RHUMATOID ARTHRITIS: A REVIEW

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Abstract:
Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disease, affecting the joints with various severity amongst patients. The hazard factors consist of age, gender, genetics and environmental exposure (cigarette smoking, air pollution and occupational). Prognosis of RA may additionally be expected based totally on the presence of some medical and laboratory evidences. New criteria for classification of RA provide possibility for before treatment.
Initiation of therapy especially by combination of DMARDs concurrent with short period of corticosteroidis predicted to prevent modern path andeven alternate the natural route of RA. At current any patients with clinical synovitis in at least one joint may also have definate RA, requiring aggressive treatment.

Keywords: Rheumatoid arthritis, Inflammation, autoimmune disease, disease modifying anti-rheumatic drugs.

INTRODUCTION:

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disorder that at first influences small joints, progressing to large joints, and in the end the skin, eyes, heart, kidneys, and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken. [1]
The disorder influences women two to three times greater than men and occurs at any age

RA led to disability, lack of ability to work, and increased mortality. Recent enhancement in results has been achieved through a better understanding of RA pathophysiology and development of higher consequence measures and healing proceed.[2]All this damage to the joints causes deformities and bone erosion, typically very painful for a patient. Common signs and symptoms of RA include morning stiffness of the affected joints for > 30 min, fatigue, fever, and weight loss, joints that are tender, swollen and warm, and

rheumatoid nodules under the skin. The onset of this disease is typically from the age of 35 to 60 years, with remission and exacerbation. It can additionally afflict younger young people even earlier than the age of sixteen years, referred to as juvenile RA (JRA), which is comparable to RA barring that rheumatoid element is now not determined.[3] The disorder is allied with the molecules of most important histo compatibility complex, dependent T- Cells. This sickness is greater severe in the case of female alternatively than guys and in the elder populace.

The result of the disease is irritation of the joints systemically, persistent synovitis, injury of the tissues due to the launch of cytokines and irritation due to imbalance between the autoimmune cells. The autoimmune antibodies will harm the tissues.[4]

Signs and Symptoms:

- Signs and symptoms of RA usually appear in the wrists, hands, or toes and include:
- pain or achiness in more than one joint
- stiffness in more than one joint that lasts longer than 30 minutes
- swelling in more than one joint
- symmetrical joint involvement
- a usual feeling of being unwell
- a low-grade fever
- appetite loss
- weight loss
- weakness
- joint deformity
- loss of feature and mobility
- unsteadiness when walking[5]

Etiology: The cause for the occurrence of rheumatoid arthritis is unknown. It would possibly be due to a change in response of a genetically prone host to an infectious agent. The causative agents may include Mycoplasma, cytomegalovirus, Epstein- Barr virus, rubella virus, and parvovirus. The distinctive spreading of an infectious agent that motives chronic inflammatory arthritis is unknown.

