

Rheumatoid Arthritis: An Updated Overview of Latest Therapy and Drug Delivery

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Key Words

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Abstract

Rheumatoid arthritis is a severe autoimmune disorder, related to joints. It is associated with serious cartilage destruction. This causes disability and reduces the excellence of life. Numerous treatments are existed to combat this disease, however, they are not very efficient and possess severe side effects, higher doses, and frequent administration.

Therefore, newer therapies are developed to overcome all these limitations. These include different monoclonal antibodies, immunoglobulins, small molecules used for immunotherapy and transgenes for gene therapy. One of the main goals of these new generation therapeutics is to address the underlying distressing biological processes by specifically targeting the causative agents with fewer systemic side effects and greater patient console. It is very fortuitous that loads of progressive investigations are going on in this field and many of them have entered into the successful clinical trial. But till date, a limited molecule has got FDA clearance and entered the market for treating this devastating disease.

This review highlights the overview of conventional therapy and advancements in newer therapeutics including immunotherapy and gene therapy for rheumatoid arthritis. Further, different novel techniques for the delivery of these therapeutics of active and passive targeting are also described.

1. Background

The word arthritis came from the Greek word "for joint inflammation". It mainly affects the joints of the body. But sometimes other tissues of the body, such as the kidneys, eyes, skin, etc. are also getting affected [1]. Arthritis belongs to the category of T cell-mediated autoimmune disorder in which the immune system of the body attacks its own tissues. It is a disease in which the body fails to recognize the self-molecules from foreign molecules [2].

In rheumatoid arthritis, the immune responses influence the secretion of rheumatoid factors and evoke destruction of cartilage and bones in progression. Both the environmental factors and genetic factors are implicated in the progress of clinical indication of RA [2-4]. Joint damage occurs due to the auto-reaction of different immune modulators like effector cells and cytokines. It starts at membranes of synovium and then progressively attacks the adjacent structures. The activation of dendritic cells, T cells, plasma cells, B cells, mast cells, macrophages, and angiogenesis cause sinusitis [5-6]. Amongst these, persistently

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activated synovial macrophages are one of the leading factors for producing inflammation in RA. Fig. 1 explains the progression of rheumatoid arthritis. However, the intensity of inflammation on the joints and degradation of tissues depends on the number and level of macrophage activation [6-7]. Therefore, over the last few decades, the RA treatment has been progressed by considering its internal mechanisms so that drugs can be developed to target at the molecular level. Table 1 depicts different molecular targets explored for drug targeting [8-11].

These novel targeted drugs have proved the enormous potential for countering disease.

However, distinguished side effects, long-term treatment challenges and cost of treatment are till have to be considered. The most important reason behind this is the nonspecific delivery of drug molecules. So nowadays the research is turned towards the development of targeted delivery strategies to the inflamed joints [12]. Although intra-articular injection is one of the best options as targeted therapy, repeated joint needling limits its utility which enhances the risk of infection. As well as it offers the local administration of the inflamed joints this cannot be a choice in case of polyarthritis and systemic disease [13]. The detailed study of inflammatory diseased tissue shows an abnormal increment of macrophages and other cellular factors. This leads to enhancing the targeting of therapeutics by different novel delivery techniques. These targeted delivery systems accumulate passively into inflamed tissues via different mechanisms like the enhanced permeability and retention, surface conjugation with a ligand and others. Surface conjugation helps in the active attachment

to receptors which are proliferated by affected cells so that systemic side-effects can be reduced and efficacy can be increased [14-15].

In this review, the overview of conventional drugs for RA and advancements in the newer therapies as medical options for management are discussed. Clinical trial updates of different treatment are also reviewed and special consideration is given to different novel delivery systems for their delivery.

2. OVERVIEW OF CONVENTIONAL RA THERAPEUTICS

The present-day treatment for RA can be classified into four classes:

- i. Non-steroidal anti-inflammatory drugs (NSAIDs)
- ii. Glucocorticoids
- iii. Non-biologic Disease Modifying Anti-rheumatic Drugs (DMARDs)
- iv. Biologic Disease Modifying Anti-rheumatic Drugs (DMARDs)

These recognized therapies are summarized in Table 2. Under each section the mechanism of action, side effects, dose and new drug candidates of each class of the drug. Different NSAIDs are generally the first choice of drugs for the treatment of RA as well as for osteoarthritis and other musculoskeletal disorders. They are generally used for the symptomatic relief of the disease and do not have any effect on the cause of the disease. These drugs reduce pain and swelling by inhibiting the cyclooxygenase enzyme which is responsible for inflammation. Cyclooxygenase -1 and Cyclooxygenase -2 are the two isoforms of the enzyme [16-17]. Corticosteroids are the second leading prescribed drug for the treatment of RA. These agents possess strong anti-inflammatory effect as well as analgesic effect. An established Guideline for RA known as “National Institute for Health and Clinical Excellence (NICE)” states that corticosteroids should be used only after the application of all other treatment options and after gaining the complete knowledge about the side effects as these drugs produce severe osteoporosis and fractures, Cushing’s syndrome, weight gain, cataract, hypertension, etc. [18-19].

DMARDs are the drug of choice for RA treatment. These drugs mainly work on the progression of the disease, hence agents prevent further joint destruction and loss. This therapy has been found successful in many cases. It eliminates the need for any other treatment. Other drugs can be used for symptomatic relief until the completion of therapy [20-22]. Mainly the biologic and non-biologic disease modifying anti-rheumatic drugs (DMARDs) are the important pharmacological therapies for RA. DMARDs of non-biologic origin is also popular as small molecule DMARDs or low molecular weight DMARDs and a wide variety of chemically diverse drugs are in this group. These drugs are further divided into two classes: traditional and novel. In this section, only traditional DMARDs will be discussed. Traditionally DMARDs have been used since the 1920s are

