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RHEUMATOID ARTHRITIS: A REVIEW

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ABSTRACT

The process of life is related with blood and the cells present in blood, like red blood cells, white blood cells and platelets. For diagnosis of any disease blood cells and some other factors must be identified. Due to the development in technology, good resolution images are found to diagnose & confirm the disease. Rheumatoid arthritis is a chronic long lasting autoimmune disease which can weaken our immune system. It is a common inflammatory joint disease characterized by articular destruction which affects the joints, tendons & bones of the body. Most commonly the hand, wrists, and knee joints are affected. The rheumatoid arthritis is predominantly affected between the ages 20-60 years with an unsure course. About 1% of the world's population is suffering from rheumatoid arthritis. And the rheumatoid arthritis is more common in women than men by two to three times. Due to the side effects of allopathic drugs the medicinal plants are recommended. 1/4th of world's population depends on traditional medicine. There is no side effect for herbal medicine. Hints for control of rheumatoid arthritis and tracking of drug remedy had been 1st developed in 1996. Since then, there had been a predominant advance within side the remedies of rheumatoid arthritis. The purpose of this review is to spotlight the latest key advances in our understandingof rheumatoid arthritis.

KEYWORDS: Rheumatoid arthritis, Autoimmune disease, Herbal medicine, Joints, Treatment.

INTRODUCTION

Autoimmunity is found in all people to a few extents. It is usually non dangerous and a universal fact of vertebral life. However, autoimmunity may be the motive of an extensive spectrum of human illness recognized as autoimmune. About 5% of people, living in industrialized nation are affected by autoimmune disease. Out of these 80% are "auto-aggressive" diseases which are now recognized. The one of the diseases in them is rheumatoid arthritis. Rheumatic disease had been acknowledged in formative years of 5th century BC under the general word arthritis. In western countries the disease is known as Hippocrates "The father of modern medicine". The disorder became additionally recognized in India from the ancient instance and it was related as "vata vyadhi" in Ayurveda. The scientist Garrod (1859) proposed the name "Rheumatic arthritis.[1-3]

Rheumatoid arthritis is an autoimmune, inflammatory, chronic disease which can lead to several disabilities. The disease affects the joints, bones & tendons of the body. It mostly affects the wrists, knees, and hands joint. Rheumatoid arthritis results in swelling, pain, and destruction of cartilage and bone. Rheumatoid arthritis affects 0.3-1 % of the world's population, according to World Health Organization. Rheumatoid arthritis is mostly seen in women than men and women are affected three times more as compared to males. 20 to 30% people with rheumatoid arthritis disease are permanently unable to work within 2 to 3 years of diagnosis. Figure 1 depicts the normal joint and Rheumatoid arthritis affected joint.[4-6]

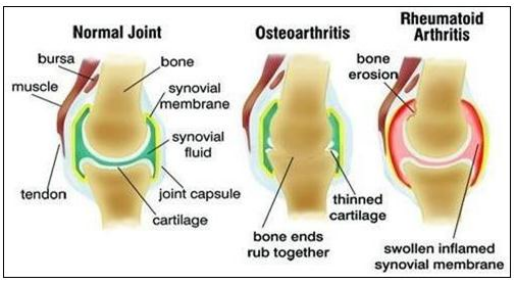

Figure 1: Normal Joint and Rheumatoid Arthritis affected Joint.

There are some laboratory tests and image studies which helps to diagnose the disease. For the treatment of rheumatoid arthritis, anti-rheumatic drugs are suggested. Also, some modifying drugs are useful to treat the diseases. The drugs like non-steroidal, anti-inflammatory drugs, corticosteroids and non-pharmacologic modalities are used for the treatment. Due to the side effects of allopathic drugs, medicinal plants are used to treat many human diseases. The herbal drugs like Harpagophytum procumbens, Bauhinia variegate, Leucas aspera, Phyllanthus amarus, Acalypha indica are used for treatment of rheumatoid arthritis. The purpose of this review is to spotlight the latest keys advances in our understanding of rheumatoid arthritis.[7]