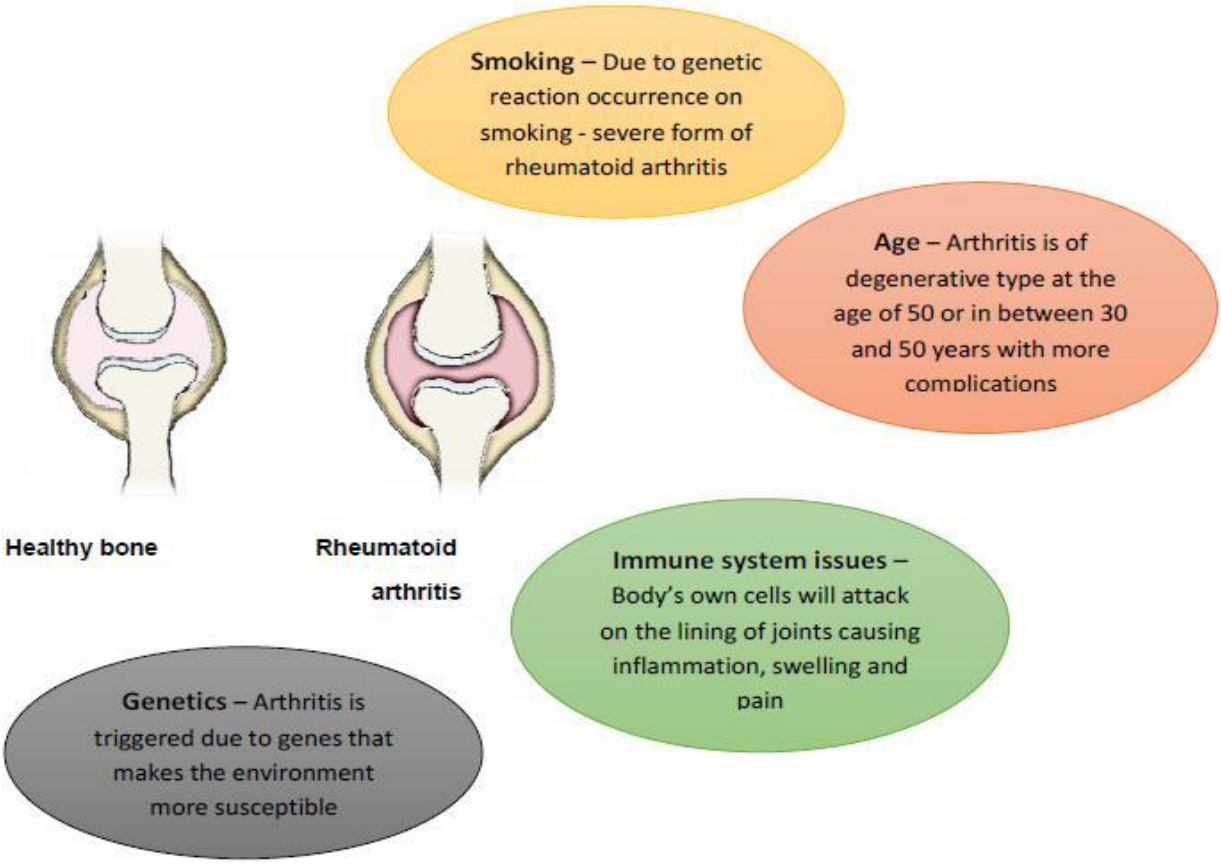
The different factors influencing rheumatoid arthritis:

a. Genetic and environmental factors
b. Smoking
c. Human microbiome

a. Genetic and environmental factors: The genetic influence for rheumatoid arthritis is between 30% and 60% from the more than one genetic study. The most large genetic factor related to rheumatoid arthritis is “shared epitope” which is existing in the DRB1 allele. The threefold increase in the incidence of rheumatoid arthritis is in relation to the presence of a shared epitope.

b. Smoking: Smoking is the major threat factor for the development of many chronic diseases. According to a few cohorts, the chance for the development of rheumatoid arthritis is greater in ACPA-positive people who take coffee.
A Swedish cohort says that work-related exposure to mineral oil is the hazard aspect in men. The Swedish population whose career is to work in mineral oil sources confirmed a 57% increase in the incidence of rheumatoid arthritis. APCA positive individuals will increase rheumatoid arthritis in case of work publicity to silica. Other elements consist of lesser consumption of vitamin D and antioxidants and much more intake of sugar, sodium, crimson meats, proteins and iron which confirmed an increased chance of rheumatoid arthritis.

c. Human microbiome: The switch from a symbiotic to a dysbiotic microbiome is the contributing hazard issue for the development of rheumatoid arthritis as it is characterized by the severe increase of the microbes and lack of bacteria/organisms. The outcome of this is responsible for deviations in innate and adaptive immunity



