IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

# Evaluationofsynthetic Drugs Through Oral Route Of Administration For Rheumatoid Arthritis

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ABSTRACT

Rheumatoid arthritis (RA) is a painful, debilitating disease characterized by inflammation of the joints, with the proliferation of the synovium and the progressive erosion of cartilage and bone. The treatment of RA is still unsatisfactory, but a number of powerful disease-modifying antirheumatic drugs have become available, such as methotrexate (MTX). RA results from the body's own immune system attacking its own tissues. Currently, there are various treatments available for RA including disease-modifying antirheumatic drugs (DMARDs) and NSAIDs. Leflunomide (LEF) is a USFDA-approved synthetic DMARD which is being widely prescribed for the management of RA; however, it faces several challenges such as prolonged drug elimination, hepatotoxicity, and others. The step down approach has been proposed for the treatment of patients with recent onset rheumatoid arthritis who have clinical features predictive of an adverse prognosis. More efficient 'targeting' of drugs at the site of desired action should help to minimize the adverse effects of therapy. Dehydroepiandrosterone (DHEA) treatment provides diverse anti-inflammatory benefits in rodent models of diseases, including rheumatoid arthritis.

Objective: To investigate the anti-arthritic activity of ethanolic extract of Caesalpinia pulcherrima (ECP) in adjuvant arthritic (AA) rat model induced by Freund's complete adjuvant (FCA). CFA/CIA Model (Collagen-Induced Arthritis)Another major model used in Wistar rats.PurposeMimics autoimmune components of human RA more closely.General Composition (conceptual)Type II collagen (usually from bovine or chicken cartilage)Emulsified in an adjuvant (complete or incomplete)Used to stimulate an autoimmune response targeting joint cartilage.

Methods:Thirty healthy albino rats were selected and randomly divided into five groups. Arthritis was induced by Freund's complete adjuvant (FCA) and then treated with ethanolic extract of Caesalpinia pulcherrima for 28 days. The various parameters like paw volume, haematological parameters (RBC, WBC, Hb and ESR), and radiological studies were assessed.

Results:1] TAPC (50, 100 and 200 mg/kg) significantly alleviated paw swelling ($p < 0.05$), arthritis scores ($p < 0.05$) and thymus and spleen indices ($p < 0.05$) of CIA rats, when compared with the control rats. In addition, TAPC significantly decreased serum levels of the pro-inflammatory cytokines TNF-α, IL-6 and IL-17 ($p < 0.01$); and down-regulated their mRNA expressions in synovial tissues ($p < 0.01$).

2] MTXSuch delivery systems provide prolonged plasma profile, enhanced and specific activity in vitro and in vivo in animal models. Nevertheless, more complementary studies are needed before they can be applied in human.

KEYWORDS:Methotrexate, RheumatoidArthritis, Anti-Rheumatic Agents, Drug Therapy, Clinical Protocols, Leflunomide; Drug Delivery; Formulation; DMARDs; Glucocorticoids; NSAIDs; Drug Deliver.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease characterised by pain, inflammation, and potential erosion of the joints. Approximately 0.39 to 1% of the population is affected by RA, making it one of the most prevalent chronic inflammatory diseases [1]. Unfortunately, the debilitating effects of RA have a long-term impact on patient's physical and psychological well-being, decreasing their quality of life [2]. Its symptoms include energy loss, fatigue, muscle pain, joint pain, and rigidity of the joints. It usually begins at the small joints of feet and hands and finally spreads to the other larger joints. Inflammation at the joint lings or in the synovial membrane damages the articular cartilage and the tissues of the joint, thereby causing rigidity of the joints and physical disability[3 -5]. In the United States alone, it is estimated that 2.5 million people suffer from the disease, with a monetary cost measured in billions [6]. The community studies stated the prevalence of 0.5% to 0.75% in India [7].

The primary therapeutic goal in RA is to achieve a target of sustained clinical remission or low disease activity (LDA) in each patient [8, 9], and this is typically only possible with the help of disease-modifying anti-rheumatic drugs (DMARDs). DMARDs have the potential to prevent or reduce joint damage and preserve joint integrity and function, controlling synovitis and slowing or stopping the radiographic progression [10, 11]. Various DMARDs are currently available for the treatment of RA, including conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targated synthetic DMARDs [8, 9].

It affects three times more women than men. RA is an autoimmune disorder elicited by exposure of genetical factors from the host to unknown antigens causing arthritogenic complaints. It also includes the activation of lymphocytes as well as CD4+ helper T cells along with local release of chronic inflammatory mediators and cytokines like tumor necrosis factor (TNF-α) and various cytokines like interleukins (IL) that enormously affect the joints. In the present era, researchers and healthcare professionals have moved toward natural medicine obtained from plants and other nat ural sources. The research based on development of phytomedicine has globally increased. Evidence has been collected to show massive therapeutic potential of medicinal plants used in various traditional systems against many pathological complications [12,13]. In the present scenario, researchers have focused on the therapeutic potential of natural products used for treatment and counteracting various disorders along with their complications having negligible adverse effects.[14] Freund's complete adjuvant (FCA) animal model is already used in anti-arthritic studies of various plants such as Celastrus pa niculatus Willd,4 Xanthium srtumarium L.,5 Premna serratifolia Linn [15]. Inflammation of the synovium causes the activation of macrophages and fibroblast to occur, and pro duction of inflammatory cytokines, tumor necrosis factor (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-17 (IL-17), macrophage colony-stimulating factor (M-CSF) was also observed. Inflammation leads to the activation of osteoclasts, which ultimatelycauses bone destruction [16].

