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Formulation Approaches and Long-Term Implications of Therapeutics in Rheumatoid Arthritis: Current Trends and Future Outlook

Shivam[1], Ravinesh Mishra[2], Sheetal Sharma[3]*, Milind Thakur[4]

[1]Research Scholar, School of Pharmacy and Emerging Sciences, Baddi University, Baddi, District-Solan, H.P., India
[2]Associate Professor, School of Pharmacy and Emerging Sciences, Baddi University, Baddi, District-Solan, H.P., India
[3]Assistant professor, School of Pharmacy and Emerging Sciences, Baddi University, Baddi, District-Solan, H.P., India
[4]Research Scholar, School of Pharmacy and Emerging Sciences, Baddi University, Baddi, District-Solan, H.P., India
Department of Pharmaceutics, School of Pharmacy and Emerging Sciences, Baddi University of Emerging Sciences and technology, Baddi Makhnumajra- 173205, H.P. India
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ABSTRACT

The main sign of rheumatoid arthritis, an autoimmune inflammatory disease, is synovitis. It can also cause extra-articular organ involvement, like interstitial pneumonia, in addition to the clinical symptoms of pain, swelling, stiffness in several joints, fever, and malaise. Age, gender, heredity, and environmental exposure (cigarette smoking, air pollution, and occupational exposure) are risk factors. Therefore, from the earliest stages of the disease, accurate diagnosis and therapy are necessary. Despite the use of glucocorticoid and anti-inflammatory medication palliative therapy, disease-modifying antirheumatic medications (DMARDs) are now utilized to suppress immunological abnormalities and regulate disease activity. DMARDs are categorized into various classes, including biologic, targeted, and standard synthetic DMARDs. Remission is now the therapeutic objective for every patient thanks to the proper use of these medications. These medications have also been demonstrated to stop the long-term progression of joint degradation and physical disability by preserving remission. Future developments are expected to include the advent of precision medicine, safer and more efficient therapies, and therapeutic approaches targeted at curing or preventing drug shortages

KEY WORDS: Rheumatoid arthritis, Synovitis, Pro-inflammatory cytokines, HLA-DR4, Disease-modifying anti-rheumatic drugs (DMARDs), Joint destruction, Future direction.

1. INTRODUCTION

1. Rheumatoid arthritis (RA)

It is a systemic autoimmune chronic disease which processed by inflammation of the synovial membranes lining the joints, leading to joint damage, deformities, and, in some cases, systemic manifestations. It is an inflammatory arthritis that affects primarily joints symmetrically, but its effects can extend to various organ systems, regulates the lungs, blood vessels, skin and heart. It is linked to an aberrant immune response in which the body's defenses target its own tissues, particularly the joints, causing injury and inflammation [1].

The main pathological feature of RA is the inflammatory infiltration of the synovial lining of joints, which leads to synovitis (inflammation of the synovial membrane), subsequent joint destruction, and loss of function over time. The immune response in RA involves many cytokines, enter tumor necrosis factor (TNF)-α, interleukin-1 (IL-1), and interleukin-6 (IL-6), which are key drivers of inflammation and tissue damage [2].

1.1 Key Features

1.1.1. Chronic Inflammation:

The hallmark of RA is chronic inflammation in the synovial joints. This leads to pain, swelling, and stiffness, particularly in the hands, wrists, knees, and feet.

1.1.2. Autoimmune Nature:

It is a disorder autoimmune in which immune system mistakenly targets the body's own tissues, specifically in the case of synovial membrane in the joints.

1.1.3. Symmetrical Joint Involvement:

RA typically effects on both sides' joints in the body symmetrically, with early involvement of the smaller joints (e.g., fingers, wrists, knees).

1.1.4. Extra-Articular Manifestations:

RA can affect organs outside the joints, leading to complications such as rheumatoid nodules, cardiovascular disease, lung issues (e.g., interstitial lung disease), and more.

1.1.5. Joint Deformities:

If untreated or inadequately managed, RA can cause irreversible joint damage, resulting in deformities such as "swan neck" deformities and ulnar deviation in the hands [3].

