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Rheumatoid Arthritis: A Overview of Current Emergent Thearpies

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Abstract
Rheumatoid arthritis (RA) is a chronic, inflammatory, system- ic 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 arthro-plasty, rheumatoid vasculitis, and Felty syndrome requiringsplenectomy 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.

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I. 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 lig- aments 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, andrheumatoid nodules under the skin. The onset of this dis- ease is usually from the age of 35 to 60 years, with remis-sion 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 fac- tor is not found [2–5]. In the West, the prevalence of RAis 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 metacarpopha- langeal (MP) joints; OA typically affects the distal inter-phalangeal (DIP) joint (Fig. 1). OA is the most commontype of arthritis and is caused by wear and tear rather thanan autoimmune condition. It has no effects on the lungs,

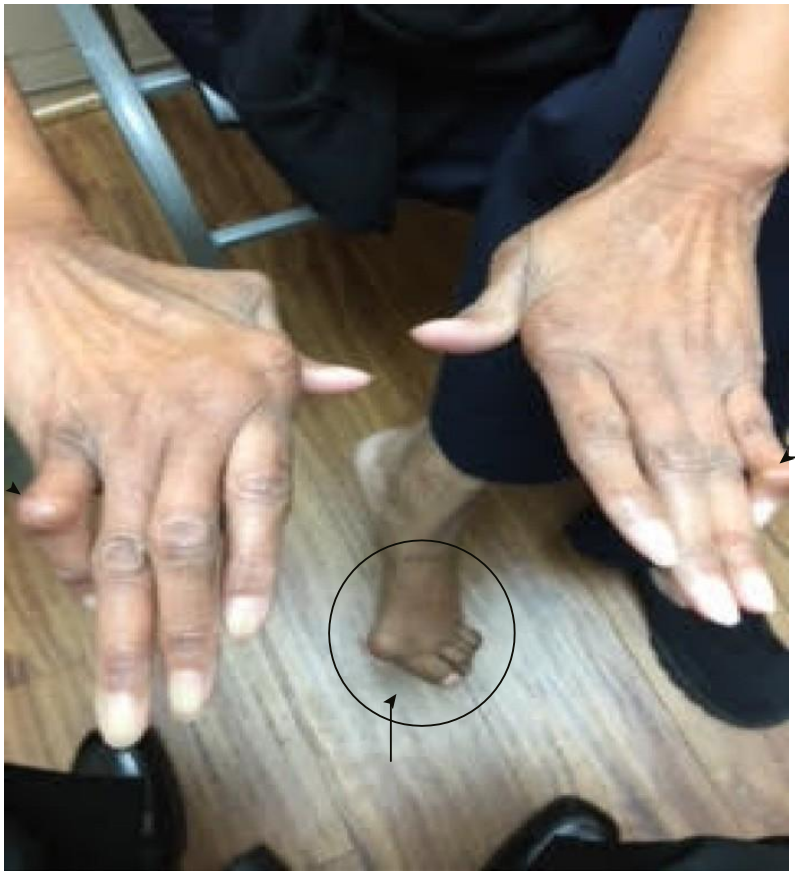

Fig. 1. A classic example of joint deformities associated with rheumatoid arthritis. Boutonniere deformity is visible in the 5th digit of the right hand, Swan neck deformity in the 5th digit of the left hand, and hallux valgus can be seen in the foot.

Heart, or immune system. In addition, OA typically af- fects only one side of the body, as opposed to the sym- metrical 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 in- flammation and pain, maximize joint function, and pre- vent joint destruction and deformity. Treatment regi- mens 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 in- cludes factors such as disease progression, the joints in- volved, age, overall health, occupation, compliance, and education about the disease [10]. This review briefly high- lights the classic and current treatment options available to address the discomfort/complications of RA. An ex- haustive review was recently published by Smolen et al.[11].

1.1 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 pros-taglandins. 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-oxygen- ase to prevent the synthesis of prostaglandins, prostacy- clin, and thromboxanes. Common side effects are nausea, abdominal pain, ulcers, and gastrointestinal (GI) bleed- ing. These symptoms can be reduced if taken with food, antacids, proton pump inhibitors, or misoprostol (Cyto- tec), An even newer NSAID called celecoxib (Celebrex) is a selective Cox-2 inhibitor that has less risk of GI side ef-fects [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 flaresof RA. Intra-articular injections of corticosteroids can beused for the local symptoms of inflammation [13].

They work by preventing the release of phospholipids and de- creasing the actions of eosinophils, thereby decreasing in- flammation. Their side effects include bone-thinning, weight gain, diabetes, and immunosuppression. Advisingthe patient to take calcium and vitamin D supplementa- tion can prevent thinning of the bone. Side effects can bereduced by gradually tapering doses as a patient's condi- tion improves. It is important to not abruptly discontinue injected or oral corticosteroids as this can lead to suppres- sion of the hypothalamic-pituitary-adrenal axis (HPA) orflares of RA [14].