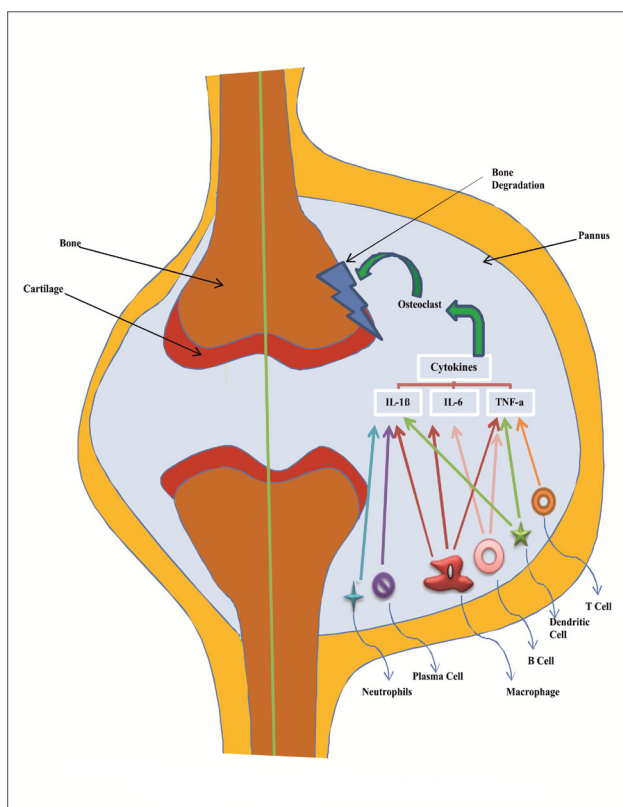


Figure 1

Table 1 Molecular Targets in Rheumatoid Arthritis

S. No.	Molecular Targets	Role	Occurrence	Example of Targeting Drugs
1.	Cyclooxygenase pathway	Biosynthesis of prostanoid, biologically active substances, involved in pathological conditions inflammation.	Cytosol and tissue	Celecoxib, Piroxicam, Naproxen, Valdecoxib
2.	Tumor Necrosis Factor- α	Activation of macrophages, synovial fibroblasts, endothelial cells, MMPs and adhesion molecule expression and release of other cytokines and PGs.	Synovial fluid and tissue	Infliximab, Etanercept, Adalimumab, Golimumab, Certolizumab pegol
3.	Interleukin-1	Potent inducer of MMPs, eicosanoids, and receptor activator of NF- κ B Ligand, Hyaline cartilage synthesis inhibitor.	Synovium	Anakinra
4.	Interleukin- 6	Activation of osteoclasts, bone resorption, upregulates intercellular cell adhesion molecules 1 expression.	Serum and synovial fluid	Tocilizumab, lactoferin
5.	Interleukin- 8	--	Synovium	ABX-IL8
6.	Interleukin- 10	Inhibit the production of cytokines and Enhancement of production of IL-1RA	Synovial tissue	
7.	Interleukin-12	Act in synergy with anti-TNF- α antibodies	Synovial fluid	ABT-874
8.	Interleukin-15	Activates T-cells, Stimulation of macrophages to release TNF-alpha	Joint Synovium	HuMax-IL-15
9.	Interleukin-17Alpha	Activation of IL-1, 6 and 8, implicated in osteoclast activation causing bone resorption in RA	Synovium	--
10.	Interleukin-18	IL-1 and TNF production enhancement	Synovium	IL-18bp
11.	Matrix Metalloproteinase	Involved in bone and cartilage degradation	Joint Synovium	Trocade (Ro 32-3555)
12.	Nuclear Factor- κ B		Cytosol	Iguratimod
13.	Cathepsin- B	Cleaves aggrecan and enhancement of RA	Synovial tissue	--
14.	Aggrecan	Maintainance of cartilage integrity	Synovium	--
15.	Osteopontin	Stimulates cell adhesion, migration, and specific signaling function.	Extracellular fluid, and inflammation site	--
16.	Prostaglandin (PG)	Bone resorption stimulator	Osteocyte	Celecoxib, Piroxicam, Naproxen, Valdecoxib
17.	ϵ 38MAPKs	Inhibition affects TNF production	Synovial tissue	Pamapimod, VX-702 and SCIO-469
18.	Oncostatin M	Synergistic with IL-1, promote cartilage damage	Synovial fibroblasts	--
19.	Collagen I	Osteoblastic differentiation of the bone marrow cells	Bone cell	--
20.	Collagen II	Maintain the integrity of cartilage	Cartilage	--
21.	T lymphocyte	essential for the continued activity of inflammation in RA	Thymus	Abatacept
22.	B lymphocyte	Antigen presentation Secretin of pro-inflammatory cytokines	Bone marrow, synovial membrane	Rituximab
23.	Janus Kinase (JAK)	affect intracellular signaling through their association with transcription factors known as STATs	Synovium	Tofacitinib, VX-509, Baricitinib (formerly LY3009104/ INCB028050), Ruxolitinib (formerly INCB018424)
24.	Spleen Tyrosine Kinase (Syk)	Syk is theoretically connected to inflammation and bone resorption.		Fostamatimib (formerly R406; R788 is the prodrug),

Table 2 Overview of Conventional RA Therapeutics

S. No.	Category	Drug	Brand name	Adult Dose	Mechanism	Side effects	Company	FDA Approval
1.	NSAIDs	Celecoxib	Celebrex	Tablet 100 to 200 mg orally twice daily.	COX-1 and COX-2 inhibitor	Dyspepsia, peptic ulcer disease, bleeding, myocardial infarction, Increased Blood pressure, Heart failure.	G.D. Searle	FDA 1998
		Piroxicam	Feldene	20-4-mg daily			Pfizer	FDA 1982
		Nabumetone	Relafen	1000 mg daily			Teva Pharmaceuticals Ltd.	FDA 2000
		Naproxen	(i) Anaprox	500- 1000 mg daily			Atnahs Pharma Inc.	FDA 1980
			(ii) Neprelan	375mg, 500 mg daily				
		Etodolac	Lodine	100- 200 mg not more than 1000mg/day			Teva	FDA 2000
		Rofecoxib	Vioxx	25 mg Daily			Merck	FDA 2002
		Valdecoxib	Bextra				Pharmacia, Pfizer	FDA 2001
Ibuprofen and Famotidine	Duexis	800 mg/26.6 mg	Horizone Pharma	FDA 2011				
2.	Glucocorticoids	Prednisone	Deltasone, Liquid Pred, Sterapred	5- 60 mg/day in divided doses	Inhibition of macrophage accumulation, reduction of capillary permeability	Osteoporosis Stomach ulcer Increased blood pressure Irritability and/or excitability Increased blood sugar/glucose Cataracts (clouding of eye lenses)	Pharmacia and UP John	FDA 1955
		Methyl Prednisone	Depopred, Medrol, Methacort, Predacorten	2-60 mg/day				
		Hydrocortisone	A-Hydrocort, Cortef	10-320 mg/day			Hospira	FDA 2006
		Dexamethasone	Decadron, Dexpak, Hexadrol, Taperpak	0.75 – 9 mg/day			Merck	FDA 1958
3.	Nonbiologic DMARDs	Methotrexate	(i) Trexall (ii) Xatmep	Maximum weekly dose: 20 mg.	Inhibition of aminoimidazole carboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase	Nausea, mouth ulcer, hair loss, cytopaenias, elevated liver enzymes, rarely pneumonitis	Silvergate Pharms	(i) FDA 2001 (ii) FDA 2017

