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Review on Recent Advances in Nano Particles Based Drug Delivery System for Rheumatoid Arthritis

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Abstract: *Rheumatoid arthritis (RA) is the most prevalent autoimmune inflammatory joint disorder, characterized by chronic synovial inflammation, autoantibody production, and progressive destruction of cartilage and bone. This complex condition often leads to systemic complications affecting the cardiovascular, pulmonary, and skeletal systems. The pathogenesis of RA is largely driven by pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α,. Interleuki1 (IL-1), interleukin-6 (IL-6), and interleukin-8 (IL-8), which sustain inflammatory processes and disease progression. Current therapeutic strategies, such as disease-modifying anti-rheumatic drugs (DMARDs) and biologics, have improved patient outcomes but are hindered by variable efficacy, systemic side effects, and high costs.Nanotechnology has increasingly emerged as a promising tool for exploring new approaches, from treating complex conditions to early detection of the onset of multiple disease states .Recent advancements in treatment have significantly slowed the progression of the disease and improved the lives of many RA sufferers..*

Keywords: Rheumatoid Arthritis, Nano particles, Macrophages, Intra articular

I. INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by significant synovial joint inflammation and osteocyte and cartilage destruction. This results in long-term impairment, inability to interact effectively in social life and daily employment, and greater death rates, all of which have a significant influence on the patient's quality of life.(1)RA is a group of joint diseases characterised by chronic joint inflammation that affects the smaller joints of hands and foot, such as wrists, fingers, and toes. The following are the main clinicopathological features: inflammatory cells infiltrate the joint, creating synovial inflammation and hyperplasia, a spike in inflammatory factors, and invasion of neighbouring cartilage, resulting in bone erosion and cartilage tissue loss. Despite significant advances in understanding and experience in the treatment of RA in recent years, effective therapy for RA continues to be a challenge.Presently, the primary goals of pharmacological therapy are to relieve RA symptoms and reduce disease activity. The European League Against Rheumatism recommends a number of medicines to treat RA. The guidelines recommend the onset of early treatment with therapeutic drugs such as synthetic and biological disease-modifying anti-inflammatory drugs (DMARDs), which include biological DMARDs like certolizumab pegol, etanercept, and adalimumab as well as traditional synthetic DMARDs like leflunomide, methotrexate (MTX), and also sulfasalazine. Certolizumab pegol encapsulated in nanocarriers with PEGylation augments the time required to reach half of its concentration to fourteen days and it also depicts encouraging outcomes in RA patients.This emphasises that DMARDs play a critical role in pharmacological approaches to RA treatment that cannot be substituted. Glucocorticoids (GCs) can, however, be utilized as a bridge treatment till traditional synthetic DMARDs show detectable therapeutic

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properties.Many nanoparticles have recently been discovered to be capable of delivering RA medicines *via* influencing immune cells such as macrophages in inflamed joints.(2) as shown in fig (1).