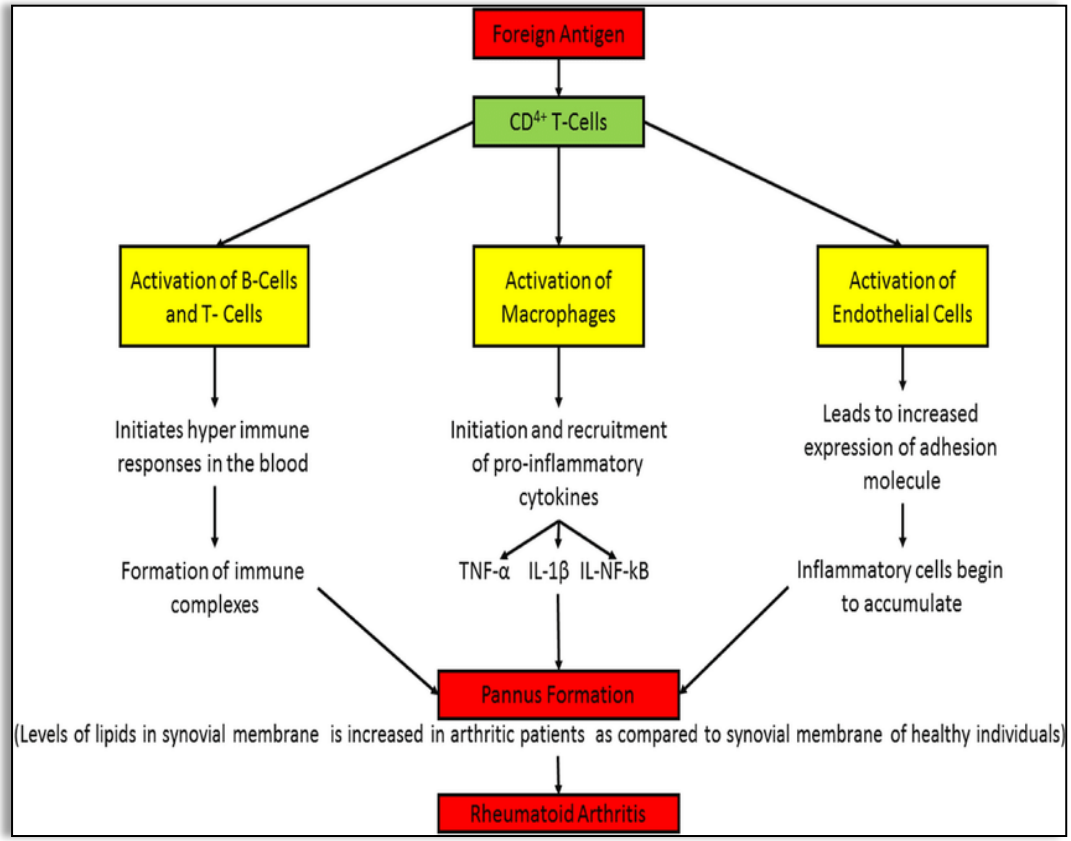
Pathophisology:

RA is characterized by using infiltration of the synovial membrane in multiple joints with T cells, B cells, and monocytes. This method is preceded by using activation of endothelial cells; neovascularization (growth of new blood vessels) is another hallmark of RA synovitis. Expansion of synovial fibroblast-like and macrophage-like cells leads to a hyperplastic synovial lining layer. This elevated synovial membrane, frequently termed "pannus," invades the periarticular bone at the cartilage-bone junction and leads to bony erosions and cartilage degradation .Molecules such as receptor activator of nuclear component κB ligand(RANKL), prostaglandins, and matrix metallo proteinases are induced by means of pro-inflammatory cytokines, including tumor necrosis factor (TNF) and interleukin (IL)-6, and mediate signs and symptoms and symptoms of the disease, including ache and swelling, and degradation of cartilage and bone.6 Stimulation by RANKL, TNF, and IL-6 generates osteoclasts inside the synovial membrane and promotes bony damage.[7]

