



## Drugs in Rheumatoid Arthritis

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Received: 08-07-2017; Revised: 24-08-2017; Accepted: 12-09-2017.

### ABSTRACT

Rheumatoid arthritis is an autoimmune disorder which mainly affects the joints. In this review, we aim at highlighting the various classes of drugs used in rheumatoid arthritis, various mechanisms of actions of these drugs, alternative systems of medicine in rheumatoid arthritis as well as a brief pathogenesis of the disease. We have attempted to briefly summarise the different types of drugs in rheumatoid arthritis from ancient gold salts to the present day biological under one heading. The article is an attempt to throw light on the journey made by anti-rheumatoid drugs research until now, the current scenario and the anticipatory future of these life modifying drugs.

**Keywords:** Rheumatoid arthritis, inflammation, immunomodulation, biosimilars, intraarticular, pannus, corticosteroids, disease modifying anti rheumatic drugs (DMARDS).

### INTRODUCTION

Rheumatoid Arthritis is a chronic inflammatory disorder having articular as well as extra articular manifestations. It is primarily an autoimmune disorder where such mechanisms cause synovial inflammation and joint destruction. The disease affects women more than men and is often diagnosed in the mid twenties to mid thirties of life.

The disease typically affects multiple joints throughout the body, causing warmth, stiffness, and swelling.<sup>1</sup> Apart from the joints rheumatoid arthritis can also affect the heart, lungs, eyes and skin. Degradation of the synovial membrane in the joints can lead to functional disability, reduced quality of life (QoL), collateral damage, and increased morbidity and mortality.<sup>2</sup> Approximately 1% of the world adult population and 0.75% of Indian population are affected by RA.<sup>3</sup>

### Pathophysiology

Many factors contribute towards disease progression in Rheumatoid Arthritis. There is persistent synovial inflammation and associated damage to the articular cartilage and underlying bone. Inflammation associated with overproduction and over expression of tumour necrosis factor (TNF), causes synovial inflammation and joint destruction, interaction between T & B lymphocytes, synovial like fibroblasts and macrophages which ultimately leads to an overproduction of cytokine like interleukin (IL) -6. The dominant local cell populations in joints affected by RA are synovial and cartilage cells. Macrophages like synoviocytes and fibroblast like synoviocytes leads joint destruction. IgM and IgA Rheumatoid factors are key pathogenic markers directed

against the F<sub>c</sub> fragment of IgG. Additional types of antibodies are those directed against citrullinated peptides. 50% of risk of developing RA is attributed to genetic factors.<sup>4</sup>

Therapy of Rheumatoid Arthritis in the past viz until the 1980's involved only the symptomatic management of pain and inflammation by the use of NSAIDS (Non Steroidal Anti Inflammatory Drugs). The introduction of biological Disease Modifying Anti Rheumatoid drugs (DMARDS) for the treatment of rheumatic disease significantly improved patient outcomes.<sup>10</sup>

Discovery of the DMARDS (Disease Modifying Anti Rheumatoid Drugs) promised for the first time an alteration in the progression of the disease. However these agents too do not completely halt the progression of the disease, but rather decrease the onset of disability by about 30%.<sup>11</sup> It is now acknowledged that early aggressive therapy with a combination of drugs or biological agents may be warranted for the effective treatment of RA.

Treatment of RA is aimed to reduce pain, joint swelling, prevent joint deformity, and improves QoL and well-being.<sup>12</sup> The treatment consists of both non-pharmacological and pharmacological approach. Non-pharmacological treatments include physical therapy, weight reduction, exercise programs, use of assistive devices, and lifestyle changes (eating healthy diet and reducing emotional stress)<sup>13</sup>. Pharmacological treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, synthetic disease-modifying ant rheumatic drugs (DMARDs), biologic DMARDs, biosimilars, and most recently a small molecule—to facitininib. Commonly about 80% of RA patients can be treated only



with combination synthetic DMARDs and that only in about 10% biologics/biosimilars can be considered because of acceptability/limited incomes.<sup>1</sup>

