Review Article

Functionalized nanoliposomes for the synergistic treatment of rheumatoid arthritis: Monotherapy with quadrilateral approach

Asiya Mahtab[1], Shweta Pandey[1], Syed Arman Rabbani[2], Mohd. Aqil[1], SushamaTalegaonkar[1,3]*

ABSTRACT

Rheumatoid arthritis is a chronic, immune-mediated disease characterized by severe progressive inflammation followed by destruction of joints and related structures. It is an autoimmune disease of unknown causes and a number of information regarding the pathogenesis are still unexplored, thus at present prevention of disease progression is very challenging. Although the treatment has evolved from non-steroidal anti-inflammatory drugs to biological disease-modifying antirheumatic drugs, yet single therapy of any of these drugs is not effective to totally cure the disease and also associated with severe adverse effects. Therefore, to avoid side effects and to make the single therapy more effective and patient friendly, we proposed a hypothesis based on targeted delivery of ligand-appended nanoliposomes of teriflunomide by intravenous route. The proposed nanoliposomes will follow four-pronged synergistic treatment approaches that are targeting through synovial macrophage system uptake, chondroitin sulfate-coated long-circulating effect, CD44 receptor-mediated cellular internalization, and chondroitin sulfate-oriented articular structure regeneration.

KEY WORDS: CD44, Chondroitin sulfate, Disease-modifying antirheumatic drugs, Lipid nanoparticles, Rheumatoid arthritis

INTRODUCTION

Rheumatoid arthritis (RA), a chronic, autoimmune inflammatory disorder that causes continual arthritic pain and characterized by synovial inflammation, hyperplasia, autoantibody production, bone, and cartilage destruction.[1] It is the most common inflammatory joint disease seen in practice and affects around 0.8% of the world's population.[2] Pathophysiology of RA involves polyarticular inflammation along with hyperplasia of the synovial lining cells.[3] The pannus tissue comprises synovial fibroblasts, synovial macrophages, and infiltrating inflammatory cells such as activated B and T lymphocytes.[4] Endogenous receptors such as tyrosine kinase and adenosine play their important role in inflammation, as they are overexpressed on vascular endothelial growth factor.[5-8]

There are various receptors overexpressed on inflammatory cells such as CD44 receptor, toll-like receptor, endothelial protein C receptor (EPCR), interleukin-26 (IL-26), etc. CD44 receptor is cell surface glycoprotein, and it is involved in various inflammatory immune-mediated diseases including RA.[9-11] EPCR plays an important role by inhibiting the activation and migration of RA monocyte. Major histocompatibility complex (MHC) also plays an essential role in the genetic susceptibility of the disease. MHC is a vast genetic region attached on the chromosome-6 short arm and the shared site in the HLADRB1/DR4 alleles has been constantly associated to the severity and risk of the disease. These include arachidonic acid metabolites such as prostaglandins and leukotrienes, vasoactive amines, kinins, endothelins, complement fragments, reactive

Access this article online

Website: jprsolutions.info | ISSN: 0974-6943

[1]Department of Pharmaceutics, School of Pharmaceutical Education and Research, Jamia, Hamdard, New Delhi, India, [2]Department of Clinical Pharmacy and Pharmacology, RAK College of Pharmaceutical Sciences, RAK Medical and Health Sciences University Ras Al Khaimah, UAE, [3]Department of Pharmaceutics, Delhi Pharmaceutical Sciences and Research University, Pushp, Vihar, New Delhi, India

***Corresponding author:** Dr. Sushama Talegaonkar, Department of Pharmaceutics, Delhi Pharmaceutical Sciences and Research University, Pushp Vihar, Sector 3, New Delhi -110017, India. Phone: 91-9818453518. E-mail: stalegaonkar@gmail.com

Received on: 19-12-2017; Revised on: 20-01-2018; Accepted on: 15-03-2018

oxygens, neutral proteinases, and proinflammatory cytokines which include IL-1, IL-6, IL-8, platelet-derived growth factor, tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor, and macrophage colony-stimulating factor.[12]

RA management has experienced major advances in past few years, both in respect of therapeutic strategy and drugs collection. Increasing evidences have revealed that early diagnosis, early treatment initiation, and prompt achievement of remission are the foremost predictors of continuing clinical, radiographic, and functional outcomes. Although various drugs for instance non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), corticosteroids, and biologics are indicated to treat RA, it is difficult to envisage which patient will respond to which treatment regimen.[4,13] Since RA is disease of unknown etiology, insufficient treatment modalities and new approaches to such type of arthritis are challenging to the rheumatologist; therefore, it is necessary to develop a wise formulation for effective management to achieve a higher symptomatic relief in RA. Therefore, development of functionalized lipid nanoparticles having multifaceted targeting potential may help to attain the treatment goals.