S. No.	Category	Drug	Brand name	Adult Dose	Mechanism	Side effects	Company	FDA Approval
		Leflunomide	Arava	Initial dose: 100 mg orally once a day for 3 days	Inhibits T-cell proliferation and production of autoantibodies by B cells.	GI disturbance, hair loss, weight loss, rash and itch, mouth ulcer, headache, cytopaenias, hypertension	Sanofi Aventis US	FDA 1998
		Sulfasalazine	Azulfidine	0.5-2gm/day	Inhibits the release of inflammatory cytokines,	Nausea, abdominal pain, hair loss, cytopaenias, elevated liver enzymes, agranulocytosis, skin rashes.	Pharmacia & Upjohn	FDA 1996
4.	Biologic DMARDs	Tocilizumab	Actemra	Dose - 4 mg/kg followed by an increase to 8 mg/kg	Inhibits Interleukin – 6 receptor	Upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased AL, injection site reactions	Genentech	FDA 2017
		Golimumab	Simponi	Dose-50mg			Centocor Ortho Biotech	FDA 2009

mainly non-biologic. They are including Sulphasalazine, Chloroquine, Methotrexate, Azathioprine, Cyclosporine A, Minocycline, and others. Even in the new era of biologic, methotrexate (MTX) still remains the drug of choice for RA and prepared as a standard to probate many other new disease-modifying drugs.

Novel Non-biologic DMARDs are further divided into four classes: phosphoinositide 3-kinases (PI3Ks) inhibitors, glycosidase inhibitors, matrix metalloproteinases (MMPs) inhibitors and cathepsin inhibitors [23].

2.1. Current FDA status of conventional RA therapeutics

It is very unfortunate that till 2017 only 25 (approx) drugs got approval for the RA treatment by the Food and Drug Administration (FDA). These drugs include corticosteroids, NSAIDs, different antibodies, and immunoglobulins. Methotrexate is one of the prime and vintage RA drugs of the mainstays for its dual capacity to reduce pain-swelling and modify joint damage to prevent disease progression over time. Methotrexate was first applied in 1947 as folate antagonist in pediatric leukemia. In 1951, its effect on RA was established by Gubner and it got approved by the FDA in 1988. In the last 25 years, this drug has become a primary standard in the treatment of adult RA. Another pioneer drug prednisolone or methylprednisolone was the drug of

choice in RA in most chronic cases and to date, they are in the system. The FDA approved methylprednisolone in October 1957 for treatment of RA [24].

The approval of Lodine by Wyeth containing etodolac was a remarkable confrontation in the year 1996. Immediately after that Azulfidine enteric coated tablets of sulfasalazine and Naprelen containing naproxen came into the market in the same year. However, sulfasalazine was permitted for medical application in 1950 in the United States. Initially, this drug was formulated as an enteric-coated formulation marketed as AZULFIDINE EN-tabs. These tablets were specifically intended to control nausea and stomach upset. Till date, this tablet is the only FDA approved formulation of sulfasalazine for the treatment of both juvenile and adult RA [25-27].

In the year of 1997, the first generic equivalent of Lodine came into the market just after one year by Royce Laboratories was Etodolac. Another three NSAIDs got approval in this year: Arthrotec by Searle, Ketoprofen by Schein Pharmaceutical which is a generic equivalent of Oruval and Tolmetin Sodium by Teva Pharmaceutical [28-29].

Hoechst Marion Roussel company launched Arava containing Leflunomide tablet in 1998. Leflunomide is an immunosuppressive disease-modifying antiarthritic drug, used in RA and psoriatic arthritis [30]. In 2001 Valdecocix (NSAIDs) tablets under the brand name Bextra got approval launched by Pharmacia Pfizer. However, because of the increased risk of heart attack and stroke, it was removed from the U.S. market in 2005. The same incidence

also happened with Vioxx containing rofecoxib drug (approved April 2002, withdrawn October 2004) [31-32].

After a long gap in 2010, Vimovo a combination product of naproxen and esomeprazole by AstraZeneca got permission for RA in patients at threat for NSAID linked ulcers [33]. In 2011, another combination product of ibuprofen and famotidine got approved under the name Duexis for the relief of RA as well as osteoarthritis by Horizon Pharma. It was also indicated for gastric ulcers associated with therapy. By this time, many monoclonal antibodies, immunoglobulins got the green signal from the FDA for treating this devastating disease. Immediately after one year, in 2012 delayed-release tablets of prednisone (Rayos) get underway by Horizon Pharma for curing different inflammatory diseases, including rheumatoid arthritis, psoriatic conditions, COPD, and asthma [34].

3. ADVANCES IN NEW GENERATION RA THERAPEUTICS

The autoimmune characteristics of RA which is primarily evident as 'chronic inflammatory arthropathy', create this treatment challenging for years. Conventional drugs have no (NSAIDs) or limited (Corticosteroid) authority on this autoimmune nature of the disease. Moreover, corticoids and other non-biologic DMARDs are inadequate and only capable of achieving clinical remission in combination. Further, they possess common unwanted side effects such as stomach upset, nausea, vomiting, diarrhea, liver problems, etc. In addition to this, approximately half of the RA patients don't show any promising reaction to traditional DMARDs [21].

