

Deciphering Rheumatoid Arthritis: A Detailed Review of Clinical Features, Disease Progression, and Treatment Strategies

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation primarily affecting the joints, leading to significant morbidity and potential systemic complications. This detailed review explores the multifaceted nature of RA, highlighting its clinical features, progression, risk factors, and contemporary treatment strategies. The analysis begins with an overview of the disease's pathophysiology, emphasizing the role of immune dysregulation and genetic predispositions. Clinical symptoms are discussed, including joint tenderness, stiffness, and systemic manifestations which may arise throughout the disease course. Various risk factors, such as gender, age, genetic background, and lifestyle choices, contribute to RA's onset and severity. Treatment approaches for RA have evolved, guided by the principles of the treat-to-target (T2T) strategy aimed at achieving low disease activity or remission through regular monitoring and individualized care. Current pharmacologic therapies include nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, traditional and biologic disease-modifying antirheumatic drugs (DMARDs), and newer targeted agents such as Janus kinase (JAK) inhibitors. Beyond pharmacotherapy, lifestyle modifications and comprehensive management strategies are crucial for improving patient outcomes. This review concludes by emphasizing the importance of early diagnosis and a multifactorial approach to RA management that incorporates patient education, lifestyle modifications, and ongoing research into innovative treatments to enhance the quality of life for individuals living with this debilitating condition.

Keywords: Naproxen; Salivary Glands; Rheumatoid Arthritis; lymphoma; seronegative; metalloproteinases; glucocorticoids; sulfasalazine

Abbreviations: RA: Rheumatoid Arthritis, T2T: Treat-to-Target, NSAIDs: Nonsteroidal Anti-Inflammatory Drugs, DMARDs: Disease-Modifying Antirheumatic Drugs, COX: Cyclooxygenase, LDAS: Low Disease Activity States, ACPA: Autoantibodies, Particularly Anti-citrullinated Protein Antibodies, GWAS: Genome-wide Association Studies, MMPs: Matrix Metalloproteinases, ACR: American College of Rheumatology, EULAR: European League Against Rheumatism

Introduction

Rheumatoid arthritis (RA) is a chronic auto immune joint disease primarily affecting the hands and feet, characterized by immune cell infiltration, synovial hyperplasia, pannus formation, and destruction of cartilage and bone. Its exact cause remains unclear, but both genetic and environmental factors play a role, with an estimated prevalence of 0.5% to 1.0% globally, and

a higher incidence in females. RA leads to symptoms such as morning stiffness and, if untreated, can result in severe joint damage and disability. Various treatments have been explored in clinical trials, with nonsteroid ante-inflammatory drugs (NSAIDs) like acetylsalicylate, naproxen, ibuprofen, and etodolac commonly used to alleviate inflammation and pain by inhibiting cyclooxygenase (COX) enzymes. While NSAIDs and corticosteroids

are effective for reducing symptoms, they do not modify the disease's progression. Disease-modifying antirheumatic drugs (DMARDs) have gained attention for their potential to effectively manage RA and achieve low disease activity states (LDAS) and remission, which require regular monitoring and adjustment of treatment plans. Composite scales, such as CDAI, SDAI, and DAS-28, are utilized to assess disease activity [1].

Symptoms

- i. Tender, warm, and swollen joints
- ii. Joint stiffness that tends to be worse in the mornings or after periods of inactivity
- iii. Fatigue, fever, and loss of appetite

Early rheumatoid arthritis typically impacts smaller joints first, particularly those connecting the fingers to the hands and the toes to the feet. As the condition progresses, larger joints such as the wrists, knees, ankles, elbows, hips, and shoulders may also be affected. Generally, symptoms are symmetrical, meaning the same joints on both sides of the body are usually impacted. Approximately 40% of individuals with rheumatoid arthritis may also experience non-joint-related symptoms, which can involve: Skin, Eyes, Lungs, Heart, Kidneys, Salivary glands, Nerve tissue, Bone marrow and Blood vessels. The severity of rheumatoid arthritis symptoms can vary and may be episodic, with periods of relative remission-where symptoms subside or disappear-alternating with flare-ups, characterized by increased disease activity. Over time, rheumatoid arthritis can lead to joint deformation and displacement. If left untreated, it can infiltrate and damage cartilage, the connective tissue that cushions the ends of the bones. Moreover, the ligaments and tendons stabilizing the joint may stretch and weaken, ultimately leading to significant joint damage and alteration in shape. The exact cause of the immunity's function leading to RA remains unknown [2].

