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AN OVERVIEW OF NOVEL DRUG DELIVERY SYSTEMS FOR NSAIDS IN THE TREATMENT OF RHEUMATOID ARTHRITIS.

Asmita B. Zodage, Shital S. Mahamuni, V. M. Gaikwad[1*]

Department of pharmaceutics, Channabasweshwar Pharmacy College (degree), Latur 413512, Maharashtra, India.

ABSTRACT

Rheumatoid arthritis (RA) is a systemic autoimmune disease that causes chronic joint inflammation, resulting in severe disability and premature death. It has a global prevalence of around 1%, with women being affected 2-3 times more than men. The pathogenesis of the disease involves preclinical RA, genetic factors, and environmental factors. The RA has no known cure and the primary aim of treatment remains to attain lowest possible disease activity and recovery if possible. The present review highlights the literature on the different treatment options available for the treatment of RA, their mechanisms of action, side effects, and novel drug delivery systems that are in use for drug administration with the main focus on novel drug delivery systems of non-steroidal anti-inflammatory drugs. Different drug classes are discussed, including corticosteroids, NSAIDs, DMARDs, and biologics, with examples of the most commonly used drugs in each class. Many disadvantages of conventional drug therapy include low solubility and permeability, poor bioavailability, degradation by gastrointestinal enzymes, first pass metabolism, food interactions, and toxicity. Novel drug delivery systems such as microspheres, nanoparticles, cubosomes, liposomes, ethosomes and so on are promising tools because they have overcome the drawbacks of traditional drug delivery systems. The current review squares the various novel drug delivery systems that have been investigated for the administration of anti-rheumatic drugs.

1. INTRODUCTION

Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic joint inflammation, eventually leading to severe disability and death. RA causes chronic inflammation of the synovial membrane, which leads to periarticular bone erosion, cartilage destruction, and permanent deformities, as well as extra-articular disease manifestations. Ageing is one of the most important risk factors for the development of RA.

The global prevalence of RA is estimated to be around 1%, with women experiencing 2-3 times the incidence of men. The prevalence of RA in India ranges from 0.28 to 0.7%, which is comparable to the prevalence in developed countries. RA affects people of all ages, but it is most common in people between the ages of 30 and 50 .RA can

affect any joint in the body. There are some differences in the prevalence of swelling and tenderness, with tenderness occurring primarily in large joints such as the elbow, shoulder, and knee, while swelling occurs in small joints such as the metacarpophalangeal joints. Different predictors of RA are represented in Fig.1.

