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A REVIEW ON PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS IN CONJUNCTION WITH MODERNISTIC APPROACHES OF TREATMENT

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Abstract

Rheumatoid arthritis (RA) is a constant fundamental immune system disorder that principally influences lining present with synovial joints. It is related with dynamic inability, sudden passing, and socioeconomic burdens. Inflammation, pain and stiffness of the joints which leads to the deformity and disability of these joints are the main symptoms of rheumatoid arthritis. There are a few foundations for rheumatoid joint pain these causes are unclear however, some incorporate hereditary factor, family history, age, hormones, smoking and so on. Here, we analyse etiology as well as pathology of this disease at particular stages: activating, development, targeting, and fulminant stage. Analysis incorporates X-rays and imaging, using diagnostic criteria, laboratory test and barring other medical conditions. There is no solution for this disease, treatment can enhance side effects and moderate the advancement of the illness, change in way of life, normal exercise and consumption of disease modifying anti-rheumatic drugs (DMARDs). Modernistic pharmacological therapies includes conventional synthetic, biological, and small molecule DMARDs. This review talks about on-going advances for the RA pathogenesis, illness adjusting chemotherapeutic agents and also gives viewpoints on progressive therapeutics for RA.

Keywords **:** Rheumatoid arthritis, Pathogenesis, Disease modifying anti- rheumatic drugs, Biological.

Introduction

Rheumatoid arthritis (RA) is a constant fundamental immune system disorder that principally influences the coating of the synovial joins and is related with dynamic inability, sudden passing, and socioeconomic burdens (Kay and Calabrese, 2004, Mahajan and Mikuls, 2018). RA is a relatively conjoint inflammatory arthritis and as per data monitor, RA influences roughly 2% individuals in U.S. furthermore, has no known reason. Rheumatoid joint pain is more predominant among women as compare to men and usually matures in the fourth and fifth decades of life whereas 80% of the cases happening in the age of 35 and most generally RA influence the old age. It is most essential to remember that it is not an infectious syndrome (Kumar *et al*., 2015; Dudics *et al.,* 2018). As the interval may goes on rheumatoid joint inflammation can extent to an ever-increasing number of joints on the two verges of the body in a symmetrical way (Jones *et al.,* 2017). The two chief pathophysiological actions prominent to RA are mononuclear cell and hyperplastic synovial lining cells (Saylor and Steiner, 2018). RA can't be determined to have just a single included joint. While there is extensive variety, either immune response is certain in around half of patients on performance, with some cover constructing around 25% seronegative. The intention for RA stays obscure, and numerous qualities have been ensnared. Every quality (except for human leukocyte antigen) clarifies just a little measure of illness hazard, however the association of a hereditary pathway has demonstrated valuable for anticipating reaction to treatment; for instance, genetic factor related to interleukin 6 (IL-6) receptor and tumour necrosis factor, yet not interleukin 17 receptor, have been elaborate to give helplessness to RA. RA was not generally reflected a way of life related sickness, however rather late courses give pieces of information about conceivable way of life alteration. There are numerous natural elements contributing to RA, however smoking is most convincingly identified with rheumatoid arthritis (Jones *et al.* 2017).

Warning symptoms of RA

Swollen joints, morning stiffness, fatigue, fever, anaemia, depression and weight reduction are the main symptoms that are reported in case of rheumatoid arthritis. According to the affliction advances, symptoms constantly spread to the knees, bring down legs, elbows, wrists, hips and shoulders. A greater part of time, a symptom occurs in similar joints on the dual sides of human body. Rheumatoid joint pain marks and indications might differ in seriousness and may even come and go. After some time, rheumatoid joint agony can make joints to distort and move strange.