### Classification of Drugs in Rheumatoid Arthritis<sup>5-9</sup>

**Table 1:** Treatment of Rheumatoid Arthritis (Disease Modifying Anti Rheumatic Drugs (DMARDs))

Immuno suppressants	Methotrexate, Azathioprine Cylosporine
<b>Antibiotics</b>	Sulfasalazine Minocycline
<b>Purine Pyridine Inhibitors</b>	Azathioprine Leflunomide Mycophenolate mofetil 6 mercaptopurine
<b>Gold Salts</b>	Auranofin Gold sodium thiomalate
<b>Alkylating Agents</b>	Cyclophosphamide Chlorambucil
<b>Clacineurin Inhibitors</b>	Cyclosporine Tacrolimus Sirolimus
<b>Glutamic Acid Derivatives</b>	Thalidomide
<b>d- penicillamine</b>	
<b>I. Biological Modifiers (BRM)</b>	<b>Response</b>
<b>TNF –α inhibitors</b>	<b>Etanercept infliximab adalimumab</b>
<b>IL-1 Antagonist</b>	<b>Anakinra</b>
<b>II. Antibiotics</b>	<b>Tetracyclines Chloroquine/ Hydroxychloroquine</b>
<b>III. Antimetabolite Hormones</b>	Corticosteroids Dexamethasone Prednisolone Triamcinolone
<b>IV. Nonsteroidal Antiinflammatory Drugs</b>	Salicylates aspirin and Derivatives Celecoxib Rofecoxib

#### NSAIDS

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen and diclofenac are commonly used as the first line drugs to provide symptomatic relief in conditions of pain and inflammation.

As first line drugs, these offer little protection against tissue degeneration. They do, however, reduce the levels of prostaglandins, bradykinins, and oxygen radicals; contributing to pain relief.

They however suffer from the drawback of having many side effects leading to side effects such as peptic ulceration, impairment of renal blood flow, renal papillary necrosis, nephrotic syndrome, and hepatic injury.

Selective COXII inhibitors like celecoxib and rofecoxib have also been used. They may be preferred over COX 1

inhibitors due to their selective action and thereby lesser adverse effect profile.

#### Corticosteroids

Their anti-inflammatory and immunosuppressive effects provide relief for many patients and are especially useful for those patients refractory to treatment with NSAIDs. Unfortunately, corticosteroid therapy is often accompanied by numerous side effects, including bone loss, increased susceptibility to infection, osteoporosis, and peptic ulcers. Additionally, weaning patients from corticosteroids can be difficult and relapses of particular degeneration are frequent once the steroid is discontinued.<sup>15</sup> Intra-articular application of these drugs has been implemented (in order to diminish the complications of oral administration) and has proven effective in reducing symptomatic joint inflammation.<sup>16</sup>



### Disease-Modifying Anti-Rheumatic Drugs (DMARDs)

In addition to the drugs mentioned previously, current therapy also involves the **DMARDs**, which are often given simultaneously with NSAIDs. DMARDs include gold, hydroxychloroquine, methotrexate, auranofin, sulfasalazine, d-penicillamine, cyclosporine, azathioprine, cyclophosphamide and leflunomide. Combinations of these agents produce increased toxicity.

Early biologics, particularly TNF inhibitors such as infliximab, were given in combination with methotrexate because this approach improved sustained efficacy. Most biologics are now combined with methotrexate.

**Table 2**

DMARD	Mechanism
Sulphasalazine, for example	Inhibits translocation of NF-kappa B into the nucleus. <sup>17</sup> This in turn inhibits transcription of various inflammatory cytokines, adhesion molecules, and chemokines.
Methotrexate	Induces apoptosis and clonal deletion of activated T-cells
Hydroxychloroquine	Interference with "antigen processing" in macrophages and other antigen-presenting cells
Auranofin (gold salts)	Inhibition of reduction/oxidation (redox) enzymes reducing ROS
Cyclophosphamide	Decreases the immune response.
d-Penicillamine	Promotes phagocytosis, suppression of immunoglobulin synthesis, reduction of circulating alpha-1 antitrypsin - IgA complexes, alteration in prostaglandin synthesis.
Leflunomide	Suppresses the effects of IL-2 (and other cytokines) and inhibits adhesion and migration of inflammatory cells

### Immunomodulation

T-lymphocytes play an important role in the initiation and modulation of immune responses in RA. RA is characterized by accumulation of T-cells in the synovial compartment. Autoantigenic regions too are thought to be present on the TCR. Hence, vaccinations, immunizations, monoclonal antibodies targeting surface receptors of T-cells, and induction of apoptosis in specific T-cells are potential drug targets in rheumatoid arthritis. TCR vaccination is presumed to induce inactivation, tolerance, suppression, or deletion of the auto reactive TCR.<sup>18</sup>

Another approach to slow the autoimmune process may be through genetically engineered monoclonal antibodies. Antibodies that target the CD4 surface

receptors of helper T-cells may help to dampen T-cell activity without affecting the normal immune functions of the patient.

