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Original Research Article

Comparison of combination therapy of methotrexate with etanercept and etanercept alone in psoriasis in Tertiary care center in South India

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ABSTRACT

Introduction: Psoriasis is a disorder of chronic nature. But the present day systemic therapies for psoriasis of moderate to severe nature are associated with toxicity and also have a greater level of displeasure in the patients. Hence the current focus for treatment is with intermittent or combination therapy that helps to overcome the loss of effectiveness in treatment over time and decrease the side effects as a result of cumulative toxicities during monotherapy.
Aim: To assess the effectiveness of oral Methotrexate and Etanercept combination therapy in comparison to Etanercept monotherapy for treatment of moderate to severe plaque type of psoriasis among patients.
Materials and Methods: This was a prospective analytical study conducted in dermatology OPD of Madras Medical College, a tertiary care centre in south India between August 2015 and July 2016. About Forty subjects clinically diagnosed with plaque type of psoriasis based upon the clinical history and morphology of the dermatological lesions were included in this hospital based study depending on inclusion and exclusion criteria and were randomly allocated into two groups. Group C: Combination therapy with oral methotrexate and Etanercept and Group M:Monotherapy with Etanercept alone. All the patients were reviewed every 4 weeks at intervals of 0,4,8 and 12 weeks for complaints and for assessment of clinical response using PASI scoring and DLQI scoring and other investigations. Data was compiled and analyzed with the help of Statistical Package for Social Science (SPSS) Version 20.0.
Results: Mean age of the study population was 37.43 ± 10.1 years. Twenty two subjects were males (55%) and eighteen subjects were females (45%). The subjects who received Group C (Methotrexate and Etanercept combination therapy) therapy achieved 75% reduction of PASI in comparison to subjects who received Group M (Etanercept monotherapy) after 8 weeks (30% vs 5%) and after 12 weeks (100% vs 50%). Also Group C showed good response to treatment after 12 weeks in comparison to Group M (85% vs 50%) and this difference in proportion of treatment response between the two groups was statistically significant. Subjects who received Group C showed greater decline (77.4% vs 68.7) in DLQI score after 12 weeks in comparison to subjects who received Group M.

1. Introduction

Psoriasis is a disorder of chronic nature[1] which is noncontagious, multisystem and immune mediated with a genetic predisposition. Psoriasis usually expresses itself typically as scaly plaques over the subject's elbows, knees, scalp, in lumbosacral areas or intergluteal clefts and glans penis. Many types of psoriasis are usually identified in common practice, and the most common type being the plaque type and about twenty percentage of the patients suffer from a disease of moderate to severe intensity.[2] Psoriasis of any severity seems to have an intense effect on the health related QOL. Although the use of topical treatments may be sufficient for the control of mild type, psoriasis of moderate-to-severe nature will mostly require the use of systemic drugs or use of phototherapy or both.[3]

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But the present day systemic therapies for psoriasis of moderate to severe nature are connected with toxicity and they also have a greater level of displeasure in the patients.[3] Hence the current focus for treatment is with intermittent or on combination therapy mainly to overcome loss of effectiveness in treatment over time and the side effects as a result of cumulative toxicities during monotherapy.[4–8] Etanercept[9–14][16] and Methotrexate[15] are commonly used for systemic therapies in subjects with psoriasis. Both of them have a satisfactory level of safety individually, are tolerated well and improve the QOL.[16] Combining Etanercept along with methotrexate is permitted for treatment of psoriatic arthritis,[17] for those who do not react to any single drug sufficiently, and "The European League Against Rheumatism" has also recommended the same.[18] But the use of this combination has not been investigated widely in psoriasis.[15,19] So, in this study, we evaluated the Combination of Etanercept plus Methotrexate vs Monotherapy of etanercept in patients with plaque psoriasis of moderate to severe intensity.

