A Review on The Recent Advancement for Rheumatoid Arthritis Drug Delivery Approaches in Anti-Rheumatic Treatment.

By

Faria Bin Ta Anika Nower
ID: 19146065

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy.

School of Pharmacy
Brac University
November, 2023

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Student Full Name
Student ID :19146065

Approval

The thesis titled "A Review on The Recent Advancement for Rheumatoid Arthritis Drug Delivery Approaches in Anti-Rheumatic Treatment.", submitted by Faria Bin Ta Anika Nower (19146065) of Spring 2019 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on November 2023.

Examining Committee:

Supervisor:

Dr. Mohd. Raeed Jamiruddin
Associate Professor,
School of Pharmacy
BRAC University

Program Coordinator:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Departmental Head:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

No human or animal tests are involved in this study.

Abstract

This review has been designed to have a very clear concept on rheumatic diseases, its mechanism, symptoms, reasons and clinically trialed medications for rheumatoid arthritis and other approaches. Rheumatoid arthritis has been and continues to be one of the most common reasons for inability in walking ,working and low quality of life each year. As time goes on, various anti-rheumatic drug formulations and different therapeutic approaches are being released on the market, raising the concern of medical professionals due to their superiority, toxicology, and cost-effectiveness compared to the traditional formulation of the same drugs. Moreover, biologics are now effective rheumatic drug that comes in different forms but it is more expensive and gives toxic effects to patients. Biologics has been shown to have a more favorable toxicological profile than conventional. The cost and side effects has not been thoroughly investigated due to the small number of research that have been conducted. Apart from that this systematic review highlights the use of therapies that has been somewhat restricted due to the adverse effects it can produce whereas normal anti-anti-rheumatic drugs has favorable safety profile. In the overall treatments of rheumatoid arthritis, there has no chance of fully heal but can have relaxation which is less harmful to the heart, better tolerated, and just as effective, expands the therapeutic alternatives available. The long-term usage of these medicines can affect other body organs. Using these approaches to have a better health could be a new addition of technology in recent eras, which may ensure the rational safety.

Keywords: Rheumatic disease, Rheumatology, Rheumatoid arthritis, Anti-rheumatic agents, Anti-inflammatory agents, Therapy**,** Prevention.

Dedication

Dedicated to myself & to my parents who could do anything for our happiness and to my beloved husband for sure.

Acknowledgement

I would like to proceed by thanking Almighty Allah to give me the knowledge, strength and patience I needed to accomplish my research. Also, I am grateful to my parents for supporting me throughout this journey.

Moreover, I would like to express gratitude to my supervisor, **Dr. Mohd. Raeed Jamiruddin** (Associate Professor, School of Pharmacy, Brac University) for his continuous guidance throughout this systematic review, whose constant supervision and motivation helped me to accomplish this project efficiently. Also, I want to thank him for inspiring my passion for my desired work.

Also, I sincerely express my gratitude to **Dr. Eva Rahman Kabir** (Professor and Dean, School of Pharmacy, Brac University) and **Dr. Hasina Yasmin** (Professor and Assistant Dean, School of Pharmacy) for their sincere monitoring and motivational approaches throughout this research.

Subsequently, I would like to thank my respected teachers, seniors, juniors and everyone else for making my undergrad life enjoyable.

I would like to acknowledge my family and friends who keep motivating me in every sector of life. Undoubtedly without their support, motivation, prayers and affection I would not do this much. Lastly, I would like to thank all the people who helped me whenever I needed and always keep supporting me.

Table of Contents

List of Tables

List of Figures

List of Acronyms

RDs	Rheumatic diseases
RA	Rheumatoid Arthritis
OA	Osteoporosis
AxSpA	Axial spondylarthritis

Chapter 1

Introduction

1.1 Rheumatic Disease

Among so many strong ancient diseases, rheumatic diseases are the oldest diseases recognized and acknowledged.(Sangha, 2000) This specific phenomena “rheumatic disease” can be subsume various kinds of autoimmune disorders which can be defined with severe inflammation, first and foremost poignanting the joints, tendons, ligaments, bones, and muscles. (E. Kocyigit & Kocak, 2023) There are some specific sign and symptoms which are very co-related with joint pain, motion loss of the joint or between joints, swelling, red-ness, and warmth are some inflammations in joints and affected area. "Rheumatology" is term of the medical special sector which only focuses on these kinds of illnesses. Doctors who specialize with necessary training to treat rheumatism are known as rheumatologists. Rheumatological diseases represent a diverse group of diseases that are related with some factors like environmental . (Kröner et al., 2019) The extra risk of cardiovascular disease are also co-related with inflammatory rheumatic diseases which has been recognized earlier .(Symmons & Gabriel, 2011)

1.2 History of Rheumatic Disease

Rheumatic disorders were mainly addressed by Hippocrates during fourth century B.C. Nearly 18 of published aphorisms mention about joint diseases where the word "rheuma" was described thoroughly about pain . Parisian physician Guilliaume Baillou has first recognized rheumatism as a musculoskeletal condition. Bernard Comroe has introduced the term "rheumatologist" nine years after. The phrase "rheumatology" used first in text-book written by Joseph L. Hollander in 1949.(Sangha, 2000) Disease definition can be a huge problem while

studying the etiology of rheumatoid arthritis as now, classification basis were gathered from patients with their established diseases. This causes from the genetic susceptibility along with revelation of environmental trigger. Genetic component can be mostly oligogenic in nature. (Ollier et al., 2001)

1.3 Epidemiology

Rheumatic diseases impose a significant economic and social burden of cost. Low and reduced standard of life, health efficiency, high and enlarged health-care expenditures are the effects they have on people and at the same time on society. This impact on people and society is anticipated to weak and worsen as the population ages with inappropriate approaches to patient administration and illness management.

According to four studies report, the crude incidence rates of epidemiology of 2 report, rural Bangladesh populations, the rate was 0.48 per 100 person- year (95% confidence interval [95% CI] 0.27–0.85) and 0.12 per 100 person-years (95% CI 0.1–0.7).(Pianarosa et al., 2022)

The epidemiology of this disease showed a population prevalence of 0.5% to 1% with highly variable yearly incidence (12-1200 per 100,000 population) which depends on gender, ethnicity within the calendar year.(Gabriel, 2001)

Finding the epidemiological informative data that can be analyzed and utilized for having a better and genuine understanding on the elements that help in contributing to the onset and progression of rheumatic diseases. Significant advancements in patient diagnosis, management and treatment can only be made with such an understanding and by analyzing the data. (Sangha, 2000)

Disease	Point prevalence/1000	Incidence/1000	Age ratio (65:25 year)	Gender ratio(female: male)	References
Rheumatoid arthritis	8.0	0.5	6:1	2.5:1	(Sangha, 2000)
Osteoarthritis (knee)	100	N/A	0	2:1	(Sangha, 2000)
Juvenile chronic arthritis	0.7	0.1	N/A	2:1–7:1	(Sangha, 2000)
Ankylosing spondylitis	2.0	0.07	0	1:3	(Sangha, 2000)
Systemic lupus erythematosus	0.4	0.05	1.5:1	3:1 to 9:1	(Sangha, 2000)
Systemic sclerosis	0.1	0.01	3:1	4:1	(Sangha, 2000)
Gout	N/A	1.0	2:1	1:6	(Sangha, 2000)

Table 1. Epidemiology of major rheumatic diseases.(Sangha, 2000)

a. Children <15 yr.
b. Prevalence among persons aged 35–74 yr.
(Sangha, 2000), (Goemaere et al., 1990)

1.4 Prevalence

According to a research report, they went through in Bangladeshi rural and urban communities to evaluate the burdens of rheumatic disorders in adults (age >/= 15 years) to reach a diagnosis which was carried out in a community of rural people with samples of 2635, 1317, and 1259 adults by surveys, questionnaires with the help of trained interviewers, internists and rheumatologists identified subjects with most and common affected sites were low back, osteoarthritis of the knees, hips, and shoulders with definite rheumatic disorders where women are recognized as most affected one respectively 26.2% (women 31.3%, men 21.1%), 24.9% (women 27.5%, men 22.6%), and 27.9% (women 35.5%, men 18.6%).(Haq et al., 2005) Knee osteoarthritis is prevalent musculoskeletal obstruction in Bangladeshi adults which has connection with work loss. Most important risk factors of knee osteoarthritis are increasing of age, poor education and overweight . (Haider et al., 2022) Some research on rheumatoid

arthritis showed about those people who live in rural areas had more functional impairment related disease which are more active. (Haq et al., 2005)

1.5 Classification

The classification of rheumatic diseases are not easy because of their not known etiology and heterogeneity factors in medical demonstration and theoretical appearance. Categorization of rheumatic states is harmed due to the lack of firm etiological proof and evidence for maximum disease conditions. More than hundred different conditions types are identified and categorized as rheumatic diseases.(Sangha, 2000)

1. Rheumatoid arthritis
2. Juvenile Idiopathic Arthritis/Juvenile rheumatoid arthritis
3. Psoriatic arthritis
4. Axial spondyloarthritis or AxSpA(non-radiographic)
5. Ankylosing spondylitis(radiographic AxSpA)
6. Systemic lupus erythematosus
7. Osteoarthritis