EPIDEMIOLOGY

Rheumatoid arthritis affects almost 0.3 to 1% of the world's population. Rheumatoid arthritis is most common in females. Females are affected 3 times more than males. Current research file shows that rheumatoid arthritis activity and severity can be reduced with oral contraceptives. Women with rheumatoid arthritis can render a protecting effect because these medications are used for contraception.[8,9] Arthritis is one of the most common chronic health diseases. And it causes disabilities. In 2002, 43 million US adults are affected by arthritis. Chopra *et al*. performed a study of a village Bhigwan (Pune District, Maharashtra) in 1996, using population survey which is organized by World Health Organization – International league of associations for Rheumatology (WHO-ILAR) Community oriented program for the control of rheumatic diseases (COPCORD).[10] The rheumatoid arthritis is more common disease in smokers. It is three times more in smokers then non-smokers, specifically in men, heavy smokers, and those who are containing the positive factor of rheumatoid. An examinee in 2010 found that those who drank modest quantity of alcohol regularly were 4 times much less prone to suffer from rheumatic arthritis than those who never drunk.[11]

ETIOLOGY

Arthritis means the breakdown of cartilage. The joints are protected by the cartilage which allow the joints to move smoothly. The pathology of disease involves the destruction of the articular cartilage and alkalosis of the joints. The cause of the rheumatic arthritis is unknown but autoimmunity plays an important role in its chronicity and progression, therefore rheumatoid arthritis is a systemic autoimmune disease. The cause of rheumatoid arthritis is not known but it may depend on the mixed result of genetic and environmental factors. By using the genetic factor one can determine about 50% to 60% of susceptibilities, severity, and the phenotype of the disease. There are some non-genetic factors like ageing, acquired genomic variability, possible bacterial or viral triggers and environmental factors. Smoking is also important factor for the development of rheumatoid arthritis. Ageing is another factor responsible for the development of rheumatoid arthritis.[12-14]

PATHOPHYSIOLOGY

Rheumatoid arthritis seems to develop from a de-regulated immune reaction that ends in revolutionary synovial infection and joint destruction. Rheumatoid arthritis is related to numerous genetic and environmental elements that contributes the phenotype in specific combinations. Rheumatoid arthritis progresses via a way of immune complicated and supplement system, perpetuated through cytokines and influenced metalloproteinase. Antigen activated CD4+, t cells stimulate monocytes, macrophages, and synovial fibroblast which in turn results in the manufacturing of cytokines, Interleukin-1, Interleukin-6, TNF alpha and secretion of matrix metalloproteinase via cell surface signaling. Large number of neutrophils are present in synovial fluid, in early stage of rheumatoid arthritis. Synovial fluid contains immune complexes and they are IgG/anti IgG antigen-antibody complex. Rheumatoid factors (IgG and IgA) are fundamental pathogenic makers. Osteoclast and proteolytic enzymes cause cartilage dissolution and bone erosion in rheumatoid arthritis. Joint harm in rheumatoid arthritis starts with the proliferation of synovial macrophages and fibroblast after triggering incidents like autoimmune or infectious lymphocyte infiltrates, perivascular regions and endothelial cells proliferate & then neovascularization occur. Blood vessels within the affected joint become occluded with small clots or inflammatory cells, over time & infected synovial tissue starts to develop irregularly, forming invasive pannus tissue & this pannus invades and destroy cartilage and bone.[15-19]

ENVIRONMENTAL FACTORS

Rheumatoid arthritis is an autoimmune illness that is primarily influenced by two factors: genetics and the environment. The few historical reports of rheumatoid arthritis before industrialization suggest that changing environmental variables may play a role in its development. In rheumatoid arthritis, a thorough examination of environmental influences is critical. Cigarette smoking, occupational and atmospheric pollutants, and a variety of infectious diseases are all examples of environmental variables. Long-term smoking is a risk factor for rheumatoid arthritis, and the DBRI'S shared epitope is linked to it. The infectious etiology includes Epstein-bar virus (EBV), mycobacterium tuberculosis, Escherichia coli, proteus mirabalis, retrovirus and paravirus B19(20).

