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Short Communication

Rheumatoid Arthritis: General Approach to Early Diagnosis and Novel Treatment Options

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Rheumatoid Arthritis (RA) is a condition that causes inflammation in synovial joints. While patients experience pain, stiffness, and swelling in their hands and feet, it may also manifest as a systemic disease affecting the heart, lungs, and eyes in some patients. It is more common in women than men, and is diagnosed at the peak age around seventy (70) years; however, it may affect individuals of any age. Early diagnosis and treatment should be initiated to reduce the possibility of permanent joint damage which may cause functional impairment, and can affect the quality of life [1]. Medications utilized must be taken consistently to be effective, and are generally continued long term [2]. A potential benefit in using these types of medications early on is the ability to reduce cardiovascular disease associated with advanced RA progression [3].

Diagnosis of RA presently depends on symptom presentation followed by confirmation from inflammatory markers [4].

Current treatment options include the use of DMARDs and other biologics drugs, and glucocorticoids in the management of RA [5, 6]. Mesenchymal stem cells are emerging as a promising alternative to manage RA symptoms [7].
While therapies can reduce the progression of RA, lifestyle changes to exercise, diet, and tobacco use are also significant in RA management [8].

It is important to approach treatment and management protocols for RA in a multi modal sense due to the common recurrence of RA patients seen in the clinical setting. An integrative approach must be used, and this article is meant to reinforce the importance of a general approach to RA patients and discuss some of the more novel treatment options that are arising.

Discussion

RA, an inflammatory disease, has a progressive course that manifests in articular and extra-articular structures [1]. Constant inflammation results in joint erosion and damage with functional impairment, deformity, and increases mortality rates. The presentation and the progression of the disease varies from individual to individual with numerous factors such as genetic background, environmental background, frequency of flare ups, and the presence of diagnostic autoantibodies in serum affecting its course [2]. Surprisingly, patients with RA were observed to have 4 times the risk of non-RA patients to experience CVD events despite treatment with aspirin and NSAIDs that have anti-inflammatory and antiplatelet effects [3]. This suggests that traditional CVD risk factors (diabetes mellitus, body mass index, hypercholesterolemia) were not the sole contributors but potentially systemic inflammation resulting in early atherosclerosis. Early diagnosis of RA is crucial as the initial presentation of RA does not differ from other inflammatory arthritis. Early detection leads to early initiation of treatment, and better therapeutic outcomes, and treating-to-target along with novel therapeutics have all improved the quality of life of those living with RA [4].

Diagnosis:

The current American College of Rheumatology/European League Against Rheumatism classification criteria for RA rates 4 signs and symptoms on a scale in use for diagnosis. These signs and symptoms include joint involvement, serology, acute phase reactants and duration of symptom. A diagnosis of RA is made if the patient scores 6 or more total points. The patient must have at least one or more joints with clinical synovitis that cannot be explained or attributed to any other cause for the synovitis [1].

This criterion is useful to rule out other differentials. The use of this criteria helps identify patients presenting with short duration of symptoms that may benefit from an early start of DMARD therapy. No specific test currently exists for the diagnosis of RA but criteria for diagnosis of RA have been developed to differentiate patients who may progress to RA from those who may not. Early diagnosis of RA is important to slow disease progression, prevent joint damage and erosions and may increase the likelihood of treatment leading to a state of remission for the patient. There are, however, limitations in recognizing and diagnosing early RA. Laboratory and clinical evidence at the early onset of arthritis is not sensitive enough to definitively differentiate and diagnose early RA compared to other inflammatory arthritis. This issue of time can be detrimental to some patients due to the seemingly rapid progression of damage the disease can cause to the joint surface. In the absence of treatment, within the first two years, the inflammation caused by RA will damage articular surfaces and lead to bone erosions [2].

Although no specific laboratory diagnostic test exists for RA, RA can be suspected from a history and physical examination performed in clinic and can later be confirmed by appropriate diagnostic laboratory tests. Symptoms may appear as vague pain with joint swelling or tenderness, redness, morning joint stiffness or arthralgia. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are laboratory tests that can provide information about acute phase response during RA. CRP levels have in fact been shown to be significantly correlated with the severity of the disease (1). It should be repeated that these tests are sensitive but are not quite specific for RA diagnosis and should not be used alone to make the diagnosis. Other laboratory values and tests that are very useful to confirm RA diagnosis and

with high diagnostic specificity for prediction of RA in patients with undifferentiated arthritis (UA) are autoantibodies such as rheumatoid factor (RF) and anticyclic citrullinated peptide (anti-CCP). Anti-CCP antibodies have a greater specificity than RF for diagnosis of RA, while the combination of the presence of anti-CCP and RF increase the diagnosis specificity for RA [3]. The levels of serum anti-CCP, can also predict the progression of UA to RA. These tests along with acute phase reactants such as ESR and CRP are useful in confirming the diagnosis of RA, the severity and progression of the disease, and can be used to evaluate treatment efficacy. A good sign of treatment efficacy has been correlated to acute phase reactants decrease in DAS value [4].

