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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 an individual basis. Here, we succinctly summarize the classic and current treatment options available for the management of patients suffering from this complex disease.

Keywords
Rheumatoid arthritis · Boutonnière deformity · Swan neck deformity

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 Felty 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 further damage. Here, we present a brief summary of various past and present treatment modalities to address the complications associated with RA.

Introduction

Rheumatoid arthritis (RA) is a chronic, symmetrical, inflammatory autoimmune disease that initially affects small joints, progressing to larger joints, and eventually 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, usually very painful for a patient. Common symptoms of RA include morning stiffness of the affected joints for >30 min, fatigue, fever, weight loss, joints that are tender, swollen and warm, and rheumatoid nodules under the skin. The onset of this dis-

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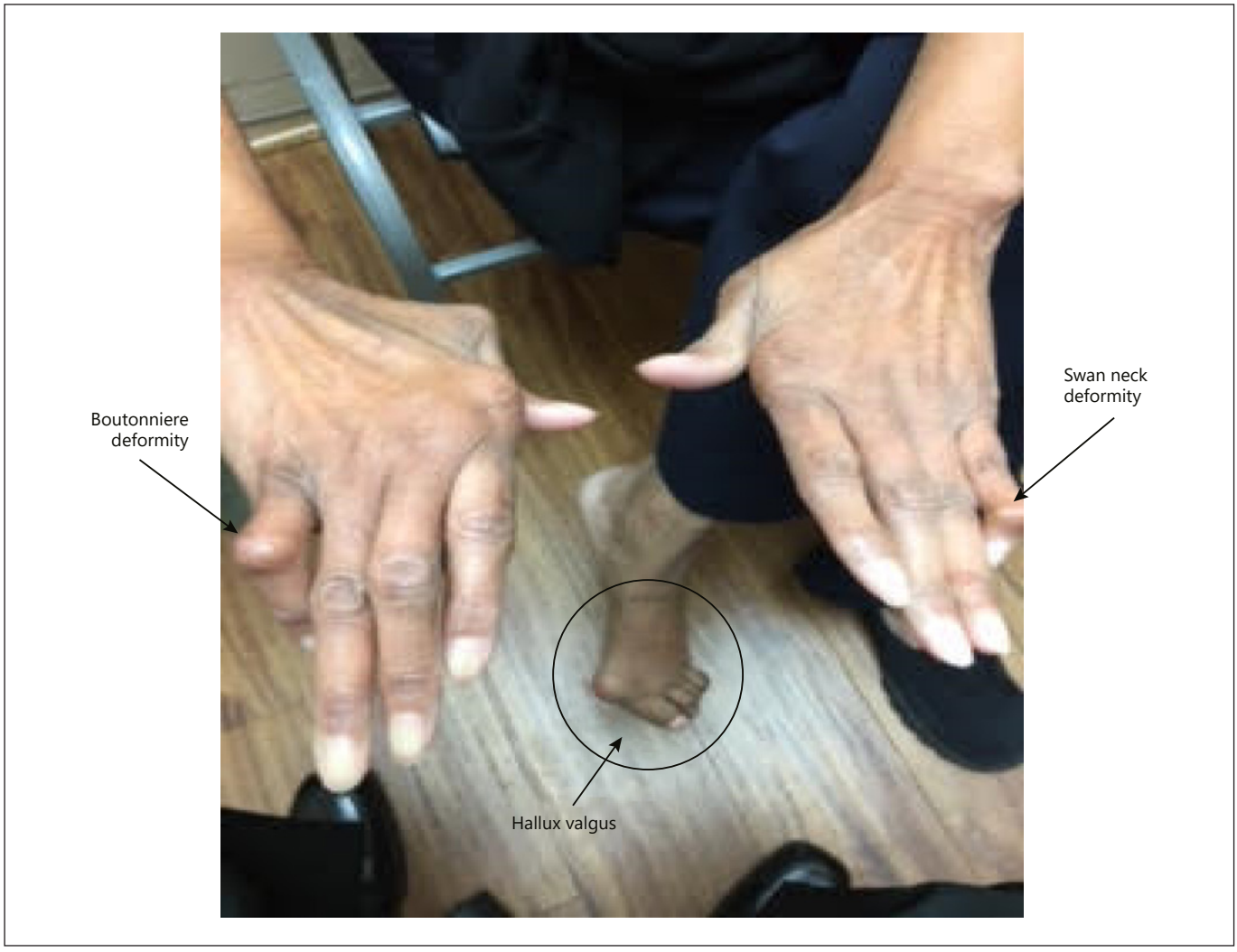

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Fig. 1. A classic example of joint deformities associated with rheumatoid arthritis. Boutonniere deformity is visible in the 5th digit of the right hand, Swan neck deformity in the 5th digit of the left hand, and hallux valgus can be seen in the foot.

ease is usually from the age of 35 to 60 years, with remission and exacerbation. It can also afflict young children even before the age of 16 years, referred to as juvenile RA (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, 6], and 1% worldwide [7].

