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Review article

Management of Rheumatoid arthritis

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ABSTRACT

Rheumatoid arthritis (RA) can be defined as an autoimmune inflammatory disease which is represented in about1% of the world population and occurs in the middle age with increasing frequency in older population. RA has several types which can be caused by joint inflammation,bone or joint damage. Scientists were unable to determine the causes of such inflammation until few years ago when some evidences or clues were unveiled that involved mainly genetics and environmental factors. Although there is no known complete cure of RA, treatment aim to achieve several goals which are pain relief, slow joint degeneration and improve patient well-being. To achieve that, several approaches could be applied including lifestyle, medication, routine monitoring and surgery.

keywords: RA, DMARDs, methotrexate, NSAIDs, corticosteroids.

INTRODUCTION

Rheumatoid arthritis (RA) is a common autoimmune disease. It is mainly characterized by persistent joint inflammation that results in loss of joint function.[1].

RA is a systemic disease, associated with progressive joint destruction and deformity. Depending on the severity, there may also be extra-articular manifestations including blood vessels, skin, and internal organs. If untreated appropriately, RA leads to a significant impairment of the quality of life [2].

The definite reason of RA is unknown. Moreover, there are some factors participating in the development of the disease. Infections are thought to be a causative agent of RA.There is an evidence relate Epstein–Barr virus and the incidence of RA. Rheumatoid factor, which exists usually in RA, is associated with higher morbidity rate, and obviously can be considered an amplifier of rheumatoid inflammation. Consequently, this finding support the autoimmunity theory of RA pathophysiology [3]. Its clinical diagnosis made on the basis of medical history, symptoms, physical exam, radiographs (X-rays) and laboratory tests [4].

Treatment strategy for rheumatoid arthritis

There is no cure for RA, but treatment can improve symptoms and slow the progress of the disease. Disease-modifying anti-rheumatic drugs (DMARDs) considered the mainstay of RA therapy. When DMARDs are started early, they give suitable results in many cases. The goals of treatment are to decrease incidence of symptoms such as pain and swelling, to avoid bone deformation and to maintain day-to-day activities [5].

RA should generally be treated with at least one specific anti-rheumatic medication [6].The use of

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benzodiazepines to treat the pain is not recommended as it does not aid the patients and is associated with several side effects [7]. Analgesics, other than NSAIDs, offer lesser benefit regarding to pain, while not producing similar gastrointestinal irritation [8].

Management approaches in RA

Lifestyle

Regular exercise is prompted as both safe and efficient to maintain muscles strength and overall physical function. Based on the evidence, aerobic capacity training combined with muscle strength training is recommended as routine practice in patients with RA.[9].

Drugs

DMARDs

DMARDs are the primary treatment for RA. They are a collection of drugs. They have been found to ameliorate symptoms, reduce joint damage, and improve overall functional abilities. Physicians should prescribe them in the earlier stages of disease as they result in disease remission in approximately half of people.

The most commonly used agent is methotrexate with other frequently used agents including sulfasalazine and leflunomide. Other agents like cyclosporin and sodium aurothiomalate (Gold)are less commonly used due to their adverse effects. Agents may be used in combinations in case of single medication does not show adequate response [8].

Methotrexate is the most important and useful DMARD and is usually the first option unless contraindicated or not tolerated. It was among the first agents for its protective effect on joints[10]. Adverse effects including hematological, gastrointestinal,and hepatic toxicity. Side effects such as nausea, vomiting or abdominal pain can be reduced by taking folic acid. The most common undesirable effect is that it increases liver enzymes in some patients. It is not recommended for those who consistently demonstrate abnormal levels of liver enzymes or have a history of liver disease [11]. Different clinical trials established the efficacy of sulfasalazine for relieving symptoms and for slowing radiological damage. This drug is considered a suitable alternative to methotrexate in certain patients, particularly those who have contraindications to the latter, and can be combined with methotrexate or an antimalarial agent, or both, for additional efficacy [12][13]. leflunomide owns many of the same possible adverse effects as methotrexate and can also cause or aggravate hypertension. The use of leflunomide has been mainly as a substitute to methotrexate, but one controlled study has also supported the use of the combination of both drugs [14].

DMARDs pharmacology and adverse effects are summarized in table 1 [12].

