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Original Research Article

Leflunomide versus Methotrexate and Hydroxychloroquine Combination Therapy in Rheumatoid Arthritis: A Prospective Study on Effectiveness and Quality of Life

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Abstract:

Introduction: Several newer drugs are available for rheumatoid arthritis including leflunomide (LEF). Comparative studies of treatment with LEF (against methotrexate) report a better quality of life. With this background we have conducted this study to evaluate and compare the effectiveness of drugs leflunomide (LEF) with combination therapy of methotrexate (MTX) and hydroxychloroquine (HCQS) in treatment of patients suffering with rheumatoid arthritis (RA).

Methodology: This was a prospective, observational and comparative study in the Department of Medicine, VIMSAR, Burla. Patients diagnosed with RA as per ACR-EULAR criteria aged >14yrs were conventionally sampled to receive leflunomide (20mg/day P.O) or a combination of methotrexate and hydroxychloroquine (7.5 mg/week P.O and 200 mg/day P.O respectively) with folate supplementation for 12weeks. The EULAR criteria of improvement according to DAS_{28} score was considered as primary efficacy variable. Baseline and end of study values were evaluated. The total study period was of 2 years.

Results: When DAS_{28} was compared between the two groups it was insignificant at baseline, 6 weeks and 12 weeks with a P-value 0.47, 0.91 and 0.86 respectively suggesting that both the groups were comparable throughout the study.

Statistical analysis: The data were analysed with Chi-square test, unpaired-t test and one way ANOVA. Values were expressed as numbers, percentages and mean ± SD. ANOVA was used to analyse the variables within the group and unpaired-t test to find the difference between the two groups.

Conclusion: LEF was found to have equal efficacy as the combination of MTX+HCQS in reducing DAS_{28} score with similar safety profile during our study and so may be considered as an initial therapy in active RA.

Keywords: DAS_{28}, Hydroxychloroquine, Leflunomide, Methotrexate, Rheumatoid Arthritis.

Introduction

Rheumatoid arthritis (RA) is a chronic, recurrent inflammatory disease of unknown etiology characterized by a symmetric, peripheral polyarthritis that leads to substantial disability, loss of productivity and increased mortality.[1] The global prevalence of RA is 0.5-1% and its incidence among females is 2 to 3 times than that of in males.[2-5] Disease activity is potentially reversible with drugs but the joint damage due to joint cartilage erosion and bony destruction is mostly irreversible.[6] Both these components cause physical function disorder, which severely reduces the quality of life (QoL).

The clinical diagnosis of RA is based on signs and symptoms of chronic inflammatory arthritis with laboratory and radiological findings. However the 2010 ACR-EULAR classification criteria is used for diagnosis of early disease and predict the prognosis. In advanced stages joint erosions and/or subcutaneous nodules may be found. [7] The ideal treatment of RA should aim at quick control of the inflammatory process, prevent joint erosions, preserve functioning with minimal toxic effects, be economical and accessible to majority of patients.

Disease-modifying anti-rheumatic drugs (DMARDs) are the fundamental treatment for inflammatory arthritis, and all other drugs such as non-steroidal anti-inflammatory drugs (NSAIDS) and glucocorticoids (GCs) should be considered as adjunctive therapies.[8] DMARD therapy generally begins with traditional molecules, such as methotrexate (MTX), hydroxychloroquine [HCQ],

or sulfasalazine [SSZ]. These agents are of proven benefit, generally well tolerated with known side-effect profiles. Of the three agents, MTX is the anchor drug. [9] But it is seen that in many of the patients on MTX alone, the signs and symptoms of RA are not controlled in the therapeutic doses, so the practice of combination therapy has increased. [10]

Study comparing combination therapy of MTX with HCQ versus MTX alone concluded the former to be more efficacious in terms of achieving 65% higher area under the curve values for MTX. In addition, C-max was lower and T-max longer for MTX on the day the combination of drugs was administered. This indicates that HCQ increases the potency of MTX and also sustains the effect. [11]

Leflunomide [LEF] is now being increasingly used by rheumatologists across the world. LEF is an effective, safe and well tolerated drug with an early onset of action. It is being used increasingly in both early and late stages.[12] In clinical trials, LEF was confirmed not only to improve measure of inflammatory markers such as erythrocyte sedimentation rate [ESR] and C-reactive protein, but also to improve subjective symptoms and objective findings of RA e.g. joint pain and swelling and measure of physical function and health related quality of life [QoL] and to inhibit joint damage. [13] The improvements in both functional ability and physician based efficacy measures seen with LEF after 1 year were maintained up to 5 years, demonstrating that early efficacy of LEF in patients with RA is sustained long-term. [14]

Based on the above literature, this study has been conducted to find out the effectiveness of the drugs MTX in combination with HCQ versus LEF by measuring Disease Activity Score (DAS_{28}) as well as their impact on quality of life (QoL) of the patient.