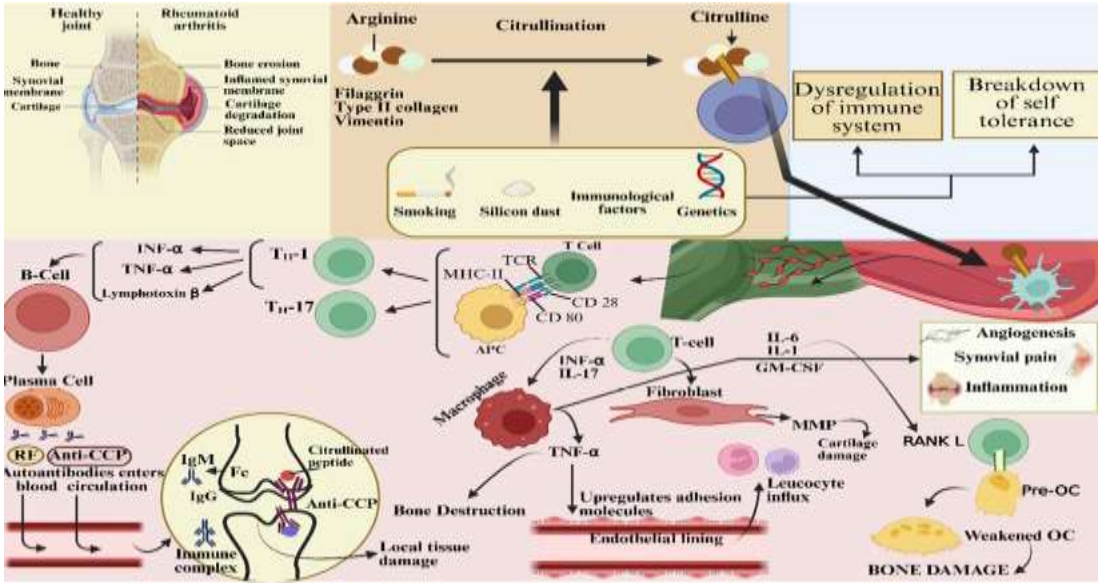



Figure 1. A diagrammatic illustration of pathophysiological events involved in rheumatoid arthritis.

Other Organ also affected like skin and lungs [17].

Articular cartilage type of connective tissue that act like protective cushion a lubricated surface for bone to smoothly glide against [17].

Knee Joint = Synovial joint; connect 2 bone with a fibrous joint capsule periosteum (outer layer of bone. It help lubricate joint [17].

INDUCING AGENT :

Genetics:

- A person with a certain gene for human protein like human leukocytes antigen or HLA-DR1&HLA-DR4 might develop rheumatoid arthritic after getting exposed to something in the environments.
- Due to susceptibility gene HLA-DR1 & HLA-DR4; immune cell get confused by this change.
- No longer recognise this protein as self antigen.

Environmental:

- Like Cigarettes smoking or specific pathogen like a bed bacteria that live in the intestine.
- This environment factor cause modification of our own antigen such IgG Antibody or other protein like type II collagen or vimetin.
- Can get modifiedthrough the process of citrullination. Amino acid convert into citrulline.
- Amino acid like arginine found in this [17].

FCA MODEL: **Freund's Complete Adjuvant (FCA)Composition:**

- *Heat-killed Mycobacterium tuberculosis* (typically 0.5–1 mg/mL)
- Mineral oil (paraffin oil)
- Emulsifier (Arlacel A / mannide monooleate)

This combination produces a strong and persistent **cell-mediated immune response**[18].

Cytokine: Inducing Agents these agents activate immune cells and stimulate release of cytokines such as TNF-α, IL-1β, IL-6, IFN-γ, etc [18].

Lipopolysaccharide:A component of Gram-negative bacterial cell wallsstrong inducer of TNF-α, IL-6, IL-1βWidely used to trigger innate immune activation [19].

Ionomycin: Calcium ionophoreenhances T-cell activation and cytokine releaseoften combined with PMA [19].

Carrageenan: Sulfated polysaccharideinduces acute inflammatory cytokines (IL-1β, TNF-α) [19].

Chemical/Drug: Induced Arthritis Models (less common) These are used when researchers need fast-onset, localized inflammation.

Examples (high-level only)Carrageenan-based inflammatory triggers

Monosodium urate crystals (gout-like but sometimes used in comparative arthritis research) [18].

**Rheumatoid arthritis mechanism of action:**

Antigens get picked up by lymph
Antigen Presenting Cell ➔ Node
(APC)

# Antigen Presenting Cell # B- cell Proliferate
ActivatedCD4 ➔
T-helper cells # Differentiate into plasma cell
⬇Antibody

# T-helper cell stimulate Produce specific

B-cells Autoantibodies Against-self-antigens [17].

Theory:

In rheumatoid arthritis; T-helper cells & antibodies
circulate & reach joints.
⬇
Now T-cell secrete cytokine like Interference γ&Interleukin-17 to recruit more inflammatorycells
like macrophages into joint space.
⬇

Macrophages will also produce inflammatory cytokine like tumour necrosis factor TNF α, Interleukin-1& Interleukin 6, which together with T-cell cytokines.

⬇

Stimulate synovial cell to proliferate[17].

The increase in synovial call & immune cell creates a **PANNUS**, which is thick swollen synovial membrane with granulation or scar tissue [17].

**Specific Deformities in Rheumatoid Arthritis:[20]**

**1. Ulnar Deviation (Ulnar Drift)**

- Fingers drift toward the **ulnar side** (little finger side).
- Caused by MCP joint erosion and ligament weakening.

**2. Swan-Neck Deformity**

- Hyperextension of the PIP joint
- Flexion of the DIP joint
- Due to weakening of volar plate & tendon imbalance.

**3. Boutonnière Deformity**

- Flexion of PIP joint
- Hyperextension of DIP joint
- Caused by rupture of the central slip of the extensor tendon.

**4. Z-Thumb (Hitchhiker Thumb / Z-Deformity)**

- Flexion at the **MCP** joint of thumb
- Hyperextension at the **IP** joint
- Subluxation at the first CMC joint.

**5. Wrist Deformities**

**a. Radial Deviation of the Wrist**

- Wrist deviates toward the **radius**, while fingers deviate ulnarly → "zig-zag" pattern.

**b. Caput Ulnae Syndrome**

- Prominent distal ulna ("piano-key sign")
- Dorsal subluxation of ulna
- Common in chronic RA.

**6. Hammer Toe / Claw Toe**

- Toes bend at PIP/DIP joints
- Due to chronic inflammation and tendon imbalance in the feet.

**7. Hallux Valgus (Big Toe Deformity)**

- Lateral deviation of big toe
- Often associated with bunion formation.

**8. Knee Deformities**

**a. Genu Valgum (Knock Knees)**

- Knees angle inward due to cartilage destruction.

**b. Flexion Contracture**

- Inability to fully extend the knee.

**9. Cervical Spine Involvement**

**Atlantoaxial Subluxation (AAS)**

- C1–C2 instability
- Can cause neck pain, neurological deficits if severe [20].

