

Management of Rheumatoid Arthritis: A Mini Review

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Abstract

Rheumatoid arthritis, a commonest chronic inflammatory condition that adversely affects the joint function and further advancement results in systemic adverse effects. According to WHO 0.3-1% of the world population exhibit the prevalence of the disease. Drug therapy for rheumatoid arthritis starts with disease-modifying antirheumatic drugs, biologics, nonsteroidal anti-inflammatory drugs, corticosteroids and end up with surgeries at the chronic stages. Even though these drugs are effective in therapy, they produce side effects to an extent that may risk the quality of life of the patients. These may be due to lesser bioavailability problems, higher dose requirement, nonspecific and untargeted delivery of the agent and immunosuppression produced specifically in case of biological agents.

Keywords: Rheumatoid arthritis, pathophysiology, pharmacological, non-pharmacological therapy, prophylaxis.

INTRODUCTION

Rheumatoid arthritis, a commonest chronic inflammatory disorder of genetic origin causing the destruction of different cells that contribute joints and a wide range of systemic effects (1). Pain as a result of inflammation and joint destruction and loss of functionality primarily of the knee joints are the major characteristics of the disease (2). Prevalence of musculoskeletal diseases exists as one of the biggest burdens among a current community. According to WHO the disease prevalence varies from 0.3-1%. Disease prevalence prohibited 50% of the patients to continue their job. Women are more prone to RA when compared to men and risk for the diseases elevated with improving age (3). Even though the etiology of the disease is not completely understood, diagnosis and treatment for the disease is given based on the joint involvement, inflammation, serology, symptoms, and duration of the disease (4).

Fight against rheumatoid arthritis begins with preventive measures, traditional medicines, therapies using DMARDs, NSAIDs, corticosteroids, hyaluronic acid intra articular injections and end up with surgery of the inflamed joint. Even though a large number of pharmacological and non-pharmacological therapies exist, effective cure of the disease is not well established due to the side effects, bioavailability problems and related health issues of the drug predominates at times (5). The study reports published in 'The New England Journal of Medicine' in December 2016 revealed the noninferiority of Celecoxib moderate doses over Naproxen and Ibuprofen on cardiovascular and gastrointestinal risks (6). DMARDs, the most preferred class of drugs, since they not only alleviate the symptoms but they also reduce the joint damage and resist the future complications. Delayed response and reduced bioavailability demanding their higher dose resulting in side effects such as liver damage and lung damage caused by methotrexate, eye damage caused by Chloroquine, teratogenicity and fetotoxicity produced by Leflunomide. Targeted DMARDs, the biologics suppress the immune response and reduce the symptoms and inflammation of the joint. Immune suppression produced by biologics encourages the risk of other inflammations such tuberculosis. Corticosteroids are administered to relieve the symptoms through immune suppression. Even though they alleviate sudden flare of symptoms they create side effects including weight gain, increased blood pressure, osteoporosis and elevated blood sugar level. Current medications for rheumatoid arthritis is not one size fits all due to their mechanism of action as well as their undesired effects produced during therapy (7). Nanoparticles with their physical characteristics' application in biological science emerge here as a helping hand to beat the problems encountered during the drug delivery and to overcome the unwelcome effects of the drug. Nanosize and flexibility to carry the drug within, made them the perfect carriers for drug

delivery. Controlled and targeted drug delivery of drugs to a particular site encouraged by nanoparticles improves their acceptance by reducing the total drug requirement to cure the disease, hence diminish the side effects.

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

Even though studies are going on from decades on rheumatoid arthritis, pathophysiology and etiology of the disease are not completely revealed. It has been considered that interplay of multiple factors such as genetic susceptibility and environmental stimulus, self-amplifying synovial inflammation, and age-related changes contribute to creating pathological lesions in synovium, erosion of bone and destruction of cartilage. Studies performed in monozygotic twins of families with RA reveals 15-30% concordance of the disease, in turn, give the evidence of genetic susceptibility to the disease (8).

