A REVIEW ON RHEUMATOID ARTHRITIS: DISEASE

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ABSTRACT
Rheumatoid arthritis is a chronic inflammatory joint disease, which can cause cartilage and bone damage as well as disability. Early diagnosis is key to optimal therapeutic success, particularly in patients with well-characterized risk factors for poor outcomes such as high disease activity, presence of auto antibodies, and early joint damage. Treatment algorithms involve measuring disease activity with composite indices, applying a treatment-to-target strategy, and use of conventional, biological, and new non-biological disease-modifying anti-rheumatic drugs. After the treatment target of stringent remission (or at least low disease activity) is maintained, dose reduction should be attempted. Although the prospects for most patients are now favorable, many still do not respond to current therapies. Accordingly, new therapies are urgently required. In this Seminar, we describe current insights into genetics and etiology, path physiology, epidemiology, assessment, therapeutic agents, and treatment strategies together with unmet needs of patients with rheumatoid arthritis.

KEYWORDS: Rheumatoid arthritis, path physiology, etiology, epidemiology, treatment, diagnosis, inflammation.

INTRODUCTION
Rheumatoid arthritis (RA) is a multi-systemic, chronic immuno-inflammatory disease that is manifested as destructive polyarthritis in association with serological evidence of autoreactivity. It is characterized by chronic pain and joint destruction, premature mortality, and elevated risk of disability, with high costs for those suffering from this disease and for society. It affects up to 0.5–1% of the world’s population, with a male-to-female ratio of 3:1, and is the most common inflammatory joint disease. [1] Rheumatoid arthritis is a chronic, systemic, inflammatory disease of unknown etiology that affects connective tissue. Although joints are the primary target of rheumatoid arthritis, extra-articular manifestations can have a significant impact on other organsystems. This autoimmune disorder affects approximately 1% of the population worldwide, making it the most common form of inflammatory arthritis. Rheumatoid arthritis typically has an insidious onset that occurs between 35-50 years of age in 80% of patients. It tends to run in families and occurs more commonly in women than men (~3:1 ratio). Men tend to have more severe systemic effects. The course is variable, ranging from mildbrief illness affecting a few
joints with minimal damage, to a progressive polyarthritis that leads to pronounced functional impairment and deformity.\textsuperscript{[2]}

It primarily involves the joints, but should be considered a syndrome that includes extra-articular manifestations, such as rheumatoid nodules, pulmonary involvement or vasculitis, and systemic co-morbidities. A therapeutic revolution in the treatment of rheumatoid arthritis in the past decade—with the advent of novel therapeutics, introduction of early therapy, development of new classification criteria, and application of new effective treatment strategies—has transformed articular and systemic outcomes.\textsuperscript{1–6} In this Seminar, we highlight recent insights into most aspects of rheumatoid arthritis, from diagnosis to treatment strategies, and from etiology to novel therapies. There is still a considerable unmet need in rheumatoid arthritis; full or stringent remission is not typical, nor is it usually sustained without continuing treatment, and as such it should now be the priority of research efforts.\textsuperscript{[3]}

The disease may be diagnosed as early as within 3 months of onset to 2 years when the disease is established. However this time duration has relevance to the concept of therapeutic window: 0–3 months, very early RA (VERA); 3 months–1 year, early established RA; 1–2 years, late established RA (LERA); and more than 2 years, established stable RA. Clinically, RA is symmetrical polyarticular arthritis marked by chronic systemic inflammation, synovial infiltrates, and progressive cell-mediated destruction of the joints and adjacent chronic inflammation of the synovium, along with various clinical features of a systemic disease. The disease is characterized by persistent and progressive synovitis of peripheral joints, leading to the destruction of cartilage and subchondral bone. The pathogenic basis of RA is a sustained specific
immune response against as-yet-unknown self-antigens. It is believed that in RA the persistent auto - immune response mediates local synovial inflammation and cellular infiltration, which ultimately result in tissue damage. The two main pathophysiological events leading to RA are (1) hyper plastic synovial lining cells, the layer in direct contact with the intra-articular cavity, and (2) mononuclear cell infiltration in the subintimal layer. The hyperplastic lining is composed of macrophage-like type I synoviocytes and fibroblast-like type II synoviocytes (FLSs). Many cell groups exist in the infiltrate of the subintimal synovial layer, including T cells, B cells, dendritic cells (DCs), fibroblasts, granulocytes, macrophages, and mast cells. Another major pathological phenomenon of RA is the formation of a destructive type of tissue that invades the interface between cartilage and bone, and is known as pannus. Pannus formation is one of the distinctive characteristic features of RA, which makes it distinct from other inflammatory arthropathies. Eventually, chronic synovitis can progress to the destruction of adjacent bone and cartilage, leading to joint deformity and disability.\textsuperscript{4}

Recent advancements in the field of immunology and rheumatology have helped in the development of a better understanding of immune dysfunction in RA. Treatment has evolved from nonspecific immunosuppressive therapy to specific molecule-targeted biologics such as anti-cytokine agents, T-cell co stimulator blocking agents, and anti-B-cell agents and signal kinase inhibitors. More drug targets based on immune mechanisms are on the horizon. However, in daily practice, the use of recently developed therapeutic agents as well as traditional disease modifying anti-rheumatic drugs (DMARDs) is based on the clinical course and response to previous therapy rather than the individual features of immune dysfunction. The search for disease markers to predict outcome and therapeutic response in individual patients is of great interest. Here we will describe the current under-standing of immune dysfunction in RA and the lessons learned from animal models of autoimmune arthritis.\textsuperscript{5}

**Epidemiology**

Rheumatoid arthritis is found throughout the world, affecting slightly less than 1% of the population. Women are approximately 3 times more likely than men to acquire the disorder, and older people are more likely than younger to develop the condition. The peak age of onset is between 30 and 50 years of age. The incidence of rheumatoid arthritis varies among different populations. It is especially high in some Native Americans (e.g., ~6.8% in Chippewa Indians) and is lower in sub-Saharan blacks and among some Chinese and Japanese. There is some evidence that the disorder was introduced into Europe from North America in the 17th Century.
There is a genetic component to rheumatoid arthritis, with monozygotic twin’s being over 4 times more likely to both develop rheumatoid arthritis than di-zygotic twins. Nonetheless, only 15-20% of monozygotic twins are concordant for rheumatoid arthritis, suggesting additional environmental factors contribute to the development of this disorder. Overall, approximately 10% of rheumatoid arthritis patients have an affected first-degree relative.\textsuperscript{[6]}

The major histocompatibility complex on chromosome 6 produces gene products involved in self-recognition. These products also bind peptide fragments that are displayed on the cell surface for scrutiny by the T cells. There are numerous alleles for most of the alpha and beta chains contained in the HLA genes. HLA-DP, HLA-DQ, and HLA-DR are genes contained in this region that code for the class II major histocompatibility complex antigens, which are expressed primarily on the B-cells and other antigen-presenting cells of the immune system. Each of these genes codes for an alpha and a beta chain of the antigen. Because the DR gene also includes a second beta chain that can pair with the alpha chain, these three genes can give rise to four distinct class II molecules. The HLA-DR4 gene is associated with rheumatoid arthritis in a number of populations, including North American and European whites, some Native Americans, such as the Chippewa, and various other South American, Japanese, and Chinese populations. HLA-DR1 is associated with rheumatoid arthritis in Asian Indians and Israeli Jews, as is HLA-Dw16, which is a specific beta chain allele of DR1, in Yakima Indians. The susceptibility epitope has been further identified as being the QKRAA or QRRAA amino acid sequence in the third hypervariable region of the beta chain of these HLA-DR alleles.\textsuperscript{[7]}

RA affects approximately 1% of the population worldwide and leads to significant morbidity and mortality. It increases in incidence with age and affects women about three times more often than men. However, after the age of 60, RA affects both genders equally.

