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Research Article

ROLE OF NEW GENERATION CORTICOSTEROIDS IN TREATMENT OF RHEUMATOID ARTHRITIS: METHYLPREDNISOLONE VERSUS DEFLAZACORT

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A B S T R A C T

Introduction: Rheumatoid arthritis (RA) is an auto-immune disease and is the most common type of inflammatory arthritis worldwide. Disease modifying anti-rheumatic drugs (DMARDs) and NSAIDs have been the mainstay of treatment of rheumatoid arthritis.

Objectives: To compare the effects of low dose methylprednisolone and deflazacort, in addition to DMARDs, on clinical progression of RA and to evaluate the side-effects of the same.

Methods: 60 patients of active RA of less than 12 weeks duration were included and divided into 2 groups of 30 each. Diagnosis was established using 2010 ACR/EULAR criteria. Patients were treated with 2 DMARDs along with one of these two corticosteroids. The remission was defined using the SDAI SCORE; and the effect of steroids was noted and the dose tailored accordingly. RESULTS: At 12 weeks, remission was attained in 80% of patients in methylprednisolone group as compared to 63.33% in deflazacort group.

Conclusion: We concluded that addition of low dose steroids to conventional DMARDs lead to rapid symptomatic improvement, earlier remission with no side-effects in short term. The difference in remission rate of both both groups was statistically insignificant.

INTRODUCTION

RA is an autoimmune disease of unknown cause and interaction between genetic and environmental factors play an important role in the development of disease in susceptible individuals. RA most commonly involves the small joints of hands and feet, often in asymmetrical distribution resulting in pain, stiffness and loss of function. The treatment options for RA include NSAIDs, DMARDs, Corticosteroids and Biological agents/ immunomodulators.

The cornerstone of Rheumatoid Arthritis treatment involves DMARDs, either as mono-therapy or in combinations, with or without corticosteroids. The modern approach of Rheumatoid Arthritis treatment includes a very early start of treatment, because even a delay of 4 months can affect the long-term outcome of treatment[1]. Nowadays, the strategy of corticosteroids treatment includes three possibilities:

1. Step-down with a high initial dose, later tapered off [2].
2. Bridge- therapy aimed at controlling symptoms in the period of high disease activity before newly started DMARDs start to have an effect [3] or
3. Long -term low dose strategy of oral corticosteroids together with a single or a combination of DMARDs[4].

Low dose corticosteroids together with DMARDs are able to reduce the rate of erosion progression in RA patients substantially[5]. In the present study, corticosteroids were used as a bridge therapy, in addition to conventional two DMARD therapy.

MATERIAL AND METHODS

Patients: 60 patients between age 18-60 years and having confirmed diagnosis of RA using 2010 ACR/Eular Criteria were included into study. Pediatric and juvenile patients, pregnant females, immune-compromised patients were excluded.

Diagnosis and Monitoring: Diagnosis was established using the 2010 ACR/Eular Criteria for RA. Disease activity and remission was monitored using SDAI (Simple Disease Activity Index).

Intervention: After routine hematological investigations, patients were initially started with 2 DMARD therapy which consisted of Methotrexate 15mg/week and Sulfasalazine 2000mg/day. Folic acid supplements were given. In addition, group 1 paitents were given methylprednisolone 4 mg/day and group 2 patients were given deflazacort 6 mg/day. Steroids were continued for 6 weeks and then tapered off over next 6

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weeks. Nonsteroidal antiinflammatory drugs (NSAIDs) and osteoporosis prophylaxis with calcium and vitamin D were permitted. Treatment with bisphosphonates and calcitonin was not allowed. Patients were followed up every 2 weeks for 12 weeks. Remission was noted using SDAI index [Figure-1].

Measurements: The following parameters were noted at baseline, and at 2,6,12 weeks:-

- Duration of morning stiffness (in minutes)
- Grip strength (in mm Hg)
- Swollen joint count
- Tender joint count

The Following Investigations Were Done

- Haemogram
- RA Factor
- Anti CCP Titre
- Liver function tests
- Renal function tests
- ESR (m at the end of one hour)
- CRP Titre (mg/L)
- S. Uric Acid

ESR and CRP were repeated at 2,4,6 and 12 weeks to monitor disease activity.

SDAI index was calculated at baseline and at 2, 6 and 12 weeks

Statistical evaluation of data was done using GRAPHPAD Software system.

