Rheumatoid arthritis: A debilitating battle with the human immune system

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ABSTRACT

Rheumatoid arthritis (RA) is an autoimmune disease in which the immune system mistakenly attacks different regions of the body, notably joints in the hands, knees, elbows, and feet. As a result, these regions become inflamed and lead to pain, swelling, and subsequent joint damage. This can affect daily activities, mental well-being, quality of life, and may decrease expected life span. As of today, there is no cure for RA and its etiology remains elusive. RA is classified using the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Criteria and treated according to the Canadian Rheumatology Association (CRA) Guidelines, which mainly focus on pharmacological interventions. Three classes of pharmaceutical agents have been effective in treating RA symptoms - disease modifying antirheumatic drugs (DMARDs), including conventional synthetic and advanced therapeutics (eg biologics, JAK inhibitors), non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. DMARDs, specifically methotrexate, hydroxychloroquine, and sulfasalazine, are usually used early to treat the underlying course of the disease. However, potential adverse drug reactions may cause some patients to discontinue or experience lack of benefit over time. Non-traditional therapy, such as diet modification, physical activity, and mindfulness-based stress reduction activities, may be adjunctive treatment for pain, fatigue, and overall mental health. Nevertheless, finding optimal treatments remains largely empirical and patient-specific. A better understanding of RA progression is needed to accurately treat the underlying disease, while improving symptoms and minimizing adverse effects. An integrated approach that incorporates both pharmacological and nonpharmacological therapies may provide more comprehensive management of RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that results in inflammation and pain, affecting more than 350,000 Canadians (1% of the population) as well as 24.5 million people worldwide.¹ RA symptoms are predominated by inflammation, particularly at joints resulting in progressive joint deterioration, but can also affect other parts of the body, specifically the lungs, eyes, heart, and blood vessels.^{2,3} In RA, most patients have joint pain and stiffness, and the stiffness often worsens following periods of rest. As a result, the chronic pain in addition to joint inflammation and/or damage associated with RA has been shown to affect daily activities, mobility, fatigue, mental well-being, and quality of life.^{3,4}

RA is classified using the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Criteria points system.^{4,5} The Canadian Rheumatology

Association (CRA) Guidelines have focused on pharmacologically-based algorithms for assessing and treating patients with RA depending on level of disease activity, though they are currently being updated.⁶ As of today, there is no known prevention or cure for RA. However, three classes of pharmacological therapies have been shown to be effective in treating the underlying disease: disease modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and corticosteroids.³⁻⁵

DMARDs are the cornerstone of treatment and include traditional (conventional synthetic), biologics, and other small molecules (Janus kinase; JAK inhibitors). Although not specified in the CRA guidelines, there is some evidence that changes to lifestyle such as diet modifications, physical exercise, and mindfulness-based stress reduction may help alleviate some symptoms associated with RA as adjunctive non-pharmacological treatment.⁵ Many individuals with RA experience significant emotional, social, and financial burdens affecting their overall quality of life. Therefore, it is important to identify symptoms when they emerge and start treatment early to slow joint damage and improve pain and fatigue.

The objective of this article is to investigate the mechanisms of action of pharmacological interventions used in managing symptoms associated with RA, while examining evidence of possible lifestyle modifications that could be used in conjunction.

PHARMACOLOGICAL INTERVENTIONS

According to the CRA Guidelines, DMARDs are the primary treatment for RA.⁶ DMARDs target the disease by decreasing joint damage, thereby improving range of motion and decreasing pain associated with inflammation. DMARDs should be started immediately after diagnosis in order to increase the probability of remission.⁷ Commonly used traditional DMARDs include methotrexate, sulfasalazine, and hydroxychloroquine. First-line therapy consists of methotrexate with or without a combination of other DMARDs. Methotrexate is an immunosuppressant that decreases inflammation by blocking production of inflammatory cytokines (eg interleukin-1) via several mechanisms including inhibition of dihydrofolate reductase, an enzyme involved in folic acid metabolism.^{7,8} Although originally devised as a chemotherapeutic agent, methotrexate has been shown to be well-tolerated and generally safe in the treatment of autoimmune diseases. O'Dell and colleagues reported that symptom severity improved and was maintained in 33% of RA patients treated with methotrexate.⁹ Additionally, symptoms improved for 77% of patients treated with triple therapy: a combination of methotrexate, hydroxychloroquine, and sulfasalazine. Triple therapy was more effective than either methotrexate alone or a combination of hydroxychloroquine

and sulfasalazine. Despite their well-established benefits, not all patients respond favourably to these medications and at least 1 in 6 patients using methotrexate discontinue treatment due to side effects including nausea, CNS effects, oral ulcers, hair loss, headaches, cytopenias, and/or transaminitis.¹⁰ Leflunomide is another DMARD that is commonly used in patients failing methotrexate and other combination therapy.¹¹

