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Methotrexate plus narrow band ultraviolet B (NBUVB) versus methotrexate alone in the treatment of moderate to severe plaque psoriasis: A randomized clinical trial

Khadka DK[1], Agrawal S[2], Dhali TK[3]

[1]Assistant Professor, Department of Dermatology and Venereology, B. P. Koirala Institute of Health Sciences, Dharan, Nepal; [2]Professor and Head, Department of Dermatology and Venereology, B. P. Koirala Institute of Health Sciences, Dharan, Nepal; [3]Associate Professor, Department of Dermatology and Venereology, ESIC PGIMSR, New Delhi, India

Abstract

Introduction: Psoriasis is a chronic, recurring inflammatory disease affecting the skin, joints and nails that has a significant negative impact on the quality of life. Efficacy of combination of methotrexate/narrowband ultraviolet B (NBUVB) phototherapy in the treatment of psoriasis has been rarely assessed.

Objectives: To compare the therapeutic efficacy of methotrexate plus NBUVB phototherapy combination vs. methotrexate in the treatment of moderate to severe chronic plaque psoriasis.

Material and methods: Seventy-nine patients with chronic plaque-type psoriasis (body surface area involvement >2%) were randomized to receive either methotrexate/NBUVB phototherapy (group A) or methotrexate (group B). End point of treatment was 75% reduction in Psoriasis Area and Severity Index (PASI75) Score or up to 12weeks, whichever was earlier. Patients were then followed up for a period of 12 weeks for assessment of adverse effect, DLQI and relapse.

Results: Of 79 patients, 69 completed the treatment period and follow-up. PASI 75 was achieved in 35/39(89%) patients in group A and 34/40(85%) patients in group B (P=0.052). The mean number of weeks (P = 0.031), the mean cumulative dose of NBUVB (8.2±3.5J/cm2)) and the mean number of phototherapy sessions (12±3)) required to achieve PASI 75 were less in group A compared with group B. There was no significant difference in the number of patients who relapsed during the follow-up period (P = 0.68).

Conclusion: Combination of methotrexate and NBUVB phototherapy provides more rapid clinical improvement compared with methotrexate monotherapy in the treatment for chronic plaque-type psoriasis.

Keywords: *DLQI, Methotrexate, NBUVB, PASI, Psoriasis*

Address for correspondence
Dr Dhan Keshar Khadka
Assistant Professor
Department of Dermatology and Venereology
B. P. Koirala Institute of Health Sciences, Dharan, Nepal
Ph. No: 9842026086
Email: dhankesharjung@gmail.com

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Introduction

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin and has remitting and relapsing course. The characteristic lesion consists of red, scaly, sharply demarcated, indurated plaque, presents particularly over the extensor surface of the extremities and scalp. The disease is variable in duration, periodicity of flares and extent. Morphological variants are common.[1] The prevalence of psoriasis varies from 1.5 to 3% and incidence indicated to 60 individuals per 100 000 per year.[2] The prevalence of psoriasis is 2% in a study conducted in eastern Nepal to identify the patients profile and belief regarding the disease psoriasis.[3] Psoriasis may have a major impact on quality of life and self-esteem. It can lead to limitations with daily activities, occupational functioning and relationship.[4] The severity of the disease determines the therapeutic approach.[5] Monotherapy with systemic agents may be insufficiently effective or produce many side-effects. In these cases, combination, rotational or sequential treatment strategies may be utilized for better results.[3] Methotrexate a folic acid antagonist though effective produces many side effects. Narrowband Ultraviolet B phototherapy has shown good efficacy in the treatment of psoriasis and currently represents the most effective UVB phototherapy for psoriasis.[4] But the study comparing methotrexate plus NBUVB with methotrexate alone is not published as far as our knowledge till this date. Therefore, we had planned to undertake the study to compare the therapeutic effecacy of methotrexate plus NBUVB verses methotrexate alone in the treatment of moderate to severe plaque psoriasis and identify the adverse effects, DLQI, and relapse associated with these regimes.

Material and methods

Patients with plaque psoriasis attending the dermatology department, BPKIHS, Dharan with more than 2% BSA involvement were included and patients with less than 2% BSA, pregnant and lactating women, patients with systemic diseases and those who received PUVA/UVB treatment for psoriasis within the past 4 weeks and topical treatment within the past 2 weeks, those with history of skin cancer and immunosuppression due to disease or drugs were excluded in the study. This study is an observer blinded, randomized, parallel group clinical trial and was approved by the Institutional Ethical Committee.