In early days, some evidences show the possible correlation between the development of rheumatoid arthritis and the exposure to occupational and atmospheric agents. Illar et al. discovered an increased risk of developing rheumatoid arthritis in electronic workers, bricklayers, concentrate workers, materials handling operator among men and assistance nurse, and attendants among women in Swedish era.[20-21]

CLASSIFICATION

Rheumatoid arthritis can be classified as:

1) Palindromic rheumatoid arthritis
2) Juvenile rheumatoid arthritis
3) Rheumatoid spondylitis
4) Ankylosing spondylarthritis
5) Osteoarthritis
6) Gout and gout arthritis
7) Infectious arthritis

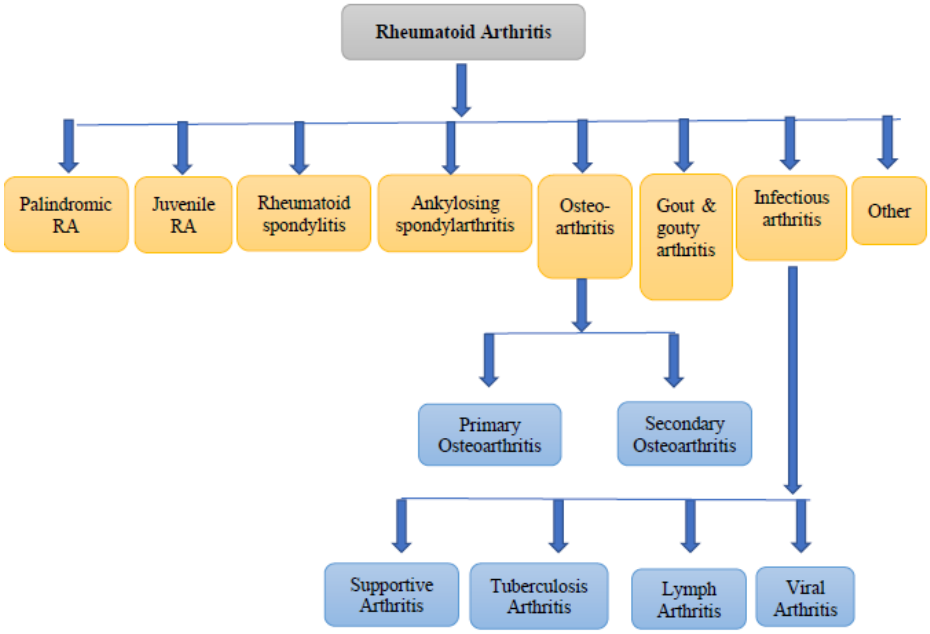

Figure 2: Classification of Rheumatoid Arthritis.

8) Other types of arthritis

Osteoarthritis – It is classified into two types

a. Primary osteoarthritis – It develops in older persons.
b. Secondary osteoarthritis – It develop at any stage.

Infectious arthritis – It is classified in four types

a. Supportive arthritis
b. Tuberculous arthritis
c. Lymph arthritis
d. Viral arthritis

Signs and symptoms

The main symptom associated with rheumatoid arthritis is the stiffness and pain at the joints. Symptoms are developed in gradual manner. The first and main symptom of our RA is observed in joints mainly at small joints, i.e., fingers and toes. Following to it, it effects to the shoulders and knee. Figure 3 represents the symptoms of Rheumatoid arthritis.[22]

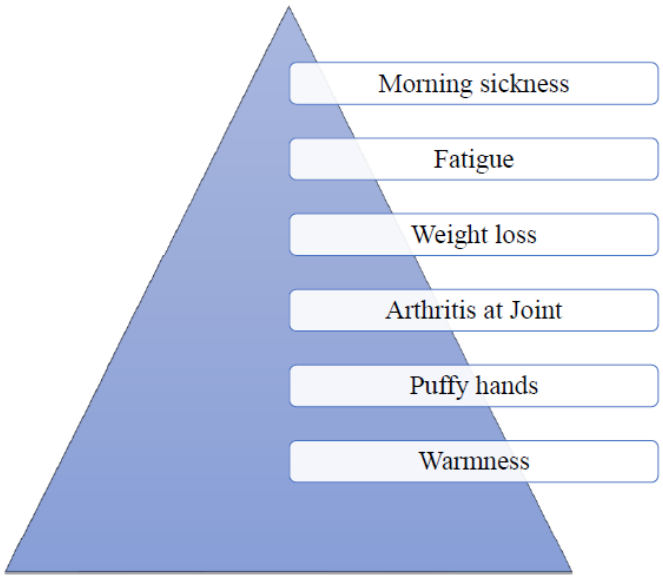

Figure 3: Symptoms of Rheumatoid Arthritis.