Normal joint Rheumatoid arthritis joint

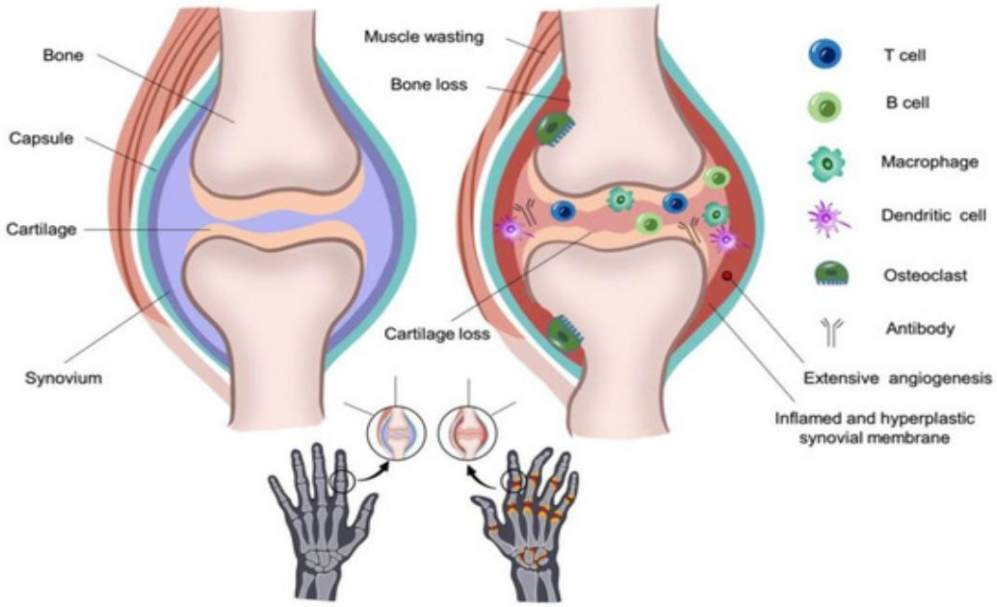

Fig1: Normal joint and Rheumatoid Arthritis Joint

Drugs used in Rheumatoid Arthritis :

Conventional DMARDS

- Methotrexate (MTX)
- Leflunomide
- (Hydroxy)chloroquine
- Sulfasalazine

Biologic DMARDs (biologics or bDMARDs)

- Abatacept
- Adalimumab
- Anakinra
- Certolizumab pegol
- Etanercept
- Golimumab
- Infliximab
- Rituximab
- Tocilizumab

Targeted synthetic drugs (tsDMARDs).

The Janus kinase (JAK) inhibitors are:

- Tofacitinib
- Baricitinib
- Upadacitinib

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- Filgotinib.(3)

Nanoparticles:

The emergence of nanotechnology has garnered increasing attention and has provided new avenues for diagnosis and treating major diseases, including RA. Studies have shown that nanoparticles present obvious advantages in the management of RA, particularly in drug targeting and slow-release delivery systems.By delivering bioactive compounds with enhanced bioavailability directly to the target site, nanoparticles can potentially improve the efficacy and safety of RA therapies, as well as reduction. In addition, the small size and high surface area of nanomaterials contribute to increased solubility and intracellular uptake of active substances.Nanoparticle systems, particularly those based on polymers, are increasingly utilised as drug delivery systems in RA therapy. Many researchers have used poly(lactic-co-glycolic acid) nanoparticles to increase circulation time and regulate the release rate of encapsulated drugs. It has been observed that when injected intravenously into arthritic rats and mice, the poly(lactic-co-glycolic acid) betamethasone system is more effective than free glucocorticoids in reducing inflammation. In another approach, Gandhi et al. fabricated poly(lactic-co-glycolic acid) nanoparticles with gold and MTX as core components and coupled with anti-CD64 antibody on their surface. The results indicated that these antibody-coupled nanoparticles displayed good stability and homogeneity. Animals treated with antibody-coupled nanoparticles showed significant improvement in clinical indicators and arthritis scores compared to non-coupled nanoparticles and free drugs. This approach enhances therapeutic efficacy while limiting dose-related side effects.(4) as shown in fig (2).

