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Review Article

A REVIEW ON VARIOUS TREATMENT MODALITIES OF RHEUMATOID ARTHRITIS: A PERSPECTIVE STUDY

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ABSTRACT

Rheumatoid arthritis is a systemic disease that causes progressive joint damage and disability. The macrophage is an important pathogenic mediator in rheumatoid arthritis, and cytokines such as tumour necrosis factor alpha (TNFα) and interleukin-1 are therapeutic targets. Drugs that block TNF a decrease joint inflammation and slow radiographic progression. There are various strategies for treatment of rheumatoid arthritis such as Allopathy, Homeopathy, Ayurveda etc. In this review we discussed about the potency and side effects of various treatment approaches of RA. Allopathy is a first line of treatment especially in acute conditions which provides both symptomatic and root cause relief. But it is supplemented with an array of side effects which limits their use chronically. It can also be cured through Complementary and Alternative Medicine (CAM) like yoga, Ayurveda, Naturopathy, Homeopathy, Unani, Siddha, acupuncture, etc. which has enough potential and remedial measures in treating arthritis. Home remedies, preventions and precautions are also important aspects in minimizing the effect of arthritis.

Keywords: Rheumatoid arthritis, Allopathy, Complementary and Alternative Medicine (CAM), Interleukin-1, Tumour necrosis factor alpha (TNFα)

INTRODUCTION

Rheumatoid arthritis is a chronic, systemic, inflammatory, autoimmune disease that causes progressive articular destruction and associated co-morbidities in vascular, metabolic, bone, and psychological domains. Rheumatoid arthritis affects about 1% of the population, alongside 5 and 50 per 100,000 people newly developing the condition each year, can present at any age, and is more prevalent in women than in men. It is characterised clinically by joint pain, stiffness, and swelling due to synovial inflammation and effusion. By contrast with other forms of arthritis, rheumatoid arthritis synovitis has a high propensity to disobey tissue boundaries, infiltrating articular bone and cartilage (then called pannus).The disease causes disability (with loss of working capacity and early retirement) and premature death if insufficiently treated.

The process is driven by antigen-presenting cells, T cells and B cells that result in the expansion of inflammatory cytokines, such as interleukin (IL)-1, IL-6 and TNF-α. It is identified that chronic joint inflammation is induced by the activated T cells infiltrating in the synovial membrane. T cells are activated by the antigen–presenting cell, presenting the antigen to the T-cell receptor. Activated T cells, in turn activate B cells either directly or via pro-inflammatory mediators. These activated B cells then get differentiated into antibody-producing plasma cells. The anti-citrullinated C peptide (anti-CCP) and rheumatoid factor (RF) antibodies form complexes to activate, attract and complement other inflammatory cells to the synovium. Activated B cells also produce a number of pro-inflammatory mediators including IL-1, IL-21, IL-6, TNF-α, interferon gamma, and lymphotoxin. T cells and B cells activate macrophages via pro- inflammatory mediators. Macrophages produce TNF-α, IL-1, IL-6 and interferon-γ. Dendritic cells produce IL-1, IL-6, TNF-α attracting cell to the inflammatory cell infiltrating the synovium. In addition to this, macrophages directly secrete matrix metalloproteinase and other proteolytic enzymes damaging synovial tissue. A cluster of cell types are drawn into the downstream effector mechanisms like endothelial cells and synoviocytes undergoing morphological changes and resulting in inflamed, synovial hyperplasia leading to joint destruction and damage[1-4].

Early diagnosis helps in preventing severe destruction of joint tissue but is difficult to accomplish. Diagnosis of RA depends on the symptoms and some blood tests can also help to confirm RA.

1. C-reactive protein test (CRP)- show inflammation and activity of the disease
2. Cyclic Citrullinated Peptide Antibody (CCP)
3. Erythrocyte Sedimentation Rate (ESR) - show inflammation in the body.
4. Ultrasound or MRI
5. Joint X-rays
6. Synovial fluid analysis
7. Complete Blood Count (CBC)-evaluate and monitor complication of RBC and WBC.
8. Rheumatoid factor (RF) – used to help diagnose RA.

The management of rheumatoid arthritis is a multidisciplinary approach in order to lessen the pain, reduction of inflammation and restoration of joints function.