Summary Table [20]

| Region | Deformity | Key Feature |
|---|---|---|
| Hand | Ulnar drift | Fingers deviate outward |
| Hand | Swan-neck | PIP hyperextension, DIP flexion |
| Hand | Boutonnière | PIP flexion, DIP hyperextension |
| Thumb | Z-thumb | MCP flexion + IP hyperextension |
| Wrist | Radial deviation | Wrist moves inward |
| Wrist | Caput ulnae | Prominent ulna, subluxation |
| Foot | Hammer/claw toes | Toe deformities |
| Foot | Hallux valgus | Big toe lateral deviation |
| Knee | Genu valgum | Knock knees |
| Spine | AAS | C1–C2 instability |

❖ FELTY SYNDROM:

Serious condition in rheumatoid arthritis TRIADAL of rheumatoid arthritis,splenomegaly & granulocytopenia.

It may lead to life threatening Infections[17].

❖ **OTHER BODY ORGANS AFFECTED BY RHEUMATOID ARTHRITIS [21].**

**1. Skin**

- Rheumatoid nodules (firm lumps over elbows, fingers)
- Vasculitis ulcers
- Palmar erythema

**2. Eyes**

- Keratoconjunctivitis sicca (dry eyes; most common)
- Scleritis
- Episcleritis
- Uveitis
- Risk of corneal ulceration in severe disease

**3. Lungs**

RA often affects the respiratory system:

Lung Conditions:

- Interstitial lung disease (ILD)
- Pleural effusion
- Rheumatoid lung nodules

- Bronchiolitis obliterans
- Increased risk of infections (due to immunosuppressive drugs)

**4. Heart**

RA increases cardiovascular risks:

- Pericarditis
- Myocarditis
- Atherosclerosis (accelerated)
- Increased risk of heart attack and stroke
- Valve disease (rare)

5**. Blood & Immune System**

- Anemia of chronic disease
- Thrombocytosis
- Leukopenia (especially in Felty's syndrome)
- Lymphadenopathy

**6. Nervous System**

- Peripheral neuropathy
- Carpal tunnel syndrome
- Cervical spine instability (atlantoaxial subluxation)

**7.Endocrine & Metabolic**

- Increased risk of:
    - Osteoporosis
    - Fatigue syndrome
    - Weight loss and muscle wasting (cachexia)

**8. Spleen**

In Felty's syndrome:

- Enlarged spleen (splenomegaly)
- Low WBC count (neutropenia)

**9. Kidneys**

Not directly affected by RA, but:

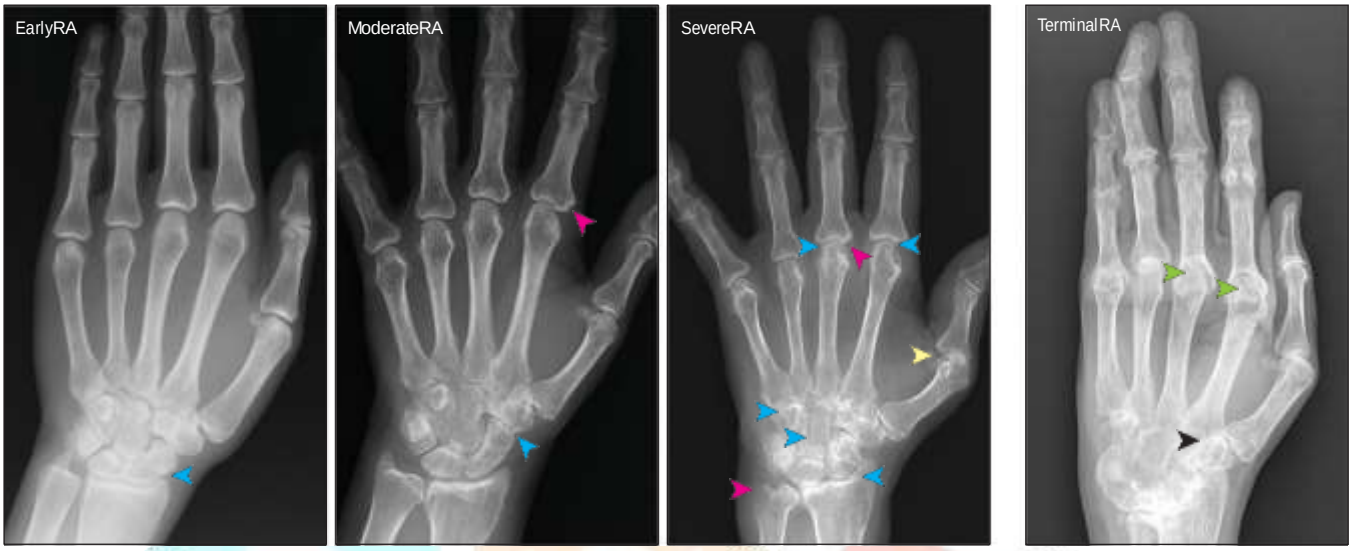
- RA drugs can cause kidney impairment
- Secondary amyloidosis can affect kidneys in long-standing RA.

MORE RARELY (HEART, LUNGS, SCLERA)

ALSO INCREASE RATE OF ARTHERESCLEROSIS ( HEART, VESSEL, STROKE) [17].

Diagnosis of Rheumatoid Arthritis:

1) Confirmatory blood test:
   Looking for the presence of rheumatoid factor & anti-citrullinated peptides antibody.
2) X-ray: Decrease in bone density around affected joints soft tissue swelling, narrow of joints space, bony erosion [17].




Radiologic findings Joint space narrowing Bone erosion Subluxation Ankylosis [22]

**Figure2.**Differenttypesofx-ray

RAisadynamicdiseasecausing creasing damagetoincreasingnumbersof joints over time, as depicted by the increasing radiographic abnormalities seen fromleft to right. In early disease (left 2 images), there is no or at most minimal bonyorcartilage damage(ascanbeseenintheseradiographs,whicharealmost normal). In severe, established RA (second image from the right), joint damage progresses in affected joints and spreads to additional joints—to additional joints—in this image, damagehasaccrued,bothintermsoft cartilage (joint spacenarrowing)andbonechanges in insufficiently treated patients. Coloured arrowheads refer to specific abnormalities exemplified here, and many more changes exist in the right 2 radiographs.

**Material and Method:**

The PRISMA extension for Scoping Reviews (PRISMA ScR) [24] Checklist and the framework proposed by Ark say and O'Malley [23]. Checklist and the framework proposed by Ark sey and O'Malley [24] were used to guide this review. The following five steps have been followed in this scoping review: (i) identifying the research question, (ii) identifyflying relevant studies, (iii) selecting eligible studies, (iv) charting the data.

**Identifying the research question**

The main research question was: "What are the efficacy and safety of different therapeutic strategies utilising different dosages and routes of administration of MTX in RA patients? . The research sub-question was as follows: What are the efficacy and safety of utilising different dos ages and routes of administration of MTX in individuals with early RA?.

