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Original Article

A Comparative Study on Efficacy of Methotrexate and Sulphasalazine in Spondyloarthropathies

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Abstract

Background: Spondyloarthropathies include a wide spectrum of disease. The study was conducted with the aim of observing the efficacy of SSZ and MTX in different subclasses of spondyloarthropathies and to compare the treatment response of the two drugs.

Methods: This study was conducted in the Department of Medicine and Rheurnatology clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) between January 1999 and July 2001.A total number of one hundred twenty five patients was included in the study. Patients with active disease more than three months, regularly taking NSAIDs and not on DMARD in the last three months were included in the study. Monthly follow up of the patients was done for 6 months.

Result: One hundred twenty five patients were included in this study. Male female ratio was 11.5:1. Mean age of patients was 24.17±7.15 years. The mean disease duration was 47.8±32.8 months. The present study categorized the patients into responder and non responder. Among the 78 patients in AS subclass, after completion of 6 month trial 55.6% patients in SSZ group and 39.4% patients in MTX group were categorized responder.

The difference of response between drug groups was not significant (p=0.158). In the JCA subclass 81.82% in SSZ and 50% in MTX group were responder. The numbers of patient in Reiter's/Reactive Arthritis in our study were too small to make a definite comment.

Conclusion: It can be concluded from this study that both the SSZ and MTX are effective DMARDs for spondyloarthropathies. Statistical analysis did not prove superiority of one drug over another, though the response rates were numerically higher in SSZ group. Key words: SSZ; MTX; DMARD; NSAID; SNSA

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Introduction

The seronegative spondyloarthropathies (SpAs) form a group of disorders, which are characterized by: involvement of the sacroiliac joints, peripheral arthropathy and absence of rheumatoid factor[1].The other features or spondyloarthropathies include enthesopathy, extra articular involvernnt, and an association with HLA-B27. These disorders include: Ankylosing Spondylitis (AS), Reiter's syndrome (RS) Reactive arthritis (ReA) Psoriatic arthritis, Enteropathic arthritis, Juvenile Chronic arthritis (JCA) and undifferentiated spondyloarthropathy[2]. Ankylosing spondylitis being the prototypes of this group of inter related disorders[3,] .The monitoring and treatment of these disorders are related more to their presenting symptoms than to their clinical diagnosis[4]. The spondyloarthropathies are a world wide distributed

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disease[5]. It almost affects all races with very few exceptions[6]. The reported prevalence of AS varied from virtual nil to 4.2% in several community studies[7]. The incidence of JCA was shown to be 12 per 100.000 and the prevalence varied from 56 to 100 per 100.000 in western population[8, 9]. In Bangladesh the exact data of prevalence of SpAs or it's subclasses in lacking. Because of the variability in presentation, the methodology for conducting clinical trials is much more complicated. One of the difficulties is the choice of assessment criteria. More over, the evolution of spondyloarthropathies is characterized by consecutive periods of flares and remissions, whatever the treatment[10]. Sondyloarthropathies are normally treated with NSAIDS, NSAIDS and physiotherapy has been the basis for AS therapy in recent decades[1].There is a clear need for effective new drug therapies in this disease and the onset of a second line drug can be considered. Sulphasalzine is the most investigated second line drug in the' field of spondylarthropathy and in the last two decades several studies have been undertaken and reports have been published of benefit to both axial and peripheral symptoms[11]. Sulpahsalzine also shown to be effective in JCA and in Reiter"s/ Reactive arthritis[12]. MTX is also tried as a second line drug in several studies[13, 14].This study was conducted to see effectiveness of SSZ and MTX with various presentations and response in the three subclasses of spondyloarthropathy.