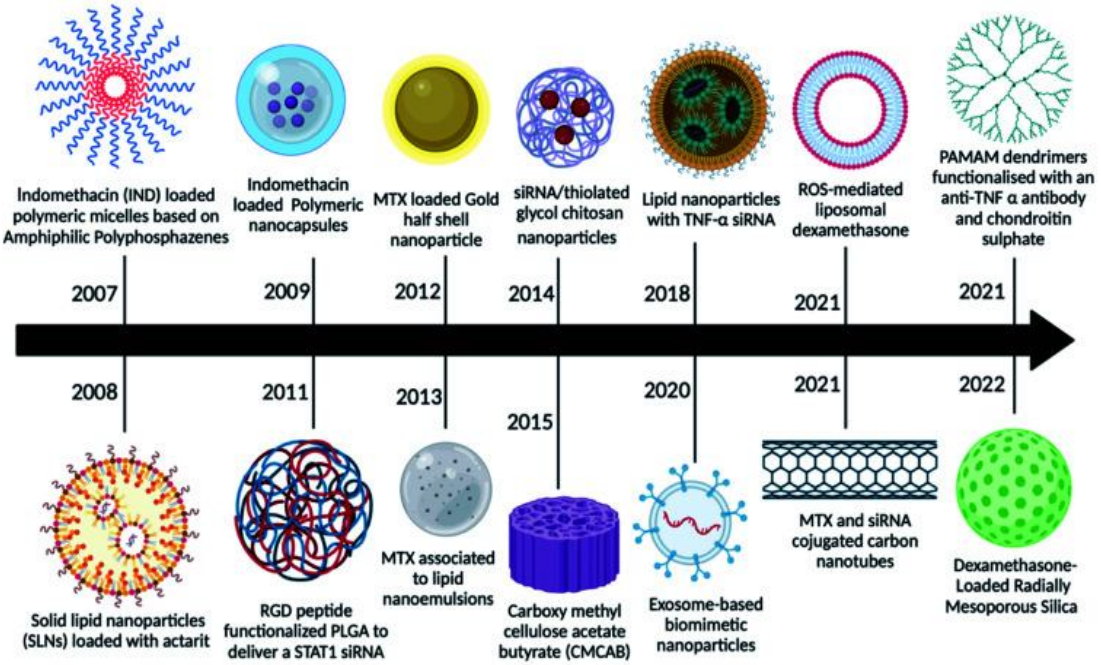

Fig 2: Various Nano particles

Nanoparticles for passively targeting macrophages

Increased vascular permeability and macrophage infiltration are two pathologic features of RA, both of which might provide favourable circumstances and target cells for nanomedicine delivery systems. The ELVIS effect (Extravasation *via* Leaky Vasculature and Inflammatory Cell-mediated Sequestration) allows the nano-drug carrier to preferentially concentrate and release medications in synovial tissue, comparable to the improved permeability and retention effect reported in the therapy of tumours. Because nano-drug particles are bigger than 200 nm and smaller than 10 nm, they can be removed by the spleen and renal tract. Hence, the particle size is an important factor to

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consider when developing a passive targeting method. As a consequence, only nanoparticles conjugated with drugs with a size range of 100 to 200 nm were able to escape from being removed by the mononuclear phagocyte system and the reticuloendothelial system (RES) and stay in blood circulation for an extended period of time in RA patients. The following are some nanoparticle modifications for better passive delivery of drugs and fewer off-target effects.

Nanoparticles for actively targeting macrophages:

Active drug delivery represents particular communications between the therapeutic agents and nano-carrier with the cells of the target, frequently *via* a certain ligand-receptor communication. The interactions between the ligand and receptor are feasible when these constituents are in direct contact with each other.The carrier system transporting the drug moves to a targeted location with the help of surface modification that was functionalized on the surface and not get biologically taken up by the RES. The alteration method involves a coating of the surface with a biological bonding agent, non-ionic surfactant and specific cell or antibodies or by albumin protein. Particular interactions of the ligands on the external area of nanoparticles and specific receptors present on the target cells

Effects of nanoparticles targetting synovial macrophages in RA

The mutual regulation of different cytokines forms a complicated network in the pathogenesis of RA. Cytokines are tiny molecular proteins that operate as intercellular communication mediators. Throughout the inflammatory process, they play a critical role in responding to numerous stimuli. The development of RA is thought to be caused by an imbalance of pro-inflammatory and anti-inflammatory cytokines. Overproduction of pro-inflammatory cytokines, as well as a lack of anti-inflammatory cytokines, can easily result in RA.(5) as shown in fig (3).