Rheumatoid arthritis has an incidence of 0.5% to 1%, with an apparent reduction from north to south and from urban to rural areas. Some Native American populations have a very high prevalence. A positive family history increases the risk of rheumatoid arthritis roughly three to five times; concordance rates in twins are increased, implicating genetic factors in pathogenesis. The heritability of rheumatoid arthritis is currently estimated as 40–65% for seropositive rheumatoid arthritis, but lower (20%) for seronegative disease.\textsuperscript{[6]}

**Etiology**

While the precise cause of rheumatoid arthritis is unknown, like other autoimmune diseases it probably occurs when a genetically susceptible host is exposed to an environmental antigen.
Although various viral (e.g., Epstein-Barr virus, parvovirus) and bacterial (e.g., Proteus, Mycoplasma) infections have been identified as potential culprits, the data remain inconclusive. Stimulation of the immune system presumably leads to the production of antibodies against the antigen which, in turn, leads to the formation of immune complexes in synovial joints and chronic inflammatory arthritis. Three possible mechanisms have been proposed for this inflammatory response. Thus, the infection, and/or long-lasting products of it, persists in the synovial tissues, or the infection damages synovial tissues in a manner that uncovers hidden antigenic determinants, or there is molecular mimicry between the environmental antigen and molecules produced by synovial joint tissues. Whatever the exact mechanism, the inflammation is sustained by a vicious cycle. Tumor necrosis factor alpha is among the more important inflammatory mediators. Increased blood flow and capillary permeability facilitate the entry of antibodies and complement components into the joint, immune complexes form, the complement cascade is activated, and phagocytes are recruited. Phagocyte activation leads to localized tissue destruction, which causes more inflammation, which, in turn, leads to more immune complexes being formed. This cycle continues until the joint is destroyed.\[8\]

Development of rheumatoid arthritis is associated with environmental factors. Consistently reported risk factors include smoking and low socioeconomic status or educational attainment. Rheumatoid arthritis is associated with periodontal disease, although the causality and nature of this relationship remains ill defined. One hypothesis proposes that Porphyromonas gingivalis (a bacterium frequently found in periodontitis) promotes aberrant citrullination and provokes local breach of tolerance to citrullinated peptides via endogenous expression of its PADI4, which converts arginine to citrulline. Indeed, other infectious agents (eg, Proteus mirabilis, Escherichia coli, and Epstein-Barr virus) have been suggested to trigger rheumatoid arthritis, generally via molecular mimicry; however these proposed mechanisms have not yet been substantiated.\[8\]

As is the case with many autoimmune diseases, there is now considerable interest in the effect of the microbiome on disease risk and progression (figure 2). Data from animal models of arthritis suggest an essential role for the gut microbiome in the development of disease. Initial studies in humans have implicated gastrointestinal dysbiosis in rheumatoid arthritis, particularly in early disease. One study detected alterations in common microbial populations in oral, salivary, and gastrointestinal sites, which were associated with C-reactive protein and ACPA status, and further altered by therapy with disease-modifying anti-rheumatic drugs. The mechanisms underpinning such observations and their importance remain to be elucidated.\[9\]
Signs and Symptoms[10]

RA primarily affects joints, but it also affects other organs in more than 15–25% of individuals. Rheumatoid arthritis progress in three stages.

- The first stage is the swelling of the synovial lining, causing pain, warmth, stiffness, redness and swelling around the joints.
- Second is the rapid division and growth of cell, or pannus, which causes the synovium to thicken.
- In the third stage, the inflamed cell releases enzyme that may digest the bone and cartilage, often causing the joints to loses its shape and alignments, more pain and loss of movements.

Symptoms include:

- Pain, swelling, limited motion, warmth and tightness around affected joints, which most commonly include the hands and wrists, feet and ankles, elbows, shoulders, neck, knees and hips, usually in a symmetrical pattern. Over time, joints may develop deformities.
- Fatigue, soreness, stiffness and aching, particularly in the morning and afternoon (described as morning stiffness and afternoon fatigue)
- Lumps or rheumatoid nodules below the skin
- Weight loss
- Low-grade fever and sweats
- Trouble sleeping
- Weakness and loss of mobility
- Depression
- The incidence of lymphoma is increased in RA,
- Local osteoporosis occurs in RA around inflamed joints.
- Constitutional symptoms including fatigue, low grade fever, malaise, morning stiffness, loss of appetite and loss of weight are common systemic manifestations seen in people with active RA.
- Low red blood cell count, inflammation around the lungs, and inflammation around the heart.
- Fever and low energy may also be present.
- An increased platelet count occurs when inflammation is uncontrolled.
- A low white blood cell count usually only occurs in people with an enlarged liver and spleen.

Joints:
Arthritis of joints involves inflammation of the synovial membrane. Joints become swollen, tender and warm, and stiffness limits their movement. With time, multiple joints are affected (polyarthritis). Most commonly involved are the small joints of the hands, feet and cervical spine, but larger joints like the shoulder and knee can also be involved. RA typically manifests with signs of inflammation, with the affected joints being swollen, warm, painful and stiff, particularly early in the morning on waking. \[^{11}\]
Pathophysiology: [12]

The cause of rheumatoid arthritis is unknown but appears to be multifactorial. It is an autoimmune disease triggered by exposure of a genetically susceptible host to an unknown arthrogenic antigen. It is the continuing autoimmune reaction with activation of CD4+ helper T cells and other lymphocytes, and the local release of inflammatory mediators and cytokines that ultimately destroys the joints.

The joint inflammation in RA is immunologically mediated. The disease is initiated, in genetically predisposed individual, by activation of CD4+ helper T cells responding to some arthrogenic agent, possibly microbial, or to some self-antigen. The activated T cells produce cytokines that (1) activate macrophages and other cells in the joint space, releasing degradative enzyme and other factors that perpetuate inflammation, and (2) activate B cells, resulting in the production of antibodies, some of which are directed against self-antigens in the joint. The rheumatoid synovium is rich in both lymphocyte and macrophage derived cytokines. [10] The activity of this cytokines counts for many features of rheumatoid synovitis; some, such as TNF, promote leukocyte recruitment, others activate macrophages, and yet others, such as IL-1, use proliferation of synovial cells and fibroblast. The cytokines also stimulate secretion by synovial cells and chondrocytes of proteolytic and matrix-degrading enzymes.
Activated T cells in RA lesions have also been shown to express impressive mounts of cytokines called RANK ligand, which induces osteoclast differentiation and activation and may play a key role in the bone resorption seen in destructive joint lesions. Despite the plethora to play pivotal role. This is demonstrated by the remarkable effectiveness of TNF antagonists in the disease, even in patients who are resistant to other therapies. The role of antibodies in the disease is suspected from a variety of experimental and clinical observations. About 80% of patients have serum IgM auto antibodies that bind to the Fc portion of their own IgG. These auto antibodies are called rheumatoid factor. They may form immune complexes with self-IgG that deposite in joints and other tissues, leading to inflammation and tissue damage. However, the role of RF in the pathogenesis of the joint or extra-articular lesions has not been established, and about 20% of patients do not have RF, suggesting that these auto antibodies are not essential for tissue injury in RA.