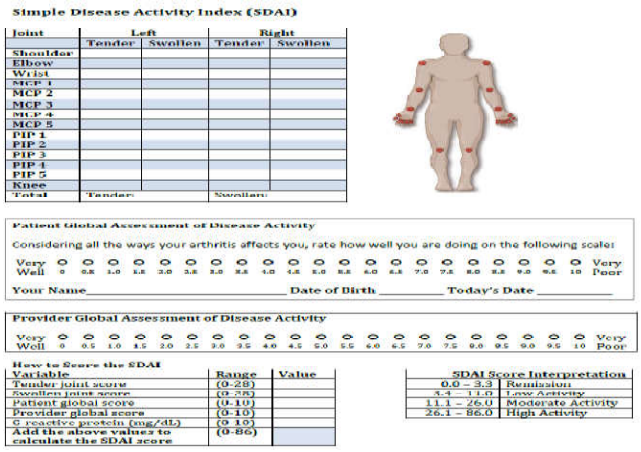

Figure 1 Simple Disease Activity Index

RESULTS

The total population of patients treated with DMARDs + Methylprednisolone (Group 1) and DMARDs + Deflazacort (Group 2) were 60. The average age of the patients was found to be 44.76 years, with the male to female ratio being 1:3.3.[Table -1]

About 83.33% patients in Group-1 and 80% patients in Group-2 were found to be positive for RA Factor. Overall, RA Factor was positive in 81.67% patients. [Table-2]

About 93.33% patients in Group-1 and 96.67% patients in Group-2 were found to be positive for Anti-CCP Antibodies. Overall, Anti-CCP was positive in 95% patients. [Table-2]

The mean duration of morning stiffness was noted in both groups as shown in Table 3. At 12 weeks, morning stiffness disappeared completely in 27 out of 30 (90%) patients in group 1 as compared to 19 out of 30 (63.33%) patients in group 2.
The Tender Joint Count and Swollen Joint Count was recorded at baseline, 6 weeks and 12 weeks, as given in Table-4. None of the patients in either group was free from tender or swollen joints at study entry. At 12 weeks, 24 (80%) patients in group 1 and 20 (66.67%) patients in group 2 had no tender joints. At 12 weeks, 24 (80%) patients in group 1 and 19 (63.33%) patients in group 2 had no swollen joints. The mean grip strength at study entry, 6 and 12 weeks is shown in table-5. At 12 weeks, the grip strength increased by an average of 50.87mm of Hg in group 1 as compared to 38.27 mm of Hg in group 2.

ESR (mm at end of 1 hour) of all patients was measured at study entry, 6 weeks and 12 weeks, as shown in table-6. None of the patients had normal ESR at the time of presentation. In group 1, 6(20%) patients had normal ESR at 6 weeks and 20(66.67%) patients had normal ESR at 12 weeks. On the other hand, in group 2, 5(16.67%) patients had normal ESR at 6 weeks and 17(56.67) patients had normal ESR at 12 weeks. The mean reduction in ESR at 12 weeks was 52.9 (mm of Hg at end of 1 hour) in group-1 and 45.2 (mm of Hg at end of 1 hour) in group-2.

The mean CRP in group-1 was 28.53mg/L at study entry, 3.99 mg/L at 6 weeks and 1.67 mg/L at 12 weeks. On the other hand, in group 2, the mean CRP was 35.65 mg/L at study entry, 3.78 mg/L at 6 weeks and 2.07 mg/L at 12 weeks. At 12 weeks, 26 (86.67%) patients in group 1 and 25 (83.33%) patients in group 2 had normal CRP.

None of the patients in either group were in remission or having low disease activity at study entry. 53 (88.33%) of 60 patients had high disease activity at time of first presentation. At 6 weeks, 15 patients (50%) in group 1 and 13 patients (43.33%) in group 2 attained remission. At 12 weeks, 24 patients (80%) in group 1 and 19 patients (63.33%) in group 2 attained remission. None of the patients in either group had high disease activity at 12 weeks.

