Drug Treatment in Rheumatoid Arthritis

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Abstract— **Introduction: Rheumatoid arthritis is the most common inflammatory autoimmune rheumatic disease that without proper treatment can cause permanent lesions and deformities of the joints resulting in long-term functional disability or disability.**

Purpose: In this review study is provided the pharmaceutical treatment of rheumatoid arthritis in order to promote the quality of life of these patients.

Material & Methods: The material of the study was a recent article on the topic found mainly in the Medline database and the Hellenic Academic Libraries Association (HEAL-Link).

Results: Early diagnosis of the disease, as well as early onset of treatment, helps significantly in the successful management of the disease. Conventional treatment for rheumatoid arthritis includes non-steroidal anti-inflammatory anti-rheumatic drugs or other disease-modifying drugs such as methotrexate and corticosteroids. The goal of medication is to reduce pain and inflammation, minimize loss of function, and prevent complications and joint damage.

Conclusions: The goal of pharmaceutical therapy is the recession of inflammation. Treatment planning is also different for each patient; both because the disease is not as severe in everyone as the needs of each patient are different.

Index Terms— **medicines, treatment, treatment of rheumatoid arthritis, pharmaceutical treatment**

I. INTRODUCTION

Rheumatoid Arthritis is a systemic inflammatory autoimmune disease of unknown etiology. It results in inflammation of the joints, and it is manifested by swelling, pain, reduced function of joints and muscle weakness. Also, it is associated with an increased risk for cardiovascular disease and osteoporosis. [1, 2] It is well known that when the cardiovascular system alters, many serious complications and diseases appear [3].

Rheumatoid Arthritis obviously affects people at 30-50 years old. Women are affected 2-3 times more often than men. Aside from this, it is highlighted that 24 million people in the world suffer from rheumatoid arthritis. In Europe, over 6,2 million people suffer from rheumatoid arthritis. It is estimated that there are 70.000 - 100.000 adults suffering from rheumatoid arthritis in Greece. [4]

Rheumatoid Arthritis may begin with mild symptoms, so patients do not realize that these symptoms are due to arthritis. Thus, patients rarely consult medical specialists when they are in the initial stage. In addition, the lack of methods for monitoring early cases of rheumatoid arthritis and the incompetence of patients' prognosis regarding the patients who will potentially manifest the progressive form of the disease play an important role. [5]

Rheumatoid arthritis is the most common disease that is a potentially treatable cause of disability. Disability may be a consequence of deformations or developmental failures or the result of functional damages or traumatic effect of the posture or motion systems. [6] The treatment is aimed at relieving symptoms like pain and stiffness; retaining functions, preventing damage of joints, deformities and disability, but also aiming at the patients' maintenance of leading a common way of life. The therapeutic approach of the disease may be conservative, pharmaceutical and surgical. [7]

Moreover, early therapeutic intervention is vital, whilst the early manifestation of the disease will have a significant impact on long-term disability and the social and economic cost of the disease. However, there are two factors that are essential prerequisites for the success of therapeutic goals. Firstly, it is the early diagnosis provided by the early visit of patients to a medical specialist's surgery in order that the specialist will be able to intervene early combining drugs used as the modifiers of disease. [4]

II. PURPOSE

The pharmaceutical treatment of rheumatoid arthritis is provided in this review study, targeting the promotion of the quality of life for these patients.

III. REVIEW METHODS

The material of the study consists of recent articles on the subject that have been found mainly in the electronic database Medline and the link of Hellenic academic libraries Link (HEAL-Link), with the following keywords: drugs, treatment, therapy of rheumatoid arthritis, pharmaceutical treatment. The language except for Greek and English was a criterion for exclusion of articles.

IV. DRUG TREATMENT IN RHEUMATOID ARTHRITIS

The early diagnosis of the disease as well as the early onset of therapy helps significantly the successful management of the disease. The conventional treatment for rheumatoid arthritis includes Nonsteroidal Anti-Inflammatory drugs (NSAIDs), antirheumatic drugs or disease-modifying drugs such as methotrexate and corticosteroids. The aim of medication is to reduce pain and inflammation, minimize the loss of functions of the joints and the prevention of complications and joint destruction. [8]

Three approaches are mainly followed throughout the pharmaceutical treatment of patients with rheumatoid arthritis [9]:

- The first approach is to reduce the symptoms, with the administration of aspirin and other non-steroidal anti-inflammatory and mild analgesics so as to reduce the

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inflammatory process and deal with the symptoms of the disease. Although these drugs are effective against the clinical manifestations of rheumatoid arthritis, they do not seem to affect the progress of the disease.