Few theories suggest the initiating factors for rheumatoid arthritis as epigenetic modifications, smoking, bacterial (porphyromonas gingivalis) infection of the synovium or synovial injury. These factors have the ability to modify autoantigens (citrullination). Citrullinated antigens are recognized as foreign antigens by antigen presenting cells (APC) and trigger the immune response. APCs move to the lymph nodes and activate CD4 T Cells, in turn, activate B cells in lymph nodes. Activated CD4 T cells migrate to the synovium and produce IL-17 that acts as a proinflammatory cytokine, induce the release of INF α , IL-1, IL-6, neutrophils and RANK L (9). Activated B cells produce two different antibodies, anticitrullinated protein antibody against the citrullinated autoantigen and IgM antibody (10). These antibodies produce proteases and reactive oxygen species that precipitate cartilage damage. Matrix metalloproteinases and cathepsins and cystatins contribute the destruction of cartilages and bones in antigen-induced arthritis. (11) IgM antigen (rheumatoid factor) and anticitrullinated protein antibody are the major indicators used in the diagnosis of RA. Bone degradation is induced by the RANK-L generated by the induction of macrophages and CD4 T Cells. Neovascularization of the inflamed joint enhances the migration of inflammatory mediators to the joint and progression of inflammation. Inflammation causes pain, swelling and form nodules in the joint. Progression of the inflammation leads to the degradation of bones and cartilages of the joint results in restricted movement of the joints that in turn affect the quality of the patients' life (12,13) (Figure.1). As the inflammation progresses inflammation also spreads to the different organs of the body indicates extra articular manifestations (14). 17.8 – 40.9% of RA patients exhibit extra-articular manifestations including cardiopulmonary diseases, glomerulonephritis, rheumatoid nodules, ophthalmologic manifestations, amyloidosis, neuropathy, Felty's syndrome, musculoskeletal manifestations and insulin

resistance. In 1.5 – 21.5% of cases extra-articular manifestations are severe with increased morbidity and mortality. These are generated as the result inflammation and the inflammatory cytokines released in the synovial joint and their presence mainly IL-1, IL-7 and INF α in the systemic circulation. On skin they contribute to nodule formation, in liver induces production of the excess of CRP or ESR and hepcidin that contribute anemia and atherosclerotic plaque formation leads to myocardial infarction and stroke. Neurological effects involve fatigue and depression that attributed to anemia. Musculoskeletal manifestations involve osteoporosis, osteopenia and in the muscles inflammation and insulin resistance. Early diagnosis and treatment are necessary to prevent the disease progression and to prevent mortality (15,16).

TREATMENT OF RHEUMATOID ARTHRITIS

Complete remission of RA from a patient still exists as a research topic. Treatment or therapies for RA is concentrated mainly on arresting inflammation, relieve symptoms, prevent or reduce the progression of joint and organ damage and improve physical function and overall well-being. Individualization of the treatment is done based on a degree of disease activity, joint function, age, sex, occupation, family responsibility and cost of a drug. Pharmacological, nonpharmacological and combination of pharmacological and nonpharmacological therapies are suggested to RA patients based on the disease state. Nonpharmacological therapy involves heat or cold therapy, exercise, physical therapy and occupational therapy and nonsteroidal anti-inflammatory drugs (NSAIDs), traditional and biologic disease modifying anti-rheumatic drugs (DMARDs) and corticosteroids comprises pharmacologic options (17).

NONPHARMACOLOGICAL THERAPY

Nonpharmacological therapy for arthritis is suggested at the early stages of the disease or along with drug therapy to enhance the effectiveness and adherence to the early treatment. This helps in delaying the appearance of new symptoms, reducing movement disabilities and sequelae and improve patient's functionality. These therapies include occupational therapy, exercise or physical activity, patient education and complementary and alternative medicine (18). The main objective of occupational therapy is to improve and maintain functional capacity, prevent progression of the disease, understanding the disease and cop up with the disease characteristics so that the patient can involve in a meaningful occupation. An occupational therapist studies the lifestyle and the daily activities of a RA patient and give suggestions and advises on how to perform the activities in a different easier manner to accomplish their normal tasks. Patients are provided with assistive devices such as cooking utensils, bathroom supporters, reachers, canes and walkers (19). Studies performed on the effect of occupational therapy in RA for the first 10 years proved the beneficial effect of occupational therapy in all the stages of rheumatoid arthritis. Prescription of assistive devices and orthoses, patient education and hand-training instructions could result in a positive result (20). Occupational therapists are more interest to introduce new technology, engineering and monitoring the effectiveness of these systems. Rehabilitation Engineering Society of North America is the only agency giving training programs on for rehabilitation engineers and concerned about the quality assurance issues (21). Application of physiotherapy is based on functional assessment, the range of range of joint motion, muscle strength, postural assessment and respiratory function. Physiotherapy modalities included in RA are cold/hot application, electrical stimulation and hydrotherapy. Physiotherapist helps the patient in joint protection, use assistive devices and performance of assistive exercises (flexibility/range of motion, conditioning/resistance therapy and aerobic exercise) (22). These approaches will help in managing chronic pain and