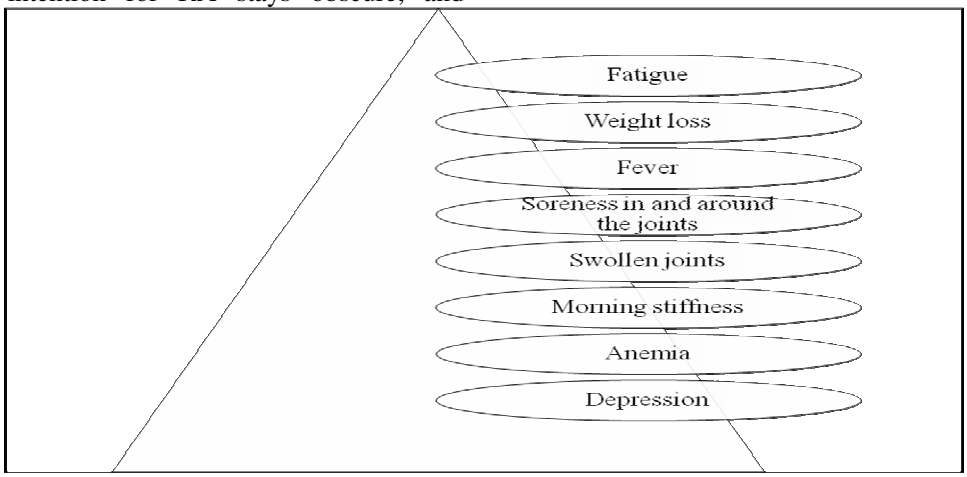


Fig.1 : Warning symptoms of RA (Malia and Coleiro, 2016, Neumann *et al.,* 2018)