**Diagnosis:**

In 1987, the American Society of Rheumatology developed revised seven Criteria for the Classification of RA.
Guidelines for classification

A. Four of seven criteria are required to classify a patient as having rheumatoid arthritis (RA).

B. Patients with two or more clinical diagnoses are not excluded.

Criteria

A. **Morning stiffness:** Stiffness in and around the joints lasting 1 h before maximal improvement.

B. **Arthritis of three or more joint areas:** At least three joint areas, observed by a physician simultaneously, have soft tissue swelling or joint effusions, not just bony overgrowth.

C. **Arthritis of hand joints:** Arthritis of wrist, metacarpophalangeal joint, or proximal interphalangeal joint.

D. **Symmetric arthritis:** Simultaneous involvement of the same joint areas on both sides of the body.

E. **Rheumatoid nodules:** Subcutaneous nodules over bony prominences, extensor surfaces, or juxta articular regions observed by a physician.

F. **Serum rheumatoid factor:** Demonstration of abnormal amounts of serum rheumatoid factor by any method for which the result has been positive in less than 5% of normal control subjects.

G. **Radiographic changes:** Typical changes of RA on posterior anterior hand and wrist radiographs that must include erosions or unequivocal bony decalcification localized in or most marked adjacent to the involved joints.

The new criteria, developed using cohorts and case scenarios of patients with early arthritis, require at least a single clinically swollen joint as entry criterion in the absence of other diseases explaining the clinical symptoms. Thereafter, the classification criteria allow for sensitive assessment of extent of joint involvement (tender joints or joints positive by ultrasound or MRI can be classified as active joints, just as well as clinically swollen joints). Additional features are serological markers (RF and ACPA), long symptom duration, and laboratory markers of systemic inflammation. The criteria have been validated in many settings and offer 21% higher sensitivity than the former criteria, at the cost of 16% lower specificity. However, classification is not synonymous with diagnosis. Whereas diagnosis has the ultimate goal of being correct at the level of the individual patient, classification aims to maximize homogeneous populations for study purposes, but can be used to support diagnosis.
The presentation and course of RA is variable. Typically, patients present with an insidious onset of symmetric joint pain, swelling, and morning stiffness worsening over several weeks. The severity and duration of morning stiffness often correlate with overall disease activity. Less common presentations include acute, rapidly progressive polyarthritis and, more rarely, monoarthritis. RA commonly involves the small joints of the hands (metacarpophalangeal [MCP] and proximal interphalangeal [PIP] joints), wrists, and feet (metatarsophalangeal [MTP] joints). Large joints can also be affected and include the shoulder, elbow, hip, knee, and ankle. Physical findings in RA involve the identification of symmetric joint inflammation early in the course of disease, as well as manifestations of joint destruction with chronic disease. Active synovitis is characterized by warmth, swelling, pain, and palpable effusions. Synovial proliferation is determined on physical examination by the presence of soft or rubbery tissue around the joint margins.[14]

Severe RA can manifest with sequelae of systemic inflammation, especially in RF-positive patients. These include rheumatoid nodules and vasculitic skin ulcerations and ocular, pulmonary, cardiac, neurologic, and hematological abnormalities. Renal and gastrointestinal manifestations are rare. With early recognition and treatment of RA, the incidence of extra-articular manifestations diminishes. The American College of Rheumatology (ACR) classification criteria for the diagnosis of RA was designed for inclusion of patients in clinical studies and not for clinical diagnosis. It is also pertinent to point out here that these criteria were formulated using data from hospitalized patients and thus are not very useful in the outpatient setting. Despite these caveats, these criteria are helpful to a physician unfamiliar with RA as a tool to evaluate a patient in the office. Most of the articular destruction occurs in the early years of disease, so it is important to diagnose and treat RA early.[15]

**Laboratory and imaging findings associated with RA:**[16]

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>Associated findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>Typically increased to &gt;0.7 picograms per mL; may be used to monitor disease course.</td>
</tr>
<tr>
<td>ESR</td>
<td>Often increased to &gt;30 mm per hour; may be used to monitor disease course.</td>
</tr>
<tr>
<td>Hemoglobin/hematocrit</td>
<td>Slightly decreased; hemoglobin averages around 10 g</td>
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<tr>
<td>Test</td>
<td>Description</td>
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<tr>
<td>------------------------------------------</td>
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</tr>
<tr>
<td>Liver function</td>
<td>Normal or slightly elevated alkaline phosphatase</td>
</tr>
<tr>
<td>Platelets</td>
<td>Usually increased</td>
</tr>
<tr>
<td>Radiographic findings of involved joints (X-ray)</td>
<td>May be normal or show osteopenia or erosions near joint spaces in early disease; wrist and ankle films are useful as baselines for comparison with future studies.</td>
</tr>
<tr>
<td>Rheumatoid factor (Latex test)</td>
<td>Negative in 30 percent of patients early in illness; if initially negative, can repeat six to 12 months after disease onset; can be positive in numerous other processes (e.g., lupus; scleroderma; Sjögren's syndrome; neoplastic disease; sarcoidosis; various viral, parasitic, or bacterial infections); not an accurate measure of disease progression.</td>
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<tr>
<td>White blood count</td>
<td>May be increased</td>
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<tr>
<td>Anticycliccitrullinated peptide antibody</td>
<td>Tends to correlate well with disease progression; increases sensitivity when used in combination with rheumatoid factor; more specific than rheumatoid factor (90 versus 80 percent); not readily available in many laboratories.</td>
</tr>
<tr>
<td>Antinuclear antibody</td>
<td>Limited value as a screening study for RA</td>
</tr>
<tr>
<td>Complement levels</td>
<td>Normal or elevated</td>
</tr>
<tr>
<td>Immunoglobulin</td>
<td>Elevated alpha-1 and alpha-2 globulins possible.</td>
</tr>
<tr>
<td>Joint fluid evaluation</td>
<td>Consider if an affected joint can be tapped and diagnosis is uncertain; straw-colored fluid with fibrin flecks often seen; fluid may clot at room temperature; 5,000 to 25,000 white blood cells per mm$^3$ (5 to 25 X 10$^9$ per L) with 85 percent polymorphonuclear leukocytes a common finding; in rheumatoid arthritis,</td>
</tr>
</tbody>
</table>

per dL (100 g per L); normochromic anemia, also may be normocytic or microcytic.
cultures are negative, there are no crystals, and fluid glucose level typically is low.

| Urinalysis | Microscopic hematuria or proteinuria may be present in many connective tissue diseases. |

Treatment:
The goals of therapy of RA are

(1) Relief of pain,
(2) Reduction of inflammation,
(3) Protection of articular structures,
(4) Maintenance of function, and
(5) Control of systemic involvement

The goals of RA treatment are to alleviate pain, control inflammation, preserve and improve activities of daily living, and prevent progressive joint destruction. Medical treatment includes the use of nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and corticosteroids. Equally important in the management of RA is nonmedical treatment, including patient education, physical therapy, occupational therapy, orthotics, and, rarely, surgery.

