Rheumatoid Arthritis: A Brief Overview of the Treatment

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Significance of the Study

Rheumatoid arthritis not only affects the joints, but can also affect internal organs thus causing permanent disability in many instances. Currently, there is no cure for this autoimmune disease, rather symptoms are addressed on individual basis. Here we succinctly summarize the classical and current treatment options available to manage the patients suffering from this complex disease.
Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory systemic autoimmune disease, affecting the joints with varying severity among patients. The risk factors include age, gender, genetics and environmental exposure (cigarette smoking, air pollutants and occupational). Many complications can follow such as permanent joint damage requiring arthroplasty, rheumatoid vasculitis and elty’s syndrome requiring splenectomy if it remains unaddressed. As there is no cure for RA, the treatment goals are to reduce the pain and stop/slow the further damage. Here we present a brief summary of various past and present treatment modalities to address complications associated with rheumatoid arthritis.
Introduction

Rheumatoid arthritis is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually affecting the skin, eyes, heart, kidneys and lungs. Often, the bone and cartilage of joints are destroyed, and tendons and ligaments weaken [1]. All this damage to the joints causes deformities and bone erosion, that is usually very painful for a patient. Common symptoms of rheumatoid arthritis include morning stiffness of the affected joints for more than 30 minutes, fatigue, fever, weight loss, joints that are tender, swollen and warm, and rheumatoid nodules under the skin. The onset of this disease is usually from ages 35-60 with remission and exacerbation. It can also afflict young children even before age 16 and is referred to as juvenile rheumatoid arthritis (JRA), which is similar to RA except that rheumatoid factor is not found [2-5]. In the West, the prevalence of RA is believed to be 1–2% [5], and 1% worldwide [7].

Clinically, the diagnosis of rheumatoid arthritis can be differentiated with osteoarthritis (OA) as, the affected areas in RA are the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints, unlike osteoarthritis, which typically affects the distal interphalangeal (DIP) (Fig. 1.) Osteoarthritis is the most common type of arthritis, and is caused by wear and tear rather than an autoimmune condition. It has no effects on the lungs, heart or immune system. Also, osteoarthritis typically affects only one side of the body, as opposed to the symmetrical nature of rheumatoid arthritis. Another differentiating factor is that the patient suffers from persistent morning stiffness for at least one hour or more. Osteoarthritis may have morning stiffness, but it typically resolves or decreases within 20-30 minutes [8, 9].

The goals of treatment for rheumatoid arthritis are to reduce joint inflammation, pain,
maximize joint function, and to prevent joint destruction and deformity. Treatment regimen consists of combinations of pharmaceuticals, weight-bearing exercise, patient education, and rest. Treatments are generally customized to the patient’s need depending on their overall health. This includes factors such as disease progression, joints involved, age, overall health, occupation, compliance, and education about their disease [10]. This review briefly highlights the classical and current treatment options available to address the discomfort/complications from rheumatoid arthritis. An exhaustive review was recently published by Smolen et al [11].

**First Line Management: NSAIDS and Corticosteroids**

The overall goals of first line treatment are to relieve pain and decrease inflammation. Medications considered as fast-acting drugs are non-steroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin is an effective anti-inflammatory for rheumatoid arthritis when used at higher doses, due to inhibition of prostaglandins. This is one of the oldest NSAIDs used for joint pain. Side effects of aspirin at high doses include tinnitus, hearing loss and gastric intolerance. There are other NSAIDs that are newer to the market than aspirin but are just as effective. In addition, these drugs require a patient to take fewer dosages a day. NSAIDs work by inhibiting cyclooxygenase to prevent synthesis of prostaglandins, prostacyclin and thromboxanes. Common side effects are nausea, abdominal pain, ulcers and gastrointestinal (GI) bleeding. These symptoms can be reduced if taken with food or with antacids, proton pump inhibitors, or misoprostol (Cytotec) An even newer NSAID called celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side effects [12].