2. Materials and Methods

This was a prospective analytical study conducted in dermatology OPD of Madras Medical College, a tertiary care centre in south India between August 2015 and July 2016. About Forty subjects clinically diagnosed with plaque type of psoriasis based upon the clinical history and morphology of the dermatological lesions were included in this hospital based study. The protocol of the study was approved by the Institutional ethical committee before commencing the study. Informed written consent was obtained from all the patients before inclusion into the study. The Inclusion criteria for the study were 1. Patients of above 12 years and below 60 years of age 2.Patients of both sexes 3.Patients willing for systemic therapy 4.Primary case of moderate to severe plaque type of psoriasis 5.Patients willing for follow-up in the 4,8 and 12 weeks. The exclusion criteria were1.Children below 12 years and elderly patients more than 60 years 2.Pregnant and lactating women 3.Patients who were not willing to come for follow-up 4.Any serious systemic illness and infections 5.Concurrent immunodeficiency state 6.Patients with impaired renal function or renal disease 7. Patients with hepatitis, severe anaemia, leukopenia or thrombocytopenia. Informed written consent was obtained from all patients before initiation of treatment. The 40 clinically diagnosed psoriasis cases were randomly allocated into two groups of 20 cases each. Group C: Combination therapy with oral methotrexate and Etanercept. They are given Tab. Methotrexate 7.5 mg weekly as 2.5mg tablet three tablets a week according to Weinstein-Frost regimen and up titrated gradually till 15mg according to the response and Inj. Etanercept 50mg subcutaneously once a week after the preliminary investigations. Patients were instructed properly to consume the tablet after food in divided doses. After one week, all the hematological investigations for ruling out myelosuppression and also liver enzymes were tested for elevation. Chest X-ray was repeated at the end of 12 weeks. Group M:Monotherapy with Etanercept alone. They were given only Inj. Etanercept 50mg subcutaneously once a week after the preliminary investigations. All the patients were reviewed every 4 weeks at intervals of 0,4,8 and 12 weeks for complaints and for assessment of clinical response using PASI scoring and DLQI scoring and other investigations. Data was compiled and analyzed with the help of Statistical Package for Social Science (SPSS) Version 20.0.

3. Results

Fourty cases from the outpatient department of age group above 12 years and below 60 years of age, diagnosed clinically as moderate to severe plaque type of psoriasis and not undergone any treatment prior were enlisted in the study. The mean age Mean age ($\pm$ S.D) group of the study population was: 37.43 (10.18) years. Of these 40 cases, 22 (55%) were male sex, 18(45%) were female sex. The inferential statistics for all the statistical tests of significance, p value of <0.05 was considered to reject the null hypothesis. The association between categorical variables was determined by using chi-square test and continuous variables by using parametric tests like student t test.

The mean PASI score at baseline, 4, 8 and 12 weeks according to group of treatment (n=40) for Group C (Methotrexate + Etanercept combination therapy) were 33.94,19.66, 9.88 and 2.59. For Group M (Etanercept monotherapy) were 30.02, 21.46, 14.04 and 6.88. Group I showed greater decline in PASI score in comparison to subjects who received Group M during 4,8 and 12 weeks. Based on the distribution of the study population the subjects who received Group C had a low mean PASI score at 4, 8 and 12 weeks in comparison to subjects who received Group M and this difference in mean PASI score was statistically significant at 8 weeks ($p= 0.002$) and 12 weeks ($p= <0.001$) ($p<0.05$) but not at 4 weeks($p=0.280$). The subjects who received combination therapy had a high mean PASI score at baseline (33.94) in comparison to subjects who received monotherapy (30.02) but this difference was not statistically significant ($p>0.05$) (Table 1). According to the reduction of mean PASI score the subjects who received Group C had a higher reductions of mean PASI score at 4, 8 and 12 weeks in comparison to subjects who received Group C and this difference in reductions of mean PASI score was statistically significant at all time period ($p<0.001$). The combined therapy showed almost 8 points higher decline in PASI score when compared to monotherapy after 12 weeks (Table 2).

The Percentage Mean reduction of PASI score at baseline, 4, 8 and 12 weeks for Group C showed greater percentage decline in PASI score (0, 42.29%, 71.09% and 92.74%) in comparison to subjects who received Group M (0, 28.78%, 53.61% and 77.76%) and this difference in reductions of mean PASI percent score was statistically significant at all time periods ($p<0.001$). The subjects who received combination therapy showed almost 15% higher decline in PASI score than subjects who received monotherapy after 12 weeks (Table 3).

