TREATMENT OF RHEUMATOID ARTHRITIS IN BASRAH: CLINICAL EFFICACY AND TOXICITY OF SULFASALAZINE USED ALONE OR IN COMBINATION WITH DICLOFENAC SODIUM

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ABSTRACT

Background: **Racial variation in the clinical presentation of rheumatoid arthritis (RA) and its response to treatment is well known. Ethnicity and associated socioeconomic factors make it necessary to study the effectiveness of the anti-rheumatic drugs such as sulfasalazine (SSZ) in our RA patients, and to what extent it interacts with the non-steroidal anti-inflammatory drug (NSAID); diclofenac.**

Objective: **To investigate the efficacy and toxicity of sulfasalazine alone or in combination with diclofenac in the treatment of moderate to severe RA.**

Methods: **A three month-randomized clinical trial was conducted on patients with moderate to severe RA: Group I: received SSZ (500 mg orally twice daily), and Group II: received SSZ plus diclofenac sodium 100mg SR tablets once daily. Evaluation involved: pain, morning stiffness, joint function, patients and physician global assessment, radiological assessment, ACR criteria, laboratory findings and drug adverse effects.**

Results: **Only 17 patients out of 20, managed to complete the 12 week treatment course. Oral SSZ (500mg twice daily for 3 months) resulted in a statistically significant clinical improvement after 12 weeks of treatment. The average percent improvement in six clinical parameters was 21.1%. The 20% improvement using ACR criteria involved 11% of patients. The improvement occurred especially in the number of swollen joints and in joint pain. The overall improvement that occurred two weeks after treatment with SSZ continued at the same level over the 12 week treatment period. No statistically significant changes were detected in the laboratory parameters measured including ESR. No radiological progression was found 12 weeks after treatment in joint space narrowing and joint erosion. SSZ reduced symptoms reported by patients before treatment by 57.4%. Diclofenac as a sustained release formulation administered concomitantly with SSZ did not change the improvement caused by SSZ as measured by the six clinical parameters (23% versus 23.4%). However, the ACR20 increased from 11% to 25%. No effect on laboratory measurements was found. Diclofenac in combination with SSZ reduced the symptoms reported by patients by 70.6% compared with 57.4% by SSZ alone.**

Conclusion: **SSZ treatment for 12 weeks caused mild to moderate improvement in all measured clinical parameters, especially in the number of swollen joints and in joint pain. Diclofenac as a sustained release formulation, given with SSZ, did not change the improvement caused by SSZ as measured by six clinical parameters, although it increased the ACR20 of SSZ from 11% to 25%.**

INTRODUCTION

Sulfasalazine (salazopyrine, SSZ) is one of the widely used disease modifying antirheumatic drugs in the UK and Asia.[1] It is used for treatment of rheumatoid arthritis, seronegative spondyloarthropathy and reactive arthritis.[1] It takes approximately 6 weeks-2 months before benefit is noted. Meta-analysis of 15 randomized clinical trials from three medical centers in USA, to assess the efficacy and safety of SSZ in comparison to placebo or other disease-modifying antirheumatic drugs (DMARDs), showed that sulfasalazine treatment, in comparison with placebo, resulted in improvement in ESR, morning stiffness, pain visual analogue scale, number of swollen joints, number of the painful joints and in patient global assessment. This meta-analysis supports the effectiveness of SSZ as a treatment of rheumatoid arthritis (RA).[2] Short term efficacy and toxicity of SSZ in RA treatment were evaluated in comparison with a placebo.[3] It appeared to have a clinically and statistically significant benefit on the disease activity in patients with RA. Its effects on overall health status and radiological progression are not clear but would appear to be modest.[3] A comparison between the efficacy and toxicity of medium to long term SSZ and gold treatment of active RA showed that SSZ was more likely to be continued for 5 years, suggesting better tolerability and/ or efficacy than gold and produced evidence of continuing benefit.[4] Efficacy of SSZ had also been shown to be better than chloroquine, gold, penicillamine but less than methotrexate (MTX).[1] In addition, SSZ has useful antirheumatic activity in patients with juvenile RA and can contribute to the care of selected