- The second approach comprises of the administration of low-dose corticosteroids in order to reduce pain and inflammation. The oral administration of corticosteroids in low doses may slow down the development and progression of bone erosions associated with rheumatoid arthritis. [8]
- Some certain drugs called disease-modifying anti-rheumatic or slow acting drugs (DMARDs) are administered in the third approach. These drugs, such as gold salts, D-penicillamine, sulfasalazine and other ones seem to modify the course of the disease by limiting the articular destruction.

Treatment usually begins with anti-inflammatory drugs and painkillers for six months, with frequent monitoring of blood tests. Aspirin is considered the drug of choice. Aspirin is often the first drug used for the treatment of rheumatoid arthritis. [2] It is a cheap and effective anti-inflammatory analgesic drug. The dose required to reach therapeutic levels in the blood and unleashing the high anti-inflammatory action is approximately 4gr daily in divided doses. [10]

The following notes are highlighted regarding medicinal preparations [11, 12]:

- Non-steroidal anti-inflammatory drugs (NSAIDs) remain the cornerstone of drug therapy in rheumatoid arthritis for the 70% of patients. Their action lies in the inhibition of the synthesis of prostaglandins. [11] They usually have a rapid onset. However, their action is limited while they do not prevent the progression of the disease and deformity of joints. [12]
- Therefore, disease-modifying antirheumatic drugs (known as DMARDs) contribute significantly to the modification and suspension of the disease. They are widely used and administered in the early stages of the disease to prevent its proliferation. [13] These drugs, such as gold salts, sulfasalazine, D-penicillamine, etc. have many beneficial effects. Their benefits are not only limited to relieve symptoms, but they also slow the course of the disease. Their anti-inflammatory effect is limited, and as a result, they are administered parallel with the NSAIDs. [14]

In particular [15-18]:

- Gold salts can be orally administered, but they are usually administered intramuscularly because of their greater efficiency. These drugs may achieve clinical regression of the disease and limit the emergence of new bone erosions in some patients. The weekly administration of gold salts continues until significant improvement is observed or side effects occur.
- The sulfasalazine inhibits free radical production O2, the proliferation of endothelial cells and cytokine production.
- Cyclosporine has a direct effect on lymphocytes and inhibits the production of Interferon-gamma (IFN-gamma) and Interleukin-2 (IL-2)
- The D-penicillamine is an effective drug for the treatment of rheumatoid arthritis and displays the same indications with salts of gold but it has an advantage over the fact that it is taken orally.
- Hydroxychloroquine stabilizes the lysosomes and inhibits the production of free radicals O2 as well as the actions of b lymphocytes.
- Methotrexate is the most effective drug and a disease modifier administered for more than 5 years to about 70% of patients. Its administration on a weekly basis can lead to the desirable result even after 2 to 4 weeks. It affects the chemotaxis and inhibits the production of immunoglobulins and Cytokines, particularly of IL-1. [19]

Finally, biological factors are a newer type of medication. They aim to bring quick relief from inflammation and reduce pain and swelling in the joints. In addition, the destruction of the joints is slowed down significantly. [20]

Biological factors are major inhibitors of tumor necrosis factor alpha which is considered to contribute to the stimulation of inflammation. They are usually administered when the patient has tried other treatments that have proven to be ineffective. They can be used as an early stage treatment. [21]

V. RHEUMATOID ARTHRITIS MEDICATION SIDE EFFECTS

The active daily 4gr dose of aspirin is slightly less than the toxic dose causing tinnitus and hearing loss. The most common side effects of taking aspirins involve the gastrointestinal and the platelet function disorder. [11] Nevertheless, there are enteric-coated forms of aspirin, as well as non-acetylated salicylates that cause less gastrointestinal disorders, while reducing the risk of gastric ulcers. However, they are more expensive. All salicylates are contraindicated in patients with a history of allergy to aspirin. [22]

As regards the nonsteroidal anti-inflammatory drugs (NSAIDS), they restrict, but they do not eliminate completely the signs and symptoms of inflammation, as there is a risk of their comeback. In addition, there are considerable variations regarding the response of different patients as well as their preference for NSAIDs. [14] They are usually administered in combination with modifiers. The most common side effects involve erosive gastritis of the gastric mucosa, creation of gastric ulcer and duodenum ulcer, gastrointestinal bleeding and gastrointestinal perforation. It is estimated that 15-30% of patients receiving NSAIDs on long-term basis, they will experience stomach or duodenal ulcer. [12]

However, there are other rare side effects observed, regarding to [23]:

- the central nervous system: headache, dizziness or confusion
- the cardiovascular system: edema, hypertension, heart failure.
- respiratory system: asthma, pneumonia
- the hematopoietic system: thrombocytopenia, aplastic anemia, hemolytic anemia
- kidney: acute renal failure, hematuria, nephrotic syndrome
- hypersensitivity reactions.

