IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
January 2020 Vol.:17, Issue:2

A Review on Rheumatoid Arthritis and Current Trends of Methotrexate in Arthritic Management

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

PRADNYA N. JAGTAP*[1], PALLAVI S. SHELKE[2], RAVINDRA Y. PATIL[3]

[1]HOD of Pharmacology Department, PDEA's S.G.R.S. College of Pharmacy, Saswad.

[2]Student of M Pharm 2nd Year, Pharmacology Department, PDEA's S.G.R.S. College of Pharmacy, Saswad.

[3]The Principal of PDEA's S.G.R.S. College of Pharmacy, Saswad.

Submission: 25 December 2019
Accepted: 31 December 2019
Published: 30 January 2020

Keywords: Rheumatoid Arthritis; Arthritic potential; DMARD's; Management; Methotrexate

ABSTRACT

Rheumatoid arthritis is a chronic multi-auto system disease of unknown cause. It affects the people in their prime of life, predominantly between the ages of 20-50 years with an unpredictable course. However, in general, it leads to the destruction of the tissues within joints and consequent physical disability in the greater majority, if unchecked. Methotrexate (MTX) is a type of disease-modifying anti-rheumatic drug (DMARD) most popularly used nowadays. MTX therapy has been a major advance in the treatment of rheumatoid arthritis and is now the cornerstone of therapy. Without disease-modifying therapy, patients with this disease do not enjoy adequate health-related qualities of life nor a normal life. This review provides a scientific perspective regarding the development of MTX and why it has become the most popular drug in the world for the management of rheumatoid arthritis (RA).

HUMAN JOURNALS
www.ijppr.humanjournals.com

INTRODUCTION

Rheumatoid arthritis is a chronic, systemic, inflammatory disease of unknown etiology that affects connective tissue[1]. Although joints are the primary target of rheumatoid arthritis, extra-articular manifestations can have a significant impact on other organ systems. This autoimmune disorder affects approximately 1.5- 2% of the population worldwide, making it the most common form of inflammatory arthritis. Rheumatoid arthritis typically has an insidious onset that occurs between 20-50 years of age in 80% of patients[2]. It tends to run in families and occurs more commonly in women than in men (~3:1 ratio). The content of this review has been taken from various journals archiving services such as PubMed, Science Direct, Springer, and Scopus. The search criteria were provided to recent research in arthritic management & understanding it's a pathology [3].

1. Etiology :

The cause of rheumatoid arthritis is unknown. It has been suggested that it might be a manifestation of many factors like hereditary, environmental, possible infectious agents like mycoplasma, rubella virus which has convincing evidence [4]. One possibility is a persistent infection of articular structures or retention of microbial products in synovial tissue which induce an immune response to components of the joint by altering its integrity and revealing antigenic peptides. Here micro-organism linked because bacteria express reactivity to type II collagen and heat shock proteins. Recent evidence is that micro-organism might prime the host to cross-reactive determinants within joints and similarity between products of certain gram-negative bacteria and HLA-DR molecules supports the possibilities. Finally, the products of infecting micro-organisms might induce the disease but still the role in the etiology of rheumatoid arthritis remaining speculative [5].

2. Pathophysiology :

It is currently believed that RA is triggered by exposure of an immunogenetically susceptible host to an arthritogenic microbial antigen, by this continuing autoimmune reaction, the activation of $CD4^{+}$ helper T cells, and local release of inflammatory mediators which destroys joints[6].