The main symptoms are as follows.

1. Morning stiffness: Stiffness is felt in or around the area of affected joints. This symptom longs for 45 minutes or an hour after some initiative moments of joints.
2. Fatigue: This symptom is observed in most of the patients. Feeling extreme tiredness is one among them which is caused because our body starts to use all its energy in order to fight against the inflammation.
3. Weight loss: This one is one of the early symptoms in which unexplained weight loss occurs. Tiredness and feverish causes to loss the appetite which eventually causes to loss the weight.
4. Arthritis at joint: The fluid filled or swelling of soft tissue is observed. This occurs at three or more joint areas mainly at Proximal interphalangeal (PIP), Metacarpophalangeal (MCP), Metatarsophalangeal (MTP) and also at wrist, elbow, knee, ankle as well.
5. Puffy hands: Swollen or puffed hands is signed at some patients of RA, which is due to increased flow of blood towards the inflamed area.
6. Warmness: RA joints are boggy, tender to touch and are warmer. As the flow of blood is increased at affected joints, it causes the rise in temperature of the site.

DIAGNOSIS

Diagnosis is one of the main steps in detecting any diseases. By studying the symptoms shown by the body of patients, it can be assumed but can't be confirmed. Hence, to make confirmation of any disease, diagnosis or check-up is necessary. When it comes to RA, it is difficult to assume by studying its symptoms because the symptoms of RA in its early stage make mimic to many other diseases. Hence Blood test becomes the major diagnosis which gives accurate condition and helps in confirming the diseases.

Blood tests

To confirm the presence of an inflammatory process in body, blood tests are carried through which elevated erythrocyte sedimentation rate (ESR or SED) or C-reactive protein (CRP) can be known. Rheumatoid factor and anti-cyclic citrullinated peptide (anti-CCP) antibodies are also some of the blood tests. Level of Hemoglobin, change in number of WBC and platelets also accounts in diagnosis of RA.

Imagine tests

To track the progression of RA in joints over time, X rays are made. To check the severity of disease some other test along X rays like magnetic resonance image (MRI) and ultrasound tests are carried out.[23]

TREATMENT

The main goal of treatment is focused on the decreasing the inflamed condition or decreasing the activity of the drug. It also minimization of joint destruction. Because ofcorrect treatment we can improve physical condition and quality of life. We can use allopathic drug treatment, herbal drug treatment, and last option is surgery.[24-28]