Table 1. Current arsenal of DMARDs

Adverse effects	Mechanism of action	Drugs
Hepatotoxicity, myelotoxicity, fibrosing alveolitis	Antimetabolite	Methotrexate
Hepatotoxicity, myelotoxicity, hypersensitivity reactions	Anti-inflammatory and antimicrobial	Sulfasalazine
Retinopathy	Interference with antigen-processing	Antimalarial drugs
Hepatotoxicity, myelotoxicity, hypertension	Antimetabolite	Leflunomide
Hypersensitivity reactions, nephritis, fibrosing alveolitis	Unknown	Gold salts (parenteral)
Nephrotoxicity, hypertension	Tcell activation inhibitor	Ciclosporin A
Hepatotoxicity, myelotoxicity, gastrointestinal	Cytostatic	Azathioprine

Biological agents

Biological agents should generally only be used if methotrexate and other conventional agents are not effective after a trial of three months.These agents include: 1- tumor necrosis factor alpha (TNFα) blockers such as infliximab which considered the first biological agent approved by food and drug administration (FDA). Etanercept and adalimumab are two examples of this class. This group believed to play an important role in the treatment as TNF-α is a key cytokine in the inflammatory process in RA. 2- monoclonal antibodies against B cells such as rituximab. This biological agent can be used to treat diseases which are characterized by having too many or overactive B cells, overactive B cells such as lymphoma, leukemia and RA. 3- T cell co-stimulation blocker such as abatacept 4-interleukin-1 blockers such as anakinra which used as monotherapeutic agent or in combination with DMARDs. Anakinra should not be used in combination with anti-TNF agents. TNF blockers and methotrexate appear to have similar effectiveness when used alone and better results are obtained when used together.

All biologic agents carry an increased risk of infections. RA patients using these medications who suffering from elevated temperature should be examined by a physician to determine the source of the fever, and the administration of the appropriate antibiotic if needed [12][15]. Some biologics are summarized in table 2 [12]

Table 2. Selected biologic agents in the today market.

Side effects	Mode of action	Drugs
Infusional reactions, infections	Tcell co-stimulation blocker	Abatacept
Injection site reactions, infections, neutropenia	IL1 receptor blockade	Anakinra
Injection site reactions, infections (including tuberculosis)	TNF blockade	Etanercept
Infusional reactions, infections (including tuberculosis)	TNF blockade	Infliximab
Infusional reactions, infections	Bcell depletion	Rituximab
Infusional reactions, infections, cytopenias, elevated cholesterol	IL6receptor blockade	Tocilizumab

Abbreviations: IL, interleukin; TNF, tumor necrosis factor.

Anti-inflammatory agents and NSAIDs

Anti-inflammatory drugs and NSAIDs decrease pain and stiffness in those with RA. They do not have significant effect on people's long term disease course. NSAIDs should be used with caution in those with gastrointestinal, cardiovascular, or kidney problems [8] [16]. NSAIDs help control the inflammation, chronic pain and swelling accompanied to RA.

Cyclooxygenase-2 enzyme inhibitors (COX-2 inhibitors); for example: celecoxib, and NSAIDs are equally effective. There is less gastrointestinal effects to celecoxib compared with diclofenac and ibuprofen. Moreover, there is an increased risk of myocardial infarction with COX-2 inhibitors [17]. Anti-ulcer medications are not recommended routinely but only in those high risk of gastrointestinal distress[18].

Glucocorticoids can be used in the short term for flare-ups, while waiting for slow-onset drugs to take effect. Earlier in 1980s, a group of scientists suggested that low-dose, long-term glucocorticoids

might lower the development of radiological damage. On the other side, long-term use reduces joint damage. It also results in osteoporosis and reduced immunity [8][19].

Surgery

Surgery In early phases of the disease may be performed. Surgical intervention consists of the removal of the inflamed synovia and avoids the rapid destruction of the inflamed joints. Severely affected joints may need joint replacement surgery, such as knee replacement [8].

Prognosis

RA is a chronic autoimmune disease, which has serious complications. There are a high number of anti-rheumatic agents; however, there is no complete cure for this serious disease till now.

Increase in mortality is associated with patients suffering from RA. Due to this unmet need in the management of this serious disease, a lot of research organizations have invested in the non-clinical and clinical trials to develop additional treatments with satisfied response.

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