Corticosteroids or glucocorticoids also have the potential to substantially reduce the inflammation in human organism and significantly improve the symptoms of the disease. They are effective for short periods of time. Over the course of time,

their effectiveness is reduced. [24] Long-term use can lead to side effects such as skin thinning, weight gain, risk of developing osteoporosis, high blood pressure and increased blood glucose (hyperglycemia) with a likelihood of developing diabetes. [6] There is also the risk of resurgence of the disease in case of abrupt interruption. Corticosteroids can be used as injectable and intra-articular injection in the joint suffering. Regarding short-term administrations, these injections relieve, but in the long term, they increase joint destruction. [25]

The disease-modifying drugs (known as DMARDs) have some degree of toxicity, and for this reason, it is essential the patient be monitored during his treatment. [13]

In particular [26]:

- About 30% of patients treated with gold present side effects, such as dermatitis, stomatitis, bone marrow suppression. Gold salts exhibit multiple actions in phagocytes, inhibit the actions of T and B lymphocytes, cytokine production and proliferation of endothelial cells and fibroblasts. [18]
- Using ciclosporin, the patient is not only at risk of burdening renal function but also of developing hypertension.
- The D-penicillamine may cause serious adverse effects such as gastrointestinal disorders, bone marrow suppression and nephrotic syndrome. [25]
- Although hydroxychloroquine has no particular toxicity, it may cause retinopathy, and even vision loss. That's why patients should undergo eye tests at regular intervals.
- Cyclophosphamide and azathioprine increases the risk of cancer. Cyclophosphamide can cause bleeding from the bladder (hematuria). [25]
- Methotrexate also causes side effects. The most frequent ones are gastric irritation and stomatitis. [19]
- Finally, with regard to biological agents, the most common side effects that may occur include hypersensitivity reactions. [21]

VI. CORTICOSTEROIDS AND RHEUMATOID ARTHRITIS

The use of cortisone in the treatment of rheumatoid arthritis, has experienced periods of glory but also decline. First and foremost, it was isolated for the first time by Tadeus Reichstein and his colleagues Edward Calvin Kendall and Philip Showalter Hench in1937. They found out its therapeutic value in the treatment of rheumatoid arthritis. It should be noted that for their discovery they were awarded the Nobel Prize in Physiology and medicine in 1950. [27, 28]

Cortisone was first used in the treatment of rheumatoid arthritis in 1948 with spectacular results. Bad news came most quickly for it was administered in large doses. These were the frequent and dose-related side effects of cortisone and loss of therapeutic effect by reducing the dosage. [29]

Thus, the period of decline began and the use of cortisone had been limited to the flare ups of rheumatoid arthritis or intra-articular injections, when 1-2 joints do not correspond the applicable therapeutic program. [30]

According to study results conducted during the last few years, the administration of cortisone in low doses in combination with other modifier drugs causes fewer side effects and contributes significantly to the prevention of rheumatoid arthritis lesions. [27] Nowadays, cortisone is administered frequently in patients with rheumatoid arthritis as "bridge therapy" in low dose (prednisolone 7.5 mg or less per day). In other words, it is administered during the period of waiting for the therapeutic effects of modifier drugs, which usually occur after about 2 months. [31]

Therefore, cortisone can be regarded as a modifier of the disease drug and can, when necessary, be administered in combination with one of the other synthetic disease-modifying drugs or, when appropriate, and with one of the organic disease-modifying medications for treating both early (duration of the disease up to six months) and established rheumatoid arthritis. [25]

Long-term use of cortisone often leads to side effects that relate mostly to gastrointestinal disorders and loss of bone mass. As a result, patients are turning more and more to modern alternative therapies and dietary supplements. [32]

VII. CONCLUSIONS

Rheumatoid arthritis is the most common inflammatory autoimmune rheumatic disease that without proper treatment can cause permanent damage and deformities of the joints resulting in long-term functional incapacity or disability. [1]

The focal point in its treatment is the aggressive treatment as soon as the disease is diagnosed because the intensive and aggressive treatment from the beginning of the disease prevents or greatly reduces erosion and consequently, the destruction of the joint. The objective of the pharmaceutical treatment is the remission of inflammation. Planning of the treatment is different for each patient, both because the disease is not so serious at all and because each patient's needs are different. [4]

The encouraging message, is that nowadays, thanks to modern therapeutic possibilities and conditions of early diagnosis and early therapeutic intervention can achieve remission; in short, stopping the disease.

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