Causes of Rheumatoid Arthritis:

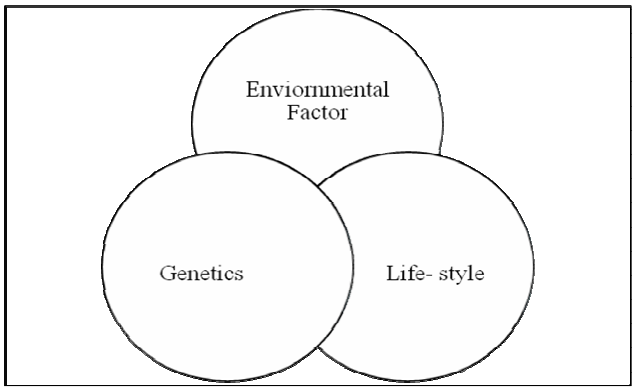
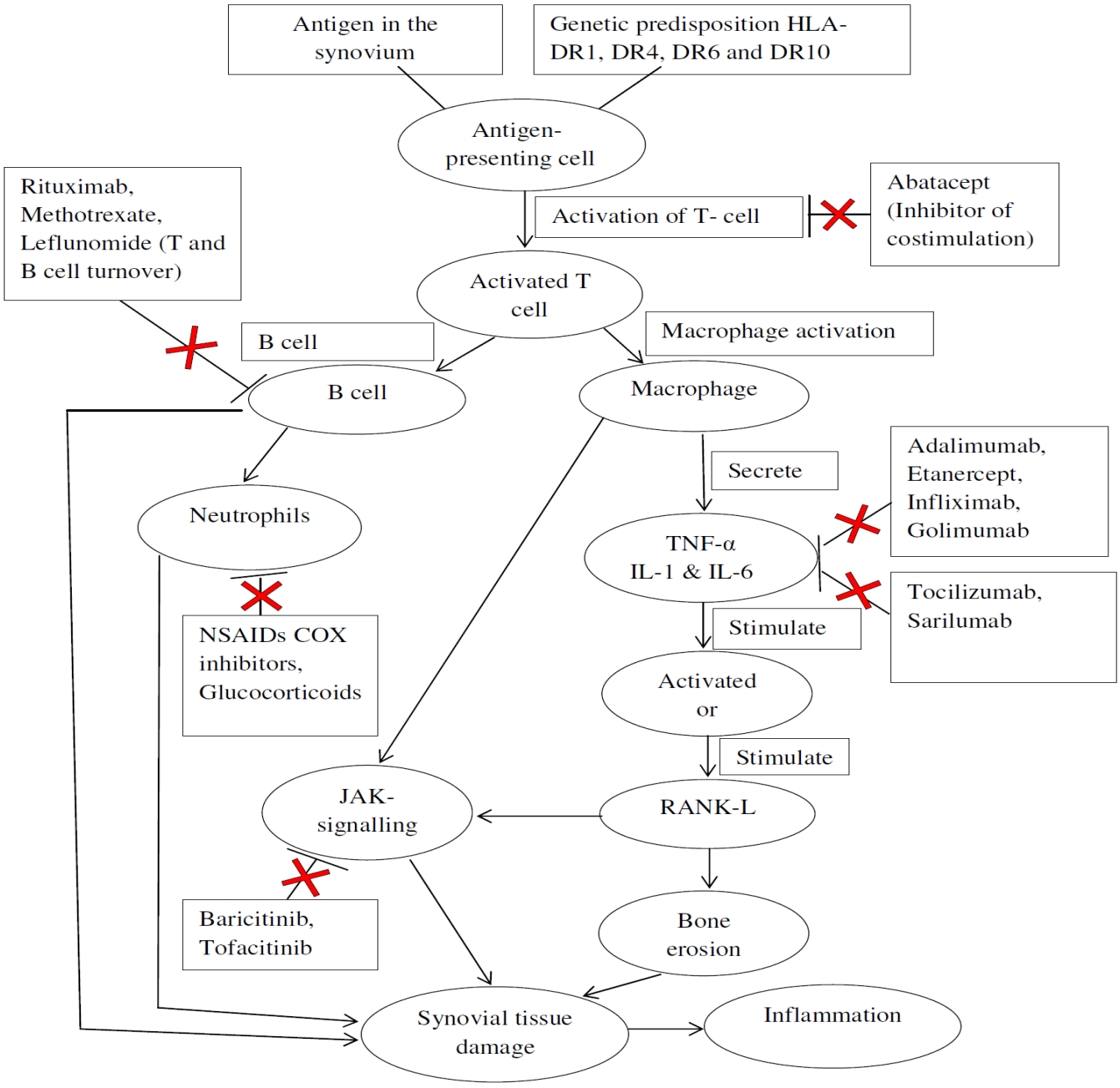