A higher proportion of subjects who received Group C achieved 75% reduction of PASI in comparison to subjects who received Group M after 8 weeks (30% vs 5%) and after 12 weeks (100% vs 50%) and this difference between the two groups was statistically significant ($p<0.05$) (Table 4). According to response to treatment in percentage reduction the subjects who received Group C showed good response after 12 weeks in comparison to subjects who received Group M (85% vs 50%) while 50% of subjects who received Group M showed only moderate response and this difference in proportion of treatment response between the two groups was statistically significant ($p<0.001$)

(Table 5). The study subjects according to DLQI (Dermatology Life Quality Index) from baseline, 4, 8 and 12 weeks Subjects who received Group C showed greater decline in DLQI score (38, 25, 14 and 9) after 12 weeks in comparison to subjects who received Group M (34, 26, 18 and 11). The adverse effect reported among subjects who received Group M were nausea (2 cases) while gastritis and pain at injection site was reported by 1 case each. Among subjects who received Group M, headache and pain at injection site was reported by 1 case each.

4. Discussion

This was a prospective analytical study conducted among 40 clinically diagnosed subjects with plaque type of psoriasis based upon the clinical history and morphology of the dermatological lesions with a view to compare the therapeutic efficacy of combination therapy consisting of oral methotrexate and etanercept against the use of monotherapy with etanercept for treatment of moderate to severe plaque type of psoriasis. There were very few research studies comparing the above two groups of treatment and not many especially in India. The age group of 40 cases ranged from 20 to 56 years. The Mean age ($\pm$ S.D) group of the study population was: 37.43 (10.18) years. Of these 40 cases, 22(55%) were male sex, 18(45%) were female sex. The 40 cases in the study were randomly allocated to each of the two groups with one group receiving combination therapy consisting of oral methotrexate and etanercept (there were 11 male cases and 9 female cases) and the other group receiving monotherapy with etanercept (there were 11 male cases and 9 female cases) for treatment. Both the groups were matched for age, gender distribution and also duration of the disease and baseline PASI score. They were followed for 12 weeks with an interval of four weeks in between. Hence there were 3 follow-up visits at 4 weeks, 8 weeks and 12 weeks after the baseline visit. The endpoint used in this study to compare the therapeutic efficacy of above mentioned treatments was achievement of 75% reduction in baseline PASI score.

The subjects who received combination therapy had a mean PASI score at baseline of 33.94 in comparison to 30.02 among subjects who received monotherapy but this difference was not statistically significant ($p>0.05$). These mean scores are lower than Gottlieb et al[20] as he observed mean scores of 18.3 and 18.2 respectively in both groups, respectively. The subjects who received combination therapy had a low mean PASI score at 4, 8 and 12 weeks in comparison to subjects who received monotherapy and this difference in mean PASI score was statistically significant 8 and 12 weeks ($p<0.05$) but not at 4 weeks. The subjects who received combination therapy had a higher reductions of mean PASI score at 4, 8 and 12 weeks in comparison to subjects who received monotherapy and this difference in reductions of mean PASI score was statistically significant at all time period. On the contrary, Combe B et al[21] found that difference in reductions of mean PASI score between the groups was not statistically significant although he studied only psoriatic arthritis patients. The subjects who received combination therapy showed almost 8 points higher decline in PASI score than subjects who received monotherapy after 12 weeks. The subjects who received combination therapy showed 92.7% decline in PASI score in comparison to 77.7% decline in subjects who received monotherapy after 12 weeks and this difference between the 2 groups was statistically significant. These findings are similar to Spuls et al.[21] The subjects who received combination therapy showed almost 15% higher decline in PASI score than subjects who received monotherapy after 12 weeks. This decline in PASI score % was lower than 24% as reported by C.Zachariae et al.[19] High proportion of subjects who received Methotrexate and Etanercept combination therapy achieved 75% reduction of PASI in comparison to subjects who received Etanercept monotherapy after 8 weeks (30% vs 5%) and after 12 weeks (100% vs 50%) and this difference between the two groups was statistically significant. The achievement of PASI 75 was in concurrence with Dhiret al[22] but the difference in achievement of PASI 75 was higher than in comparison to Gottilieb et al[20] who reported PASI 75 reduction of 69% vs 48.9% in the groups after 12 weeks. C.Zachariaeet al[19] reported PASI 75 reduction of 57% vs 29% in the groups after 12 weeks.