Clinically, the diagnosis of RA can be differentiated from osteoarthritis (OA) as the affected areas in RA are the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints; OA typically affects the distal interphalangeal (DIP) joint (Fig. 1). OA 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. In addition, OA typically affects only one side of the body, as opposed to the symmetrical nature of RA. Another differentiating factor is that RA patients suffer from persistent morning stiffness for at least ≥1 h. Patients with OA may have morning stiffness, but this typically resolves or decreases within 20–30 min [8, 9].

The goals of treatment for RA are to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight-bearing exercise, educating patients about the disease, and rest. Treatments are generally customized to a pa-

tient's needs and depend on their overall health. This includes factors such as disease progression, the joints involved, age, overall health, occupation, compliance, and education about the disease [10]. This review briefly highlights the classic and current treatment options available to address the discomfort/complications of RA. An exhaustive review was recently published by Smolen et al. [11].

First-Line Management: NSAIDS and Corticosteroids

The overall goal of first-line treatment is to relieve pain and decrease inflammation. Medications, considered to be fast-acting, are nonsteroidal anti-inflammatory drugs (NSAIDs) including acetylsalicylate (Aspirin), naproxen (Naprosyn), ibuprofen (Advil and Motrin), and etodolac (Lodine). Aspirin is an effective anti-inflammatory for RA when used at high doses, due to the inhibition of prostaglandins. It 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 on the market than aspirin and just as effective. In addition, these drugs require fewer doses per day. NSAIDs work by inhibiting cyclo-oxygenase to prevent the 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, 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 a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses, during exacerbations or flares of RA. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation [13]. They work by preventing the release of phospholipids and decreasing the actions of eosinophils, thereby 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 the bone. Side effects can be reduced by gradually tapering doses as a patient's condition improves. It is important to not abruptly discontinue injected or oral corticosteroids as this can lead to suppression of the hypothalamic-pituitary-adrenal axis (HPA) or flares of RA [14].

Opioid Analgesics

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

Second-Line Management: Disease-Modifying Antirheumatic Drugs

The overall goal of second-line treatment is to promote remission by slowing or stopping the progression of joint destruction and deformity. Medications are considered to be slow-acting because they take from weeks to months to be effective. Disease-modifying antirheumatic drugs (DMARDs) can also reduce the risk of developing lymphoma that can be associated with RA [17].

Methotrexate (MTX) is the initial second-line drug (also considered an anchor drug). It is an analog to folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for converting FH2 to folinic acid (FH4). Without FH4, the metabolism of purine and pyrimidine is impaired, and the synthesis of amino acids and polyamine is inhibited. MTX is an immunosuppressive drug that requires regular blood tests due to its side effects, i.e., liver problems, cirrhosis, and bone marrow deterioration. Folic acid supplementation can reduce the risk of side effects. It is an effective DMARD, has a lower incidence of side effects than other DMARDs, and has dosage flexibility, meaning that doses can be adjusted as needed [18]. Until now, there is convincing data showing the benefits of combinations of conventional synthetic DMARDs over MTX monotherapy. However, biological and synthetic DMARDs in combination are reported to be better than MTX but with more side effects and greater costs [11, 14, 19].