An increase in several synovial lining cells causes lesions in rheumatoid synovitis along with perivascular infiltration with mononuclear cells which projects to oedematous and protrudes

into joints cavity as villous projections [7]. The inflamed synovium becomes hypertrophied, hyperplasia including microvascular injury, thrombosis and neovascularization edema and infiltration with mononuclear cells, often collected into aggregates around small blood vessels. Synovial endothelial cells increase adhesion molecules in the process. The predominant infiltrating cell is T-lymphocyte $CD4^+$ Tcells predominate over $CD8^+$Tcells which is proximity to HLA-DR^+ macrophages and dendritic cells. These CD4, CD8, T cells activate antigen CD69. Besides this, infiltration of B cells that differentiate locally into antibody-producing plasma cells, this produce polyclonal immunoglobulins and auto anti-body result in the formation of immune complexes. Synovial fibroblasts manifest enzymes such as collagenase and cathepsins, that can degrade articular matrix1. Some of the mediators which bring about destructive-proliferative synovitis which includes, cytokines, tumor necrosis factor α, IL-1, IL-6, IL-5, interferon-γ, TGFP, GM-CSF. TNF α and IL-1 upregulate the expression of adhesion molecules by endothelial cells, resulting in the accumulation of white cells in synoviums[8].

3. Signs & Symptoms :

Signs and symptoms of rheumatoid arthritis may include:

- Tender, warm, swollen joints
- Joint stiffness that is usually worse in the mornings and after inactivity
- Fatigue, fever, and loss of appetite

Early rheumatoid arthritis tends to affect your smaller joints first — particularly the joints that attach your fingers to your hands and your toes to your feet. As the disease progresses, symptoms often spread to the wrists, knees, ankles, elbows, hips, and shoulders. In most cases, symptoms occur in the same joints on both sides of your body [9].

4. Causes :

Rheumatoid arthritis occurs when your immune system attacks the synovium - the lining of the membranes that surround your joints. The resulting inflammation thickens the synovium, which can eventually destroy the cartilage and bone within the joint. The tendons and ligaments that hold the joint together weaken and stretch. Gradually, the joint loses its shape and alignment [10].

5. Autoimmune Arthritic Classification:

Osteoarthritis

This is the most common chronic degenerative form of arthritis. It is most commonly affected by age and results in the softening, fraying and eventual breaking of joints and bones. Over time these broken down joints and bones thicken with the build-up of extra bone tissue. The joints fuse with bone spurs and movement is restricted [11].

Rheumatoid arthritis

Beginning to affect individuals between the ages of 30-60 (and on average affecting three times as many women as men) rheumatoid arthritis works symmetrically, affecting the function and health of the fingers, wrists, feet, and ankles. The synovial fluid that encases the joints becomes inflamed, eventually leading to the thickening of the membrane, growth of the joint cavity and fusion of bone ends leading to joint and bone deformity[11]. Symptoms of this autoimmune disease include; joints are painful, warm and swollen, stiffness, fatigue, weight loss and general weakness[12].

Gouty Arthritis

This form of arthritis mainly affects the feet though sometimes it may have an effect on the fingers, hands, and wrists as well as knees. The inflammation occurs as a result of increased uric acid levels in the body, which are often due to too much being produced, or too little being excreted from the body[13].

Ankylosing spondylitis

This form of arthritis results in the fusion of the vertebrae of the spine, resulting in a less flexible spine and a posture that is hunched. It begins to affect the individual in early adulthood (mainly men). When the disease becomes very severe there can be complications with eye inflammation, heart health and compression fractures[14].

Lupus

This form of arthritis affects far more than just the joints of the body, it can affect the skin, kidneys, lungs, blood, cells, heart and brain. The disease often mimics symptoms of

other illnesses (such as rashes) so it can be tricky to diagnose. Some of the symptoms include; a butterfly-shaped rash on the face, joint pain, fatigue, chest pain and dry eyes[15].

Sjogren's syndrome

This form of arthritis can develop at any age but is often diagnosed later in life. Its main symptoms are dry eyes and mouth. Other symptoms include joint pain, swollen salivary glands, persistent coughing and vaginal dryness[14].

Reiter's syndrome (or Reactive Arthritis)

This form of arthritis affects the joints of the body as well as, the urethra, eyes, and skin. Caused as a result of an infection or sexually transmitted disease. It is most common amongst sexually active men between the ages of 20-40[15].