These molecular and cellular events result in the clinical disease expression. Progression of joint harm is intrinsically associated with joint swelling.[8]The reason of RA is unknown. However, genetic and environmental factors both make contributions to RA. Many gene loci are related with RA [9]. However, certain HLA type II antigens, such as HLA-DRB1*01 and HLA DRB1*04, contain the "shared" epitope—a stretch of 5 amino acids in the region responsible for antigen presentation to T lymphocytes—and are most closely related with RA. Genes with weaker association may also contribute, mainly through gene-gene and gene-environment interactions.**10**. Environmental risk factors for RA are smoking, periodontitis, and traits of the microbiome of the gut, mouth, and lungs, as nicely as viral infections. **11** Regarding the microbiome, Prevotella species, which are increased in the gastrointestinal tract in early RA, and Porphyromonas gingivalis, which is associated with periodontitis, may additionally have a function in pathogenesis. New data advice that bacteria may also translocate from the gut to tissues, causing irritation and autoimmunity. The relationship between genetics and environment is evident primarily based on recent observations that HLA-DR molecules of patients with RA present peptides of auto antigens having sequence homology with epitopes from proteins of commensal bacterial species present in RA. Similarities between amino acid sequences of auto antigens and bacterial or viral proteins have been described Epstein-Barr virusinfectio has additionally been implicated, further supported by means of recent observations that transcription factor EB nuclear antigen (EBNA2) binds preferentially to genetic loci related with RA and other autoimmune diseases.12.Epigenetic changes such as DNA methylation and histone acetylation also promote inflammatory responses. Posttranslational protein changes such as citrullination of arginine by peptidyl arginine deiminase or carbamylating of lysine contribute to breaking immunological tolerance by means of creating neoepitopes of various auto logous proteins (eg, collagen, vimentin,fibrinogen), resulting in formation of auto antibodies against auto antigens (eg, anticitrullinated peptide antibodies [ACPAs]),antibodies to IgG (rheumatoid factor [RF]), nuclear antigens, or autoantigens that cross-react with bacterial or viral antigens, such as Prevotella or Epstein-Barr virus.13,21 These auto antibodies can form immune complexes that may also activate complement,

further increasing inflammatory responses.[13] RF and ACPAs together can promote a substantial inflammatory response, whereas ACPAs alone cause little inflammation. RFs expand Immune complexes formed through ACPAs and enlarge the inflammatory response elicited by means of immune complexes and complement activation.[14, 15]

Auto antibodies increase earlier than symptoms and signs occur. This stage is termed "pre-RA" and can last between much less than 1 and more than 10 years. The size of time earlier than look of RA symptoms is related to the autoantibody profile. Individuals who only express ACPAs increase signs and symptoms 5 to 10 years after the autoantibody appearance, whereas human beings who develop ACPAs and RF and also expanded C-reactive protein (CRP) stages develop symptoms within a few months after the 0.33 of these factors appears. Inflammatory modifications in the synovium have been cited in some patients with pre-RA. Even in established RA, overt inflammatory changes identified by histology are now not always accompanied by clinical signs and symptoms.[16]Early manifestations of RA range from mild arthritis with few involved joints to extreme poly articular disorder and from a state of terrible auto antibodies to more than one positive auto antibodies. Very early disease does now not but exhibit structural damage, whereas later stages are characterized by erosive disease or joint space narrowing as an indicator of cartilage degradation. If now not adequately treated, RA progresses into a greater homogeneous, destructive disease.



First Line Management: NSAIDS and Corticosteroids

The aim of first line remedy is to relieve pain and reduce inflammation Medications considered as fast-acting drugs are non-steroidal anti-flammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin is an tremendous anti-inflammatory for rheumatoid arthritis when used at higher doses, due to inhibition of prostaglandins. This is one of the oldest NSAIDs used for joint pain. Side effects of aspirin at excessive doses encompass tinnitus, hearing loss and gastric intolerance. There are different NSAIDs that are more recent to the market than aspirin however are just as effective. NSAIDs work through inhibiting cyclooxygenase to stop synthesis of prostaglandins, prostacyclin and thromboxanes.

Common side outcomes are nausea, stomach pain, ulcers and gastrointestinal (GI) bleeding. These symptoms can be decreased if taken with food or with antacids, proton pump inhibitors, or misoprostol (Cytotec) An even more recent NSAID known as celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side effects .[17]

Corticosteroids are extra potent anti-inflammatory medicines compared to NSAIDs however; they come with larger side effects. For this reason, they are solely indicated for a short period of time at low dosages, during exacerbations or flares of rheumatoid arthritis. Intra-articular (IA) injections of corticosteroid can be used for local signs and symptoms of irritation [18] They work by preventing phospholipids release and decreasing actions of eosinophils, therefore decreasing inflammation. Their side effects consist of bone thinning, weight gain, diabetes, and immune suppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of bone. Side effects can be decreased through gradually tapering the doses as the patient achieves improvement. It is important not to suddenly discontinue injected or oral corticosteroids as it can lead to hypothalamic-pituitary-adrenal axis suppression (HPA) or flares of rheumatoid arthritis **[19]**

Second Line Management: Disease-modifying Anti-rheumatic Drugs (DMARDs)

The general goals of 2nd line therapy are to promote remission via slowing or stopping the progression of joint destruction and deformity.