VARIOUS TREATMENT STRATEGIES FOR RHEUMATOID ARTHRITIS

Allopathy

It is a conventional treatment in which drugs are used to cure acute and life-threatening illness or infections. It is scientifically proved system of medicine and most widely followed one. But it is associated with many untoward effects which limits its usage for some chronic conditions. In spite of these drawbacks it still occupies the first place as far as treatment is concerned.

NSAIDs are particularly helpful during the first few weeks in which a patient has symptoms, because the drugs provide partial relief of pain and stiffness. NSAIDs should be used together with DMARDs. NSAIDs exert their actions by inhibiting enzymatic activity of the COX enzymes. Aspirin, ibuprofen, or naproxen are non-steroidal anti-inflammatory drugs (NSAIDs) that can relieve arthritis pain[5].

Gold therapy has been shown to attenuate the destructive process in RA, until the introduction of Methotrexates precursor, aminopterin. Gold compounds were the standard for RA treatment.

T cells also have an important role in rheumatoid arthritis. A fusion protein — cytotoxic T-lymphocyte–associated antigen 4–IgG1 (CTLA4Ig) binds to CD80 and CD86 on antigen-presenting cells, blocking the engagement of CD28 on T cells and preventing T-cell activation and is a promising new therapy for rheumatoid arthritis. Combination of CTLA4Ig and methotrexate improved the signs and symptoms of disease, physical function, and quality of life in patients who had active rheumatoid arthritis despite ongoing methotrexate therapy[6].

Corticosteroids are potent suppressors of the inflammatory response in rheumatoid arthritis. Predictable side effects of corticosteroid drugs include thinning of the skin, cataracts, osteoporosis, hypertension, and hyperlipidaemia [7,8].

Optimal management of rheumatoid arthritis requires rapid and sustained suppression of inflammation with DMARDs, which are defined as medications that retard or halt the progression of disease. Disease modification is most convincingly demonstrated by the ability of the medications to decrease radiographic progression. DMARD is applied to medications which can alter the course of disease and thus prevent joint erosion. The mechanisms through which DMARDs act are varied but a collective outcome is to help stem the destructive process of intertwined inflammatory cascades resulting in the degradation of soft tissue, cartilage and bone.

DMARDs have a delayed onset of action, whereas glucocorticoids relieve signs and symptoms within days, appear to have some disease-modifying potential.

Methotrexate is thought to be multifactorial, with inhibition of cell maturation and to show reduce TNF levels in synovial tissue of patients. It is now the drug of choice to maintain remission.

Three biologic products that inhibit the actions of TNF-α (infliximab, etanercept, and adalimumab) and one that inhibits the action of interleukin-1 (anakinra) and to treat rheumatoid arthritis.

The biologics used in inflammatory arthritis are genetically engineered proteins derived from human genes. They mainly inhibit specific components of the immune system that play pivotal roles in driving or inhibiting inflammation in arthritis[9].

The modern treatment strategy for RA involves early and highly effective treatment with frequent clinical follow-up (tight control) aiming at reaching a target of clinical remission in patients with early RA and to achieve a target of low disease activity in patients with long-standing RA. This, so called treat to-target strategy has been shown to inhibit joint inflammation, preventing progressive joint damage and future functional loss.

Quinine derivatives such as chloroquine and hydroxychloroquine are very safe to use. They are used commonly in the treatment of RA, but efficacy has not been demonstrated to be comparable to Methotrexate[10].
Sulphasalazine has anti-inflammatory and antimicrobial effects and is suitable for mono- or combination therapy with e.g. hydroxychloroquinine and MTX[11].

Cyclosporine is mainly used in low-dose in combination with MTX and reduces radiographic progression. It acts via T lymphocytes, which are considered to be central in the pathogenesis of early RA.
Leflunomide blocks pyrimidine synthesis. Its clinical and radiographic effects match those of MTX.
Modern treatment strategies aim at reducing inflammation and halting erosive damage.

Homeopathy

Homeopathy is effective in reducing the symptoms of joint inflammation in RA. There was a significant improvement in subjective pain, articular index, stiffness and grip strength in those patients receiving homoeopathic remedies[12].