The sample size of 40 patients were recruited in each arm of the study, considering 80% power, 5% alpha error, two sided and percentage of PASI 75 reduction at 12 weeks in methotrexate group 50% and methotrexate plus NBUVB group 80%.

Subject enrollment

A prior informed and written consent was taken from all patients. Particulars of an individual patient and detailed history with respect to the chief complaints, duration of illness, associated symptoms and site of involvement were documented in a preset proforma for each patient. Seasonal variation, precipitating factors, joint involvement, family history and past treatment taken were also recorded. A complete clinical examination was done in all patients. The sites involved and the morphology of the lesion were documented in the proforma. Body surface area (BSA) was measured using the rule of nine as in burn. Severity of the disease was assessed using PASI (Psoriasis Area and Severity Index).

Baseline investigations of routine blood counts (Hemoglobin, Total Leucocyte Count, Differential Leucocyte Count, platelets), liver function test (total bilirubin/conjugated, SGOT, SGPT, ALP) and renal function test (Serum Urea, Serum Creatinine), routine urine examination and microscopy and X-ray chest Posterior Anterior view were done to rule out any systemic involvement. A HIV test was done after sending the patient for the pre-test counseling only in high risk patients. All females of reproductive age group underwent the pregnancy test and were also advice to use contraceptives during the treatment period.

A wash off period of 4-8 weeks was given to patients on any kind of past treatment (i.e. 4 weeks for topical and 8 weeks for any systemic

treatment).
No concomitant therapy was allowed except for emollients and anti-histamines during treatment and follow-up period.

Two parallel groups (1:1) generated with the help of Ralloc software and were randomized into two intervention group. Group A (Methotrexate plus NBUVB) and Group B (Methotrexate alone).

Interventions
Methotrexate plus Narrow Band UVB (Group A)
Prior to the initiation of MTX-NBUVB treatment, the minimal erythema dose (MED) of NBUVB was determined in each patient. MED is defined as the smallest dose of radiation required to achieve just perceptible erythema read after 24 hours. After the MED was determined, NBUVB was administered thrice weekly using "Dermaindia, Chennai Lightning" cubicles which are equipped with 24 UVB lamps emitting a radiation spectrum of 290-320nm of which NBUVB absorption is at maximum at 311±2nm. The dose increment was done at each visit based on the percentage of previous dose and erythema response as mentioned below:

a) No erythema -20% increment at each visit
b) Mild (Grade I, barely perceptible erythema) - repeat previous dose
c) Moderate (Grade II, well defined asymptomatic erythema) – postpone one treatment, repeat previous dose at next visit and reduce to 10% increment to achieve barely perceptible erythema.
d) Severe (Grade III, painful erythema persisting for more than 24 hours, edema or bullae) – no treatment until recovery and further treatment by reducing exposure dose by half: thereafter 10% increment at each visit.

The dose of NBUVB was continued till lesion was clear (which was defined as 90% reduction in PASI scores) or completion of 12 weeks of therapy. After achieving clearance or 12 weeks of therapy, all forms of therapy were discontinued without tapering or maintenance. Patients wore UV protective goggles and male patient were provided with the genital protection in the cabinet. Since NBUVB was given on every alternate day, methotrexate at a dose of 0.4mg/kg/week was given with maximum dose of 25 mg/week on a day when the patients did not receive the NBUVB.

Methotrexate alone (Group B)
Oral MTX was given in the dose of 0.4mg/kg/week with maximum of 25 mg/week for a period of 12 weeks. No changes were permitted in the dose of MTX used during the study.

Assessment was done by calculating PASI and TBSA during follow-up. DLQI were assessed at 12 and 24 weeks using Nepali version. Relapse assessed at 16, 20 and 24 weeks of follow-up.TLC, DLC, Hb, platelets, LFT repeated twice weekly for first 4 weeks and every 4 weekly for remaining 8 weeks. Cumulative dose of methotrexate and number of session calculated for NBUVB. The primary end point was change in PASI at 12week and secondary end point was adverse effect, DLQI, and Relapse. Level of outcome measured as:

1. Excellent/good : clearance/minimal residual disease, or PASI 90
2. Satisfactory: PASI 75
3. Improvement: PASI 50
4. Mild improvement: PASI 1-<50
5. No improvement: PASI 0
6. Relapse: PASI >25 from baseline

Treatment discontinuation was done if there were any serious adverse effect and if there were any abnormal laboratory findings.