DMARD therapy within three months of diagnosis is currently recommended because it can slow or arrest progression of the disease. DMARDs suppress immune-mediated inflammation by decreasing the activity of target cells (e.g., lymphocytes) or specifically targeting cytokine pathways. Commonly used DMARDs include methotrexate, leflunomide, sulfasalazine, and hydroxychloroquine. When maximal dosing of one DMARD provides suboptimal disease control, the addition of other DMARDs often improves effectiveness [17, 18]. Monitoring for RA disease activity and drug toxicity is important as well.

Biologic DMARDs targeting the inflammatory cytokine TNF-α include the fusion protein etanercept; the monoclonal antibodies infliximab, adalimumab, and golimumab; and the pegylated TNF receptor fusion protein certolizumab pegol. Other currently available biologic DMARDs include abatacept (a cytotoxic T-lymphocyte antigen 4 fusion protein that blocks T-cell costimulation by antigen-presenting cells); rituximab (a monoclonal antibody to CD20 that depletes B cells); the IL-1 receptor antagonist anakinra; and tocilizumab, a monoclonal antibody...
to the IL-6 receptor. Recently, an oral biologic, tofacitinib, which is a janus kinase 3 (JAK 3) inhibitor was approved for RA treatment.

Corticosteroids in low doses (e.g., prednisone, 5–10 mg) are extremely effective in promptly reducing the symptoms of RA and are useful in helping patients recover their previous functional status, but care should be taken to use the lowest effective dose. Corticosteroids are appropriate in patients with significant limitations in their activities of daily living or in an acute disease flare while awaiting the efficacy of the generally slower-acting DMARDs [1]. NSAIDs, including the selective cyclo oxygenase (COX)-2 inhibitors, are commonly added to treatment regimens for pain relief and to decrease inflammation. NSAIDs do not prevent progression of bone and cartilage damage and should be used with caution because of their potential for gastrointestinal (GI) and renal toxicity and effects on cardiovascular risk, especially since RA patients may have an increased incidence of cardiovascular events [19].

A historic viewpoint of rheumatoid arthritis treatment:

Both the objectives and the results of treatment for RA have changed profoundly over the past 25 years, dictated largely by an enhanced understanding of the pathogenesis of the disease. In 1890, Koch showed that gold cyanide inhibited the growth in vitro of tubercle bacilli, and gold compounds were subsequently used to treat the chronic infection tuberculosis [20]. Hypothesizing chronic infectious etiology for RA, Forestier pioneered the use of gold salts in RA [21], and they were subsequently shown to be effective by controlled studies [22, 23]. Despite years of investigation, we know rather less about how gold evokes its anti-rheumatic effect than we do for most other drugs used in RA. Gold interferes with lymphocyte and monocyte function in vitro but not in vivo and reduces levels of immune complexes and rheumatoid factor (RF). The standards of older trials, such as those originally showing the short- and long-term efficacy of gold salts, were not always up to the standards employed today. The methodology applied in conducting clinical trials in RA is continually subject to improvement [24]. Until the introduction to the rheumatology clinic of methotrexate (MTX), intramuscular (IM) gold, effective in the short and long term, was considered the standard disease-modifying anti-rheumatic drug (DMARD) with which all other drugs were to be compared [25]; its major limitation, however, is its toxicity. Adverse effects occur in approximately one third of patients treated with IM gold. Common are trivial reactions such as post-injection reactions, mucocutaneous reactions (dermatitis, stomatitis, pruritus), deposition of gold into the cornea or lens, and dysgeusia. Less commonly seen, but potentially serious, are nephrotic syndrome, cytopenias including marrow aplasia, interstitial lung disease, and peripheral neuropathies. Thus, although undoubtedly effective in some
patients, approximately one third of patients treated with parenteral gold stop the drug because of side effects, another third achieve a good clinical and radiographic response, and in the rest no response or toxicity is seen. In the era of biologic DMARDs and with the plethora of therapeutic options for RA patients nowadays, many clinicians no longer recommend it.\textsuperscript{[26]}

D-penicillamine, used in RA since the first successful case in 1964, is a degradation product of the antibiotic penicillin and acopper chelator, leading to the dissociation of immune complexes. It controls RA in inflammation possibly by suppressing T cell function. D-penicillamine has never been shown to have the radiographic efficacy of parenteral gold and has many side-effects (bone marrow suppression, dysgeusia, anorexia, vomiting and diarrhea), including a weird spectrum of autoimmune phenomena (nephropathy, hep-atotoxicity, membranous glomerulonephritis, aplastic anemia, antibody-mediated myasthenia gravis, Lambert-Eaton myasthenic syndrome, drug-induced systemic lupus erythematosus, elastosis perforans serpiginosa, toxic myopathies). Interestingly, a subpopulation of anti-Ro(SSA) positive patients with RA who receive D-penicillamine are of higher risk for developing side-effects, including skin rashes, proteinuria, leukopenia and autoimmune phenomena such as myasthenia gravis\textsuperscript{[27, 28]}. Few prescribe it actively now, and many younger rheumatologists have never done so. There appear to be no advantages when D-penicillamine is used in combination with other drugs\textsuperscript{[29]}

Sulfasalazine (SSZ), the third oldest drug or drug class still in use in the treatment of RA, was the first to be synthesized specifically for that disease. Reflecting the then still prevailing notion that RA had an infectious etiology, a complex of salicylic acid and the antibacterial agent sulfapyridine linked by anazo bond was synthesized and early data showed efficacy against RA and ulcerative colitis\textsuperscript{[30, 31]}. How SSZ works is unknown. By design, it possesses anti-inflammatory and antibacterial moieties that are released via cleavage by colonic bacteria; 30\% of the drug, however, is absorbed as a whole. Most of the released sulfapyridine is absorbed, whereas most of the 5-aminosalicylic acid is retained in the feces\textsuperscript{[32]}. In RA the 5-aminosalicylic acid moiety alone has failed to control disease, whereas sulfapyridine does\textsuperscript{[33]}. Interestingly, 5-aminosalicylic acid seems to be the active moiety in ulcerative colitis\textsuperscript{[34]}. The parent drug SSZ is a potent de novo purine synthesis enzyme inhibitor, resulting in increased intracellular adenosine, which has potent anti-inflammatory properties, shown most convincingly for neutrophils\textsuperscript{[35, 36]}. In terms of cell biology, SSZ has effects on T and B-cell populations and suppresses levels of IL-1 and TNF-\textalpha\textsuperscript{[37]}. Although several initial trials showed good results in open trials, lack of efficacy is the main reason for discontinuation of SSZ treatment. The question where SSZ stands in the hierarchy of other agents in use in RA is only partially answered. SSZ is more effective than the antimalarials.
and azathioprine; it is as effective as IM gold and penicillamine and possesses considerably less toxicity. In summary, SSZ possesses the efficacy of gold and penicillamine but with a more favorable side effect profile. It may be as efficacious as MTX, with less severe toxicity. It is fairly rapid acting and dose adjustments are straightforward.