Fig. 2 : Causes of RA (Mustafa *et al*., 2018)

Pathophysiology of Rheumatoid arthritis with mechanism of action of different drug molecules:



COX- Cyclooxygenase, JAK-Janus kinase, TNF- Tumour necrosis factor, IL-Interleukin, RANK-L-receptor activator of nuclear factor kappa-B ligand, NSAIDs- Non steroidal anti-inflammatory drugs.

Fig. 3: Pathophysiology of Rheumatoid arthritis with mechanism of action of different drug molecules (Kay and Calabrese, 2004, Sharkey *et al*., 2011, Kumar *et al.,* 2016)

Diagnosis of RA:

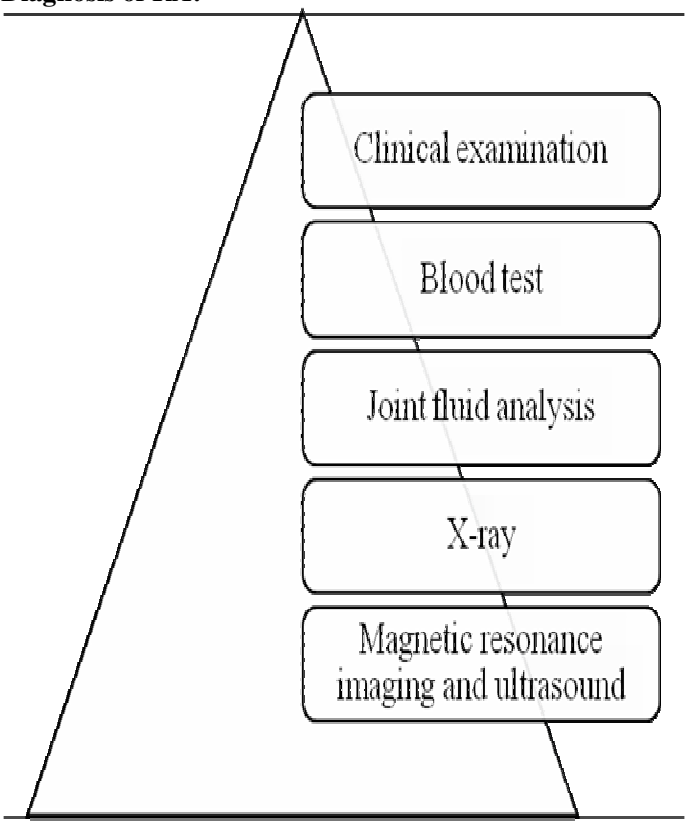


Fig. 4 : Diagnosis of RA (Neumann *et al*., 2018, Kumar *et al*., 2016)

Chemotherapy for Rheumatoid Arthritis:

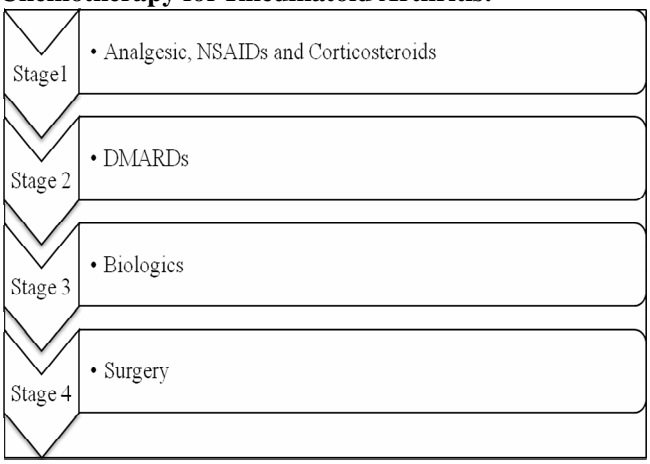


Fig. 5 : Chemotherapy for Rheumatoid Arthritis (Choy *et al*., 2014, Kourilovitch *et al*., 2014)

The general methodology for treating RA is to predict long-term injury to the joints and decrease irritation. As of now accessible helpful methodologies comprising NSAIDs, glucocorticoids (GCs), DMARDs and biological agents, for example; TNF-α blockers and IL-1 receptor antagonist that works by diminishing the joint aggravation and severe pain (Kourilovitch *et al*., 2014, Majithia and Geraci, 2007).