2. PATHOPHYSIOLOGY

The pathogenesis of RA involves the activation of immune cells such as T-cells, B-cells, and macrophages, which infiltrate the synovial lining and release inflammatory cytokines and autoantibodies (e.g., rheumatoid arthritis and anti-citrullinated protein antibodies (ACPAs)). These molecules promote further inflammation, main role in the formulation of pannus (abnormal tissue growth) that destroys cartilage and bone. The process of pathophysiology of the disease is described by an onset of usually symmetrical inflammation with stiffness and pain predominantly by hands and feet of small joints although any cartilage-covered bone and synovial joint effect. The process begins with inflammation of the starting phase the joint capsule, leading to excessive synovial fluid accumulation containing the enzyme metalloproteinase which attacks and erodes the cartilage.

It has been discussing on the role of cytokines in the pathophysiology and treatment regimens of RA, in particular their role in synovitis. These chemicals control the immune responses responsible for cell growth, tissue repair and remodeling, and also inflammation, as they have pro- and anti-inflammatory effects.

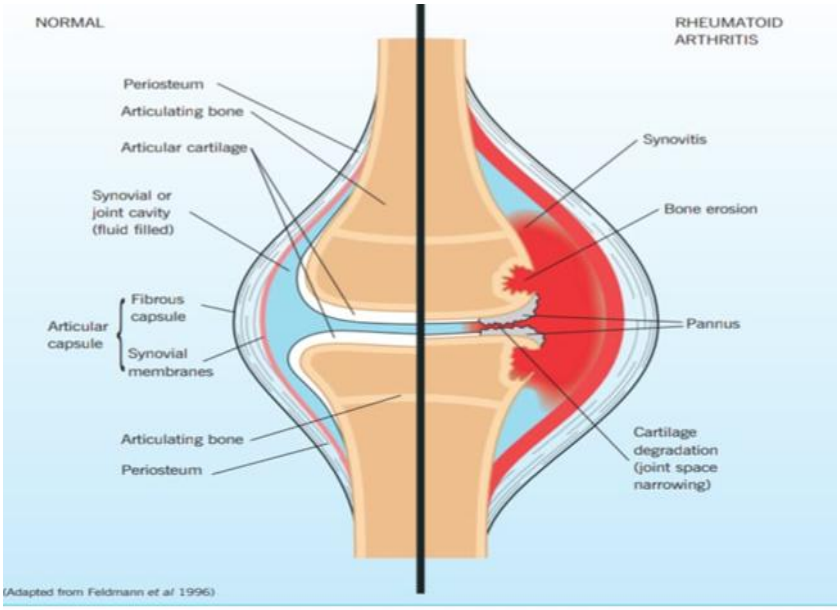


Fig no.1: Pathophysiology of Rheumatoid Arthritis

It is having been divided into two groups:

- Th1: promotes T-cell mediated immunity.
- Th2: determines B-cell humeral (antibody) response.

The body's immune system is reliant on self-regulating levels in these cytokines, has been important as per point view of healthy operational immune system. The levels are controlled by the visual in genes which are influenced by environmental factors, in case of pathogens in the joints. An excess or inadequate production of interleukins (a type of cytokine) and interferon (such as an anti-viral biomarker) which make up Th1 and Th2, leads to a failure in the homeostatic roles of cytokines resulting in synovitis associated with RA [4].

Table 1. Some Stages of Rheumatoid Arthritis [5]

Stage	Pathologic Process	Sign	Phenomenal Sign	Radiographic Changes
1	Presentation of antigen to T cells.	Probably none	-	-
2	T-cells proliferation B-cells proliferation Angiogenesis in synovial membrane.	Malaise, mild joint tension and inflamed	Swelling of hand in a small joint of wrists or pain in hands, wrists, femur and toes.	none
3	Accumulation of neutrophils in synovial fluid, synovial-cell proliferation without polarization or spreads of cartilage.	Joint pain and swelling, morning stiffness, malaise and weakness.	Warm, swollen joints, excess synovial fluid, soft-tissue proliferation under the joints pain and disadvantages of movement in a rheumatoid nodule.	Soft -tissue swelling
4	Polarization of synovitis into a centripetally invasive pannus Activation of chondrocytes Initiation of enzyme [proteinase] debasement of cartilage.	Under the sign stage 3	Cover up with as stage 3, but more pronounced swelling.	MRI reveals proliferative pannus; radiographic evidence of periarticular osteopenia.
5	Erosion of subchondral bone Invasion of cartilage by pannus chondrocyte proliferation stretched ligaments around joints.	Under the sign 3, plus misplacement of function and early deformity [e.g., ulnar deviation at metacarpophalangeal joints].	Same at stage 3, plus instability of joints, flexion contractures, low range of the motion, extraarticular complications.	Early erosions and narrowing of joint spaces.