    - Knee
    - Hand
    - Hip

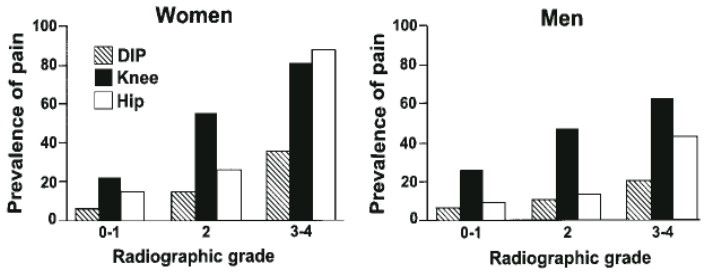

***Figure 1**: Prevalence of pain among individuals with radiographically diagnosed osteo-arthritis.(Sangha, 2000)*

8. Fibromyalgia
9. Vasculitis
10. Scleroderma
11. Rheumatic fever
12. Reiter's syndrome
13. BehCet's disease/ BehCet's syndrome

14. Acute gout
15. Polyrnyositis/dermatomyositis
16. Sjogren syndrome
17. Polymyalgia rheumatica
18. Bacterial arthritis
19. Mixed connective tissue disease (MCTD)

(Rosenthal, 1978), (Tamási & Szekanecz, 2007), (Sangha, 2000), (Johnson et al., 2007)

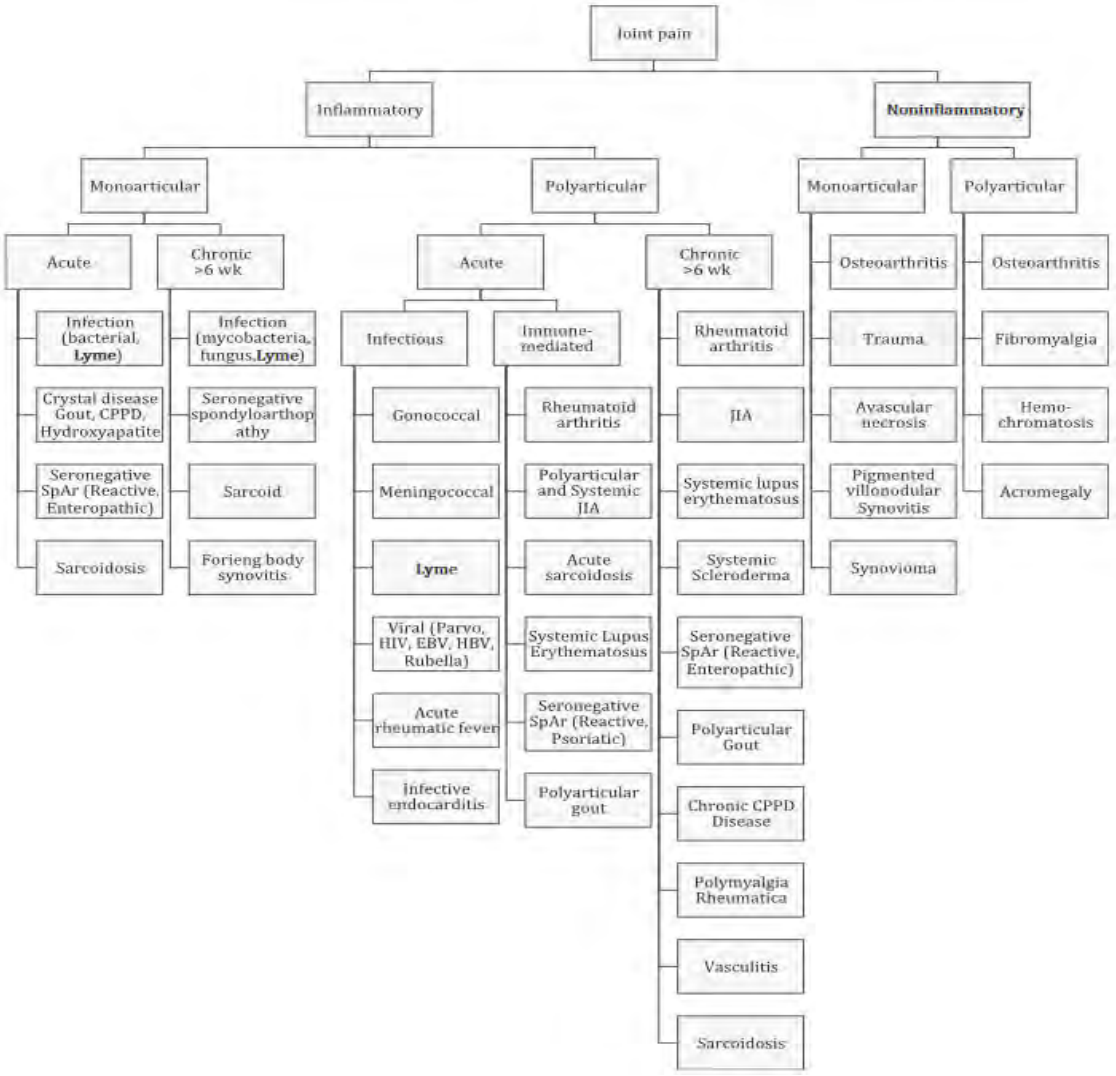

Figure 2: *Arthralgia. EBV(Epstein-Barr virus), HBV(hepatitis B virus), HIV(human immunodeficiency virus), JIA(juvenile idiopathic arthritis).(Ventura et al., 2018)*

Chapter 2

Clinical Overview

2.1 Symptoms

Patients who have this rheumatic disease are prone to have a very high and increased risk of infection with low immune system.(Listing et al., 2013) Some important features such as- age not more than 45 years , insidious onset and present for greater than 3 months , morning back stiffness around , pain at second half of the night also buttock pain . (Ventura et al., 2018) The most common residual symptoms are- pain, fatigue and morning-stiffness , mental-health , inappropriate sleep and less work productivity, impairment in standard of life , and functional disability (Ishida et al., 2018) Symptoms that can focus on the correct diagnosis are- the location of the joint pain, the nature of discomfort, duration of pain and associated symptoms. Pain is limited to one or a few joints is mainly common in gout, traumatic arthritis, osteo-arthritis, spondylo-arthropathy, or early rheumatoid arthritis. More significant joint discomfort has a history of trauma to the knees or ankles, swelling and pain in the forefeet or ankles may be the first symptom of an inflammatory arthropathy such as rheumatoid arthritis or ankylosing spondylitis and reactive arthritis.(Ventura et al., 2018) It is necessary to know the exact and accurate history for early diagnosis of systemic rheumatic diseases with foot and ankle symptoms. (Whisler et al., 2002)

2.1.1 Factors associated with chronic pain

Chronic pain can be associated and related with physical, psychological, and social factors which was classified as ‘modifiable’ and ‘non-modifiable. (Mills et al., 2019)

Factors associated with the development of chronic pain

Demographic	Age
	Gender
	Ethnicity and cultural background
	Socio-economic background
	Employment status and occupational factors
Lifestyle and behaviour	Smoking
	Alcohol
	Physical activity
	Nutrition
	Sunshine and vitamin D
Clinical	Pain
	Multi-morbidity and mortality
	Mental health
	Surgical and medical interventions
	Weight
	Sleep disorders
	Genetics

***Figure 3**: Factors associated with the development of chronic pain.(Mills et al., 2019)*

2.1.2 Diagnosis

Rheumatoid arthritis is an well-known autoimmune disease of multifactorial etiology which can be characterized by inflammation of the joints and presence of auto-antibodies that is directed against multiple auto-antigens.(Yu & Lu, 2019) Initial laboratory evaluation should also include complete blood count with differential and assessment of renal and hepatic function. Patients taking biologic agents should be tested for hepatitis B, hepatitis C, and tuberculosis.(Wasserman, 2011) Although laboratory testing and imaging studies can help confirm the diagnosis and track disease progress, rheumatoid arthritis primarily is a clinical diagnosis and no single laboratory test is diagnostic. (Rindfleisch & Muller, 2005)

2.1.3 Laboratory studies and imaging

There are some laboratory tests like- rheumatoid factor, erythrocyte sedimentation rate, anti-nuclear anti-bodies, and C-reactive protein are helpful in diagnosis to recognize potential autoimmunity.(Whisler et al., 2002); (Kim et al., 2018) The importance of laboratory testing in the diagnosis and evaluation of the more prevalent rheumatologic diseases from the perspective of the working clinician.(Percy & Russell, 1975)

2.2 Pathogenesis

The exact mechanisms which may be responsible for rheumatic disorders development are unknown. Maximum rheumatic diseases are complex disorders which are not easy to understand for which understanding the pathogenetic mechanisms are hard and tough. Although many hypotheses claim that environmental exposure is responsible for the occurrence of autoimmune disease such as interference with immune tolerance, molecular mimicry, activation of the immune system, exposure to infectious agents and toxic chemicals, trauma, diet, occupation, physical activity, lifestyle and socioeconomics. These are some factors that affect disease occurrence which influence epidemiological risk factors such as gender and age. Loss of self-tolerance, causing an auto-inflammatory state, is crucial for the development of systemic rheumatic diseases. The immune system directly gets activated through environmental exposure and results in autoimmune disease. (Cheleschi et al., 2022); (Schur, 1977); (Gourley & Miller, 2007)