6. Important Risk Factors for Developing Rheumatoid Arthritis[16,17]

- Female gender; the impact of the X chromosome, microchimerism, lifestyle
- Age; associated with accelerated immune aging
- Inheritance of genetic variants, e.g., HLADRB1 and PTPN22
- Autoantibodies to citrullinated protein antigens (ACPAs), rheumatoid factor
- Family history; first-degree relatives have a higher prevalence of genetic and serological risk factors
- Hormonal factors; nulliparity, the first 3 months postpartum, low androgen or high estrogen status (in males); longer-duration breastfeeding
- Smoking status; >25 cigarettes/day for >20 years confers a 15-fold risk in subjects who carry disease-associated human leukocyte antigen (HLA)-DRB1 alleles
- Low alcohol intake
- Environmental antigens (the "exposome"); dietary factors; exposure to infectious (and noninfectious/microbiota) pathogens at mucosal surfaces such as the lung, periodontium, and gut; noninherited maternal antigens (NIMA)

7. Complications: Rheumatoid arthritis increases your risk of developing[18]:

- **Osteoporosis.** Rheumatoid arthritis itself, along with some medications used for treating rheumatoid arthritis, can increase your risk of osteoporosis — a condition that weakens your bones and makes them more prone to fracture[11].

- **Rheumatoid nodules.** These firm bumps of tissue most commonly form around pressure points, such as the elbows. However, these nodules can form anywhere in the body, including the lungs.

- **Dry eyes and mouth.** People who have rheumatoid arthritis are much more likely to experience Sjogren's syndrome, a disorder that decreases the amount of moisture in your eyes and mouth.

- **Infections.** The disease itself and many of the medications used to combat rheumatoid arthritis can impair the immune system, leading to increased infections[17].

- **Abnormal body composition.** The proportion of fat to lean mass is often higher in people who have rheumatoid arthritis, even in people who have a normal body mass index (BMI).

- **Carpal tunnel syndrome.** If rheumatoid arthritis affects your wrists, the inflammation can compress the nerve that serves most of your hand and fingers.

- **Heart problems.** Rheumatoid arthritis can increase your risk of hardened and blocked arteries, as well as inflammation of the sac that encloses your heart.

- **Lung disease.** People with rheumatoid arthritis have an increased risk of inflammation and scarring of the lung tissues, which can lead to progressive shortness of breath.

- **Lymphoma.** Rheumatoid arthritis increases the risk of lymphoma, a group of blood cancers that develop in the lymph system[17].

8. New development in imaging for diagnosis in rheumatic disease[19]

The availability of therapeutic modalities that can stop inflammatory joint damage has also markedly influenced recent developments in musculoskeletal imaging. One focus of interest is the detection of joint pathology as early as possible to prevent erosive bony changes ultrasonography and magnetic resonance imaging are the most valuable technologies. In addition to these recent advances in peripheral and axial joint imaging.

Radiography [19]

X-ray as Rontgen called, conventional radiography is still the most relevant imagining technology for the assessment of rheumatic disorders. Knowledge about the pathological alterations that are visible on plain radiographs. The differentiation of inflammatory and degenerative process and the combination is important to determine the pattern of joint involvement. However, in many rheumatic diseases, valuable additional diagnostic information can be obtained from joint radiographs.

Magnetic resonance imaging (MRI) [19]

MRI allows excellent imaging of intra and periarticular soft tissue structures and pathophysiological concepts of inflammation. For peripheral joints, the development of MRI-units has been a major advantage. The information about synovitis, erosions and bone edema obtained with these smaller, transportable machines appears and the advantage of smaller units is lower costs, easier patient positioning and elimination of potential contraindication, such as claustrophobia (or) metal implants. This gives ample evidence that synovitis changes demonstrated by MRI are prerequisites for joint damage. Also used in the assessment of atlantooccipital and atlantoaxial inflammation, an extremely helpful and sometimes life saving diagnostic modality.