These medications are considered slow acting drugs because they take weeks to months to be effective. DMARDs can also decrease the chance of developing lymphoma that can be associated with rheumatoid arthritis.[20] Methotrexate (MTX) is the preliminary second-line drug (also considered as an anchor drug). It is an analogue to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for changing FH2 to folinic acid (FH4). Without FH4, purine andpyrimidine metabolism is impaired, and amino acid and polyamine synthesis is inhibited. MTX isan immunosuppressive drug that requires regular blood tests due to its facet effects of liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can minimize the risk of side effects. It is an effective DMARD, has decrease incidence of side effects in contrast to the other DMARDs, and has dose flexibility, that means that dosages can be adjusted as needed .Until now, there is convincing date available showing the advantages of combination of conventional synthetic DMARDs (csDMARDs)overMTXmonotherapy.However biological DMARDs(bDMARDs) combined

with csDMARDs, are mentioned to be higher thanMTX however with greater sideeffects and is very expensive .Hydroxychloroqyine (Plaquenil) is an antimalarial drug and can be used long term in the treatment of rheumatoid arthritis.

This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common aspect outcomes consist of troubles in the gastrointestinal tract,skin, and central nervous system. In particular, the eye can be affected when used at higher dosages. Patients onthis medication require pursuits consultation with an ophthalmologist. Sulfasalazine (Azulfidine) is a DMARD commonly used in the therapy of irritable bowel disease. Combined with anti-inflammatory medications, this DMARD can be to treat rheumatoid arthritis. The mechanism of action of this drug in the therapy of rheumatoid arthritis has now not been identified. It is concept that sulfapyridine, a decreased form of the medication after administration, may decrease secretions of interleukin 8 (IL-8) and monocyte chemo attractant protein(MCP).Thisdrug consistsof side effects ofgastrointestinalandcentral nervous system si gnsandsymptoms as well asrash.Itis generally well tolerated amongst patients, but it must be prevented in patients with sulfa allergies since it includes sulfa and salicylate compounds.[21] Gold salts, such as aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen, Cuprimine) have been used regularly in the treatment of rheumatoid arthritis. These DMARDs require regular blood and urine checks due to damage to the bone marrow and the kidneys.

These medicines have not beenused recently dueto more effective treatments, especially meth otrexate. Other immunosuppressive medications, azathioprine (Imuran), cyclophsphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune), can also be employed but are usually reserved for patients with very aggressive rheumatoid arthritis or problems of the disorder [22, 23]

Current Drug Therapy: The current pharmacologic treatments for the therapy of RA are categories Because RA is an inflammatory condition, first-line therapy has historically covered medicines that suppress inflammation, such as non steroidal anti inflammatory drugs (NSAIDs) and glucocorticoids. These classes of medications also act hastily to enhance pain and swelling due to RA. Disease modifying antirheumatic drugs (DMARDs) include methotrexate, hydroxychloroquine, sulfasalazine, and, more recently, leflunomide. Unlike NSAIDs, these slower-acting compounds now not only improve signs and symptoms however gradual clinical and radiographic progression.Because their time to onset ranges from various weeks to months, more rapid-acting agents. The newest category of medications used to treat RA—biological-response modifiers—has been available for nearly 10 years. These agents, designed to goal the inflammatory mediators of tissue injury in RA, include infliximab, etanercept, adalimumab, anakinra, abatacept, and rituximab. Many greater are in different phases of clinical lookup and might also be available in the subsequent few years.

With the creation of new therapies for RA, ACR developed uniform measures for assessing response to therapy that evaluate the degree of clinical improvement, described by specific variables (e.g., number of tender or swollen joints, patient and physician assessments of disease activity).A20% enhancement ina mixture of these variables is called the ACR20; similarly, 50% and70% are known as the ACR50 andACR70, respectively. NSAIDs. This usually used class of medications is effective for controlling the pain, inflammation, and stiffness related to RA. NSAID scan be very beneficial in the first weeks after the onset of RA signs and symptoms while a diagnostic workup is undertaken, before a analysis is certain, and as bridge therapy while ready for a slow-acting DMARD to become like NSAIDs and glucocorticoids, are regularly used as "bridge" therapy when initiating therapy with DMARDs effective. Leflunomide is an oral medicine that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotide uridine monophosphate pyrimidine. It relieves signs and retards the progression of RA. It is encouraged to be used in combination with MTX however can constitute a monotherapy if patients do now not respond to MTX. Side effects consist of hypertension, GI upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow injury.[24, 25]