Risk Factors

- a. **Sex:** Women are more likely than men to develop rheumatoid arthritis.
- b. **Age:** While RA can emerge at any age, it most frequently begins in middle age.
- c. **Family History:** A family history of rheumatoid arthritis can increase your susceptibility to the disease.
- d. **Smoking:** Cigarette smoking is linked to a higher risk of developing RA, especially for those with a genetic predisposition. It is also associated with more severe disease progression.
- e. **Excess Weight:** Obesity may slightly elevate the risk of rheumatoid arthritis.
- f. **Osteoporosis:** This condition, which weakens bones and makes them more susceptible to fractures, may be related to RA.

g. **Rheumatoid Nodules:** These firm tissue bumps commonly arise around pressure points, such as elbows, but can occur anywhere in the body, including the heart and lungs.

h. **Dry Eyes and Mouth:** People with rheumatoid arthritis are at a higher risk for Sjögren's syndrome, a disorder that reduces moisture in the eyes and mouth.

i. **Infections:** Both rheumatoid arthritis and many of its treatments can compromise the immune system, leading to increased susceptibility to infections. Getting vaccinated against illnesses like influenza, pneumonia, shingles, and COVID-19 is important for protection.

j. **Abnormal Body Composition:** Individuals with rheumatoid arthritis often have a higher fat-to-lean mass ratio, even with a normal body mass index (BMI).

k. **Carpal Tunnel Syndrome:** Inflammation in the wrists caused by RA can compress the nerve that serves most of the hand and fingers.

l. **Heart Problems:** Rheumatoid arthritis can raise the risk of artery hardening and blockage, as well as inflammation of the fibrous sac that encases the heart.

m. **Lung Disease:** There is an increased risk of lung tissue inflammation and scarring in people with rheumatoid arthritis, potentially leading to progressive shortness of breath.

n. **Lymphoma:** RA has been associated with a higher risk of lymphoma, a type of blood cancer that develops in the lymphatic system.

The Immune System and the Pathophysiology of Rheumatoid Arthritis

In rheumatoid arthritis (RA), both memory and naïve B cells infiltrate and accumulate in the synovial tissue, where specific B cell clones with a pronounced tendency to migrate appear to undergo continuous activation. According to flow cytometry studies, peripheral B cells from RA patients demonstrate significantly lower levels of FcγRIIb (an inhibitory receptor essential for feedback inhibition of IgG immune complexes) and elevated levels of CD86 (a costimulatory protein). These marked changes suggest that inflammation in RA can dysregulate the expression of CD86 and FcγRIIb, potentially contributing to a breakdown of immune tolerance and the subsequent emergence of humoral autoimmunity. A transcription factor, FOXO3a, plays a crucial role in regulating cell survival and controlling the cell cycle. Microarray studies have shown that RA patients have increased levels of FOXO3a mRNA in their peripheral blood, predominantly with in polymorphonuclear cells. This finding was further confirmed in T lymphocytes found in the inflammatory aggregates of the RA synovial tissue sub lining. This overexpression of FOXO3a likely contributes to the chronic inflammation characteristic of RA by prolonging the survival of these immunece allotypes.