Eg: Arnica, Nux vomica*, Arsenicum album,* Opium*, Bryonia alba, Pulsatilla Calcarea carbonica,* Rhododendron*, Causticum,* Rhustoxicodendron*, Ignatia ruta,* Lachesis, Sepia, *Lycopodium sulphur,* Morgan, *Sycotic co, Natrum muriaticum,* Thuja are homeopathic Remedies of wide action in rheumatoid arthritis[13].

a) Arnica may help to soothe arthritic pain when applied externally to areas of inflammation and soreness[14].
b) It has known to show significant reduction in swelling and pain and some of the active ingredients of Boswellia (boswellic acids) have shown good anti-inflammatory effects[15].
c) Bryonia is an excellent remedy in cases of acute pains of rheumatoid arthritis. Causticum that is used in homeopathic treatment of individuals suffering from rheumatoid arthritis has symptoms that include the development of deformities in the joints, contractures and weakness in the muscles of the body in general[16].
d) *Calcarea fluoricum* medicine works for these patients of arthritis who tend to have large or medium joint infections such as knee joint, spine or shoulders[17].
e) Rhododendron basically helps with rheumatic and symptoms. It prevents stiffness of neck, pain in shoulders, arms, wrists. It also provides relief of swollen joints and gouty inflammation of the great-toe joint[18].

Naturopathy

Herbal medicinal drugs that interact with the mediators of inflammation are used in the treatment of rheumatoid arthritis (RA). Herbal remedies can form an alternative source to relieve symptoms in patients having RA as well as to address the

drawbacks associated with present treatment methods with allopathic drugs.

a) The antiarthritic property of *Aloe vera* is due to the anthraquinone compound. It stimulates the immune system and it is an anti-inflammatory agent[19,20,21].
b) Oral administration of *Withania somnifera* Linn., root powder showed the antiarthritic effect in adjuvant induced arthritic rats[22,23].
c) Extract of *Boswellia serrata* have natural anti-inflammatory activities at sites where chronic inflammation is present by switching off pro-inflammatory cytokines and mediators which initiates the process. *Boswellia serrata* Linn., reduces the breakdown of glycosaminoglycan synthesis[24,25,26].
d) Piperine isolated from black pepper decreases the arthritic symptoms[27,28].
e) Black cohosh decreases the inflammation produced due to the arthritis[29,30].
f) Ginger extract is one of the effective arthritis joint pain remedies recommended by physicians. Main constituents are sesquiterpenoids, with (-) zingiberine. Sesquiterpene Lactones (SLs) are natural products responsible for its anti-inflammatory activity[31,32].
g) Curcumin, a natural compound present in the rhizomes of plant *Curcuma longa,* demonstrated its anti-inflammatory action. Curcuminoids inhibits joint inflammation in both the acute and chronic phase of arthritis[33,34,35].
h) Hydro-alcoholic extract of *Terminalia chebula* Retz., shows the anti-arthritic activity in formaldehyde or Complete Freund's Adjuvant (CFA) induced arthritis. The anti-arthritic activity of *Terminalia chebula* Retz., is due to its modulatory effect on pro-inflammatory cytokine expression in the synovium[36].

Ayurveda

Ayurveda is very systemic and considered to be the best Indian system of Medicine, having more approachable ways of treatment. According to Ayurveda, RA is caused due to an imbalanced Vata Dosha (Airy Bioelement) that leads to the accumulation of Ama (toxin) in the body.

The classical ayurvedic formulation treatment includes several pharmacological forms of internal herbal medicines [Arishtams (Alcoholic preparations), Bhasmas (Ash), Choornas (Powder), Grithams (Medicated Ghee), Gulikas (Tablet) Lehyams (Herbal Jam), Kashayams (Water Extract) and Thailams (Oil)] which eliminates the toxins and retaining back to the balance to VataDosha (Airy Bioelement) in the body[37,38].

The concept of Ayurveda suggesting the production of ama or impaired metabolism invites the attention of researchers of to combat the disease by eliminate this causative factor as such the treatment. According to Ayurveda in addition to alleviation of disease it also aims at augmenting the process of digestion both at intestinal and cellular level.

Ayurvedic treatment (Ashwagandha powder and Sidh Makardhwaj) has a potential to be used for the treatment of rheumatoid arthritis[39]. A formula comprising *B. serrata, T. cordifolia, W. somnifera,* and *Z. officinalis* patented for treating RA and osteoarthritis [46].