Identifying relevant studies A primary electronic literature search was conducted in the three major biomedical databases (PubMed, EMBASE, and Cochrane) to identify relevant publications on using different therapeutic strategies with MTX in RA patients. The search strategies were adapted for each database using a combination of free-text terms and medical subject headings (MeSH and Emtree terms).

Articles published between database inception to 4th April 2022 were included in the review. In addition to this search with a more global approach aimed at patients with a time from RA diagnosis of any duration, a specific search strategy was developed to identify studies explicitly addressing the efficacy and safety of utilising different dosages and routes of administration in initial treatment with MTX only for patients' early RA (disease duration ≤ 2 years). Thus, a total of two searches (one for each research question) were conducted, combining the following main search terms based on inclusion and exclusion criteria: "methotrexate", "rheumatoid arthritis", "drug administration routes", "methotrexate/administration and dosage", and "randomised controlled trial". Most of the articles were found using combinations between Boolean operators "AND/OR", search terms, and synonyms for the keywords. Further search for any other relevant studies was per formed through a hand search of reference lists of the selected and review articles. The searches were restricted to studies in humans, but no language or time restrictions were imposed. The final selected studies from the obtained references were screened by a single reviewer. The complete search strategies are available in Additional File 1 in the supplementary materials.

**Study selection**

Following the manual removal of duplicates, the titles and abstracts of retrieved articles were screened for relevance. Full texts of retrieved publications were reviewed and marked for inclusion if they met the inclusion criteria. The inclusion criteria were as follows: (1) the study design was a randomised clinical trial (parallel arm and cross-over) published in any format (full paper, conference abstracts) with sufficient data available to estimate outcomes, (2) enrolled adult patients (> 18 years) with RA diagnosis according to validated criteria, irrespective of clinical stage or disease duration; and (3) compared two or more treatment strategies at treat ment initiation and later on, by using different dosages or routes of administration, whether or not combined with other drugs. We consider an additional inclusion criterion on RA disease duration (≤ 2 years) to answer the research sub-question about a specific population (early RA patients) in accordance with prior publications [25]. Papers were excluded if (1) enrolled paediatric or mixed populations, (2) focused on the use of MTX in combination with other agents or on the splitting dosing strategy (administering the totalprescribed dose more frequently and in smaller increments over one week), (3) included a single arm or with any other design (narrative reviews, editorial comments, and letters). Quality appraisal was not performed in accordance with the standard approach to conducting scoping reviews [24, 26]. The PRISMA study flow diagram is illustrated in Fig. 1

**Charting data and reporting the results**

A data extraction template was developed to determine which variables to extract for each study. The following data were extracted from full-text publications selected for inclusion in the review: author(s), year of publica tion, study location, the title of the publication, follow up (number of patients randomised, follow-up period, frequency of withdrawals), study population (i.e., age, gender, RA duration, baseline severity of RA, baseline functional status, MTX- or other DMARD-exposure), intervention type (i.e., treatment(s) received, dosage and dose schedule), outcome measures and critical results of the publication on the effectiveness and safety of MTX. All data were entered and verified onto a specifically designed 'data form' using the database program Excel. T he most recent or complete report was used when multiple articles describing the same sample or study were published. We categorised the included studies based on the following three pre-identified themes: (1) initiating MTX therapy, (2) optimising MTX therapy, and (3) optimising MTX therapy in early RA patients, consider ing different starting doses, dose escalation strategies and routes of administration for each of them. We considered MTX therapy optimisation when the MTX dose or route of administration was modified after a failed first treat ment with MTX.

**Animals**

Healthy Wistar albino rats (body weight 150–200 g) were used for the study. These animals were fed with standard pellet diet and were provided water ad libitum. Animals were weighed before and after the experiment. The rats were intensely observed for any infection, and those showing signs of infection were replaced with healthy animals. All animal studies were approved by the Institutional Animal Ethical Committee (IAEC) (approval no. 192/PhD/2012/ IAEC/BRNCP/12-13/Mandsaur). The animals were randomly divided into groups of six each for study.

Drugs classes for rheumatoid arthritis treatment

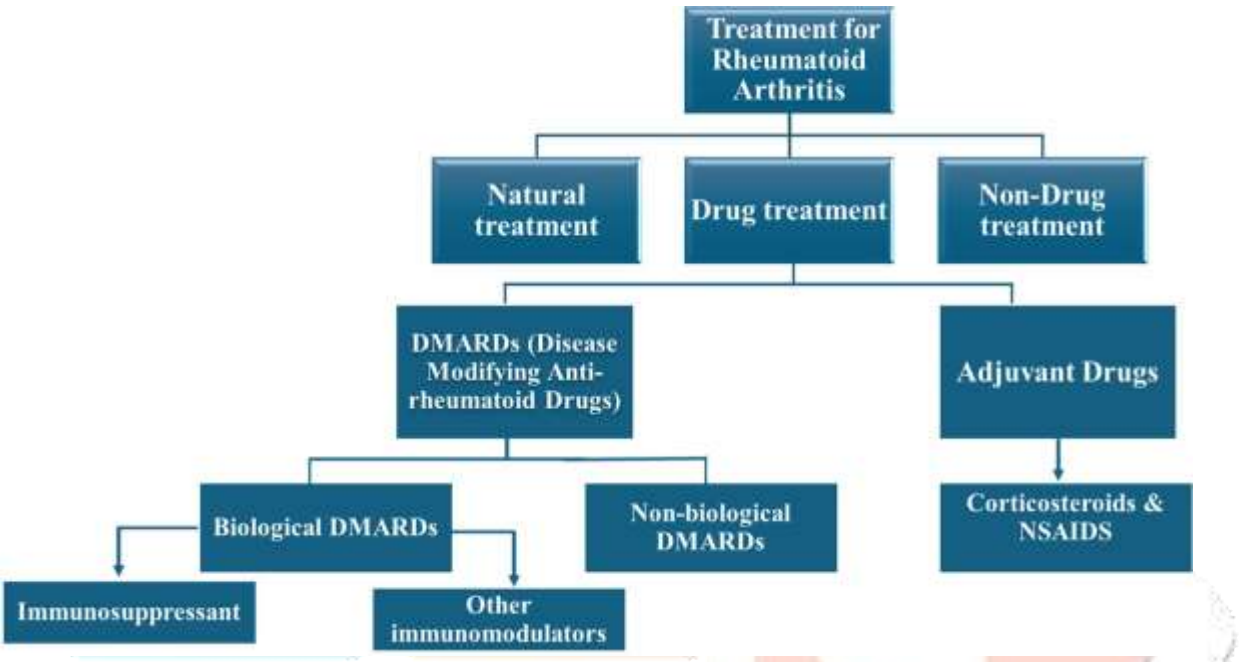



**Figure3.**DifferenttypesofcurrentlyavailabledrugclassesforRAtreatment.

*Note*. CD: cluster of differentiation; COX: cyclooxygenase; CTLA: cytotoxic T lymphocyte antigen; DMARD: disease-modifying rheumatic disease;

GC: glucocorticoid; HAT: histone acetyltransferase; HDAC: histone deacetylase; IL: interleukin; JAK: Janus-activated kinase; MSC: mesenchymal stem cell; NF-κB: nuclear factor-κB; NSAID: nonsteroidal anti-inflammatory drugs; TNF, tumor necrosis factor; Treg, regulatory T cell.

