REVIEW ARTICLE
MANAGEMENT OF RHEUMATOID ARTHRITIS : A NANOMEDICINE PERSPECTIVE

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Abstract

Rheumatoid arthritis (RA), a chronic and joint-related autoimmune disorder, leads to immune dysfunction and destruction of joints and cartilages. Little molecules and biological therapies are applied in a very wide variety of inflammatory disorders; however, their utility as a therapeutic agent is proscribed by poor absorption, speedy metabolism, and serious side effects. To improve these limitations, nanomedicines, that are capable of encapsulating and protective medicine from degradation before they reach the target site in vivo, could serve as drug delivery systems. The current studies demonstrated that the efficacy gets improved when a drug is administered in a nanoparticle formulation as compared to the free drug, mainly in three aspects: selective accumulation, controlled drug release, and reduced systemic toxicity. The newly developed nanocarriers significantly enhance the therapeutic effectiveness of current drugs to treat RA in experimental models by overall dose reduction and higher local drug localization by passive and active drug targeting. Therefore, in this review we explore newly discovered nanomedicines and their role in rheumatoid arthritis.

Keywords: Nanomedicine; Inflammatory disorders; Rheumatoid Arthritis; Therapeutic agentPolycyclic aromatic hydrocarbons, Vegetable oils, High-performance liquid chromatography.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disorder predominantly affects the synovial membrane that results in systemic destruction of bone and cartilage (Tak and Kalden, 2011). It affects approximately 0.5-1% of the total world population (Silman and Pearson, 2002). RA is characterised by inflammation of the synovium which leads to pannus formation. The inflammation caused in RA is due to the invasion of various pro inflammatory mediators in the joints which results in the cartilage destruction and bone erosion. The most important mediators which play an important role in the inflammation process are fibroblasts, macrophages, lymphocytes, pro-inflammatory cytokines, prostaglandins and enzymes. The immunological response in RA is produced by B cells, T cells and macrophages. RA pathogenesis consists of several stages which generally starts outside the joints.

It involves the activation of dendritic cells, macrophages and neutrophils by various etiological factors with the activation of inflammation process as well as T and B cells regulation. This hereby induces the production of autoantibodies to the cells of immune system that recognises various modified proteins with citrulline residues (Rantapaa *et al.*, 2003). Moreover, immunological changes in RA are also triggered when there is an interaction between genetic and environmental factors, leading to an inflammatory arthritis (Yarwood *et al.*, 2016; Ruiz-Esquide and Sanmarti, 2016). It has been shown that there is a genetic susceptibility factor in RA which contributes 60% to the development of this disease. Most of the immune effectors or regulatory gene products in RA have been well characterized through a genome-wide association study (Okada *et al.*, 2014) providing novel insight into RA pathogenesis.

Nanotechnology has become a boom in the treatment of various inflammatory diseases. It has produced various tools in medical and biological research such as target drug delivery system, numerous types of implants and many types of diagnostic tools for the diagnosis of various types of diseases (Murthy *et al.*, 2006). Nanomedicines are used for specific drug targeting which allows having improved pharmacokinetics and pharmacodynamics of the drug with reduced toxicity. On comparing with the ongoing drugs nanomedicines present numerous advantages such as improved delivery of lipophyllic drugs, reduced toxicity, selective targeting, controlled release of drugs and protection of drug from deterioration in the body. The application of nanotechnology which is highly used in RA is nanomedicines which include several types of particles such as nanoparticles, dendrimers, solid lipid nanoparticles, liposomes, niosomes, transferosomes (Moghimi *et al.*, 2005). Therefore, in this review we explore the role of lipid nanoparticles in rheumatoid arthritis and newly discovered nanomedicines for the treatment of rheumatoid arthritis.

Pathogenesis of rheumatoid arthritis

Rheumatoid arthritis is caused by the improper balance between the immune system and pro and anti-inflammatory proteins of the body which ultimately induces the destruction of its own body cells which leads to the inflammation in the synovium and destruction of joints (Strand *et al.*, 2016) the pathogenesis of RA consists of 3 stages:

1. Initiation: It consists of initiation and activation of the entire pro and anti-inflammatory cytokines.

2. Propagation: This includes the propagation of all these cytokines to the joints and pannus formation takes place.

3. Tissue damage: the activated cytokines damage the tissues and inflammation is produced in response to this.

Etiology

The etiology of RA is still not known properly but some genetic and environmental factors seem to triggers the immunological reaction in RA (Okada Y *et al.*, 2014). Some hormones such as thyroid or other endocrine hormones can

influence RA by acting on macrophages. Sex hormones also plays a role in the etiology of RA as the women are more prone to most of the autoimmune disorders as compared to the men. A genome wide association study characterises the regulatory gene products or immune effectors in RA. The patients who are positive for rheumatoid factor or RA factor or anti citrullinated protein antibody (ACPA) consists of HLA-DRB1 allele on some distinguished genes (Eyre *et al.*, 2012). RA alters the immune system which in turns affects the inflammatory pathways such as STAT4 pathway (Takasugi *et al.*, 2006). Different types of environmental factors such as infections and other factors such as smoking, alcohol intake, hormones, and obesity are more prone to RA. Among all the factors smoking is the major issue which further increases the risk for RA. Besides all of this smoking and tobacco causes mutations in deoxyribonucleic acid

(DNA) or genetic polymorphism due to the presence of high concentration of free radicals in it (Ruiz-Esquide and Sanmarti, 2012; Pedersen *et al.*, 2006).

Treatment of rheumatoid arthritis

Previously the most widely used drugs in RA was NSAIDs, but due to their increasing adverse effects, their long term use has been limited. Various other drugs therapy used in the treatment of RA are Glucocorticoids, DMARDs, biologics and their combinational therapy (Keystone, 2005). The recently approved drugs are Sarilumab are given to the patients with moderately to severely active RA or to those patients who are not tolerant to DMARDs (Rahman *et al.*, 2016) (Table 1). Various therapeutic agents used in RA along with their complications are discussed (Table 2).

Table 1: Shows some names of vegetable oils used in the study.

Therapeutic classifications	Therapeutic category	Therapeutic agent	Mechanism of action
Non-biological agents	Glucocorticoids	prednisone, methylprednisolone, dexamethasone	inhibits many process involved in immune responses and inflammation block T-cell activation and IL-2 production.
	Calcineurine inhibitor	cyclosporine	interfere with synthesis of nucleic acid and cell proliferation.
	Antimetabolite	azathioprine, leflunomide, mycophenolate, mofetil and methotrexate	
Biological agents	Anticytokines	Anakinra	they direct against IL-1 receptor they inhibit IL-6 signaling they inhibit T-cell proliferation
		Tocilizumab	
		Infliximab, adalimumab, golimumab, certolizumab and etarnacept	It blocks CTLA4, target CD20 and deplete B cells
	Anti-cell surface ligands	Abatacept	It direct against α4 integrin and block cell adhesion and migration
		Rituximab and crelizumab	
		Natalizumab	It act against IFN-β and suppress T cell activity
		Sarilumab (recently discovered)	It is an interleukin-6 (IL-6) antagonist.

Table 2: Various therapeutic agents used in rheumatoid arthritis and their complications.

S.No.	Therapeutic agents	Target	Complications produced due to long term therapy
1.	NSAIDs (First line therapy), for example, Ibuprofen, Naproxen, Indomethacin, Diclofenac sodium,	COX-2 (NON SELECTIVE)	Peptic ulcers, Dyspepsia, Anorexia, Abdominal pain, Nausea, Flatulence, Diarrhea, Renal ulcers, Myocardial infarction
2.	Injectable corticosteroids	COX-2	Skin atrophy
3.	DMARDs, for example, Gold salts, Leflunomide, Sulfasalazine, Methotrexate, Azathioprine, Minocycline, Hydroxychloroquine, Cyclosporine	TNF-α. IL	Digestive organ dysfunction, Liver dysfunction, Kidney dysfunction, Stomatitis, Depilation and myelosuppression
4.	Coxibs, for example, Celecoxib, Etoricoxib	COX-2(Selective)	Peptic ulcers
5.	Glucocorticoids, for example, Prednisone, Methyl prednisone, Hydrocortisone, Dexamethasone, Betamethasone	COX-2	Impaired wound healing, Skin atrophy, Osteoporosis, Muscle atrophy, Cataract, Glaucoma, Peptic ulcer, Manifestation of latent diabetes, Premature mortality
6.	Biologics	TNF-α, IL-1,IL-6	Malignancy, Tuberculosis

Nanotechnology

Nanotechnology refers to the technology which deals with the various dimensions of atoms and molecules. It has wide applications of which nanomedicines are widely used as they have enormous benefits (Mukharjee, 2013). Nanomedicine is composed of nano which means a very small particle and medicine which means drugs which are the main components of nanoparticles. Nanomedicines have a greater advantage regarding drug delivery system as they deliver drugs to the targeted sites actively or passively.

To be an ideal nanomedicine, a nanocarrier must fulfil all the requirements stated:

1. Size ranging from 1-100 nm and has a surface charge neutral or anionic.

2. It must be coated with a suitable polymer and has a long circulation time within the systemic circulation of the patient.