Unani

As per Unani conventional and literal explanations, arthritis is defined as the pain which occurs in different joints of the body especially in the joints of arms and legs etc.[40,41, 6-11] and the description of disease is based on the four-humor doctrine of Unani Medicine. The pathological changes in the joints are caused mainly by derangement of temperament of humors, which leads to accumulation of morbid materials into the joint spaces[40, 42, 43,44]. The pain in the joints is sometimes accompanied by with or without swelling. The morbid materials develop contractures also. Hippocrates says that the chronic illness like arthritis arises from the accumulation of toxic materials. The principal of treatment of arthritis is 'tanqiya' i.e., cleansing and evacuating of morbid materials out of the body through munzijwamus' hil (concoctive and purgative) drugs which help correct deranged temperament [44] by the complex process of detoxification [45]. The mode of action of concoctive and purgative drugs may be detoxification and excretion of morbid materials out of the body.

Tanqiya is a complex process in the body by which the morbid and diseased materials are taken out of the body by way of evacuation, a complex phenomenon under certain environmental conditions under vigil of a physician with the help of various simple Unani drugs having munzij and mus'hil (concoctive and purgative) effects under a very specific set of Unani guidelines (Unani principles for this complex process) for a certain period of time depending upon the chronicity, nature of the disease and type of khilt (humor) involved therein.

It has analgesic and anti-inflammatory effects. It could also be due to the anti-oxidant and energizing effects of the drugs which maintain a balance between the formation of free radicals and their utilization in the body or elimination from the body by the complex mechanism of concoction and purgation since free radicals are responsible for the development of RA. It helps in keeping a correct balance between the formation of free radicals and their utilization within the body. The treatment helps in bringing pH level of urine from 4(higher acidic) to 6.5(nearly alkaline) which is indicative of the fact that it had facilitated the morbid materials to be excreted out of the body thus providing a near balance of pH inside the body because a balance of pH is must for the maintenance of health.

This medication acting as anti-oxidant must be reducing the level of oxidative stress and acting as scavengers to mop out the free radicals from the body leading to the stress-free state to the already loaded damaged tissues and muscles of the joints in RA thus maintaining near balance pH in the body and of course in the urine. A number of gut induced toxins including endo-toxins (cell wall compounds of bacteria, by-products of bacteria, candida albicans, and yeast compounds) are also evacuated out due to purgation [46] thus bringing a balance of pH inside the body free of diseases.

The medication acting as anti-oxidants must be reducing the level of oxidative stress and acting as scavengers to mop out the free radicals from the body leading to the stress-free state in the body including urine and it is here that free radicals are acting as morbid materials which disturb the pH of the body also of urine. It is also possible that the test formulation had helped in keeping a correct balance between the formation of free radicals and their utilization within the body that is why a considerable balance of pH inside the body had been maintained.

Siddha Formulation

Interestingly, the Siddha system of treatment is being increasingly recognized as an alternate approach to arthritic treatment. Herbal mixtures have long been used in traditional medicine because of

the synergism that takes place among the phytochemicals on the herbs utilized.

A significant increase is observed in the activities of glycohydrolases in RA. Furthermore recently a strong association was found between RA and -d-glucuronidase and *N*-acetyl- -d-glucosaminidase activities that were reported to be the foremost glycosidases of stimulated chondrocyte supernatants and RA sera[47,48].

The increased activities of these lysosomal enzymes RA might result in the degradation of proteoglycans and subsequently might lead to the loss of collagen [49]. This decrease in the level of collagen might be due to declined collagen synthesis accompanied by an increase in the catabolism of newly formed collagen in acute phase and soluble to insoluble collagen in chronic phase of the arthritis[50].

HA (hyaluronic acid), a large glycosaminoglycan is a predominant component of the articular surface. The most probable mechanism of depletion of GAGs from matrix by -d-glucuronidase and *N*-acetyl- -d-glucosaminidase is the degradation of hyaluronate supplemented with the removal of terminal monosaccharides of GAGs such as CS, resulting in the decreased level of GAGs and its constituents. The decreased level of hyaluronic acid in arthritic condition might also be due to cleavage by hyaluronidases, since the catabolic contribution of -d-glucuronidase and *N*-acetyl-d-glucosaminidase was reported to be restricted to hydrolyze the oligosaccharides produced by the action of hyaluronidase restoration of hyaluronic acid to normal level by the treatment. By this it might have inhibited the destruction of cartilage, bone and synovial tissue *via* regulating the expressions of proinflammatory cytokines (TNF-α and IL-1) [59] and downregulating the chemical mediators such as arachidonic acid [51] and PGE_2 [52,53]. This results in the downregualtion of MMPs (MMP-1) and increases the production of TIMPs (TIMP-1) [53], consequently resulting in the increased synthesis of collagen [55]and proteoglycans [54,56,57] by the treatment.