1.2 Opioid Analgesics

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

2. Second-Line Management: Disease-Modifying Antirheumatic Drugs

The overall goal of second-line treatment is to pro- mote remission by slowing or stopping the progression ofjoint destruction and deformity. Medications are consid-ered 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 developinglymphoma 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 dihydrofo-lic acid (FH2) to the enzyme that is responsible for con- verting FH2 to folinic acid (FH4). Without FH4, the me-tabolism of purine and pyrimidine is impaired, and the synthesis of amino acids and polyamine is inhibited.

MTX is an immunosuppressive drug that requires regularblood tests due to its side effects, i.e., liver problems, cir- rhosis, and bone marrow deterioration. Folic acid supple- mentation can reduce the risk of side effects. It is an ef- fective DMARD, has a lower incidence of side effects than other DMARDs, and has dosage flexibility, meaning thatdoses can be adjusted as needed [18]. Until now, there isconvincing data showing the benefits of combinations ofconventional synthetic DMARDs over MTX monothera-py. However, biological and synthetic DMARDs in com-bination 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. Thisdrug decreases the secretion of monocyte-derived proin-flammatory cytokines. Common side effects include prob- lems in the GI tract, skin, and central nervous system. Theeyes, in particular, can be affected when this drug is takenat high doses. Patients on this medication require routineconsultation with an ophthalmologist [20]

3. Newer Medications

Leflunomide is an oral medication that is converted tomalononitrilamide, which inhibits the synthesis of ribo- nucleotide uridine monophosphate pyrimidine. It re- lieves 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 rap- idly 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 com- mon 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 medica- tions such as etanercept (Enbrel), infliximab (Remicade),adalimumab (Humira), golimumab (Simponi), and cer- tolizumab pegol (Cimzia) are all TNF inhibitors that pre- vent the recruitment of the cells that cause inflammation, bringing rapid symptom relief. They are recommended if other second-line medications are not effective. Unfortu- nately, 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 continu- ous 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]

4. Surgery

Joint surgery in patients with RA reached a peak in the1990s. However, a 2010 study showed decreased rates ofjoint surgery in RA patients 40–59 years of age. In con- trast, 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 func- tional decline due to joint destruction after all nonsurgi- cal approaches have failed. At this point, the disease is considered "end-stage." The goal of surgical managementis to relieve pain for the patient and restore the function of the joints. A patient needing surgical treatment shouldbe evaluated based on their customized needs because there are many different types of surgery.

A tenosynovectomy involves the excision of inflamedtendon sheaths or repairing a recent tendon rupture, most commonly in the hand [42]. Radiosynovectomy is an alter-native to surgical synovectomy; it involves intra-articularinjection 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. Exci-sion of an inflamed synovium via arthroscopy or open syn-ovectomy is no longer commonly used due to the availabil-ity of more effective options

A procedure for soft-tis-sue 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 andimprove hand function, most commonly in the metacar- pophalangeal joints. Metatarsal-head excision arthroplasty is done to alleviate severe forefoot pain. Lastly, a total joint replacement involves removing the damaged joint and re-placing 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 contraindicationfor surgical joint replacements is the presence of active sys- temic articular infection.

5. Other Therapies

It has been found that, in contrast to suggestions in thepast, there are no specific foods that patients with RA should avoid. The idea that diet can "aggravate" symp- toms 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. Fishoils and omega-3 fatty acid supplements are beneficial forthe 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 behelpful in preventing osteoporosis. Lastly, folic acid canhelp to prevent the side effects of MTX [49].

Patients with RA also benefit from physical and occu- pational therapy. It is recommended that they perform exercise regularly to maintain joint mobility and strength-en 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 minimizespainful symptoms. Studies are being done on different types of connective tissue collagen, to better understand and reduce RA disease activity. Lastly, with the scientificadvancements and enhanced understanding of the mo- lecular mechanisms, newer and better treatment options should become available in the near future [50–55].

6. Conclusion

RA is a debilitating, chronic, inflammatory disease, ca- pable of causing joint damage as well as long-term dis- ability. Early diagnosis and intervention are essential forthe 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, earlyreferral to a specialist can help to ensure better treatmentoutcomes. With advances in the field of molecular medi- cine, we have a better understanding of disease mecha- nisms which can aid in the designing of more effective treatments. Old treatment modalities have been opti-mized and new ones have been produced.

Gene array analysis is proving beneficial in finding out which pa- tients will be more responsive to specific medications. This customization will allow for more rapid treatment aswell as decrease the likelihood of disease progression dur- ing the experimental phase to seek an appropriate treat- ment for a particular patient. Gene array analysis is also being used to determine which patients are at greater riskfor more aggressive forms of RA. It is foreseen that treat-ment methods will face tremendous improvements in themanagement of RA.

Significance of the Study

Rheumatoid arthritis not only affects the joints but can also affect internal organs, thus causing per-manent 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.

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