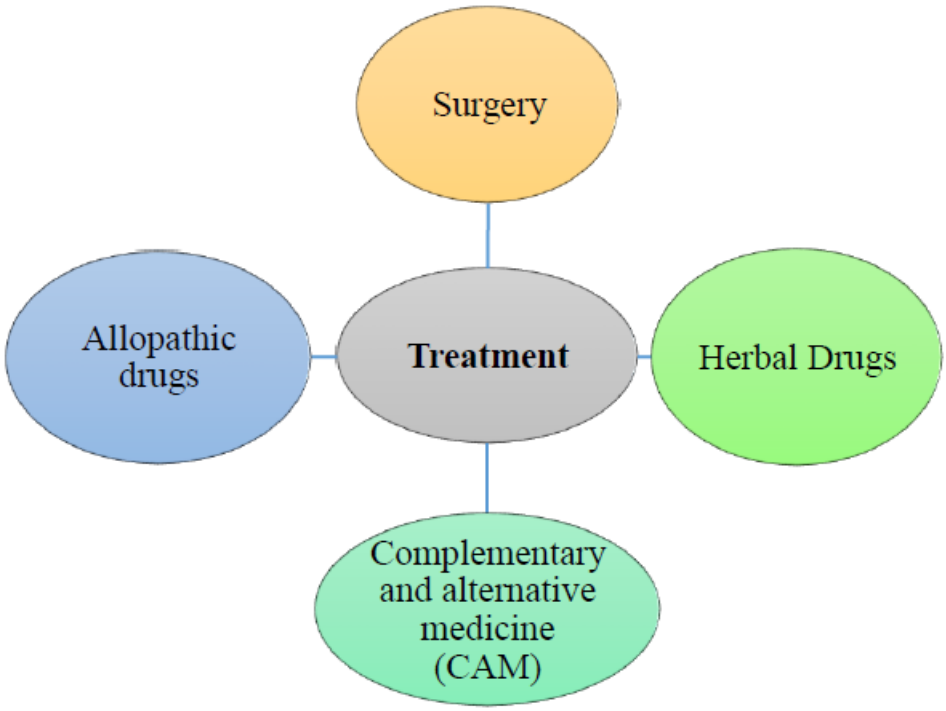

Fig. 4- Treatment of Rheumatoid arthritis.

a. Allopathic drugs

The drug used in treatment of rheumatoid arthritis Acetaminophen (tylenol), aspirin, ibuprofen naproxen, Methotrexate, gold salts, penicillamine, sulfasalazine, and hydroxychloroquine, hydroxychloroquine, methotrexate sulfasalazine, Sulfasalazine –

hydroxychloroquine and methotrexate – hydroxychloroquine – sulfasalazine, Paracetamol, ibuprofen, naproxen, meloxicam, etodolac, nabumetone, sulindac, tolmetin, choline magnesium salicylate, diclofenac, diflunisal, indomethacin, ketoprofen, oxaprozin, and piroxicam.

There are 4 types of therapy used in treatment of rheumatoid arthritis are over the counter drug therapy, Disease modifying anti-rheumatic drugs (DMRDs) therapy, non- steroidal anti- inflammatory drugs (NSAIDs) therapy and biological agent therapy.[29]

b. Surgery

When herbal and the allopathic drugs not able to prevent or slow joint damage, one can prefer the surgery to repair the damaged joint. Due to the surgery ability to use of joint is restored. And the main cause of surgery is to reduce the pain and correct the deformities.

1. Synovectomy- This surgery includes the removal of the inflamed synovium joint means lining of the joint. Synovectomy used in wrists, fingers, elbow, knees, and hip joints.
2. Tendon repair- The tendons are formed around inflammation and joint damage to loosen or rupture. These tendons are repaired by surgery.
3. Total joint replacement- In this surgery, the surgeon removes the damaged part of joint and insert a metal and prosthesis.
4. Joint fusion- In this surgery fusion of joint may be recommended for the relief of the pain and it also stabilize a joint and it is used when there is no option of replacement of joints.[30]

c. Herbal drugs

Herbal drugs treatment is used due to the side effect of the allopathic drug. Some plants which are able to show anti-rheumatic activity and they are as follow:[31-33]

1. Harpagophytum procumbens

It is also known as "devil claws" plant. This plant found in Kalahari Desert and Namibia steppes in southern Africa. The root of this plant shows anti- inflammatory and analgesic activity in rat by Freund's adjuvant induced arthritis both in the acute and chronic phase and then there are may test like Behavioral test, bodyweight, hot-plate test, and paw volume are measured. Because of this drug extract increased the animals 'latency of paws' withdrawal also this drug shows protective effect to reduce the pain. This drug used in acute and chronic rheumatoid arthritis.

2. Bauhinia variegate

The leaf of Bauhinia variegates show the anti-inflammatory activity using 3 in vivo animal models. The activity of this drug found more in petroleum ether fraction. The traditional use of this plant used to treatment of both acute and chronic inflammatory condition.

3. Leucas aspera

Leucas aspera used as analgesic, anti-pyretic, anti-rheumatic, anti- inflammatory and anti-bacterial treatment. The paste of drug is applied externally to inflammed areas. Due to this herbal medicine treatment to the complete cartilage regeneration is formed and near normal joint.