Materials and Methods

This study was a prospective, observational, comparative study conducted in Department of Pharmacology, VIMSAR, Burla and patient data was obtained from OPD/IPD of Department of Medicine, VIMSAR, Burla. Study was conducted from February 2021 to December 2022 [24 months] and a total of 50 number of patients of RA were selected in the study by convenience sampling methods, after satisfying the pre-defined inclusion and exclusion criteria.

Method of Data Collection:

Inclusion Criteria:

1. All the patients of age >14 years suffering from rheumatoid arthritis (RA).
2. ACR-EULAR score ≥6

Exclusion Criteria:

1. Pregnant and lactating women
2. Patients with history of any bleeding disorder
3. Patients with hepatic and renal disorders
4. Patients with cardiac disease
5. Patients with retinopathy
6. Patients with myelosuppression
7. Patients with any infective foci in the body

After selection of the patients, they were classified into two groups according to treatment protocol. Each group consisted of 25 no of patients. Patients in monotherapy group were treated with tablet leflunomide 20mg once daily. Loading dose of leflunomide was not utilized as efficacy ranging from 50% - 87% with monotherapy has been observed in various situations irrespective of absence of loading dose. The combination group received a combination of tablet methotrexate 7.5mg once weekly and tablet hydroxychloroquine 200mg twice daily.

At the start of the study all the baseline laboratory parameters were recorded, such as CBC, ESR, CRP, LFT, RFT, FBS, 2hPPBS, HbA1C, Anti-CCP and RA factor. Digital X-ray of wrist was done to rule out bony erosions and joint defects. Brief clinical history was taken and general clinical examination was done and DAS_{28} score was calculated accordingly. RAQoL score was calculated for each patient at the start of the study as per the response received through preformed questionnaire. All the patient related data was recorded as per the case report format. The blood investigations were repeated at 6 weeks and 12 weeks to assess treatment response and to monitor possible adverse effects. The baseline DAS_{28} score indicated the disease activity at the start of the study and the improvement in disease activity following therapy was assessed at 6 weeks and 12 weeks of treatment.

DAS28 score interpretation

Score	Interpretation
0 to <2.6	Remission
2.6 to ≤ 3.2	Low disease activity
>3.2 to ≤5.1	moderate disease activity
>5.1	high disease activity

The RAQoL consists of 30 questions with binary responses to be completed by the patient at the start and the end of their assessment with scores varying from 0(best) to 30(worst) indicating RA specific quality of life. [15] All the treatment emergent

adverse events were recorded at each visit in ADR reporting form (ver. 1.3) and were analysed at the end of the study.

Statistical analysis:

- Data was entered in Microsoft Excel version 2017.
- Data was analyzed with the IBM SPSS version 23.
- Chi-square test was used for comparison of qualitative variables.
- Unpaired t-test was used for comparison of quantitative variables.
- One way ANOVA was used for analysis of intra-group data.

Results

Out of the 50 patients selected 90% were females. The age distribution was most common in the 4th decade with a mean age of 39.46 years.

The baseline demographic parameters did not vary between the two groups [Table-1].

