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Original Article

Comparative evaluation of efficacy of leflunomide versus combination of methotrexate and hydroxychloroquine in patients of rheumatoid arthritis – An Indian experience

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ABSTRACT

Introduction: Methotrexate (MTX) is most widely used both as monotherapy and in combination therapy for the treatment of rheumatoid arthritis (RA). Combinations of different disease modifying anti-rheumatic drug/s provide additional or even have potentiating effects and therefore have become widely used. Leflunomide (LEF) alone has been seen to improve both the subjective symptoms and the objective parameters in RA.

Material and methods: An open label, prospective, comparative clinical study was conducted with 100 patients, divided into two groups of 50 patients in each. Subjects in group-1 were given LEF (20 mg/day) and group-2 received a combination of MTX (initial dose of 7.5 mg/week escalated to 25 mg/week) and hydroxychloroquine (HCQ) (200 mg twice a day). The various scores and parameters of disease activity were compared every 4 weeks for 12 weeks using Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI) scores.

Results: At 4 weeks, in group-1, DAS28 improved by 1.28 and CDAI improved by 16.82; while in group-2, DAS28 and CDAI improved by1.02 and 14.39 respectively. At 12 weeks, DAS28 and CDAI improved by 2.22 and 25.33 in group-1 and 2.35 and 26.53 in group-2 respectively. When DAS28 was compared in between groups, it was insignificant at baseline, 4 weeks, and 12 weeks with a *p*-value of 0.547, 0.960 and 0.182 respectively, which suggested that both groups were comparable throughout the study. The comparison of CDAI between the groups was insignificant at baseline, 4 weeks and 12 weeks with a *p*-value of 0.634, 0.893 and 0.333 respectively, which also suggested that disease activity in both group were comparable from baseline to 12 weeks.

Conclusions: LEF was found to have equal efficacy as the combination of MTX and HCQ in reducing DAS28 and CDAI score (i.e. from severe to moderate disease activity) and so may be considered as initial therapy in RA.

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown aetiology marked by a symmetric, peripheral polyarthritis that often results in joint damage and physical disability.[1] Disability may result from disease activity-related component that is potentially reversible with therapy and a joint damage-related component owing to the cumulative and largely irreversible effects of cartilage and bone breakdown.[2]

Disease modifying anti-rheumatic drugs (DMARD/s) are the fundamental treatment for inflammatory arthritis, and all other therapeutic approaches such as non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids should be considered as adjunctive therapies.[3] DMARD therapy generally begins with the traditional molecules, such as methotrexate (MTX), hydroxychloroquine (HCQ), or sulfasalazine (SSZ). These agents are of proven benefit, are generally well tolerated with known side-effect profiles and incur low cost. Of the three agents, MTX is the anchor drug.[4] But since in many patients MTX alone does not adequately control the signs and symptoms of RA at tolerated doses, the practice of combination DMARD therapy has increased.[5]

A study of combination of MTX with HCQ versus MTX alone concluded that MTX + HCQ are more effective than MTX alone. In this study, co-administration of MTX + HCQ resulted in area under curve ($AUC_{0-\infty}$) values for MTX that were on average 65% higher than those achieved, when MTX was administered alone, either orally or intravenously. In addition, C-max was lower and *t*-max longer for MTX on the day the combination of drugs was administered. Thus HCQ increases the potency of MTX and also sustains its effect.[6]

Leflunomide (LEF) is now being increasingly used by rheumatologists worldwide. LEF is an effective, safe and well tolerated drug with an early (4 weeks) onset of action and is being increasingly used in patients in both early and late stages.[7] 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 and to inhibit joint damage.[8] 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 in long-term.[9]

Based on the above literature, it was planned to conduct a study to compare the efficacy of MTX in combination with HCQ versus LEF by measuring Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI) in patients of RA.

2. Materials and methods

A total of 100 patients of active RA as per American College of Rheumatology-1987 criteria, reporting to outpatient department of Rheumatology Clinic of Pt. B.D. Sharma, P.G.I.M.S., Rohtak, Haryana, a tertiary care institute in North India, were enrolled in the study after approval from ethical committee. Patients with hepatic diseases, renal diseases, pulmonary diseases, uncontrolled hypertension and diabetes mellitus, pregnant or lactating mothers and those belonging to the reproductive age group and not willing to practice contraception (known or detected on baseline investigations) were excluded from the study. An informed consent was taken from all the subjects included in the study and informed them about all possible adverse effects related to drugs. RA patients with high disease activity (DAS28 >5.1 and CDAI >22) were enrolled in each group. A detailed history and clinical examination including routine laboratory investigations such as complete hemogram, ESR, serum creatinine, Sgot/Sgpt (IU/L) and baseline radiographs of hands were done.

The patients were categorised into two groups of 50 patients in each according to random no. table. Group-1 was put on LEF at a dose of 20 mg per day for 3 months while group-2 was put on a starting dose of 7.5 mg/week of MTX and patients were told to increase the dose by 2.5 mg/week to the maximum of 25 mg/week or depending on tolerability; along with HCQ 200 mg twice a day for 3 months. DAS28 and CDAI scores were calculated. Disease activity was calculated in both groups by DAS28 and CDAI at baseline, 4 weeks and at 12 weeks, was assessed at each visit by same individual to avoid inter-observer variation. All patients were followed till the completion of study except the patients who were withdrawn from the study as they develop side effects of drugs (one patient group-1 and two patients in MTX and HCQ group-2). Three new patients were enrolled (one in group-1 and two in group-2) and these were followed according to their parent group (Fig. 1). On every visit, patients of both the groups were evaluated for any drug side effects by history, clinical examination, and biochemical investigations. Data were collected and analysed by using Friedman ANOVA to compare variables within group and Mann–Whitney was used to analyse variables between two groups. Values were expressed as numbers, percentage, Mean ± SD. Statistical significance was measured by *p*-value <0.05 = significant.

3. Observations

Age in both the groups was comparable. The male:female ratio was 1:24 and 3:9.5 in group-1 and group-2 respectively. Mean disease duration of group-1 was 2.83 ± 1.3 years and of group-2 was 2.88 ± 1.4 years (Table 1).

The DAS28 score for both the groups showed significant reduction from baseline to 12 weeks in both group-1 and 2 ($p < 0.001$) (Table 2). When DAS28 was compared between two groups, both groups were comparable at baseline, 4 weeks and 12 weeks with *p*-value at baseline, 4 weeks, and 12 weeks 0.547, 0.960 and 0.182 respectively (Tables 1 and 2).

Similar to DAS28, CDAI score for both the groups showed significant reduction from baseline to 12 weeks in group-1 and group-2 ($p < 0.001$) (Table 2). The comparison of CDAI between the groups was insignificant at baseline, 4 weeks and 12 weeks with a *p*-value of 0.634, 0.893 and 0.333 respectively (Tables 1 and 2). This comparison also showed that both groups were comparable from baseline to 12 weeks. There were significant reduction in tender joint count (TJC), swollen joint count (SJC), patients global assessment (PGA), evaluator global assessment (EGA), global health (GH), ESR from baseline to 12 weeks in both groups ($p < 0.001$) however, the comparison of TJC, SJC, PGA,