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patients (good response in pauciarticular and polyarticular types with poor one in the systemic onset type).[5] SSZ was found by one study to produce marked decrease in radiographic progression compared with pre-diagnosis progression.[6] Ethnicity is important in RA.[7] There is an evidence of ethnic variation in the clinical presentation of RA. It was found that disability and disease activity were higher in African-Americans than Caucasians in the USA.[8] However, ethnicity was not independently associated with these outcomes when socioeconomic and psychological factors were taken into account. American-Indians and Alaska native populations showed an increased prevalence of RA and more severe disease with early age of onset, high frequency of radiographic erosions, rheumatoid nodules and positive rheumatoid factor.[9] Hispanics in comparison to non-hispanic whites in the USA had significantly more tender and swollen joints, more frequent rheumatoid factor positivity, high ESR, and lower number of lifetime disease modifying anti rheumatic drugs.[10] Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used drugs in RA. SSZ is metabolized into 5-aminosalicylic acid and sulfapyridine. Therefore, protein binding displacement by the highly protein bound NSAIDs beside that, 5-aminosalicylic acid being itself a NSAID- like compound, could be a source of interaction. Therefore the present study was performed to investigate the clinical efficacy and adverse effects of SSZ in treatment of patients with moderate to severe RA in Basrah as a monotherapy or in combination with a NSAID; diclofenac sodium.

PATIENTS AND METHODS

A 3-month randomized, comparative clinical trial was conducted at the Rheumatology Unit at the Teaching Hospital, Basrah, and the Department of Pharmacology, College of Medicine, University of Basrah (Iraq) during the period from October 2005 to June 2006. Patients with moderate to severe RA (classified according to the American College of Rheumatology (ACR) criteria) were randomly allocated into:

Group I: receiving SSZ (Salazopyrin-EN, Kahira Pharm), 500mg twice daily orally.

Group II: receiving SSZ plus diclofenac sodium 100mg SR (Refen Retard, Hemofarm) tablets once daily.

Measurements

1. *Clinical evaluation (including laboratory investigations and monitoring of adverse effects).*
2. *Radiological evaluation.*

Clinical evaluation

Pain (using 11-point numerical rating scale), morning stiffness (duration in minutes), joint function (number of tender and swollen joints), and patient and physician global assessment, using horizontal visual analogue scale), laboratory investigations (including complete blood picture and ESR, liver enzymes, blood urea, Hb electrophoresis), American College of Rheumatology (ACR) criteria, and drugs adverse effects (according to a check list).

Radiological evaluation

X-rays before and 3 months after treatment were assessed blindly by a specialist in radiology using modified Sharp score involving joint space narrowing and erosion (Van der Haijde DM. Bailliere's Clin Rheumatol 1996; 10: 435-453).

Treatment allocation

Drugs were randomly allocated according to a randomization list. Follow-up was made by two rheumatologists: the first prescribed the drugs, and the second, blindly, assessed the patient response and the adverse effects

Ethical approval

The study design was approved by the College Council and the Ethical Committee of the College of Medicine, University of Basrah (Iraq).

RESULTS

1. Characteristics of patients

Twenty patients with moderate to severe RA were randomly allocated into two treatment groups: SSZ (500mg tablets twice daily), and SSZ plus diclofenac (100mg SR tablets). Only 17 patients managed to complete the 12-week course of treatment. Patients characteristics with respect to age, gender, duration of disease and others are shown in table-1.

Table 1. ***Characteristics of patients.***

Parameter	SSZ group n = 9	SSZ + Diclofenac n = 8
Age (years)	45.4 ± 8.4	44.5 ±6.4
Gender	9 females	7 females, 1 male
Duration of disease (years)	11.2 ± 9.1	13.8 ± 8.2
Severity *Severe* *Moderate*	 5 4	 4 4
Hb type HbA HbAS	8 1	7 1
Defaulters	1	2

2. The effects of sulfasalazine (SSZ, 500 mg twice daily) on clinical and laboratory parameters in patients with rheumatoid arthritis

(A) Effects of sulfasalazine on clinical parameters

Although, there is a trend towards reduction in the scores of all measured clinical parameters (joint pain, morning stiffness, number of the swollen joints, number of the tender joints, patients and physician global assessments) after SSZ treatment, this reduction is more clear and reached statistical significance in the joint pain (where there was a statistically significant reduction at 2, 6, and 12 weeks after treatment with SSZ), and in the number of swollen joints (45.5% reduction at 12 weeks). This is in addition to a small but significant reduction that reflects improvement in patient and physician global assessment (Table-2).