Inflammation of sacroiliac joints, vertebral bodies, intervertebral discs, vertebral joints and enthuses are visible on MRI before they develop into the bony lesions seen on conventional radiographs.

Sonography [19]

Sonography is the other imaging technology that gives excellent information about soft tissue pathology in the musculoskeletal system. This provides information and procedure for detecting pathological findings of the musculoskeletal system in rheumatic disease. The availability of equipment using frequencies of 10MHZ with modern equipment, it is possible to see the minute amount of fluid in a healthy tendon sheath allowing tendon movement without friction or to identify single tendon fibrils, justifying the term acoustic microscopy.

Nuclear medicine [19]

Another imaging method has the potential to predict rheumatic joint destruction long before this becomes visible on plain radiographs. Increased tracer uptake in three-phase bone has been shown to proceed erosions by years radiolabelled polyclonal human immunoglobulins accumulate in inflamed joints and allow the scintigraphical imaging of synovitis. The availability of single-photon emission computed tomography (SPECT) for data acquisition and processing helped for indications such as avascular necrosis.

9. Management of disease

Non-steroidal anti-inflammatory drugs (NSAID)

The first class of drugs used to treat rheumatoid arthritis is NSAID. These are agents having analgesic and anti-inflammatory effects but are believed to not be capable of preventing erosions or altering the progression of the disease [20]. Several NSAIDs available include ibuprofen, naproxen, indomethacin, piroxicam, diclofenac, meclofenamate sodium, etc. These drugs relieve pain and inflammation. But the major side effects of nonselective NSAIDs, are significant damage to the upper and lower gastrointestinal tract [21]. However, to minimize side effects, Cox-1 and Cox-2 inhibitors is the choice of drug namely celecoxib and rofecoxib.

Disease-modifying antirheumatic drugs (DMARD's):

These are a major class of drugs used to treat and should be considered as early as possible once a diagnosis has confirmed. It slows the progress of the disease. The commonly used 'DMARD' are methotrexate, hydroxychloroquine, sulfasalazine, and leflunomide. These drugs thought to influence the abnormalities of the immune system responsible for the disease[22].

Biological response modifiers:

These are the newest rheumatoid arthritis medications that interfere with the autoimmune response in RA. These drugs are genetically engineered to target the immune factor known as cytokines, (particularly tumor necrosis factor) proteins of body immune system that trigger inflammation during a normal immune response and certain interleukins that play a major role in the destructive. RA process and helps in reducing structural damage to the joint. The

drugs include are, intercept, infliximab, anakinra, and adalimumab. These drugs are the most powerful and make patients less susceptible to infection. The high cost of these drugs may prohibit many by using them[23].

Others

a) Corticosteroids:

These are hormones effective in treating inflammation but can cause many side effects. Prednisone is the corticosteroid given orally for rheumatoid arthritis Corticosteroids are given by injection into the affected joint to stop the pain, only once (or) twice a year because it may cause damage to the cartilage [24].

b) Gold salts:

These are effective when methotrexate cannot be tolerated, used for the erosive disease but contraindicated in hepatic, renal, hematopoietic, dysfunction[21].

c) Another new treatment is a device called the prosorba column. It mechanically removes inflammatory antibodies from the blood. The blood is removed from the body through the catheter (a process called apheresis) and then passes through a column coated with a substance called protein A, which binds the antibodies. The blood is then returned to patients[21].

Table No. 1: Currently used rheumatoid arthritis medications along with their uses, side effects and monitoring requirements [25,26]