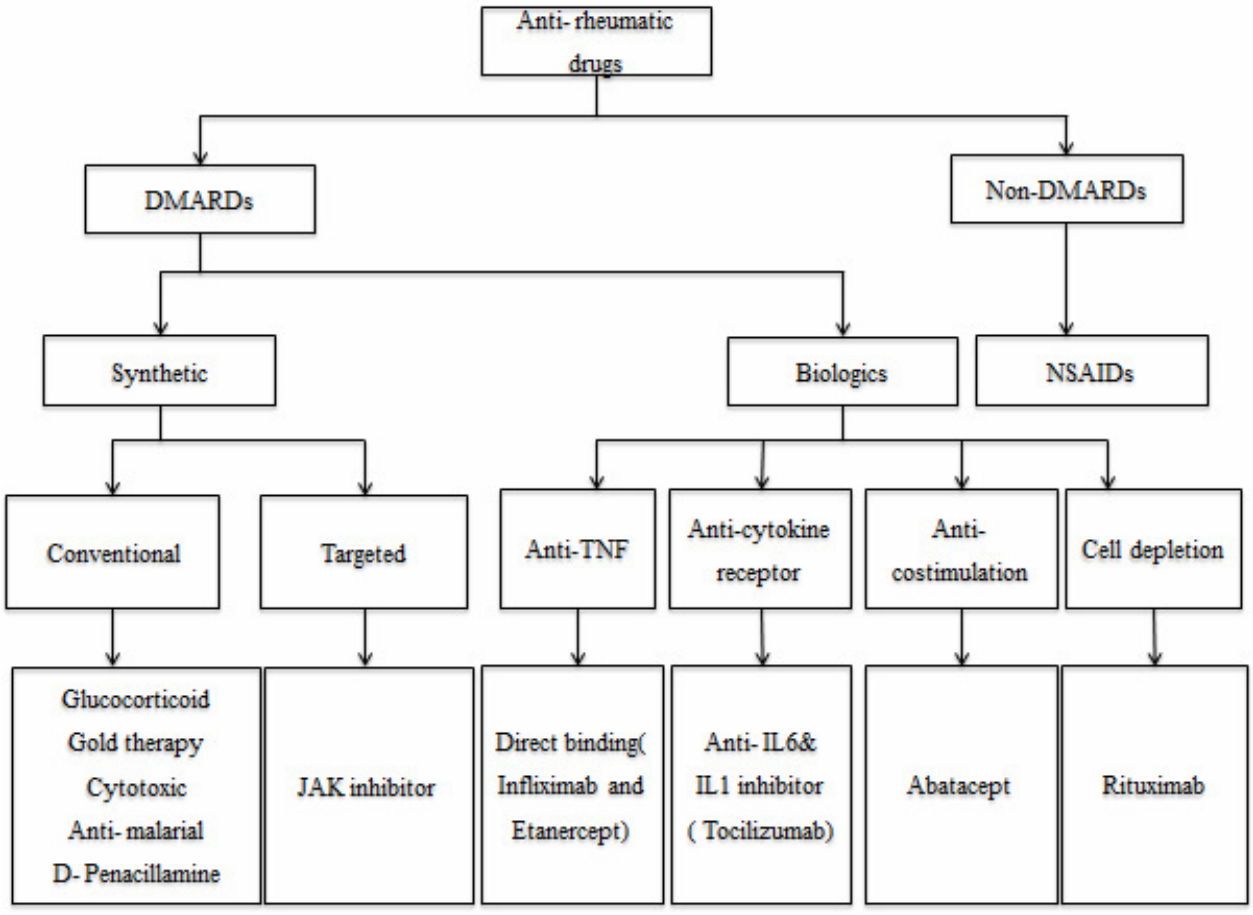


Fig. 6 : Classification of drugs according to their sources and mechanism of action (Dudics *et al*., 2018; Kourilovitch *et al*., 2014; Rahman *et al.,* 2017)

Corticosteroids:

Cortisol is a steroid hormone created normally by the body's adrenal organs. One of critical capacity of cortisol is its anti- inflammatory activity. Since, steroids have more potential long term side effects. In this way, they are regularly utilized as a measure to help control irritation while slower-acting DMARDs can produce results or might be utilized in case of inflammatory arthritis. In a perfect world, steroids ought to be utilized for the shortest period of time at the least dose to maintain a strategic distance from side effects (Joseph *et al*., 2016).

NSAIDs:

This is a class of treatments used to delight irritation and soreness of arthritis. These pharmaceuticals can control the side effects; however they don't avert movement or damage. NSAIDs can smother or diminish pain in the joints however they can't repair or prevent the disorder (Alam *et al*., 2017).

Table 1: Non-steroidal anti-inflammatory drugs and corticoids

S.no.	Drug	Mechanism of action	Side- effects	References
1	Diclofenac	COX1 and COX2 inhibitors	Asthma, nausea, rapid weight gain	(Kumar *et al*., 2016, Alam *et al*., 2017, Crofford, 2013)
2	Ibuprofen		Diarrhoea, rash, nausea	
3	Indomethacin		Nausea, vomiting, stomach discomfort	
4	Ketoprofen		Headache, rash, dizziness	
5	Naproxen		Nausea, fluid retention	
6	Meloxicam		Nausea, abdominal pain.	
7	Prednisolone, dexamethasone	Macrophage growth inhibitor	Nausea, stomach pain, sleep problems, increase sweating	(Joseph *et al*., 2016)