disability by improving the flexibility of the joints, range of motion, aerobic condition, endurance, bone integrity, strength, coordination, risk of fall and coordination. Occupational therapy and are recommend by the UK clinical guidelines adjunct to drug treatment. Patient education The American pain society has recommended consideration of patient education as first in the management of rheumatoid arthritis before considering any pharmacological intervention. It is necessary for the patient to understand the disease to adhere completely to the medication and choose a lifestyle necessary to alleviate the disease. Programs such as 'arthritis self-management program' create awareness in patients regarding the medication, techniques to cop up with pain and symptoms, healthy lifestyle behavior and effective communication with the physicians and family (23). Complementary and alternative medicine Complementary and alternative medicine have attained an importance in the treatment of RA. US NIH (National Institute of Health) categorized CAM into four classes such as biologically based treatments, Alternative medicine systems, mind-body medicine and manipulative and body-based treatments. Four of these classes have a role in the therapy of RA. A double-blind randomized controlled pilot study performed comparing classic Ayurvedic medicine, methotrexate and their combination reveal no significant difference in efficacy measures of three groups although methotrexate group exhibited more side effects and ayurvedic medicine exhibited numerically few side effects (24). This reveals the acceptance of the complementary therapy in rheumatoid arthritis. Acupuncture is also employed in rheumatoid treatment to manage the pain.

PHARMACOLOGICAL THERAPY

Pharmacological therapy for RA starts immediately after the diagnosis of arthritis by the identification of the disease markers such as rheumatoid factor (RFs) or anticitrullinated protein antibody (anti-CPAs) in the body in spite of the differentiation RA (25). Assessment of the articular as well as extra articular manifestations and comorbidities are the basic requirement to fix on the medication (26). DMARDs (disease modifying anti-rheumatoid drug), NSAIDs (nonsteroidal anti-inflammatory drugs), Corticosteroids are the different classes of drugs used in the treatment of rheumatoid arthritis. There are biological and Nonbiological classes of DMARDs are employed in the treatment of rheumatoid arthritis. Traditional DMARDs are first preferred drugs for the treatment of RA. DMARDs or their combination with other drugs is preferred for most of the patients since they reduce the disease progression, bone degradation and the cardiovascular risks. Hydroxychloroquine (HCQ), sulfasalazine (SSZ), methotrexate (MTX), leflunomide (LEF), minocycline, azathioprine and D-Penicillamine are the DMARDs proved efficacy in slow down the disease progression. Results of safety and efficacy data of LEF promote it in to a first line drug for RA along with methotrexate. HCQ, MIN and SSZ are recommended only in mild RA cases. Methotrexate is the most prescribed and the first line drug in the treatment of RA. Proofs of safety and efficacy data of LEF promote the drug into the first-line agent. The side effects of DMARDs include hepatic cirrhosis, hypersensitivity, allergic reactions, intestinal pneumonitis and retinopathy (28). Biological DMARDs/Biologic agents/biologic response modifiers, a class of DMARDs targeting their action on inflammatory mediators (TNF- α , IL-1, IL-6, T cells and B cells) inhibit the proinflammatory and joint damaging effects. Biologics action based on the ability of the genetically engineered proteins in the inhibition of larger size protein cytokines that is not effectively performed by normal drug molecules. Their affinity towards specific components of immune system helps in their targeted therapy. TNF inhibitors, IL-1 receptor antagonist, B cell