Medications	Uses	Side Effects	Monitoring
Analgesics & NSAIDs	Analgesics relieve pain. NSAIDs relieve pain and inflammation	Upset stomach, peptic ulcer, bleeding, renal failure, NSAIDs many increases in the rate of miscarriage for pregnant women	For all traditional NSAIDS, Doctor wants to the council about patients habits, (or)Previous medications
Traditional NSAIDs, Ibuprofen, Ketoprofen, Naproxen	Reduce pain & Inflammation	Abdominal cramp, pain, discomfort diarrhea, dizziness	-Do-
Corticosteroids	Reduce pain and inflammations,	Increase appetite, indigestion,	For corticosteroid therapy, doctor councils

	redness, itching and allergies	nervousness or restlessness	for any fungal infection, tuberculosis, herpes simplex of the eye, blood pressure.
Methylprednisolone, prednisone	Available as a pill form or injection into the joint. Improvement was seen in several hours up to 24 hrs. used when the disease does not respond to NSAIDs.	Osteoporosis, mood changes, fragile skin, easy bruisons, weight gain, muscle weakness, risk increased disk of Infection	Monitoring for continued effectiveness and for side effects is needed.
Disease-modifying antirheumatic drugs (DEMARD'S)	Relieves pain in swollen joints. Slows joint damage and take a few weeks or month to affect.	Increase the risk of infection, hair loss, kidney or liver damage	Monitoring reduces risk of toxicities.
Biological response Modifiers	Selectively block parts of the immune system called cytokines.	Increased risk of infection especially tuberculosis, pneumonia, listeriosis (foot born illness) caused by a bacterium.	Avoid eating undercooked foods, because, it may cause listeriosis
Gold sodium Thiomalate	One of the 1st DEMAND to treat Rheumatoid arthritis.	Redness or soreness of tongue, swelling or bleeding.	Counseled for lupus skin rashes, kidney disease, colitis.
Eg. Leflunomide	Reduces signs, symptoms, slow structural damage to joints.	Bloody, cloudy, urine, congestion in chest, cough, diarrhea, burning, painful urination.	Before taking this Medication counseled for immune deficiency, renal insufficiency or underlying malignancy.
Sulfasalazine	Reduces the signs and symptoms by suppressing immune system.	Abdominal pain, aching joints, diarrhea, sensitivity to sunlight, loss of appetite.	Monitored, by counseling for allergen to sulphas or aspirin, Kidney or liver blood disease.
Interleukin inhibitor Anakinra	Given daily injections long term efficacy and safety are uncertain	Redness, swelling, bruising or pain at site of injection, headache, stomach upset, running nose.	Doctor monitoring is required.

Table No. 2: Herbal drugs used in rheumatoid arthritis [27]

Drug Name	Uses	Company Name
Sallaki tablets	Osteoarthritis, myositis, fibrositis, effective herbal treatment for musculoskeletal disorder.	Gufic Bioscience Ltd.
Rumanyl Capsules	Osteoarthritis, and musculoskeletal disorders.	Charaka pharma Pvt. Ltd.
Rumalaya forte tablets	Gout, arthralgia, osteo arthritis, cervical and lumbar spondylosis, frozen shoulder.	Himalaya herbal health Care.
Rumedap with gold	Used in joint pain, backache, sciatica and muscle spasm.	Bajaj consumer care Ltd.
Arthur care tablets	Joint pain, osteoarthritis and muscle spasm.	Sami labs.
Arthnexforte tablets	In articular inflammatory disease, musculoskeletal inflammatory conditions.	Sagar pharmaceuticals herbal health care division.

10. Methotrexate

Methotrexate is one of the most effective and widely used medications for treating **rheumatoid arthritis (RA)**and other inflammatory types of arthritis. It's also one of the safest arthritis drugs, insist rheumatologists, despite a common misconception among many patients and even some primary care physicians that methotrexate is highly toxic[28].