3. Proper ligands should be used to modify them (Parveen *et al.*, 2012).

Polyethylene glycol (PEG) or PEGylated is the mostly used polymer to prevent opsonisation. A proper modification should be done in an ideal PEGylated nanocarrier. Different types of nanocarrier system are used in the treatment of rheumatoid arthritis they are: nanoparticles, metallic nanoparticles, polymeric nanoparticles, dendrimers, solid lipid nanoparticles (Parveen *et al.*, 2102).

Nanoparticles have various advantages over the other conventional drugs (Albuquerque *et al.*, 2015-16). Drugs that are poorly soluble, highly toxic, indefinite quantity, not specific in delivery, has shorter half lives, nanoparticles has the application of target drug delivery system (Garud *et al.*, 2012).

- Nanoparticles improve the solubility of poorly soluble drugs by increasing their surface area and escalating their dissolution rate.

- Nanoparticles increase the half lives of the drugs in the systemic circulation: nanoparticles has the major advantage of sustained release and deliver the drugs as per the target, to attenuate the side effects and thereby reduces the markers of inflammation (Neda Naseri *et al.*, 2015).

Drugs such as non steroidal anti inflammation drugs, methotrexate, dexamethasone, clodronate are embedded in nanoparticles in different ways using different techniques for a particular type of disorder. Nanomedicines are widely used in the treatment of various diseases such as asthma, allergy, cancer and infection (Garud *et al.*, 2012). The targeted delivery approach of nanoparticles depends on the ability to pass through various barriers and to release their contents on the targeted sites. Polymeric nanoparticles have a major disadvantage of penetration, to overcome this advantage lipids are chosen as another

carrier for oleophillic prescribed drugs. They are known as solid lipid nanoparticles. It has various advantages over polymeric nanoparticles such as physical stability, protection of incorporated drug, good tolerability, less toxic, more biodegradable, easy to manufacture, better stability, low cost. They can be incorporate through various routes such as parenteral, oral etc (Shah *et al.*, 2011).

Liposomes

Liposomes are small sized vesicles spherical in shape composed of lipids, cholesterol, drug and a stabilizing agent. It consists of lipid bilayers (Bonifácio *et al.*, 2014). The liposomes can be classified in many ways according to their surface areas, charge, lipid composition and their method of preparation. It is a very promising approach as it reduces the side effects of medicine (Oleiveira *et al.*, 2018).

Metallic Nanoparticles

As the name suggests it consists of metals such as lithium, gold, platinum, zinc, iron. They are unique as they have the major advantage of constraining a large amount of medicines and they highly increases the half lives of the drugs. They possess some exceptional characteristics such as optical and electrical properties (Yaser *et al.*, 2017).

Dendrimers

They are the mostly recognised category of nanoparticles. They are characterised by their arboresque branches i.e. tree like branches. It mainly consists of a central core that begins from inside and grows outwards with many functional groups attached to it. They possess wide applications in the field of pharmacy (Abbasi *et al.*, 2014).

Polymeric Nanoparticles

Polymeric nanoparticles can be designed in two different ways according to their need: as a nanosphere or a nanocapsule. Their size ranges from 10-1000 nm. They can be made from artificial or natural biodegradable polymers. The polymers mainly used in their preparation are poly lactic acid and poly lactic-co glycolic acid (Bonifácio *et al.*, 2014).

Nanoparticle approaches in RA

Various anti-inflammatory drugs such as non steroidal anti inflammatory drugs produces side effects and sometime produces toxicity to the cells which is the most important issur to be addressed while implementing the nanoparticle approach. The drugs can be targeted into two ways: Passive targeting and active targeting (Yang *et al.*, 2014). Currently used nanoparticles are shown in (Table 3).

