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Nanofacilitated synergistic treatment for rheumatoid arthritis: A 'three-pronged' approach

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, inflammatory, autoimmune disease of unidentified etiology that affects the joints and causes pain, swelling, stiffness and redness in the joints. The exact cause of rheumatoid arthritis has not yet been discovered and, consequently, treatment methods have not been optimally effective. It has long been treated with anti-inflammatory and immunosupressants including modern biologics either alone or in combination but all of the drugs have severe life threatening consequences with impaired immune function due to nonspecific targeting. Therefore, a three-pronged approach of local, active and synergistic targeting can be used to optimize delivery of therapeutic agents to reduce toxicity and patient outcome without compromising patient's immunity.

Introduction

Rheumatoid arthritis (RA) is characterized by symmetrical polyarticular inflammation of the joint synovium resulting in pain and stiffness which can lead to progressive joint damage due to cartilage and bone destruction, organ deformities and functional loss [1,2]. The synovium, or membrane present in the synovial joints that lines the joint capsules (commonly in the hands and feet), is the first structure affected. The synovial membrane or synovial lining, is an irregular membrane that is 3–5 cell-depth thin and is free from intercellular junctions [3]. In normal conditions it provide nutrients to the cartilage cells and secrete synovial fluid for lubricating the joint. It consists of numerous cell types such as fibroblast, macrophages, lymphocytic cells, dendritic and epithelial cells which overexpress their specific receptors in pathologic condition, among which CD44 receptors, folate receptors, toll like receptors, endothelial protein C receptors (EPCR) are most prominent. Some endogenous receptors of adenosine, tyrosine kinase and receptors overexpressed on vascular endothelial cells (VEGFR) also play their important role in inflammation [4–7].

RA affects 1–4% of the worlds and 1.4–5.2% of Indian adults [8,9]. Etiology of RA is not very clear, therefore, its cause is still the major area of research. Some factors such as environmental, genetic and hormonal, were initially reported as cause of occurrence but later on considered only responsible for triggering and severity of the disease [10]. Induction of autoimmunity by environmental trigger involve certain viruses and bacterial agents that contain identical peptide sequence to auto antigen and infection with these microbial agents can induce an immune response that crossreacts with auto antigen termed "antigen mimicry" [11]. Genetic susceptibility of the disease is related to major histocompatibility complex (MHC) which is a large genetic region on the short arm of chromosome-6 and the shared epitope in the HLADRB1/DR4 alleles has been constantly linked to the risk and severity of the disease and are also responsible to modulate the risk of several environmental agents. It is reported that RA occurrence is more in female than men in the ratio of 3:1 that presents strong evidence of the involvement of female hormones estrogen and progesterone [12–14].

Rheumatoid arthritis (RA) is a complex disease involving humoral and innate immune responses including numerous cell types markedly T cells, B cells, macrophages, neutrophils, fibroblasts, chondrocytes and dendritic cells [11,15]. Established rheumatoid arthritis is characterized by synovial hyperplasia of synovial membrane that is mainly composed of fibroblast like synviocytes combined with massive infiltration of lymphocytes and macrophages, resulting into the formation of an abnormal granulation tissue called "pannus" that adheres to the surface of articular cartilage and sometimes erode the cartilage completely. When cartilage is destroyed fibrous tissue joins exposed bone ends, the tissue ossifies and fuses the joint so that it become immovable [12]. Cytokine networks involving TNF-α, interleukins (IL-1, IL-6) and many other mediators participate in disease perpetuation and can be targeted by therapeutic agents [16]. The most important challenge associated with rheumatoid arthritis is to improve and

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optimize the medical treatment because the cause of rheumatoid arthritis is not known and no treatment cures the disease. Although treatment has evolved from non-steroidal anti-inflammatory drugs (NSAIDs) to disease modifying anti-rheumatic drugs (DMARDs), including modern biologics but all of the drugs have severe life threatening consequences [17,18]. It remains one of the most important challenge to improve and optimize the medical treatment of RA because it is currently impossible to predict which patient will respond to which medication regimen. Current research is being done to develop genetic and proteomic approaches to specifically identify patient disease on the genetic basis, however, practically the applications of such advances has not been attained. RA has been a debilitating disease with few, insufficient treatment modalities, so there is an immense need to develop an effective treatment for prevention or control of joint damage, achievement of remission or low disease activity, improvement in quality of life. Therefore, development of nanocarrier for local targeting *via* intra-articular route, CD44 mediated active targeting and overall synergistic effect of drugs and excipients may achieve the above treatment goals by increasing the residence time only in the synovial cavity and reducing the systemic side effects without affecting one's immunity.

