Section A-Research paper

STUDY ON TREATMENT USED IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT

Rheumatoid Arthritis is a long-term inflammatory systemic autoimmune disorder that shows its effect on symmetrical joints as well as other body organs. Mostly, women are susceptible to the rheumatic disorder as compared to opposite sex, which is depicted as in ratio 3:1. There are two subtypes of RA out of which ACPA-positive is found in 67% of the patients as compared to the other and also, the effect of drugs is more in positive type than other. The treatment plan targets the reduction in the inflammation, pain and decelerate the damage of the joints, as the RA is non-curable in modern era. The treatment of the RA has undergone remarkable conversion since decades and now it is treated with the strategy known as treat to target. The Anti-Rheumatic drugs, such as DMARD's, corticosteroids etc. are classified and prescribed according to the symptoms of the patient. The treatment of RA of prescribing drugs should be according to the guidelines (national essential list of drugs, WHO guidelines etc.) or on the basis of patient symptoms. (DOI: 10.3892/etm.2016.3045) Hence, we scrutinize the treatment for controlling the symptom of RA in patients.

KEYWORDS: RHEUMATOID ARTHRITIS, DMARDs, NSAIDs

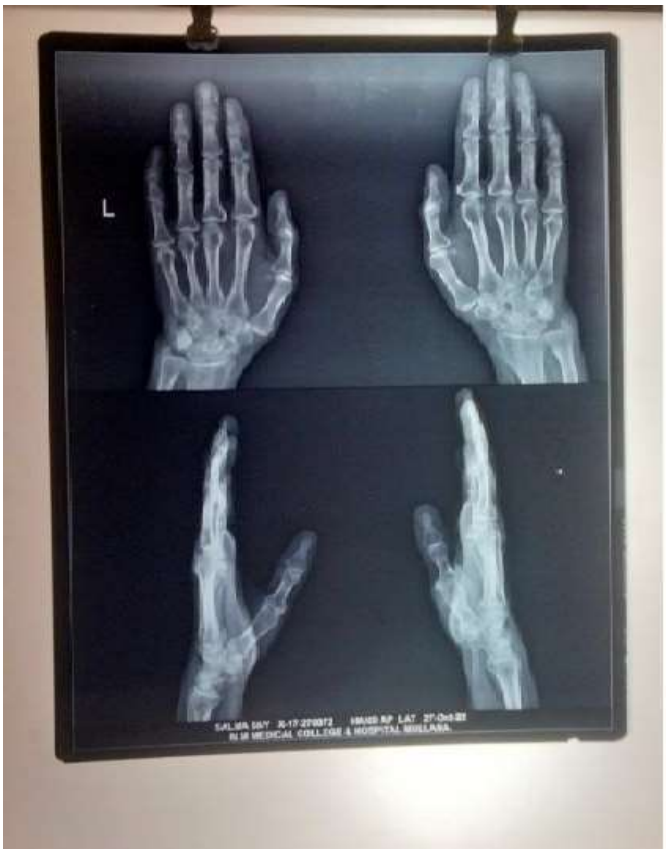
ARTHRITIS:

Arthritis is a joint of inflammation swelling, and pain in one or more joints. [1]

RHEUMATOID ARTHRITIS:

RA is an inflammatory autoimmune joint disease that affects symmetric joints [Fig.1] and it is likely to affect more women than men and is typically seen in elderly people. Rheumatoid Arthritis is a polyarthritis and multisystem disease [2]. The characterized inflammation of the