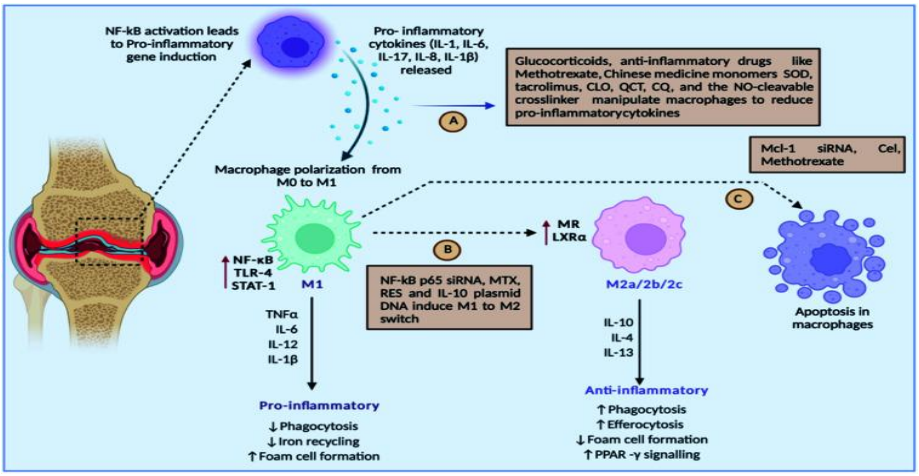

Fig 3: Pro-inflammatory and Anti-inflammatory Cytokines

The basic causes of RA are pro-inflammatory cytokines. As a result, targeting pro-inflammatory cytokines has been suggested as the main treatment strategy for RA. Also known as M_1 macrophages, activated macrophages boost inflammation and speed up the clearance of intracellular infections, and in RA, M_1 macrophages are overproduced, causing increased inflammation and bone damage.Repolarising M_1 macrophages into M_2 macrophages has gained awareness in the therapy of RA. Downregulation of apoptosis can lead to a larger number of macrophages in RA. Hence, targeted inhibition of macrophages and activating apoptosis can augment the treatment regimen.

Delivery strategies for Different types of agents:

The synovial in inflamed joints is abnormally expanded, accompanied by angiogenesis and inflammatory cell infiltration. Thus, the emergence of endothelial gaps in microenvironment of RA allows for the leakage of colloidal nanoparticles into the affected joints, subsequently followed by the sequestration of exogenous nanoparticles mediated by various inflammatory cells This passive targeting mechanism is similar to the famous enhanced permeability and

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retention (EPR) effect occurred in tumor tissues due to the analogous leaky vessels presented in disease sites. Unlike EPR in tumors, the retention mechanism in RA mainly relies on the sequestration of local inflammatory cells. In order to improve the efficacy of current available agents in RA therapy, researchers have developed diverse drug carriers by taking advantages of this passive targeting mechanism. The designing and construction of favorable drug delivery systems should be based on the physicochemical properties of therapeutic agents, as well as their dilemma *in vivo*. In this section, various drug vehicles for encapsulating and delivering different types of drugs will be summarized and classified in which aims to provide general principles and inspiring insights for further explorations.(6)

Encapsulation of drugs with in nano-carriers

The encapsulation of drugs within nanocarriers is a direct and useful approach to provide the protection of drugs from environments and tailor their *in vivo* performance by manipulating the size, shape, and surface properties of nanocarriers. Liposomes are a well-known nanocarrier in improving the bioavailability of drugs for RA treatment Liposomes have sparked great interests in drug delivery for a long time, for it can incorporate both hydrophilic and hydrophobic agents simultaneously. In order to systematically explore how the physical and chemical properties of liposomes affect their *in vivo* fate, Ren et al.prepared a series of liposomes with different sizes, surface charges, PEG lengths. They found that liposomes with the diameter of ∼100 nm, a slightly negative charge, and the 10% incorporation of 5 kDa PEG had superior *in vivo* circulation time and inflamed joint targeting. PEG or other functional ligand modified liposomes also showed the significant improvement of the delivery efficiency in RA therapy Nevertheless, these conventional liposomes still face the challenges such as poor stability and drug leakage *in vivo* Recently, Wang et al. designed a polymerized liposome composed of 1,2-bis(10,12-tricosadiynoyl)-*sn*-glycero-3-phosphocholine ($DC_{8,9}PC$) and DSPE–PEG, in which $DC_{8,9}PC$ molecules were cross-linked in the bilayer of the liposomes upon UV irradiation and the PEG present at the surface of the liposome provided a stealth layer. The polymerized stealth liposome was highly stable and showed long circulation time *in vivo*. After being administrated into arthritic rats, the Dex-loaded polymerized stealth liposomes significantly suppressed the proinflammatory level in joint tissues and reduced the swelling of inflamed joints.(7)