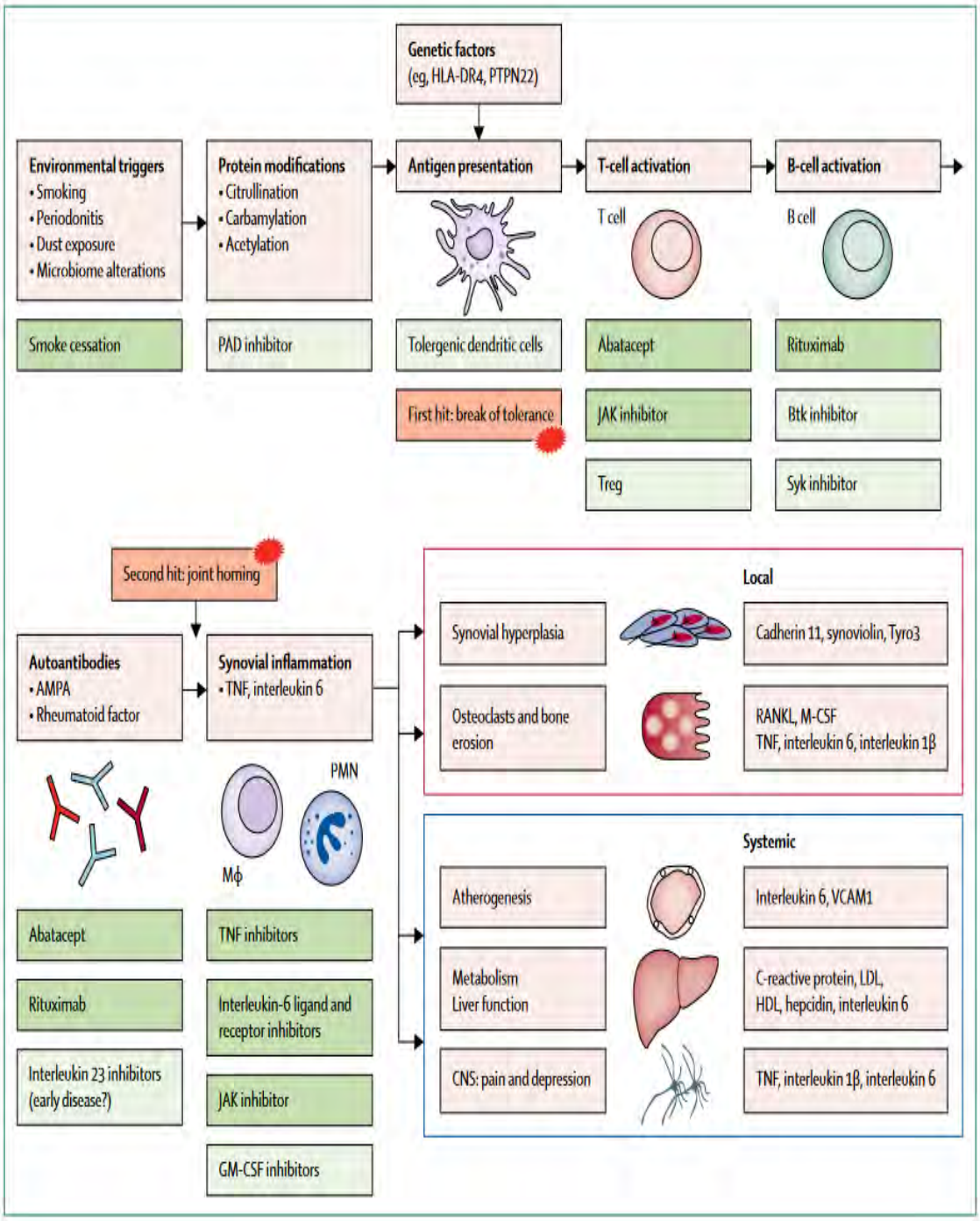

Figure 4: *Roadmap by developing RA and key possible therapeutic intervention steps.(McInnes & Schett, 2017)*

Chapter 3

Drug Regimen

3.1 Anticipatory Guidance

Agents	Reference
Methotrexate(MTX)	(Zhao et al., 2022)
Leflunomide	(Alfaro-Lara et al., 2019)
Sulfasalazine	(Choi & Fenando, 2023)
Injectable gold	(Clark et al., 2000)
Antimalarial agent	(Mackenzie, 1983)
Kinase inhibitors	(Palominos et al., 2021)
Glucocorticoids	(H. B. Townsend & Saag, 2004)
TNF inhibitors	(Tamási & Szekanecz, 2007)
B- & T-lymphocyte targeting agents • Rituximab • Abatacept	(M. J. Townsend et al., 2010);(Isaacs, 2009)
Other inflammatory cytokine inhibitors: • Anakinra (IL-1 inhibitor) • Tocilizumab (IL-6 receptor inhibitor)	(Cavalli et al., 2021);(Sebba, 2008)
Combination therapy of DMARDs	(Krüger, 2011); (O'Dell, 1998)
Biological agents for rheumatoid arthritis.	(Vollenhoven, 2010);(van Vollenhoven, 2010)

Table 2: *List of common drugs groups and representative drugs within the groups.*

3.2 Uses of drugs

1. Methotrexate(MTX) : For the treatment of rheumatoid arthritis (RA), methotrexate (MTX) is an important disease-modifying anti-rheumatic medication (DMARD) due to its strong efficacy and tolerability.(W. Wang et al., 2018) Since it has been used for almost 40 years, methotrexate (MTX) has been a part of the global standard of treatment for rheumatoid arthritis (RA). There are several different ways that MTX works to treat RA.(Zhao et al., 2022) Folate inhibitors most important and frequently prescribed substance for the treatment of RA, higher doses of MTX (20–30 mg) are more effective than lower ones (7.5–15 mg) , MTX monotherapy is effective and in the long-term safety profile is clinically acceptable . This is why the quality of efficacy and safety data puts MTX in first place. MTX is the 'anchor drug' in the treatment of RA and the adequate first choice in most DMARD-naive patients .(Pincus et al., 2003)

2. Leflunomide : Leflunomide is also a disease-modifying antirheumatic drug which is isoxazole derivative.(Sehgal & Verma, 2013) Use of leflunomide (LEF) has been proved effective in the treatment of active rheumatoid arthritis (RA). However, it have shown and associated with increased incidence of liver toxicity. (Chen et al., 2013)

3. Sulfasalazine : In the treatment and management of autoimmune diseases, sulfasalazine is a disease-modifying anti-rheumatic agent which can be used . In such case- rheumatoid arthritis and inflammatory bowel disease. (Choi & Fenando, 2023) Some toxic responses of sulfasalazine are sickness, migraine, anorexia and hemolysis are related with high serum sulfasalazine .Gentle hypersensitive responses, like rash and fever, might be overwhelmed by continuous desensitization.(Peppercorn, 1984) Sulfasalazine is the medication of choice in women who desire to have children. (Rains et al., 1995)

4. Injectable gold : Gold is most effective and toxic during the first 2 years of treatment. Both efficacy and toxicity appear to be dose-dependent . Gold compounds are one of the rare agents

that reduce the rate of erosion progression.(Jones & Brooks, 1996) In spite of the fact that its utilization can be restricted by the frequency of serious harmfulness, injectable gold has a significant clinically and genuinely critical advantage in the transient treatment of patients with rheumatoid joint pain. (Clark et al., 2000) Gold salts are used in the treatment of rheumatoid arthritis.(Uhm et al., 2000)

5. Antimalarial agent: The anti-malarial drugs chloroquine and hydroxychloroquine are among the most commonly used DMARDs in the treatment of RA. They have been shown to be significantly more effective than NSAIDs alone in several clinical trials and are characterized by mild toxicity. The combination of hydroxychloroquine and methotrexate appears to significantly reduce methotrexate hepatotoxicity.(Khraishi & Singh, 1996) Anti-malarial drugs are almost similar to chrysotherapy in terms of potency. Anti-malarial are prescribed in the treatment of active rheumatoid arthritis that is not optimally controlled with nonsteroidal anti-inflammatory drugs and in all cases of disease progression. The safe use of these medications depends on the daily dosage.(Mackenzie, 1983)

6. Kinase inhibitors : Tyrosine kinase inhibitors are investigational medicines in the treatment of rheumatoid arthritis. They inhibit immunological cell signal transduction which helps in preventing pro-inflammatory cytokines so that it cannot produced and released.(Palominos et al., 2021)

7. Glucocorticoids: These are the drugs that are used for reducing pain and inflammation for a short time but if it taken for a pro-long time, can have severe side effects.(Spies et al., 2010) It has been recognized for long because of its beneficial effects in rheumatoid arthritis . The specific efficacy is to relive inflammation and to prevent radiographic erosions in early diseases .(H. B. Townsend & Saag, 2004)

8. Combination therapy of DMARDs in RA:

- Biological agents + any DMARDs agent: The combination therapy of a biologic agent with MTX is quite effective than monotherapy.(Krüger, 2011)
- Triple therapy of MTX, sulfasalazine and hydroxychloroquine.(O'Dell, 1998)

9. TNF inhibitors : TNF inhibitors are drugs that help to stop inflammation and used worldwide to treat inflammatory conditions like- RA , psoriatic arthritis ,juvenile idiopathic arthritis. Anti-tumor necrosis factor-alpha (TNF-alpha) agents play a central role in biological therapy as these agents have been successfully tried in most of these diseases.(Tamási & Szekanecz, 2007)