Table 1 Demographics of Patients

	Mean age (years)	Males	Females
GROUP-1	44.63	8	22
GROUP-2	44.9	6	24
TOTAL	44.76	14	46

Table 2 Distribution of RA Factor and Anti-CCP Antibodies

	RA Factor		Anti-CCP Antibodies	
	Positive	Negative	Positive	Negative
GROUP-1	25 (83.33%)	5 (16.67%)	28 (93.33%)	2 (6.67%)
GROUP-2	24 (80%)	6 (20%)	29 (96.7%)	1 (3.3%)
TOTAL	49 (81.67%)	11 (18.33%)	57 (95%)	3 (5%)

Table 3 Duration of Morning Stiffness

Duration (in minutes)	Group 1 (Methylprednisolone)			Group 2 (Deflazacort)		
	0 Weeks	6 Weeks	12 Weeks	0 Weeks	6 Weeks	12 Weeks
Mean±SD	73.83±36.99	6.83±13.80	1.83±5.64	74.00±33.89	9.83±13.80	5.67±8.17

Table 4 Tender And Swollen Joint Counts

	Group 1 (Methylprednisolone)			Group 2 (Deflazacort)		
	0 Weeks	6 Weeks	12 Weeks	0 Weeks	6 Weeks	12 Weeks

No. of Tender Joints (Mean±SD)	12.03±2.44	1.96±2.68	0.56±1.54	12.03±2.54	3.83±4.19	1.73±2.78
No. of Swollen Joints (Mean±SD)	3.40±1.16	1.03±1.35	0.30±0.60	3.43±1.54	1.86±1.71	0.73±1.20

Table 5 Grip Strength (Mmhg)

Grip Strength (in mmHg)	Group 1 (Methylprednisolone)			Group 2 (Deflazacort)		
	0 Weeks	6 Weeks	12 Weeks	0 Weeks	6 Weeks	12 Weeks
Mean±SD	76.13±17.71	106.40±18.90	127.00±19.50	75.73±18.22	96.67±17.48	114.00±21.43

Table 6 Esr (In Mm At The End Of 1 Hour)

ESR (mm/ HR)	Group 1 (Methylprednisolone)			Group 2 (Deflazacort)		
	0 Weeks	6 Weeks	12 Weeks	0 Weeks	6 Weeks	12 Weeks
Mean±SD	74.80±20.95	42.77±18.73	29.27±19.00	75.47±20.89	52.37±22.01	40.37±19.58

Table 7 Sdai Score

SDAI SCORE	Group 1 (Methylprednisolone)			Group 2 (Deflazacort)		
	0 Weeks	6 Weeks	12 Weeks	0 Weeks	6 Weeks	12 Weeks
0.0-3.3 (Remission)	0	15	24	0	11	19
3.4-11.0 (Low Activity)	0	8	3	0	6	6
11.1-26.0 (Moderate Activity)	4	6	3	3	11	5
26.1-86.0 (High Activity)	26	1	0	27	2	0

DISCUSSION

The mean age at presentation was 44.76 years. This was comparable to a study by Imanaka *et al*[6] (1997) who found it to be average of 46.9 years. However, it was lower than the mean age of 57.1 years studied by Frank Buttgereit *et al*[7] (2012) in the CAPRA 2. The female: male ratio for rheumatoid arthritis was found to be 3.3:1. Doran *et al*[8] (2002) found this ratio to be 2.7:1, Kvien *et al*[9] (2006) found it to be 4.5:1 and Owino *et al*[10] (2009) found it to be 6.5:1.

RA Factor was positive in 49 (81.67%) of 60 patients. This corroborates with the study by Kuriachan *et al*[11] (2012) who found a Positive RA Factor in 89% patients. St.Clair *et al*[12] (2004) found RA factor positive in about 72% of patients and Verhoeven *et al*[13] (2001) found RA factor positive in about 78% patients.

Anti-CCP was positive in 57 (95%) of 60 patients. This is fairly corroborating with the study by Kuriachan *et al*[11] (2012) who found it positive in 86.25% of subjects.The anti-CCP test is more specific than the commonly used RA Factor test (95% versus less than 90%) and has a comparable sensitivity (more than 70%).[14] These antibodies are detectable very early in the disease and widely accepted as an indispensable tool for diagnosis and management of rheumatoid arthritis patients.