**TABLE: 1 Categorization of treatment options for RA therapy**

| Drug names | Functions | Outcome |
|---|---|---|
| NSAIDs | COX inhibitors | Resolution of inflammation and pain |
| Glucocorticoids | Inhibition of inflammatory genes | Resolution of inflammation and pain |
| DMARDs | Suppression of immune cell proliferation<br>Reducing the accumulation of toxic elements in joints<br>Decrease intracellular levels of glutathione, resulting in diminished tissue damage due to toxic oxygen metabolites<br>Promoting the extracellular levels of adenosine | Resolution of inflammation and pain |
| Adalimumab Infliximab Etanercept | Targeting TNF Targeting TNF Targeting TNF | Anti-inflammatory properties |
| Abatacept | Targeting CTLA4 | Reducing effector T cells |
| Tofacitinib | Inhibition of JAK | Reducing inflammatory cytokine production |
| Rituximab | Targeting CD20 molecule on B cells | Reducing B-cell count and function |
| Trichostatin A | Inhibition of HDACs | Reducing IL-6 level and inflammation |
| Givinostat | Inhibition of HDACs | Reducing IL-6 level and inflammation |
| Vorinostat | Inhibition of HDACs | Suppression of fibrosis |
| Entinostat | Inhibition of HDACs | Suppression of NF-κB |
| Valproic acid | Inhibition of HDACs | Stimulation of Tregs |
| Mesenchymal stem cell | Cell–cell contact<br>Soluble mediator production | Decreasing inflammation |

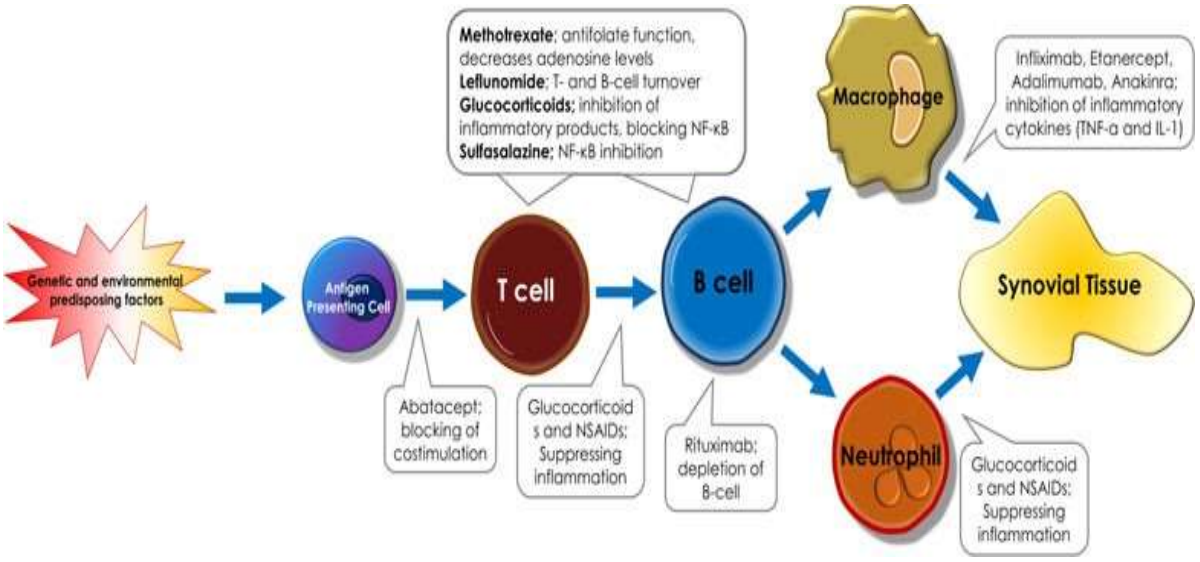
## 1 AN OVERVIEW ON RA

Nowadays, less is still discovered with respect to the precise mechanisms of tissue damage in RA, but it is believed that both genetic and environmental factors exert vital roles in the onset of an immunologic stimulation against the self-antigens with synovium,

leading to inflammation and joint damage. Polymorphisms of the genes, especially those in major histocompatibility complex II locus, have been reported in susceptibility to RA in various populations.

Human leukocyte antigens (HLAs) that have strongly been associated with RA predisposition are HLA-DR1, HLA-DR4, HLA-DR6, and HLA-DR10 (Nepom, 1998). Environmental factors, on the other side,

Like infections and smoking have been suggested as major triggering factors in individuals with the susceptible genetic background (Albani, 1997; Albert, 2000) [27].




Schematic overview of the therapeutic strategies in RA therapy aiming to alleviate inflammation. RA: rheumatoid arthritis [Color figure can be viewed at wileyonlinelibrary.com]

TREATMENT OF RHEUMATOID ARTHRITIS:

AsummaryofmedicationsusedcurrentlyandthosewithprospectsinthefuturearelistedinTable1.SinceRAisaninflammatorysetting,first-line medication has traditionally been agents that sootheinflammation, like GCs and NSAIDs. This type of therapy functions rapidly to alleviate pain and improve swelling in RA patients. DMARDs are predominantly methotrexate, sulfasalazine, leflunomide, hydroxy- chloroquine. DMARDs are slow-acting agents that are beneficent inimproving the symptoms and radiographic progression (Figure 1)[28].