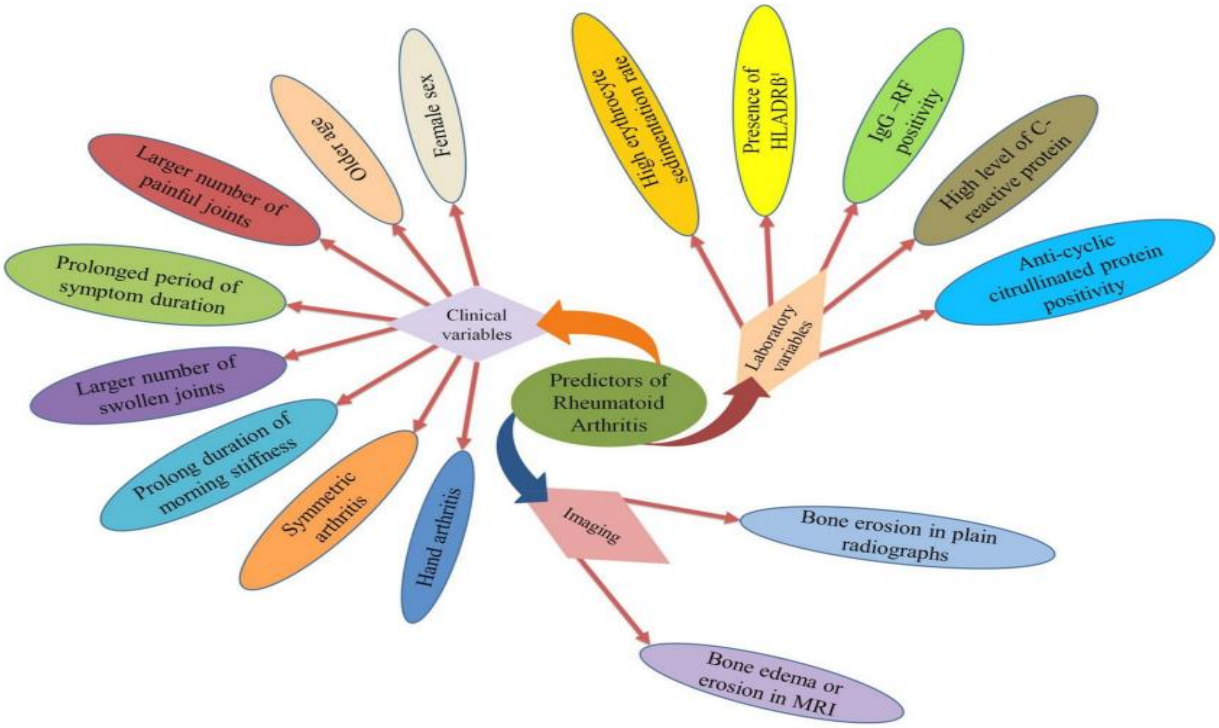

Figure 1: depicts various predictors of RA.

2. PATHOGENESIS OF RA

The exact pathogenesis of RA is unknown, but it has been reported that various inflammatory mediators such as tumour necrosis factor- (TNF-), C reactive protein (CRP), CD40 L, interleukins (IL-18 and IL20), monocyte chemoattractant protein-1 (MCP-1) fractalkine, matrix metalloproteinase-9 (MMP-9) and adhesion molecules play an important role in disease development [9]. Preclinical RA, genetic factors, and environmental factors are the three broad categories of well-known factors involved in the pathogenesis of RA (Fig. 2).