Statistical analysis
Data from all randomized patients were included on intent-to treat basis. T-test was used where equal variance was demonstrated. Chi square test was used in the initial exploration of the data. Otherwise, equivalent nonparametric statistics (Wilcoxon rank sum test) was used. Kaplan-Meir test used to assess the relapse after completion of the treatment period.

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Results

Among 80 randomized patients (40 in each group), one patient in group A refused for participation so a total 79 patients, 39 in Group A (Methotrexate plus NBUVB) and 40 in Group B (Methotrexate) were studied. A total of 69 (36 in Group A and 33 in Group B) completed the treatment and follow-up (Figure 1).

A baseline demographic comparison of the 2 groups (Group A and B) of patients is shown in Table 1. The patients of both groups were not statistically different in regards to age (p=0.698), duration (p=0.13), and PASI (p=0.086).

Psoriasis area severity index (PASI)

There was marked reduction in percentage score of PASI between the two treatment groups, with greater reduction in the combination treatment (Group A) than methotrexate (Group B), however there was no statistical significance (Figure 2). During the follow-up period of 12 weeks carried at 4 weekly interval, the median PASI reduction at 24 weeks was greater in Group A than in Group B, which was statistically significant (P=0.003)(Table 2).

PASI 75 was achieved earlier in Group A (i.e. at 3rd week), where it was at 8th week in group B (p=0.031) and the total cumulative dose of methotrexate was lower in Group A than Group B (p=0.046). Both were statistically significant favoring the combination group (Group A) (Table 3).

Total body surface area (TBSA)

Reduction in percentage of total body surface area was statistically significant (P=0.032), at 12 weeks favoring Group A over Group B (Figure 3). At the end of follow-up period of 12 weeks after completion of treatment (i.e. at 24 weeks) the mean reduction in total body surface area was statistically significant (P=0.003) and favored the combination group (Group A) (Table 4).

Dermatology life quality index (DLQI)

Marked reduction in DLQI was present both at 12 weeks and at 24 weeks, however statistically significant reduction was at 12 weeks (P=0.022) and favored Group A over Group B (Table 5).

Adverse effect (ADRS)

In methotrexate plus narrowband UVB, 9(23%), patients developed the side effects, in methotrexate, 11(27.5%). There was no statistically significant difference in side effects at the end of study among the two treatment group (P=0.270)(Table 6).

Relapse

There was no significant difference in number of patients who relapsed at the end of study among the two groups (p=0.095, 0.084, 0.069 at 16, 20 and 24 weeks respectively) (Table 7).

Discussion

Many therapeutic agents are used for the treatment of psoriasis vulgaris with variable efficacy but none is a definite treatment. Methorexate has been in use for more than five decades as monotherapy and in combination with other agents in the treatment of psoriasis, despite its potential short-term and long-term side-effects.[14] Kumar *et al* reviewed data on 244 psoriatics who were put on weekly oral methotrexate at full therapeutic dose (0.3–0.5 mg/kg/week) from 1981 to 2000 and found marked improvement to occur in 88% of patients in 8.5 ± 5.1 weeks.[15] In the field of phototherapy, an important milestone was the introduction of NBUVB phototherapy by van Weelden *et al* and Green *et al*, which over the years has been proven to be equally effective, safer and more practicable than PUVA (psoralen plus UV-A phototherapy).[6,7]

However, the option of combining methotrexate with narrowband UVB phototherapy has been relatively less exercised. Advantage of such a combination could be a more rapid clearing of lesions because of the synergistic action. Both methotrexate and NBUVB have an anti-mitotic and anti-proliferative action on infiltrating T lymphocytes.[8] In addition, both possess significant anti-inflammatory properties.[9]

We were unable to find any study comparing the

efficacy, DLQI, ADRS and relapse rate between methotrexate plus narrowband UVB verses methotrexate, till the time of completion of this study. There were two studies[11,12] where methotrexate plus narrowband UVB versus narrowband UVB were compared.

In our study, there was no statistical significant difference in the number of patients who achieved marked improvement in PASI between the two groups (methotrexate plus narrowband UVB and methotrexate) at 12 weeks (P =0.815). The mean total cumulative dose of methotrexate (56.5±12.5 mg in methotrexate plus narrowband UVB and 140.75±60.5 mg in methotrexate) received by the patients in the two groups to achieve marked improvement was statistically significant (P=0.046). The lower mean total cumulative dose of methotrexate in combination group to that of methotrexate was due to earlier improvement in PASI score and lesser weeks of treatment required. We also found the difference in the time (3.5±1.5 weeks in Group A and 8.5±4.5 weeks in Group B) required to achieve marked improvement in PASI to be statistically significant (P=0.031) favoring the combination group (Group A). In our study 34/39 in combination (87%), and 33/40(82.5%) in methotrexate achieved PASI 90 (P=0.053). PASI 75 was achieved in 35/39(89%) in combination, and 34/40(85%) in methotrexate (P=0.052). During the follow-up period of 12 weeks carried at 4 weekly interval after stopping treatment, the median PASI reduction at 24 was statistically significant (P=0.003). This shows the persistence of response for long period in the combination group.