Corticosteroids are more potent anti-inflammatory medications compared to NSAIDs,
however, they come with greater side effects. For this reason, they are only indicated for a short period of time at low dosages, during exacerbations or flares of rheumatoid arthritis. Intra-articular (IA) injections of corticosteroid can be used for local symptoms of inflammation [13]. They work by preventing phospholipid release and decreasing actions of eosinophils, therefore decreasing inflammation. Their side effects include bone thinning, weight gain, diabetes, and immunosuppression. Advising the patient to take calcium and vitamin D supplementation can prevent thinning of bone. Side effects can be reduced by gradually tapering the doses as the patient achieves improvement. It is important not to abruptly discontinue injected or oral corticosteroids as it can lead to hypothalamic-pituitary-adrenal axis suppression (HPA) or flares of rheumatoid arthritis [14].

**Opioid Analgesics**

Whittle *et al.*, addressed the question of the use of opioid analgesics in patients with pain due to rheumatoid arthritis [15]. From their conclusions, weak opioids such as codeine, dextropropoxyphene, and tramadol may have an effective role in short term management of pain caused by rheumatoid arthritis, however the adverse effects outweigh the benefits. They recommend that other analgesics be considered first [16].

**Second Line Management: Disease-modifying Anti-rheumatic Drugs (DMARDs)**

The overall goals of second line treatment are to promote remission by slowing or stopping the progression of joint destruction and deformity. These medications are considered slow acting drugs because they take weeks to months to be effective. DMARDs can also reduce the risk of developing lymphoma that can be associated with rheumatoid arthritis [17].

Methotrexate (MTX) is the initial second-line drug (also considered as an anchor drug). It is an analogue to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the
enzyme that is responsible for converting FH2 to folic acid (FH4). Without FH4, purine and pyrimidine metabolism is impaired, and amino acid and polyamine synthesis is inhibited. MTX is an immunosuppressive drug that requires regular blood tests due to its side effects of liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can reduce the risk of side effects. It is an effective DMARD, has lower incidence of side effects compared to the other DMARDs, and has dose flexibility, meaning that dosages can be adjusted as needed [18].

Until now, there is convincing data available showing the benefits of combination of conventional synthetic DMARDs (csDMARDs) over MTX monotherapy. However, biological DMARDs (bDMARDs) combined with csDMARDs, are reported to be better than MTX but with more side effects and is very costly [11, 14].

Hydroxychloroquine (Plaquenil) is an antimalarial drug and can be used long term in the treatment of rheumatoid arthritis. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the gastrointestinal tract, skin, and central nervous system. In particular, the eye can be affected when used at higher dosages. Patients on this medication require routine consultation with an ophthalmologist [20].

Sulfasalazine (Azulfidine) is a DMARD typically used in the treatment of irritable bowel disease. Combined with anti-inflammatory medications, this DMARD can be to treat rheumatoid arthritis. The mechanism of action of this drug in the treatment of rheumatoid arthritis has not been identified. It is thought that sulfapyridine, a reduced form of the medication after administration, may reduce secretions of interleukin 8 (IL-8) and monocyte chemoattractant protein (MCP). This drug carries side effects of gastrointestinal and central nervous system symptoms as well as rash. It is usually well tolerated among patients, but it should be avoided in patients with sulfa allergies since it contains sulfa and salicylate compounds [21].
Gold salts, such as aurothioglucose (Solganal), auranofin (Ridaura), gold sodium thiomalate (Myochrysine), and D-penicillamine (Depen, Cuprimine) have been used frequently in the treatment of rheumatoid arthritis. These DMARDs require frequent blood and urine tests due to damage to the bone marrow and the kidneys. These medications have not been used recently due to more effective treatments, particularly methotrexate. Other immunosuppressive medications, azathioprine (Imuran), cyclophosphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune), can also be employed but are typically reserved for patients with very aggressive rheumatoid arthritis or complications of the disease [22, 23].