10. Other inflammatory cytokine inhibitors: Anakinra (IL-1 inhibitor), Tocilizumab (IL-6 receptor inhibitor) (Sebba, 2008)

11. B- & T-lymphocyte targeting agents(M. J. Townsend et al., 2010)

- Rituximab and Abatacept: rituximab for lyses B-cells, and abatacept for T-cell co-stimulation modulator.(Isaacs, 2009)

12. Biological agents for rheumatoid arthritis

Agent	Structure	Pharmacology	Usual Dosage	Specific Side Effects and Risks	References
Abatacept	Recombinant CTLA4 molecule dimerized on Ig-frame	T-cell co-stimulation blocker	500-1000 mg(monthly)	Infusional reactions, infections	(Vollenhoven, 2010)

Adalimumab	Human monoclonal	TNF blockade	40 mg s.c. biweekly	Injection site reactions, infections including tuberculosis	(Vollenhoven, 2010)
Anakinra	Recombinant IL-1 receptor antagonist	IL-1 receptor blockade	100 mg s.c. daily	Injection site reactions, infections, neutropenia	(Vollenhoven, 2010)
Certolizumab pegol	Pegylated Fab' fragment from humanized monoclonal	TNF blockade	200 mg s.c. biweekly or 400 mg s.c. monthly	Injection site reactions, infections including tuberculosis	(Vollenhoven, 2010)
Etanercept	Recombinant TNF receptor (p75) dimerized on Ig-frame	TNF blockade	50 mg s.c. weekly	Injection site reactions, infections including tuberculosis	(Vollenhoven, 2010)
Golimumab	Human monoclonal	TNF blockade	50 mg s.c. every 4 weeks	Injection site reactions, infections including tuberculosis	(Vollenhoven, 2010)

Infliximab	Chimeric monoclonal	TNF blockade	3-10 mg/kg i.v. every 4-8 weeks	Infusional reactions, infections including tuberculosis	(Vollenhoven, 2010)
Rituximab	Chimeric monoclonal	B-cell depletion	1000 mg, 2 i.v. infusions 2 weeks apart	Infusional reactions, infections	(Vollenhoven, 2010)
Tocilizumab	Humanized monoclonal	IL-6-receptor blockade	8 mg/kg i.v. every 4 weeks	Infusional reactions, infections, cytopenias, elevated cholesterol	(Vollenhoven, 2010)

Table 3: *Approved Biological drugs for Rheumatoid Arthritis(RA).(Vollenhoven, 2010)*

Current treatment for rheumatic diseases:

Treatment options include-

Treatment options	References
1.Medicine • Herbal supplement : Back pain, fibromyalgia, osteoarthritis, and rheumatoid arthritis. o Turmeric o Ginger o Boswellia serrata o Devil's claw o Green tea o Aloe vera	(Ernst, 2011a);(Ernst, 2011b);(Kolasinski, 2012);(Marcus, 2009);(Li & Zhang, 2020);(Conrozier et al., 2014);(Tomaras et al., 2022);(Sterzi et al., 2016);(Akbar et al., 2017);(Heidari et al., 2019);(Guan et al., 2020);(Dehghan, 2015);(van Laar et al., 2012);(Todd & Clissold, 1990);

o Cat's Claw o Eucalyptus o Thunder God Vine o Willow bark (Salix alba) extracts o Capsicum creams o Phytodolor o Rose hip (Rosa canina) o Fish body oil • Vitamins: o Glucosamine and chondroitin o Omega-3 fatty acids o SAM-e o Curcumin o Vitamin D : lack of vitamin D is linked to rheumatoid arthritis. o Vitamins B3, Vitamin E might be of some benefit for treating osteoarthritis. ● Over-the-counter pain medications : o Acetaminophen o Ibuprofen o Naproxen sodium o Aspirin	

2) Weight reduction	(Kreps et al., 2018);(Sadeghi et al., 2022)
3) Exercise	(Benatti & Pedersen, 2015);(Fallon, 2021);(B. F. Kocyigit et al., 2023)
4) Surgery	(Ronald MacKenzie et al., 2018);(Bird, 1990)
5) Injection: ● Corticosteroid injections ● Sacroiliac joint injections ● Ultrasound guided major joint injection ● Hydrocortisone injections	(Gvozdenović et al., 2014);(Hunter & Blyth, 1999);(Wu et al., 2023);(Kokar et al., 2021);(Hartung et al., 2011);(S. Wang et al., 2019);(Martin et al., 2017)
6)Acupuncture	(Amezaga Urruela & Suarez-Almazor, 2012);(Berman et al., 2000);(Chou & Chu, 2018)
7)Ayurvedic treatment	(Krishna, 2011);(Park & Ernst, 2005)
8) Homoeopathic treatment	(Jonas et al., 2000);(Brien et al., 2011);(Fisher & Scott, 2001)
9)Electricity	(L. U. Brosseau et al., 2002);(L. Brosseau, Judd, et al., 2003)
10)Chiropractic or osteopathic or spinal manipulation	(Fiechtner & Brodeur, 2000);(Chung & Mior, 2015)
11) Therapy : • Physical therapy	(Tamási & Szekanecz, 2007); (Cheleschi et al., 2022);(Vervoordeldonk & Tak, 2001);(Engel,

• Occupational therapy • Immunotherapy • Hot or cold compresses • Gene therapy • Megavitamin therapies • Energy healing therapy • Biological therapy: Anti-tumor necrosis factor-alpha (TNF-alpha) is vital and central drugs of the biological therapy as these have been successfully tried in most of these diseases. • Balneotherapy(BT): It is mostly used for non-pharmacologic complementary therapies for treating rheumatic diseases.	2012);(Galon & Bruni, 2019);(L. Brosseau, Yonge, et al., 2003);(Pozsgay et al., 2017);(Miller & Ranatunga, 2012);(Phang et al., 2018);(Bliddal et al., 2014)

Table 4: *Current treatment for rheumatic diseases.*

Chapter 4

Future drug consideration

The anti-rheumatic therapies are recently getting medical and commercial successes about a huge number of healing drugs which are now in developmental early and late-stage of rheumatic disease's symptoms .(Vollenhoven, 2010)

Treatment(Agents)	Conditions	Benefits and efficacy	Clinical trial	References
BI 695501	Rheumatic arthritis		Completed	(Boehringer Ingelheim, 2018)
ADX-102 1% Topical Dermal Cream (reproxalap) and Vehicle of ADX-102 Topical Dermal Cream	Sjogren-Larsson Syndrome.		Completed	(Aldeyra Therapeutics, Inc., 2023)
Placebo, M2951 and M2951	Rheumatic arthritis		Completed	(EMD Serono Research & Development Institute, Inc., 2018)
Elsubrutinib , Upadacitinib , Placebo for elsubrutinib and Placebo for upadacitinib	Rheumatic arthritis		Phase II	(AbbVie, 2021)
Kinase inhibitor JAK-3{Tasocitinb (CP690-550)}	Rheumatic arthritis	Less side effects.	Last stage phase III development.	(Vollenhoven, 2010)
Biological: HB-adMSCs	Rheumatic arthritis		Completed	(Hope Biosciences, 2022)
Biological: Adalimumab - GP2017 and Adalimumab - US licensed Humira	Rheumatic arthritis		Completed	(Sandoz, 2018)
Anti-TNF-alpha , Methotrexate , Placebo and RO7123520	Rheumatic arthritis		Phase II	(Hoffmann-La Roche, 2020)
Biological: Adalimumab	Rheumatoid Arthritis,		Phase IV	(AbbVie, 2019)

Other: Placebo	Musculoskeletal and Connective Tissue Diseases			
Naltrexone and Placebo	Osteoarthritis, Psoriatic Arthritis and Rheumatoid Arthritis		Completed	(VA Office of Research and Development, 2021)
Syk inhibitor (PRT062607)	Chronic lymphocytic leukemia.		Phase I	(Spurgeon et al., 2013)
Abatacept and DMARDs	Rheumatic arthritis		Phase IV	(NYU Langone Health, 2023)
Fostamatinib disodium (R788)	Rheumatic arthritis	Good safety profile and efficacy is not very encouraging.	Phase II and III stage development.	(Vollenhoven, 2010)
• MSB11022 • EU-Humira	Moderate to Severe Rheumatoid Arthritis.		Phase III	(Fresenius Kabi SwissBioSim GmbH, 2019)
Ofatumumab and ocrelizumab	Rheumatic arthritis	Less allergic reactions than rituximab.	Completed	(Vollenhoven, 2010)
Methotrexate , Sulfasalazin , Hydroxychloroquine , Etanercept and Adalimumab	Rheumatic arthritis		Phase 4 and completed.	(Solomon, 2022)
Anti-IL-17	Rheumatic arthritis	More specific activity is expected.	Two types of anti-IL-17 molecules entered phase II/III development.	(Vollenhoven, 2010)
Drug: Upadacitinib Biological: Pneumococcal 13-valent conjugate vaccine (PCV-13)	Rheumatic arthritis		Completed	(AbbVie, 2022)

Methotrexate, Leflunomide , Hydroxychloroquine, Prednisolone , Folic Acid and Sulfasalazine	Rheumatic arthritis		Phase III	(Negi, 2021)
GDC-0853 , Adalimumab , Folic Acid , MTX and Placebo	Rheumatic arthritis		Completed	(Genentech, Inc., 2020)