Thus, one of the foremost goals of new generation RA therapeutics is to repress the fundamental biological processes which cause bone erosion, joint destruction, and progression of physical comorbidities. These medicines have a fast therapeutic action and possess comparatively less systemic side effects than former treatments. Most significantly, these therapeutic substances can modify the fundamental cause of inflammation and cell damage. These amazing therapeutic agents are including biologic DMARDs or biotech drugs used in immune therapy and specific transgenes for gene therapy [21]. In this section, introduction, advancements, clinical aspects and other details of these newly introduced agents have been discussed.

3.1. Immunotherapy for RA

The amendment of immune therapies as especially do target the molecules and cells accountable within the immunopathogenesis is very essential for RA treatment. The preceding endeavors at RA immunotherapy had been cells targeted rather than molecules. The detected T lymphocyte values into the investiture about RA resulted in endeavors according to alternate the immune replication by denotes of depleting T lymphocytes [35]. However, this method was once generally unfruitful. It was found rational to aim at T cells, so those hold a sanctioned role

among initiates or directing immune replications. During this length, many other researchers have been focused on provocative cytokines, along a most important attempt focused regarding the provocative TNF- α . At the beginning of the 1980s, TNF- α was recognized in the synovial film of RA patients. 27 years later in 1980s new TNF- α blockers had been produced. The drug named CA2 (infliximab) was first in this category.

Last study of few years shows that many patients impasive to established therapies have proved effective in treatment with novel biological agents. The rationale behind this may be the efficiency of highly specific targeting approach to provocative cytokines and other involved cells and along with their surface molecules in the RA pathogenesis. They mainly act by three mechanisms:

First, prevention of binding of the cytokines to its cell-surface receptors in different ways, including monoclonal antibodies, soluble receptors, and natural antagonists. Second, inhibition of production/proliferation of provocative cytokines by anti-inflammatory cytokines such as interleukin-4, 10 or 13. Third, exclusion of the inflammatory cells or interference with cell function by targeting either biological agent against differentiation or cell-surface antigens attached functionally.

Presently used biologic DMARDs are including TNF antagonists (etanercept, infliximab, golimumab, adalimumab), IL-1 and IL-6 inhibitor (tocilizumab), T cell inhibitors (abatacept), B cell inhibitors, anti CD20 (Rituximab). However, latest biologic DMARDs under investigation are phospholipase A2 (PLA2) inhibitors, vascular endothelial growth factor (VEGF) inhibitors, chemokines blocker, colony stimulating factor" (CSF) inhibitors and others [36].

Amongst recently used DMARDs TNF blockers are much more extravagant and consequently payers endeavor to restrain their exploitation of patients whose disease cannot otherwise be controlled. Therefore, traditional therapy is a junction point in RA treatment where cost considerations become very authentic. While biologic therapies are efficacious, they are sumptuous. The alternative approach of amalgamation therapy with conventional DMARDs, such as hydroxychloroquine and sulfasalazine together with methotrexate (soi-disant "triple therapy") and the utilization of glucocorticoids as bridge therapy, is additionally efficacious. It is much less extravagant, but it involves several medicines and the insertion of glucocorticoids and their associated side effects [37].

3.1.1. Current FDA status of immune-therapeutics

Table 3 depicts the FDA approved immune-therapies for RA with their mechanism and side effects. Initially, Enbrel (Etanercept) was launched in November 1998. It was the first targeted biologic for RA. It reduces the symptoms and inhibits the progression of structural damage in patients facing moderate to highly active rheumatoid arthritis. It is also useful in juvenile polyarticular type RA. It is basically a TNF antagonist. Further, in January 2002, it received approval for diminishing the symptoms of arthritis in pa-

Table 3 FDA Approved Immunotherapeutic For Treatment Of RA

S. No.	Approval year	Brand name	Biologics	Company	Dosage form	Mechanism	Side effects
1.	November 1997	Rituxan	Rituximab	Genentech	IV solution	antiCD20 antibody	Skin Rashes
2.	November 1998	Enbrel	Etanercept	Immunex Corporation	SC injection	TNF inhibitors	Serious infections including tuberculosis, upper UTI
3.	November 2001	Kineret	Anakinra	Amgen	Injectable	IL-1 receptor antagonist	Diarrhea, stomach pain, Headache
4.	June 2002	Remicade	Infliximab	Centocor Ortho Biotech	Intravenous infusion	TNF inhibitors	Chest pain, sore throat, dizziness, fatigue
5.	December 2002	Humira	Adalimumab	Abbott Laboratories	SC injection	TNF inhibitors	Bruising at the injection site, upper respiratory infection, nausea
6.	December 2005	Orencia	Abatacept	Bristol-Myers Squibb	SC injection	CTLA4-Ig fusion protein	Increase risk of serious infections, Skin irritation, itching rashes, swelling and pain
7.	April 2009	Simponi	Golimumab	Centocor Ortho Biotech	SC injection	TNF inhibitors	Increase the risk of serious infections including tuberculosis,
8.	May of 2009	Cimzia	Certolizumab pegol	UCB	SC injection	TNF inhibitors	Tuberculosis, UTI, headache
9.	June 2009	Ilaris	Canakinumab	Novartis	Powder for injection	anti-IL-1 β receptor antibody	Bronchitis, Diarrhoea, Gastroenteritis, vertigo, weight increase
10.	September 2009	Stelara	Ustekinumab	Janssen Biotech	SC injection	Human IgG1k monoclonal antibody	Nasopharyngitis, diarrhea, upper UTI, nausea
11.	January 2010	Actemra	Tocilizumab	Genentech	IV infusion	anti-IL-6 receptor antibody	Serious infections, elevated liver enzymes neutropenia, decreased platelet counts
12.	November 2012	Xeljanz	Tofacitinib	Pfizer	Tablet, extended release	Janus Kinase inhibitor	Upper respiratory tract infection, Diarrhoea, Nasopharyngitis
13.	March 2014	Otezla	apremilast	Celgene	Tablet	PDE4 inhibitor	Diarrhoea, nausea, headache
14.	March 2016	Taltz	Ixekizumab	Eli Lilly	SC injection solution	Anti IL- 17A receptor antibody	Injection site reactions, tinea infection, nausea
15.	May 2017	Kevzara	sarilumab	Sanofi	SC injection	IL- 6 receptor antagonist	Neutropenia, increased ALT, injection site erythema, UTI

tients with psoriatic arthritis for which it's the first therapy [38].