3. EPIDEMIOLOGY

The study of how diseases spread and what causes them in human communities is known as epidemiology. Two basic tenets underlie this definition: first, that human disease does not arise randomly, and second, that there are preventive and causative factors for human disease that can be found by methodically examining various populations or subgroups of people within a population in various settings or at various times. Therefore, basic explanations of how disease manifests in a population (i.e., disease frequency, incidence, and prevalence levels, mortality, time trends, geographic distributions, and clinical features) as well as explanations of the probable risk factors for disease occurrence are included in epidemiologic studies [6].

3.1 Danger Factors of Epidemiology:

3.1.1. Genetic factor

Twin and family studies strongly imply that shared genetic variables influence disease risk among affected individuals' relatives. Studies were conducted on Caucasian patients with developed RA who contained alleles encoding a "shared epitope" known as a rheumatoid epitope. These investigations also revealed a substantial link between "rheumatoid epitope" and disease severity and outcome [7,8].

3.1.2. Age and Sex

Women are very chances develop RA than males. Most studies report a sex ratio ranging from roughly 2:1 to 3:1. The discrepancy shows that reproductive and hormonal factors important role in a disease’s occurrence. The main of epidemiological studies show that in case of age disease onset peaks in the fifth decade of life.

3.1.3. Smoking

Smoking is believed to affect both the chance of developing RA and the development in the disease. The increased risk of RA related with smoking has been reported in both cross-sectional and data reveal an association of adverse socioeconomic status with worse prognosis of the disease [9].

3.1.4. Hormonal Factor

The evidence occur on the females are more mainly to develop RA than males shows that hormonal variables may important in disease vulnerability. Furthermore, estrogens are known to stimulate the immunological system. Epidemiological studies attempted to investigate this link by looking into the potential protective role of pregnancy parity has been connected with a lower chance of developing RA. However, it is unclear is connect visual a protective impact of pregnancy or an increased chance of infertility prior to the onset of RA. Pregnancy has also been linked to RA patients going into remission. This impact reverses in the postpartum period [10].

3.1.5. Dietary factor

There are many studies occur on eating fish, olive oil, and cooked vegetables throughout one's life may have a protective effect. The preventive effects of fish eating have been related to the changes of omega-3 large chain process polyunsaturated fatty acids on poly-inflammatory diseases. The Mediterranean diet as a whole has also been identified as a lifestyle component that lowers the risk of acquiring RA and protects against a severe course of the illness. Basic observations have been partially verifying the geographical variations of disease occurrence and severity [11].

4. MARKET FORMULATION AND ITS ROUTE AND MECHANISM [12]

Category	**Preparation Type**	**Example**	**Route**	**Mechanism /Use**
Biologics	Injectable	Adalimumab (Humira), Etanercept (Enbrel)	Subcutaneous (SC)	TNF - inhibitors
		Tocilizumab (Actemra), Rituximab (Rituxan)	Intravenous (IV)	IL-6 Receptor/Anti-CD20
JAK Inhibitors	Oral	Oral	JAK pathway inhibitors	
	Topical	Diclofenac gel	Topical	Pain relief, anti-inflammatory
Corticosteroids	Oral	Prednisone	Oral	Anti-inflammatory
	Injectable	Methylprednisolone	IV	Anti-inflammatory
Emerging Therapies	Injectable	SMO3(Anti-CD22 monoclonal antibody)	IV	Immune modulation
	Oral and Subcutaneous (pipeline	Novel therapies in clinical trials Upadacitinib	Various	Target -specific inhibition
DMARDs	Oral	Methotrexate, Hydroxychloroquine, Leflunomide	Oral SC/IM	Immune -modulator
	Injectable	Methotrexate		Immune
NSAIDs	Oral	Ibuprofen, Naproxen	Oral	Pain relief anti-inflammatory

5. SYMPTOMS

Rheumatoid arthritis symptoms and indicators can include:

- Swollen
- Heated and tender joints Usually worst at the mornings or after inactivity.
- Joint stones Fatigue.
- Fever and appetite loss smaller joints especially those connecting your fingers or in your hands by your toes to your feet, are typically the first to be affected by early rheumatoid arthritis.