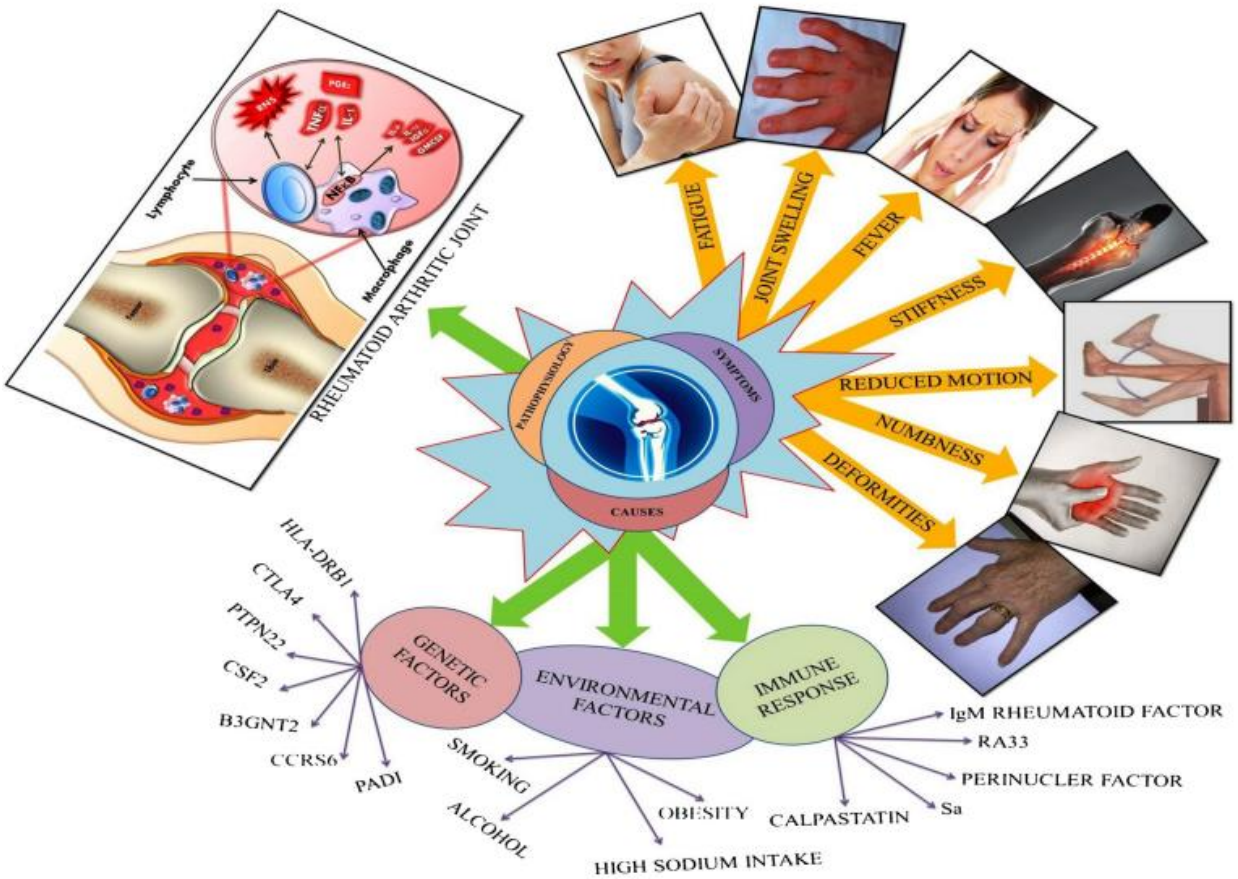

Fig. 2. Factors involved in pathogenesis of Rheumatoid arthritis.

2.1. Preclinical RA

There is an increased level of disease-related biomarkers, including auto-antibodies, in the body in preclinical RA (the period preceding the development of arthritis). IgM-Rheumatoid factor, RA33, SA, p68, calpastatin, and perinuclear factor are some of the disease-specific autoantibodies. Rheumatoid factor (RF) is a key player in the pathogenesis of RA.

2.2. Genetic influences

The development of RA is dependent on the interaction of genetic background and a variety of environmental factors. Molecular biology studies confirmed the importance of major histocompatibility complex (MHC) genes in disease pathogenesis. In RA, the HLA-DRB1 gene has been identified as one of the most important MHC genetic associations, with'shared-epitope' sequences within the DRB1 molecule encoded by specific alleles within the DRB1.

2.3. Environmental factors

Recent research has linked some environmental factors to an increased risk of RA. Smoking and alcohol consumption are the most common risk factors. Long-term smoking is linked to an increased risk of developing seropositive RA. High sodium intake, autoimmune thyroid disease (AITD), atopic dermatitis (AD), schizophrenia, cigarette smoking, and endometriosis are all risk factors for developing RA.

3. RA Treatment

There is no known cure for RA. The primary treatment goal remains to achieve the lowest possible disease activity and, if possible, recovery. minimize joint injury and to improve physical function as well as quality of life. The available treatment options for RA include nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, disease modifying anti-rheumatic drugs (DMARDs), and biological..

3.1. Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most commonly and widely used drugs for the management of arthritis disorders due to their analgesic as well as anti-inflammatory actions. These act by inhibiting cyclooxygenase (COX) enzyme which is involved in the conversion of arachidonic acid to prostaglandins. Most of the NSAIDs are non-selective COX inhibitors that inhibit both COX-1 and COX-2. Nevertheless, there has been ever growing concerns about the adverse effects of this class of drugs. The adverse effects include acute kidney ischemia due to vasoconstriction, caused by inhibition of prostaglandins, changes in blood pressure, and increased bleeding due to platelet inhibition. The non-selective NSAIDs have been reported as ulcerogenic causing serious upper gastrointestinal (GI) complications including perforation, obstruction and gastrointestinal hemorrhage. The NSAIDs are also associated with increased cardiovascular risks such as myocardial infarction and strokes, however NSAIDs are still widely used drugs in management of RA. Commonly used NSAIDs for the treatment of RA are represented in Fig. 3.

