Annals of King Edward Medical University

Research Article

Comparison of Effectiveness of Leflunomide against High Dose Methyl-Prednisolone in Multiple Sclerosis

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Abstract

Background: Leflunomide is a disease-modifying, anti-rheumatic drug, whose active metabolite Teriflunomide is licensed drug therapy for reducing progression in Multiple sclerosis. Intravenous high dose Methyl-Prednisolone is an established treatment for acute relapses of multiple sclerosis that escalates recovery. Intravenous methyl-prednisone also being used anecdotally for the prevention of relapses.

Methods: Each patient after enrollment in the study received treatment for 1 year. A total of 30 patients, 15 patients in each group were taken. Patients fulfilling inclusion criteria and giving written informed consent were randomly divided into 2 groups (Group A and Group B) using a computer-generated random numbers table. Group A patients received Leflunomide 20mg with a loading dose of 3 tablets for 3 days and then once daily for one year. And group B patients received high-dose intravenous Methyl Prednisolone 1g monthly for a period of one year.

Results: Methyl Prednisolone group, 5 (33.3%) had only 1(%) relapse and 10 (66.7%) cases had no relapse. In contrast, Leflunomide group, no relapse was recorded. The frequency of relapse was consequently statistically higher in Methyl Prednisolone group, p-value < 0.05. In respect of, a number of lesions on MRI; Methyl Prednisolone group demonstrated no change in 4 (26.67%) cases and 11 (73.33%) cases had lesions increased from baseline. Whereas, in the Leflunomide group the number of lesions significantly decreased (p-value < 0.05). Significant improvement in Expanded disability status was observed leflunomide group (p-value < 0.05).

Conclusion: Leflunomide was more effective in preventing relapses and in decreasing disease activity on MRI, as compared with high dose monthly Methyl-prednisone in patients with Multiple Sclerosis.

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Key Words: Demyelinating disease, Multiple Sclerosis, Leflunomide, Intravenous Methyl Prednisolone (IVMP), Lesions on MRI, Relapse.

Introduction

Multiple sclerosis is a chronic, progressive inflammatory disease with accumulating disability due to relapses and thus can lead to the deteriorating quality of life.[1] The main aim of therapy in multiple sclerosis always has been to hinder progression and minimize disability.

There is currently a myriad of drugs approved by the FDA in relapsing forms of multiple sclerosis.[2]. Cost-effectiveness of drugs has always been a concern in developing nations.[2] The expense of conventional drugs is almost identical to contemporaneous approved therapies in multiple sclerosis.[3] Besides, there are numerous drugs which are effective but are not

readily available in developing countries, such as Pakistan, and those drugs which are accessible, their annual cost per person is quite high. Teriflunomide is available with a brand name of Aubagio in Pakistan with a monthly cost of more than a hundred thousand[4]. Conversely. Leflunomide's average cost per tablet is approximately 20 rupees.

Intravenous high dose Methyl Prednisolone (IVMP) is an established treatment for acute relapses of multiple sclerosis, therefore accelerate recovery[5]. However, whether it prevents further relapses hasn't been studied appropriately. A five-day course of a high dose of IV methylprednisolone every four to six months slowed progression of brain atrophy as measured on MRI, as compared to treatment for relapses only in relapsing-remitting MS 6 Intravenous high dose of Methyl Prednisolone every two months showed partial, dose-dependent benefit in secondary progressive MS[5].

Leflunomide is an oral disease-modifying drug used in patients with rheumatoid arthritis and psoriasis. 4 It is not an approved FDA treatment in the relapsing form of multiple sclerosis. Though, its active metabolite teriflunomide has been licensed by the FDA as a first-line oral drug treatment in the relapsing-remitting form of multiple sclerosis.[7] Leflunomide and teriflunomide both are similar in structure and are inhibitors of pyrimidine synthesis.[7] Leflunomide is a pro-drug that is converted into active metabolite teriflunomide.[7] Leflunomide 20mg is equivalent to 14mg of teriflunomide.[8] Efficacy of leflunomide has not been much studied in the treatment of multiple sclerosis. Whether Leflunomide alters or modulates disease progression or disease activity is unknown.

In contrast to leflunomide, the effectiveness of teriflunomide has been assessed extensively in two Phase III clinical trials: Teriflunomide in Multiple Sclerosis Oral (TEMSO, Clinical Trials) and Teriflunomide Oral in people with relapsing multiple sclerosis (TOWER).[9] Teriflunomide has been proven safe with consistent results across both studies and at both doses i.e., 7mg and 14mg; no adverse events (AEs) have been reported regarding Teriflunomide use for up to 10 years or more[9].

Teriflunomide decreased the annualized relapse rate (ARR) with relative risk reductions of 31.2% and 31.5%, at doses of 7mg and 14mg respectively (P< 0.001 for both in comparison with placebo). Teriflunomide also is shown to decrease total lesion volume by 39.4% and 67.4% at 7mg and 14mg respectively.[7,8,9]

This study was designed to evaluate the clinical efficacy of leflunomide and role of high dose Methylprednisolone in lowering relapse rate and impact on disease activity on MRI.