Hydroxychloroqyine (Plaquenil) is an antimalarial drug and can be used for long-term treatment of RA. This drug decreases the secretion of monocyte-derived proinflammatory cytokines. Common side effects include problems in the GI tract, skin, and central nervous system. The eyes, in particular, can be affected when this drug is taken at high doses. 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 used to treat RA. The mechanism of action of this drug in the treatment of RA has not been identified. It is thought that sulfapyridine, a reduced form of the medication after administration, may reduce secretions of interleukin (IL)-8 and monocyte chemoattractant protein (MCP). This drug has side effects of GI and central nervous system symptoms as well as rash. It is usually well-tolerated among patients, but 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 and Cuprimine) have been used frequently in the treatment of RA. These DMARDs require frequent blood and urine tests due to damage to the bone marrow and kidneys. They have not been used recently due to the more effective treatments, particularly MTX. Other immunosuppressive medications like azathioprine (Imuran), cyclophsphamide (Cytoxan), chlorambucil (Leukeran), and cyclosporine (Sandimmune) can be employed but are typically reserved for patients with very aggressive RA 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. It relieves symptoms and retards the progression of RA. It is recommended to be used in combination with MTX but can constitute a monotherapy if patients do not respond to MTX. Side effects include hypertension, GI upset, liver damage, leukopenia, interstitial lung disease, neuropathy, rash, and bone marrow damage [24, 25].

Biologics, also known as biological DMARDs, are rapidly effective in retarding the progression of the joint damage caused by RA. They are considered to be a more "direct, defined and targeted" method of treatment [26]. Nonetheless, biologics pose the problem of serious side effects, such as increased risk of infections. Other common side effects include neurologic diseases like 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 that prevent the recruitment of the cells that cause inflammation, bringing 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 RA and with various mechanisms of action is a matter of continuous investigation. They are often used in combination with other DMARDs, especially MTX. TNF inhibitors are contraindicated in patients with congestive heart failure of demyelinating diseases. Each biologic medication has a different mode of administration [30–32].

Anakinra (Kineret) is a drug that is injected subcutaneously daily. It works by binding to IL-1, a chemical messenger of inflammation. It can be used in combination with other DMARDs or as a monotherapy, but due its low response rate compared to other biologics, it is not used as frequently [33, 34]. Rituximab (Rituxan) is useful in RA because it depletes the B cells responsible for inflammation and the production of abnormal antibodies. Typically used in the treatment of lymphoma, this drug can be used in cases of RA where TNF inhibitors have failed. In addition, rituximab has shown benefits in treating the complications of RA, such as vasculitis and cryoglobulinemia. It is administered as an intravenous infusion in 2 doses, 2 weeks apart, every 6 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 have not been effectively treated with traditional DMARDs [37].

Tocilizumab (Actemra) is a biologic that works by blocking 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 DMARDs [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 have not been effectively treated with MTX. Tofacitinib is taken orally twice daily, alone or in combination with MTX. It should not be used in combination with traditional biologic medications or other potent immunosuppressants [39, 40].

Surgery

Joint surgery in patients with RA reached a peak in the 1990s. However, a 2010 study showed decreased rates of joint surgery in RA patients 40–59 years of age. In contrast, patients older than 60 years had increased rates of

surgery [41]. Surgery is a last resort for the treatment of RA. 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 restore the function of the joints. A patient needing surgical treatment should be evaluated based on their customized needs because there are many different types 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; it involves intra-articular injection of small radioactive particles, is cost-effective, and can treat multiple joints 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 no longer commonly used due to the availability of more effective options. Another surgical option is 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 decreased range of motion; this 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 arthroplasty is done to alleviate severe forefoot pain. Lastly, a total joint replacement involves removing 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 suggestions in the past, there are no specific foods that patients with RA 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 RA, although they are not as effective as DMARDs. Fish oils and omega-3 fatty acid supplements are beneficial for the short-term symptoms of RA. Cumin has been shown to have anti-inflammatory effects in patients with this disease. Calcium and vitamin D supplementation can be helpful in preventing osteoporosis. Lastly, folic acid can help to prevent the side effects of MTX [49].

Patients with RA also benefit from physical and occupational therapy. It is recommended that they perform exercise regularly to maintain joint mobility and strengthen the muscles around the joints. Movement exercises that are less traumatic for joints but 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, to better understand and reduce RA disease activity. Lastly, with the scientific advancements and enhanced understanding of the molecular mechanisms, newer and better treatment options should become available in the near future [50–55].

Conclusion

RA is a debilitating, chronic, inflammatory disease, capable of causing joint damage as well as long-term disability. Early diagnosis and intervention are 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 implementing the protocols to achieve and assess them. Furthermore, early referral to a specialist can help to ensure better treatment outcomes. With advances in the field of molecular medicine, we have a better understanding of disease mechanisms which can aid 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 as well as decrease the likelihood of disease progression 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 RA. It is foreseen that treatment methods will face tremendous improvements in the management of RA.

Disclosure Statement

The authors declare no conflict of interest.

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