Morning stiffness is characteristic to head the diagnostic criteria for rheumatoid arthritis.[15] At 12 weeks, morning stiffness disappeared completely in 90% patients in group 1 as compared to 63.33% patients in group 2. The mean duration of morning stiffness at study entry in both groups was lower than that studied by CARRA-2 study by Buttgereit *et al*[7] who found it to be 152 minutes at study entry. Nearly 50% of the patients had duration of morning stiffness of >1 hour. This corroborates with a study by Yazici*et al*[16] (2004), in which 49% patients had morning stiffness of >1 hour. The results in both groups were better than those obtained by a similar study with prednisolone by Buttgereit *et al*[17] (2008) in the CAPRA -1 study, where the patients in the prednisone modified-release group achieved a mean improvement of 44·0 min compared with baseline. The results of reduction in duration of morning stiffness were comparable with those seen in CAPRA 2 study by Buttgereit *et al*[7], in which the improvement in median duration of morning stiffness in prednisolone group was 81 minutes.

Grip strength is a composite measure and may be influenced by dysfunction in muscles, tendons, and any of the small joints of the hand and wrist. At 12 weeks, the mean grip strength was 127 mm of Hg in group 1 as compared to 114 mm of Hg in group 2. p value = 0.017 which is statistically significant. The grip strength at study entry is comparable with that studied by Helliwell *et al*[18] (1987). At 12 weeks, the grip strength increased by an average of 50.87mm of Hg in group 1 as compared to 38.27 mm of Hg in group 2.

Swollen and tender joints are the most characteristic features of RA, and disease severity is directly related to the number of swollen and tender joints. A joint count assessment is the most specific quantitative clinical measure to assess the status of the patient with inflammatory arthropathies, particularly RA.

At 12 weeks the difference in mean number of tender joints was found to be statistically significant in favour of group 1 (p value = 0.049). At 12 weeks, 24 (80%) patients in group 1 and 20 (66.67%) patients in group 2 had no tender joints. The mean number of tender joints at 12 weeks was lower than that studied in separate studies by Buttgereit *et al*[7] and by Kuriachan *et al*[11] (2012) where the mean number of tender joints at 12 weeks was 7.9 and 3.13 respectively.

At 12 weeks, the mean number of swollen joints was comparable in both groups (p value = 0.088). The results at 12 weeks were better than those studied by Kuriachan *et al*[11] where the swollen joint count at 3 months in their third group was 3.03 joints.At 12 weeks, 24 (80%) patients in group 1 and 19 (63.33%) patients in group 2 had no swollen joints.

The mean ESR at 12 weeks was 29.27 (mm at end of 1 hour) in group 1 as compared to 40.37 (mm at end of 1 hour) in group 2. p value = 0.030 which was statistically significant. The mean ESR at study entry was higher than that in CAPRA 2 study by Buttgereit *et al*[7], Montecucco *et al*[10], as well as the study by Lipsky *et al*[20].

At 12 weeks, 24 patients (80%) in group 1 attained remission, 3 patients (10%) had low disease activity and 3 patients (10%) had moderate disease activity.On the other hand, 19 patients (63.33%) in group 2 attained remission, 5 patients (16.67%) had low disease activity and 6 patients (20%) had moderate disease activity. None of the patients in either group had high disease activity at 12 weeks.Remission was achieved in 24 patients in group 1 as compare to 19 patients in group 2. Using the chi-square (pearson test) p value = 0.152, which is statistically not significant. Good results using combination of two DMARDs with low dose corticosteroids have also been reported by Kuriachan *et al*[11] (2012).

Out of 60 patients included in the study, 51 patients did not complain of any adverse drug reaction throughout the study. Nausea and vomiting occurred in 2 patients in group 1 and 3 patients in group 2. This side effect was most probably due to methotrexate. Symptomatic relief was attained in all these

patients using rabeprazole (proton pump inhibitor) 20 mg once daily. Diarrhea occurred in 1 patient in each group at 2 weeks but it subsided spontaneously. Headache occurred in 2 patients in group 2 for about 2 weeks. This was probably a side effect of deflazacort. However, it subsided spontaneously.

CONCLUSION

Addition of low dose steroids to the first line DMARDs potentiated their action, leading to early remission, which further minimizes the chances of developing deformities. It should be emphasized that the DMARDs remain the mainstay of treatment of rheumatoid arthritis; and steroids were added to enhance their action.

Out of the two new generation steroids, it was seen that methylprednisolone group had statistically better parameters at 12 weeks, including duration of morning stiffness, grip strength, tender joint count and ESR. However, the attainment of remission was statistically comparable in both groups.

Since steroid drugs were used in low dose, No Side Effects of these steroid drugs were noted. Steroids were withdrawn in nearly 80% of patients by 6-12 weeks. (governed by achievement of remission).

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