Based on the above research, we hypothesized to prepare multifaceted liposomes of DMARDs along with surface functionalization with proper ligand CS to make them effective for RA treatment. These multifaceted long-circulating lipid nanoparticles will target CD44 receptor and therefore will overcome the systemic effect of the drug. Hence, the suggested formulation will be effective in the management of RA in four ways (four-pronged approach): (a) Drug-loaded liposomal nanoparticles for the treatment of RA will be prepared [Figure 1]. Liposomes can be used as vehicles for intracellular delivery of teriflunomide (TFL) into phagocytic cells.[14] Uncoated hydrophobic TFL-loaded liposomes will be efficiently taken up by the synovial macrophages and will lower the inflammation by releasing TFL in the cells after lysosomal degradation. It exerts its cytostatic action by reversibly inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), important for the *de novo* synthesis of pyrimidine. The released TFL will also show its cytostatic effect on proliferating T and B cells by inhibiting activity of protein tyrosine-kinase, which also leads to the reduction of proinflammatory cytokine production,[15] (b) CS-coated hydrophilic liposome will act as long-circulating vesicles by reducing the adsorption of different blood proteins and thereby prolonging their circulation time. It will act as stealth lipid vesicles which avoid detection and destruction through phagocytes by the cloaks of hydrated CS molecules, (c) the second aspect of CS-coated liposome is CD44-mediated active-targeting through cellular internalization of nanoparticles.[16] CS-CD44 binding to the targeted cells will increase the concentration of drug at the targeted site and will minimize the chances of toxicity to other organs, and (d) the remaining unbound (not bound to CD44) CS-coated liposomes will play an important role in CS-oriented cartilage regeneration and healing. Thus, this multifaceted approach will provide effective and sustained treatment for the painful joint degenerative disorder and will serve as a potential prophylactic against the advancement of cartilage degeneration [Figure 2].

EVALUATION

Persistent synovitis, systemic inflammation, and autoantibodies are characteristics of RA.[17] On the one hand, its treatment options aim at symptomatic pain relief through NSAIDs, corticosteroids, and on the other hand, it focuses on slowing down disease activity, along with aiming for remission by combination therapy of DMARDs.[3,18] Recommendations (national and international) highlight the importance of initiating a DMARD therapy as soon as RA is diagnosed. Detailed understanding of RAs pathophysiology has led to identification of new therapeutic targets such as proinflammatory cytokines, adhesion molecules, T cells and B cells, and chemokine, along with intracellular and extracellular signaling pathways. The two most important diagnostic and prognostic markers of RA are rheumatoid factor and anti-citrullinated peptide antibodies and their existence in a variety of autoimmune diseases suggest that they may be valuable therapeutic targets.[19] Liposomes have been widely investigated as drug delivery vehicles for therapeutic index enhancement of encapsulated drugs, and their flexibility to house a range of therapeutic agents has been demonstrated in preclinical and clinical settings.[20] Traditional liposomes have short blood circulation time after intravenous (I.V.) administration due to quick and effcient uptake by macrophages of mononuclear phagocyte system, mainly those in the liver and spleen. While by preparing functionalized liposomes, we can actively target drug on inflamed area post-systemic administration. Moreover, inflamed tissues permit small, long-circulating drug carrier systems to extravasate by the EPR effect, referred as passive targeting. The aim of clinical management of RA has been focused on prevention of disease progression through treatment with disease-modifying antirheumatic drugs such as sulfasalazine, TFL, methotrexate, and hydroxychloroquine. In recent times, biologic agents aiming specific inflammatory cytokines such as IL-1 and TNF-α have been prescribed.[21] DMARDs were believed to reduce the damage shown on radiographs

and act through direct or indirect suppression of cytokines.[22] TFL is the drug used in the formulation for the treatment of RA. It is the newest DMARD for the treatment of the disease, leading to the inhibition of DHODH which act as a rate-limiting step in the pathway for pyrimidine production. Ligand such as CS is a natural component of extracellular matrix (ECM) and is a sulfated glycosaminoglycan made up of long unbranched polysaccharide chain with a repetition of disaccharide structure of N-acetyl-galactosamine along with glucuronic acid. It is capable of reducing the proinflammatory cytokine, IL-6, etc.[23] CS functionalized liposome may represent a superior mode of drug administration as compared to conventional forms owing to high drug intracellular uptake, improved biodistribution and controlled release.[24] Long-circulating liposome system is one of the most important carriers for drug targeting. I.V. injection of liposomes could induce a strong, speedy, and long-lasting therapeutic advantages.[25] Hence, nanolipid carriers can be easily prepared with help of these excipients and will lead to an increase in therapeutic index. Therefore, four-pronged treatment approach will be used to achieve the desired targets:

(a) TFL helps in blocking the formation of DNA, which is important in the development of cells such as the ones in immune system. Liposomes extravasate through leaky vasculature into synovial tissues and are immersed by macrophages within inflamed tissues, further supporting utilization of enhanced permeability for targeted delivery of anti-inflammatory agents.[26] After macrophage uptake, noteworthy reductions will be observed in the expression of proinflammatory cytokines including TNF-α, IL-8, and IL-1β.