4. Phyllanthus amarus

The aqueous extract of Phyllanthus amarus extract (PAE) (2.5% phyllanthin and hypophyllanthin) become tested in opposition to Freund's entire adjuvant- induced arthritic rats. Arthritis assessment, paw volume, joint diameter, mechanical hyperalgesia, and nociceptive threshold had been measured. PAE extensively reduced arthritis which become evident with arthritis index, paw volume, and joint diameter. It additionally extensively improved the mechanical hyperalgesia and nociceptive threshold. The histopathology additionally found out the manage in irritation with PAE 24.

5. Acalypha indica

Acalypha indica (AI) methanol extract turned into evaluated the use of 3 unique in-vitro fashions to discover anti-arthritic potentials such as inhibition of protein denaturation, proteinase inhibitory motion, and anti-hyaluronidase activity. The concentrations of 10 to 2 hundred µg/ml of AI methanol extract had been organized the use of DMSO. Diclofenac turned into used as high-quality control. All in- vitro determinations had been performed in triplicate. A dose-established growth in percent inhibition turned into located for all of the 3 fashions. The inhibitory concentration (IC50) turned into located to be 52 µg/ml for protein denaturation assay, 37µg/ml in proteinase inhibitory motion and 18 µg/ml for anti- hyaluronidase activity. The traditional use of the drug is it exhibit a very good anti-arthritic activity.

d. Complementary and alternative medicine (CAM)

CAM is defined as a 'diagnosis, treatment and/or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine'. Nowadays,there is an increase in use of CAM therapies not only in North America, Europe and Australia but even also in Asian countries like India. The main alternative system used inIndia are Ayurveda, Homoeopathy, Siddha and Unani medicine which are been practicing since a long period ago. In addition to thissome of other therapies those are found in India are yoga asana, pranayama, massage, acupuncture and magnet therapy. The main advantages of CAM are that there are cheaper, effective, without any side effects. The practice of yoga asana and pranayama is more when compared to Ayurveda in India.[31]

Side effects

For the treatment of RA, many methods are used. Among them DMARDs (disease- modifying antirheumatic drugs), NSAIDs (Nonsteroidal anti-inflammatory drugs),

Therapies and surgery are used mainly. Some side effects of DMARD drugs are as follows:[34]

Table 1: DMARDs (disease- modifying antirheumatic drugs) with their dosage and side effects.

Drugs (DMARD)	Dosage	Side effects
Adalimumab (Humira)	40 mg for every two weeks subcutaneously	Infusion reactions; increased infection risk, including TB reactivation Rare: Demyelinating disorders
Anakinra (Kineret)	100 to 150 mg per day subcutaneously	Infection and decreased neutrophil counts, headaches, dizziness, nausea Rare: hypersensitivity
Auranofin (Ridaura)	3 mg twice per day or 6 mg orally per day	Diarrhea Rare: leukopenia
Azathioprine (Imuran)	50 to 150 mg orally per day	Nausea Rare: leukopenia, sepsis, lymphoma
Cyclosporine (Gengraf, Neoral)	2.5 to 5 mg per kg orally per day	Nausea, paresthesias, tremor, headaches Rare: hypertension, renal disease, sepsis
D-Penicillamine (Cuprimine)	250 to 750 mg orally per day	Nausea, loss of taste, rash, reversible platelet decreases Rare: proteinuria, late autoimmune disease
Etanercept (Enbrel)	25 mg twice per week or 50 mg per week subcutaneously	Contraindicated in infection, mild infection site reactions Rare: demyelination
Hydroxychloroquine (Plaquenil)	200 to 400 mg orally per day	Nausea, headaches Rare: abdominal pain, myopathy, retinal toxicity
IM gold Gold sodium thiomalate (Myochrysine) Aurothioglucose (Solganal)	25 to 50 mg IM every two to four weeks	Mouth ulcers, rash, vasomotor symptoms after injection Rare: leukopenia, colitis, thrombocytopenia, proteinuria
Infliximab (Remicade)	3 mg per kg IV at weeks zero, 2 and 6, then every eight weeks	Infusion reactions, increased infection risk, including TB reactivation Rare: demyelinating disorders
Leflunomide (Arava)	100 mg orally per day for three days, then 10 to 20 mg orally per day	Nausea, diarrhea, rash, alopecia, highly teratogenic, even after discontinuation Rare: leukopenia, hepatitis, thrombocytopenia
Methotrexate	12 to 25 mg orally per week Intramuscular or subcutaneous route	Nausea, diarrhea, fatigue, mouth ulcers, rash, alopecia, abnormal liver function tests Rare: low WBC and platelets, pneumonitis, sepsis, liver disease, Epstein-Barr virus-related lymphoma, nodulosis
Minocycline (Minocin)	100 mg orally twice per day	Dizziness, skin pigmentation
Staphylococcal protein A immunoadsorption (Prosorba column)	Extracorporeal; weekly for 12 weeks	Hypotension and anemia during procedure, catheter site infection, joint pain,
Sulfasalazine (Azulfidine)	2 to 3 g orally per day in divided doses	Nausea, diarrhea, headache, mouth ulcers, rash, alopecia, contact lens staining, reversible oligospermia, abnormal liver function tests Rare: leukopenia