Studies reported that TNF blockade is one of the most effective methods for RA treatment. It leads to the evolution of distinct inhibitors of TNF like Infliximab, Adalimumab, Certolizumab pegol, Golimumab. In June 2002, infliximab (IFX) came into the market. It is a chimeric monoclonal antibody (mAb) against TNF- α [39]. After six months another TNF- α blocker, Humira (adalimumab) by Abbott Laboratories got approval.

Anakinra (brand name Kineret) the first biopharmaceutical drug used to treat rheumatoid arthritis got approval in November 2001. It is a recombinant human receptor antagonist acting on IL- 1 and nonglycosylated form of protein.

A specific co-stimulation modulator named Abatacept is accepted in 2005. It binds to CD80/86 and inhibits T-cell activation and thus it modulates its interaction with CD28 which initiates, the co-stimulatory signal required for the T cell activation. This drug is suggested for patients not responding to different DMARDs or TNF inhibitors, takes an approach that differs from the TNF inhibitors [40].

It is notable that amongst these immune-therapeutics, etanercept, adalimumab, and anakinra are self-injectable drugs, while infliximab, rituximab, and abatacept are infused products [41]. A product of Novartis, Canakinumab (ACZ885, Ilaris) acts by neutralizing 1β signaling. It is a human anti-IL- 1β monoclonal antibody. It suppresses inflammation in patients with autoimmune disorders [42]. STELARA[®] is a human IgG1k monoclonal antibody. It attaches specifically to the protein on p40 subunit and utilized by both the cytokines interleukin -12 and 23. STELARA[®] (ustekinumab) is prescribed to the patients of active psoriatic arthritis. A combined form of it and methotrexate is also frequently suggested [43].

Tocilizumab denoted as TCZ was the first biological DMARD and it targets to IL-6. The clinical trials for other inhibitors of Interleukin-6 are also in progress. These include sarilumab the monoclonal antibody (REGN88/SAR153191), and nanobody (ALX-0061), sirukumab, olokizumab, and MEDI5117. EVZARA targets and binds with high affinity to IL-6 receptors (sIL-6R and mIL-6R) came into the market in 2017 [44].

Janus kinase pathway inhibition is an advanced mechanism. It inhibits the intracellular effects of several inflammatory cytokines and completely modulates the immune and inflammatory response. Tofacitinib is the first oral non-biologic DMARD, approved in 2012. Baricitinib is another one from the same group. For the patients with an unsuccessful DMARD history tofacitinib is the best drug [45].

3.2. Gene therapy for RA

In the understanding of the molecular mechanisms behind RA pathogenesis cause a continuous advancement over the past years. It results in the development of many kinds of targets of novel gene therapy. It is an established fact that RA pathogenesis is involved with activation of specific T cells, osteoclasts, monocytes, fibroblasts, B

cells, endothelial cells and macrophages [46]. Along with this excess production of pro-inflammatory factors like cytokines and chemokines, rheumatoid factor and matrix metalloproteinases are also responsible. Each of these factors can be manipulated as a target in multiple ways using gene therapy. This section presents a review of the latest advances in gene therapy for RA treatment.

Therapeutic genes are generally delivered by two methods: in vivo and ex vivo. These methods can accomplish the need of local as well as systemic delivery of genetic material. Generally, the intraarticular route is used for gene transfer in local in vivo strategies [47]. However, ex vivo strategies include three steps:

- i. Exclusion of synoviocytes from the affected area usually joint
- ii. In- vitro Transduction
- iii. Transduced cells are re-injected into the joints.

The systemic gene therapy consists of the transfer of genes to the cells and these cells synthesize the gene product. These gene products are then secreted into the circulation. This approach is beneficial as rheumatoid arthritis has its systemic nature and it has the capacity to target more than one joint simultaneously. This also leads to non-specific immune suppression with increased susceptibility to infection [48]. Many transgenes are available which are utilized for RA in different methods some of the important examples are summarized here.

In a report 'IL-1 Ra' transgene was introduced by naked DNA method to DBA/1 mice. Arthritis was induced by using an adjuvant-induced arthritis method. Four sites of hind limbs were injected intramuscularly. The results depicted that the onset of collagen-induced arthritis was completely prevented with decreased synovial inflammation, cartilage destruction, with a lesser expression of IL- 1β in ankle joints [49].

One more study administered 'IL-1 Ra co-expressed with GFP' by i.e. injection into mice via adenovirus. The results reveal the severity of arthritis was reduced along with reduced foot-pad swelling, inflammatory cell infiltration, and synovial proliferation. Additionally, it increased Th1 driven IgG2a antibodies and Th2driven IgG1 antibody and conserved the proteoglycan concentration [50]. It was observed that impediment in enduring provocative autoimmune disease after intravascular tail injection of a single-chain antibody into 'DBA/1 LacJ' mice [51]. A study on 'adoptive cellular gene therapy' where T-cell was hybrid and transduced with RT administered CIA by intravenous tail injection. They reported transgene expression was constrained to the paw and decreased the level of IL-6 [52]. One more study conducted on both IL-1Ra and SiL-1RacP. They were injected CIA by i.v. Via adenovirus into DBA/1 mice. The result disclosed sIL-1RacP refurbished CIA without affecting T cell immunity, whereas IL-1Ra refurbished CIA and repressed lymphocyte propagation [53]. In a motivating study, researchers used variants of hTNFR-Is as monomeric, dimeric and 'chimeric hTNFRIs/mIgG1' type. These were introduced via ET of plasmids DBA/1 mice, CIA by intramuscular injection. Researchers found hTNFR-Is/mIgG1 at the beginning of CIA condensed clinical and histological manifestations of the disease. Dimeric form demonstrated the effective-

ness of local expression in a dose-dependent manner and lasted a minimum of 6 months. Researchers found after intraarticular injection of an adenovirus (over-expressing IL-18BP) to mouse knees before the sign of CIA offer many favorable effects on the course of RA disease. These include the control incidence of bone damage, occurrence of disease, and collagen II-specific IgG2a antibody levels [54].

In RA patients 08 clinical trials of gene therapy have been initiated. One of these clinical trials was closed that was aimed to conduct genetic synovectomy, due to inadequate enrollment. The only clinical trial data on rheumatoid arthritis have published by Evans and coworkers. It came from a phase I protocol of arthritic patients. This data approved the safety and ease of gene transfer to arthritic joints [55].