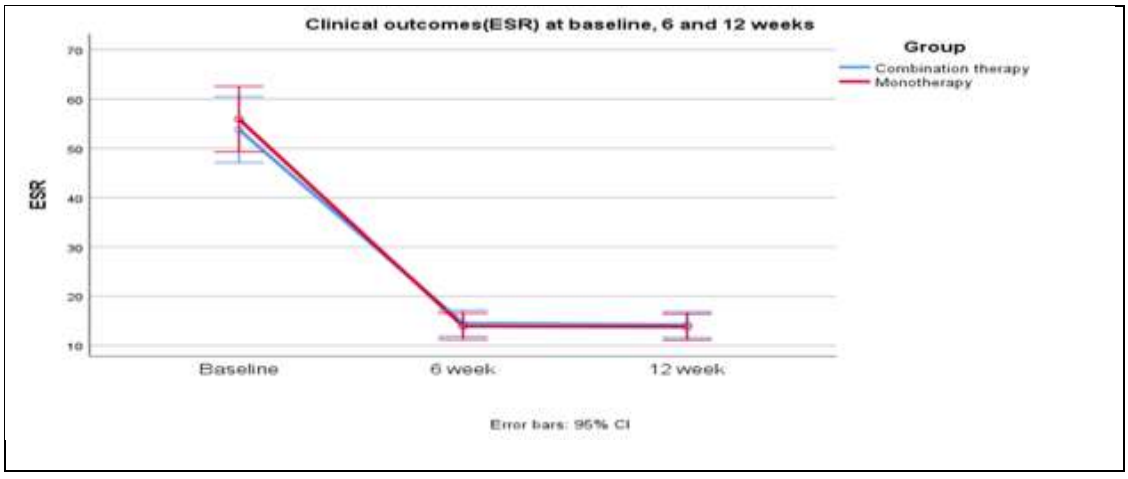
Table 1: Baseline demographic data and clinical characteristics of the patients

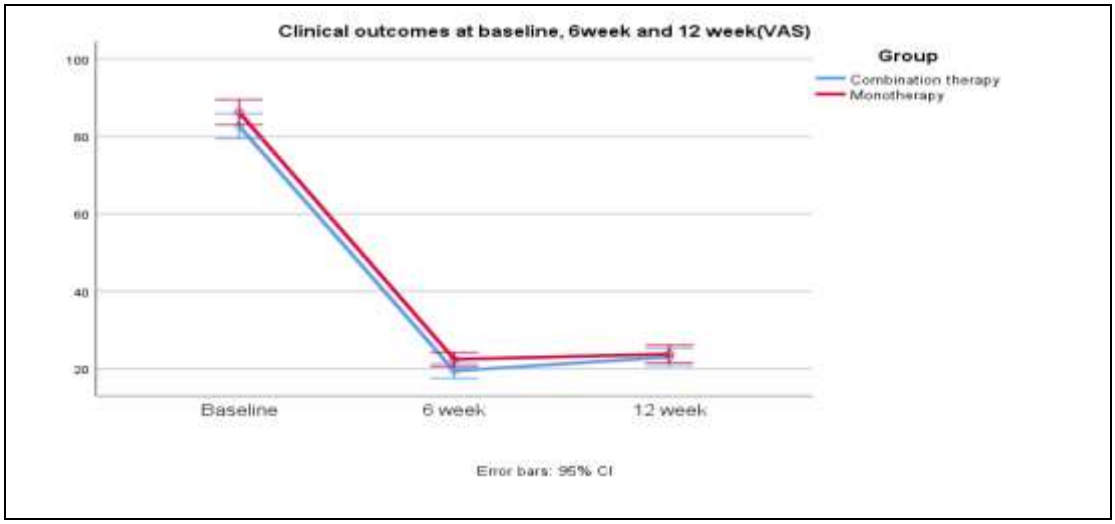
Characteristics	LEF group	MTX+HCQS group	P value
Number of patients	25	25	
Female sex[%]	88	92	
Age [years]	40±12.88	38.92±13.2	0.771
TJC	17.28±4.24	17.16±5.32	0.93
SJC	10.52±3.49	10.64±4.11	0.912
ESR	55.92±15.94	53.8±17.19	0.653
VAS	86.28±7.44	82.72±8.76	0.128
DAS_{28} score	7.21±0.44	7.1±0.61	0.47
RAQoL score	25±3.12	25.72±2.83	0.39
Data shown is Mean±SD, LEF=leflunomide,MTX=methotrexate,HCQS=hydroxychloroquine,TJC=tender joint count, SJC=swollen joint count, ESR=erythrocyte sedimentation rate, VAS=visual analogue score, DAS_{28}=disease activity score, RAQoL=rheumatoid arthritis specific quality of life score.			