Methods

The study was a prospective, therapeutic, randomized parallel-group, open-label, pilot study of one-year duration conducted in King Edward Medical University, Department of Neurology. Patients between ages of 18-55, who met revised 2017 McDonald's criteria[10] for diagnosis, had a relapsing form of multiple sclerosis[10], with or without progression were enrolled in the study. Relapse was defined as the appearance of new symptoms or reappearance of old symptoms once they have improved. Patients were excluded from the study if they had any other systemic illness, pregnant women and women who were breastfeeding.

Patients presented in outpatient and inpatient department of Neurology were taken. The protocol was approved by the university ethical committee and institutional review board; all patients gave written informed consent, upon hospital admission, before enrollment in the trial study.

Subjects were randomly divided into 2 groups (Group A and Group B) using a computer-generated random numbers table. As recommended by the Board of Studies of Dept. of Neurology, each group consisted of 15 patients and the total number of patients were 30. Group A patients received Leflunomide 20mg with a loading dose of 60mg for 3 days consecutively followed by once-daily dose for one year. Group B patients received IV Methyl Prednisolone 1g once a month for 1 year. Researcher himself assessed a number of relapses. Change in a number of lesions was reported by radiologist. Patients were followed every 3 months regularly & physical and neurological examination was carried out at each visit. Blood pressure of patients was recorded at baseline and then at every visit. Complete Blood count /peripheral blood picture, liver function tests, serum creatinine, blood urea nitrogen, and serum electrolytes were performed at baseline and then

every month for the first 3 months and then every 3 months until 1 year. MRI scans (for both groups) were obtained at baseline and on the completion of study. Disability was assessed by Expanded disability status scale (EDSS)[9] at baseline and at the end of a trial. All tests of patients were done free of cost.

Patients visited the hospital after the onset of a relapse. Suspected and confirmed relapses were treated with intravenous high dose Methyl Prednisolone 1g for 3 days followed by oral prednisolone tapering for both groups.

Data Analysis Procedure:

Data were analyzed by SPSS 20.0. Data for age, gender, type of MS were described by using frequency and percentages. Chi-square test was used to see the relation of relapses and increase, decrease or no change in a number of lesions at end of a treatment trial. P-value ≤ 0.05 was considered significant.

Results:

There was a total of 30 patients of Multiple Sclerosis.

14 (46.7%) male and 16 (53.3%) female participants. The mean age of cases in Leflunomide group and in Methyl Prednisolone group was 29.67 ± 4.86 years and 35 ± 6.55 years respectively. There were 7 (46.7%) males and 8(53.3%) females in each group.

There were 12 (80%) subjects with Relapsing Remitting (RRMS) subtype and 3 (20%) with Secondary Progressive (SP) subtype in Leflunomide group. There were 14 (93.3%) patients with Relapsing Remitting (RR) subtype and 1 (6.7%) with Secondary Progressive (SP) subtype in Methyl Prednisolone group. There were total of 26 patients with Relapsing Remitting (RR) subtype among them 14 were males and 12 were females. There was a total of 4 patients with Secondary Progressive (SP) subtype and all were females. Mean age of cases in Relapsing Remitting (RR) subtype was 31.58 years and in Secondary Progressive (SP) subtype was 37.25 years.

Table 1: *Comparison between MS subtype and relapse*

Relapse	MS Subtype		
	RR subtype	SP subtype	Total
No relapse	22 (84.6%)	3 (75%)	27 (90%)
1 relapse	4 (15.4%)	1 (25%)	3 (10%)
Total	26 (100%)	4 (100%)	30 (100%)

Leflunomide significantly reduced annual relapse rate compared to high dose methyl-prednisolone. In Methyl Prednisolone group, 5 (33.3%) cases had only 1 relapse and 10 (66.7%) cases had no relapse while in Leflunomide group, 15 (100%) cases had no relapse, the frequency of relapse was statistically higher in Methyl Prednisolone group, p-value < 0.05. Only 4 patients of Relapsing Remitting Subtype and 1 patient with Secondary Progressive Subtype had a relapse.

Table 2: *Comparison between High dose Methyl-prednisolone and Leflunomide*

		Study Groups		Total
		High dose Methyl-Prednisolone (n = 15)	Leflunomide (n = 15)	
Relapse	No relapse	10 (66.7%)	15 (100%)	25 (83.3%)
	1 relapse	5 (33.3%)	0 (0%)	5 (16.7%)
	Total	15 (100.0%)	15 (100.0%)	30 (100.0%)

Patients in Leflunomide group showed an ample reduction in total lesion volume on MRI in contrast to group B. In Leflunomide group; number of lesions decreased in 4 (26.67%) ($p < 0.05$), in 60% of patients no changes in number of lesions were perceived on MRI cases. Increase disease activity was demonstrated in only 2 (13.33%) in Leflunomide group. While in Methyl Prednisolone group, no changes were observed on MRI in 4 (26.67%) subjects. But, rather 11 (73.33%) showed a high frequency of lesions comparative to baseline.