Stimuli-responsive nanoparticles and dual delivery system

Target-specific delivery approaches are stimulated by various stimulants such as thermal regulations, pH, and oxidation–reduction potential and a few ailments have dual stimulants nearby the preferred surroundings at the same moment. Smart drug transport approaches are potential candidates for temperature-sensitive and pH-reactive stimulated areas of drug transport. Several bifurcated polymers hold the capability of combining binary stimulation that have been formulated exhibiting rational applications in various diseases. Various studies have concluded the sustained and maintained release of drug delivery systems by enzyme-degradable polymers sensitive to varying pH, temperature responsive hydrogels, dual receptive micelles for varying redox environments, and high-intensity focused ultrasound. Hydrolases like proteases, lipases and glycosidases, and oxidoreductases are utilized in the enzyme link to overcome the challenges faced because of variations in pH and enzymatic reactions in between each tissue which can essentially be exploited and serve as triggers for gradually releasing the active drug in the site of action. This would increase the cellular internalization of the nanoparticles at different penetration depths of NPs to release the drug at the site of action. Flurbiprofen encapsulated polymeric nanoparticles responded to a change in pH levels at the site of inflammation. Chitosan glycerin borax was used to formulate thermo-sensitive hydrogels to encapsulate dexamethasone that decreased the pain and progression of inflammation in mice models. Polyethylene glycol−phenylboric acid−triglycerol monostearate was used as a dual stimuli vehicle for targeting dexamethasone at the inflammation area, by pH stimuli and elevated levels of MMPs.(8) as shown in fig (4).

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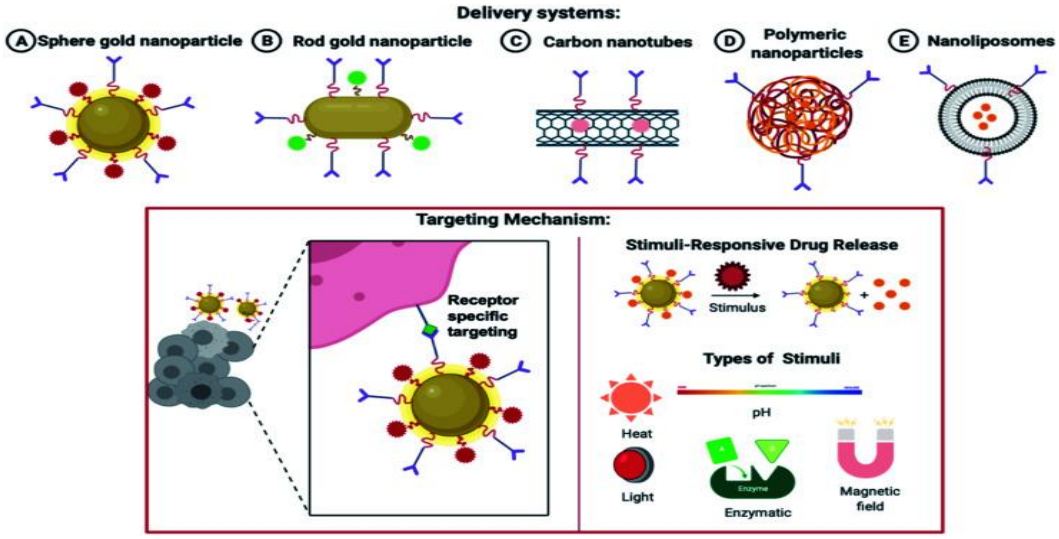

Fig4: Delivery systems

Various delivery systems ranging from gold nanoparticles to polymeric and liposomal-based delivery systems are widely accepted. As shown in , the nanoparticles are decorated with a targeting ligand and directed to a specific RA marker. On reaching the site of action, the nanoparticles can be made sensitive to a particular stimulus like pH, temperature, heat, enzymatic degradation, ultraviolet light, *etc*, which mediates a site-specific and more profound delivery of nanocarriers.