1.1 | NSAIDs

NSAIDs can be beneficial in the early weeks after the onset of RA clinical symptoms and as a bridge treatment before the beginning of slow-acting DMARDs (O'dell, 2004; Singh et al., 2016). Mechanism ofNSAIDs action is to inhibit cyclooxygenase (COX) enzymes, [29]

Whichfunction in the metabolism of arachidonic acid to produce the proinflammatory prostaglandins (Vane & Botting, 1998). Chronic use of NSAIDs may result in gastrointestinal (GI) abnormalities like perforations, ulcer, and bleeding (Chiba et al., 2005), which have been account for the considerable rate of death (Wolfe, Lichtenstein, & Singh, 1999). Alongside the use of NSAIDs, the administration of misoprostol is suggested to decrease the possibility of GI complica- tions (Lazzaroni & Bianchi Porro, 2001; Rostom et al., 2002). Renal complications are also seen in NSAIDs use. Vasculature in glomerulus is strictly controlled through thromboxanes and prostaglandins in arteries that control the pressure of glomeruli (Simms et al., 1996). Based on the American College of Rheumatology (ACR) guidelines, patients who are at risk for renal complications need to check their creatinine clearance before the start of treatment as well as every other week for initial months (Simms et al., 1996) [30].

Recently, researchers have concentrated mostly on NSAIDs that inhibit COX-2 selectively. Their pain alleviating and anti-inflamma- tory effects are similar to conventional NSAIDs (Bensen et al., 2002 [32];

Bombardier et al., 2000; Emery et al., 1999). Nonetheless, while their adverse effects are identical to the other conventional NSAIDs, the risk of GI complications is lower. According to randomized clinical trials (RCTs) reports, valdecoxib, rofecoxib, and celecoxib had lower adverse GI complications (Emery et al., 1999; Lisse et al., 2003; Silverstein et al., 2000) [32].

The Vioxx Gastrointestinal Outcomes Research (VIGOR) study reported the possible cardiovascular complications with the use of COX-2 inhibiting NSAIDs. This study evidenced that RA patients under 50mg of rofecoxib medication daily demonstrated an increased rate of nonfatal myocardial infarction (MI) compared with patients treated with 500mg of naproxen twice a day (Bombardier et al., 2000). Moreover, a meta-analysis reported a 2.3 times higher risk of MI in patients taking rofecoxib than patients taking other NSAIDs or placebo (Jüni et al., 2004). Furthermore, valdecoxib and parecoxib were associated with the increased risk of cardiovascular complications, including MI, cardiac arrest, and stroke, given to cases with coronary artery bypass transplantation as analgesics (Nussmeier et al., 2005) [33]. Due to these observations, rofecoxib and valdecoxib were stopped prescribing in 2004 and 2005, respectively (Food and Drug Administration, 2005; Sibbald) [34].

2.1 | GCs

GCs are reduced activation, proliferation, differentiation, and survival of several cells involved in the production of inflammatory mediators (Gøtzsche &GCs were discovered 80 years ago and used for the first time in patients with RA in 1948 (Neeck, 2002). The mechanism of action of GCs are through two main mechanisms, namely genomic and nongenomic actions. During the genomic mechanism, the hormone agent in the plasma diffuses through the lipid membrane. A binding site of the hormone is located on receptors in the cytoplasm and on the nucleus.pores and then attaches to the DNA molecules, culminating in the modulation of gene transcription. Moreover, the complex of GC receptor is able to impress posttranscription occurrences, eventuating in modification of activity and structure of cell-like increased neutrophil count while decreased of other leukocytes (Buttgereit, Straub, Wehling, & Burmester, 2004 [35]; Spies, Bijlsma, Burmester, & Buttgereit, 2010). On the other side, the nongenomic events occur immediately and engage in receptors located on cell membrane (Spies et al., 2010). Beneficial effects of GCs in RA patients Johansen, 1998). GCs can suppress the function and proliferation of T helper 1 (Th1) cells, and thus result in decreased production of proinflammatory cytokines, such as interleukin (IL)-1β, IL-2, IL-3, IL-6, tumor necrosis factor-α (TNF-α), interferon-γ, and IL-17 (Buttgereit et al., 2004). Furthermore, the predominant beneficial effect of GCs [35].

3.1| DMARDs

3.3.1 | Methotrexate

Methotrexate has been the predominant therapy for RA in the United States for >20 years (Cronstein, 2005). This drug has several advantageous, including reliability, effectiveness, sustained long-term effect, low cost, and high tolerability. Studies have established the understanding that methotrexate might decrease mortality, especially cardiovascular-related deaths, in comparison to other DMARDs (Choi, Hernán, Seeger, Robins, & Wolfe, 2002). Methotrexate exerts its function through over four mechanisms, which all seems to beneficial in RA therapy. First, it is an antifolate compound and can interfere with the proliferation of immune cells, such as lymphocytes and other inflammatory cells (Quéméneur et al., 2003) [36]. Second, tissue injury in RA due to the accumulation of toxic compounds can be decreased by methotrexate, which is mediated by tetrahydrofolate (Cronstein, 2005; Hawkes, Cleland, Proudman, & James, 1994)[37]. Third, this drug may decrease intracellular levels of glutathione, resulting in diminished tissue damage due to toxic oxygen metabolites (Phillips, Woollard, & Griffiths, 2003) [38]. Fourth, methotrexate cause promoting the extracellular levels of adenosine, which reduces inflammation (Cronstein, Naime, & Ostad, 1993; Montesinos et al., 2003). In RA patients, methotrexate is usually used orally with the dose of 15–25mg one time a week (Fosså et al., 1988). Methotrexate may also be administered in intramuscular and subcutaneous ways, which is thereby associated with improved efficacy, as the bioavailability in oral route is decreased (Matherly & Goldman, 2003). After absorption, methotrexate is polyglutamylated and deposited in the tissues, which sustains for days to weeks (Dervieux et al., 2003). Among the potential disadvantageous effects of methotrexate are oral ulcers, cirrhosis, hepatitis, interstitial pneumonitis, and cytopenias (Kremer & Lee, 1986). Because 80% of the methotrexate is excreted through the kidneys, the complications due to drug are more prevalent and serious in cases with renal dysfunction (D. Felson, 1995). Efficacy of methotrexate can be compared with other conventional DMARDs but seems

to be less effective than newer biological agents (Bathon et al., 2000; Emery et al., 2000; D. T. Felson, Anderson, & Meenan, 1992[39]; Hamdy, McKendry, Mierins, & Liver, 1987; Hurst, Kallan, Wolfe, Fries, & Albert, 2002; Lipsky et al., 2000; Weinblatt et al., 1990). Nevertheless, considering its advantageous aspects of its acceptable toxicity, high efficacy, and low cost, it seems to be the first-choice therapy for the near future.