Additionally, elevated levels of soluble B7-H4 (sB7-H4) have been detected in the sera of RA patients. Research in mouse models suggests that sB7-H4 exacerbates arthritis by competing with B7-H4, an inhibitory molecule involved in the B7-CD28 signaling pathway. ZAP-70 is a vital player in their curation of downstream effectors or molecules during T cell receptor (TCR) signaling. A series of sophisticated transgenic experiments that involved mutating key scaffolding residues in ZAP-70 demonstrated diminished T cell growth and sensitivity to TCR stimulation, as well as disruptions in both positive and negative thymic selection processes, resulting in fewer regulatory T cells (Tregs). Interestingly, these mice did not develop arthritis, although they did produce circulating rheumatoid factors. This response contrasts with SKG mice, which are predisposed to arthritis and possessed different ZAP-70 mutations despite having similar T cell developmental defects. The distinct TCR repertoires in these two strains seem to delineate the boundary between autoreactivity and overt autoimmunity. Regulatory T cells (Tregs) are fundamental in maintaining immune tolerance. Compared to effector T cells, Tregs have been observed to transport lower levels of protein kinase C θ (PKC θ) to the immunological synapse following TCR signaling, which results in reduced activation of NF- κ B downstream. Interestingly, PKC θ appears to negatively regulate Treg function. In RA, TNF α is known to promote Treg localization to the immunological synapse, further complicating their regulatory role in this context.

****Genetic and Familial Risk Factors for RA****

There is substantial evidence to suggest that genetic factors play a pivotal role in the onset and development of RA. A notably higher incidence of RA in families indicates that heritability might account for approximately 40 to 50 percent of cases of seropositive RA, with first-degree relatives facing the highest risks. Furthermore, increased RA prevalence in certain racial groups, such as Native Americans where prevalence rates can reach 5-7%-points to the involvement of genetic predispositions. Specific genetic loci have been identified that correlate with an increased risk for RA, although non-genetic familial or environmental characteristics may also contribute significantly. The so-called "shared epitopes" (SEs)-a group of alleles within the major histocompatibility complex (MHC) that predict similarities in the structure of the human leukocyte antigen (HLA) peptide-binding groove-are the most robust genetic risk factors associated with RA. While some studies suggest a lower contribution, SE alleles are generally believed to contribute roughly 40% to the overall genetic risk. Previously established nomenclature for SEs has transitioned to a new classification system that centers on specific amino acids at positions 70 and 71, which are now used to categorize risk alleles into five groups: S1, S2, S3P, S3D, and X. Within this framework, S2 and S3P are recognized as high-risk groups, correlating notably with elevated levels of autoantibodies, particularly anti-citrullinated protein antibodies (ACPA).

Interestingly, several studies have indicated that citrullinated

proteins preferentially bind to SEs, enhancing their presentation to T cells compared to their arginine-containing counterparts. This interplay appears critical to the pathophysiology of RA, especially in ACPA-positive cases. Over 100 genetic loci have been associated with RA through genome-wide association studies (GWAS), which together explain about 5% of the genetic predisposition to the disease outside of the SEs. Most of these loci exert relatively modest effects, with odds ratios typically below two. Alongside genetic factors, emerging evidence points to epigenetic modifications associated with RA disease activity. Specifically, methylation changes in regions of the genome in fibroblast-like synoviocytes (FLS) derived from RA joints have been linked to increased disease aggressiveness, although it remains unclear whether these changes arise early in the disease process or are secondary to more established disease states. In summation, while the SE represents the strongest identified genetic risk factor, there are significant distinctions in its relationship with seropositive versus seronegative RA. Overall, heritability estimates suggest that genetics contribute roughly 40-50% of seropositive RA cases and about 20-30% of seronegative cases. Importantly, the known genetic and environmental factors together account for less than 100% of heritability, implying the existence of unrecognized genetic, environmental, or stochastic factors that may further influence RA risk.