Table 3: *Comparison of Changes in Lesions in both groups*

		Study Groups		Total
		Methyl-Prednisolone (n=15)	Leflunomide (n=15)	
Change in Lesions (on MRI) from baseline	Decreased	0(0%)	4(26.67%)	4(13.3%)
	No change	4(26.67%)	9(60%)	13(43.33%)
	Increased	11(73.33%)	2(13.33%)	13(43.33%)
Total		15(100.0%)	15(100.0%)	30(100.0%)

Before treatment the mean EDSS in was Methyl Prednisolone group 6.60 ±4.37 while after treatment was 6.80 ± 4.57, p-value > 0.05 while the mean EDSS before treatment in Leflunomide group was 5.47 ± 1.73 and after treatment, the mean EDSS was 3 ± 3.02 respectively, p-value < 0.05. The mean EDSS was same, before and after treatment in high dose intravenous Methyl-Prednisolone group. Although, it was significantly lower in the Leflunomide group at the end of study, p-value < 0.05.

Table 4: *Comparison of EDSS between Group A and Group B*

	Study groups	t-test	P-Value
EDSS (before)	Methyl Prednisolone (n = 15)	1.38	(0.189)
EDSS (after)	Methyl Prednisolones (n = 15)		
EDSS (before)	Leflunomide (n = 15)	4.34	(0.001)
EDSS (after)	Leflunomide (n = 15)		

No adverse events in high dose Methyl-prednisone were reported during the trial period. Mild elevation in transaminases was observed in 2 patients, that eventually improved with decreasing the dose for some time, but did not lead to discontinuation of therapy.

Discussion

Leflunomide showed marked benefit in reducing in clinical annual relapse rate in relapsing forms of multiple sclerosis in this study as compared with monthly high dose methyl-prednisone. Moreover, it showed modest improvement in lesion volume on MRI after the trial. In 4 (26.67%) cases the number of lesions decreased, and in 9 (60%) cases no change in existing number of lesions was demonstrated. Significant improvement in EDSS was demonstrated in the leflunomide group. while no change in disability scale was noted in (IVMP) intravenous high-dose methyl-prednisolone subjects. These findings conclude that high dose methyl-prednisolone does not have a long-term disease modifying effects. The benefits that are observed with leflunomide in this study are similar to other licensed oral disease-modifying treatments in relapsing forms of multiple sclerosis.

There is multitude of studies on the clinical efficacy of teriflunomide in multiple sclerosis, TOWER, TEMSO, TOPIC to name a few[8]. However, there is scarce or no data available on the use of leflunomide in relapsing forms of multiple sclerosis to compare with our study. There is a one case series on off-label use of leflunomide; Leflunomide in multiple sclerasis conducted in the United States by Daniel Kantor and et al, presented in a consortium of multiple sclerosis centres in 2018, reported that leflunomide can be a supplement to a teriflunomide in efficacy. They enrolled a total of 53 patients from five different MS centres, of which 85% were women. Mean age at the time of initiation of therapy was 61 years. Concerning MS subtype, 64% of patients had relapsing-remitting MS, while 32% had secondary-progressive MS and 2 had primary-progressive MS. Only 17% of

patients had comorbid RA, and the leflunomide was being used to treat both the MS and RA; another 6% had comorbid Crohn's disease. Almost half of the patients were started on leflunomide due to financial constraints in the study.

Adverse effects of leflunomide include diarrhoea, nausea, hepatotoxicity or raised transaminases levels, hypertension, interstitial lung disease, rash, alopecia, hair thinning, pancreatitis, leukopenia can lead to infections, and peripheral neuropathy.[11] In previous studies, 2-3% of patients reported raised alanine aminotransferase (ALT) levels that resulted in discontinuation of the drug.[12] In our study, no adverse effects caused by leflunomide were reported. A mild increase in liver function tests was observed in 2 patients but therapy was not discontinued. During one-year exposure of therapy with leflunomide, a rare adverse event such as progressive multifocal leukoencephalopathy 13 was not reported by any of our patients in the leflunomide group.

Although MP is a recognized treatment of acute relapses, the long-term effects of the MP can be seen over an extended period. High doses of ivMP are considered to be effective in reducing the number of MRI contrast-enhanced lesions at 30 and 60 days, mainly by decreasing the rate of new lesion formation 14. In contrast, in our study, high dose ivMP did not decrease total lesion volume on MRI and did not have any effect on EDSS. An increase in MRI disease activity was observed in 73.3%. Adverse effects such as hypertension, diabetes mellitus, cataracts and avascular necrosis of femoral head 15 were not observed in any of our patients during or after the study.

Limitations of the Study

The study has some potential limitations. First and foremost, the sample size is too small for generalization of results. Secondly, limited research is available on leflunomide in multiple sclerosis. Furthermore, no head to head trials has been done previously to compare the efficacy of leflunomide with methylprednisolone.

Conclusion

In conclusion, leflunomide showed superior efficacy to high dose Methyl-prednisolone as it was associated with a fewer number of relapses and the number of lesions on MRI. Therefore, it can be considered as a surrogate, in low income or middle-income countries, to teriflunomide. Further research on leflunomide with bigger sample size is needed.

Ethical Approval: Given
Conflict of Interest: The authors declare no conflict of interest
Funding Source: None

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