Biologics, also known as biological DMARDs, are unexpectedly effective in retarding the progression of the joint damage caused by using RA. They are regarded to be a more "direct, defined and targeted" method of therapy.[26] Nonetheless, biologics pose the hassle of serious facet effects, such as increased hazard of infections. Other common side effects consist of neurologic diseases like multiple sclerosis and lymphoma[27] Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira), golimumab (Simponi), and certolizumab pegol (Cimzia) are all TNF inhibitors that prevent the recruitment of the cells that cause inflammation, bringing rapid symptom relief. They are endorsed if other second-line medications are now not effective. Unfortunately, these medicinal drugs tend to be very expensive and their function in treating patients at various stages of RA and with a number of mechanisms of action is a matter of continuous investigation. They are regularly used in mixture with other DMARDs, especially MTX. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each biologic remedy has a exclusive mode of administration.[28]

Anakinra (Kineret) is a drug that is injected subcutaneously daily. It works through binding to IL-1, a chemical messenger of inflammation. It can be used in combination with other DMARDs or as a monotherapy, but due its low response rate compared to other biologics, it is not used as frequently. Rituximab (Rituxan) is useful in RA due to the fact it depletes the B cells responsible for inflammation and the manufacturing of abnormal antibodies. Typically used in the treatment of lymphoma, this drug can be used in cases of RA where TNF inhibitors have failed. In addition, rituximab has shown benefits in treating the problems of RA, such as vasculitis and cryoglobulinemia. It is administered as an intravenous infusion in two doses, two weeks apart, each and every 6 months. Abatacept (Orencia) is a biologic medication that

works by blocking T cell activation. This is given as an intravenous infusion as soon as a month or subcutaneously once a week. It is used in patients who have not been effectively treated with traditional DMARDs.[29]

Tocilizumab (Actemra) is a biologic that works by using blocking IL-6, a chemical messenger of inflammation. It is administered via intravenous infusion given monthly or via weekly subcutaneous injections. It is additionally used for patients who have now not been effectively treated with traditional DMARDs [38]. Lastly, tofacitinib (Xeljanz) has a specific mechanism of action and works by means of blocking Janus kinases within cells, which are enzymes of inflammation. For this reason, it is regarded as a JAK inhibitor. This medication is used for patients who have not been effectively treated with MTX. Tofacitinib is taken orally twice daily, by myself or in aggregate with MTX. It should now not be used in combination with normal biologic medications or other potent immunosuppressants. **30**

References:

1. Lee, Ji-Eun, et al. "A case of rheumatoid vasculitis involving hepatic artery in early rheumatoid arthritis." Journal of Korean medical science 32.7 (2017): 1207-1210.).
2. (Aletaha, Daniel, and Josef S. Smolen. "Diagnosis and management of rheumatoid arthritis: a review." Jama 320.13 (2018): 1360-1372.ures.
3. Bullock, Jacqueline, et al. "Rheumatoid arthritis: a brief overview of the treatment." Medical Principles and Practice 27.6 (2018): 501-507)
4. Nithyashree, R. S., and R. Deveswaran. "A Comprehensive Review on Rheumatoid Arthritis." (2020).)
5. https://www.medicalnewstoday.com/articles/323361)
6. (Martins, Patrícia, and João Eurico Fonseca. "How to investigate: Pre-clinical rheumatoid arthritis." Best Practice & Research Clinical Rheumatology 33.4 (2019): 101438.)
7. Redlich, Kurt, and Josef S. Smolen. "Inflammatory bone loss: pathogenesis and therapeutic intervention." Nature reviews Drug discovery 11.3 (2012): 234-250)
8. (Aletaha, Daniel, and Josef S. Smolen. "Joint damage in rheumatoid arthritis progresses in remission according to the Disease Activity Score in 28 joints and is driven by residual swollen joints." Arthritis & Rheumatism 63.12 (2011): 3702-3711.)
9. Viatte, Sebastien, and Anne Barton. "Genetics of rheumatoid arthritis susceptibility, severity, and treatment response." Seminars in immunopathology. Vol. 39. No. 4. Springer Berlin Heidelberg, 2017.
10. Dekker, Joost, Gabriella M. van Dijk, and Cindy Veenhof. "Risk factors for functional decline in osteoarthritis of the hip or knee." Current opinion in rheumatology 21.5 (2009): 520-524.
11. Scher, Jose U., et al. "Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis." elife 2 (2013):e01202.
12. (Aletaha, Daniel, and Josef S. Smolen. "Diagnosis and management of rheumatoid arthritis: a review." Jama 320.13 (2018): 1360-1372.
13. Ospelt, Caroline, Steffen Gay, and Kerstin Klein. "Epigenetics in the pathogenesis of RA." Seminars in immunopathology. Vol. 39. No. 4. Springer Berlin Heidelberg, 2017.