For instance, elevated levels of the cytokine MCP-1 have been observed in autoantibody negative first-degree relatives of RA patients from Native American populations, suggesting a potential biomarker role or response to environmental triggers. Moreover, research has revealed several inflammatory pathway abnormalities in arthritis-free first-degree relatives of RA patients, including those related to PTPN22 function, even in the absence of known autoimmunity-associated alleles. There is also increasing acknowledgment that subtle genetic factors, such as predispositions to inflammation or autonomic dysfunction, may contribute to RA susceptibility. Although our understanding of the functional roles of the SE genetic factors in RA development is still evolving, it is clear that the SE influences aspects like citrullinated antigen presentation and may significantly affect intracellular functions related to autoimmunity and inflammation. There is currently ongoing investigation into the role of the SE in autoantibody generation and the transition from a preclinical state to clinically apparent RA, underscoring its potential significance in disease development. In longitudinal studies, the presence of the SE has been associated with approximately a twofold increase in the risk of developing inflammatory arthritis and classifiable RA in ACPA-positive individuals, highlighting the importance of genetic predisposition in this complex disease process. Rheumatoid arthritis (RA) develops through several distinct stages, each characterized by specific immune and pathological changes [3].

Triggering Stage

In this stage, the immune system's anomalous response leads to the production of anticyclic citrullinated peptide antibodies

(ACPAs), crucial for RA diagnosis and prognosis. Several factors contribute to ACPA production:

a. Genetic factors: Notable genes include HLA-DR1 and HLA-DR4, which are significant risk factors, along with PTPN22 polymorphisms influencing T cell activation.

b. Environmental factors: Exposure to substances such as tobacco smoke, silica dust, and certain pathogens (e.g., *Porphyromonas gingivalis* and *Aggregate bacteria* *ctinomyces* *comitans*) act as triggers by activating immune pathways. These exposures may lead to citrullination of proteins, promoting autoantibody synthesis.

c. Family history: The risk of developing RA increases significantly among first-degree relatives of affected individuals, underscoring genetic predispositions.

d. Epigenetic influences: Mechanisms such as DNA methylation may modify gene expression in response to environmental factors [4].

Maturation Stage

The maturation of the immune response occurs in secondary lymphoid tissues or the bone marrow, marked by epitope spreading. Autoantibodies against citrullinated proteins are produced, often preceding clinical symptom manifestation. During this phase:

i. ACPA production indicates a breakdown of immunological tolerance and leads to enhanced T cell activation. Organization of immune responses continues, with gradual increases in anti-citrullinated protein antibodies over years.

ii. Microbial immunity appears linked to auto immune responses, as some auto antigen influence the immune response in the joints [4].

Targeting Stage

In this stage, clinical RA becomes evident with synovitis, characterized by symmetrical joint swelling and inflammation of the synovial membrane:

i. Immune cell infiltration leads to chronic synovitis, driven by interactions between innate and adaptive immune systems. Key players include macrophages, T cells, and dendritic cells, which perpetuate inflammation and autoimmunity.

ii. Structures within the joints, such as fibroblast-like synoviocytes (FLS), are activated, leading to an abnormal immune response and sustaining inflammation [4].

Fulminant Stage

The fulminant stage is marked by more severe pathological changes, including:

a. Synovial hyperplasia: This process leads to a

dysfunctional synovial lining and the excessive production of inflammatory cytokines, perpetuating joint damage.

b. Cartilage damage: Direct invasion of the cartilage by hyperplastic synovium occurs, involving matrix metalloproteinases (MMPs) that lead to degradation of the cartilage

c. Bone erosion: This characteristic feature of RA involves increased osteoclast activity due to pro-inflammatory cytokines, coupled with reduced osteoblast function, resulting in localized bone loss [5].

Systemic Implications

RA extends beyond joints, potentially leading to systemic health issues including cardiovascular disease, lung fibrosis, and increased mortality risk due to associated comorbidities such as osteoporosis and malignancies. In summary, RA is a complex autoimmune disease characterized by multiple interrelated stages, ranging from the initial triggering of immune responses to the fulminant stage of significant joint and systemic damage. Understanding these stages is crucial for early diagnosis and effective treatment strategies (Figure 1).