Basically, it depends upon knees, ankles, wrists, elbows, hips, and shoulders are frequently affected as the illness worsens. Usually, the joints on both sides same of your body experience the same sensations [13].

About 40% of people have been rheumatoid arthritis also effect physical sign and symptoms that don't participate the joints. Areas that may be acted include: Skin Eyes Lungs Products & Services A it has a Book: Mayo Clinic Guide to Arthritis present more products by Mayo Clinic heart, kidneys, Salivary Glands, Nerve Tissue, Bone marrow, Blood vessels.

Rheumatoid arthritis signs and symptoms may vary in severity and may even come and go. Periods of increased disease activity, called flares, alternate with periods of relative remission when the swelling and pain fade or disappear. Over time, rheumatoid arthritis can cause joints to deform and shift out of place [14].

Pain and swelling feet and the hands are common symptoms of RA. The wrists, knuckle and knuckle, toe knuckles, and proximal hinge joints are where the swelling is most noticeable. This is followed by stiffness in the morning joints that lasts longer than thirty minutes and typically for several hours. In case of swelling is usually "soft" due to effusion and synovitis, as opposed to the "hard" (bony) by the osteoarthritis. Swelling occurs in a under joints in case of finger involved [15].

6. CAUSES

An autoimmune condition is rheumatoid arthritis. Your immune system often aids in defending your body against illness and infection. Your immune system targets healthy joint tissue when you have rheumatoid arthritis. Additionally, it may result in health issues with your skin, eyes.
The main cause of this process doctors, however it seems likely to be genetic. Although your genetic makeup may not directly cause rheumatoid arthritis, it may increase your susceptibility to environmental triggers, such as bacterial and viral infections.

7. DIAGNOSIS

The usual patient has morning joint stiffness, recently developed sore and swollen joints, and abnormal laboratory results like increased C-reactive protein or erythrocyte sedimentation rate [16].

When no other conditions can account for the clinical symptoms, the new criteria, which were created using cohorts and case studies of early with the patients, require at once upon a minimum clinically joint effusion as an admission criterion. Following that, the classification criteria enable a sensitive evaluation of the degree of joint involvement (painful joints or joints that test positive on MRI or ultrasound can be classified as active joints, just as well as clinically swollen joints). Long illness duration, test indicators of systemic inflammation, and serological markers (RF and ACPA) are additional characteristics. At the expense of 16% less specificity, by the standard has been selected in several scenarios, offer 21% more sensitivity than the previous criteria [17].

7.1. Joint Manifestations:

The main clinical characteristic of RA is soft synovial joint enlargement, which is usually accompanied by morning stiffness and discomfort upon examination. It is notable that RA is not present in the axial joints or distal interphalangeal joints. The participation of the spine's C1–C2 joint is the most significant exception to this rule (FIG. 4g). The highly destructive character of RA sets it apart from other types of arthritis by causing articular and periarticular bone damage as well as inflammatory cartilage degradation [18].

7.2. Systemic manifestations:

The joints are not the only parts affected by RA. RA is a systemic illness that can cause a variety of extra-articular symptoms in the heart, lungs, eyes, and other organs. It is also linked to an elevated acute-phase response. In case they are minimum on these days, rheumatoid nodules and vasculitis (FIG. 4h) may be seen in severe RA. Moreover, fibromyalgia may accompany RA. Effective treatment can attenuate or minimize the disease's extra-articular symptoms and consequences [19].

Taking a medical history, doing a physical examination, ordering laboratory tests, ordering imaging procedures like ultrasounds or x-rays are the methods that doctors use to diagnose RA. Because rheumatoid arthritis progresses over time by the less symptoms in a present days or early stages. It has been be challenging to identify the condition in its early starting process. The condition cannot be diagnosed with a single test. The symptoms may

resemble those of other joint diseases and forms of arthritis. The symptoms may resemble those of other joint disorders and forms of arthritis. Individual differences in symptom [20].

