act by nonselective inhibition of cyclooxygenase enzyme which exists in two distinct isoforms, COX-1 and COX-2. Both these enzymes have nearly 60% amino acid homology, similar tertiary structure, and similar but nonidentical active sites. COX enzyme catalyses the transformation of arachidonic acid into prostaglandins which are the mediators in the inflammatory process. Thus, inhibition of COX by NSAIDs leads to reduction in pain and inflammation. COX-1-derived prostaglandins regulate many physiological processes such as protection of stomach lining from gastric acid erosion and vascular haemostasis. In contrast, COX-2 is principally an inducible enzyme which is highly expressed in inflammatory conditions. Therefore, selective inhibitors of COX-2 are preferred over nonselective inhibitors. The use of NSAIDs in RA is currently limited due to high risk of gastrointestinal complications. The gastrointestinal adverse effects range from minor discomfort to life-threatening peptic ulcers. The minor adverse effects include dyspepsia, heartburn, anorexia, abdominal pain, nausea, flatulence, or diarrhoea in 10% to 60% of patients. It has been reported that 15% to 35% of peptic ulcer complications are due to NSAIDs. NSAIDs are also cause renal and cardiovascular complications like acute kidney failure, hypertension, electrolyte abnormalities, myocardial infraction, and stroke.

MACROPHAGE ACCUMULATION IN AUTOIMMUNE DISEASES

Glucocorticoids such as prednisone, methyl prednisone, hydrocortisone, triamcinolone, and dexamethasone are used to suppress the inflammation in RA and other autoimmune diseases. They act by multiple mechanisms including inhibition of macrophage accumulation and reduction of capillary permeability. Although they are most potent anti-inflammatory drugs and exhibit rapid onset of action, long term use of steroids is associated with severe side effects, including impaired wound healing, skin atrophy, osteoporosis, muscle atrophy, cataract, glaucoma, peptic ulcer, manifestation of latent diabetes, and ultimately premature mortality[26]. These side effects can be minimised by using glucocorticoids at low dose particularly in patients unresponsive to NSAIDs and DMARDs or by administration of selective glucocorticoid receptor agonists that selectively target the immune and inflammatory pathways in order to reduce systemic toxicity or by intra-articular injection.

POTENT INHIBITORS ACTING TOWARDS ANTI-INFLAMMATORY ACTIVITY

Natural agents including flavonoids, terpenes, quinones, catechins, alkaloids, anthocyanins, and anthoxanthins are known to exhibit anti-inflammatory activity. Curcumin, resveratrol, and 6- shogaol are some of the polyphenols that have been tested for the treatment of arthritis. All these herbal drugs suppress the activation of nuclear factor-kB and thus lead to downregulation of the expression of metalloproteinase, cyclooxygenase-2, 5-lipoxygenase, and other inflammatory intermediates, all of which are associated with arthritis. The antiarthritic activity of curcumin has been supported by *in vitro* and *in vivo* studies.

Serological features in targeting and biosynthesis

Rheumatoid factor and ACPA are two most important markers used to diagnosis of RA. Antinuclear antibodies and anti-double-stranded DNA antibodies may also be present in patient with RA[27].

Targeting stage

The involvement of RA in joints usually has a characteristic presentation with synovitis occurring in symmetrical small joints. Joint swelling is the external reflection of synovial membrane inflammation following immune activation. The normal synovial compartment is infiltrated by leukocytes and the synovial fluid is inundated with pro-inflammatory mediators that interact to produce an inflammatory cascade, which is characterized by the interactions of fibroblast-like synoviocytes with the cells of the innate immune system, including monocytes, macrophages, mast cells, dendritic cells, and as well as cells of adaptive immune system such as T lymphocytes (cell-mediated immunity) and B cells (humoral immunity), endothelial cells contribute to the extensive angiogenesis. The two immune systems and their interactions are intimately involved in the development of ACPA [Anti citrullinated protein anti bodies] positive RA, which results in the failed resolution of inflammation in chronic synovitis. Monocytes or macrophages have been found to massively infiltrate synovial membrane and be central to the pathophysiology of inflammation. Enolase on the surfaces of monocytes and macrophages induces production of pro inflammatory mediators. The imbalances between pro inflammatory.M1 macrophage and anti-inflammatory M2 macrophage must also be considered in the context of inflammatory RA. The accumulation of dendritic cells in the articular cavity has also been reported. As an especially myeloid dendritic cells have been shown to induce T cell differentiation.CD4 effector T cells are major abnormal immunity in RA by sustaining chronic synovitis and supporting antibody production and a lack of reactive oxygen species could pro inflammatory Tells, which on the importance of energy metabolism in RA as shown in Figure 4. Therefore, better understanding of the mechanisms of disordered innate immunity, including immune complex mediated complement activation, adaptive immune responses against self-antigens and abnormal cytokine networks may new avenues to restore immunologic homeostasis.