(b) By coating the liposome shell with CS, hydrophilic longer-circulating liposomes formation can be done that would reduce the adsorption of various blood proteins, thus extending their circulation time.[27]

(c) CS-coated liposomes will recognize the CD44 receptors overexpressed markedly on synovial leukocytes, lymphocytes, and other immune-mediated cells and targeting will also reduce the toxicity potential.[28] CS-coated liposome possesses high anti-inflammatory activity in stimulated cells as it reduces the levels of TNF-α proinflammatory cytokine and IL-8.[21]

(d) The remaining unbound CS-coated nanoliposomes in the synovial region will lead to articular regeneration and will modify cellular death process and further enhance the anabolism-catabolism balance of cartilage ECM.

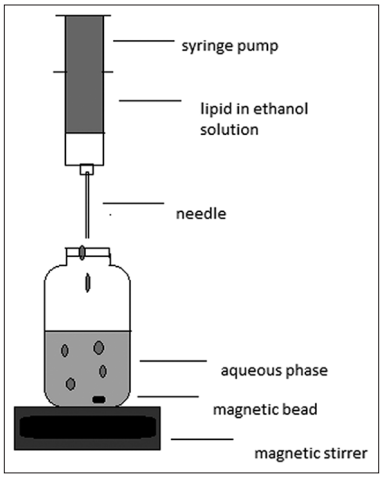

Figure 1: Schematic representation of assembly used in nanoliposome preparation

CONCLUSION

There are various treatment modalities available for RA such as NSAIDs, glucocorticoids, and biologics; however, their safety, stability, and efficacy are still questionable. Thus, we make an approach to develop a drug delivery system that will provide sustained localized release with less side effects. Hence, we will develop lipid nanocarriers with four-pronged approach to target the disease having multifaceted therapeutic

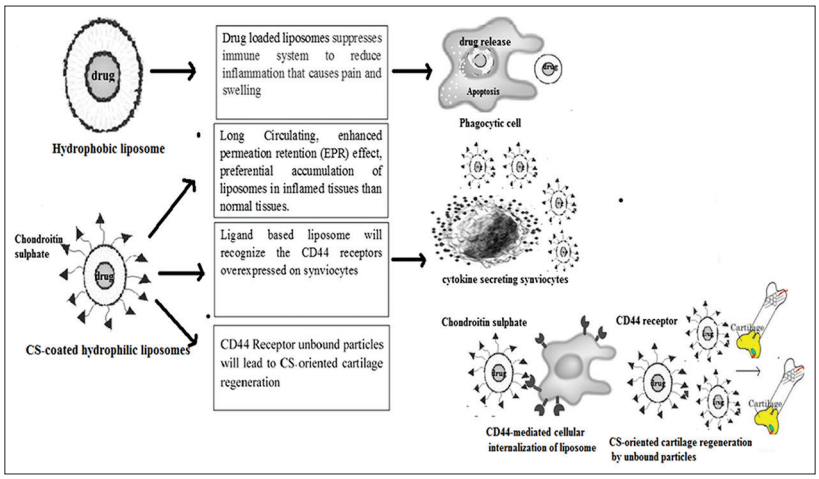

Figure 2: Diagrammatic representation of hypothesized four-pronged approach of rheumatoid arthritis treatment

effects such as pain relieving, preventing the disease progression, articular regeneration, increasing safety, and cost-effectiveness.

ACKNOWLEDGMENT

The authors would like to thank Jamia Hamdard, New Delhi, for providing Hamdard National Foundation fellowship.