8. TREATMENT

Phase	**Standard strategy**	**Different strategy**	**Result and further outcome**		
First-line treatment	Start initial csDMARD (methotrexate) plus less-term glucocorticoids	If methotrexate is contraindicated, use an alternate csDMARD (leflunomide or sulfasalazine)	Target reached continued first -line treatment	Target sustained Moved to remission phase	Target failure Moved to second line treatment
Second-line treatment	Continued csDMARD or adding Bdmad (combination csDMARD + bDMARD	Poor in case prognostic factor is present, switch to another csDMARD monotherapy	Continue second -line treatment	Moved to remission phase	Moved to third -line treatment
Third-line treatment	Adding some any other bDMARD or tsDMARD, in continued csDMARD	Not applicable	Continued 3rd line treatment	Moved to a discharge phase	Repeat the 3rd line treatment on another drug until target it reached
Remission phase	Consider tapering existing therapy by reducing does or by extending time period in the treatment	Continued therapy based on patient or physician preference	Not applicable patients already at target	Continue tapering and reverse remission phase basic and different plan	Retry previously effective strategy

As rheumatoid arthritis treatment advances, many people might experience symptom alleviation and an improvement in their quality of life. To treat RA, doctors may employ the following strategies:

- Remedy
- Exercise and rehabilitation
- Operation
- Pattern monitoring and continuous care
- Complementary therapies have been doctor suggest a many of treatments, change a large time plan on a symptom in a several diseases. There is no treatment in plan of doctor suggest all goal to help:
- Analgesic
- Minimum inflammation and less swelling
- Stop, less or terminate joint and organ impairment
- By doing activity enhance ability

9. CRYSTAL FORMULATION IN JOINTS

It must identify that uric acid and gout are related, and it is a pathological connection between the two [21]. Fatness or older is the dangerous factor that are common to both gout and may complicate the relationship between the two illnesses [22]. It has long been known that uric acid and gout are related, and there is a pathological connection in a two [23]. It is not clear how both prevalent disorders are pathologically related [24, 25].

Chronic hyperuricemia leads to the deposition of monosodium urate crystals in the joints, which causes arthritis. It is the most prevalent inflammatory arthritis in men and affects 1% to 2% of individuals in affluent nations. The prevalence of gout appears to be increasing, according to epidemiological

data. Primary gout appears to be primarily caused by genetic polymorphisms in renal transporters of urate and diet. Metabolic syndrome hypertension diabetes mellitus, or cardiovascular and renal disorders are linked to gout and hyperuricemia [26].

One of the most prevalent types of crystalline urate, the primary sediment in gouty arthritis, is monosodium urate (MSU) monohydrate (NaC5H3N4O3.H2O), in which a urate molecule links to sodium and a water molecule [27]. Clinical symptoms, such as excruciating pain, erythema, and edema, are brought on by crystal deposit in the articular joints and periarticular tissue in serum uric acid level are elevated over the local solubility limits [28, 29]. The key to acute gout arthritis is MSU crystals, and hyperuricemia is the essential biological basis of a gout attack [30].

Gout can be "cured" by first totally dissolving MSU crystals and then preventing the production of new crystals. After the crystal burden has been removed [31]. Tactical actions or interventions to accomplish strategic goals provide the foundation of the entire plan [32].

10. LONG TERM TOXICITY CAUSE BY CONSUMPTION OF ARTHRITIS DRUG

Rheumatoid arthritis is a chronic, autoimmune, inflammatory, and systemic condition that primarily affects the joints but also affects the skin, blood vessels, muscles, heart, and lungs [33]. The hallmark of RA is the inflammation of the synovial membrane, which results in redness, swelling, and the creation of autoantibodies. This triggers inflammatory synovitis, which in turn destroys articular cartilage and eventually erodes bone joints [34].

For example, Methotrexate have many harmful effects includes are vomiting, diarrhea, myelosuppression, liver dysfunction, renal failure, pancytopenia, pulmonary symptoms, mucositis, stomatitis, gastrointestinal ulcers, and cutaneous ulcerations, are caused by the antifolate properties even when used at low dosages. Increases in aminotransferase, uric acid, thrombocytopenia, leukopenia, and anemia were observed in the serum of RA patients receiving methotrexate [35].

Anti-rheumatic medications have very opposite effect than positive ones, and prolonged use of methotrexate has been linked to multiorgan toxicity. Leflunomide was suggest in children with severe disease, whereas methotrexate was appointed among the children early disease. Compared to those treated with leflunomide, patients treated with methotrexate gained more weight. Long-term use of leflunomide increases the risk of hepatotoxicity, but it has been shown to have less detrimental effects on the respiratory system and cardiac output. Conversely, methotrexate is more harmful to the cardiovascular and kidney systems, which raises blood pressure. However, by lowering urea and uric acid, it lessens inflammation. Therefore, it can be said that the two medications are interchangeable and can be prescribed in different ways for less severe side effects [36].