Systemic side-effects may arise if the premature and rapid release of the drug takes place from the nanoparticles. Similarly, a very relaxed release of the therapeutic molecule may shrink the effectiveness of the medicine, elevate the toxic effects due to prolonged exposure and lead to multiple drug resistance. This strategy helps in enhancing the effectiveness and the bio-accessibility of the drug. This area is keenly investigated to attain target delivery and regulated and monitored release of the encapsulated drug. Both endogenous and exogenous stimuli can be utilized. Some endogenous stimuli are pH varying-sensitive, ROS (reactive oxygen species) level-sensitive,environmental redox level-sensitive, responsive to a particular enzyme and thermo-sensitive delivery strategies pertaining to a few disease locations. Widely utilized exogenous stimuli contain photo-triggeredand thermo-triggered strategies.Magnetic field-activatedand X-ray generated drug delivery schemes are also utilized in the device of such trigger-responsive structures. Different stimuli-responsive techniques holding sensitive fragments can be utilized for transferring therapeutic agents to a specific tissue and attaining a drug release as and when required. The characteristics and structures of the trigger-responsive nanoparticles can be altered *via* endogenous or exogenous triggers for enhanced intake by the cellular compartments and the permeation efficacy (9)

Actively targeted delivery systems:

In RA pathology, cells involved in RA onset and development would go through a series of alterations such as the up-regulation of specific surface receptors or transformation of phenotype As a result, nanocarriers with the special binding affinity to these inflammation-related cells would consequently further promote the targeted drug delivery in inflamed sites. In the past five years, enormous progress has been made in the actively targeted drug delivery in various inflammatory disorders. Herein, nanomedicines engineered with small molecules, polymers, peptides, or proteins to achieve the active targeting are comprehensively summarized in . In the following sections, several representatives of actively targeted strategies in RA therapy. (10) as shown in fig (5).

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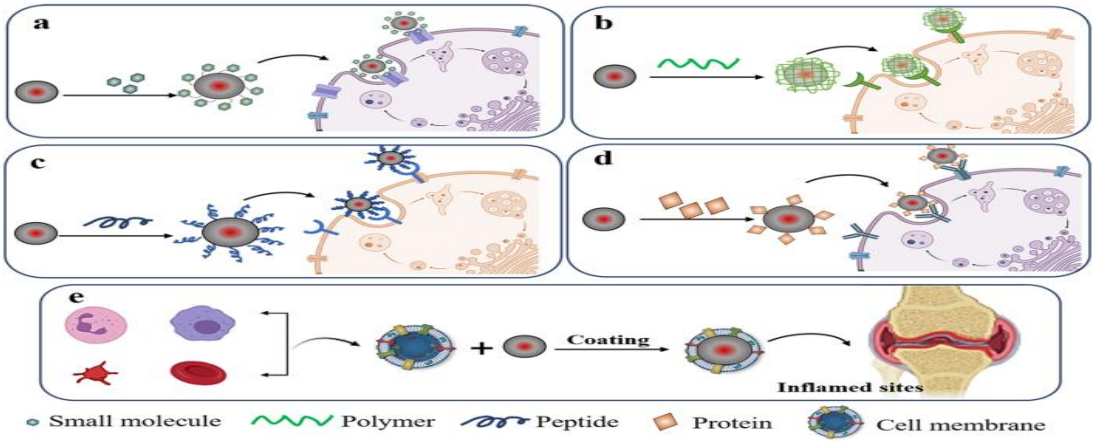

Fig5: Targeted delivery systems

Treatment for Rheumatoid Arthritis :

Current treatments for RA primarily aim to alleviate pain, and discomfort of arthritis, and minimise joint damage, deformity, and loss of function, ultimately improving the patient's quality of life.Early-stage RA is commonly treated with long-term oral or intra-articular injections of therapeutic drugs for pain relief. These drugs are typically categorised into four main groups: non-steroidal anti-inflammatory drugs, glucocorticoids, disease-modifying anti-rheumatic drugs (DMARDs), and biologics.(11)

Non steroidal anti inflammatory drugs: Non-steroidal anti-inflammatory drugs are a mainstay in the early therapy of RA as they effectively inhibit cyclo-oxygenase, providing anti-inflammatory, analgesic, and anti-swelling effects. However, these drugs do not alter the course of the disease or prevent joint destruction, nor do they specifically target inflamed tissue. And their prolonged use is associated with gastrointestinal side effects, limiting their long-term use.