Modulation in the treatment strategies of rheumatoid arthritis

Effective strategies which can be predominantly adopted towards RA therapy include pharmacological and non-pharmacological therapies [19], receptor mediated targeted therapy, angiogenesis inhibition and inhibition of intracellular signal transduction pathways such as janus kinase pathways, mitogen-activated protein kinases (MAPKs), p38 MAPK, c-Jun N-terminal kinase, nuclear factor-κB (NF-κB), and receptor activator of NF-κB ligand (RANKL) [20,21]. The medications needed for ideal management of RA are also referred to as disease-modifying anti-rheumatic drugs or DMARDs [22]. Because cartilage damage and bony erosions frequently occur within the first two years of disease, rheumatologists now refer insistently to a DMARD agent early in the course of disease, till the diagnosis is confirmed. The cause of RA is multifactorial therefore an ideal management of disease necessitate an effective approach which can be fulfilled by developing a nanoformulation that has efficiency of suppressing more than one factors associated with the disease. Therefore, it will be propitious to develop multifunctional nanoparticles having efficiency for synergistic, active and local targeting. Synergistic and active targeting would be achieved by using the bioaccepatable excipients which will be the integral part of bone and tissue itself and also have disease ameliorating capacity. Local targeting will be achieved by intra-articular drug delivery of nanoparticles [23–25].

Encapsulation of drug in nanoparticles functionalized with ligand allows them to be recognized by receptors expressed on synovial cells facilitating its delivery to inflamed synovial cavity. Intra-articular drug delivery for administration of immunomodulatory drug along with receptor mediated targeting may enable the localization of drug at tissue and cellular level. This can explore the utility of receptors overexpressed on activated synovial cells in disease condition and reduce the required dose of drug for more efficient therapeutic action hence, reduce associated side effects and increase patient compliance.

Some classes of pharmaceutical excipients from both synthetic and natural origin exhibit disease preventing activity. These functional excipients may be the polymer which acts as the building materials for the nanoparticles as well as the components that stabilizes the particles. Confirmation of role of excipients as immunomodulators can lead to new formulation design approach. As these pharmaceutical excipients inherently modulate immune responses, hence they can be used in development of anti-arthritic drug formulation. Use of excipients as the potential immunomodulator is associated with many advantages like (i) Devoid of the formulation related complexity due to the incorporation of additional immunomodulator; (ii) As pharmaceutical excipients are already acceptable up to higher concentrations, additional toxicity induced by immunomodulators is limited by this approach and (iii) This approach virtually adds no or very less cost to the formulation. The drug needs to be temporally localized in the synovial cells for optimal effect these objectives, *viz.* minimal exposure of the normal tissues to the drug and temporal localization can be achieved by ligand functionalized targeted delivery system.

Hypothesis

Based on the above research envisaged we proposed the development of a bioceramic based nano-sized drug delivery device containing DMARDs, also having inherent immunomodulation activity due to functional excipients along with receptor targeting capabilities. We hypothesize that: (a) since no ideal treatment is available till date to cure the disease therefore, targeting the immune system by combination of disease modifying anti-rheumatic drugs will be a good approach towards the treatment of RA; (b) along with DMARDs, the immunodulators could be the formulation excipients, which are generally used in the nanoparticle preparation and they also have bone and joint protection ability (c) an additional ligand based targeting nature of these carrier nanoparticles will reduce the toxicity potential of the nonspecific immunomodulators (d) overall effect of the nanoformulation will be synergistic towards RA. Hence, the above said hypothetized drug delivery system aims to develop a wise combination of drugs, excipients and ligand to achieve a higher symptomatic relief in RA model (Fig. 1).

Evaluation and discussion of the hypothesis

In RA inflammatory cell proliferation is an active process and often associated with chronic synovitis and bone damage which results in long survival of the disease. On one hand, older conventional treatments such as NSAIDs and corticosteroids are particularly helpful during the first few weeks, providing partial relief of pain and stiffness and on the other hand, recent effective biological DMARDs are much more expensive, therefore combining two cost effective non-biological DMARDs to achieve greater efficacy, would be a good approach. A number of excipients involved in the formulation of the nanoparticles also possess the immunomodulation activity. These include surfactants, polymers and lipid excipients. Chitosan, a natural polymer, has ability to promote neovascularization and this action of angiogenesis is responsible for cartilaginous tissue repairing. It also acts as antioxidant, metalloproteinase inhibitor and immune-enhancer [26–28]. Polymers of dextrin derivate produced by the hydrolysis of starch obtained from natural products have been described to have anti-inflammatory properties. Pebisut is a biodegradable and nontoxic natural glue that may exert anti-inflammatory activity [29,30]. In addition there is new establishment of immunomodulation and cytotoxicity-promoting properties of a hydrophilic nonionic surfactant, Poloxamer 407, revealing considerable pharmacological interest and hence, clinical trials are in progress to explore its potential applications [31]. Some biomaterials such as bioceramics protect bone and joints by scavenging H_2O_2, inhibiting PGE_2, and increasing the viability of osteoblast cells [25,32]. Hyaluronic acid (HYA) is a biodegradable hydrophilic polymer used as viscosupplement in RA [33]. Hence, nanoformulation can be easily prepared by these functional excipients with wide range of choice and availability. RA treatment protocols undergo with multiple medications for prolonged time