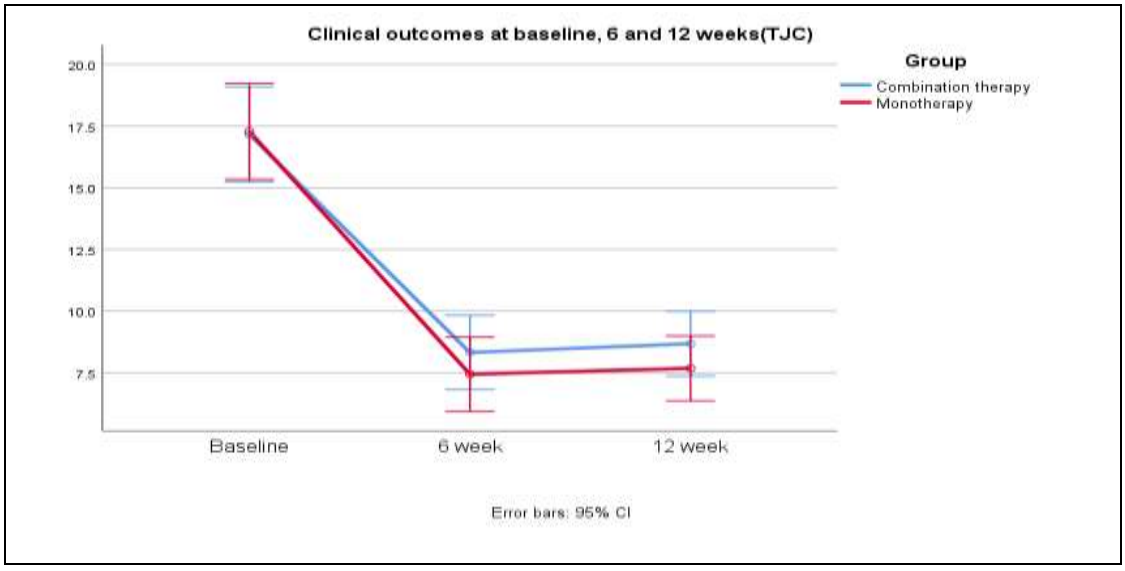
There was significant improvement in disease activity score in the leflunomide as well as in the methotrexate-hydroxychloroquine combination treatment group. Disease activity was reduced from high to moderate activity after 12 weeks of therapy in both the groups. Disease activity score within the groups decreased, while it didn't show any statistical significance between the groups [Table-2 and 3].

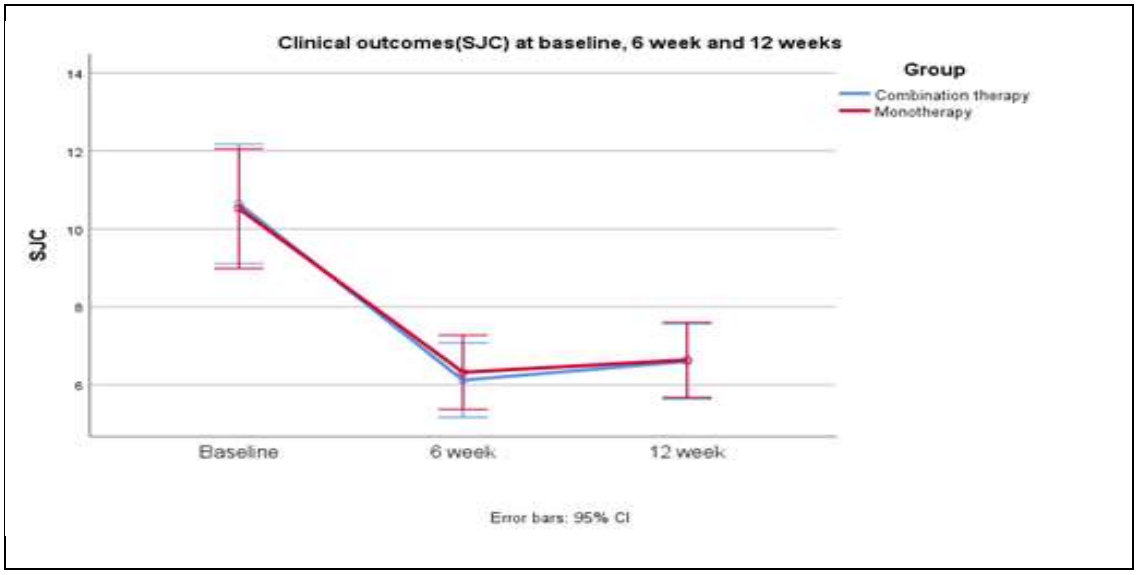
Table 2: Analysis of various parameters of DAS_{28} and its comparison in LEF group & MTX+HCQS group at baseline, 6weeks and 12weeks