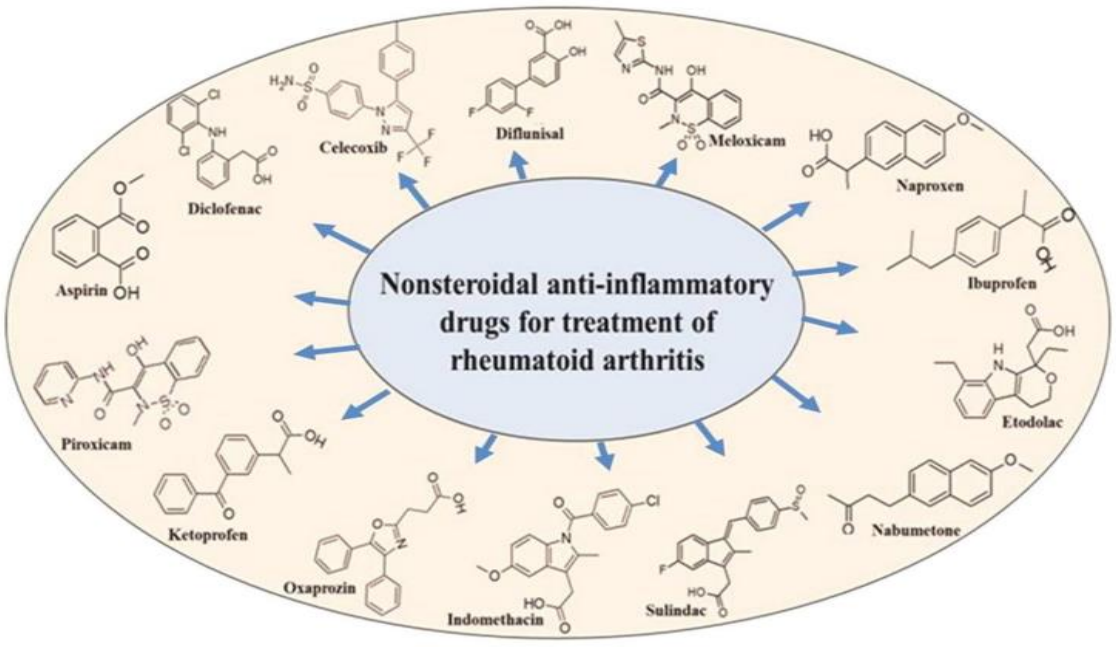

Fig. 3. Commonly used non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of Rheumatoid arthritis.

3.2. Corticosteroids

Corticosteroids, specifically glucocorticoids, are widely used for the treatment of inflammatory disorders like asthma, RA and other autoimmune diseases. Prolonged use of corticosteroids is related with numerous side effects like impaired wound healing, osteoporosis, osteonecrosis, peptic ulcers, candidiasis, and pancreatitis. These side effects can be minimized by using a low dose of glucocorticoids in patients unresponsive to NSAIDs and DMARDs or by administration of selective glucocorticoid receptor agonists.

3.3. Disease-modifying antirheumatic drugs & Biologics

Disease-modifying antirheumatic drugs (DMARDs) are a class of drugs used for the treatment of RA. These are slow acting drugs and may take weeks or months to produce any pharmacological effect. DMARDs do not have a common mechanism of action and the side effects also vary from drug to drug. The DMARDs therapy is associated with various side effects like digestive organ dysfunction, liver dysfunction, kidney dysfunction, stomatitis and myelosuppression. Various biologics used for RA management are IL-1 receptor antagonist, antiIL-6 receptor antibody, B cell depleting antiCD20 antibody, T cell signaling inhibitor, TNFα-receptor fusion protein, anti-TNFα PEGylated antigen-binding fragment, and anti-TNFα monoclonal antibodies.

4. Novel drug delivery systems in RA management

Conventional drug delivery systems show advantages along with several disadvantages like low solubility and permeability, poor bioavailability, degradation by GI enzymes, first pass metabolism, food interactions, high dose requirement and associated drug toxicity. To overcome these disadvantages, extensive researches have been done leading to the advent of novel drug delivery systems (NDDS). A decade ago, NSAIDs and analgesics were the first-line medications in the medical intervention of RA. As the disease progresses, they become largely ineffective and intra-articular (i-a) steroid depot is required to suppress pain and inflammation. These were followed by DMARDs like salazopyrine and chloroquine along with immunosuppressive agents such as methotrexate (MTX) and azathioprine. Newer second-line medications like leflunomide and tacrolimus have been found to reduce activated CD4 T-cells proliferation, which plays a pivotal role in pathogenesis of RA. I-a injection of drugs encapsulated in NDDS like liposomes, nanoparticles and microparticles have shown to decrease i-a drug clearance and increased mean residence time.

4.1. Nanoparticles

Nagai et al. created novel topical formulation (nanogel ointment) containing ketoprofen (KET) solid nanoparticles of 83 nm mean particle size by bead mill strategy for the examination of the anti-inflammatory effect in adjuvant-induced arthritis (AA) rats. The in vitro skin penetration experiment exhibited fundamentally higher penetration coefficient and penetration rate for KET nanogel ointment when contrasted with the gel ointment containing KET microparticles of 7.7 μm particle size. Furthermore, as per in vivo percutaneous absorption experiment, areas under KET concentration-time curve and apparent absorption rate constant for rat skin were found to be greater in rats getting KET nanogel ointment than those receiving KET microgel ointment . The IMC nanogel ointment also showed a significantly larger accumulation of IMC than the IMC microgel ointment. However, the plasma concentration of IMC remained same for both the gel formulations.