The use of cyclosporine A (CSA) in RA began in 1980. CSA inhibits the nuclear translocation of NF-AT, which is critical in the activation of T lymphocytes. A major effect appears to be the inhibition of transcription of IL-2 and other early T-cell activation genes. The history of CSA use in RA is like that of the GCs, in which early efficacy at high doses was shown, but enthusiasm was dampened by toxicity concerns. Unlike the GCs, CSA has proven less toxic but still effective at lower doses. But although GCs are widely used by practicing rheumatologists despite uncertainties about their precise role in the scheme of RA treatment, CSA is not, and is virtually never used as a first-line DMARD. Its future as mono-therapy seems doubtful, and it remains unclear whether its efficacy in combination therapy outweighs the toxicities, still present even at low doses.

Leflunomide (LEF), approved by the FDA in September 1998 for the treatment of active RA, inhibits de novo pyrimidine synthesis, and its major effect in RA and animal models of RA appears to be related to the inhibition of activated T-cell proliferation. It appears not to suppress bone marrow nor predispose to opportunistic infections. Limited data, of which more are pending, suggest short- and long-term (radiographic) efficacy comparable with that of SSZ. It is an expensive alternative to MTX and SSZ but may indeed prove to have a better toxicity/tolerability profile.

**From pathophysiology to therapeutic targets:**

Finding an effective targeted therapy seemed for many years to be no more than a game of chance within the logic derived from dissecting pathophysiologic pathways. Despite many uncertainties, dramatic advances have occurred in the RA therapeutic arena. Blockade of TNF-α and IL-6, inhibition of T-cell co-stimulation and B-cell depletion are all highly effective and currently available therapies for RA. Interestingly, however, all these approaches seem to have very similar clinical efficacy, at least when administered in combination with methotrexate, in any given population of patients with RA, early or late disease, and with the exception of B-cell depletion patients who test positive or negative for the presence of autoantibodies. Although no head-to-head trial comparing these four approaches has been performed, and bearing in mind that most studies ignore or omit the fact that patients included in the studies were also receiving...
small doses of steroids, this observation raises the question of whether all effective therapies actually target a common final pathway in the pathogenesis of RA. \[43\]

**Targeting B-cells:**

Improvement in clinical signs and symptoms of RA through B-cell depletion has highlighted the importance of B-cells in the pathogenesis of the disease. Hindering the impact of B-cells to disease activity has been achieved by B-cell-depleting therapies with great success. Rituximab, a monoclonal chimeric anti-CD20 antibody, recognizes a determinant expressed on intramedullary pre-B- to B-memory stage lymphocytes. It was originally used in non-Hodgkin's lymphoma, while the first controlled trial on RA was published in 2004\[44\]. Rituximab induces antibody-dependent cell-mediated cytotoxicity, complement-dependent cytotoxicity, and apoptosis of B-cells in various stages of development\[45, 46, 47\] leading to their transient but almost complete depletion in peripheral blood, although only partially in the bone marrow and synovial tissue niches\[48, 49\]. Serum biomarkers of B cell activation, such as the presence of RF, or ACPA and elevated serum IgG levels, were identified as potential predictors of response to rituximab\[50\]. Patients seronegative for RF and ACPA have worse responses, suggesting that these patients have non-B-cell-mediated disease and require a different therapeutic approach\[51, 52\]. Despite the fact that rituximab does not deplete fully matured plasma cells, repeated administration of the biologic agent frequently induces a reduction of immunoglobulin, particularly immunoglobulin G (IgG), which may carry an increased risk of infection. Peripheral blood B cell re-population after rituximab therapy mainly involves a subset of naïve or antigenically inexperienced transitional B cells derived from an immature population. Eliminating B cells by targeting the CD20 cell surface differentiation antigen might remove a large population of cells full with pathophysiologically important cytokines, such as TNF-A and IL-6. Concurrent depletion of CD20\+non-B cells and prevention of antigen presentation by eliminating B cells might convey an additional effect by leading to a reduction in T-cell activation without primarily affecting co-stimulation\[53\]. Thus, the role of B cells in the pathogenesis of RA might also have to be considered in the general context of intercellular communication: B-cell depletion might not only lead to a reduction in autoantibodies, but also to an inhibition of T-cell reactivity either via deficient antigen presentation, elimination of a cell population capable of conveying co-stimulatory signals or even activation of TREG cells. Rituximab has shown to be effective as monotherapy, but considerably less so when used in combination with methotrexate, both in the magnitude and duration of response\[54\]. The use of
rituximab with other DMARDs, mainly leflunomide, has been evaluated as producing similar results\textsuperscript{[55]}, but large head-to-head randomized trials are still lacking.

In Europe, rituximab was approved in RA patients with severe disease, but only after failure of at least one anti-TNF agent (and always in association with methotrexate). However, in the more recent 2012 ACR guidelines, rituximab has already been recommended as a first-line biologic agent after synthetic DMARD failure for patients with moderate to severe disease activity and for those with low disease activity and poor prognostic markers\textsuperscript{[56]}.

**Targeting T-cells:**

T cells require at least two signals to become fully activated\textsuperscript{[57, 58]}. The first signal is antigen specific and is delivered by engagement of the T-cell receptor with an MHC-peptide complex on an antigen-presenting cell. The second signal is delivered by the binding of a co-stimulatory receptor on T cells to a ligand on the antigen-presenting cell.\textsuperscript{[59]} A key co-stimulatory signal is provided by the interaction of CD28 on T cells with CD80 or CD86 on antigen-presenting cells\textsuperscript{[60, 61]}. In the presence of optimal T-cell receptor and CD28 signals, T cells proliferate and produce cytokines that can activate other inflammatory cells, such as macrophages. With only a T-cell receptor signal and no CD28 signal, T-cell activation is not optimal, and T cells may be rendered poorly responsive to otherwise optimal subsequent stimulation or they may undergo apoptosis\textsuperscript{[62]}. Cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) is expressed on the surface of T cells hours or days after they become activated. CTLA4 is the high-avidity receptor for both CD80 and CD86, binding approximately 500e2500 times as avidly to these ligands as to CD28\textsuperscript{[63, 64]}. CTLA4-Ig is constructed by genetically fusing the external domain of human CTLA4 to the heavy-chain constant region of human IgG1. CTLA4-Ig binds both CD80 and CD86 on antigen-presenting cells, thereby preventing these molecules from engaging CD28 on T cells. By blocking the engagement of CD28, CTLA4-Ig prevents the delivery of the second co-stimulatory signal that is required for optimal activation of T cells.