Table 5: *New & upcoming agents for the treatment of Rheumatic diseases.*

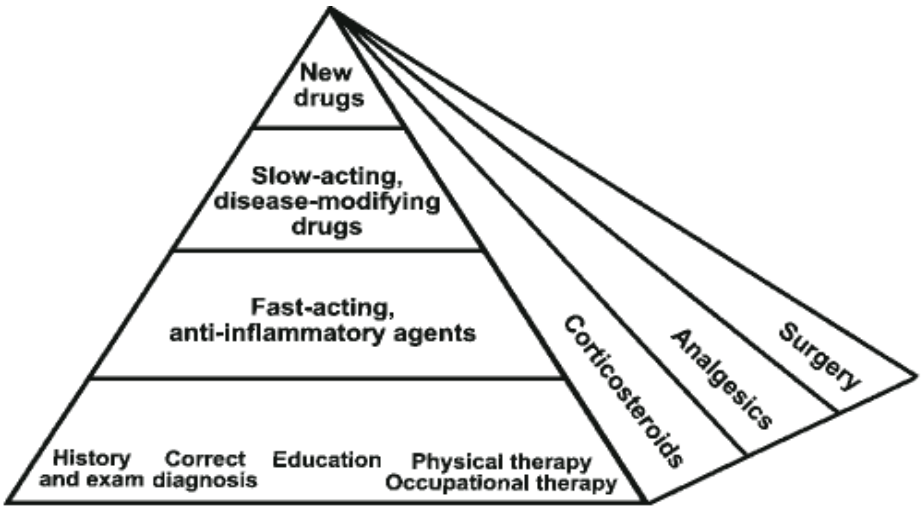

Figure 5 *: Treatment of Rheumatoid Arthritis(RA),(Sangha, 2000)*

4.1Common concerns

Health surveillance through screening, counselling by giving some exercise, and provision of anticipatory guidance is among the most important functions of a rheumatologist. Criteria

such - classification criteria, sub-classification criteria, prognostic criteria, status indexes, activity indexes, damage indexes and outcome entreat sets give legal and formal status for the study of the etiology, course, and controls of rheumatic diseases and also which can provide a basic for future developments, improvements and to upgrade in clinical supervision. For understanding the motive and desired purposes of these particular criteria sets and the contrasts or difference of opinion between these criteria categories is main and pivotal to interpret the rheumatic disease literature, written works, published writings and for the blueprint for managing of clinical and epidemiologic investigations.(Fries et al., 1994)

4.2 Prevention

Intensifying rheumatology education within medical school and accommodation programs can encourage trainees to learn rheumatology and pursue careers on this field which may improve the ability of initial care providers to recognize and treat the growing number of patients who have musculoskeletal conditions. (Lewandowski et al., 2020); (Finckh & Deane, 2014). Based on evidence, it is an ongoing effort which need continue emendation and update of recommendation. It may currently be used to address a wide variety of clinical questions. In this field, initiatives that need to be taken on practice-based research to establish standard indicators and need to link the areas where rheumatology practice can be enhanced . (Kerr, 1995);(Klareskog et al., 2010)

Chapter 5

Conclusion

In conclusion, the main objective of this entire systematic review is to understanding diseases, disease types, symptoms, developmental needs, abilities, and common concerns. This review addresses anticipatory guidance, normal development, and common issues that arise in patients. This review is all about disease mitigating highly efficacious therapeutic Anti-rheumatic medicine in Rheumatic Arthritis for the riddance of synovitis equals & joint demolition by Using effective complementary approach.

References

AbbVie. (2019). A Phase 4 Trial Assessing the ImPact of Residual Inflammation Detected Via Imaging TEchniques, Drug Levels and Patient Characteristics on the Outcome of Dose TaperIng of Adalimumab in Clinical Remission Rheumatoid ArThritis (RA) Subjects (PREDICTRA) (Clinical Trial Registration NCT02198651). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02198651

AbbVie. (2021). A Phase 2, Multicenter, Double-Blind, Parallel Group Long Term Extension Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial With ABBV-105 Given Alone or in Combination With Upadacitinib (ABBV-599) (Clinical Trial Registration NCT03823378). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03823378

AbbVie. (2022). Phase 2 Study, Multicenter, Open-Label Extension (OLE) Study in Rheumatoid Arthritis Subjects Who Have Completed a Preceding Phase 2 Randomized Controlled Trial (RCT) With Upadacitinib (ABT-494) (Clinical Trial Registration NCT02049138). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02049138

Akbar, U., Yang, M., Kurian, D., & Mohan, C. (2017). Omega-3 Fatty Acids in Rheumatic Diseases: A Critical Review. Journal of Clinical Rheumatology: Practical Reports on Rheumatic & Musculoskeletal Diseases, 23(6), 330–339. https://doi.org/10.1097/RHU.0000000000000563

Aldeyra Therapeutics, Inc. (2023). A Phase 3 Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of ADX-102 1% Topical Dermal Cream (Reproxalap) in Subjects With Sjögren-Larsson Syndrome (SLS) (Clinical Trial Registration NCT03445650). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03445650

Alfaro-Lara, R., Espinosa-Ortega, H. F., Arce-Salinas, C. A., & PRECIS study group, all physicians belong to Division of Internal Medicine. Hospital Central Sur de Pemex. (2019). Systematic review and meta-analysis of the efficacy and safety of leflunomide and methotrexate in the treatment of rheumatoid arthritis. Reumatologia Clinica, 15(3), 133–139. https://doi.org/10.1016/j.reuma.2017.07.020

Amezaga Urruela, M., & Suarez-Almazor, M. E. (2012). Acupuncture in the treatment of rheumatic diseases. Current Rheumatology Reports, 14(6), 589–597. https://doi.org/10.1007/s11926-012-0295-x

Benatti, F. B., & Pedersen, B. K. (2015). Exercise as an anti-inflammatory therapy for rheumatic diseases-myokine regulation. Nature Reviews. Rheumatology, 11(2), 86–97. https://doi.org/10.1038/nrrheum.2014.193

Berman, B. M., Swyers, J. P., & Ezzo, J. (2000). The evidence for acupuncture as a treatment for rheumatologic conditions. Rheumatic Diseases Clinics of North America, 26(1), 103–115, ix–x. https://doi.org/10.1016/s0889-857x(05)70124-1

Bird, H. A. (1990). Medical treatment for rheumatic diseases. Journal of the Royal Society of Health, 110(5), 157–160. https://doi.org/10.1177/146642409011000503

Bliddal, H., Christensen, R., Højgaard, L., Bartels, E. M., Ellegaard, K., Zachariae, R., & Danneskiold-Samsøe, B. (2014). Spiritual healing in the treatment of rheumatoid arthritis: An exploratory single centre, parallel-group, double-blind, three-arm, randomised, sham-controlled trial. Evidence-Based Complementary and Alternative Medicine: eCAM, 2014, 269431. https://doi.org/10.1155/2014/269431

Boehringer Ingelheim. (2018). Long-term Assessment of Safety, Efficacy, Pharmacokinetics and Immunogenicity of BI 695501 in Patients With Rheumatoid Arthritis (RA): An Open-label Extension Trial for Patients Who Have Completed Trial 1297.2 and Are

Eligible for Long-term Treatment With Adalimumab (Clinical Trial Registration NCT02640612). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02640612

Brien, S., Lachance, L., Prescott, P., McDermott, C., & Lewith, G. (2011). Homeopathy has clinical benefits in rheumatoid arthritis patients that are attributable to the consultation process but not the homeopathic remedy: A randomized controlled clinical trial. Rheumatology (Oxford, England), 50(6), 1070–1082. https://doi.org/10.1093/rheumatology/keq234

Brosseau, L., Judd, M. G., Marchand, S., Robinson, V. A., Tugwell, P., Wells, G., & Yonge, K. (2003). Transcutaneous electrical nerve stimulation (TENS) for the treatment of rheumatoid arthritis in the hand. The Cochrane Database of Systematic Reviews, 2003(3), CD004377. https://doi.org/10.1002/14651858.CD004377

Brosseau, L. U., Pelland, L. U., Casimiro, L. Y., Robinson, V. I., Tugwell, P. E., & Wells, G. E. (2002). Electrical stimulation for the treatment of rheumatoid arthritis. The Cochrane Database of Systematic Reviews, 2002(2), CD003687. https://doi.org/10.1002/14651858.CD003687

Brosseau, L., Yonge, K., Welch, V., Marchand, S., Judd, M., Wells, G. A., & Tugwell, P. (2003). Thermotherapy for treatment of osteoarthritis. The Cochrane Database of Systematic Reviews, 2003(4), CD004522. https://doi.org/10.1002/14651858.CD004522

Cavalli, G., Larcher, A., Tomelleri, A., Campochiaro, C., Della-Torre, E., Luca, G. D., Farina, N., Boffini, N., Ruggeri, A., Poli, A., Scarpellini, P., Rovere-Querini, P., Tresoldi, M., Salonia, A., Montorsi, F., Landoni, G., Castagna, A., Ciceri, F., Zangrillo, A., & Dagna, L. (2021). Interleukin-1 and interleukin-6 inhibition compared with standard management in patients with COVID-19 and hyperinflammation: A cohort study. The Lancet. Rheumatology, 3(4), e253. https://doi.org/10.1016/S2665-9913(21)00012-6

Cheleschi, S., Tenti, S., Seccafico, I., Gálvez, I., Fioravanti, A., & Ortega, E. (2022). Balneotherapy year in review 2021: Focus on the mechanisms of action of balneotherapy in rheumatic diseases. Environmental Science and Pollution Research International, 29(6), 8054–8073. https://doi.org/10.1007/s11356-021-17780-0

Chen, Z., Li, X.-P., Li, Z.-J., Xu, L., & Li, X.-M. (2013). Reduced hepatotoxicity by total glucosides of paeony in combination treatment with leflunomide and methotrexate for patients with active rheumatoid arthritis. International Immunopharmacology, 15(3), 474–477. https://doi.org/10.1016/j.intimp.2013.01.021

Choi, J., & Fenando, A. (2023). Sulfasalazine. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557809/

Chou, P.-C., & Chu, H.-Y. (2018). Clinical Efficacy of Acupuncture on Rheumatoid Arthritis and Associated Mechanisms: A Systemic Review. Evidence-Based Complementary and Alternative Medicine: eCAM, 2018, 8596918. https://doi.org/10.1155/2018/8596918

Chung, C. L. R., & Mior, S. A. (2015). Use of spinal manipulation in a rheumatoid patient presenting with acute thoracic pain: A case report. The Journal of the Canadian Chiropractic Association, 59(2), 143–149.