A higher proportion of subjects who received Methotrexate and Etanercept combination therapy showed good response after 12 weeks in comparison to subjects who received Etanercept monotherapy (85% vs 50%) while 50%

Table 1: Distribution of the study population according to mean PASI score at baseline, 4, 8 and 12 weeks and group of treatment (n=40)

PASI Score	Group	Mean	Std. Deviation	Mean difference	p value
Baseline	C	33.940	6.2016	3.920	0.051
	M	30.020	5.9597		
4 Weeks	C	19.660	4.6231	-1.800	0.280
	M	21.460	5.7045		
8 Weeks	C	9.875	3.4333	-4.165	**0.002**
	M	14.040	4.4863		
12 Weeks	C	2.585	1.9225	-4.295	<**0.001**
	M	6.880	3.4630		

Table 2: Distribution of the study population according to reduction of mean PASI score from baseline after 4, 8 and 12 weeks and group of treatment (n=40)

PASI Score reduction	Group	Mean	Std. Deviation	Mean difference	p value
Reduction after 4 weeks	C	14.280	3.1825	5.720	<**0.001**
	M	8.560	2.9343		
Reduction after 8 weeks	C	24.065	5.0355	8.085	<**0.001**
	M	15.980	4.2790		
Reduction after 12 weeks	C	31.355	5.2786	8.215	<**0.001**
	M	23.140	4.4652		

Table 3: Distribution of the study population according to reduction in percentage of PASI score from baseline after 4, 8 and 12 weeks and group of treatment (n=40)

PASI Score reduction in percentage	Group	Mean % reduction	Std. Deviation	Mean % reduction difference	p value
Percent reduction after 4 weeks	C	42.29	6.966	13.51 %	<**0.001**
	M	28.77	9.453		
Percent reduction after 8 weeks	C	71.08	8.821	17.47 %	<**0.001**
	M	53.61	11.328		
Percent reduction after 12 weeks	C	92.74	4.952	14.98 %	<**0.001**
	M	77.75	9.694		

Table 4: Distribution of the study subjects according to achievement of 75% reduction of PASI after 8 and 12 weeks (n=40)

75% reduction in PASI Score		Group C		Group M		p value
		N	%	N	%	
After 8 weeks	Not achieved	14	70.0%	19	95.0%	0.037
	Achieved	6	30.0%	1	5.0%	
After 12 weeks	Not achieved	0	0.0%	10	50.0%	<0.001
	Achieved	20	100.0%	10	50.0%	

Table 5: Distribution of the study subjects according to response to treatment in percentage reduction of PASI after 12 weeks (n=40)

Response to treatment (% reduction in PASI)	Group C		Group M	
	N	%	N	%
Excellent (100%)	3	15.0%	0	0.0%
Good (75 to 100%)	17	85.0%	10	50.0%
Moderate (50 to 75%)	0	0.0%	10	50.0%
Poor (<50%)	0	0.0%	0	0.0%
Total	20	100.0%	20	100.0%
Chi-square value: 14.815	df = 2		p value = 0.001	

of subjects who received Etanercept monotherapy showed only moderate response and this difference in proportion of treatment response between the two groups was statistically significant. Subjects who received Methotrexate and Etanercept combination therapy showed greater decline (77.4%) in DLQI score after 12 weeks in comparison to subjects who received Etanercept monotherapy (68.7%). This finding is comparable to the finding of C.Zachariae et al[19] who reported 74% and 48% in the two groups, respectively.

5. Conclusion

The study shows that combination therapy with methotrexate and etanercept is superior to etanercept monotherapy in treatment of moderate to severe plaque type of psoriasis as it achieved greater reductions in PASI score and greater achievement of PASI 75% reduction after 12 weeks without any significant difference in occurrence of adverse events. Even though this study was not large enough to be of reasonable precision as it has been carried out over a limited period of time with a limited number, all the cases of this study were collected from a tertiary level hospital in South India and hence has some credentials in reflecting the facts regarding the available treatment options and the most favourable modality for treatment of moderate to severe plaque type of psoriasis.

6. Source of funding

None.

7. Conflict of interest

None.

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