4. ADVANCES IN DRUG DELIVERY SYSTEMS FOR THE RA THERAPEUTICS

Despite the presence of a wide variety of therapeutics for RA, the major challenge lies in their successful delivery to the affected area. Along with this, most of these therapeutics often cause side effects and drug resistance. The most important reason behind this is the nonspecific delivery of drug molecules. So nowadays the research is turned towards the development of targeted delivery strategies to the inflamed joints [41]. The changed properties of the inflammatory site, such as a change in pH, temperature, EPR effect and overexpression of various cells have the greatest potential for targeting. Therefore, different delivery systems are establishing their arena by targeting the drug to the site, reducing the amount of drug and adverse effect [56]. Fig. 2 shows some novel carriers used and fig. 3 illustrates the mechanism of different newer delivery systems for targeting RA. Advancements of these delivery systems and their efficacy in carrying the therapeutic molecule to the target site are described here.

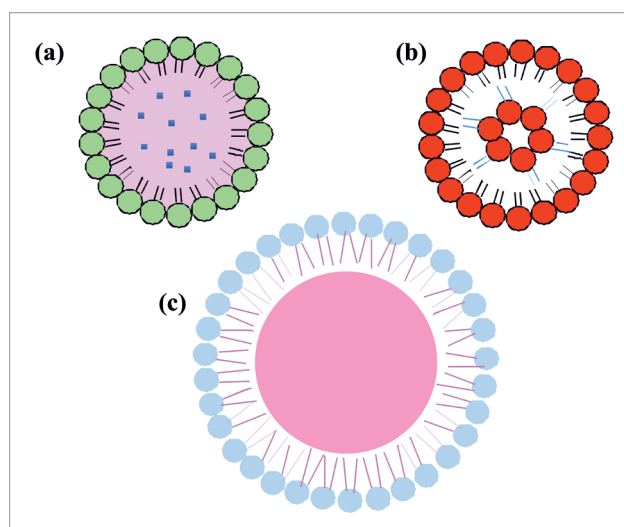


Figure 2

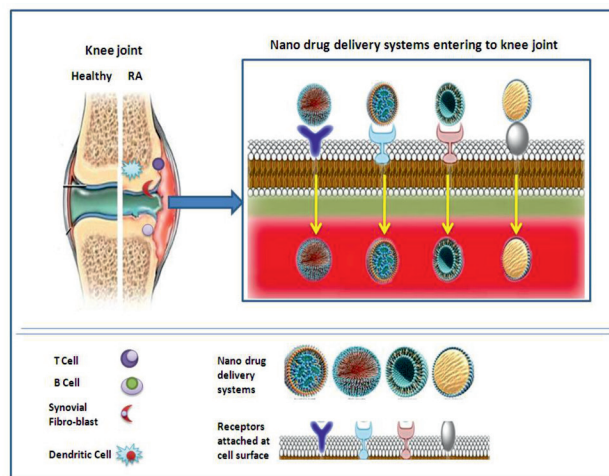


Figure 3

4.1. Nanoparticles

Nanoparticles are the particles microscopic in size and smaller than 1micron. They generally measure approximately 1 - 1000 nm in size and differ their properties from their macroscale forms. The drug can be embedded in the nanoparticles matrix or it can be adsorbed onto the surface. Nanoparticles also enhance the solubility and bioavailability of poorly soluble drugs. These nanocarrier systems also have properties of the high surface to volume ratio, enhanced permeability and retention effect, sustained action, etc. similar to other nanocarriers [56-57]. Due to these unique properties, they are successfully used for drug targeting in different diseases including RA.

Solid Lipid Nanoparticles (SLN) are suitable colloidal carriers. These are used for delivery of poorly soluble drugs. These colloidal carriers are differentiated from nanostructured lipid carriers (NLC) by the composition of the solid matrix. They are alternative carriers to liposomes and emulsions. As the SLN are prepared from biocompatible and biodegradable lipids, these systems are highly acceptable and tolerable. The lipid nanoparticles are the safest nano-carrier system [58].

Lee et al., 2013 have developed half-shelled gold nanoparticles attached with Arginine- Glycine- Aspartic peptide (RGD) for RA treatment. The active constituent was methotrexate. Methotrexate belongs to DMARDs class of antirheumatic drugs. RGD peptide was used as a ligand for targeting the inflamed tissue. They concluded that the prepared nanocarrier system minimized the adverse effects of methotrexate and enhanced its efficacy. On the basis of obtaining results, they suggested that this nano-carrier can also be used for the delivery of other DMARDs efficiently [59]. Satya Prasad et al., 2016 explained that multifunctional nanoparticles are used for Rheumatoid arthritis or other inflammatory diseases. They described the Zinc oxide and Zinc sulfate nanoparticles, gold nano compounds such as auranofin, aurothioglucose, silver nanoparticles, and metallic copper nanoparticles were used to improve the clinical status of arthritic patients.

They concluded that GOLD nanoparticles are the best remedy for rheumatoid arthritis [60]. Hwiwon Lee et al., 2014 prepared hyaluronate gold nanoparticles and Tocilizumab complex for rheumatoid arthritis treatment. Gold nanoparticles are used as a carrier with an antiangiogenic effect. The effect of the complex was approved by ELISA and western blot analysis in mice using adjuvant-induced arthritis [61]. Homma et al., 2010 told that Hyaluronic Acid (HA)-conjugated methotrexate (MTX) nanoparticles reduced the proliferation of fibroblast-like synoviocytes (FLs) in vitro, and symptoms of arthritis were consequently alleviated [62]. Zheng et al., 2015 successfully prepared oil, water nanoemulsion of curcumin for improving the low oral bioavailability of curcumin, which can facilitate the formulation of oral dosage forms [63]. Shailaja A.K. et al., 2016 prepared polymeric nanoparticles containing Mefenamic acid. They used the ionotropic gelation technique. After the development of the nanoparticles, they characterized these nanocarriers and found that these systems possessed excellent properties such as less particle size, greater stability and controlled drug release for 12 hours [64]. Pang-hu Zhou et al., 2018, synthesized hyaluronic acid-chitosan nanoparticles containing plasmid DNA encoding Cytokine response modifier A (HA/CS-Crma). They used the method of complex coacervation of cationic polymers. The nanoparticles qualified different evaluation parameters. The result showed that the prepared nanoparticles safely transfected arthritic cells and released the drug with sustained effect. It can be concluded that the prepared nanoparticles prevent cartilage destruction and inflammation [65]. Wenshuai Fan et al., 2018, used kartogenin (KGN) molecule that is reported to show a protective and regenerative effect on cartilage, and polyurethane nanoparticles were prepared. The kartogenin conjugated polyurethane nanoparticles showed a sustained release of drug with regular spherical shape and size. The intra-articular (IA) injection of KGN conjugated polyurethane nanoparticles proved efficacious with less cartilage degeneration as compared to IA injection of plane KGN [66]. Jiesheng Ye <<http://www.sciencedirect.com/science/article/pii/S0378517307008435>> et al., 2008, studied in detail about SLNs loaded with actarit and incorporated in the intravenous injection formulation. Actarit is an anti-rheumatic drug with a poor water-solubility profile.