Abatacept is a human CTLA4-IgFc fusion protein, binds to CD80/86 on antigen-presenting cells and competitively prevents its binding to the T-cell CD28 molecule (CTLA). The blocking of CD80/CD86-CD28 interaction limits and down-modulates T cell activation. Administration of abatacept subsequently leads to impaired B-cell activation and reduced levels of autoantibodies, together with a reduction in T-cell-mediated activation of osteoclasts and diminished cytokine release from T-cells, B-cells, and macrophages\textsuperscript{[65, 66]}. This translates into reduced disease activity, a decrease in inflammatory markers and halted bone erosion, as seen in various randomized...
clinical trials supporting its use, with benefits being present as early as 1e4 months of continued administration\textsuperscript{[67]}. Abatacept is more effective in ACPA-positive patients\textsuperscript{[68]} the reason for this is unknown, and emphasize that RA is a syndrome with multiple subtypes that may respond differently to different therapies.

Direct targeting of T cells by cyclosporine A (CsA) has shown limited or no efficacy. The immunosuppressive action of CsA is primarily due to the inhibition of antigen/mitogen-induced secretion of lymphokines at the transcriptional level from T cells. CsA acts by forming a complex with immunophilin, which inhibits the Ca\textsubscript{2+}/calmodulin-dependent serine/threonine phosphatase calcineurin. Inactive calcineurin is unable to activate the nuclear factor of activated T cells (NFAT), which downstream appears to shut down lymphokine-gene transcription. This pathway is induced via CD28, which would explain why CsA inhibition of calcineurin signaling can be overcome by CD28 costimulation\textsuperscript{[69]}.

Tacrolimus, a macrolide calcineurin inhibitor, initially developed and used to prevent organ transplant rejection reactions. Its mechanism of action is similar to that of CsA. It acts by binding to specific intracellular proteins after entering T cells and this complex inhibits calcineurin phosphatase, which prevents the activation of NFAT. There is little evidence to support its use as first-line therapy, but when conventional DMARDs have failed or biological agents are not an option, tacrolimus 3 mg per day could be an alternative option as monotherapy or in combination with MTX. Further analysis of the role of tacrolimus when used alongside other DMARDs or biologics in patients with resistant RA would be helpful. Finally, the lack of evidence regarding the effect of tacrolimus on radiographic progression of RA needs to be addressed with further studies\textsuperscript{[70, 71]}.

Targeting the cytokines:

TNF-\textalpha

It is an old, well-established notion that TNF-\textalpha is an inflammatory mediator which induces itself, pro-inflammatory cytokines, activates polymorph nuclear leukocytes, natural killer cells, and cytotoxic T cells, drives osteoclastogenesis, inhibits collagen synthesis, and enhances cartilage breakdown\textsuperscript{[72]}. Since TNF-\textalpha is an important mediator responsible for joint inflammation and destruction, it was the first cytokine to be targeted in the treatment of RA\textsuperscript{[73]}. TNF-\textalpha is overexpressed in the synovial fluid of patients with RA\textsuperscript{[74]}. Moreover, TNF-\textalpha transgenic mice spontaneously develop arthritis\textsuperscript{[75]}. Clinical trials have proved that TNF blockade is highly efficacious in the treatment of RA and this led to the development of five TNF inhibitors.
The first biologic disease modifying anti-rheumatic drugs (bDMARD) generated was infliximab, a chimeric monoclonal antibody composed of a murine variable region and a human constant region, against TNF (soluble and membrane bound). Clinical trials of infliximab proved that TNF blockade is highly efficacious in the treatment of RA and led to the development of other TNF inhibitors.

Infliximab is usually administered intravenously every 4-8 weeks. Ensuing randomized controlled trials showed that infliximab in combination with methotrexate produced a rapid reduction of signs and symptoms, reduced radiographically measured disease progression and improved physical function. In addition, the reduced radiographic progression was shown to be independent of clinical response[76].

Etanercept, approved in 1998 for the use in RA, is a recombinant fusion protein, consisting of two TNF receptor 2 (also known as p75TNF receptor) extracellular domains and a human Fc fragment of the human immunoglobulin (Ig) G1 class. As TNF-α and lymphotoxin bind to TNF receptor 2, etanercept works as a decoy receptor, binding to soluble TNF and blocking the binding to its receptor, while neutralizing the biological activity of both cytokines. It has a short half-life (3-6 days), and is usually administered subcutaneously 50 mg once a week or 25 mg twice a week. The clinical efficacy of etanercept has been shown both as monotherapy[77] and in combination with methotrexate[78], the combination providing better results than methotrexate or etanercept alone. Several recent studies have suggested that in patients with established RA who have achieved a long-lasting low disease activity state on the combination of methotrexate plus etanercept, the latter drug can in many cases be continued at half the usual dose or at more sparse treatment intervals[79].

Adalimumab was the first fully human monoclonal antibody binding TNF. It is administered subcutaneously and has a longer half-life than etanercept (approximately 13 days), allowing a less frequent injection interval (every second week). The clinical efficacy of adalimumab in combination with methotrexate was shown in patients with early aggressive RA. As well as in patients who had previously failed to respond to other biologic or non-biologic DMARDs[80]. A recent study evaluated the use of methotrexate and adalimumab as first line treatment for patients with early RA, with a unique trial design that rerandomized patients who had achieved a low disease activity state with the combination after 24 weeks[81]. After 76 weeks, around 90% of patients who continued on both (versus around 80% of patients who continued with only methotrexate) had maintained low disease activity. While this difference was statistically significant, the most important conclusion might well be that, for
at least a subset of patients with early RA, induction-maintenance is a highly successful therapeutic strategy with an obviously favorable health-economic profile.

Golimumab is a human monoclonal antibody, binding to both soluble and membrane bound TNF. It has a half-life of approximately 13 days and is administered subcutaneously once a month. Recently, the Food and Drug Administration (FDA) approved an intravenous format of this drug for the treatment of RA, to be administered at 0 and 4 weeks, thereafter every 8 weeks. Golimumab has been shown to be effective in the treatment of moderate to severe RA patients who failed to respond or were naïve to methotrexate, as well as in patients who failed to respond to at least one anti-TNF therapy.

Certolizumab pegol is a pegylated, humanized anti-TNF Fab fragment. Since it lacks the Fc portion, it does not induce apoptosis through complement activation or antibody-dependent cell-mediated cytotoxicity. The pegylation process (addition of polyethylene glycol) delays the elimination of this small antibody-derived protein, prolonging its half-life (approximately 14 days). Certolizumab is administered subcutaneously every second week and can be given either as monotherapy or in combination with methotrexate.[81]

**IL-6**

IL-6 is a pleiotropic cytokine. Serum levels of IL-6 and soluble IL-6 receptor (IL-6R) are elevated and correlate with disease activity in RA patients and so blocking IL-6/IL-6R has been considered beneficial for the treatment of RA.