synovium and any joint including the mini joint of hands and feet and the big joint of shoulder and knees.[3] The synovitis annihilation of bones and cartilage results in radiographic damage.[4] It is a long-time inflammatory disease derivative from an autoimmune disease of the synovial membrane reducing the production of pro-inflammatory cytokines.[3-5]. The joint tissues strong membrane lining that surrounds all the splinters is attacked by the body's immune system firstly act on the peripheral and synovium joints. Ultrasonography examines most frequently joint space widening, synovium hypertrophy, fluid accumulation, bone erosions, cartilage defects, tendon sheath widening, and tendon rips are ultrasound abnormalities that can be found in RA patients.[6] According to the definitions set by the ACR in 1987 Rheumatoid Arthritis (RA) is defined as a persistent non-supportive swelling of the synovial joints. Criteria for the diagnosis of Rheumatoid Arthritis (Arnett. et al, 1988).[7] Arthritis of three or more joints this including the wrists, knee, elbow,(MTP)Metatarsophalangeal, (PIP) Proximal interphalangeal, (MCP) Metacarpophalangeal Lumber Spine, and Cervical Spine. [7], [8] Deformities and bone rudeness are move on by all this joint depletion, which is usually a bit burning for the patient.[9] Rheumatoid nodules beneath the skin weariness, fever, weightless, and morning rigidity of the afflicted joints for more than 30 minutes are all common symptoms of RA[10]. [11], [12]



[X-Ray on Rheumatoid Arthritis]

[Fig.no.1 symmetric symptoms shown in RA]

This illness often begins from the age of 35 to 60 that can go into remission or worsen. Juvenile RA (JRA), it is similar to RA but there is absence of rheumatoid factor which can also affect teenagers [13]. The percentage of RA is approximated to be 1% globally and 1-2% in the West. [14], [15]. Chronic RA is the irreversible that causes rough damage of the bone. RA is a clinically very heterogeneous disease [16], [17]. The American College of Rheumatology and Subcommittee on Rheumatoid Arthritis (ACR-SRA) recommends a baseline laboratory data evaluation and clinical test inflammatory marker which involves a (CBC) complete blood count, (ACCP) Anti-Cyclic Citrullinated Peptide, (RA) Rheumatoid factors, (ESR) Erythrocyte Sedimentation Rate, (CRP) C - reactive protein and Radiographic x-ray. [18]Rheumatoid Arthritis is the first well-known Rheumatoid Arthritis immunologic marker[19], [20] It is noticed in 80-85% of RA patients that increased disease activity radiographic progression and the occurrence of extra-articular symptoms have all been linked to elevated serum RF levels. RF has a sensitivity range of 50-90% and a specificity range of 50-95%. Compared to RF, Anti-CCP antibodies seem to be a more focused marker. They frequently exist even years or even years before the first symptoms of the disease. Anti-CCP antibodies have established prognostic significance. The amount of anti-CCP in the serum are matched up with earl joint degradation and a bad prediction. Deformities and bone intersection are brought on by all this joint depletion, which is a bit painful for the patient. [21]–[23] The main etiological factor is still unknown and the research explains that the causing factors of RA is associated to genes, hormones, and environmental factors, that involves: Women hormones (70 percent of RA suffer are women), obesity, infectious diseases those are caused due to bacteria, and viruses. Some other reasons environmental elements involve exposure to cigarette smoke, insecticides, mineral oil, or silica in the workplace. Smoking can cause bone desorption. This can hasten the disease's course in persons with osteoporosis. Additionally,[22], [24]–[26] it lowers estrogen levels in women, which might hasten menopause and contribute to further bone loss. [17]–[19].The epidemiology of spreading of RA in the adult population in India is approximately 0.75%. Rheumatoid Arthritis has occurred an alarming concern affecting more than the worldwide population. [27]. The aim of the treatment are to relieve from swelling and pain in joints, also maximizing the functioning of the joints and preventing them from getting deformed or destruction of the joints. [28]. In the decade, there had been a great revolution in treatment of RA with more aggressive and initial treatment strategies likewise, treat-to-target also, introduction to the biologics and other target therapies resulting in notably improvised clinical outcomes for most of the patients [29]. Therefore, the review aims to is study the treatment options for RA in the modern era, including the new drug treatment and other new therapies that has recently developed for the RA treatment such as biologics etc.