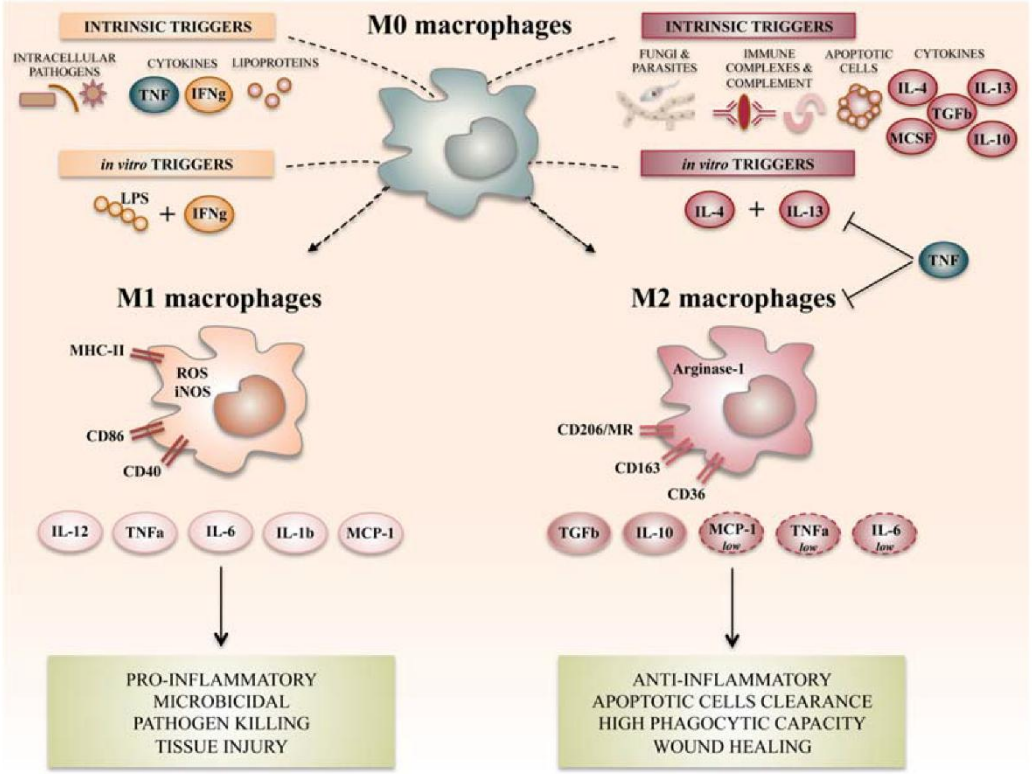

Figure 4: Macrophage polarization states of activated macrophages. Different stimuli and signalling pathways have been described as inducers of M1 like or M2 like activated states, which the most widely referenced ones are summarized here. M1 or M2 polarization has been reported in humans as being related to distinct defensive or healing schemes.

ATTAINMENT IN ABILIBITY BY IMPROVING THERAPY AND PREVENTING COMORBIDITIES

The acute therapy for rheumatoid arthritis is to control the underlying inflammatory disease. Attainment of this goal will alleviate pain, improving patients' quality of life, and preserve independence and ability to perform activities of daily living and vocational and avocational pursuits. Furthermore, major long-term goals of treatment are to prevent joint destruction and prevent comorbidities of disease and treatment, including heart disease and osteoporosis. There are four main groups of drugs are used to treat RA. These are painkillers (analgesics), non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and steroids.

Analgesics

As explained earlier, that one of the major symptoms of RA are joint pain. This condition will really disrupt the patients, because the joint is the main organ of the movement. Analgesics works as a painkiller. Among analgesics commonly used are type of opioid, paracetamol and aspirin, the other is co-codamol, coproxamol. Some analgesics containing codeine can cause constipation.