Materials and methods

This study was conducted at the department of Medicine and Rheumatology clinic of Bangabandhu Sheikh Mujib Medical University (BSMMU) between January 1999 and July 2001. A total number of one hundred twenty five patients were included in the study. Among these patients ninety two had AS, twenty two had JCA and the other eleven were suffering from Reiter's/Reactive arthritis. All the patients of each subgroup of spondyloarthropathy were divided in two groups randomly to be included in sulphasalazine & MTX group. To each group of patients NSAIDs were added whenever required. Patients with active disease more than three months, regularly taking NSAIDs and no DMRD in the last three months were included in the study. SSZ was started in a dose of 500mg/day in two divided doses. The dose was increased at weekly interval till the full dose of 40-50mg/kg (maximum 2 gm) was reached**.** MTX was given in a dose of 7.5mg/wk; which was administered in three 12 hourly spaced doses of 2.5mg of tablets. A 5mg of folic acid was given on the following day of MTX to avoid adverse effects. If there was no desired response to this dose within two months, the dose was increased by 2.5mg at monthly intervals up to 15mg/wk. Monthly follow up of the patients was done for 6 months.

Clinically disease course was monitored by morning stiffness, nocturnal awakening frequency, visual analog scale, number of involved joints, joint swelling index, tenderness index, functional index, modified Schober's test, finger. to floor distance, NSAID score, physician's global assessment, ESR. At each follow up the subjects turned up with reports of urine R/E, CBC, Serum Creatinine and SGPT.

The patients were categorized responder and non responder to the drugs when the disease was inactive or active respectively. One hundred twenty five patients were randomly assigned to SSZ and MTX group following the random table. The numerical data obtained from the study were analyzed using computer based SPSS/PC programme. $P<0.05$ was taken as minimum level of statistical significance.

Results

A total number of 125 patients were included in the study. Finally 106 patients completed the trial for six months duration, of them 78 patients were AS, 19 JCA and 9 Reiters/Reactive arthritis. A total of 19 cases dropped out, 14 in AS group, 3 in JCA and 2 in Reiter’s/Reactive arthritis. 11 patients developed side effects, 3 in SSZ group and 8 in MTX group. 8 patients failed to attend follow up. In the AS subclass 45 received SSZ and 33 received MTX, in JCA 12 received SSZ and 7 received MTX, in Reactive arthritis 6 received SSZ and 3 received MTX. The mean age of these

total numbers of one hundred twenty five patients was 24.17±7.15 years. The mean disease duration was 47.86±32.81 months. There were no statistically significant differences in demographic data or clinical and laboratory variables between the two treatment groups in the intent-to-treat population. After completion of six months trial, the patients of AS subgroup (n=78) showed remarkable improvement in most of the clinical parameters. Both the group showed significant decrease in disease activity in all parameters except chest expansion in case of MTX. A comparison of treatment response between SSZ and MTX showed no statistically significant difference but there was a tendency in favour of SSZ for two variables: NSAID score and physician's global assessment (Table1). Twenty five patients (55.6%) in SSZ group and thirteen patients (39.4%) in MTX group were categorized responder. Twenty (44.4%) of SSZ group and twenty (60.6%) of MTX group were categorized nonresponder. The difference of response between drug groups was not significant (P=0.158) .At the end of six months, almost all the variables showed significant improvement except modified Schober's test, chest expansion and ESR of both groups and finger to floor distance of MTX group. Improvement in visual analogue scale, Schober's test and NSAID scores showed results in favour of SSZ, on the other hand ESR improved significantly in MTX group. Treatment response of JCA after 6 months with the SSZ and MTX groups were significant but no significant difference between groups observed. Nine patients (81.82%) in SSZ group and 4 patients (50%) in MTX were categorized responder. Two patients (18.18%) of SSZ group and 4 patients (50%) of MTX group were categorized non responder. The treatment response of Reiter's/Reactive arthritis in SSZ and MTX groups and comparison of response in between groups were statistically significant. Thirty four patients (51.57%) in SSZ group and 30 patients (58.82%) in MIX group developed at least one adverse drug reaction during the trial period. The difference was insignificant (P = 0.617).