Second-line therapies include biological agents, also known as biological response modifiers, which are the newest class of drugs given by injection used to treat RA.⁴⁻⁶ Biologics are non-traditional DMARDs that are genetically engineered to mimic natural proteins within the immune system and target specific inflammatory mediators.^{12,13} Not only can biologics help dramatically decrease RA progression, they have been shown to have fewer adverse reactions associated with them compared to DMARDs.¹¹ They are often used concomitantly with other medications, usually methotrexate, for dual therapy. One common class of biologics is tumor necrosis factor- α (TNF α) inhibitors, which inhibit the release of the pro-inflammatory cytokine TNF α by macrophages and lymphocytes.^{11,14} Other biologics target IL-6, T cells, and B cell mediators.^{12,16} Studies show that treatment with TNF α inhibitors significantly improved outcomes in patients with RA, reducing swelling in joints and levels of pro-inflammatory cytokines.¹² This suggests that the use of biologics may be a good alternative for patients who do not respond to or develop adverse reactions to traditional DMARDs. A newer, but costly, class of non-traditional DMARDs recently approved in Canada are JAK inhibitors, oral drugs that inhibit signalling along the JAK-STAT pathway.¹³ They have similar indications to biologics, where the RA disease is active and has not fully responded to traditional DMARDs.

Lastly, NSAIDs and corticosteroids manage RA symptoms by temporarily reducing inflammation. However, these drugs generally do not modify the disease (ie alter joint destruction).^{16,17} Ideally, these drugs are used only as adjunctive treatment and for a short time due to risk of adverse events. However, many patients with RA take NSAIDs and/or oral corticosteroids chronically. Complications with chronic NSAID and steroid use include gastric ulcers, renal impairment, hypertension, osteoporosis, diabetes, and cardiovascular events. NSAIDs inhibit prostaglandin synthesis, another key mediator in inflammation, by blocking cyclooxygenase (COX) enzyme COX-2 as well as some COX-1.¹⁶⁻¹⁸

LIFESTYLE INTERVENTIONS

While pharmacotherapeutics are necessary in the treatment of RA, there is some evidence that symptoms can be improved with lifestyle changes including smoking cessation, physical activity, weight loss in overweight patients, and stress reduction.¹⁹⁻²¹ A balanced diet not only maintains a healthy weight to reduce physical pressure on weight-bearing joints but can also reduce the percentage of fat cells that release pro-inflammatory substances into the body.¹⁹ Diet modifications, such as increasing fish oil, eating a Mediterranean diet, and/or eliminating meat, may mildly reduce the symptoms, most likely by reducing the production of inflammatory mediators and by increasing anti-inflammatory cytokines. In addition, Olaf and colleagues reported that a diet

low in arachidonic acid reduced prostaglandin metabolites and leukotriene B4 (both inflammatory cytokines) by 5% and 25%, respectively.²⁰ Furthermore, supplementation with fish oil (Omega-3) reduced joint tenderness and swelling by 17% and 12%, respectively, by blocking COX enzymes.²¹ Vitamin D has been shown to be inversely associated with RA disease activity, with a stronger correlation with supplemental Vitamin D than dietary. Animal models of RA show that Vitamin D functions in a paracrine manner to reduce cytokine production and T cell responsiveness, thus decreasing the incidence of inappropriate immune responses.²²

Smoking is a risk factor that can increase the risk of RA by promoting the production of reactive oxygen species, which may lead to the generation of autoreactive pro-inflammatory T cells.²³ A positive correlation exists between smoking and gene expression of pro-inflammatory mediators like interleukins, which could exacerbate disease and symptom progression.²⁴ Lastly, moderate alcohol consumption could help prevent or decrease RA symptoms in the early stages; however, it is also a risk for liver toxicity with methotrexate.²⁵ Conversely, some studies have shown that alcohol may exacerbate symptoms.^{24,25}

Physical exercise also improved outcomes in patients with RA. Regular movements of joints (eg walking, stretching) can improve joint stiffness and range of motion by strengthening muscle, improve tone, and reduce overall pain.²⁶ Regular physical exercise can delay the onset of disability by improving flexibility, weight, and independence, which has been correlated with increased overall quality of life.²⁷

Patients training with mindfulness-based stress-reducing activities such as yoga and meditation are better able to cope with RA compared to patients who have not.²⁸⁻³⁰ Stress-reducing practises can decrease pain perception, fatigue, and depressive symptoms while improving overall balance and range of motion.^{28,29} A study conducted by Pradhan and colleagues described a 35% reduction in psychological distress and an increase in overall well-being in patients who completed a 6-month mindfulness-based stress reduction program.²⁸ This suggests that cognitive behavioural therapies could be a beneficial adjunct to pharmacological treatment in patients suffering with RA.³⁰

CONCLUSION

RA is a lifelong disease that can affect individuals of any age.^{2,3} The etiology of RA is not fully understood but both genetic and environmental factors have a role. Patients with RA often suffer from inflammation in multiple areas of the body (eg joints), and damage usually worsens over time.⁴ A variety of pharmacological treatment options exist to help reduce disease progression and manage symptom outcomes. Non-pharmacological treatments, which could be used concomitantly with DMARDs, are also being investigated. These include changes in diet and supplements (eg fish oil and vitamin D), physical exercise, and cognitive behavioural therapy. Incorporation of non-pharmacologic interventions may improve the quality of life associated with RA. Additional studies are needed to determine optimal combinations of pharmacological and non-pharmacological interventions to slow down disease progression while managing symptoms associated with RA.

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