Steroids

Some steroid or corticosteroid produced in the body, currently steroids are widely produced and used to reduce pain. This medication can be used intravenously or orally. As for the side effects can result from steroid medications are facial flushing, interference in menstrual cycle, thinning, and other change in the site of injection. But oral tablet has more side effects including weight gain, osteoporosis, muscle weakness, cataract, a rise of blood sugar or blood pleasure, and increased of developing infections.

A delivery system that delivers the drug directly to the synovial cavity is found to be more effective than those that are delivered systemically. However, most of the current therapies for RA do not exhibit joint specificity. Therefore, to achieve effective drug concentrations in affected joints, high systemic doses of drug need to be administered, which may lead to significant systemic side effects. Reduction in drug doses may attenuate toxicity but on the other hand may lead to decreased therapeutic efficacy. To strike a balance between efficacy and side effects, several approaches have been reported that specifically target drugs to affected joints. In view of this, the novel drug delivery systems like controlled release pellets, liposomes, sustained release pellets, microspheres, microcapsules, soft gels, nanocomposites, topical formulations, microemulsions, nanosuspensions, suppositories, micro sponges, and solid dispersions have been formulation[28-33].

POLYMERIC TECHNOLOGIES EMPHASISING IN TARGETING AND CONVENIENT DRUG DELIVERY SYSTEM

Though many novel drug delivery systems have emerged in the last two decades for the targeted delivery of anti-rheumatoid drugs to the synovial fluid, liposomes provide an effective and convenient drug delivery capable of reducing the side effects due to following advantages.

(1) Liposomes are biocompatible, completely biodegradable, nontoxic, flexible, and nonimmunogenic.
(2) They offer both a lipophilic and an aqueous environment “milieu interne” in one system and are, therefore, suitable for delivery of drugs with varying solubility profiles including hydrophobic, amphipathic, and hydrophilic molecules.
(3) They have the ability to protect the encapsulated drug from the external environment.
(4) They act as sustained release depots.
(5) They can be formulated into a number of dosage forms, for example, a suspension, an aerosol, or in a semisolid form such as gel, cream, and lotion, as a dry vesicular powder for reconstitution.
(6) They can be administered through ocular, pulmonary, nasal, oral, intramuscular, subcutaneous, topical, and intravenous routes.
(7) Apart from entrapment of small molecules, liposomes are also capable of encapsulating macromolecules like superoxide dismutase, haemoglobin, erythropoietin, interleukin-2 and interferon gamma
(8) They offer reduced toxicity as the exposure of nontargeted sites to the drug is reduced.
(9) They alter the pharmacokinetic and pharmacodynamic profiles of drugs (e.g., reduced elimination, increased circulation life time)
(10) They exhibit flexibility to couple with site-specific ligands to achieve active targeting (e.g., anticancer and antimicrobial drugs)[34-36].

PARENT MOLECULE AND CORNER STONE AFFINITY IN THE BUILDING OF CLINICAL AND MONITORING THE HEPATO TOXIC EFFECTS

MTX is modified form of folate designed to have an increased binding affinity for dihydrofolate reductase compared with its parent molecule. MTX is the corner stone in the treatment of RA either as a single agent or in combination with other DMARDs. In a recent meta-analysis, MTX showed a substantial clinical and statistically significant benefit compared to a placebo in the short-term treatment of people with RA, although it uses was associated with a 16% discontinuation rate due to adverse effects. MTX has been proposed to participate in the process of folate antagonism, adenosine signaling, the blocking of methyl donor production involved in reactive oxygen species, down regulation of the adhesion molecule expression, modification of cytokine profiles, and the down regulation of eicosanoids and MMPs[37-39]. MTX for RA is administered as a low -dose (5-25) mg weekly regimen with dosing conditional to the disease state and side effects. Oral MTX has a more variable uptake than subcutaneous administration, which leads to fewer significant side effects. Sub cutaneous MTX administration also demonstrated a greater bioavailability compared with oral MTX. MTX requires regular monitoring to optimize dosing and asses its immunosuppressive and hepatotoxic effects through frequent blood tests (monthly, initially) as shown in Figure no 5. There are a few well established drugs interactions for MTX, including cotrimoxazole, which causes pancytopenia, combined with azathioprine or leflunomide, which causes liver and lung complications[40-41]. NSAIDs can be safely used in conjunction with MTX for symptoms control after over 30 years of routine use of the two agents. It is inconclusive that MTX enhances the risk of malignancy beyond the increased relative risk of neoplasia associated with RA. Adverse effects associated with the use of MTX additionally include the development of accelerated nodulosis, also known as MTX - induced accelerated nodulosis, which occurs in (1-10)% of patients on MTX .However , most adverse effects can be reversed by supplementation with calcium or sodium folinate[42-43].