To improve the therapeutic efficacy of the poorly soluble drug and to reduce its nephrotoxicity and GIT disturbances were the primary objectives of the study. They concluded that actarit SLN in the form of injectable was promising passive targeting therapeutic agent for RA [67]. Antônio Luiz Boechat et al., 2015 developed MTX-Lipid core nanocapsules and MTX solution. They evaluated their efficiency for the reduction of inflammation. MTX-LNC were shown better results than the MTX solution for reducing different inflammatory agents. Along with this, they found that the nanocarrier system has reduced the dose of MTX. From the found results, they concluded that the LNC containing MTX are a very propitious system for treatment of inflammatory disorders [68]. Meiling Zhou et al., 2018, developed a targeted system of solid lipid nanoparticle (SLN) containing glucocorticoid prednisolone.

The SLN particles were coated with Hyaluronic acid (HA) shown as HA-SLNs/PD. Hyaluronic receptor CD44 found over-expressed on the surface of synovial lymphocytes, macrophages and fibroblasts in arthritic inflamed joints and HA efficiently binds to these receptors. The results showed that prepared nanoparticles (HA-SLNs/PD) accumulated and persisted longer in circulation. The formulation was found better in efficacy and safer than the free drug and from SLN of a drug without coating for the treatment of inflammatory disorders [69].

4.2. Liposomes

Liposomes are extensively used as drug carriers for rheumatoid arthritis treatment. They are basically vesicular concentric lipid bilayers. They enclose hydrophilic components inside them. They are highly biocompatible, biodegradable poses less toxicity and commercially important as they have the ability to entrap both the lipophilic and hydrophilic drugs [70].

Many drugs used for the treatment that RA possesses low bioavailability, limited selectivity, high clearance, etc. And that's why to require frequent and high dosing to maintain the therapeutic effect. High doses are also the cause of side effects. Liposomes are the solution for these drawbacks. Weak pharmacokinetic profiles of many drugs can be improved by entrapping the drug in liposomes. They enhance the drug absorption too. Different types of liposomes possess different specific properties like large liposomes to show enhanced retention, small liposomes are good for passive targeting and PEGylated liposomes also enhance circulation time by reducing the uptake by the liver and spleen. By all these actions the localization of liposomes enhances by enhanced permeability and retention (EPR) effect [70-71]. William et al., 1995 developed liposomes containing methotrexate and compared its efficacy with the free methotrexate. They found that methotrexate containing liposomes have shown a significant effect on established arthritis. From the obtained results it can be concluded that the liposomal preparations show better results than the free drug [72]. Metselaar et al., 2003 developed PEG encapsulated liposomes containing glucocorticoids.

They followed single intravenous treatment and observed its effect on both the joint inflammation and cartilage destruction. They have also studied the targeting of these formulations to the inflammatory site. They concluded that the anti-inflammatory activity of glucocorticoids can be strongly enhanced by the development of long-circulating liposomes [73]. Prabhu et al., 2012 prepared and evaluate the methotrexate nano lipid vesicles for their antirheumatic activity. They successfully prepared methotrexate nano lipid vesicles with high efficiency, selectivity, and reduced toxicity [74]. Gottschalk et al., 2015 developed cationic liposomes containing MTX and compared their impact with the free MTX. They found that the liposomal MTX showed promising effects on inflamed sites than the free MTX [75]. Rahman et al., 2016 explained that over the conventional carriers, liposomal systems have many advantages related to the delivery of drugs, including merits

in both passive and active targeting of drug molecules to the inflammatory sites [76]. Mengdi Jia et al., 2018 developed liposomal carriers to deliver dexamethasone and 1,1'-dioctadecyl-3,3,3',3'-tetramethylindodicarbocyanine by thin film hydration technique. The liposomal carriers for both the molecules were proved efficacious on the basis of results obtained. Both the formulation, taken together, a safe liposomal delivery system was developed to achieve inflammation targeted therapy against arthritis [77].

4.3. Polymeric micelles

These are self-assembled amphiphilic block polymers. They are biocompatible and biodegradable. They possess a hydrophilic shell and a hydrophobic core. The shell material generally utilized is polyethylene glycol. When polymeric micelles are compared with free drugs they show higher drug loading, stability and biocompatibility, circulation time and localization. Polymeric micelle is an ideal carrier system for both the passive and active targeted drug delivery as they improve the therapeutic window and reduce the toxic side effects. By using polymeric nanocarriers the Active Pharmaceutical Ingredients can be protected against biodegradation in the blood circulation and consequently the circulation and the action can be prolonged. The drug molecules are directly and selectively delivered to the targeted area by using both active and passive delivery methods. Polymeric micelles show specific strength in solubilizing hydrophobic drugs and reduce the limitations associated with the toxic solvents [78-79].

Crielaard et al., 2012 developed novel derivatives of dexamethasone. These derivatives are covalently entrapped in polymeric micelles. They are hydrolytically cleavable and specially designed to achieve effective glucocorticoid targeting. The release rate of dexamethasone tried to be controlled by varying the degree of oxidation the thioether in the drug-linker [80].

