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Efficacy of two Versus three Drug Regimen in Induction of Remission in Early Active Rheumatoid Arthritis: A Comparative Study

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Abstract

Introduction: Rheumatoid arthritis is the most common inflammatory disease of the joints with an incidence of about 4-13 in 100,000 males and 23-36 in 100,000 females. It is recommended that the drug treatment should start within short period of 6 weeks to arrest progression of disease, joint erosion and deformation. Aggressive treatment in the initial stage of the disease with DMARDS reduces the disease progression. The responses of patients with rheumatoid arthritis to treatment with a single so-called disease-modifying drug, such as methotrexate, are often suboptimal. Despite limited data, many patients are treated with combinations of these drugs. *Objective:* The aim of the study was to compare the efficacy of hydroxychloroquine, methotrexate and combination of hydroxychloroquine, methotrexate and sulfasalazine in induction of remission in early rheumatoid arthritis. *Methodolgy:* The present study included 50 randomly selected cases of rheumatoid arthritis, who presented at PES Hospital, during July 2014 to July 2016 fulfilling the inclusion and exclusion criteria. Following collection of data in a pretested proforma, which included brief history, physical examination and ACR criteria, the patients were divided randomly into two groups. The first group, Group A, was treated with once a week oral methotrexate 7.5 mg and twice daily oral Hydroxychloroquine. The second group, Group B, was treated with once a week oral methotrexate 7.5 mg and twice daily oral Hydroxychloroquine 200 mg and salfasalazine 500 mg twice daily. Patients in both the groups received additional oral folic acid 5 mg thrice daily once a week. Patients in both the study group received oral sustained release aceclofenac and paracetamol twice daily for the first 10 days. All the patients were followed up in the out-patient department of the hospital at 4 weeks interval for 12 weeks and evaluated by the ACR criteria for remission and improvement in symptoms. Blood investigations like haemoglobin level, RA factor, ESR, and liver enzyme levels were done before initiating treatment for all patients. All patients underwent haemoglobin level, ESR, and liver enzyme levels at every follow-up visit. *Results:* At the end of three months group A which was treated with two drug regimen had remission in 32% and group B patients treated with three drug regimen had 52% remission rate according ACR criteria for remission. Remission was more in seronegative arthritis than seropositive. *Conclusion*: Remission was induced in higher number of patients on combination therapy with methotrexate, hydroxychloroquine and sulfasalazine when compared to patients on treatment with methotrexate and hydroxychloroquine.

Keywords: RA factor; methotrexate; Rheumatoid arthritis; Hydroxychloroquine.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory disease affecting articular and extra articular structures with significant morbidity and mortality rates if left untreated [1,2]. Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients [2,3]. Identification of RA at initial presentation and treatment at earlier stage can affect disease course, prevent the development of joint erosions or retard

progression of erosive disease [4,5]. Early diagnosis and treatment may affect disease outcomes even to a remission state [6,7]. Mainstay of treatment is pharmacotherapy [8]. The commonly used drugs are analgesics, non-steroidal anti-inflammatory (NSAIDS), glucocorticoids, biologic and disease-modifying antirheumatic drugs (DMARDS). Combinations of these therapies are tried and found to be more effective.

There are many studies comparing efficacy of monotherapy with methotrexate and combination therapy of DMARDS. Many studies showed combination therapy gives better results. Whereasonly few studies are foundcomparing efficacy of two drugs regimen and three drugs regimen. In our study we compared the efficacy of 2 drug regimen and 3 drug regimen in induction of remission in early rheumatoid arthritis.

Methodology

The present study is aprospective randomised study which included 50 cases of rheumatoid arthritis, who presented at PES hospital, during july 2014 to july 2016 fulfilling the inclusion and exclusion criteria. Clinically diagnosed and patients whose age is above 18 years, fulfilling the criteria of american rheumatology association 2010 guidelines were included in study [9]. Patients who are already on DMARD drugs, patients using DMARD drugs with side effects, patients with elevated liver enzymes, patients who are having deformities with rheumatoid arthritis were excluded from study.

Following collection of data, which included brief history, physical examination and ACR criteria, laboratory investigations, the patients were divided randomly into two groups. Randomisation was done by choosing every alternate patient for same treatment. The first group, group A was treated with once a week oral methotrexate 7.5 mg and twice daily oral hydroxychloroquine 200 mg. The second group, group B, was treated with once a week oral methotrexate 7.5 mg and twice daily oral hydroxychloroquine 200 mg and salfasalazine 500 mg twice daily. Patients in both the groups received additional oral folic acid 5 mg daily. Both groups were given oral paracetamol for pain relief until good response to DMARDs wasachieved (around 10 days) [10]. Group A received a placebo oral drug to avoid bias.

All the patients were followed up in the out-patient department of the hospital at 4 weeks interval for 12 weeks and evaluated by the ACR criteria [8] for remission and improvement in symptoms. Blood investigations hb%, RA factor, ESR and liver enzyme levels were done before initiating treatment for all patients. All patients underwent hb%, ESR, and liver enzyme levels at every follow-up visit.