Treatment Strategies for Rheumatoid Arthritis (RA)

Rheumatoid arthritis (RA) management has evolved significantly with a focus on treatment strategies rather than simply the medications themselves. Key elements of effective treatment strategies include: [6]

Treat-to-Target (T2T)

This approach emphasizes setting specific therapeutic targets (like remission or low disease activity) and involves meticulous monitoring of disease activity. It incorporates shared decision-making with patients, aiming for a proactive response to the therapeutic adjustments if targets are not met. Recommended by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), T2T strategies are inspired by successful management protocols in chronic diseases such as diabetes and hypertension [6].

Sequential Therapy after TNF Inhibitor Use

In cases where conventional synthetic DMARDs (cs DMARDs) fail, there has been a trend to move away from switching between TNF inhibitors. Instead, clinicians have started using a range of drugs that target different immune pathways, such as:

i. Interleukin-6 inhibitors

ii. Oral JAK inhibitors

iii. Abatacept

iv. This shift is driven by evidence showing that these alternatives often have better efficacy and safety profiles.

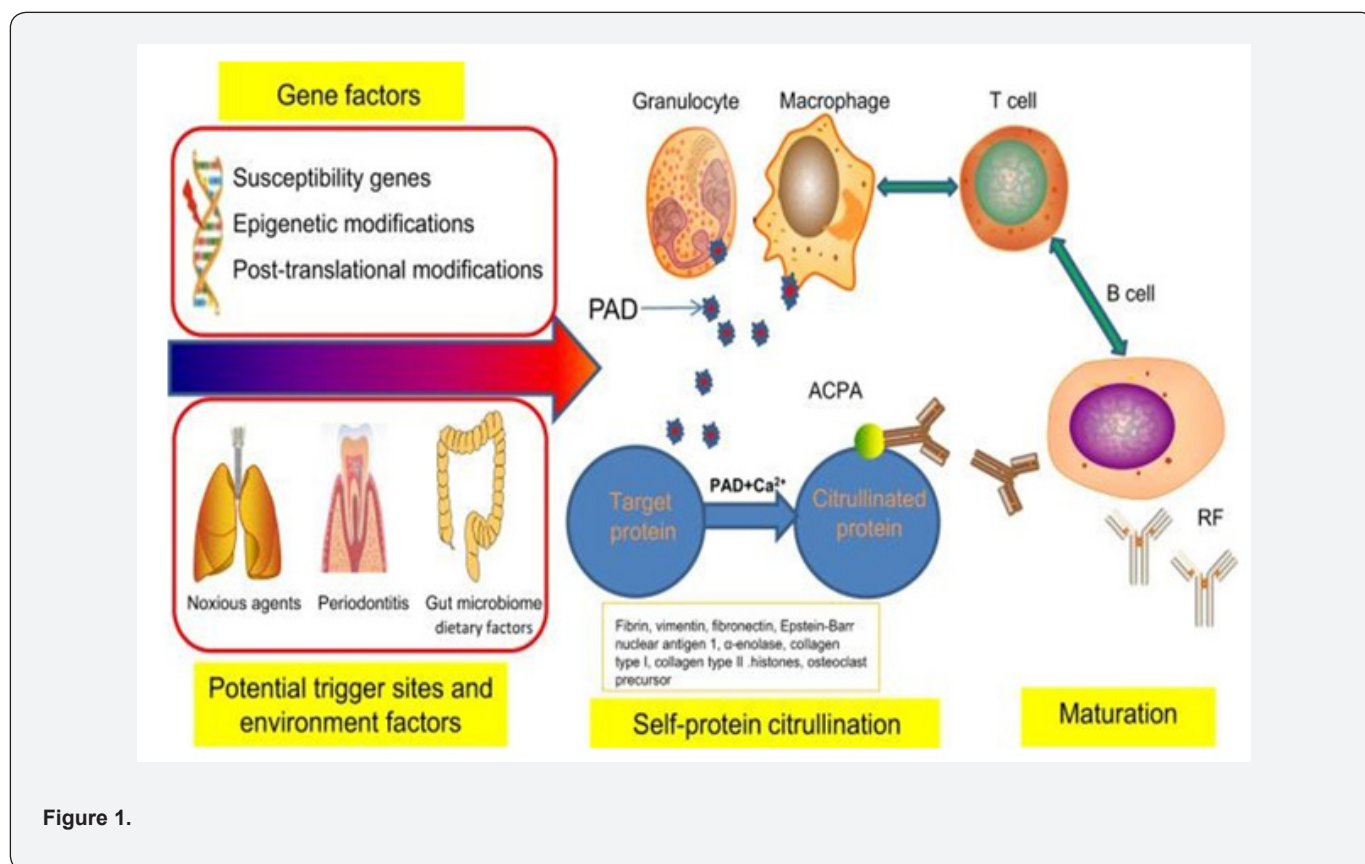
Current Pharmacologic Therapies

a. First-Line Treatments: Include nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, which provide rapid relief of symptoms.

b. Disease-Modifying Anti rheumatic Drugs (DMARDs): Methotrexate, hydroxy chloroquine, and sulfasalazine are examples. These agents not only alleviate symptoms but also slow

the progression of the disease.

c. Biologics: More recent innovations in RA treatment include biologic response modifiers (b DMARDs) which target specific aspects of the inflammatory process, including agents like infliximab and adalimumab.



NSAIDs in RA Management

i. Traditionally used for pain and inflammation control, NSAIDs are not deemed sufficient as monotherapy because they do not prevent the progression of RA.

ii. They are typically used as bridge therapy while waiting for DMARDs to take effect [7].

Glucocorticoids (GCs)

Short-term glucocorticoid therapy in combination with DMARDs can significantly improve clinical outcomes, reduce joint damage, and hasten the onset of therapeutic effects. The use of glucocorticoids, however, must be carefully managed to avoid long-term side effects.