3.3.2 | Hydroxychloroquine

Hydroxychloroquine is an antimalarial agent that was proposed as treatment for RA and systemic lupus erythematosus. Although of vague mechanism of action, hydroxychloroquine seems to inhibit deoxyribonucleotides metabolism, impair the antigen presentation, and increase stabilization of lysosomal membrane (Fox & Kang, 1993; Weber & Levitz, 2000) [40]. This drug is efficiently absorbed orally and has a half-life of about 40 days. The adverse effects of deoxyribonucleotides are predominantly related to GI, like diarrhea and nausea and retinopathy (Markakis et al., 2003)[41].

3.3.3 | Sulfasalazine

Sulfasalazine was first developed for RA therapy with the notion that infection played a role in the etiopathogenesis of RA. The drug is broken to 5-aminosalicylic acid and sulfapyridine in intestine through bacteria (Chatham, 2005)[42]. Sulfapyridine appears to be responsible for a major part of sulfasalazine's therapeutic function (Pullar, Hunter, & Capell, 1985). Among the action mechanisms of the drug, are decreasing immunoglobulin levels, inhibition of neutrophil function, and inhibition of nuclear factor-κB(NF-κB) activation and, therefore, interfering with the function of T cell (Carlin, Djursäter, & Smedegård, 1992; Gadangi et al., 1996)[43]. The starting dosage of sulfasalazine is typically 500mg once or twice daily. The most prevalent adverse effects of sulfasalazine are related to GI, such as diarrhea, nausea, and vomiting, and hematologic, such as thrombocytopenia and neutropenia (Symmons, Salmon, Farr, & Bacon, 1988) [44].

3.3.4 | Leflunomide

Leflunomide is an immunomodulatory agent that interferes with the synthesis of pyrimidines, which are essential for lymphocyte activation (Kremer, 1999; Olsen & Stein, 2004) [45]. The drug is administered at dosages of 10–20mg daily and its half-life is 15 days. Leflunomide is less excreted by kidneys and its administration dosage does not need to be adjusted in cases with renal dysfunction (Rozman, 2002) [46]. Hepatotoxicity seems to be the most serious adverse effect of leflunomide. In 2–4% of patients, liver enzymes are elevated (Gaffo, Saag, & Curtis, 2006) [47]. Other adverse effects are diarrhea, nausea, abdominal pain, weight loss, and hypertension. Clinical trials have reported that the efficacy of leflunomide is identical to sulfasalazine and methotrexate (Emery et al., 2000; Smolen et al., 1999; Strand et al., 1999). This drug is commonly prescribed as an alternative for patients who show tolerance to methotrexate. Mechanism of leflunomide's action seems to be complementary to methotrexate function. Although combination therapy of leflunomide-methotrexate improves joint symptoms, elevation of liver enzyme appears to be major drawback in administration for most of the patients (Kremer et al., 2002; Weinblatt et al., 1999) [48].

4 | NEW GENERATION OF RA THERAPY

4.1 | Biological agents

The newest class of treatments used to RA therapy are biological compounds or biological response modifiers, which has been used for almost 10 years. These drugs have been designed to target the inflammatory molecules, cells, and pathways that confer tissue damage in RA patients. Currently, several new agents are in different phases of clinical trials and might be introduced in the future.

Infliximab is a chimeric mAb that binds to the Fc region of human IgG1 and contains the variable region (Fab) of a mouse antibody against TNF-α. It was the first anti-TNF-α compound that was assessed for RA therapy. Infliximab binds to both soluble and membrane-attached TNF-α and inhibits cytokine binding to the related receptors and, therefore, triggers an antibody and complement-dependent response toward the cells expressing TNF-α (Elliott et al., 1993)[49]. Infliximab is administered intravenously at a dose of

3mg/kg and takes over 2hr. The standard infusion timetable for RA patients is at weeks 0, 2, and 6, which is then continued through a maintenance administration at every 8 weeks (Buch et al., 2005) [50].

Etanercept is another anti-TNF mAb that contains TNF-receptor (Nestorov, 2005) [51], which is conjugated to the Fc portion of human IgG1, conferring them a prolonged half-life. This agent binds to both TNF-α and TNF-β (lymphotoxin) and, therefore, interfere with the binding of cytokine to its natural receptors on cells. The difference between etanercept and infliximab is that the earlier one cannot target membrane-attached TNF-α molecules. Etanercept is administered subcutaneously at 25mg dosages twice weekly or 50mg dosages once weekly (Keystone, Schiff, et al., 2004) [52]. The half-life of the etanercept is about 4 days (Korth-Bradley, Rubin, Hanna, Simcoe, & Lebsack, 2000) [53].

The choice of TNF-α inhibitor is often under the impression of drug cost, patient choice for self-injection or by physician. Several unfavourable events have been observed in medication with TNF-α inhibitors, in which occurrence of infections is most prevalent (Elliott et al., 1993; Lipsky et al., 2000; St. Clair et al., 2004) [54]. Evidence has reported that infliximab may result in granulomatous infections, especially tuberculosis, compared with etanercept (Wallis, Broder, Wong, Hanson, & Beenhouwer, 2004) [55]. Moreover, reactions after administration, such as nausea, headache, anaphylaxis, and urticaria, can be experienced during the infusion of infliximab (Sany, Kaiser, Jorgensen, & Trape, 2005)[56]. Etanercept infusion has been reported to be accompanied with redness and itching at the site of injection. Adalimumab administration was associated with pain at the injection site (Furst et al., 2003) [57]. Moreover, it has been associated with an insignificant reduction in leukocyte, mainly neutrophil counts, and increased haemoglobin concentration (Keystone, Kavanaugh, et al., 2004)[58]. Additionally, TNF-α inhibitors have been associated with the increased rate of malignancies, such as lymphomas (Bongartz et al., 2006) [59]. Demyelination of the central nervous system (CNS; Mohan et al., 2001; Sharief & Hentges, 1991) and heart failure (Anker & Coats, 2002) are considered other undesired events due to treatment with TNF-α inhibitors. Although real lupus-like complicationhave rarely been observed, development of autoantibodies against DNA, such as antinuclear antibodies, has been observed after treatment with all the mentioned TNF-α inhibitors (Moreland et al., 1999; Weinblatt et al., 2003) [60]. Anti-infliximab antibodies have been reported to be produced in 61% of patients with Crohn's disease treated with infliximab (Hanauer et al., 2002). The prevalence of antibodies against TNF-α inhibitors has been reported to be ranged from 5% to 20% in RA patients but the clinical importance of these antibodies is still unclear (Keystone, Schiff, et al., 2004) [61]. However, these antibodies have been associated with decreased efficacy and increased prevalence of infusion reactions (Baert et al., 2003) [62].