The rise of CRP with RA progression may also contribute to atherothrombosis where the protein activates macrophages to produce procoagulants that formulate atherosclerotic plaques [5]. While CRP cannot be used to diagnose RA directly, the persistent elevation suggests a causative relationship between RA and cardiovascular symptoms and mortality. Alongside the elevation in acute phase reactants, there should also be accelerated atherosclerosis amongst RA patients. With systemic inflammation, there is a greater risk of developing fatty streaks with inflammatory cytokines such as tumor necrosis factor α, interleukin-1, interleukin-2 and adhesion molecules [6]. Greater levels of cytokines and growth factors suggest advanced atherosclerotic lesion formation and higher risk of myocardial infarction and ischemia when paired with elevated ESR and CRP [6].

Imaging has also been useful in confirming RA diagnosis. On radiographs, signs of joint space narrowing, erosions, cartilage loss and subluxations can confirm RA diagnosis.

Treatment Options:

The gold standard treatment option for RA is the use of DMARD therapy. Other drugs such as biologics and steroids may also be used for the treatment and management of RA. In clinical settings, it has been recommended to "treat-to-target" meaning management for RA should involve regular assessment of disease activity, and adjustments of medical therapy if patients are not in remission and until they are in low disease activity [4, 5].

With early initiation, therapy is focused on remission rather than to control the rate of inflammation. Early identification of RA remains important because early initiation of DMARDs is essential for high-risk individuals who are at risk of developing erosive arthritis. Delay in starting DMARDs has shown to negatively affect long-term outcome significantly. Studies show that a better outcome is seen when there is an administration of a steroid in combination with DMARDs or with biological therapies in early RA [5]. Particularly with methotrexate, DMARD treatment suggested a decrease in CVD risk and mortality. However, methotrexate has the possibility of inducing hyperhomocysteinemia that can worsen atherosclerosis so folic acid should be administered concurrently [5]. This trend was similarly seen with TNF blockers along with a reduction of risk with cardiac failure not seen with DMARD administration [5, 6].

This treatment regimen has a higher rate of inducing remission when compared to DMARD monotherapy and should be considered in all patients presenting with RA to produce a low disease activity state. Systemic glucocorticoids are also used and are effective in the treatment of RA for the short-term relief of pain and swelling. As a new treatment, mesenchymal stem cells (MSCs) have been investigated as a potential therapeutic approach for the management of RA. Their ability to differentiate into multiple cell types and immunomodulatory properties make them potentially useful for treating RA [7]. MSCs have anti-inflammatory effects which may help alleviate the symptoms of RA. They may also aid in the possibility of promoting cartilage regeneration and repair. MSCs secrete growth factors and cytokines that can promote tissue repair and protect against damaged joints. There are ongoing clinical trials to investigate the safety and efficacy of MSC-based therapies for RA. Lifestyle modifications should also be considered as stress has been linked to RA flares. Individuals with RA should focus on living a healthy lifestyle which includes getting good quality sleep, being active (low impact activities) and avoiding tobacco use in conjunction with maintaining medication compliance [8].

Both smoking and obesity have been linked to increased disease activity and joint damage.

Conclusion:

In conclusion, early diagnosis and treatment of RA is pivotal for increasing long term outcome. Early DMARDs combination therapy has been proven very effective in producing remission states and limiting progression of RA bone damage. Currently, much research has been centralized on RF, ESR, and CRP markers and hopefully inflammatory cytokines and concurrent cardiovascular symptoms can also be monitored as used for future screening. Decreasing disease activity and maintaining a low activity state is the treatment goal for RA. Besides the effective DMARDs combination therapy, we anticipate further results from TNF blockers treatment as a possible alternative or even forerunner in reducing cardiovascular mortality associated with RA. Mesenchymal stem cells research is encouraging with its anti-inflammatory and regenerative properties. Notably MSCs have a restorative effect on joints which may differentiate this therapy from other blockers. It is important to note that although use of MSCs show promise, further research is needed to determine optimal protocols, long-term effects and risks associated with their use in RA management. Lifestyle changes have also shown effectiveness with RA progression and alterations to diet, exercise and tobacco use should be addressed with patients in conjunction with steroid and biologic administration. Given that RA does not have a definitive diagnostic test, this paper reiterates the significance of following the known step by step diagnosis and treatment plan for the best patient outcome.

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