ETIOLOGY

The reason for RA is thought to be mixed resulting from genetic and environmental factors. Susceptibility and severity are more in men younger then 30 years. As compared to men the women are more prone to the disease.[30] The heritability for seropositive RA is 40% to 60% and for seronegative in RA. Epigenetics is defined as heritable conversions without making change in DNA sequences. These conversions may exists in chromatin or DNA including DNA methylation, histone tampering and non-coding RNA mediated regulation. A study done on risk factors of an anti-CCP (anti-citrullinated protein antibody) positive individual patient concludes that there is an interaction between shared epitope (SE) and smoking which creates chances of burgeoning the risk of Rheumatoid arthritis.[54]

EPIDEMIOLOGY:

RA affects double the women in comparison to men. The normal age of onset is between the third and fifth decade of life which further increase in next decade. The disorder causes pain, stiffness and swelling in the joints of lower and upper extremities. Most commonly the interphalangeal joints, wrists and Metacarpophalangeal and metatarsophalangeal joints in feet are painful and swollen. Later, this disorder develops in bigger joints likewise hips, knees etc. RA leads to destruction and erosion of the bones on joints [50]. With the increase in age of patient the RA effect also continues to burgeon until 70 years of age. Almost 0.75% of Indian population is affected by the disorder that hampers the quality of life of patient. [DOI: 10.20959/wjpps20164-6406]

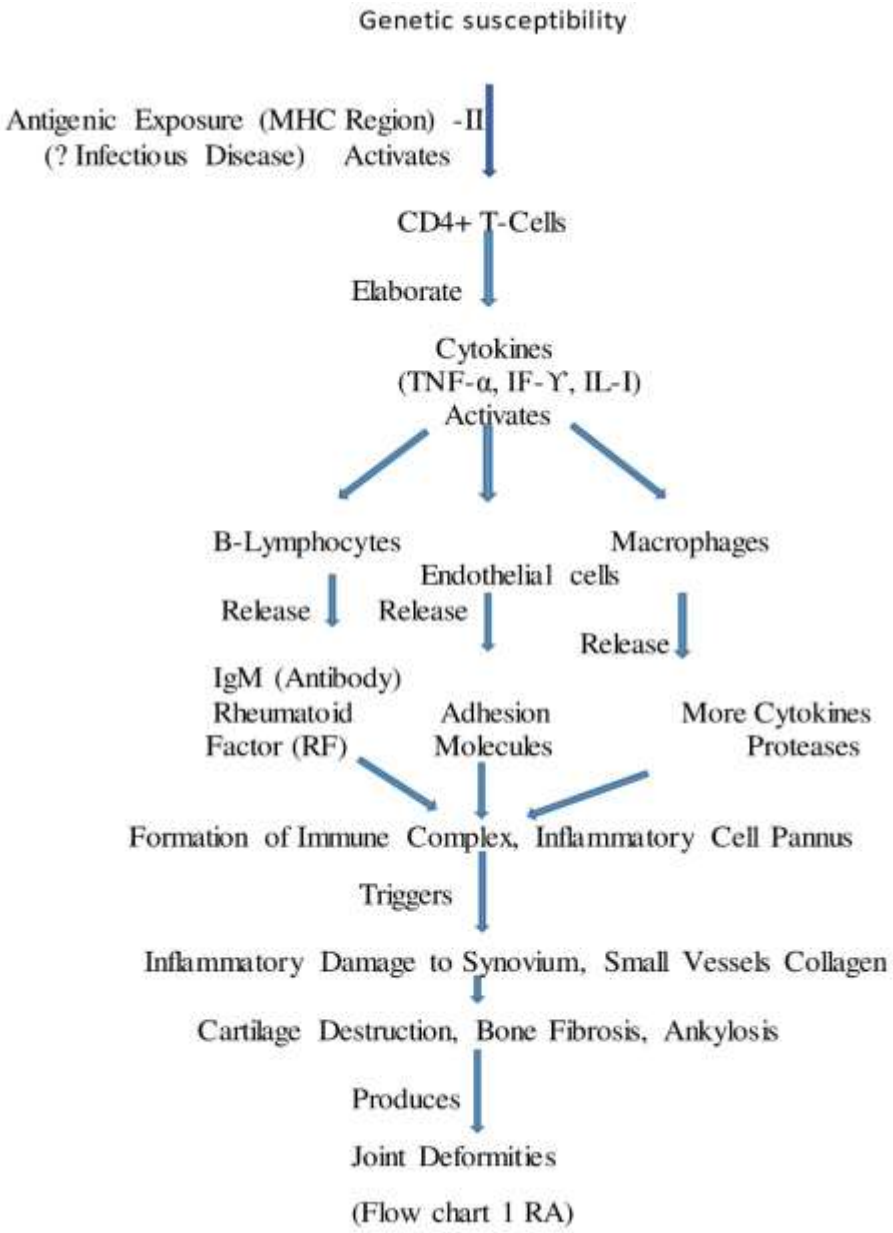
PATHOGENESIS:

There are two subtypes of RA according to the presence or absence of Anti-citrullinated protein antibodies (ACCP) Calcium-dependent enzyme peptide arginine deaminizes (PAD). Catalyze the citrullination result in changing positively charged arginine to polar, neutral citrullinated resulting in a post-translational modification. ACPA is a more aggressive clinical phenotype than ACPA-negative. [19], [20], [31]On another hand, ACPA –negative has different genetic patterns that result in different responses to other handmade cells to citrullinated antibodies. [11], [20], [31], [32] In treatment terms, MTX or Rituximab responses are less effective in ACPA-negative in Comparison to the others [11], [12], [27], [33]

The Role of CD4 and T-Cells in Rheumatoid Arthritis:

The Immune Cells CD4+ T cells are activated in response to antigenic exposure (such as an infectious agent) in genetically predisposed individual HLA-DR molecules (MHC-II region). After the activation,[24], [25], [34] these cells produce cytokines, among which tumor necrosis factor (TNF), interferon (IF), interleukin (IL)-1, and IL-6 are the most crucial. These cytokines cause macrophages, B lymphocytes, and endothelial cells to

become active. The activation of B-cell releases an anti-IgG molecule known as rheumatoid factor, which is an IgM antibody (RF).[35] Immune complexes IgG and IgM cause inflammation that damages collagen, the synovium, and tiny blood vessels. Endothelial cells that have been activated produce adhesion molecules that encourage the aggregation of inflammatory cells. More cytokines are released when macrophages are activated, damaging joint tissues and causing pannus development and cartilage vascularization. Eventually, fibrosis and ankylosis, which result in joint abnormalities, follow the deterioration and destruction of bone and cartilage. (Flow chart 1) [36]–[39]



(Flow chart 1 RA)

Treatment:-

Treatment goals:

There are several vital aims that are necessary to be achieved by the physician while prescribing the treatment medicines to the patients are:

- The first goal is to control the symptoms, including pain, inflammation.
- Preventing damage of the joints and related structure due to the disorder.
- To reduce the RA ability and helps in maintaining the proper joint movement and improvisation of quality of life of a patient.
- The other is ton reduce long term complications for the patient and burgeoning the joint movement for longer period of time.