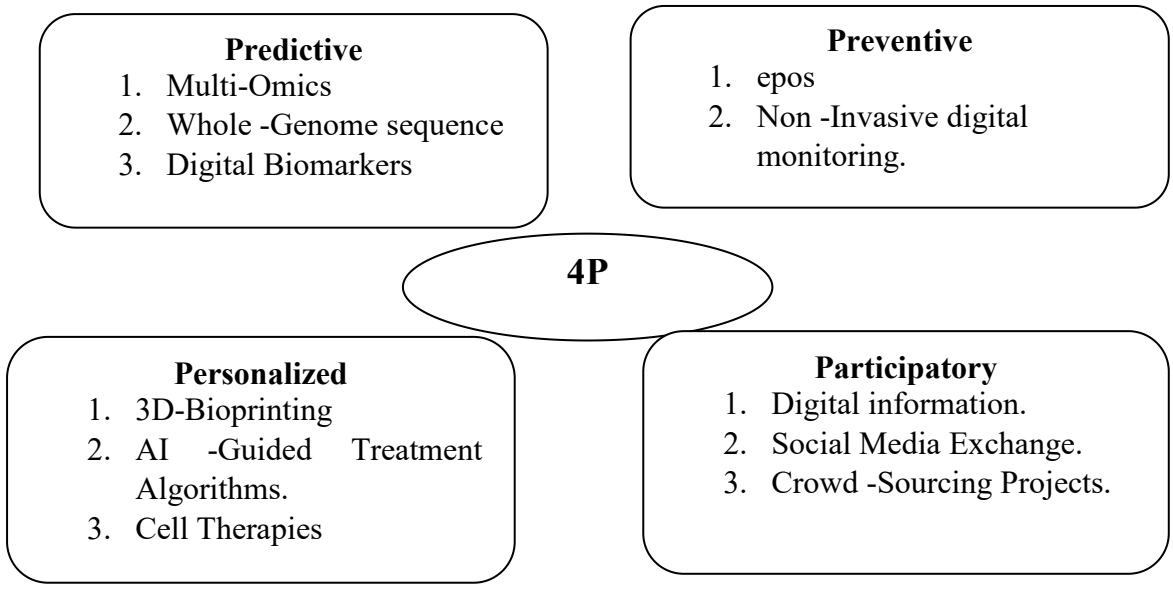
11. FUTURE DIRECTION

We still cannot prevent or cure the disease in spite of all these advancements. Diagnostic We are still unable to prevent or cure the disease in spite of all these advancements. For many patients, expensive treatments and delays in diagnosis brought on by a lack of access to a specialist continue to be significant challenges [37,38]. The terato-target concept and the objective of disease remission are frequently overlooked, even in developed nations. For many individuals, RA continues to be the cause of their disability and decreased quality of life [39].

In addition to the aforementioned advancements and paradigm changes necessary to create P4 medicine in rheumatoid arthritis Crucial issues must be resolved. Long-term, the objective is to apply the P4 method to practice more patient-centered, economical, and efficient medicine that offers each person the best care possible [40].

12. FOUR P CONCEPT FOR RHEUMATOID ARTHRITIS

Patients with RA will have a bright future. The development of biological and digital biomarkers will enable us to further identify and track the illness. Patients with RA will have a bright future. We will be able to identify and track the illness even more precisely with the advent of biological and digital biomarkers [41]. At the end there was a less source to justify combo therapy until recently, many rheumatologists still prescribe it [42,43].



CONCLUSION

RA is a chronic, inflammatory, disabling condition that can lead to long-term disability and joint degeneration. Serious harm and the loss of vital body functions can only be avoided by early diagnosis and management. As a result, early diagnosis and appropriate therapy are necessary we now understand disease pathways better thanks to developments in molecular medicine, which can help in the development of more potent treatments. DMARDs are used to treat the condition by suppressing immunological abnormalities and regulating disease activity. DMARDs are divided into three categories: biologic DMARDs, targeted synthetic DMARDs (such JAK inhibitors), and standard synthetic DMARDs (like methotrexate). These drug classes have been demonstrated to prevent structural damage to the joints and to prevent the progression of physical dysfunction. Precision medicine, cure-focused therapeutic approaches, and safer and more efficient therapies are anticipated in the future. Young researchers and doctors may find inspiration in translation research that aims to provide novel treatments and preventative measures.