Tocilizumab, a humanized anti-IL-6R monoclonal antibody, has been successfully used as monotherapy or in combination with synthetic DMARDs such as methotrexate in patients who are DMARD naïve and have an inadequate response to TNF inhibitors.[82] In the most recent EULAR recommendations for the management of RA, tocilizumab was listed as a first-line TNF inhibitor in patients not responding to synthetic DMARDs.[83] It has a half-life of 10e13 days and is administered intravenously every 4 weeks. A subcutaneous formulation of tocilizumab has been developed and was very recently approved in the United States. Tocilizumab (162 mg) injected subcutaneously once weekly has recently shown a comparable efficacy and safety profile to TCZ-IV (8 mg/kg).[84, 85] The successful treatment of RA with tocilizumab has encouraged the development of novel bDMARDs targeting IL-6 or IL-6R. In addition to tocilizumab, the phase II clinical trials of olokizumab, sarilumab and sirukumab, three new bDMARDs targeting IL-6 are reported. All these drugs were studied in RA patients with moderate-to-severe disease activity despite TNF inhibitors.[86]

**IL-1**
IL-1 is implicated in the pathogenesis of RA, its level correlates with RA disease activity.[87] IL-1 type 2 receptor is a decoy receptor which binds to circulating IL-1[88] and is not involved in signal transduction. An antagonist of this receptor has also been identified (IL1RN) which neutralizes the effects of IL-1, consequently, IL1RN acts as a physiological inhibitor of IL-1. Complete inhibition of IL-1 requires 10-fold to 100-fold molar excess of IL1RN over IL-1. The balance between IL-1 and IL1RN is important in maintaining the normal physiology of the joints and homeostasis of the immune system.

Anakinra, a recombinant form of the naturally occurring IL1RN, has a very short half-life (4e6 h) and must be administered sub-cutaneously once a day. Due to this inconvenience, as well as indirect comparative reports showing limited success of anakinra in RA compared to TNF inhibitors[89], this drug is not commonly used in adult RA. Nevertheless, anakinra has been successfully used in juvenile RA and other autoinflammatory disorders[90, 91].

Synovial Fibroblast:[92]

Synovial fibroblasts play critical roles in normal embryogenesis and mature joint functioning. During development, it is the SF that forms the main element of the nascent joint tissue and that, in response to hyaluronic acid and other signals, begins to define the joint space and capsule. In the healthy adult joint, the SF performs several functions. As the primary stromal cell of the joint, the SF appears responsible for the production of collagen and other connective tissue molecules that form and maintain the joint capsule. The SF is also the major secretor of hyaluronic acid and other molecules into the joint space itself, providing lubrication to the joint surface as well as signaling functions to the joint tissues. Healthy SF are also likely to secrete controlled amounts of enzymes, such as matrix metalloproteinases, that have the capacity to digest connective tissue and presumably maintain the structure and pliability of the joint capsule through remodeling. In RA, however, SF takes on both a different character and a different set of roles. Most prominently, one could describe the Rheumatoid Arthritis Synovial Fibroblast (RA SF) as tumor-like, in that the tissue it constitutes becomes hyperplastic. The RA SF also resembles tumor in that it becomes invasive, advancing past its normal barriers to invade bone and cartilage. In contrast to many tumors, however, the RA SF is not autonomous, instead responding to a wide range of inflammatory signals, including pro-inflammatory cytokines.

Anti-inflammatory cytokines or regulatory cytokines:[93]

IL-10: IL-10 to play mainly an anti-inflammatory role in the immune system. IL-10 was originally known as the (CSIF).cytokine synthesis inhibiting factors. Like other cytokines interleukin-10 has many effects upon the functions of cells such as lymphocytes, monocytes,
natural killer cells, and dendritic cells. Specifically, IL-10 is a cytokine that regulates immune-mediated inflammation. It appears to have two major functions: (1) to inhibit cytokine (i.e., TNF, IL-1, chemokine, and IL-12) production by macrophages and (2) to inhibit the accessory functions of macrophages in T cell activation. IL-10 accomplishes the latter function through the reduced expression of MHC class II molecules and certain co-stimulators (e.g., B7). The cumulative effect of these functions acts to inhibit T cell-mediated immune inflammation.

**IL-4:** IL-4 is a T-cell derived anti-inflammatory cytokine which inhibits the production of several pro-inflammatory cytokines, i.e. IL-1β, TNF-α and IL-6. IL-4 also reduces bone resorption in vitro and systemically injected IL-4 suppresses the chronic destructive phase in streptococcal cell-wall induced arthritis in rats.

**Matrix Metalloproteinases (MMPs):** MMPs are secreted from monocytes/macrophage and are capable of degrading a variety of extracellular matrix protein components including the collagens, proteoglycans, fibronectin and laminin. There are at least 19 known human MMPs that can be divided into four groups: collagenase, stromelysins, gelatinases and the membrane type MMPs (MT-MMPs). The most important MMPs in RA are stromelysin 1 (MMP-3) and collagenase (MMP-1). Increased levels of MMP-3 have been detected both in serum and Synovial fibroblast of RA. The main inhibitors of MMPs are the tissue inhibitors of matrix metalloproteinases (TIMPs), a class of low molecular weight proteins that form noncovalent high affinity complexes with active MMPs. TIMP-1 is increased in RA serum and SF.

**MANAGEMENT:**

- **Classification of NSAIDS:**
  
  **A. Non-selective COX inhibitors (traditional NSAIDS):**
  
  1. Salicylates: Aspirin
  3. Anthranilic acid derivative: Mephenamic acid.

  **B. Preferential COX-2 inhibitors:**
  
  Nimesulide, Meloxicam, Nabumetone
C. Selective COX-2 Inhibitors:
   Celecoxib, Etoricoxib, Parecoxib.

D. Analgesic-Antipyretics with poor anti-inflammatory action:
   2. Pyrazolone derivatives: Metamizol (Dipyrone), Propiphenazone.

Classification Of Anti-Rheumatic Drugs:

A. Disease modifying antirheumatic drugs (DMARDS):
   1. Immunosuppressants: Methotrexate, Azathioprine, Cyclosporine
   2. Sulfasalazine
   3. Chloroquine or Hydrochloroquine
   4. Leflunomide
   5. Gold sod. Thiomalate, Auranofin
   6. D-penicillamine

B. Biologic response modifiers (BRMS):
   1. TNF-α Inhibitors: Etanercept, Infliximab, Adalimumab
   2. IL-1 Antagonist: Anakinra

C. Corticosteroids: Prednisolone

Nonsteroidal Anti-inflammatory Drugs (NSAIDS):
These agents are rapidly effective at mitigating signs and symptoms, but they appear to exert minimal effect on the progression of the disease.

- **Mechanism of action:**
  - These agents have capacity to block the activity of the cyclooxygenase (COX) enzymes and therefore the production of prostaglandins, prostacyclin, and thromboxanes, they have analgesic, anti-inflammatory, and antipyretic properties.

- **Indications and General unwanted effects of NSAIDs:**
  - Unwanted effects, owing largely to inhibition of the constitutive housekeeping enzyme cyclooxygenase-1, are common, particularly in the elderly, and include:
  - Dyspepsia, nausea and vomiting; also gastric damage in chronic users, with risk of hemorrhage, resulting from abrogation of the protective effect of prostaglandin (PG) on gastric mucosa.
Skin reactions.

- Reversible renal insufficiency (in individuals who have noradrenergic- or angiotensin-mediated vasoconstriction) through lack of compensatory PGE2-mediated vasodilatation.
- 'Analgesic-associated nephropathy'; this can occur following long-continued high doses of NSAIDs (e.g. paracetamol) and is often irreversible.
- Less commonly, liver disorders, bone marrow depression.
- Bronchospasm in 'aspirin-sensitive' asthmatics.