Modernistic pharmacological therapies for Rheumatoid arthritis

The distinguishing proof of a preclinical platform and a developing comprehension of the regular past and components of RA advancement close by novel prospective remedial mediations. Oral corticosteroids are powerful and successful mitigating remedies that can add to illness alteration. Symptomatic administration stays imperative over the span of the malady and comprises of regular useful measures to manage the essential indications of joint firmness, for example, torment and weakness. Exercise is vital to help joint adaptability and capacity, while keeping away from smoking is an all-inclusive guidance to all RA patients given its effect on immune response development (Guo *et al*., 2018). DMARDs are predominantly categorized into two varieties titled as synthetic and biological. Whereas synthetic DMARDs are further characterized as conventional or targeted/synthetic. Targeted DMARDs have been twisted as to amend the specific sites involved in age of aggravation. Critical models incorporate Janus kinase inhibitor, for example, tofacitinib or baricitinib. The utilization of customary DMARDs has developed observationally and their methods of activity are still to a great extent obscure (Smolen *et al*., 2017; Suresh, 2010).

Table.2: Modernistic pharmacological therapies for rheumatoid arthritis

S. No.	Drug	Mechanism of action	Molecules type	Usual dose	Side- effects	References
Conventional/ synthetic DMARDs						
1	Methotrexate	Analog of folic acid	Small molecule	25mg once weekly	Nausea, vomiting, pulmonary damage, increased liver enzyme	(Brown *et al*., 2016)
2	Leflunomide/ Triflunomide	Pyrimidine synthesis inhibitor		20mg/day	Diarrhoea, nausea, Hypertension, hepatotoxicity	(Smolen *et al*., 1999)
3	Sulfasalazine	Immunosuppression and anti-inflammatory		3g/day	Decrease appetite, stomach pain, decreased sperm count	(Jawad H.. Ahmed, 2011)
4	Chlorquinone	Immunomodulator		400mg/day	Gastrointestinal, skin, CNS adverse effect and retinal toxicity	(Review, 2018)
5	Baricitinib	JAK 1 and 2 inhibitor		2-4 mg/ day	Increase in creatine phosphokinase level, infection, hyperlipidaemia	(Nakayamada *et al*., 2016)
6	Tofacitinib	JAK 1,2 and 3 inhibitor		10mg/day		(Yamaoka, 2016, Jensen and Fave, 2012)
Biological DMARDs						
7	Adalimumab	TNF-α inhibitor	Human monoclonal antibody	40mg each 2 week	Hypertension, skin rashes, injection site reaction	(Burmester and Pope, 2017)
8	Certolizumab		Fragment of humanized antibody	200mg each 2 weeks	Hypotension, injection site reaction, serum sickness, skin rashes	(Jones *et al*., 2017,Review, 2018)
9	Infliximab		Human chimeric antibody	3-10mg/kg every 6 months	Infection, injection site reaction, stomach pain, tiredness	(Agarwal, 2011)
10	Etanercept		Receptor fusion protein	50mg/week subcutaneously	Severe/ anaphylactoid reaction, redness, itching	(Smolen *et al*., 2016)
11	Rituximab	B-cell depleting	Human chimeric antibody	1000mg intravenously every 6 months	Infection, Hypertension, viral reactivation	(Cohen *et al*.,2006)

12	Abatacept	CD28/CTLA4 system	Receptor fusion protein	125mg/week subcutaneously	Infection, malignancy	(Suresh, 2010, Kahlenberg and Fox, 2011)
13	Tocilizumab	IL-6 inhibition	Humanized antibody	162.6mg/week subcutaneously	Infection(mostly on easy-going tissue), growth in level of serum cholesterol	(Rubbert- Roth *et al*., 2018)

Conclusion

Rheumatoid arthritis (RA) is an immune system disorder that principally influences the lining of the synovial joints involving environmental, genetic and immunological factors. In this review, we have concise the modernistic pharmacological therapies including conventional/synthetic, biologic DMARDs. These treatments have some side effects or long term risks; however the adverse effect and function of these treatments will need to be carefully estimated. So, with a superior knowledge about the pathophysiology of rheumatoid arthritis, novel therapeutic methodologies are emergent to afford precise medication to persons.

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