REFERENCE

1. **Firestein, G. S., & McInnes, I. B. (2017).** "Immunopathogenesis of rheumatoid arthritis." Immunity.
2. This review article details the immune mechanisms involved in RA, focusing on the role of immune cells and cytokines in disease progression.
3. **Aletha, D., et al. (2010).** "Rheumatoid arthritis classification criteria: and collaborative initiative." Arthritis & Rheumatism.
4. Clancy J, Hexthorpe H (2011) Pathophysiology of rheumatoid arthritis: nature or nurture
5. Epstein, F. H., & Harris, E. D. (1990). Rheumatoid Arthritis. New England Journal of Medicine, 322(18), 1277–1289.
6. Fletcher, G. S. (2019). Clinical epidemiology: the essentials. Lippincott Williams & Wilkins.
7. Weygand, C. M. (1992). The Influence of HLA-DRB1 Genes on Disease Severity in Rheumatoid Arthritis. Annals of Internal Medicine, 117(10), 801. doi:10.7326/0003-4819-117-10-801
8. Gabriel, S. E., Crowson, C. S., & O'Fallon, M. (1999). The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. Arthritis & Rheumatism, 42(3), 415–420. doi:10.1002/1529-0131(199904)42:3<415: aid-anr4>3.0.co;2-z
9. Harrison, B. J. (2002). Influence of cigarette smoking on disease outcome in `97. doi:10.1097/00002281-200203000-00003
10. Buyon, J. P., Nelson, J. L., & Lock shin, M. D. (1996). The Effects of Pregnancy on Autoimmune Diseases. Clinical Immunology and Immunopathology, 78(2), 99–104. doi:10.1006/clin.1996.0018.
11. Cleland, L. G., James, M. J., & Proudman, S. M. (2003). The Role of Fish Oils in the Treatment of Rheumatoid Arthritis. Drugs, 63(9), 845–853. doi:10.2165/00003495-200363090-00001.
12. Neil O. J Liam, Rodriguez -Alpizar Dashier, Deane. Kevin D Rheumatoid Arthritis: The Continuum of Disease and Strategies for Prediction, Early Intervention, and Prevention. The Journal of Rheumatology 2024; xx:xxxx doi:10.3899/jrheum.2023-0334 First Release February 15 2024.