Recently, specific inhibitors of the isoform of cyclooxygenase (COX) have been developed which selectively inhibit COX-2 and not COX-1, have been shown to be as effective as classic NSAIDs, which inhibit both isoforms of COX, but to cause significantly less gastroduodenal ulceration.

- None of the NSAIDs has been shown to be more effective than aspirin in the treatment of RA. However, these non-aspirin drugs are associated with a lower incidence of gastrointestinal intolerance.

- None of the newer NSAIDs appears to show significant therapeutic advantages over the other available agents.

- Recent evidence indicates that two separate enzymes, COX-1 and -2, are responsible for the initial metabolism of arachidonic acid into various inflammatory mediators.

- The former is constitutively present in many cells and tissues, including the stomach and the platelet, whereas the latter is specifically induced in response to inflammatory stimuli and is absent from the normal stomach and platelet.

- Inhibition of COX-2 accounts for the anti-inflammatory effects of NSAIDs, whereas inhibition of COX-1 induces much of the mechanism-based toxicity.

- Coxibs have been approved for the treatment of RA.

- Coxibs suppress the signs and symptoms of RA as effectively as classic COX-nonspecific NSAIDs but are associated with a significantly reduced incidence of gastroduodenal ulceration and appear to reduce the incidence of gastrointestinal bleeding, perforations, and obstruction to a variable degree compared with classic NSAIDs.

- However, the use of Coxibs is associated with sodium retention, hypertension, and peripheral edema in a fraction of patients, and the use of some Coxibs may be associated with an increased frequency of myocardial infarction.

- This suggests that Coxibs might be considered instead of classic COX nonspecific NSAIDs, especially in persons with increased risk of NSAID-induced major upper
gastrointestinal side effects, including persons over 65, those with a history of peptic ulcer disease, persons receiving glucocorticoids or anticoagulants, or those requiring high doses of NSAIDs.

<table>
<thead>
<tr>
<th>DRUG</th>
<th>M/A</th>
<th>SIDE EFFECTS</th>
<th>USES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>-Inhibit COX-1 &amp; COX-2</td>
<td>-epigestric distress -blood loss in stools -mucosal damage -peptic ulceration -nausea -vomiting</td>
<td>-Acute rheumatic fever -RA -As Analgesic -As antipyretic</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>-Irreversible cox inhibition</td>
<td>-gastric ulcer -eprgastic pain</td>
<td>-Dental surgery pain -ocular anti-inflammatory</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td></td>
<td></td>
<td>-ankylosing spondylitis -As Anti-inflammatory</td>
</tr>
<tr>
<td>Naproxen</td>
<td>-Irreversible cox inhibition</td>
<td></td>
<td>-RA -Osteoarthritis -Dysmenorrhoea</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>-Inhibiting leucocyte migration -stabilise lysosomes &amp; inhibit LOX</td>
<td>-gastric effect -G.I.T upset</td>
<td>-RA -Osteoarthritis -Dysmenorrhoea</td>
</tr>
<tr>
<td>Fenamate</td>
<td>-Inhibits COX as well as PGs</td>
<td>-Diarrhoea -Epigestic distress -CNS manifestation -Haemolytic anemia</td>
<td>-RA -RA -Osteoarthritis -Dysmenorrhoea</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>-Inhibit COX-2 Selective &amp; PGs</td>
<td>-headache -dizziness -gastric ulceration</td>
<td>-RA -Osteoarthritis -Dysmenorrhoea</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
<td>-RA -RA -Osteoarthritis -Dysmenorrhoea</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>-Selective COX-2 Inhibitor</td>
<td></td>
<td>-RA -RA -Osteoarthritis -Dysmenorrhoea</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>-Inhibit COX -Lower conc of PG &amp;-inhibit platelet aggregation</td>
<td>-Rashes -Blood loss</td>
<td>-RA -Osteoarthritis -Dysmenorrhoea -musculoskeletal injuries</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td></td>
<td></td>
<td>-RA -Osteoarthritis -Dysmenorrhoea -musculoskeletal injuries</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>-Inhibit PG synthesis</td>
<td>-Abdominal pain -Loose stools -Drowsiness -Dyspepsia</td>
<td>-dental pain -musculoskeletal pain -migrain</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>-Inhibit PG synthesis &amp; suppressed neutrophil motility</td>
<td>-Mental confusion -Hallucination -Hypersensitivity reaction</td>
<td>-Acute gout -ankylosing spondylitis -As Anti-inflammatory</td>
</tr>
<tr>
<td>Dipyrone</td>
<td>-Inhibit COX</td>
<td>-fall in BP -Gastric Irritation</td>
<td>-As Analgesic -As antipyretic</td>
</tr>
<tr>
<td>Propiphenzcape</td>
<td></td>
<td></td>
<td>-RA -Osteoarthritis -Dysmenorrhoea -musculoskeletal injuries</td>
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CONCLUSION

RA is a multifactorial disease involving genetic, immunological, and environmental factors. Animal model studies have shown diverse immune dysfunctions and different clinical features in the RA disease process. These animal models have provided valuable information for understanding the pathogenesis of inflammatory arthritis and have contributed to develop new therapeutic targets. On the other hand, none of these animal models reproduce human RA in its entirety and several new agents showing therapeutic efficacy in animal models have failed in human trials. Nonetheless, many innovative drugs have been developed based on advances in our understanding of immune dysfunction in RA. With currently available drugs, significant therapeutic responses (ACR70) are typically achieved and sustained only in some of the patients. No single drug has yet been shown to be effective in the majority of RA patients. These observations suggest that RA is a heterogeneous disease comprising several subsets of patients with variations in disease pathogenesis. Defining these differences in pathogenic mechanisms may lead to improved therapeutic modalities. The lower the disease activity achieved at 6 months, the better the long-term outcome; reaching stringent clinical remission within 3–6 months halts damage progression independent of the type of therapy used. Adding low-dose glucocorticoids to conventional synthetic DMARDs maximizes clinical, functional, and structural benefit. In higher-risk patients, using methotrexate as a first DMARD and adding a biologic, for those who do not attain at least low disease activity within 6 months and have high progression risk, optimizes benefit. And finally, if a state of low disease activity or an 80%
reduction of disease activity is achieved within 3 months from start of treatment, attainment of the target of low disease activity or remission at 6 months is highly likely. Rigorous attention to this regimen, coupled with the development of further therapeutic options for patients who remain unresponsive, should ensure within the next 10 years that most patients will achieve cessation of disease progression and disability, and retention of high levels of quality of life.

REFERENCES


30. N. Svartz, Salazopyrin, a new sulfanilamide preparation: A. Therapeutic re-sults in rheumatic polyarthritis; B. Therapeutic results in ulcerative colitis; C.Toxic manifestations in treatment with sulfanilamide preparations, ActaMed. Scand. 110 (1942) 577e598.


62. P.S. Linsley, J.L. Greene, W. Brady, J. Bajorath, J.A. Ledbetter, R. Peach, Human B7-1 (CD80) and B7-2 (CD86) bind with similar avidities but distinct kineticsto CD28 and CTLA-4 receptors, Immunity 1 (1994) 793e801.