**Newer Medications**

Leflunomide is an oral medication that is converted to malononitrilamide, which inhibits the synthesis of ribonucleotide uridine monophosphate pyrimidine (rUMP). It relieves symptoms and retards the progression of rheumatoid arthritis. It is recommended to be used in combination with methotrexate, but can be used as monotherapy if patients do not respond to methotrexate. Side effects include hypertension, gastrointestinal upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash and bone marrow damage [24,25].

The biologics, also known as biological disease-modifying anti-rheumatic drugs (bDMARDs), are rapidly effective in retarding the progression of joint damage caused by rheumatoid arthritis. They are considered to be a more “direct, defined and targeted” method of treatment [26]. Nonetheless, biologics pose the potential for serious side effects, such as increased risk of infections. Other common side effects include neurologic disease similar to multiple sclerosis and lymphoma [27-29].

Tumor necrosis factor (TNF) is a messenger protein that promotes inflammation in joints. Biologic medications such as etanercept (Enbrel), infliximab (Remicade), adalimumab (Humira),
golimumab (Simponi), and certolizumab pegol (Cimzia) are all TNF-inhibitors. These inhibitors prevent the recruitment of cells that cause inflammation, causing rapid symptom relief. They are recommended if other second line medications are not effective. Unfortunately, these medications tend to be very expensive and their role in treating patients at various stages of rheumatoid arthritis and mechanism of action is a matter of continuous investigations. These medications are often used in combination with other DMARDs, especially methotrexate. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each of these biologic medications have different modes of administration [30-32].

Anakinra (Kineret) is a drug that is injected subcutaneously daily and works by binding to interleukin 1 (IL-1), a chemical messenger of inflammation. This medication can be used in combination with other DMARDs or as monotherapy, however due to a lower response rate than other biologics, it is not used as frequently [33,34]. Rituximab (Rituxan) is useful in rheumatoid arthritis because it depletes B cells, responsible for inflammation and production of abnormal antibodies. Typically used in the treatment of lymphoma, this drug can be used in the case of rheumatoid arthritis when TNF-inhibitors have failed. In addition, rituximab has shown benefits of treating complications of rheumatoid arthritis, such as vasculitis and cryoglobulinemia. It is administered as an intravenous infusion in two doses, two weeks apart, every six months [35,36]. Abatacept (Orencia) is a biologic medication that works by blocking T cell activation. This is given as an intravenous infusion once a month or subcutaneously once a week. It is used in patients who were not effectively treated with traditional DMARD medications [37].

Tocilizumab (Actemra) is a biologic that works by blocking interleukin 6 (IL-6), a chemical messenger of inflammation. It is administered via intravenous infusion given monthly or via weekly subcutaneous injections. It is also used for patients who have not been effectively treated
with traditional DMARD medications [38]. Lastly, Tofacitinib (Xeljanz) has a different mechanism of action and works by blocking Janus kinases within cells, which are enzymes of inflammation. For this reason, it is known as a JAK inhibitor. This medication is used for patients who are not effectively treated with methotrexate. Tofacitinib is taken orally twice daily alone or in combination with methotrexate. This medication should not be used in combination with traditional biologic medications or other potent immunosuppressants [39, 40].

**Surgery**

Joint surgery in patients with rheumatoid arthritis reached a peak high in the 1990s. However, a 2010 study shows that patients aged 40 through 59 with rheumatoid arthritis had decreased rates of joint surgery. In contrast, patients over age 60 had increased rates of surgery [41]. Surgery is a last resort option for treatment of rheumatoid arthritis. Indications include intractable joint pain or functional decline due to joint destruction after all nonsurgical approaches have failed. At this point, the disease is considered “end-stage.” The goal of surgical management is to relieve pain for the patient and to restore the function of the joints. A patient needing surgical treatment should be evaluated based on their customized needs because there are many different options of surgery.