Table No. 3: Description of Methotrexate

Molecular Wt.	454.44g/mol
Molecular formula	$C_{20}H_{22}N_8O_5$
Dose	15 to 30 mg daily
Solubility	Soluble in alkali hydroxide and carbonates
Routes of administration	Oral, IV, IM, SC, Intrathecal

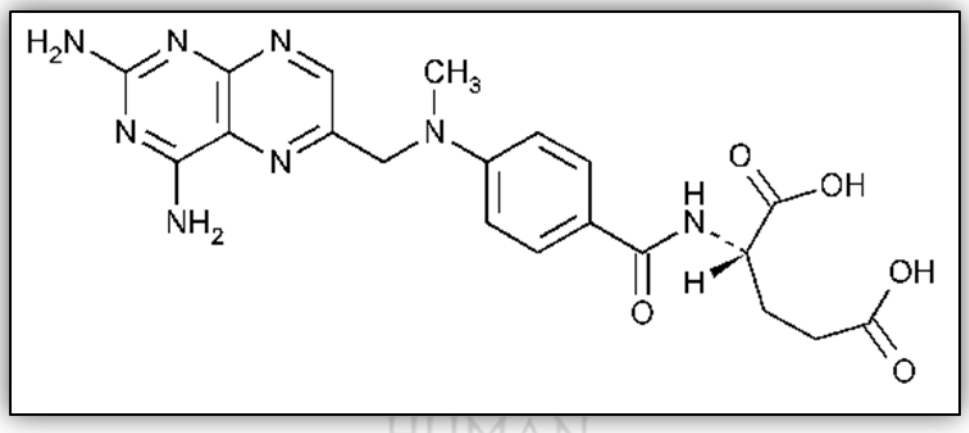

Fig 1: Structure of Methotrexate

Table No. 4: Pharmacokinetics

Bioavailability	60% at a lower dose, Less at higher dose
Protein binding	35-50% (Parent drug)
Metabolism	Hepatic and Intracellular
Half-Life	3-10 hrs (lower dose), 8-15 hrs (higher dose)
Excretion	Urine (80 – 100 % Faces (small amount)

Confusion about this important medication's safety profile seems to exist because it is also used – in much higher doses – for treating some forms of cancer. Most patients who use methotrexate to treat their inflammatory arthritis take between 10 and 25 milligrams (mg) per week. By contrast, the doses used to treat leukemia and certain other types of cancer may be hundreds of times larger.

That's not to suggest that taking methotrexate is risk-free. A 2009 review of 21 studies found that 73 percent of RA patients who used the medication experienced at least one side effect. Yet the study indicates that most of these problems were relatively minor. What's more, doctors who prescribe methotrexate for arthritis say that following a few simple steps can make this drug even safer to use[29].

Folic Acid Is a Must

Understanding how methotrexate works help explain why it can cause unwanted effects. Researchers originally developed Stabilization of hydrochlorothiazide nanocrystals using fibroin methotrexate in the 1940s as a cancer drug. It stops malignant (or cancerous) cells from rapidly multiplying and spreading by blocking their access to folate, a form of vitamin B, which these cells need to survive.

Unfortunately, depleting the body of folate can affect healthy cells, too, especially those in the gastrointestinal (GI) tract, mouth, hair follicles, and liver.

GI problems such as nausea and vomiting are the most common side effects associated with methotrexate, affecting between 20 and 65 percent of RA patients who take the drug. While hair loss is a relatively uncommon side effect in patients who take methotrexate at such doses, up to one third develop mouth ulcers or sores. Many also complain of headaches, fatigue and an overall "blah" feeling – sometimes called "methotrexate fog" – that can occur a day after receiving a dose of methotrexate (which is taken in pill form or injected once a week).

The good news: These side effects can often be short-circuited by taking a folic acid supplement. Folic acid is the synthetic form of folate. One study found that RA patients on methotrexate who took folic acid supplements lowered the risk of GI problems and mouth sores by 79 percent[30].

A few additional steps may help prevent or relieve GI and oral problems[29]:

- **Split the dose.** Most arthritis patients take methotrexate orally, in a dose consisting of several pills. Some find that splitting the dose eases GI side effects; take half the pills in the morning and the other half 12 hours later, preferably with food.

- **Ask about medication.** For very severe stomach queasiness, your doctor can prescribe an anti-nausea drug such as ondansetron (Zofran).

- **Swap your pills.** When nothing else helps, switching from oral methotrexate to the injectable version can eliminate GI distress.