inhibitor, T cell costimulation inhibitors and IL-6 inhibitors are the five classes of biologics available for treatment. Multiplex cytokine interactions and an array of targets made it difficult to assess its safety, efficacy and toxicity profiles. Higher risk of bacterial infection, high cost and loss of response to the drug exist as a barrier for convenient use of biologics (29). Normally preferred DMARDs are mentioned in Table.3. Nonsteroidal anti-inflammatory drugs are one among the classes of drugs used to reduce the symptoms of rheumatoid arthritis. They used widely due to their anti-inflammatory, analgesic and antiplatelet aggregating nature. NSAIDs reduce inflammation and sensitivity to pain by inhibiting the synthesis of prostaglandins that increase vascular permeability and bradykinin sensitivity at the site of inflammation. NSAIDs not, however, prevent or reduce the disease progression they are administered only to reduce swelling and pain. More than 20 different NSAIDs are available with or without prescription. Acetylated and nonacetylated salicylates and used in RA treatment. Nonacetylated salicylates used are salsalate, choline salicylate and magnesium salicylates. Celecoxib, Diclofenac, Ibuprofen, Ketoprofen and Naproxen (nonacetylated) are used to suppress the symptoms of rheumatoid arthritis. Due to the inability of these medications to prevent disease progression and side effects of gastrointestinal disturbances, cardiovascular risks and renal impairment limited their application in treatment (37,38). Corticosteroids are effective in RA due to their anti-inflammatory and immunosuppressant action that results from the suppression of immunomodulators including IL 1, IL 6, TNF α and interferon gamma. Inhibition and expression of proinflammatory mediator leukotrienes and prostaglandins, plasminogen activators, inducible nitric oxide synthase and adhesion molecules. At the site of inflammation glucocorticoids maintain the cell physiology by suppressing the activity of monocytes, antigen presenting cells and lymphocytes. They also suppress the proliferative response to nitrogen production of cytokines and immunoglobulin (39). Glucocorticoids are prescribed to the patients awaiting the onset of DMARDs. Combination of DMARDs, NSAIDs and corticosteroids are suggested in patients with active rheumatoid arthritis. Maintaining the disease condition and providing a better quality life is presented by a low dose long-term therapy of corticosteroids. Prolonged use of glucocorticoid can precipitate cardiovascular diseases, insulin resistance, osteoporosis, skin thinning, obesity, inhibition of wound repair and hypertension (40). Advancements in biotechnology potentiate the chances of gene therapy in human. Gene therapy deals with the transfer and expression of an absent or faulty gene. Gene therapy is targeted or localized to the joints in case of rheumatoid arthritis (41). High expression anti-inflammatory cytokine genes and suppression of proinflammatory cytokine genes are targeted in rheumatoid arthritis therapy. This approach provides persistent anti-inflammatory effect and no systemic effects as a benefit. Adeno associated viral (AAV), retroviral and adenoviral vectors are used as the major carriers (42,43). Hyaluronic acid is a major component of synovial fluid, is given as intraarticular injection in rheumatoid arthritis. It reduces the friction between the cartilage surfaces of the joint, acts as an anti-inflammatory agent, analgesic by reducing the prostaglandin or bradykinin induced pain, chondroprotective and provides the joints with the necessary oxygen and nutrients (44). It also removes the carbon dioxide and metabolic waste that results from the activity of the chondrocytes, contributing the health of the joints. During the progression disease and inflammation of the joint hyaluronic and the synovial membrane that continuously producing hyaluronic acid degrades (45). Injection of hyaluronic acid into the synovial cavity as a viscoelastic supplement reduces bone degradation and disease progression. Pain and damage to the ligaments during injection,

chances of septic arthritis and systemic sepsis and the cost of medication restrain its use (46).

PROPHYLAXIS OF RHEUMATOID ARTHRITIS

Remission of rheumatoid arthritis can be achieved effortlessly once the disease is identified in pre-rheumatoid arthritis stages. Pre-rheumatoid arthritis phase comprises a number of events preceding the clinical occurrence of RA (47). It starts with genetic and environmental factor interaction thereby initiation of the autoimmune process that ends up with inflammation and tissue injury. Presence of autoantibodies (ACPAs and RF) 3-5 years before the appearance of clinical RA increases the possibility of early identification of the disease and its remission. Preventive measures that can be considered in rheumatoid arthritis are included in the Table.1 Applicability of preventive strategies rely on the extent of understanding of the risk factors and modifying the ability of the risk factors (48,49).

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