Scoring Systems for Disease Progression:

Radiographic damage is assessed through scoring systems that measure joint and soft tissue damage to direct treatment strategies

effectively. These scores help monitor disease progression and assess the efficacy of treatment approaches. In conclusion, despite the range of pharmacological options available for RA, the emphasis on personalized treatment strategies-particularly the T2T approach-along with the integration of patient preferences and regular monitoring, are critical in the effective management of the disease Steroidal Treatment in Rheumatoid Arthritis (RA).

Overview of Corticosteroids

Corticosteroids are synthetic drugs that mimic hormones from the adrenal glands, effectively reducing inflammation and modulating immune responses. They are beneficial for all eviating pain and slowing joint damage progression, especially in acute conditions or high disease activity [8].

Indications for Use

Corticosteroids are indicated for:

a. Acute Flare-ups: Provide rapid symptom relief during exacerbations.

b. Bridging Therapy: Used during the initiation of DMARDs (e.g., methotrexate) to control symptoms while waiting for their effects.

c. Severe Disease: Essential in cases poorly controlled by DMARDs or NSAIDs to reduce inflammation and enhance quality of life.

d. Extra-articular Manifestations: Manage systemic symptoms affecting lungs, skin, and cardiovascular health.

Common Corticosteroids

a. Prednisone: The primary oral option for RA management.

b. Methyl prednisolone: Often given via injection for rapid effect in acute situations.

c. Triamcinolone: Can be injected into affected joints for localized relief [4].

Dosing and Administration

a. Low to Moderate Doses: Initial dosages usually range from 5 to 10mg/day of prednisone, adjustable based on patient response and side effects.

b. Tapering Strategy: Long-term users should taper doses gradually to prevent withdrawal symptoms and disease flare-ups.

Therapy Benefits of Corticosteroid

a. Rapid Symptomatic Relief: Quick alleviation of pain and improved joint function.

b. Anti-inflammatory Effects: Significant reduction in inflammation markers, enhancing RA management.

c. Improved Quality of Life: Effective symptom control leads to better physical functioning and well-being.

d. Adjunct to Other Therapies: Supports other treatments while DMARDs become effective.