Table 2. ***The effects of SSZ (500mg twice daily) on clinical parameters in patients with rheumatoid arthritis (n= 9)***

Variables	Before treatment	After treatment		
		2 weeks	6 weeks	12 weeks
Joint pain (severity)	4.45± 0.9	3.35 ± 1* (24.71%)	2.67 ± 1** (40%)	3.25 ±1.03* (26.9%)
Morning stiffness (in minutes)	35.55 ± 16.7	26.76 ± 14.14 (24.97%)	28.9± 14.53 (18.37%)	32.5 ± 18.32 (8.57%)
Number of swollen joints	4.55 ± 1.6	3.33 ± 1.58 (26.8%)	3.5 ± 1.6 (23.07%)	2.5 ± 1.5* (45.5%)
Number of the tender joints	6.11 ± 2.42	5.33 ± 2.3 (12.76%)	6.11 ± 3.06	4.37 ± 1.2 (28.47%)
Patient global assessment	4.89 ± 1.05	3.55 ± 0.88** (27.4%)	3.55 ± 0.88** (27.4%)	4 ± 0.00** (18.2%)
Physician global assessment	4.45 ± 0.88	4 ± 0.0* (10.1%)	4 ± 0.00* (10.1%)	4 ± 0.00* (10.1%)

Data are expressed as mean of scores of each parameter ± SD and percent reduction with respect to before treatment.
A significance difference with respect to before treatment score: *P<0.05, **P<0.01

(B) The effects of sulfasalazine (SSZ) on laboratory parameters

No statistically significant changes were found in all laboratory parameters measured in this study at 2, 6, and 12 weeks after SSZ treatment. However, monocyte count was reduced by 22.8%, and 30.3% at 6 and 12 weeks of treatment respectively. The decrease in ESR at 2 weeks and increase at 6 weeks were not statistically significant (Table-3).

Table 3. ***The effects of SSZ (500mg twice daily) on laboratory parameters in patients with rheumatoid arthritis (n=9)***

Variables	Before treatment	After treatment		
		2 weeks	*6 weeks*	*12 weeks*
Hemoglobin (gm/dl)	12 ± 1.55	11.5 ± 1.4	11.35 ±1.57	11.05 ± 1.83
ESR (mm/hr)	41.33 ± 27.6	28.11±15.7 (-32%)	56.7 ± 46 (+37.2%)	42.9 ± 28.9
WBC total count (× 1000/mm^3)	8 ± 3.2	8.57 ±1.86	7.21 ± 3.35 (-9.9%)	6.37 ± 1.88 (-20.4%)
WBC differential Count: lymphocyte	26 ± 5.48	28.5 ± 6.45	26.6 ± 4.55	25.1 ± 7.42
WBC Differential count: neutrophils	67.6 ± 6.28	64.5 ± 6.67	68.7 ± 4.38	69.7 ± 8.8
WBC Differential count: monocyte	5.33 ± 1.66	6 ± 2.5	4.11 ± 2.26 (-22.8%)	3.71 ± 1.98 (-30.3%)
SGOT (unit/ liter)	7.78 ± 1.3	9.11 ± 2.71	8 ± 1	8.71 ± 2.14
SGPT(unit/liter)	8.67 ± 2.45	7.9 ± 0.93	8.11 ± 0.93	8 ± 2
Blood urea (m mole /liter)	4.52 ±0.91	4.5 ±1.04	4.8 ±1.29	4.7 ± 1.12
Platelet count	283 ± 72	276.7 ± 73	313.3 ± 73	313.3 ± 83

Data are expressed as mean of scores of each parameter ± SD and percent reduction with respect to before treatment .

3. Effects of combined treatment with SSZ and diclofenac on clinical and laboratory parameters

(A) Effects of combined treatment with SSZ and diclofenac on clinical parameters

SSZ and diclofenac combined treatment resulted in reduction in all the six clinical parameters after 2 weeks of treatment. However, these reductions are not statistically significant, but remained consistent in extent at 6 and 12 weeks and reached statistical significance only with morning stiffness (40% reduction, $P<0.05$) and patient global assessment (25% reduction, $P<0.05$) at 6 weeks of treatment.

(B) Effects of combined treatment with SSZ and diclofenac on laboratory parameters

No statistically significant changes in all laboratory parameters measured at 2, 6, and 12 weeks of treatment, were found except a small but significant reduction (9.4%) in hemoglobin concentration detected at 6 weeks after treatment.

4. Summary of percent changes and their overall mean of the six clinical parameters in the two treatment groups

The overall average of improvement in the six clinical parameters showed that SSZ alone or in combination with diclofenac resulted in approximately comparable overall percentage of improvement ranging from 21.1% to 26.2% over a 12 week period of treatment (Table-4).

Table 4. ***Grand mean of percent improvement of all the six clinical parameters in patients with rheumatoid arthritis.***

Duration of Treatment	SSZ (N=9)	SSZ+ Diclof (N=8)
2 weeks	**21.1** ± 7.6	**21.4** ± 3.8
6 weeks	**23.9** ± 11	**26.2** ± 7.2
12 weeks	**23** ± 13.7	**23.4** ± 7

Data are expressed as mean ± SD of percent improvement of all the six clinical parameters.