- **Try a rinse.** To relieve painful mouth sores, a salt-water rinse or special mouthwash containing lidocaine (a pain reliever) may help.

Protecting the Liver

Since methotrexate blocks folate, taking folic acid – the manmade version of the vitamin – might seem like it would be counterproductive. However, methotrexate appears to relieve pain and other RA symptoms through actions that are largely unrelated to folate. Investigators discovered that methotrexate causes cells to release a molecule called adenosine, which blocks other chemicals that promote inflammation[31].

Fighting inflammation helps relieve painful, swollen joints. But it is also noted that adenosine causes fibrosis, or buildup of scar tissue, in the liver; over time, that could result in liver disease. It is important to note that alcohol also releases adenosine in the liver. In rare cases, methotrexate users may develop fibrosis and inflammation in the lungs, though this is unlikely to be related to adenosine release[32].

Regular blood tests are also necessary to detect signs of other problems that can arise in methotrexate users, including a drop in white blood cells, which normally guard against infections. Also, some people experience a dip in the production of blood platelets, which could cause abnormal bleeding. However, these changes in the blood often go away if you stop taking the drug temporarily (which should only be done under a doctor's supervision)[33].

SUMMARY

Present world scenario and growing evidence of clinical reports suggest that RA can no longer be considered as a benign disease rather it is a major health concern. Presently, a variety of antirheumatic drugs (DMARD's) are available to control the disease process of RA. The most commonly prescribed (at least 500,000 patients with RA) drug is methotrexate (MTX). This review article is focused on rheumatoid arthritis, its pathophysiology,

classification of anti-rheumatoid drugs and also discussed on Methotrexate current importance related to the management of arthritis in the pharmacy field.

REFERENCES

1. Harisons, Principles of Internal medicine, 14th edition, Library of Congress cataloguing publishers, 1998.
2. Science Direct Best Practice and Research clinical rheumatology. The treatment of rheumatism. Available from: www.science direct.com/science?-ob-article URL & udi = B6WBJ-4DIMFY4-5L-US, (Access Date: 31/12/2019).
3. www.sciencedirect.com/.../rheumatoid-arthritis.
4. Van der Heijde DM. Joint erosions and patients with early rheumatoid arthritis. Br J Rheumatol. 1995;34(suppl 2):74–78.
5. Schoels M, Wong J, Scott DL, et al. Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. Ann Rheum Dis. 2010;69:638– 643.
6. Iain B. McInnes, Georg Schett. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;365:2205–19.
7. Kelly JC. Rheumatoid arthritis: Updated recommendations released. Medscape Medical News. Available at http://www.medscape.com/viewarticle/845495. May 28, 2015; Access Date: 30/12/2019.
8. Williams RC, Jr Autoimmune mechanisms involved in the pathogenesis of rheumatoid arthritis. Adv. Dent. Res. 1996;10(1):47-51.
9. Hafstrom, I. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens. Rheumatology,40(10),2001, 1175-1179.
10. Prior P, Symmons DP, Scott DL, Brown R, Hawkins CF. Cause of death in rheumatoid arthritis. Br J Rheumatol. 1984 May;23(2):92–99.
11. Affleck, G., Tennen, H., Keefe, F.J., Lefebvre, J.C., Kashikar-Zuck, S., Wright, K., Starr, K. & Caldwell, D.S. Everyday life with osteoarthritis or rheumatoid arthritis: independent effects of disease and gender on daily pain, mood and coping. Pain, 83, 1999, 601-609.
12. Quandt, S. A., Chen, H., Grzywacz, J. G., Bell, R. A., Lang, W., & Arcury, T. A. Use of complementary and alternative medicine by persons with arthritis: Results of the National Health Interview Survey.Arthritis & Rheumatism,53(5),2005, 748-755.
13. Joshi VR. Rheumatology, past, present and future. J Assoc Physicians India 2012;60:21.
14. Zeidler H. Systemic literature review of the performance of the 2010 ACR/ EULAR classification criteria for rheumatoid arthritis: good news of debatable significance. Ann Rheum Dis 2013;72:87.
15. Fifield, J., McQuillan, J., Tennen, H., Sheehan, T.J., Reisine, S., Hesselbrock, V. & Rothfield, N. History of affective disorder and the temporal trajectory of fatigue in rheumatoid arthritis. Annals of Behavioral Medicine, 23 (1),2001, 34-41.
16. Scott IC, Seegobin SD, Steer S, et al. Predicting the risk of rheumatoid arthritis and its age of onset through modelling genetic risk variants with smoking. PLoS Genet 2013;9:1003808.
17. Hu, Y., Costenbader, K. H., Gao, X., Al-Daabil, M., Sparks, J. A., Solomon, D. H., Lu, B. Sugar-sweetened soda consumption and risk of developing rheumatoid arthritis in women.American Journal of Clinical Nutrition,100(3),2014, 959-967.
18. Heinlen L, Humphrey MB. Skeletal complications of rheumatoid arthritis. Osteoporos Int. 2017;28(10):2801-2812.
19. Bernhard Manger MD Prof. of Rheumatology.Available from: www.science direct.com (Access Date: 28/12/2019).
20. David B, Hellman MD, John H Stone MD. Arthritis and musculoskeletal disorders.Available from: www.Current-med.com.
21. Smolen JS, Landewe R, Breedveld FC, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological diseasemodifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492– 509.