Glucocorticoids: Glucocorticoids are effective in relieving arthritis symptoms and improving joint functions. The main mechanism of glucocorticoids in the treatment of RA is that they follow blood circulation, diffuse to the cells, bind to the corresponding receptors on the cell surface, participate in the regulation of cytokine expression, and inhibit the release of pro-inflammatory factors by blocking the transcription of genes such as interleukin-1β, *TNF*-α, nuclear factor-kappa B (*NF*-κ*B*), and so on, thus reducing the inflammatory response. However, their advantages are short-lived.Long-term use of these medications can lead to side effects such as hyperglycinemia and hypertension, and patients are resistant to the use of hormones.

Disease modifying anti Rheumatoid drugs : Disease-modifying anti-rheumatic drugs, such as methotrexate (MTX), are effective in controlling RA progression, reducing synovial inflammation, and alleviating the ongoing lesions and damage of joints and cartilage.Currently, DMARDs are the main drugs for the clinical RA treatment, functioning by curbing the production of antibodies and inflammatory mediators. This is achieved through the suppression of lymphocyte proliferation and dampening of inflammatory signaling pathways, ultimately aiming to slow down or halt the destruction of RA cartilage and bones. MTX, known for its tolerability, cost-effectiveness, and therapeutic efficacy, is the most commonly prescribed DMARDs. It modulates the activity of various immune cells, including T cells, B cells, monocytes, neutrophils, synoviocytes to suppress inflammation and immune reactions. However, the use of MTX and other DMARDs can induce serious toxic side effects, highlighting the need for careful monitoring and management.Additionally, the short half-life of these drugs necessitates frequent dosing, which may not always result in adequate drug concentration at the site of action. The long-term use of conventional drugscan lead to drug resistance and toxicity, such as gastrointestinal discomfort, hepatic, and renal toxicity.

Therapeutic agents: Biologics represent a distinct class of therapeutic agents that have a predetermined specific action on cytokines or molecules involved in the inflammatory cascade response in RA. Unlike the other therapeutic approaches discussed previously, biologics have a defined mechanism of action. This broad therapeutic class that can

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be split into several subgroups based on their function: co-stimulatory blockers (e.g., abatacept), TNF-α blockers (e.g., adalimumab), golimumab and infliximab, B-cell reductors (e.g., rituximab), and interleukin blockers (e.g., anabolic acid). They have disease-modifying properties but their use are often accompanied with side effects such as infection, elevated cholesterol and neutropenia.This mode works by suppressing the pro-inflammatory cytokines overproduction at the site of inflammation in RA patients.This suppression primarily targets the immune system, thereby increasing the patient's susceptibility to infections.While biologics offer promising therapeutic options, ongoing research is essential to fully understand their potential risks, benefits, and economic implications.(12)

Intra-articular administration for rheumatoid arthritis

Intra-articular injection is a widely utilised treatment method for RA.This technique involves injecting medication directly into the joints, thereby enhancing its bioavailability and allowing the drug to reach the affected area directly, which not only shortens the recovery time of the patient. This targeted approach not only expedites patient recovery but also minimises the side effects typically caused by oral medication.Currently, corticosteroids and hyaluronic acid are the most frequently used medications administered by intra-articular injection for pain management and joint lubrication.(13)

II. CONCLUSION

RA is a systemic, autoimmune, inflammatory disorder that damage cartilage and joints and drug delivery systems for RA, particularly focusing on hydrogels, microspheres, and nanoparticles. Compared to conventional treatments, these systems offer advantages such as sustained release, targeted delivery, reduced side effects, and improved patient compliance. The potential for personalised medicine, enhanced by precision delivery systems, is particularly noteworthy, offering a tailored approach to managing RA that considers individual patient needs.the delivery of therapeutic agents for the treatment of RA is still being explored and facing a variety of challenges, including biocompatibility, long-term safety, scalability, and regulatory approval processes. Further research and development are essential to overcome the current limitations of injectable drug delivery systems for RA. In addition to the design of nanocarriers, priming strategies represent a promising approach for improving drug delivery. Future studies should focus on optimising the design of these systems to enhance their efficacy, safety, and biocompatibility. Additionally, by addressing current challenges and embracing novel opportunities, researchers and clinicians can work together to usher in a new era of personalised and targeted therapies that have the potential to revolutionise patient care in the field of rheumatology.

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