A newer drug, which acts at the level of T cells, is leflunomide (LFM). LFM is an anti-inflammatory and immunomodulatory drug that has been used to treat RA.<sup>17</sup>

### Angiogenesis Inhibitors

Angiogenesis aids in the delivery of inflammatory cells to the synovium and pannus tissue -synovial proliferation over articular surfaces. Pannus blood vessels demonstrate increased expression of the integrin v3. A novel therapeutic agent, a cyclic peptide antagonist of v3, upon introduction to the joint capsule induces vascular apoptosis and decreased pannus formation, synovial infiltrates, joint swelling and protects against erosive damage. However the role of these agents has to be better explored in clinical trials.<sup>19</sup>

### Gene Therapy

Recent animal studies have also suggested that gene therapy via attenuation of hyperactive synovial cells (characteristic of RA) may hold promise in RA therapy. When hyperactive synovial cells and arthrogenic lymphocytes are eliminated, cytokines and degradation enzymes are no longer introduced into the joint and inflammation ceases. Adenovirus mediated gene transfer is used to induce expression of anti-inflammatory molecules such as IL-1Ra (a natural inhibitor of TNF- $\alpha$  and IL-1), found in synovial tissue. Transgenic expression of specific proteins in synovial joints may possibly be one of the future therapies. However these have yet to be proven in humans.<sup>20</sup>

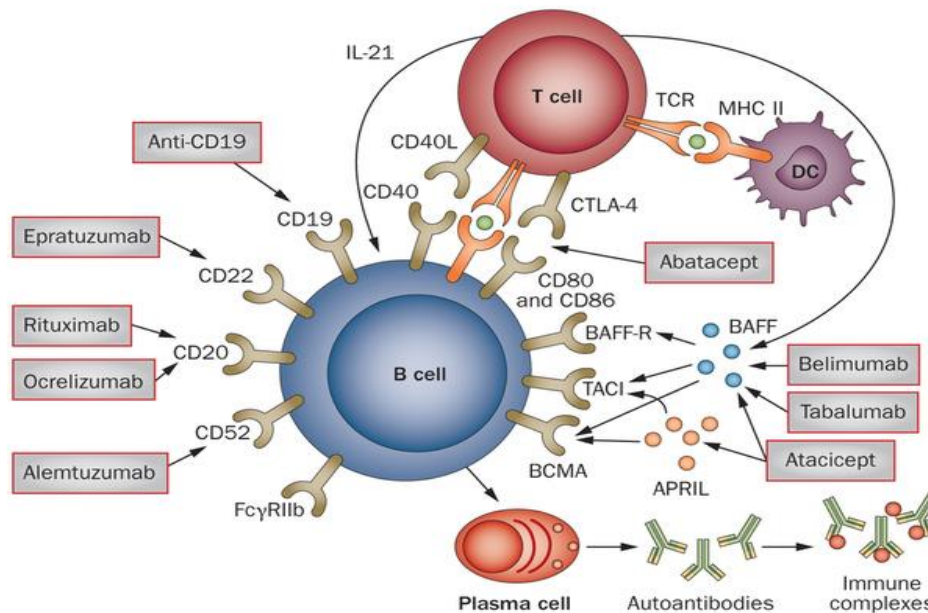
Given the autoimmune nature of the disease, emerging therapeutic research areas focusing on immune mediators of the disease are now being probed into. One such mediator is tumour necrosis factor (TNF) -  $\alpha$ , a cytokine thought to stimulate production (by RA synovial cells) of IL-1, IL-6, and granulocyte-macrophage colony stimulating factor. Therapy involving infusion of sTNFRs into RA affected joints to suppress the actions of TNF  $\alpha$  is now being explored.

**Etanercept** has already shown significant efficacy in decreasing joint pain and reducing clinical signs of inflammation and joint destruction.

A related strategy for diminishing the actions of TNF- $\alpha$  involves treatment of patients with anti-TNF- $\alpha$  monoclonal antibodies derived from marine, anti-TNF- $\alpha$  mouse and human IgG<sub>1</sub> (**infliximab**). This complex (which binds TNF- $\alpha$  and appears to reduce its activity) has been shown to significantly reduce joint pain and swelling.<sup>21</sup>



## CYTOKINE TARGETS IN RA22



**Figure 1:** Both TNFRs and anti-TNF-alpha mAbs are currently receiving a great deal of attention in RA therapy.

### Antibiotics as a Mode of Therapy

Despite insufficient evidence for the infectious etiology of this disorder, several antibacterial, such as sulfa compounds, tetracyclines and rifampicin, have been investigated in the treatment of rheumatoid arthritis. Minocycline, a semi-synthetic derivative of tetracycline, has been extensively studied as a therapeutic agent for rheumatoid arthritis. The anti-rheumatic effect of minocycline can be related to its immunomodulatory and anti-inflammatory, rather than to its antibacterial properties. Antimalarials like chloroquine and its hydroxyl derivative have action as antibiotics as well as DMARDs in Rheumatoid Arthritis.