4.1.2 | IL-1 inhibitors

Anakinra is a recombinant mAb that inhibits IL-1, a proinflammatory cytokine. The amino acid sequence of natural inhibitor of IL-1, which is reduced in the synovial tissue of RA patients, is imitated by theanakinra (Horai et al., 2000) [63]. It is administered subcutaneously and has a short half-life (Hirohata et al., 1999). According to two clinical trials, anakinra was validated to be safe and effective as monotherapy as well as in combinational therapy with methotrexate for RA therapy (Bresnihan et al., 1998; Cohen et al., 2002) [64]. Anakinra has been associated with adverse effects, such as increased proneness to infections and local reactions. Considering the small clinical efficacy of anakinra in relation to TNF-α inhibitors and the necessity to be injected daily, it is only prescribed for patients with TNF-α inhibitor intolerance (Genovese et al., 2004) [65].

4.1.3 | Anti-B-cell agents

CD20 is a calcium channel in the cell membrane, expressed on the surface of normal and malignant B cells, but not on long-lived plasma cells. Rituximab is a chimeric anti-CD20 mAb, which acts to a selective depletion of B cells. Rituximab was approved by FDA in 2006 to be administered in combination with methotrexate for RA therapy (Cross, Stark, Lauber, Ramsbottom, & Lyons, 2006) [66]. The administration protocol of rituximab is in two separate 1000-mg dosage infusions with the interval of 2 weeks (Edwards et al., 2004) [67]. According to the reports of clinical trials, rituximab was safe and effective in RA therapy in combination with cyclophosphamide or methotrexate (Edwards et al., 2004) [67]. The most common adverse event is reactions at the site of infusion. Studies indicated that rituximab therapy was not attributed to an elevated predisposition to infections relative to placebo. Moreover, it did not have adverse modifications on immunoglobulin levels (Edwards et al., 2004) [67].

4.1.4 | Janus-activated kinase (JAK) inhibitors

Although the mitogen-activated protein kinase pathway appears to be important in RA, but trials of compounds that target this pathway have not resulted in promising outcomes (Schett et al., 2000) [68]. Nonetheless, agents targeting JAK pathways have accompanied with encouraging results in RA therapy. The mechanism of JAK inhibitors action in through the interfering in the production of several cytokines that exert JAK pathways in their pathway (Heinrich, Behrmann, Müller-Newen,Schaper, & Graeve, 1998) [69]. According to RCTs in RA have indicated that JAK inhibitors had safety and efficacy (Yamaoka, 2016b) [70]. The European Medicines Agency (EMA) approved tofacitinib with methotrexate, between 2016 and 2017, for cases with moderate to severe active RA, who do not respond efficiently to other DMARDs. Moreover, tofacitinib can be prescribed as monotherapy in case methotrexate is tolerated or responded nonefficiently (Finder & Pacific, 2014) [71]. Additionally, baricitinib (JAK1/2 inhibitor) was approved by EMA for RA therapy in patients with moderate to severe active RA with nonefficacious response or tolerance to DMARDs (Richez, Truchetet, Kostine, Schaeverbeke, & Bannwarth, 2017) [72]. Studies have demon strated that the JAK inhibitors are almost identical to other biological agents in adverse events. However, tofacitinib has been associated with increased susceptibility to herpes zoster infection (Cohen et al., 2017; Curtis, Xie, Yun, Bernatsky, & Winthrop, 2016; J. Pope et al., 2017; Yamaoka, 2016a)[73-74-75-70].

### 4.3 | Biosimilars

Biosimilars are defined as biological agents that are highly similar, but not identical, to reference products that are considered for separate marketing approval after patent expiration of the reference products (Combe, Tredree, & Schellekens, 2005) [76]. Several biosimilars for RA therapy have already reached approval, such as infliximab and etanercept, or are in clinical development (Brodszky, Baji, Balogh, & Péntek, 2014) [74]. The NORSWITCH study approximated that the biosimilar CT-P13 might be replaced by infliximab, with respect to immunogenicity, efficacy, and safety in patients with RA, Crohn's disease, ulcerative colitis, psoriatic arthritis, and spondyloarthritis. The study suggested that switching from infliximab to the biosimilar CT-P13 was acceptable and continuing the therapy with the biosimilar could be performed (Jørgensen et al., 2017) [77].

## 5 | COMBINATIONAL THERAPY IN RA: METHOTREXATE AND BIOLOGICS

There is evidence indicating that patients who are treated with biologics and methotrexate simultaneously might show good responses for treatment in comparison to patients who use only biologics (Gabay, Riek, Scherer, & Finckh, 2015) [78]. When TNF inhibitors is administered in RA patients after unfavourable response to methotrexate alone, the choice of combination therapy with methotrexate is preferred to TNF inhibitor alone. However, in patients with less intense disease symptoms, treatment with only one approach might be adequate (J. E. Pope et al., 2014) [75]. Moreover, a little advantage of tocilizumab in combination with methotrexate was detected in comparison to tocilizumab alone in patients without adequate response to methotrexate alone (Teitsma, Marijnissen, Bijlsma, Lafeber, & Jacobs, 2016) [79]. In early RA patients who had not received methotrexate, the clinical findings of patients did not show the difference between those who received baricitinib monotherapy and those who were treated with combinational baricitinib and methotrexate therapy. Nonetheless, patients receiving combination therapy had only a small amelioration in radiographic outcomes (Fleischmann et al., 2017) [80].

## 10 | CONCLUSIONS AND PERSPECTIVES

In RA, there is a hyperresponsive condition of immune cells toward self-antigens, culminating in inflammation and other disease symptoms. To alleviate the manifestations, current therapies either treat symptoms or reduce disease progression through suppressing immune players and inflammatory mediators. These approaches are not yet curative or preventative. In a recent hypothesis, antigen specific immunotherapy in RA, it is tried to remove autoreactive B and T cells as well as induce immune tolerance to self-antigens.

On the contrary, a number of approaches and related recommendations can confer optimal treatment program for RA patients with a better outcome compared with those used in old generation. New treatment strategies, applying biological agents and bio similarities, alone and in combination with DMARDs have been associated with further improved course of the disease. Treatment with conventional DMARDs and biologics have been associated with several adverse effects. However, being armed with pharmacogenetic and personalized medicine studies, we could have been able to reduce the side-effects and treat patients with precision medicine approaches through identifying biomarkers to apply the right drug to the right patient. On

the other side, we need to be armed with newer strategies, such as cell therapy (MSC therapy) and epigenetic therapy, as we acknowledge different aspects of RA pathogenesis.

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