Sethi et al., 2013 prepared sterically stabilized micelles (SSM) containing low doses of the vasoactive intestinal peptide (VIP) for the treatment of RA. The interaction of SSM and VIP protected the peptide from degradation and prolonged its retention time. The low doses of VIP in SSM can be vasoactive intestinal peptide a novel nanomedicine for RA. It was found that it can down-regulate both autoimmune and inflammatory components of RA [81].

4.4. Microemulsion / Nanoemulsion

Nanoemulsions are also known as mini-emulsion or submicron emulsions. It basically consists of oil in water type of emulsion. It possesses the droplet size of 100 - 500 nm. They are the good transporter for lipophilic compounds as they possess lipophilic core. They show good stability and clarity during storage. The property of possessing a low viscosity of nanoemulsions is beneficial for preparing sprays [82]. The small size of nanoemulsions provides properties such as high surface area per unit vol-

ume, stability, transparency, and tunable rheology. Generally, two methods are used to prepare nanoemulsions i.e. high energy and low energy method. Other methods include high-pressure homogenization, phase inversion, ultrasonication, bubble bursting method, etc.

Nanoemulsions come under ultrafine dispersion systems and their properties including visual, visco-elastic and targeting properties make them highly efficient novel delivery systems. Singh et al., 2017 & Pey et al., 2006, studied and optimized the composition and preparation method of nanoemulsions. They used a factorial design for the study. They concluded that the size of the droplets and the polydispersity affected by the variation in the composition and preparation methods. They have also used a central composite design for optimization [83-84]. Shakeel et al., 2008 examined the anti-inflammatory effect of celecoxib nanoemulsions. They compared the prepared transdermal preparation of celecoxib with conventional celecoxib gel on carrageenan-induced paw edema. They used ANOVA for the study. They found that the inflammatory response can be enhanced by using nanoemulsions.

They gave a conclusion that nanoemulsions can be successfully used for enhancing the anti-inflammatory effects of celecoxib [85]. Mello S B, et al., 2016 tested the anti-inflammatory efficacy of lipid nanoemulsions containing methotrexate given intravenously in rabbits with antigen-induced arthritis. They compared their formulation with marketed methotrexate. HPLC method was used for determining the pharmacokinetics of MTX nanoemulsions. They found the result that the uptake of methotrexate nanoemulsion was increased by two folds in arthritic joints. They concluded that the intravenously administered nanoemulsion was superior to the marketed preparation of MTX [86]. Modi et al., 2011 investigated the efficiency of aceclofenac nanoemulsion applied topically. They used the spontaneous emulsification method for the preparation of oil in water nanoemulsions. They used rat abdominal skin and determined topical permeation by Franz diffusion cell. They compared nanoemulsion gel with a conventional gel of aceclofenac. The result showed an increase in permeability parameters such as permeability coefficient, steady-state flux, etc. They concluded that nanoemulsion is potential delivery vehicles for aceclofenac when applied transdermally [87].

4.5. Nanogels

Nanogels are the polymeric delivery systems having size up to about 500 nm. Generally, nanoparticles are prepared and incorporated on the gel base. These systems possess the potential for targeting different types of drugs due to their small particle size, high biocompatibility, biodegradability high drug loading, good permeation capabilities, high water retention, etc [88]. Drugs from the nanogels can be delivered passively or actively. Nanogels are basically hydrogel that can accommodate a large amount of water inside them and swell to a large volume thus increasing the capacity to load a large amount of drug. Chen et al., 2013, Samah et al., 2010 prepared nanogel of methotrexate by surfactant-free emulsion polymerization meth-

od and tested its permeation efficiency by Franz diffusion cells using a porcine ear skin. The presence of nanoparticles in the receptors was presented by the TEM study. They concluded that the enhanced permeation of the drug occurs due to the permeation efficiency of the nanogels [89-90]. Nagai, N., et al., 2015 prepared and evaluated the indomethacin nanogel ointment in adjuvant-induced arthritic rats. The indomethacin gel ointment was prepared by bead smash 12. The size of the nanoparticle of indomethacin was about 173 nm. They found the result that the increase in hind paw edema is reduced and the drug concentration in the affected tissues is increased by using nanogel ointment of the drug.

They suggested by their findings that the use of nanoparticles, especially when applied topically avoids the unwanted side effects of any drug with a variety of advantages [91]. Khurana et al. 2013 formulated and evaluated the potential of meloxicam SLN incorporated in a gel base. The formulation was optimized by using various parameters. The skin permeation was determined using Franz diffusion cells and skin tolerance was determined in vivo by histopathological examination using mice. Carageenan-induced rat paw edema method was used for determining the anti-inflammatory potential of the gel containing SLN.

The result showed that nano-sized meloxicam SLN possesses controlled-release abilities with good permeation capacity. They gave a concluding remark that SLN gel can be used as an efficient delivery system for meloxicam for the alleviation of inflammatory diseases [92]. Elkomy et al., 2018 investigated the potential of SLN gel of tenoxicam and performed a pharmacokinetic Pharmacodynamic model for determining concentration-time profile in the skin. They used 23 factorial design to study the effect of different formulation variables on the properties of SLN gel for optimization. Gel tolerance was determined by using rabbit skin irritation test and the anti-inflammatory effect was determined by the rat paw edema model. They concluded that SLN- gel is a promising delivery vehicle for tenoxicam through the skin for arthritic disorder and PK-PD modeling is an efficient approach for indirect quantitation of skin accumulation [93].

5. CONCLUSION

The pathophysiology behind rheumatoid arthritis (RA) is a complex milieu that, could not be fully described till date. However, the scientific workflow has explained several breakthroughs involved in the development of the disease. Despite this enormous advancement in the methods of treatment of the disease, there is still a lot of scope for further research as there is no therapy available which can completely cure the disease. Presently, maximum therapies work on symptoms of the disease. Along with this, they show poor efficacy, severe side effects, high doses, greater frequency of administration and high cost.

The novel drug delivery systems overcome many of the problems associated with conventional dosage forms. Passive and active targeting methods deliver the drugs directly to the inflamed site. In spite of these novel efforts,

patients do not respond at all to the therapy in many cases. At present, a large number of researches of different drugs are reported to the management of rheumatoid arthritis, but a limited number of formulations entered into clinical trials. The field still requires prodigious study.

CONFLICT OF INTEREST

No conflict of interest

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