Condition in India

This inflammatory disease is predominantly affecting people between the ages of 20 to 60 years with an unpredictable course. According to WHO, around 0.3-1% of world's total population is afflicted by RA and is about two to three times more common in woman than men. It has been noted that prevalence in Europe and North America may be higher than prevalence in Asia. Projected to whole populations, RA would give a total of about 7 million patients in India. The ratio of prevalence of women to men with RA has been consistently found to be around 3:1 though the probands from multicase families have been reported as often to be men as women. The prevalence of RA in adults has been

reported to vary from 0.5 to 3.8% in women and from 0.15 to 1.37% in men.[35]

CONCLUSION

RA is a debilitating, chronic, inflammatory disease, capable of causing joint damage as well as long-term disability. Early diagnosis and intervention are essential for the prevention of serious damage and loss of essential bodily functions. With advances in the field of molecular medicine and with a better understanding of disease mechanisms which can aid in the designing of more effective treatments. Old treatment modalities have been optimized and new ones have been produced. It is foreseen that treatment methods will face tremendous improvements in the management of RA. RA patients today can live a healthy and productive life. Today's medicines used can relieve pain and swelling and, in some cases, put the disease in remission, preventing bone damage or deformity.

REFERENCES

1. Trouw LA, Huizinga TWJ, Toes REM. Autoimmunity in rheumatoid arthritis: different antigens-common principles. Annals of the rheumatic diseases, 2013; 72(2): ii132-ii136.
2. Tracy A, Buckley CD, Raza K. Pre-symptomatic autoimmunity in rheumatoid arthritis: when does the disease start? Seminars in immunology, 2017; 39(4): 423-435.
3. Handa R, Rao URK, Lewis JFM, Rambhad G, Shiff S, Ghia CJ. Literature review of rheumatoid arthritis in India. Int. J. of Rheumatoid Diseases, 2016; 19: 440-451.
4. Tierney M, Fraser A, Kennedy N: Physical Activity in Rheumatoid Arthritis. A Systematic Review. J. Phys. Act. Health, 2012; 9: 1036-1048.
5. Malaviya AN, Kapoor SK, Singh RR, Kumar A, Pande I. Prevalence of rheumatoid arthritis in the adult Indian population. Rheumatol Int., 1993; 13: 131-134.
6. Sayah A, English JC: Rheumatoid arthritis. A review of the cutaneous manifestations. J Am Acad Dermatol, 2005; 53: 191-209.
7. Scott DL, Wolfe F, Huizinga TW. Rheumatoid arthritis. Lancet, 2010; 376: 1094-1108.
8. Alamanos Y, Drosos AA. Epidemiology of adult rheumatoid arthritis. Autoimmun. Rev., 2005; 4: 130-136.
9. Kvien TK, Uhlig T, Odegard S, Heiberg MS. Epidemiological aspects of rheumatoid arthritis: the sex ratio. Ann N Y Acad Sci., 2006; 1069: 212-222.
10. Chopra A, Patil J, Billempelly V, Relwani J, Tandle HS. Prevalence of rheumatic disease in a rural population in western India: a WHO-ILAR COPCORD study. The Journal of the Association of Physicians of India, 2001; 49: 240-246.
11. Singh TB, Ahmad, Ausaf. A hospital based epidemiological study on clinically suspected Rheumatoid Arthritis patients. Department of community Medicine, 2016.
12. Scherera HU, Thomas H, Burmesterb GR. The etiology of rheumatoid arthritis. Journal of Autoimmunity, 2020; 110: 102400.