In the present study, reduction in percentage of total body surface area was statistically significant (P=0.032), at 12 weeks of treatment and follow-up period (P=0.003).There was greater reduction in the percentage of total body surface area in methotrexate plus narrowband UVB on all weeks of treatment and reached statistical significance at the end of treatment and follow-up favoring methotrexate plus narrowband UVB over methotrexate alone. This greater reduction in total body surface area in combination treatment is due to the synergistic action of methotrexate and NBUVB.

In the present study, the median reduction in DLQI between methotrexate plus narrowband UVB and methotrexate was marked and statistically significant at completion of treatment at 12 weeks (P=0.022). Asawanonda and Nateetongrungsak in 2006 found that the combination of NB-UVB and MTX cleared more patients with psoriasis (90.9% vs 38.5%) than when NB-UVB was used alone. Kanwar et al (2010) showed methotrexate plus NBUVB phototherapy provides more rapid clinical improvement compared with NBUVB alone in the treatment of moderate to severe psoriasis, however the DLQI, adverse effects and relapse showed no significant difference. Our study also showed similar result where combination treatment cleared psoriasis early and with fewer treatments compared to monotherapy.

The greater reduction in PASI percentage and its persistence during follow up period favor the methotrexate plus narrowband UVB with statistical significance. Similarly the greater and statistically significant reduction in total body surface area and DLQI in Group A over Group B is due to the synergistic action of methotrexate and narrowband UVB. Methotrexate decreases the scaling which helps greater penetration of the NBUVB and greater reduction in T-cells.[10] NBUVB irradiation has been proven to have local and systemic immunological effects on the skin. Langerhans cells (LCs) are very important dendritic antigen-presenting cells present in the epidermis, which offer a first line of immunological defense. UVB therapy reduces the amount of LCs, which leads to an impaired antigen-presenting capacity and local immunity. Because LCs migrates to draining lymph nodes after taking up foreign antigens, treatment with NBUVB irradiation also affects the systemic Immunity.[16]

Total of 20 (25.31%) patients developed various side effects during treatment and follow up period among all patients in both group. In methotrexate

plus narrowband UVB, 9 (23%) patients developed the side effects; in methotrexate 11(27.5%) patients developed the different side effects. Majority of side effects were gastrointestinal intolerance, like anorexia, nausea, and vomiting, followed by fatigue and malaise and pruritus. These side effects were graded in a 4 point scale (from 0-no side effect to 3-severe) to know the severity of side effect. Majority of patients experienced grade 1 (mild) and few developed moderate degree of symptoms only and which disappeared on continuation of treatment. There was no statistically significant difference in side effects at the end of study among the two treatment group (P=0.088). This shows addition of NBUVB does not increase the rate of side effects and is safe for combination with methotrexate.

Relapse in any patients were said to be present when there was more than 25% increase in PASI score from that of PASI score at the end of treatment. There were no significant relapse between the two treatment group (methotrexate plus narrowband UVB and methotrexate) during follow-up period of 12 weeks (i.e P=0.095, P=0.084, and P=0.069 at 16, 20 and 24 weeks respectively). Similar rate of relapse among the two groups indicate there is no advantages of combination treatment in patients with psoriasis in case of relapse rate.

The study concludes that the combination of methotrexate and NBUVB phototherapy is a useful, safe and an effective treatment for moderate to severe psoriasis as it leads to marked improvement in patients suffering from psoriasis in fewer weeks of treatment compared with methotrexate monotherapy. In the era of biologics, methotrexate/NBUVB combination offers a cheap and clinically beneficial therapeutic option. Finally, although there is danger of skin cancer associated with methotrexate plus narrowband UVB, it may be prevented because of fewer NBUVB exposure and lower dose of methotrexate thereby reducing the cumulative dose due to faster clearance. Lastly but not the least, persistence of response for a longer duration in methotrexate plus narrowband UVB adds longer disease free interval and improvement in overall health related quality of life. With the proper selection of patients and assessment of risk factors on further study relapse rate and adverse effects can be minimized optimally.