22. O'Dell JR, Curtis JR, Mikuls TR, et al. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. Arthritis Rheum. 2013;65:1985.
23. Callhoff J, Weiß A, Zink A, Listing J. Impact of biologic therapy on functional status in patients with rheumatoid arthritisda metaanalysis. Rheumatology 2013; 52: 2127:35.
24. Duru N, van der Goes M, Jacobs J, et al. EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases. Ann Rheum Dis 19 July 2013; http://dx.doi.org/10.1136/ annrheumdis-2013-203249.
25. Chen YF, Jobanputra P, Barton P, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib, and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technol Assess 2008; 12: 1–278.
26. Donahue KE, Gartlehner G, Jonas DE, et al. Systematic review: comparative effectiveness and harms of disease-modifying medications for rheumatoid arthritis. Ann Intern Med 2008; 148: 124–34.
27. Khanna D, Sethi G, Ahn SK., Pandey MK, Kunnumakkara AB, Sung B et al. Natural Products as a gold mine for arthritis treatment. Current Opinion in Pharmacology. 2007; 7(3): 344–351.
28. Suarez-Almazor ME, Belseck E, Shea B, Wells G, Tugwell P. Methotrexate for rheumatoid arthritis. Cochrane Database Syst Rev 2000; 2: CD000957.
29. Loza E, Lopez JAM, Carmona L: Is methotrexate safe in the perioperative period in rheumatoid arthritis patients? Arthritis Rheum. 58(9), S735 (2008).
30. Morgan SL, Baggott JE, Alarcon GS, Koopman WJ. Folic acid and folinic acid supplementation during low-dose methotrexate therapy for rheumatoid arthritis: comment on the article by van Ede et al. Arthritis Rheum 2002;46:1413–4.
31. Strand V, Morgan SL, Baggott JE, Alarcon GS. Folic acid supplementation and methotrexate efficacy: comment on articles by Schiff, Emery et al., and others. Arthritis Rheum 2000;43:2615–6.
32. Chakravarty K, McDonald H, Pullar T, Taggart A, Chalmers R, Oliver S, et al. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. Rheum April 2008 http://www.rheumatology.org.uk/guidelines/guidelines_other/dmard08.
33. Pavy S, Constantin A, Pham T, Gossec L, Maillefert J-F, Cantagrel A et al. Methotrexate therapy for rheumatoid arthritis: clinical practice guidelines based on published evidence and expert opinion. Joint Bone Spine 2006; 73: 388–395.