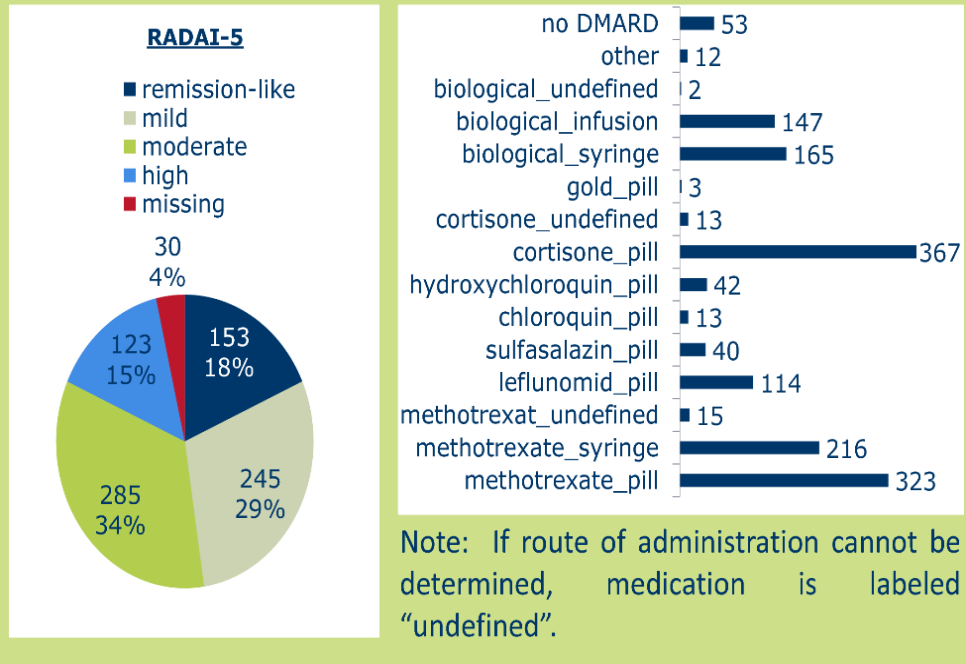

Figure 5: MTX for drug monitoring in optimizing the dosing of administration through medication.

FUTURE PERSPECTIVES

With a better understanding of the pathophysiology of RA, new therapeutic approaches are emerging to provide precision medicine for individuals. However, the function and adverse side effects of these drugs will need to be carefully evaluated and used reasonably. Gene therapy means that treating RA by inserting a gene into a patient's cells instead of using drugs[44]. Targeting gene therapy in RA is a treatment strategy that is still in early stages of development but could lead to new possibilities because of treating a disease. To prevent disease onset or relapses, smoking cessation or avoiding body exposure to environment risk factors is probably the easiest and most cost-effective method[45]. Autoimmunity develops years before the inflammatory phase of the disease, which can be considered as a period for preventing disease progression. Re-establishing immune tolerance and immunological homeostasis are ambitious goals in the way to overcome the disease. T cells and B cells can be targeted by specific drugs in the future to achieve seroconversion or delay the onset of joint destruction. Reduction of the function of APCs and modification of the pro-inflammatory properties of antibodies are being further developed. There is also a great interest in the novel approaches that have.

CONCLUSION

RA is a chronic inflammation disease, capable of causing joint damage as well as long term disability. Early diagnosis and intervention are essential for the prevention of serious damage and loss of essential bodily functions. The diagnosis should be considered treating of target recommendations by 1st outlining the aims and then implementing the protocols to achieve and asses them. The current treatments of RA include NSAIDS, glucocorticoids, liposomal technologies and biologic DMARDS. Nanotechnology indicates specific and localised delivery drug while minimising the quantity of drug used, so restrictive probable off target unwanted effects. Further well-designed human clinical trials are required to evaluate the effects of traditional and natural remedies in terms of symptomatic, functional and biological outcomes.

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