14. Aletaha, Daniel, Farideh Alasti, and Josef S. Smolen. "Rheumatoid factor, not antibodies against citrullinated proteins, is associated with baseline disease activity in rheumatoid arthritis clinical trials." Arthritis research & therapy 17.1 (2015): 1-10.
15. Sokolove, Jeremy, et al. "Rheumatoid factor as a potentiator of anti–citrullinated protein antibody–mediated inflammation in rheumatoid arthritis." Arthritis & rheumatology 66.4 (2014): 813-821.
16. De Hair, M. J. H., et al. "Features of the synovium of individuals at risk of developing rheumatoid arthritis: implications for understanding preclinical rheumatoid arthritis." Arthritis & rheumatology 66.3 (2014): 513-522.
17. Bullock, Jacqueline, et al. "Rheumatoid arthritis: a brief overview of the treatment." Medical Principles and Practice 27.6 (2018): 501-507.)
18. Combe, Bernard, et al. "2016 update of the EULAR recommendations for the management of early arthritis." Annals of the rheumatic diseases 76.6 (2017): 948-959.
19. Liu, Dora, et al. "A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy." Allergy, Asthma & Clinical Immunology 9.1 (2013): 1-25.
20. Smolen, Josef S., et al. "EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update." Annals of the rheumatic diseases 73.3 (2014): 492-509.
21. Volin, Michael V., et al. "Treatment with sulfasalazine or sulfapyridine, but not 5-aminosalicylic acid, inhibits basic fibroblast growth factor–induced endothelial cell chemotaxis." Arthritis & Rheumatism: Official Journal of the American College of Rheumatology 42.9 (1999): 1927-1935.
22. Sailaja, A. Krishna. "An overall review on rheumatoid arthritis." Journal of Current Pharma Research 4.2 (2014): 1138.
23. Kumar, Pradeep, and Snehashish Banik. "Pharmacotherapy options in rheumatoid arthritis." Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders 6 (2013): CMAMD-S5558.
24. Fox, Robert I., et al. "How does leflunomide modulate the immune response in rheumatoid arthritis?." BioDrugs 12.4 (1999): 301-3
25. Gibofsky A. Combination therapy for rheumatoid arthritis in the era of biologicals. HSS J. 2006 Feb;2((1)):30–4115.
26. Veale, Douglas J., Carl Orr, and Ursula Fearon. "Cellular and molecular perspectives in rheumatoid arthritis." Seminars in immunopathology. Vol. 39. No. 4. Springer Berlin Heidelberg, 2017.
27. Rein, P., and R. B. Mueller. "Treatment with biologicals in rheumatoid arthritis: an overview. Rheumatol Ther 4 (2): 247–261." (2017).
28. Gay, Robert D., et al. "Anti-TNFα domain antibody construct CEP-37247: full antibody functionality at half the size." MAbs. Vol. 2. No. 6. Taylor & Francis, 2010.
29. Rosman, Ziv, Yehuda Shoenfeld, and Gisele Zandman-Goddard. "Biologic therapy for autoimmune diseases: an update." BMC medicine 11.1 (2013): 1-12.
30. Hodge, Jennifer A., et al. "The mechanism of action of tofacitinib-an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis." Clin Exp Rheumatol 34.2 (2016): 318-328.