REFERENCES

1. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med 2011;365:2205-19.
2. Komano Y, Yagi N, Nanki T. Joint-targeting drug delivery system for rheumatoid arthritis: SiRNA encapsulated liposome. Pharm Anal Acta 2015;6:1-5.
3. van den Hoven JM, Van Tomme SR, Metselaar JM, Nuijen B, Beijnen JH, Storm G, *et al.* Liposomal drug formulations in the treatment of rheumatoid arthritis. Mol Pharm 2011;8:1002-15.
4. Pandey S, Rai N, Rawat P, Ahmad FJ, Talegaonkar S. Nanofacilitated synergistic treatment for rheumatoid arthritis: A 'three-pronged' approach. Med Hypotheses 2016;92:44-7.
5. Naor D, Nedvetzki S. CD44 in rheumatoid arthritis. Arthritis Res Ther 2003;5:105-15.
6. Huang QQ, Pope RM. The role of toll-like receptors in rheumatoid arthritis. Curr Rheumatol Rep 2009;11:357-64.
7. Meilang X, Lyn M, Sambrook PN, Fukudome K. Endothelial protein C receptor is overexpressed in rheumatoid arthritic (RA) synovium and mediates the anti-inflammatory effects of activated protein C in Rheumatoid Arthritis monocytes. Ann Rheum Dis 2007;66:1574-80.
8. Scott BB, Weisbrot LM, Greenwood JD, Bogoch ER, Paige CJ, Keystone EC, *et al.* Rheumatoid arthritis synovial fibroblast and U937 macrophage/monocyte cell line interaction in cartilage degradation. Arthritis Rheum 1997;40:490-8.
9. Pandey S, Mahtab A, Rai N, Rawat P, Ahmad FJ, Talegaonkar S, *et al.* Emerging role of CD44 receptor as a potential target in disease diagnosis: A Patent review. Recent Pat Inflamm Allergy Drug Discov 2017;11:77-91.
10. Rai N, Ray A, Jamil SS, Gulati K. Cellular and molecular mechanisms of action of polyherbal preparation UNIM-352 in experimental models of bronchial asthma. Indian J Exp Biol 2015;53:625-31.
11. Rai N, Gulati K, Ur-Rahman R, Ray A. Effects of a polyherbal agent on structural changes and biochemical markers during airway remodelling in experimental model of bronchial asthma. EC Pharmacol Toxicol 2016;22:99-107.
12. Miyasaka N. Cytokines and chemical mediators in rheumatoid arthritis. Nihon Rinsho 1992;50:463-7.
13. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: A synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry 2009;31:206-19.
14. van Rooijen N, Sanders A, van den Berg TK. Apoptosis of macrophages induced by liposome-mediated intracellular delivery of clodronate and propamidine. J Immunol Methods 1996;193:93-9.
15. Warnke C, Meyer zu Hörste G, Hartung HP, Stüve O, Kieseier BC. Review of teriflunomide and its potential in the treatment of multiple sclerosis. Neuropsychiatr Dis Treat 2009;5:333-40.
16. Bagari R, Bansal D. Chondroitin sulfate functionalized liposomes for solid tumortargeting. J Drug Target 2011;19:251-7.
17. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet 2010;376:1094-108.
18. Monti S, Montecucco C, Bugatti S, Caporali R. Rheumatoid arthritis treatment: The earlier the better to prevent joint damage. RMD Open 2015;1:e000057.
19. Tak PP, Kalden JR. Advances in rheumatology: New targeted therapeutics. Arthritis Res Ther 2011;13 Suppl 1:S5.
20. Metselaar JM, Mastrobattista E, Storm G. Liposomes for intravenous drug targeting: Design and applications. Mini Rev Med Chem 2002;2:319-29.
21. Kremer JM, Westhovens R, Leon M, Di Giorgio E, Alten R, Steinfeld S, *et al.* Treatment of rheumatoid arthritis by selective inhibition of T-cell activation with fusion protein CTLA4Ig. N Engl J Med 2003;349:1907-15.
22. Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. N Engl J Med 2001;344:907-16.
23. Henrotin Y, Mathy M, Sanchez C, Lambert C. Chondroitin sulfate in the treatment of osteoarthritis: From *in vitro* studies to clinical recommendations. Ther Adv Musculoskelet Dis 2010;2:335-48.
24. Craciunescu O, Moldovan L, Moisei M. Selection of an efficient Chondroitin Sulfate-liposome delivery system as chondroitin effective agent for local inflammation treatment. Stud Univ Vasile Goldiş Ser Ştiinţele Vieţii 2014;24:93-101.
25. Metselaar JM, Wauben MH, Wagenaar-Hilbers JP, Boerman OC, Storm G. Complete remission of experimental arthritis by joint targeting of glucocorticoids with long-circulating liposomes. Arthritis Rheum 2003;48:2059-66.
26. Hofkens W, van den Hoven JM, Pesman GJ, Nabbe KC, Sweep FC, Storm G, *et al.* Safety of glucocorticoids can be improved by lower yet still effective dosages of liposomal steroid formulations in murine antigen-induced arthritis: Comparison of prednisolone with budesonide. Int J Pharm 2011;416:493-8.
27. Prabhu P, Shetty R, Koland M, Vijayanarayana K, Vijayalakshmi KK, Nairy MH, *et al.* Investigation of nano lipid vesicles of methotrexate for anti-rheumatoid activity. Int J Nanomedicine 2012;7:177-86.
28. Prasad LK, O'Mary H, Cui Z. Nanomedicine delivers promising treatments for rheumatoid arthritis. Nanomedicine (Lond) 2015;10:2063-74.