Clark, P., Tugwell, P., Bennet, K., Bombardier, C., Shea, B., Wells, G., & Suarez-Almazor, M. E. (2000). Injectable gold for rheumatoid arthritis. The Cochrane Database of Systematic Reviews, 1997(2), CD000520. https://doi.org/10.1002/14651858.CD000520

Conrozier, T., Mathieu, P., Bonjean, M., Marc, J.-F., Renevier, J.-L., & Balblanc, J.-C. (2014). A complex of three natural anti-inflammatory agents provides relief of osteoarthritis pain. Alternative Therapies in Health and Medicine, 20 Suppl 1, 32–37.

Dehghan, M. (2015). Comparative Effectiveness of B and E Vitamins with Diclofenac in Reducing Pain Due to Osteoarthritis of the Knee. Medical Archives, 69(2), 103–106. https://doi.org/10.5455/medarh.2015.69.103-106

EMD Serono Research & Development Institute, Inc. (2018). Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of M2951 in Subjects With Rheumatoid Arthritis on Stable Methotrexate Therapy (Clinical Trial Registration NCT02784106). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02784106

Engel, J.-M. (2012). [Physiotherapy and ergotherapy are indispensable. Concrete prescription of remedies—Without recourse]. Zeitschrift Fur Rheumatologie, 71(5), 369–380. https://doi.org/10.1007/s00393-011-0865-8

Ernst, E. (2011a). Herbal medicine in the treatment of rheumatic diseases. Rheumatic Diseases Clinics of North America, 37(1), 95–102. https://doi.org/10.1016/j.rdc.2010.11.004

Ernst, E. (2011b). Herbal Medicine in the Treatment of Rheumatic Diseases. Rheumatic Disease Clinics of North America, 37(1), 95–102. https://doi.org/10.1016/j.rdc.2010.11.004

Fallon, K. (2021). The role of exercise in management of rheumatological disease. Australian Journal of General Practice, 50(5), 271–274. https://doi.org/10.31128/AJGP-03-21-5865

Fiechtner, J. J., & Brodeur, R. R. (2000). Manual and manipulation techniques for rheumatic disease. Rheumatic Diseases Clinics of North America, 26(1), 83–96, ix. https://doi.org/10.1016/s0889-857x(05)70122-8

Finckh, A., & Deane, K. D. (2014). Prevention of rheumatic diseases: Strategies, caveats, and future directions. Rheumatic Diseases Clinics of North America, 40(4), 771–785. https://doi.org/10.1016/j.rdc.2014.07.010

Fisher, P., & Scott, D. L. (2001). A randomized controlled trial of homeopathy in rheumatoid arthritis. Rheumatology (Oxford, England), 40(9), 1052–1055. https://doi.org/10.1093/rheumatology/40.9.1052

Fresenius Kabi SwissBioSim GmbH. (2019). A Multicenter, Randomized, Double-blind, Phase III Trial to Evaluate the Safety, Immunogenicity, and Efficacy of MSB11022 Compared With Humira® in Patients With Moderately to Severely Active Rheumatoid Arthritis (Clinical Trial Registration NCT03052322). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03052322

Fries, J. F., Hochberg, M. C., Medsger Jr., T. A., Hunder, G. G., Bombardier, C., Diagnostic, A. C. O., & Committee, T. (1994). Criteria for rheumatic disease. Different types and different functions. Arthritis & Rheumatism, 37(4), 454–462. https://doi.org/10.1002/art.1780370403

Gabriel, S. E. (2001). The epidemiology of rheumatoid arthritis. Rheumatic Diseases Clinics of North America, 27(2), 269–281. https://doi.org/10.1016/s0889-857x(05)70201-5

Galon, J., & Bruni, D. (2019). Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. Nature Reviews. Drug Discovery, 18(3), 197–218. https://doi.org/10.1038/s41573-018-0007-y

Genentech, Inc. (2020). A Two-Cohort Randomized Phase II, Double-Blind, Parallel Group Study in Patients With Active Rheumatoid Arthritis Evaluating the Efficacy and Safety of GDC-0853 Compared With Placebo and Adalimumab in Patients With an Inadequate Response to Previous Methotrexate Therapy (Cohort 1) and Compared With Placebo in Patients With an Inadequate Response or Intolerance to Previous TNF Therapy (Cohort 2) (Clinical Trial Registration NCT02833350). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02833350

Goemaere, S., Ackerman, C., Goethals, K., De Keyser, F., Van der Straeten, C., Verbruggen, G., Mielants, H., & Veys, E. M. (1990). Onset of symptoms of rheumatoid arthritis in relation to age, sex and menopausal transition. The Journal of Rheumatology, 17(12), 1620–1622.

Gourley, M., & Miller, F. W. (2007). Mechanisms of disease: Environmental factors in the pathogenesis of rheumatic disease. Nature Clinical Practice. Rheumatology, 3(3), 172–180. https://doi.org/10.1038/ncprheum0435

Guan, Y., Hao, Y., Guan, Y., Bu, H., & Wang, H. (2020). The Effect of Vitamin D Supplementation on Rheumatoid Arthritis Patients: A Systematic Review and Meta-Analysis. Frontiers in Medicine, 7, 596007. https://doi.org/10.3389/fmed.2020.596007

Gvozdenović, E., Dirven, L., van den Broek, M., Han, K. H., Molenaar, E. T. H., Landewé, R. B. M., Lems, W. F., & Allaart, C. F. (2014). Intra articular injection with corticosteroids in patients with recent onset rheumatoid arthritis: Subanalyses from the BeSt study. Clinical Rheumatology, 33(2), 263–267. https://doi.org/10.1007/s10067-013-2465-2

Haider, M. Z., Bhuiyan, R., Ahmed, S., Zahid-Al-Quadir, A., Choudhury, M. R., Haq, S. A., & Zaman, M. M. (2022). Risk factors of knee osteoarthritis in Bangladeshi adults: A national survey. BMC Musculoskeletal Disorders, 23(1), 333. https://doi.org/10.1186/s12891-022-05253-5

Haq, S. A., Darmawan, J., Islam, M. N., Uddin, M. Z., Das, B. B., Rahman, F., Chowdhury, M. A. J., Alam, M. N., Mahmud, T. A. K., Chowdhury, M. R., & Tahir, M. (2005). Prevalence of rheumatic diseases and associated outcomes in rural and urban communities in Bangladesh: A COPCORD study. The Journal of Rheumatology, 32(2), 348–353.

Hartung, W., Ehrenstein, B., Härle, P., Fleck, M., & Weigand, T. (2011). [Ultrasound-guided joint injections in patients with rheumatic diseases]. Zeitschrift Fur Rheumatologie, 70(6), 455–461. https://doi.org/10.1007/s00393-011-0837-z

Heidari, B., Hajian-Tilaki, K., & Babaei, M. (2019). Vitamin D Deficiency and Rheumatoid Arthritis: Epidemiological, Immunological, Clinical and Therapeutic Aspects. Mediterranean Journal of Rheumatology, 30(2), 94–102. https://doi.org/10.31138/mjr.30.2.94

Hoffmann-La Roche. (2020). A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Phase II Study to Evaluate The Safety and Efficacy of RO7123520 as Adjunct Treatment in Patients With Moderately to Severely Active Rheumatoid Arthritis and an Inadequate Response to TNF-alpha Inhibitors (Clinical Trial Registration NCT03001219). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03001219

Hope Biosciences. (2022). A Phase 1/2a Clinical Trial to Assess Safety of a Single IV Infusion of Autologous Adipose-derived Mesenchymal Stem Cells in Adults With Active Rheumatoid Arthritis (Clinical Trial Registration NCT03691909). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03691909

Hunter, J. A., & Blyth, T. H. (1999). A risk-benefit assessment of intra-articular corticosteroids in rheumatic disorders. Drug Safety, 21(5), 353–365. https://doi.org/10.2165/00002018-199921050-00002

Isaacs, J. D. (2009). Therapeutic agents for patients with rheumatoid arthritis and an inadequate response to tumour necrosis factor-alpha antagonists. Expert Opinion on Biological Therapy, 9(12), 1463–1475. https://doi.org/10.1517/14712590903379494

Johnson, S. R., Goek, O.-N., Singh-Grewal, D., Vlad, S. C., Feldman, B. M., Felson, D. T., Hawker, G. A., Singh, J. A., & Solomon, D. H. (2007). Classification criteria in

rheumatic diseases: A review of methodologic properties. Arthritis and Rheumatism, 57(7), 1119–1133. https://doi.org/10.1002/art.23018

Jonas, W. B., Linde, K., & Ramirez, G. (2000). Homeopathy and rheumatic disease. Rheumatic Diseases Clinics of North America, 26(1), 117–123, x. https://doi.org/10.1016/s0889-857x(05)70125-3

Jones, G., & Brooks, P. M. (1996). Injectable gold compounds: An overview. British Journal of Rheumatology, 35(11), 1154–1158. https://doi.org/10.1093/rheumatology/35.11.1154

Kerr, L. D. (1995). The impact of rheumatology in the primary care setting: One rheumatologist's odyssey. Southern Medical Journal, 88(3), 268–270. https://doi.org/10.1097/00007611-199503000-00004

Khraishi, M. M., & Singh, G. (1996). The role of anti-malarials in rheumatoid arthritis—The American experience. Lupus, 5 Suppl 1, S41-44.