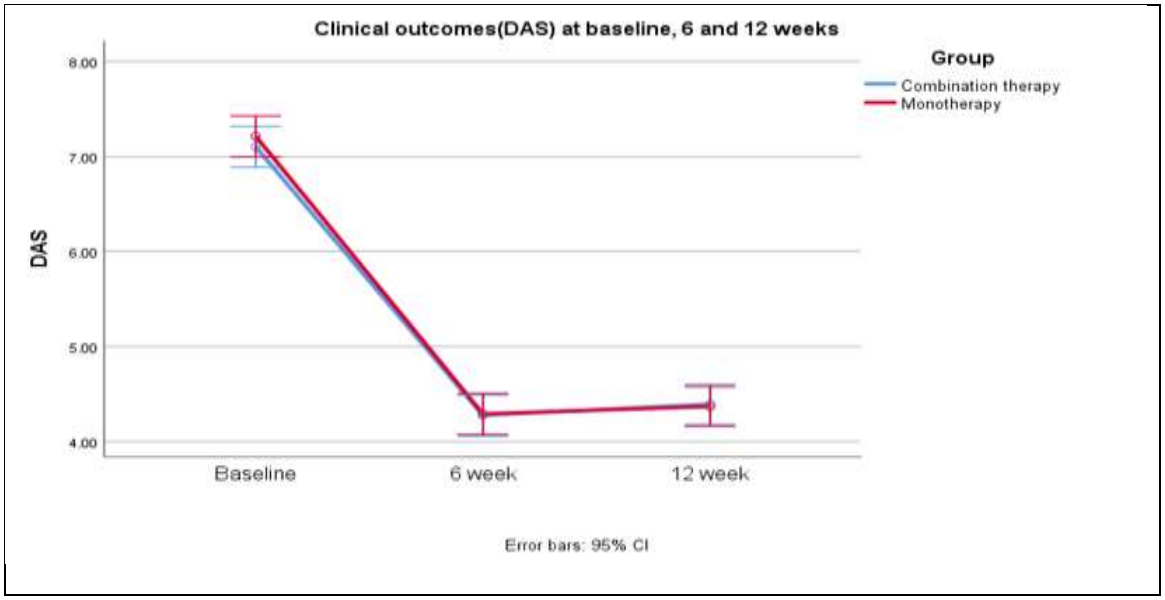
	LEF group				MTX+HCQS group			
	Baseline	6 weeks	12 weeks	P-value	Baseline	6 weeks	12 weeks	P-value
TJC	17.28± 4.24	7.44 ± 2.59	7.68 ± 2.3	.000*	17.16 ± 5.32	8.32 ± 4.61	8.68 ± 4.007	.000*
SJC	10.52 ± 3.49	6.32 ± 2.19	6.64 ± 2.09	.000*	10.64 ± 4.11	6.12 ± 2.53	6.6 ± 2.66	.000*
ESR	55.92 ± 15.94	13.88 ± 5.54	13.76 ± 4.51	.000*	53.8 ± 17.19	14.52 ± 7.55	14.24 ± 8.13	.000*
VAS	86.28 ± 7.44	22.4 ± 4.79	23.76 ± 6.19	.000*	82.72 ± 8.76	19.4 ± 4.34	23 ± 5.14	.000*
Data shown is Mean±SD, * Statistically significant, TJC=tender joint count, SJC=swollen joint count, ESR=erythrocyte sedimentation rate, VAS=visual analogue score								




Clinical outcomes at baseline, 6week and 12 week(VAS)
Group
Combination therapy
Monotherapy
100
80
60
40
20
Baseline
6 week
12 week
Error bars: 95% CI


Clinical outcomes at baseline, 6 and 12 weeks(TJC)
Group
Combination therapy
Monotherapy
20.0
17.5
15.0
12.5
10.0
7.5
Baseline
6 week
12 week
Error bars: 95% CI


Clinical outcomes(SJC) at baseline, 6 week and 12 weeks
Group
Combination therapy
Monotherapy
SJC
14
12
10
8
6
Baseline
6 week
12 week
Error bars: 95% CI



The above graphs are for individual parameters of disease activity score, showing a decreasing trend in both the treatment groups which is statistically significant [p<0.05].