4.2. Solid lipid nanoparticles

Kaur et al. formulated and assessed dermally/topically administered diclofenac (DIF) loaded solid lipid nanoparticles (SLNs). In this study, authors reported that SLNs prepared via microemulsification based hot homogenization method had a mean size of 124.0 ± 2.07 nm and were spherical in structure with a PDI 0.294 ± 0.15. DIF-loaded SLNs demonstrated a significant reduction in granuloma tissue weight, fluid volume and leukocyte count/mm3 in the mice air pouch model post administration of DIF SLN formulation. In addition, authors reported 1.29 and 2.30 times increase in percentage inhibition of oedema in rat paw oedema model and mice ear oedema model, respectively, after the application of DIF SLN formulation compared to conventional cream. Authors concluded that DIF SLNs could be potential nanocarriers for the effective treatment of arthritis-associated inflammation.

4.3. Microemulsion

For topical administration at the affected sites of inflammation, Goindi et al. developed Tenoxicam (TNX) formulations based on microemulsion. Microemulsion formulations of TNX showed significantly higher ($p < 0.001$) mean cumulative percent permeation values in comparison to conventional cream and suspension of the drug. Results suggest that the developed microemulsion formulations may be used for effective topical delivery of TNX to treat various inflammatory conditions.

4.4. Microspheres

Ramasamy et al. formulated pectin-based colon-specific microspheres (multiparticulate delivery system) by means of emulsion dehydration technique. Based on the findings, authors concluded that pectin microspheres coated with eudragit could be used as a promising carrier for colon-specific delivery of aceclofenac in chronopharmacological treatment of RA.

4.5. Nano-structured lipid carriers (NLCs) mediated delivery

Nano-structured lipid carriers (NLCs) are colloidal lipid carriers that have shown to improve drug penetration and permeation through skin. A lower systemic cytotoxicity has been reported for NLCs prepared using physiological and biological lipids.

REFERENCES:

[1] D. Aletaha, T. Neogi, A.J. Silman, J. Funovits, D.T. Felson, C.O. Bingham, N.S. Birnbaum, G.R. Burmester, V.P. Bykerk, M.D. Cohen, 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative, Arthritis Rheum. 62 (9) (2010) 2569–2581.

[2] D.P. Symmons, Epidemiology of rheumatoid arthritis: determinants of onset, persistence and outcome Best, Pract. Res. Clin. Rheumatol. 16 (5) (2002) 707–722.

[3] P. Chalan, A. van den Berg, B.-J. Kroesen, L. Brouwer, A. Boots, Rheumatoid arthritis, immunosenescence and the hallmarks of aging, Curr. Aging Sci. 8 (2) (2015) 131–146.

[4] A. Gibofsky, Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis, Am. J. Manage. Care 18 (Suppl. 13) (2012) S295–302.

[5] R. Handa, U. Rao, J.F. Lewis, G. Rambhad, S. Shiff, C.J. Ghia, Literature review of rheumatoid arthritis in India, Int. J. Rheum. Dis. 19 (5) (2016) 440–451.

[6] B.J. Crielaard, T. Lammers, R.M. Schiffelers, G. Storm, Drug targeting systems for inflammatory disease: one for all, all for one, J. Control. Release 161 (2) (2012) 225–234.

[7] W. Grassi, R. De Angelis, G. Lamanna, C. Cervini, The clinical features of rheumatoid arthritis, Eur. J. Radiol. 27 (1998) S18–S24.

[8] T. Kanazawa, J. Nishino, S. Tohma, S. Tanaka, Analysis of the affected joints in rheumatoid arthritis patients in a large Japanese cohort, Mod. Rheumatol. 23 (1) (2013) 44–49.

[9] F. Montecucco, F. Mach, Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis, Rheumatology 48 (1) (2008) 11–22.

[10] K.D. Deane, J.M. Norris, V.M. Holers, Preclinical rheumatoid arthritis: identification, evaluation, and future directions for investigation, Rheum. Dis. Clin. North Am. 36 (2) (2010) 213–241.