First-line treatment:-

NSAIDs AND Corticosteroids-

First-line therapy aims to reduce inflammation and relieve discomfort generally. Pain relief and reduced inflammation are the two main objectives of first-line therapy.[21], [22], [40] Non-steroidal anti-inflammatory drugs (NSAIDs), which include acetylsalicylic acid (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and ketorolac, are medications that are regarded as fast-acting (Iodine). [40], [41] because as its ability to suppress prostaglandins, aspirin is a potent anti-inflammatory for disorder when given at high doses. One of the earliest NSAIDs used to treat joint pain is this one. [23], [40], [42] Tinnitus, hearing loss, and gastrointestinal intolerance are a few of the side effects of aspirin when used in excessive amounts. Aspirin is not the only NSAID; other NSAIDs are also equally effective and more recent additions to the market. [27], [43]–[45] these medications also need fewer daily doses. Prostacyclin, thromboxane, and prostaglandins are not produced when NSAIDs are taken because they suppress cyclooxygenase. Abdominal discomfort, stomachaches, ulcers, and other common adverse effects.[36], [38], [46], [47]

Corticosteroids:

These medications are more powerful than NSAIDs as an anti-inflammatory, but they have greater side effects. So, these are prescribed at low doses and only for a shorter period of time, during worsening or flares of RA. [40]For the local inflammation symptoms, the corticosteroid injections could be used intra-articular. These steroids works by decreasing the action of eosinophils action by preventing the release of phospholipids that results in reduction in inflammation. These medications have side effects of bone thinning, weight increase, diabetes, and immunosuppression. So, vitamin D supplement and calcium tablets are advised to the patient so as to prevent the thinning of bones. After the, improvement in the patient's condition the dose can be tapered gradually so as to reduce the side effects. The continuous dose of steroids must

not to be discontinue suddenly because this may results to suppression of hypothalamic-pituitary-adrenal axis-(HPA) or flares of RA.[12], [24]–[26]

Opioid Analgesics

Opioids like codeine, dextropropoxyphene, and tramadol can be useful in short-term management of pain due to rheumatoid arthritis but the risks passes the benefits [17]. They advise considering different analgesics initially. A recent study published as Cochrane review included 11 studied that included 672 patients fulfilling the required quality criteria out of these studies 4 studies evaluate the success of single opioid doses and also, these studies reveals that opioids reduce more pain than the placebo. But there are very less evidence of use of opioids in treatment of Rheumatoid arthritis and hence, they are not much preferred as a treatment compliance [51].

Second-Line Management: Disease-Modifying Anti-Rheumatic Drugs

Promote remission by reducing or stopping the increase as joint damage. Medication is said to be slow-acting if it takes weeks or months to start working DMARDs are slow-acting drugs that show their effect after a long duration of time. Disease-modifying anti-rheumatic medications (DMARDs) can also lessen the possibility of getting lymphoma, which is connected to RA.

The DMARDs

These are the agents that modify the progression of disease these are also known as (SAARDs) slow-acting anti-rheumatic drugs. The DMARDs are classified the two types. Non-biological Conventional synthetic (CS DMARDS) is a small molecule drug. These drugs are Immunosuppressant are Methotrexate, Azathioprine, and Cyclosporine, and other immunomodulators are Sulfasalazine, Hydroxychloroquine, Chloroquine, leflunomide, and Tofacitinib. DMARDs are considered to be the best treatment for RA. A study conducted in Dutch for a duration of 17 weeks with immediate start of DMARDs. Constant therapy with DMARD methotrexate (MTX), resulting in decreased mortality by 60% in comparison with patient not taking MTX. [53]

Non-Biological DMARDs:

It is the medicine types that are made using chemical or are prepared in the laboratories. This include the various drugs such as methotrexate, leflunomidde, sulfasalazine, HCQ and Gold salt etc. Methotrexate being an initial second line treatment or an anchor drug and an analog to the folic acid that completely inhibits the dyhydrofolic acid binding from the enzymes which are responsible for changing FH-2 to folinic acid [FH-4]. Folic acid supplement can decrease the side effects of MTX. Also, the drug can be given in flexible doses as per the needs. So, this is the best preferred medicine for the disorder. On the other hand, HCQ that is antimalarial drug can be used in long term treatment of RA as it decrease monocyte secretion derived pro inflammatory cytokines. It causes side effects likewise, GI tract, skin etc. Sulfasalazine is used as combination

doses with other DMARDs but the mechanism of action is unknown of that of azulfidine. This drug is consumed less and mostly the patient have allergies with sulfa are not prescribed with the drug. [52]