Statistical methods applied: Statistical analysis was done using spss software (version 16.0).

Reuslts

Our study included 12 (24%) males and 38 (76%) females. The age of onset was between 41-55 years in 44% of the patients. Mean age of the patients was 46.71. RA factor was positive in 42 (84%) of the cases. All the patients in both groups had morning stiffness for more than one hour. At the follow up period of three months in group A eight patients (32%) had morning stifness where as in group B only six patients (48%) had morning stiffness and the duration of mornig stiffness reduced to less than 15 munites.

Fourty eight patients (98%) in both group A and group B had swollen joints at the start of the study. At the time of last follow-up (three months) 14 patients (56%) in group B and 12 patients (48%) in the group A had relieved of swollen joints.

At the start of the study all patients (100%) in both Group II and Group I had tender joints. At the time of last follow-up 11 patients (44%) in the Group II and 8 patients (32%) in the Group I are relieved of tender joints.

At the start of the study 18(72%) patients in the group A had an ESR level of >50 mm at the end of one hour. At the end of third month follow-up eight patients (32%) had a normal esr. At the start of the study 76% of the patients in the group B had an esr level of >50 mm at the end of one hour. At the end of third month follow-up 9 patients (36%) had a normal esr. More number of patients on the three drug had reduction in esr levels to normal when compared to the patients on double drug.

Liver enzymes of all the patients remained in the normal range through out the study period. All patients had normal range of haemoglobin at end of follow up.

Remission-

At the end of three months, remission was induced in 8 patients (32%) in the group B and 13 patients (56%) in the group A according to the ACR criteria for remission [10].

Discussion

Rheumatoid arthritis (RA) is an systemic inflammatory progressive disease which mainly involves joints and in the absence of appropriate treatment can lead to joint destruction, disability and mortality. The distribution of joints affected (synovial joints) is characteristic. It typically affects the small joints of the hands and the feet, and usually both sides equally in a symmetrical distribution, though any synovial joint can be affected. In patients with established and aggressive disease, manyjoints will be affected over time.

Persistent inflammation leads to erosive joint damage and function impairment in the vast majority of patients [2,3]. Risk factors for the development of RA include smoking, obesity, concurrent infections, advancing age, female gender, and genetic inheritance, while oral contraceptives and some dietary constituents may be protective. The onset and progression of disease depends on number of variables like genetic background, frequency, level of autoantibody in blood, severity of inflammatory process [6,7]. It is now considered as a malignant disease and with increase mortality and morbidity and poor prognosis. Life expectancy decreases by 3-10 years according to severity and age of onset of disease. It is debilitating disease and limits the patient daily activities [11]. Rheumatoid arthritis usually affects individuals in their 4^{th} and 5^{th} decade [12,13], in our study the mean age of incidence was 46 years.

Rheumatoid arthritis is more prevalent in females than compared to males. As per available literature, in western population one male patient is affected for every three female patients [14] where as in Indian population male to female ratio is 1:9 [15]. In our study male to female ratio of was 1:3, which is similar to western population. We feel there is no difference in sex ratio affected by rheumatoid arthritis in Indian and western population. However there is lack of study conducted on larger population in Indian region to support our view.

Usually blood markers like RA factor, ESR, CRP are used in diagnosis of rheumatoid arthritis (ACR criteria 2010 guidelines) [9]. Same blood markers are used in follow up visit for evaluating prognosis and remission. Higher RA factor suggest poor prognosis. RA factor is even used as a prognostic factor, where higher titrescarry a poor prognosis [16]. RA factor was foundto be positive in 70%-80% of patients of rheumatoid arthritis in a study conducted in the west [13]. In our study, RA factor is found positive in 84% of patients. Higher remission was found in patients with seronegative rheumatoid arthritis in our study.

Early diagnosis and early aggressive treatment can affect disease course, prevent joint destruction, retard joint erosions [17,18]. The longer active disease persists, the less likely the patient is to respond to therapy [19]. Achieving early remission and retarding disease progression have become foremost goal of many treatment strategies. Treatment modalities include both pharmacological and non pharmacological methods. Pharmacotherapy is the main stay of treatment of rheumatoid arthritis [8]. Many nonpharmacologic treatment options are available for this disease, including exercise, diet, massage, counseling, stress reduction, physical therapy, and surgery. Many classes of drugs are available like NSAIDS, DMARDS, steroids, biologics.

Over the past two decades, treatment of rheumatoid arthritis has been revolutinalized due to better understanding of pathology behind rheumatoid arthritis and developing drugs which target them. Various treatment protocols have been put forward by many studies which included monotherapy, combination of two or more drugs. Methotrexate was initially used as monotherapy for treatment of rheumatoid arthritis. In 2010, cochrane systemic review done by Katchamart W et al. emphasized lack of evidence of a statistically significant advantage for initial combination therapy using MTX and other conventional DMARDs over monotherapy with MTX [20]. In a study done by Davis JM et al., suggested that initial treatment for rheumatoid arthritis is a combination of methotrexate and prednisolone for three months and step up to combination therapy with non biologic DMARDS if no improvement in symptoms is found [21]. In a study by o dell JR et al. remission rate was found to be 77% in patients who received combination of methotrexate, hydroxychloroquine and sulfasalazine at the end of nine months.