It can even act *via* directly downregulating the expression of MMPs (Unpublished data) and reducing the release of lysosomal enzymes could reduce the degradation of cartilage, bone and synovial tissue, thereby enhancing the increased synthesis of collagen and GAGs. The drugs might have exerted their effect by inhibiting lipid peroxidation, reducing the ROS/RNS [58,66]and enhancing the antioxidant system and *via* suppressing the proinflammatory cytokines TNF- and IL-1 [59] and reducing PGE_2 synthesis [67,68], causing the increased stability of lysosomes.

Cell Therapy

MSCs (mesenchymal stem cells) and their role in hematopoiesis and immune modulation suggests their potential use for cell therapy.

A single intraperitoneal injection of allogeneic MSCs given at the moment of immunization with CII (type II collagen), was sufficient to prevent the occurrence of bone and cartilage erosions in the joints of immunized mice. Current therapy for RA is directed toward diminishing the inflammatory response and treating the sequelae of uncontrolled inflammation. It represents an effective new therapeutic approach to target the pathogenic mechanism of autoimmune arthritis using adult stem cells[59,60]

Acupuncture

Acupuncture needles are inserted into the skin at specific points along meridians or channels. It has been used for the relief of pain that is caused by osteoarthritis of the knee. This can be severe and maybe incompletely relieved by conventional treatments. Although the best current evidence suggests that acupuncture relieves pain, because it is an unusually potent placebo, it is safe and can be considered as an adjunct to conventional treatment[61]

Yoga for Arthritis

Yoga is a comprehensive, multidimensional approach used to improve health conditions. It has been used for reducing various musculoskeletal problems, [62]including rheumatoid arthritis. Yoga plays an important role in improving physical, mental, emotional, and spiritual well-being, as well as in managing stress and its effects[63].

a) Loosening exercises (Shithilikaranavyayama; 6 minutes)—Passive rotation of the toes, toe bending, ankle rotation, knee rotation, knee cap tightening, full butterfly, waist rotation, hip rotation, shoulder rotation, neck bending, and neck rotation.
b) Diaphragmatic breathing (3 minutes)
c) Strengthening exercises (Shakti Vikasaka Vyayama;4 minutes)
   For the wrist-Mani Bandha Shakti Vikasaka
   For the palms-Kara Tala Shakti Vikasaka
   For the fingers-Anguli Shakti Vikasaka
   For the elbows-Kaphoni Shakti Vikasaka
   For the arms-Bhuja Bandha Shakti Vikasaka
   For the back-Kati Shakti Vikasaka
   For the thighs-Jangha Shakti Vikasaka
   For the calf muscles-Pindali Shakti Vikasaka
d) Physical postures (Yogasan as 10 minutes)
   Standing postures-ArdhakatiChakrasana, ArdhaChakrasana, and Pada Hastasana
   Prone postures-Bhujangasan andShalabhasana
   Supine postures-Sarvangasana and Matsyasana
   Sitting postures-Vakrasana and Ushtrasana
   Shavasana with deep relaxation-7 minutes
e) Breathing practices (Pranayama; 11 minutes)
   Preparatory practices-Kapalabhati Kriya and Vibhagiya Pranayama
   Pranayama-Surya AnulomaViloma, NadiShuddhi, Shitali, Shitakari, and Sadanta
f) Meditation (Dhyana; 8 minutes)-Nadanusandhana and OM meditation
g) Devotional song and silence (Bhajans; 5 minutes) [64].

Surgery and other treatments

In some cases, surgery may be done if other treatments have not worked. This may include arthroplasty to rebuild the joint, joint replacement, such as a total knee joint replacement[65]

CONCLUSION

Rheumatoid arthritis is a devastating condition of joints with pandemic distribution. It adversely affects the quality of life with high morbidity. Various treatment strategies are available to control the problem but coupled with their own drawbacks. Hence, early diagnosis associated with appropriate choice of treatment helps in ameliorating the disorder.

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