Table 3: Currently used Nanoparticles in Rheumatoid Arthritis

Drugs	Liposomal type	Animal used	Animal model	Route of administration	Observed effect	Year
Indomethacin	Large unilamellar vesicles	Rat	Carrageenan induced pae edema and adjuvant arthritis	Intraperitoneal	Increase inflammatory activity, less ulcer index	2000
Diclofenac sodium	Lipogelosome	Rabbit	Antigen induced arthritis	Intra-articular	Reduced side effects, increase retention of drug at inflammatory site	2008
Cortisol palmitate	Not defined	Rabbit	Poly-D-lysine and hyaluronic acid complex	Intra-articular	Reduced temperature and diameter in arthritic joints	1979
Hydrocortisone	Multilamellar liposome	Rabbit	Antigen induced arthritis	Intra-articular	Prolong antiinflammatory effect	1984
Prednisolone phosphate	PEG-liposome	Mice	Collagen type-II and adjuvant induced arthritis	Intravenous	Reduce cartilage damage	2004
Methylprednisolone hemisuccinate	nanoliposomes	Lewis rat, beagle dog	Adjuvant arthritis	Intravenous	High encapsulation efficacy, high drug-lipid mole ration,increase therapeutic efficacy,	2008
Prednisolone phosphate	Not defined	Mice	Antigen induced arthritis	intravenous	suppression of bone erosion, less synovial immune cell infiltration, suppress metalloprotease and aggrecanass in synovium	2011
Methylprednisolone hemisuccinate	nanoliposomes	Lewis rat	Adjuvant arthritis	Intravenous or subcutaneous	Reduce arthritis, suppression of secretion of proinflammatory cytikines	2012
Betamethasone hemisuccinate	nanoliposomes	Lewis rat	Adjuvant arthritis	Intravenous or subcutaneous	Reduce arthritis, suppression of secretion of proinflammatory cytikines	1987
Dexamethasone phosphate	Oligilamellar and multilamellar vesicles	Rabbit	Antigen induced arthritis	Intra-articular	Increase retention of drug in synovium and synovial fluid	2006
Dexamethasone phosphate	RGD-PEG-liposomes	Lewis rat	Antigen induced arthritis	Intravenous	Strong and long lasting antiarthritic effect, specifically target vesicular indothelial sites at site of inflammation	2009
Dexamethasone phosphate	Non-PEGglyated liposomes	Rat	Antigen induced arthritis	Intravenous	Suppress joint swelling	2010
Dexamethasone phosphate	Non-PEGglyated liposomes	Mouse	collagen induced arthritis	Intravenous	Persistent antiinflammatory effect, suppression of hypothalamic pitutary	2011, 2013
Dexamethasone phosphate	Not defined	Lewis rat	Adjuvant arthritis	Intravenous	Suppression of histological sign of arthritis, increased residence time of drug in synovial membrane	1993
Dexamethasone budesonide prednisolone	Long circulating liposomes	Rat	Adjuvant arthritis collagen induced arthritis	Intravenous	Increase therapeutic efficacy, decrease clearance of drug from body	2009 2010 2011

Passive targeting in nanoparticles

The targeting of the drugs to a specific site depends on the properties of nanocarrier delivery system. The passive targeting strategy is to identify the targets to act in RA. The targets in RA are the leaky vessels. The size of nanoparticles ranges between 20-250 nm will accumulated in the inflammatory space and thereby releasing the drug by using sustained effect (Kapoor *et al.*, 2014). Various studies have shown very promising effects in the field of target drug delivery system. In vitro model against CD-64 a macrophage specific receptor – Methotrexate was incorporated in poly lactic co-glycolic acid. The result shows that these nanoparticles are much more effective in showing therapeutic effect as compared to the conventional drugs (Moura *et al.*, 2014). Fumagilin Prodrug nanoparticle targeted with αvβ3-integrin peptide mimetic antagonists increases the production of nitric oxide in the endothelial cells thereby decreasing the

inflammation in RA (Zhou *et al.*, 2012; Zhou *et al.*, 2014). Through all of these studies, it was found that even a small dose of nanoparticles can produce a greater therapeutic effect than the conventional dose of the drug.

Nanosponges

A newly promising potential approach in the treatment of rheumatoid arthritis

Nanosponges are the new prototypes of nanoparticles recently discovered for the treatment of rheumatoid arthritis to block the progression of the disease. Nanosponges are the newly discovered nanoparticle made of biodegradable polymers consists of neutrophil membrane which is a type of white blood cells. The primary functions of neutrophils are to respond against the infection, they also have a role in rheumatoid arthritis. When RA progresses or develops in the body, cytokines are released. These cytokines in turn

activates the white blood cells (WBCs) to enter into the joints. Once this system is activated, additional cytokines are released and attracted towards the joints causing inflammation. These nanosponges block the activation of WBC by the cytokines resulting in the reduced inflammation and joint destruction. Nanosponges have helped to manage the disease progression but they act on some certain kinds of cytokines and a variety of cytokines plays role in RA.

Conclusions

There are limited types of treatment available for rheumatoid arthritis these days that includes drugs such as non biologics and biologics which are somewhat successful in providing the beneficial effects in the patients with an active RA, but Along with the effects this long term therapy produces no. of side effects too which in turn reduces the quality of life of patients and sometimes produces remission in the patients. Lipid-based nanoparticles has somewhat reduced this disadvantage of toxicity and side effects by providing long term effects in a very small amount of drug than a conventional drug therapy. These nanoparticles have produced very advanced effects when evidenced in animals and clinical trials. Although, more research is required to get better retention time and controlled release rate of drug.

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