We compared two drugs to three drug regimen. We found higher remission rate patients (52%) treated with three drug regimen when compared to patients (32%) treated with two drug regimen at the end of three months. There was no significant side effect of drugs at follow up visit. Hence we recommend three drug combinations over two drugs for treatment and early remission of rheumatoid arthritis.

Conclusion

We recommend early and aggressive treatment with combination therapy to induce early remission and halt the disease progression in rheumatoid arthritis. We recommend three drug combinations over two drugs.

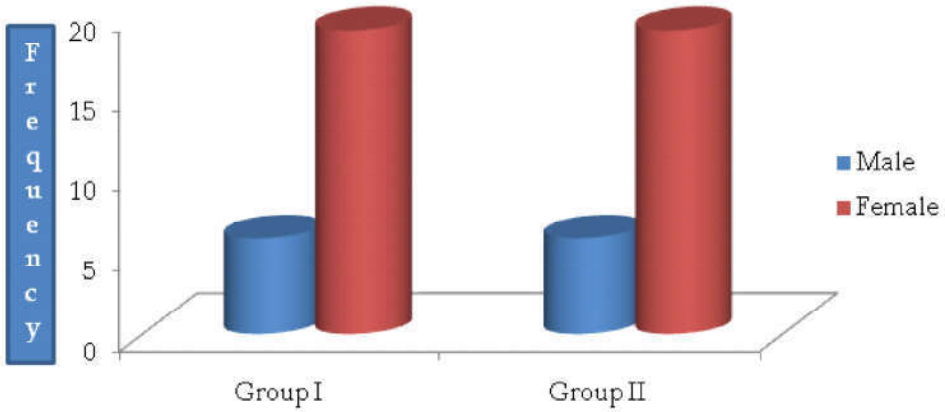

Fig. 1: Sex Distribution of Sample

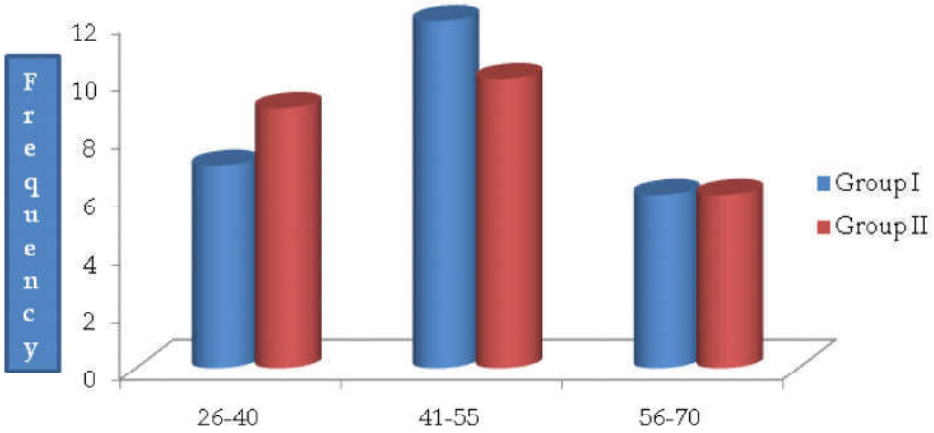

Fig. 2: Age Distribution of Sample

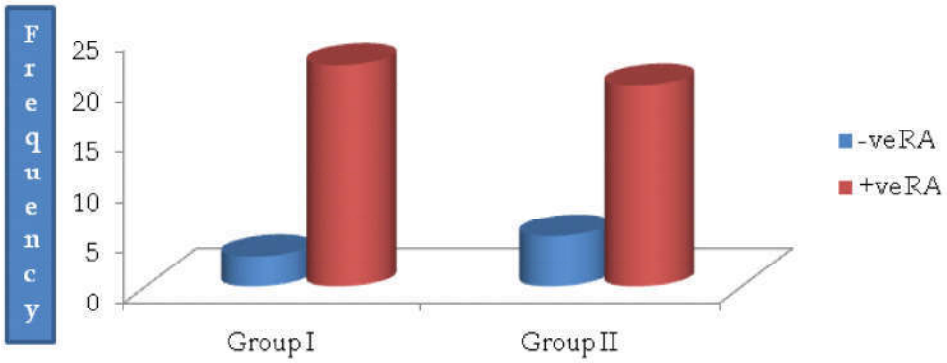

Fig. 3: Distribution of the Sample by Ra Factor

Table 1: Distribution of Cases by Remission

	Group I	Group II
No Remission	17	12
Remission	8	13

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