Risks and Side Effects:

Potential side effects of long-term corticosteroid use include:

a. Osteoporosis: Increased fracture risk due to decreased bone density.

b. Weight Gain: Caused by increased appetite and metabolic changes.

c. Hypertension: Elevated blood pressure requiring monitoring and possibly treatment.

d. Increased Infection Risk: Suppressed immune function

leads to higher susceptibility.

e. Hyperglycemia: Elevated blood sugar levels, especially in diabetic patients.

f. Psychiatric Effects: Mood swings, anxiety, or depression may occur (Figure 2).

Management strategies of rheumatoid arthritis

Management strategies for rheumatoid arthritis (RA) focus on reducing inflammation, controlling symptoms, preventing joint damage, and improving the overall quality of life. These strategies often involve a combination of medications, lifestyle changes, physical therapy, and regular monitoring. Here are key components of RA management:

Medications

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): Help relieve pain and reduce inflammation (e.g., ibuprofen, naproxen).

a. Corticosteroids: Used to quickly reduce inflammation and suppress the immune system (e.g., prednisone).

b. Disease-Modifying Antirheumatic Drugs (DMARDs): Slow disease progression and prevent joint damage (e.g., methotrexate, sulfasalazine).

c. Biologic DMARDs: Target specific parts of the immune system (e.g., adalimumab, rituximab).

d. Janus Kinase Inhibitors: A newer class of drugs, taken orally, that target specific pathways in the immune response (e.g., tofacitinib).

Life style Modifications

a. Diet: A balanced diet rich in anti-inflammatory foods (e.g., fruits, vegetables, omega-3 fatty acids) can help manage symptoms.

b. Physical Activity: Regular exercise improves joint function and reduces stiffness. Activities can include low-impact aerobics, swimming, and strength training.

c. Weight Management: Maintaining a healthy weight reduces stress on joints and improves overall health.

d. Stress Management: Techniques such as yoga, meditation, and mindfulness can help manage stress and improve well-being.

Physical and Occupational Therapy

a. Physical Therapy: Tailored exercises can improve mobility and strengthen muscles around affected joints.

b. Occupational Therapy: Helps patients maintain daily activities through adaptive techniques and the use of assistive devices.