5. Improvement after 12 weeks of treatment assessed according to the number of patients showing 20% improvement (American College of Rheumatology Criteria/ ACR-20)

ACR-20 for SSZ, and SSZ plus diclofenac groups were found in 11% and 25% of patients in the two group respectively.

6. Radiological changes, 12 weeks after treatment with SSZ or its combination with diclofenac

There was no significant progression in the radiological changes (joint space narrowing and erosion) when assessed before and three months after treatment with SSZ. Diclofenac with SSZ appeared to retard radiological progression by 42.9% but this is not statistically significant.

7. Symptoms reported by patients before and after treatment (potential adverse effects)

There was a consistent trend towards reduction in the incidence of symptoms reported by patients after 12 weeks of treatment when compared to before treatment in the two groups of treatment. SSZ reduced symptoms by 57.4%. This reduction is increased to 70.6% by the combination of SSZ and diclofenac.

DISCUSSION

Treatment of RA is directed towards relief of symptoms, suppression of active and progressive disease, and restoration of function in affected joints.[11] This may be achieved by drugs, rest, physiotherapy or surgery with modification of patient environment. The use of disease modifying antirheumatic drugs (DMARDs) should be considered in all patients with symptoms and signs of active inflammatory arthritis. The majority of rheumatologists believe that patients with RA should be treated with DMARDs earlier than later in the disease process.[12] If these drugs are used early, in addition to improving joint pain, stiffness and swelling and reducing the systemic symptoms, acute-phase proteins, ESR, and rheumatoid factor titer over a period of months, they may reduce the rate of radiological progression of the disease. However, their main benefit is, probably, in inducing asymptomatic remission for 1-2 years in 40%-60% of patients.[13] SSZ is widely used in the treatment of RA. Improvement in pain, morning stiffness, number of the swollen and tender joints, ESR and other parameters takes about 6-8 weeks to be observed.[1-2] During the 3 month period of SSZ treatment used in our study, it resulted in an overall improvement of 23%. This improvement seems to start early (2 weeks after the start of treatment) and continued at the same level at 6 and 12 weeks after treatment. The highest percentage of clinical response was in the reduction of the number of the swollen joints (decreased about 45.5%). No statistically significant effect of SSZ treatment on ESR after 12 weeks of treatment. All other laboratory parameters measured (Hb, WBC count total and differential, platelet counts, SGPT and SGOT, and blood urea) did not show any significant change with SSZ treatment. Despite normal laboratory measurements found in the present study, serious toxicity has been reported in the first 6 weeks of SSZ treatment.[14] Ten cases of hepatoxicity after SSZ therapy had been reported within 7 years in the latter study.[14] These results are in accord with what has already been reported by others.[1-3] However, when SSZ effect was compared to that of MTX[15], the latter seems to be more effective (the overall percentage of clinical improvement after 12 weeks of treatment is around 35% for MTX compared to 23% with the use of SSZ). SSZ also differs from MTX in that its effect started earlier than MTX and remains at the same level over the 12 weeks of treatment, while response to MTX increased as the duration of treatment increased. Administration of diclofenac with SSZ did not affect the overall response to SSZ except a more benefit with morning stiffness. This is in contrast to the interaction between MTX and diclofenac found by the same authors.[15] However, NSAIDs e.g. phenylbutazone can interact with SSZ through protein binding displacement.[16] Thus, diclofenac which is also highly protein bound is expected to increase SSZ concentration. In addition 5-aminosalicylic acid (the active metabolite of SSZ) is also a NSAID- related compound and may be expected to potentiate the effect of diclofenac. Despite these mechanisms of interaction, our results did not show a clinically important additive effect of diclofenac on SSZ, in the dosage regimen used in the present study, and within the three month duration of treatment. On the other hand, when evaluation was made using ACR-20 response rate, diclofenac seems to interact favorably with SSZ. It increased the ACR-20 from 11% to 25% and retard the radiological progression by 42.9%. To conclude, there is a trend towards reduction (i.e. improvement) in the scores of all measured clinical parameters after SSZ treatment. The improvement occurred especially in the number of swollen joints and in joint

pain. The overall improvement that occurred two weeks after treatment with SSZ continued at the same level over the 12 week treatment period. Diclofenac as a sustained release formulation did not change the improvement caused by SSZ as measured by six clinical parameters. However the ACR20 increased from 11% to 25%. Diclofenac in combination with SSZ reduced the symptoms reported by patients by 70.6%. Finally, it must be mentioned that randomized clinical trials have established the efficacy of methotrexate in RA.[17] In another study, we have also investigated the efficacy of methotrexate (7.5mg single oral dose per week) in our RA patients. It was found more effective than SSZ (35% versus 21.1% average improvements in the six clinical parameters after 12 weeks of treatment). These results are sent for publication at the present time.

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