Table 3: Analysis of disease activity score (Mean ± SD)

	LEF group	MTX+HCQS group	P value
Baseline	7.21 ±0.44[VA]	7.1 ± 0.61[VA]	0.47
6 week	4.29 ± 0.39[MA]	4.27 ± 0.65[MA]	0.91
12 week	4.36 ± 0.38[MA]	4.39 ± 0.62[MA]	0.86
P-value	0.000*	0.000*	
Disease activity: VA=very active, MA=moderate active, * Statistically significant, LEF=leflunomide, MTX=methotrexate, HCQS=hydroxychloroquine			

Compared with the baseline DAS_{28} score show a decreasing trend [above graph] in both the leflunomide(monotherapy) and the methotrexate-hydroxychloroquine (combination) therapy groups that is highly significant (P<0.05). RAQoL score, the instrument used in our study to assess the secondary outcome measure, i.e. quality of life (QoL).

We got mean scores of 25 and 25.72 in the leflunomide and combination therapy groups respectively prior to therapy. The post therapy scores were significantly lower in the individual study groups. The inter-group comparison of RAQoL scores revealed a significant improvement in the leflunomide recipients after 12 weeks [Table-4].

Table 4: Comparison of RAQoL

Duration	LEF group	MTX+HCQS group	P value
Baseline	25±3.12	25.72±2.83	0.39
12 weeks	6.84±2.79	8.84±3.85	0.04*
RAQoL=rheumatoid arthritis specific quality of life score, * Statistically significant, LEF=leflunomide, MTX=methotrexate, HCQS=hydroxychloroquine			

Reporting the hematological and clinical adverse events were our secondary objective. Total 8 (16% of participants) adverse events were reported in the study. None of them needed hospitalization.

In the LEF therapy group 2 cases of nausea/vomiting, 1 case of rash, 1 case of hair thinning and 1 case of asymptomatic elevation of liver enzyme was reported. In the MTX+HCQS combination therapy group 1 case of nausea/vomiting and 2 cases of skin rashes were reported.

Discussion

Inflammation is the central feature as well as the target of anti-rheumatic therapy. The optimal approach to the treatment of RA remains controversial because of high proportion of therapeutic failures noted with conventional monotherapy. The current approach to the treatment of RA is an early aggressive treatment. [16] Methotrexate remains the gold standard drug in the treatment of majority of patients with RA.[17] In our study, we have compared the efficacy of leflunomide with combination therapy of methotrexate and hydroxychloroquine in the

treatment of active RA over a period of 12 weeks. The disease activity score (DAS_{28}) was kept as the primary outcome measure. We have done a comparison of disease activity score both in the group as well as between the groups at baseline, 6 weeks and 12 weeks. The rheumatoid arthritis specific quality of life score (RAQoL) was the second outcome measure used to know the impact of the therapies on the quality of life of the patients.

The youngest patient was 16 years old and the oldest was 62 years old. The commonest age group affected was 41-50 years [38%]. It indicates that the common age group affected are of the 4^{th}-5^{th} decade. A female preponderance of 90% was seen in the study, indicates that rheumatoid arthritis commonly affects females.

The parameters of DAS_{28} score show a significant improvement in both the treatment groups, this indicates that both the regimens are effective in improving the clinical and hematological parameters in active rheumatoid arthritis. However, the comparison of individual parameters of DAS_{28} scores between the two treatment groups didn't show any significance. Which indicate that both the regimens are equally efficacious in this regard. The assessment of disease activity score [DAS_{28}] show that most of the patients had high disease activity prior to treatment, which significantly decreased to moderate values in both the treatment groups. This indicates that both monotherapy and combination therapy are effective in lowering disease activity amongst its recipients. However the comparison of the pre and post – therapy DAS_{28} scores between the two treatment groups didn't show any significance, which indicates that both these therapies are equally efficacious in lowering disease activity. On evaluation of response rates all of the patients were found to be moderate responders in both the therapeutic groups. The rheumatoid arthritis specific quality of life score [RAQoL] showed a significant improvement in the leflunomide monotherapy recipients after 12 weeks of therapy, which indicates that patients on leflunomide are experiencing better improvements in their quality of life as compared to those on methotrexate hydroxychloroquine combination therapy. The commonly encountered complication was nausea and vomiting, skin rashes in both the groups. However, none of the complications were serious. Therefore the safeties of the two groups were similar.

Conclusion

In conclusion, the efficacy of leflunomide monotherapy and methotrexate-hydroxychloroquine combination therapy was similar. However, the LEF monotherapy was a more economical treatment regimen than combination therapy.

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