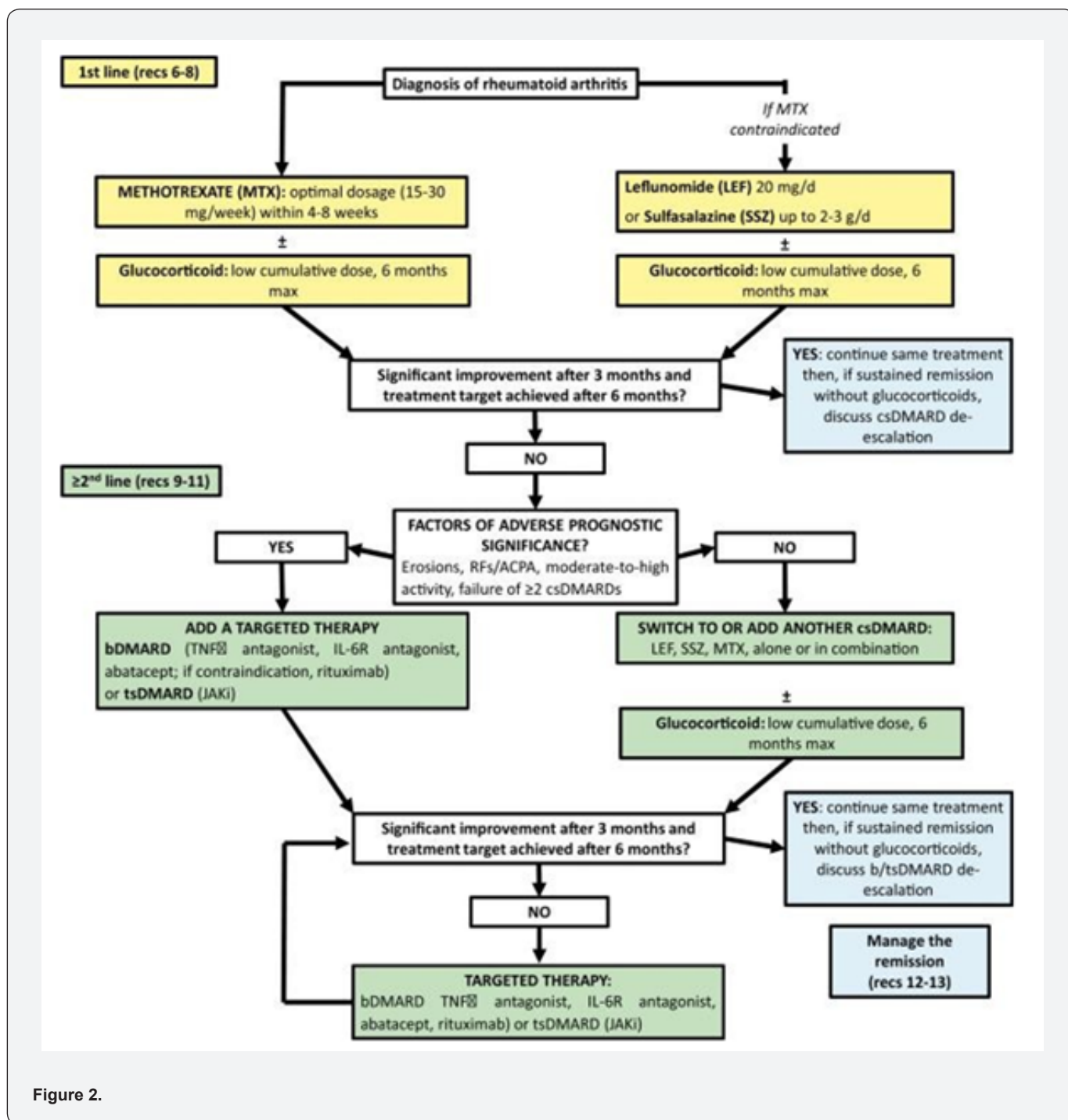


Figure 2.

Regular Monitoring and Follow-Up

- i. Frequentists rheumatologist for joint evaluations and monitoring of disease activity.
- ii. Regular blood tests to monitor the effects of medications and assess disease activity markers.

Patient Education and Self-Management

- i. Educating patients about their condition, treatment

options, and self-management techniques can empower them to take an active role in their care.

- ii. Support groups or counseling can provide emotional support and practical tips for living with RA.

Surgery (as a Last Resort)

In advanced cases where joint damage is severe, surgical options such as joint replacement or synovectomy may be considered [8].

Conclusion

In conclusion, rheumatoid arthritis (RA) presents a multifaceted challenge, necessitating a comprehensive understanding of its clinical manifestations, pathophysiology, and evolving treatment strategies. As a chronic autoimmune condition primarily affecting the joints, RA can lead to significant pain, disability, and systemic complications if not managed appropriately. Advances in our understanding of its genetic and environmental risk factors illuminate the complexity of its onset, highlighting the need for individualized patient care strategies. Recent developments in treatment paradigms, particularly the emphasis on a treat-to-target (T2T) approach, promote proactive management and close monitoring of disease activity. This strategic focus, combined with the integration of various pharmacological options—including conventional DMARDs, biologics, and novel oral agents—offers hope for enhanced patient outcomes and quality of life. Moreover, the importance of lifestyle modifications, supportive therapies, and patient education cannot be overstated, as they are essential components of a holistic approach to RA management. As research continues to unravel the intricate mechanisms underlying RA and as novel therapeutic agents are developed, the future of RA treatment is promising. Continued collaboration among healthcare providers, researchers, and patients is crucial to optimize care, personalize treatment plans,

and ultimately improve the landscape of rheumatoid arthritis management for those affected by this challenging disease.

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