13. Alam J, Jantan I, Bukhari SNA. Rheumatoid arthritis: Recent advances on its etiology, role of cytokines and pharmacotherapy. Biomedicine & Pharmacotherapy, 2017; 92: 615-633.
14. Bannatyne GA, Wohlmann AS. Rheumatoid arthritis: Its clinical history, etiology, and pathology. The Lancet, 1896; 147(3791): 1120-1125.
15. Cooles FAH, Isaacs JD. Pathophysiology of rheumatoid arthritis. Current Opinion in Rheumatology, 2011; 23: 233-240.
16. McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet, 389(10086): 2328-2337.
17. Harris ED. Rheumatoid Arthritis Pathophysiology and Implications for Therapy. The NewEngland Journal of Medicine, 2013; 322(18): 1277-1289.
18. Gibofsky A. Epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis: A Synopsis. The American Journal of Managed Care, 2014; 20(7): S128-35.
19. Calabresi E, Petrelli F, Bonifacio AF, Puxeddu I, Alunno A. One year in review 2018: Pathogenesis of rheumatoid arthritis. Clin. Exp. Rheumatoid, 2018; 36: 175-184.
20. Deane KD, Demoruelle KM, Kelmenson LB, Kuhn KA, Norris JM, Holers VM. Genetic and environmental risk factors for rheumatoid arthritis. Best Practice & Research Clinical Rheumatology, 2017; 31(1): 3-18.
21. Edward CJ, Cooper C. Early environmental factors and rheumatoid arthritis. Clin. Exp. Immunology, 2005; 143: 1-5.
22. Heidari, Behzad: Rheumatoid Arthritis. Early diagnosis and treatment outcomes. Caspian journal of internal medicine, 2011; 2(1): 161-70.
23. Rindfleisch JA, Muller D. Diagnosis and Management of Rheumatoid Arthritis. American Family Physician, 2005; 72: 1037-1047.
24. Bullock J, Rizvi SAA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid Arthritis: A Brief Overview of the Treatment. Med Princ Pract, 2018; 27(6): 501-507.
25. Guo Q, Wang Y, Xu D. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res.*, 2018; 6: 15.
26. Van Vollenhoven RF. Treatment of rheumatoid arthritis: state of the art. Nat Rev Rheumatol, 2009; 5(10): 531-541.
27. Law ST, Taylor PC. Role of biological agents in treatment of rheumatoid arthritis. Pharmacological Research, 2019; 150.
28. Emery P. Treatment of rheumatoid arthritis. BMJ., 2006; 332(7534): 152-155.
29. Nimesh S. Herbal drug is better than allopathic drug in the treatment of rheumatoid arthritis. Int J Pharmacognosy, 2018; 5(9): 539-545.
30. Lipsky, Peter E, Tao XL. A potential new treatment

for rheumatoid arthritis: thunder god vine. In Seminars in arthritis and rheumatism, 1997; 26(5): 713-723.
31. Zaman T, Agarwal S, Handa R. Complementary and alternative medicine use in rheumatoidarthritis: An audit of patients visiting a tertiary care centre. Natl Med J India, 2007; 20: 236– 239.
32. Soeken KL, Miller SA, Ernst E. Herbal medicines for the treatment of rheumatoid arthritis: a systematic review. Rheumatology, 2003; 42(5): 652-659.
33. Kaur A, Nain P, Nain J. Herbal plants used in treatment of rheumatoid arthritis: a review. Int J Pharm Pharm Sci., 2012; 4(4): 44-57.
34. American College of Rheumatology Subcommittee on Rheumatoid Arthritis Guidelines. Guidelines for the Management of Rheumatoid Arthritis. Arthritis and Rheumatism, 2002; 46: 328-346.
35. Grover S, Sinha RP, Singh U, Tewari S, Aggarwal A, Misra R. Subclinical atherosclerosis in rheumatoid arthritis in India. The Journal of rheumatology, 2006; 33(2): 244-247.