Discussion

Spondyloarthropathies (SpAs) include a wide spectrum of rheumatological .disorders. The beneficial effect of sulphasalazine (SSZ) and methotrexate (MTX) has established them as effective second line agents in the treatment of rheumatoid arthritis. In the past 20 years, SSZ and MTX have been largely employed for the treatment of AS. Though SSZ in the most studied drug, the use of MTX has also been increased in the past few years. In the present study, the average ages of the patients were 24.17 ± 7.15 years (ranging from 13 to 45 years). Mean (SD) age of the AS subclass was 25.5±7.3, of JCA 17.0± 3.4 and Reiter's/ReA was 24.4±5.5. It has similarity with the study conducted in Bangladesh by MA Haque but differed from Dougados and Biasi where the age was much higher in AS and Reiter's/RE groups[15].Out of 125 patients 10 were female; the male female ratio was 11.5:1. Among the three studied subclasses of spondyloarthropathies, frequency of female was highest in JCA which is 26.31 %(5 cases). There was no female in Reiter's/ReA group. Except one case, all the females of AS group presented with peripheral Joint involvement. At the end of 6 months trial four (80%) female patients out of five in JCA subclass became responder (3 in SSZ group and 1 in MTX group). On the other hand in AS subclass two (40%) patients responded and three remained nonresponder at the end of 6 months. The treatment outcome appears to be remarkable in females having JCA in comparison to AS. And the results were more in favour of SSZ[12]. Mean disease duration was 48.6±32.1 months of SSZ group and 49.3±37.1 months of the MTX group (ranging form 8 months 10 years). This wide range is due to the included subclasses of patients.

Detailed analysis showed that, the pretreatment nocturnal awaking frequency in SSZ group was 2.9±1.9 and post treatment was 0.78 ± 1.29. In the MTX group it was 3.4±1.8 and 0.94±1.50 respectively. The pretreatment and post treatment morning stiffness were 93.4±68.8 and 14.3±35.5 minutes respectively. It showed a highly significant improvement. The improvement was

similarly remarkable in MTX group, where the pretreatment and post treatment values were 85.4±68.5 and 19.2±25.8 respectively. The pretreatment and post treatment visual analogue scale in SSZ group in this study were 7.5±1.8 and 2.9±1.9 respectively. In the MTX group pre and post treatment VAS values were 7.9±1.1 and 2.9±1.6. Such improvement in nocturnal awakening frequency, visual analogue scale and morning stiffness were also evident in drug trials of Dougados with SSZ and D. Biasi with MTX.Patient's improvement of overall well being was reflected by the positive outcome in functional index. In SSZ group it was 5.37±1.54 and 1.80±1.34 before and after treatment; in MTX group 4.92±1.64 and 1.85±1.24 respectively. The difference was not significant (p=0.187). There was no significant change in chest expansion and less significant change in pre and post treatment ESR in MTX group. But changes in SSZ group were significant. The JCA subclass of present study in both SSZ and MTX group showed improvements in most of the parameters. Schober's test and chest expansion did not show significant difference. The other ten variables in both groups showed significant improvement. NAF, VAS, NSAIDs score and ESR showed results in favour of SSZ but statistically the difference was not significant. In the Reiter's/ReA group lower-than expected number of patients were recruited into this study. In the SSZ group VAS, tenderness index, functional index. PGA and ESR showed highly significant improvement but in the MTX group the patients failed to experience any conclusive response in any parameter except tenderness index and ESR.

The present study categorized the patients into responder and non responder following D. Biasi et al[14]. Among the 78 patients in AS group. after completion of 6 month trial 25 (55.6%) patients in SSZ group and 13 (39.4%) patients in MTX group were categorized responder. 20 (44.4%) of SSZ and 20 (60.6%) of MTX group were categorized non responder. The difference of response between drug groups was not significant (p=0.158). D Biasi also found favorable response with MTX in a 3 year open study but Corkill failed to get significant response with SSZ[16].

Conclusion

Over the last two decades SSZ and MTX have been studied separately in different subclasses of SpAs with variable success. It can be concluded from the present study that, both SSZ and MTX are effective DMARDs for spondyloarthropathies.

Statistical analysis did not prove superiority of one drug to the other and long term drug therapy in AS showed increased response rate.

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