13. Aletaha, D., & Smolen, J. S. (2018). Diagnosis and Management of Rheumatoid Arthritis. JAMA, 320(13), 1360. doi:10.1001/jama.2018.13103.
14. Smolen, J. S., Aletaha, D., Barton, A., Burmester, G. R., Emery, P., Firestein, G. S., … Yamamoto, K. (2018). Rheumatoid arthritis. Nature Reviews Disease Primers, 4, 18001. doi:10.1038/nrdp.2018.1
15. Smolen J.S Aletaha .D Mclnnes.LB Rheumatoid arthritis http://dx.doi.org/10.1016/S0140-6736(16) 30173-8
16. Radner, H., Neogi, T., Smolen, J. S., & Aletaha, D. (2013). Performance of the 2010 ACR/EULAR classification criteria for rheumatoid arthritis: a systematic literature review. Annals of the Rheumatic Diseases, 73(1), 114–123. doi:10.1136/annrheumdis-2013-203284
17. Hurd ER. Extraarticular manifestations of rheumatoid arthritis. Semin Arthritis Rheum 1979; 8: 151–76.
18. Smolen, J. S. et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum. 38, 38–43 (1995).
19. Minichiello, E., Semerano, L. & Boissier, M. C. Time trends in the incidence, prevalence, and severity of rheumatoid arthritis: a systematic literature review. Joint Bone Spine 83, 625–630 (2016). 123.
20. Theander, L. et al. Severe extraarticular manifestations in a community-based cohort of patients with rheumatoid arthritis: risk factors and incidence in relation to treatment with tumor necrosis factor inhibitors. J. Rheumatol 44, 981–987 (2017). 124. Aggarwal, R. et al. Distinctions between diagnostic and classification criteria? Arthritis Care Res. 67, 891–897 (2015).
21. Ma, C. A., & Leung, Y. Y. (2017). Exploring the Link between Uric Acid and Osteoarthritis. Frontiers in Medicine, 4. doi:10.3389/fmed.2017.00225
22. Saag KG, Choi H. Epidemiology, risk factors, and lifestyle modifi cations for gout. Arthritis Res Ther 2006; 8 (suppl 1): S2.
23. Harris CM, Lloyd DC, Lewis J. The prevalence and prophylaxis of gout in England. J Clin Epidemiol 1995; 48: 1153–58.
24. Wallace K, Riedel A, Joseph-Ridge N, Wortmann R. Increasing prevalence of gout and hyperuricemia over 10 years among older adults in a managed care population. J Rheumatol 2004; 31: 1582–87.
25. Annemans L, Spaepen E, Gaskin M, et al. Gout in the UK and Germany: prevalence, comorbidities and management in general practice 2000–2005. Ann Rheum Dis 2008; 67: 960–66.
26. Liebman SE, Taylor JG, Bushinsky DA. Uric acid nephrolithiasis. Curr Rheumatol Rep 2007; 9: 251–57.
27. Mandel NS, Mandel GS. Monosodium urate monohydrate, the gout culprit. J Am Chem Soc. 1976;98(8):2319–23.
28. Dalbeth N, et al. Gout Nat Rev Dis Primers. 2019;5(1):69.
29. Richette P, et al. 2018 updated European League against Rheumatism evidence-based recommendations for the diagnosis of gout. Ann Rheum Dis. 2020;79(1):31–8.
30. Neogi T, Gout. Ann Intern Med. 2016;165(1):ITC1–ITC16.
31. Doherty M, Jansen TL, Nuki G, Pascual E, Perez-Ruiz F, Punzi L, et al. Gout: why is this curable disease so seldom cured? Ann Rheum Dis. 2012;71:1765–70
32. Perez-Ruiz F, Herrero-Beites AM, Carmona L. A twostage approach to the treatment of hyperuricemia in gout: the ‘‘Dirty Dish’’ hypothesis. Arthritis Rheum. 2011;63:4002–6.
33. Dinesh, P., Rasool, M., 2019. Berberine mitigates IL-21/IL-21R mediated autophagic influx in fibroblast-like synoviocytes and regulates Th17/Treg imbalance in rheumatoid arthritis. Apoptosis 24, 644–661. https://doi.org/10.1007/s10495-019- 01548-6.
34. Zhang, X., Dong, Y., Dong, H., Zhang, W., Li, F., 2017. Investigation of the effect of phlomisoside F on complete Freund’s adjuvant-induced arthritis. Exp. Ther. Med. 13, 710–716. https://doi.org/10.3892/etm.2016.3995.
35. Bidaki, R., Kian, M., Owliaey, H., Babaei Zarch, M., Feysal, M., 2017. Accidental chronic poisoning with methotrexate; report of two cases. Emergency 5.
36. Zatmum T ,Rihar A, Qirat M.A Labql M.A . Comparative analysis of multiorgan toxicity induced by long term use of disease modifying anti-rheumatic drugs.
37. Mucke .J, Krusche .M and Burmester.G.R A broad look into the future of rheumatoid arthritis.
38. . Einarsson JT, Willim M, Ernestam S, et al. Prevalence of sustained remission in rheumatoid arthritis: impact of criteria sets and disease duration, a Nationwide Study in Sweden. Rheumatology 2019; 58: 227–236.

39. Matcham F, Scott IC, Rayner L, et al. The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: a systematic review and meta-analysis. Semin Arthritis Rheum 2014; 44: 123–130

40. Mucke J, Sewerin P and Schneider M. Rheumatology in 2049: the age of all data. Ann Rheum Dis 2021; 80: 825–827.

41. Burmester GR. Rheumatology 4.0: big data, wearables and diagnosis by computer. Ann Rheum Dis 2018; 77: 963–965.

42. Breedeveld .F.C Current and future management approaches for rheumatoid arthritis.`

43. Verhoeven AC, Boers M, Tugwell P: Combination therapy in rheumatoid arthritis: updated systemic review. Br J Rheumatol 1998, 37:612-619.