### New and emerging treatments for Rheumatoid arthritis:

----**JANUS KINASE (JAK) INHIBITORS:** Finally, in recent years, new orally effective kinase inhibitors, particularly JAK inhibitors, have been developed. Acitinibcitrates belongs to the class of medications called Janus kinase (JAK) inhibitors. It specifically target JAK1 and JAK3 of the Janus family of kinases (enzymes), to interfere with the inflammatory process in rheumatoid arthritis that leads to joint damage.

### ----PI3KS INHIBITORS

Phosphoinositide 3-kinases (PI3Ks), most notably PI3K $\delta$  and PI3K $\gamma$  (belong to class I PI3Ks), have crucial and specific roles at all stages of RA disease progression, including antigen signalling in B and T cells, downstream signalling of Fragment Crystallizable Receptors, cytokine receptors and chemokine receptors on mast cells, macrophages, neutrophils and synoviocytes.

### ----MMPS INHIBITORS

Matrix metalloproteinase (MMPs) seem to be important in RA, as some of them are present in increased amounts

and in active forms in RA synovial tissue. Hence inhibitors of these enzymes are beneficial.

### ----CATHEPSIN INHIBITORS

The cathepsins (e.g. cathepsin B, L, K, and S) are cysteine proteases that play major roles in intracellular protein degradation and turnover.

### ----GLYCOSIDASE INHIBITORS

Scripps Research Inst. has shown that inhibition of glycosidases in the synovial fluid has great utility as a novel chondroprotective approach in treating diseases associated with cartilage degradation. Commonly, cartilage erosion results from the over-catabolism of glycosaminoglycans (GAGs) of the proteoglycan (PG)-hyaluronate complex, which comprises the bulk of cartilage tissue.<sup>11</sup>

### Traditional Herbs used in Rheumatoid Arthritis

India is well known for its rich and traditional Ayurvedic system of medicine. A variety of herbal medicines have been used since long for the treatment of Rheumatoid arthritis. The viability in cost and low toxicity of herbal medicines make it an attractive option compared to the more expensive and toxic allopathic drugs. However their dietary restrictions, lack of scientific evidence and paucity of clinical trials have limited their applications in RA therapy. Some of the traditional plants used in rheumatism include *Boswellia seratta*, *Zingibero ffinalis*, Borage seed oil- Borage officinalis, Capsaicin, Evening primrose oil- *Oenothera blennis*, *Curcumin longa*, Curcumin (diferuloyl methane), Blackcurrant seed oil- Ribesnigrum, Feverfew –*Tanacetum parthenium*, Flaxseed oil.<sup>23</sup>

In addition to herbal medicine animal drugs like fish liver oil has potent anti-inflammatory properties. Physical

therapy is proven to be effective in improving disability and joint mobility and must accompany pharmacological measures.(Fig2) The main goals of physical therapy are to maintain or increase muscle strength around affected joints and to maintain joint range of motion. Alternative systems of medicine like Acupuncture, Yoga therapy, Ultraviolet A light therapy, Unani System of medicine have contributions in Rheumatoid arthritis.

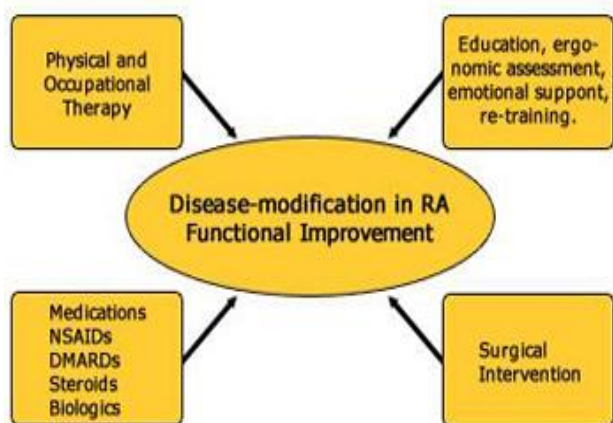


Figure 2

## CONCLUSION

The amount of research that has been carried out and yet to be carried out in the field of rheumatoid arthritis therapy is promising. Therapy in rheumatoid arthritis has come a long way from the gold salts to the emerging biologicals. One can only conclude that novel therapies will still continue to revolutionise therapy of this disease in the years to come offering solace and hope to those who endure wrath.

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Source of Support: Nil, Conflict of Interest: None.