Kim, J. R., Jo, J. H., Chung, J. W., & Park, J. W. (2018). Antinuclear antibody and rheumatoid factor positivity in temporomandibular disorders. Head & Face Medicine, 14, 26. https://doi.org/10.1186/s13005-018-0183-3

Klareskog, L., Gregersen, P. K., & Huizinga, T. W. J. (2010). Prevention of autoimmune rheumatic disease: State of the art and future perspectives. Annals of the Rheumatic Diseases, 69(12), 2062–2066. https://doi.org/10.1136/ard.2010.142109

Kocyigit, B. F., Sagtaganov, Z., & Yessirkepov, M. (2023). The effectiveness of yoga as a form of exercise in the management of rheumatic diseases. Rheumatology International, 43(5), 795–801. https://doi.org/10.1007/s00296-023-05291-9

Kocyigit, E., & Kocak, T. (2023). Rheumatic diseases and gut microbiota publications in 2002-2022: A Scopus-based bibliometric analysis. Rheumatology International, 43(11), 2115–2124. https://doi.org/10.1007/s00296-023-05408-0

Kokar, S., Kayhan, Ö., Şencan, S., & Gündüz, O. H. (2021). The Role of Sacroiliac Joint Steroid Injections in the Treatment of Axial Spondyloarthritis. Archives of Rheumatology, 36(1), 80–88. https://doi.org/10.46497/ArchRheumatol.2021.8043

Kolasinski, S. L. (2012). Herbal medicine for rheumatic diseases: Promises kept? Current Rheumatology Reports, 14(6), 617–623. https://doi.org/10.1007/s11926-012-0293-z

Kreps, D. J., Halperin, F., Desai, S. P., Zhang, Z. Z., Losina, E., Olson, A. T., Karlson, E. W., Bermas, B. L., & Sparks, J. A. (2018). Association of weight loss with improved disease activity in patients with rheumatoid arthritis: A retrospective analysis using electronic medical record data. International Journal of Clinical Rheumatology, 13(1), 1–10. https://doi.org/10.4172/1758-4272.1000154

Krishna, K. P. R. (2011). The efficacy of Ayurvedic treatment for rheumatoid arthritis: Cross-sectional experiential profile of a longitudinal study. International Journal of Ayurveda Research, 2(1), 8–13. https://doi.org/10.4103/0974-7788.83177

Kröner, P. T., Tolaymat, O. A., Bowman, A. W., Abril, A., & Lacy, B. E. (2019). Gastrointestinal Manifestations of Rheumatological Diseases. The American Journal of Gastroenterology, 114(9), 1441–1454. https://doi.org/10.14309/ajg.0000000000000260

Krüger, K. (2011). [Combination therapy using methotrexate with DMARDs or biologics—Current status]. Zeitschrift Fur Rheumatologie, 70(2), 114–122. https://doi.org/10.1007/s00393-010-0684-3

Lewandowski, L. B., Schiffenbauer, A., Mican, J. M., Moses, S. J., Fallah, M. P., Plotz, P., & Katz, J. D. (2020). Rheumatology capacity building: Implementing a rheumatology curriculum for Liberian health-care providers in 2016. Clinical Rheumatology, 39(3), 689. https://doi.org/10.1007/s10067-019-04817-6

Li, X., & Zhang, S. (2020). Herbal compounds for rheumatoid arthritis: Literatures review and cheminformatics prediction. Phytotherapy Research, 34(1), 51–66. https://doi.org/10.1002/ptr.6509

Listing, J., Gerhold, K., & Zink, A. (2013). The risk of infections associated with rheumatoid arthritis, with its comorbidity and treatment. Rheumatology (Oxford, England), 52(1), 53–61. https://doi.org/10.1093/rheumatology/kes305

Mackenzie, A. H. (1983). Antimalarial drugs for rheumatoid arthritis. The American Journal of Medicine, 75(6A), 48–58. https://doi.org/10.1016/0002-9343(83)90474-6

Marcus, D. M. (2009). Herbals and supplements for rheumatic diseases. Nature Reviews Rheumatology, 5(6), 299–300. https://doi.org/10.1038/nrrheum.2009.89

Martin, E. J., Cooke, E. J., Ceponis, A., Barnes, R. F. W., Moran, C. M., Holle, S., Hughes, T. H., Moore, R. E., & von Drygalski, A. (2017). Efficacy and safety of point-of-care ultrasound-guided intra-articular corticosteroid joint injections in patients with haemophilic arthropathy. Haemophilia: The Official Journal of the World Federation of Hemophilia, 23(1), 135–143. https://doi.org/10.1111/hae.13057

Miller, A. V., & Ranatunga, S. K. M. (2012). Immunotherapies in rheumatologic disorders. The Medical Clinics of North America, 96(3), 475–496, ix–x. https://doi.org/10.1016/j.mcna.2012.04.003

Mills, S. E. E., Nicolson, K. P., & Smith, B. H. (2019). Chronic pain: A review of its epidemiology and associated factors in population-based studies. BJA: British Journal of Anaesthesia, 123(2), e273–e283. https://doi.org/10.1016/j.bja.2019.03.023

Negi, D. V. S. (2021). Comparison of Sulfasalazine Versus Leflunomide Based Combination Disease Modifying Anti-rheumatic Drug Therapy (DMARD) in Patients With Rheumatoid Arthritis Failing Methotrexate Monotherapy: A Randomized Control Trial

(Clinical Trial Registration NCT02930343). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02930343

NYU Langone Health. (2023). Rheumatoid Arthritis Memory B Cells and Abatacept (RAMBA) (Clinical Trial Registration NCT03652961). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03652961

O'Dell, J. R. (1998). Triple therapy with methotrexate, sulfasalazine, and hydroxychloroquine in patients with rheumatoid arthritis. Rheumatic Diseases Clinics of North America, 24(3), 465–477. https://doi.org/10.1016/s0889-857x(05)70020-x

Ollier, W. E., Harrison, B., & Symmons, D. (2001). What is the natural history of rheumatoid arthritis? Best Practice & Research. Clinical Rheumatology, 15(1), 27–48. https://doi.org/10.1053/berh.2000.0124

Palominos, P. E., Lineburger, I. B., & Xavier, R. M. (2021). Emerging protein kinase inhibitors for the treatment of rheumatoid arthritis. Expert Opinion on Emerging Drugs, 26(3), 303–321. https://doi.org/10.1080/14728214.2021.1964472

Park, J., & Ernst, E. (2005). Ayurvedic medicine for rheumatoid arthritis: A systematic review. Seminars in Arthritis and Rheumatism, 34(5), 705–713. https://doi.org/10.1016/j.semarthrit.2004.11.005

Peppercorn, M. A. (1984). Sulfasalazine. Pharmacology, clinical use, toxicity, and related new drug development. Annals of Internal Medicine, 101(3), 377–386. https://doi.org/10.7326/0003-4819-101-3-377

Percy, J. S., & Russell, A. S. (1975). Laboratory diagnosis and monitoring of rheumatologic diseases. Canadian Medical Association Journal, 112(11), 1320–1328.

Phang, J. K., Kwan, Y. H., Goh, H., Tan, V. I. C., Thumboo, J., Østbye, T., & Fong, W. (2018). Complementary and alternative medicine for rheumatic diseases: A systematic review

of randomized controlled trials. Complementary Therapies in Medicine, 37, 143–157. https://doi.org/10.1016/j.ctim.2018.03.003

Pianarosa, E., Chomistek, K., Hsiao, R., Anwar, S., Umaefulam, V., Hazlewood, G., & Barnabe, C. (2022). Global Rural and Remote Patients With Rheumatoid Arthritis: A Systematic Review. Arthritis Care & Research, 74(4), 598–606. https://doi.org/10.1002/acr.24513

Pincus, T., Yazici, Y., Sokka, T., Aletaha, D., & Smolen, J. S. (2003). Methotrexate as the "anchor drug" for the treatment of early rheumatoid arthritis. Clinical and Experimental Rheumatology, 21(5 Suppl 31), S179-185.