Table 1: Baseline characteristic of the study population

Disease characteristics	MTX+NBUVB (N=39)	MTX (N=40)	Total	P-value
Males	32 (85%)	22 (60%)	54 (72.50%)	0.253
Females	6 (15%)	16 (40%)	22 (17.50%)	0.223
Mean age (years)	36.90 ± 11.48	37.30 ± 10.94	37.10 ± 11.07	0.698
Duration of illness (years)	6.80 ± 5.09	12.35 ± 8.96	9.57 ± 7.72	<0.13
Age of onset (years)	30.10 ± 10.96	24.95 ± 8.54	27.52 ± 10.04	>0.14
Mean BSA (%)	19.5 ± 8.85	14.65 ± 3.40	17.07 ± 7.06	>0.063
Mean PASI	16.02 ± 3.51	14.44 ± 2.80	15.23 ± 3.24	>0.086

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Table 2: Reduction in PASI during follow up.

Charecteristics	Group				MannWhitney U test	p-value	Remarks
PASI (weeks)	MTX+NBUVB		MTX				
	N	Mean±SD (Median)	N	Mean±SD (Median)			
PASI 16	36	0.88±2.33 (0.85)	33	1.669±1.557 (1.44)	548.000	0.490	NS
PASI 20	36	0.88±3.15 (0.85)	33	1.669±1.395 (1.44)	449.000	0.305	NS
PASI 24	36	1.00±3.14 (0.97)	33	1.909±1.724 1.65)	188.000	0.003	S

Table 3: Different PASI response

Charecteristics	Group		MannWhitney U test	p-value	Remarks
	MTX+NBUVB (N=39)	MTX (N=40)			
Attainment of PASI 75	35 (89%)	34 (85%)	570.000	0.052	N
Number of NBUVB treatments for attaining PASI 75 (mean ± SD)	12±3	-	-	-	-
No. Weeks reuired for attaining PASI 75 (mean ± SD)	3.5±1.5	8.5±4.5	388.000	0.031	S
Total NBuVB dose required for attaining PASI 75 (mean ± SD) J/cm²	8.2±3.5	-	-	-	-
Total MTX dose required for attaining PASI 75 (mean ± SD) mg	56.5±12.5	140.75±60.5	434.000	0.046	S

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Table 4: Reduction in total body surface area during follow up

TBSA	Group				Mann Whitney U test	p-value	Remarks
	MTX+NBUVB		MTX				
	N	Mean±SD (Median)	N	Mean±SD (Median)			
(16th week)	36	0.43±6.41 (0.35)	33	3.81±2.68 (2.79)	452.000	0.057	NS
(20th week)	36	1.00±7.43 (0.82)	33	3.70±2.88 (2.78)	344.000	0.075	NS
(24th week)	36	2.78±7.35 (2.26)	33	3.99±2.55 (2.92)	187.000	0.003	S

Table 5: Reduction in DLQI during study

Charecteristics			Group		Mann Whitney U test	p-value
			MTX+NBUVB	MTX		
Total number of patients (N)			39	40		
DLQI score	Baseline	Mean±SD (Median)	8.26±6.370 (6)	10.20±5.360 (11)	198.000	0.222
	Weeks 12	Mean±SD (Median)	1.31±2.462 (0.24)	1.43±2.111 (1.55)	182.000	0.022
	Week 24	Mean±SD (Median)	0.001±0.0001 (0.01)	0.46±1.484 (0.5)	202.000	0.067
Median % of improvement from baseline to 12 weeks			97	85	182.000	0.022
Median % of improvement from baseline to 24 weeks			99	95	202.000	0.067
No. and % of patients achieving DLQI score 0 following treatment			23 (59%)	19 (47%)	285.000	0.075
No. and % of patients achieving clincially meaningful improvement in DLQI			30 (77%)	25 (62%)	201.000	0.066

Table 6: Adverse effects of treatment

S.N.	ADRS	Group A	Group B	Total
1	GIT	11 (35.4%)	9 (25.7%)	20 (30.3%)
2	ERYTHEMA	8 (25.8%)	6 (17.1%)	14 (21.1%)
3	FISSURING	2 (6.4%)	0 (0%)	2 (3%)
4	PUSTULES	1 (3.2%)	0 (0%)	1 (1.5%)
5	ITCHING	7 (22.5%)	8 (22.8%)	15 (22.7%)
6	WEAKNESS	7 (22.5%)	6 (17.1%)	13 (19.6%)
7	HEPATITIS	3 (9.6%)	2 (5.7%)	5 (7.5%)