Biological DMARDs:

These are the recombinant proteins or monoclonal Anti-bodies these derived from living organisms. They are considered to be defined and target treatment method. But it is less preferred because of its more serious side effects as compared to the non-biological DMARDs such as increased risk of infection.[52] TNFα-Ihibitorsar drugs ETAnercept, Infliximab, Adalimumab, and other biological drugs are Ankianra, Abatacept, and rituximab. [22] [23]

SURGERY: After the failure of all non-surgical treatments in controlling the damage of joints it is then preferred as the 'end stage' and the patient needs the surgical treatment [26]. The evaluation of surgical treatment is done that is based on customized needs because there are many types of surgeries. For e.g. tenosynovectomy for hands, knee replacement, etc. [25]

Most 10 drugs are prescribed RA Adalimumab (Humira) is a biological medication for injection under the skin the initial dose will be administered to the patient. After then, the normal dose is self-administered once a week or every other week. A COX-2 inhibitor is a type of NSAID, and celecoxib (Celebrex) belongs to this class. Patients should normally take this capsule with food once or twice a day. ETAnercept (Enbrel) is a self-administered biologic that is injected under the skin once or twice a week. Plaquenil (hydroxichloroquine) is a DMARD. It comes in tablet form, which patients typically take once a day with food. The physician could advise dividing the dose to be taken twice daily for greater doses. The patient typically takes leflunomide (Arriva), another DMARD, once a day. During the initial few days of treatment, the doctor may instruct the patient to take it more frequently. For RA, methotrexate (Rheumatrex, Trevally) is a DMARD that works quite well. It can be obtained as a pill or an intramuscular injection. To reduce adverse effects, the doctor typically recommends a weekly dose [47]. A corticosteroid is a methylprednisolone (Medrol). The oral pill dosage might range from once daily to multiple times daily. The dosage range may be reduced by the doctor by checking the patient's health. Another corticosteroid is Prednisone (Deltasone). Both a pill and an oral solution are available.[46] The typical dosage is one time per day up to four times per day with food. Sulfasalazine (Azulfidine) is an oral DMARD. It acts by delayed-release of tablet to reduce the stomach irritation. The patient should take the tablet after the meal with glass of water.[41] Doctors usually begins at low doses and increase to max. Dose by giving tablets twicly per day [27], [34], [40], [43][21]–[23], [40], [43]

EXERSISES:

According to the German general guidelines on early RA management patients are recommended regular dynamic exercise to enhance endurance and strength that directly help in improvising the working of the joints. [48], [49] Warm up must be done so as to maintain the joints working by

rubbing the joints continuously by the palm of hands. Yoga must be preferred by the patients as it is the most effective method for improvisation of the joints working.

CONCLUSION:

The drug used in treating RA was found to be primarily NSAIDs, Corticosteroids, DMARDs, and opioid analgesics (not used much). The first line is NSAID (aspirin, naproxen), Corticosteroids, which give relief to pain and decrease swelling as these class drugs are prescribed as symptomatic relief to the patient whereas DMARDs are the second line of treatment that reduces joint damage and slower or stops further damage to the joints such as MTX, HCQ, Leflunomide etc. and these are proper treatment to DMARDs and the other treatment is a biological treatment that includes Rituximab, Ankianra. The last option remains for the surgery. Also with that, non-pharmacological therapy such as exercises, yoga, meditation etc. are much beneficial for the patient that must be continued or counsel about to the patient by the pharmacists or physician. [DOI: 10.20959/wjpps20164-6406] Thus, DMARDs are mostly prescribed and have the best effect mainly methotrexate, HCQ, etc.

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