Pozsgay, J., Szekanecz, Z., & Sármay, G. (2017). Antigen-specific immunotherapies in rheumatic diseases. Nature Reviews. Rheumatology, 13(9), 525–537. https://doi.org/10.1038/nrrheum.2017.107

Rains, C. P., Noble, S., & Faulds, D. (1995). Sulfasalazine. A review of its pharmacological properties and therapeutic efficacy in the treatment of rheumatoid arthritis. Drugs, 50(1), 137–156. https://doi.org/10.2165/00003495-199550010-00009

Rindfleisch, J. A., & Muller, D. (2005). Diagnosis and management of rheumatoid arthritis. American Family Physician, 72(6), 1037–1047.

Ronald MacKenzie, C., Goodman, S. M., & Miller, A. O. (2018). The management of surgery and therapy for rheumatic disease. Best Practice & Research. Clinical Rheumatology, 32(6), 735–749. https://doi.org/10.1016/j.berh.2019.06.003

Rosenthal, M. (1978). A critical review of the effect of levamisole in rheumatic diseases other than rheumatoid arthritis. The Journal of Rheumatology. Supplement, 4, 97–100.

Sadeghi, A., Tabatabaiee, M., Mousavi, M. A., Mousavi, S. N., Abdollahi Sabet, S., & Jalili, N. (2022). Dietary Pattern or Weight Loss: Which One Is More Important to Reduce Disease Activity Score in Patients with Rheumatoid Arthritis? A Randomized Feeding

Trial. International Journal of Clinical Practice, 2022, 6004916. https://doi.org/10.1155/2022/6004916

Sandoz. (2018). A Randomized, Double-blind, Parallel-group, Multicenter Study to Demonstrate Similar Efficacy and to Compare Safety and Immunogenicity of GP2017 and Humira® in Patients With Moderate to Severe Active Rheumatoid Arthritis (Clinical Trial Registration NCT02744755). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02744755

Sangha, O. (2000). Epidemiology of rheumatic diseases. Rheumatology (Oxford, England), 39 Suppl 2, 3–12. https://doi.org/10.1093/rheumatology/39.suppl_2.3

Schur, P. H. (1977). Pathophysiology of rheumatic diseases. Arthritis and Rheumatism, 20(2 Suppl), 500–508.

Sebba, A. (2008). Tocilizumab: The first interleukin-6-receptor inhibitor. American Journal of Health-System Pharmacy: AJHP: Official Journal of the American Society of Health-System Pharmacists, 65(15), 1413–1418. https://doi.org/10.2146/ajhp070449

Sehgal, V. N., & Verma, P. (2013). Leflunomide: Dermatologic perspective. The Journal of Dermatological Treatment, 24(2), 89–95. https://doi.org/10.3109/09546634.2011.595383

Solomon, D. H. (2022). Treatments Against RA and Effect on FDG-PET/CT (The TARGET Trial) (Clinical Trial Registration NCT02374021). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT02374021

Spies, C. M., Bijlsma, J. W. J., Burmester, G.-R., & Buttgereit, F. (2010). Pharmacology of glucocorticoids in rheumatoid arthritis. Current Opinion in Pharmacology, 10(3), 302–307. https://doi.org/10.1016/j.coph.2010.02.001

Spurgeon, S. E., Coffey, G., Fletcher, L. B., Burke, R., Tyner, J. W., Druker, B. J., Betz, A., DeGuzman, F., Pak, Y., Baker, D., Pandey, A., Hollenbach, S. J., Sinha, U., & Loriaux,

M. M. (2013). The selective SYK inhibitor P505-15 (PRT062607) inhibits B cell signaling and function in vitro and in vivo and augments the activity of fludarabine in chronic lymphocytic leukemia. The Journal of Pharmacology and Experimental Therapeutics, 344(2), 378–387. https://doi.org/10.1124/jpet.112.200832

Sterzi, S., Giordani, L., Morrone, M., Lena, E., Magrone, G., Scarpini, C., Milighetti, S., Pellicciari, L., Bravi, M., Panni, I., Ljoka, C., Bressi, F., & Foti, C. (2016). The efficacy and safety of a combination of glucosamine hydrochloride, chondroitin sulfate and bio-curcumin with exercise in the treatment of knee osteoarthritis: A randomized, double-blind, placebo-controlled study. European Journal of Physical and Rehabilitation Medicine, 52(3), 321–330.

Symmons, D. P. M., & Gabriel, S. E. (2011). Epidemiology of CVD in rheumatic disease, with a focus on RA and SLE. Nature Reviews Rheumatology, 7(7), Article 7. https://doi.org/10.1038/nrrheum.2011.75

Tamási, L., & Szekanecz, Z. (2007). [Biological therapy of arthritis and systemic autoimmune diseases]. Orvosi Hetilap, 148 Suppl 1, 63–70. https://doi.org/10.1556/OH.2007.28038

Todd, P. A., & Clissold, S. P. (1990). Naproxen. A reappraisal of its pharmacology, and therapeutic use in rheumatic diseases and pain states. Drugs, 40(1), 91–137. https://doi.org/10.2165/00003495-199040010-00006

Tomaras, S., Keyßer, G., & Feist, E. (2022). Curcumin: Useful add-on for Rheumatic Diseases? Journal of Clinical Medicine, 11(10), 2908. https://doi.org/10.3390/jcm11102908

Townsend, H. B., & Saag, K. G. (2004). Glucocorticoid use in rheumatoid arthritis: Benefits, mechanisms, and risks. Clinical and Experimental Rheumatology, 22(5 Suppl 35), S77-82.

Townsend, M. J., Monroe, J. G., & Chan, A. C. (2010). B-cell targeted therapies in human autoimmune diseases: An updated perspective. Immunological Reviews, 237(1), 264–283. https://doi.org/10.1111/j.1600-065X.2010.00945.x

Uhm, W. S., Yoo, D. H., Lee, J. H., Kim, T. H., Jun, J. B., Lee, I. H., Bae, S. C., & Kim, S. Y. (2000). Injectable gold-induced hepatitis and neutropenia in rheumatoid arthritis. The Korean Journal of Internal Medicine, 15(2), 156–159. https://doi.org/10.3904/kjim.2000.15.2.156

VA Office of Research and Development. (2021). Low Dose Naltrexone for Chronic Pain in Osteoarthritis and Inflammatory Arthritis (Clinical Trial Registration NCT03008590). clinicaltrials.gov. https://clinicaltrials.gov/study/NCT03008590

van Laar, M., Pergolizzi, J. V., Mellinghoff, H.-U., Merchante, I. M., Nalamachu, S., O'Brien, J., Perrot, S., & Raffa, R. B. (2012). Pain Treatment in Arthritis-Related Pain: Beyond NSAIDs. The Open Rheumatology Journal, 6, 320–330. https://doi.org/10.2174/1874312901206010320

van Vollenhoven, R. F. (2010). New and future agents in the treatment of rheumatoid arthritis. Discovery Medicine, 9(47), 319–327.

Ventura, I., Reid, P., & Jan, R. (2018). Approach to Patients with Suspected Rheumatic Disease. Primary Care: Clinics in Office Practice, 45(2), 169–180. https://doi.org/10.1016/j.pop.2018.02.001

Vervoordeldonk, M. J., & Tak, P. P. (2001). Gene therapy in rheumatic diseases. Best Practice & Research. Clinical Rheumatology, 15(5), 771–788. https://doi.org/10.1053/berh.2001.0193

Vollenhoven, R. F. van. (2010). New and Future Agents in the Treatment of Rheumatoid Arthritis. Discovery Medicine, 9(47), 319–327.

Wang, S., Wang, X., Liu, Y., Sun, X., & Tang, Y. (2019). Ultrasound-guided intra-articular triamcinolone acetonide injection for treating refractory small joints arthritis of rheumatoid arthritis patients. Medicine, 98(33), e16714. https://doi.org/10.1097/MD.0000000000016714

Wang, W., Zhou, H., & Liu, L. (2018). Side effects of methotrexate therapy for rheumatoid arthritis: A systematic review. European Journal of Medicinal Chemistry, 158, 502–516. https://doi.org/10.1016/j.ejmech.2018.09.027

Wasserman, A. M. (2011). Diagnosis and management of rheumatoid arthritis. American Family Physician, 84(11), 1245–1252.

Whisler, R. L., Gray, L. S., & Hackshaw, K. V. (2002). Rheumatology, a clinical overview. Clinics in Podiatric Medicine and Surgery, 19(1), 149–161, vii. https://doi.org/10.1016/S0891-8422(03)00085-5

Wu, L., Tafti, D., & Varacallo, M. (2023). Sacroiliac Joint Injection. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK513245/

Yu, H.-C., & Lu, M.-C. (2019). The roles of anti-citrullinated protein antibodies in the immunopathogenesis of rheumatoid arthritis. Ci Ji Yi Xue Za Zhi = Tzu-Chi Medical Journal, 31(1), 5–10. https://doi.org/10.4103/tcmj.tcmj_116_18

Zhao, Z., Hua, Z., Luo, X., Li, Y., Yu, L., Li, M., Lu, C., Zhao, T., & Liu, Y. (2022). Application and pharmacological mechanism of methotrexate in rheumatoid arthritis. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie, 150, 113074. https://doi.org/10.1016/j.biopha.2022.113074