A tenosynovectomy involves the excision of inflamed tendon sheaths or repairing a recent tendon rupture, most commonly in the hand [42]. Radiosynovectomy is an alternative to surgical synovectomy; involves intra-articular injection of small radioactive particles, a cost-effective procedure and multiple joints can be treated simultaneously [43]. Repair of ruptured tendons can also be done through arthroscopy, most commonly in the rotator cuff of the shoulder. Excision of an inflamed synovium via arthroscopy or open synovectomy is not commonly used any longer due to the availability of more effective medical treatment options. Another option of surgery is an
osteotomy. In this procedure, weight bearing bones are realigned to correct valgus or varus deformities, most commonly in the knee [44]. Joint fusion can be done to stabilize joints that are not easily replaceable such as the ankle, wrist, thumb and cervical spine. A procedure for soft tissue release can be done to correct severe contractures around joints causing decrease range of motion. This soft tissue release is an older procedure that is not commonly utilized [45]. Small joint implant arthroplasty can be done to reduce pain and improve hand function, most commonly in the metacarpophalangeal joints. Metatarsal head excision arthroplasties are done to alleviate severe forefoot pain. Lastly, a total joint replacement (TJR) is the removal of the damaged joint and replacing it with a metallic, plastic or ceramic prosthesis. This is most commonly done in the shoulder, elbow, wrist, hip, knee, and ankle [46,47]. The major contraindication for surgical joint replacements is the presence of active systemic articular infection.

Other Therapies

It has been found that in contrast to previous suggestions, there are no specific foods that patients with rheumatoid arthritis should avoid. The idea that diet can “aggravate” symptoms is no longer accepted as true [48]. Home remedies have been proven to be helpful for patients suffering from rheumatoid arthritis, although they are not as effective as DMARDs. Fish oils and omega-3 fatty acid supplements have been beneficial for the short-term symptoms of rheumatoid arthritis. Cumin has shown to have anti-inflammatory effects for patients with this disease. Calcium and vitamin D supplementation can be helpful for prevention against osteoporosis. Lastly, folic acid is helpful in preventing the side effects of methotrexate [49]. Patients with rheumatoid arthritis also benefit from physical and occupational therapy. It is recommended that patients perform exercise regularly to maintain joint mobility and to strengthen muscles around the joints. Movement exercises that are less traumatic for joints but are good for muscle strength include swimming,
yoga and tai chi. Applying heat and cold packs before and after exercise minimizes painful symptoms. Studies are being done on different types of connective tissue collagen in order to better understand and reduce rheumatoid arthritis disease activity. Lastly, with the scientific advancements and enhanced understanding of the molecular mechanisms, newer and better treatment options will become available in the near future [50-55].

**Conclusion**

Rheumatoid arthritis is a debilitating chronic inflammatory disease, capable of causing joint damage as well as long-term disability. Early diagnosis and intervention is essential for the prevention of serious damage and loss of essential bodily functions. The treating physician should consider adhering to treat-to-target (T2T) recommendations [56] by first outlining the aims and then implement protocols to achieving and assessing them. Furthermore, early referral to a specialist can also help ensuring better treatment outcomes. With the advances in the field of molecular medicine, we have better a understanding of disease mechanisms, thus aiding in the designing of more effective treatments. Old treatment modalities have been optimized and new ones have been produced. Gene array analysis is proving beneficial in finding out which patients will be more responsive to specific medications. This customization will allow for more rapid treatment and decrease the likelihood of progressive disease that can be avoided during the experimental phase to seek an appropriate treatment for a particular patient. Gene array analysis is also being used to determine which patients are at greater risk for more aggressive forms of rheumatoid arthritis. It is foreseen that treatment methods will face tremendous improvements for the management of rheumatoid arthritis.

**Conflict of interest:**

The authors declare no conflict of interest.
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Wilkins; 2011.


**Figure 1.** A classic example of joint deformities associated with rheumatoid arthritis. Boutonnière deformity is visible in the 5th digit of the right hand and Swan neck deformity in the 5th digit of the left hand. Also, hallux valgus can be seen in the foot.