Table 7: Rate of relapse during study

Characteristics	Group		P-value	Remarks
Relapse	MTX+NBUVB (N=36)	MTX (N=33)		
1 (16 week)	2(5.5%)	3(9%)	0.095	NS
2 (20 week)	3(8.3%)	5(15%)	0.084	NS
3 (24 week)	4(11%)	7(21%)	0.069	NS

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FIGURES

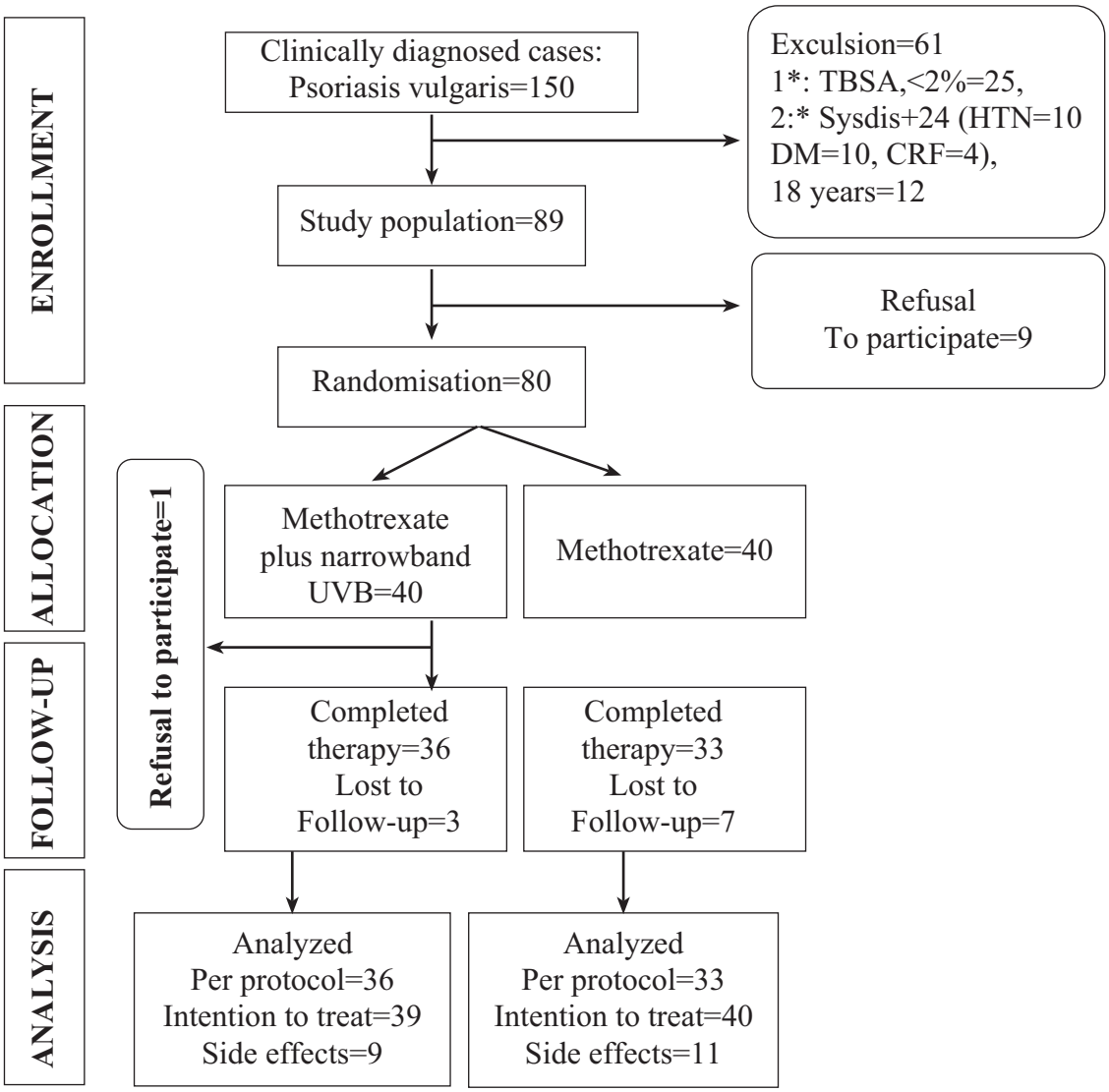

Figure 1: Flow diagram of the patients through different stages
* TBSA-Total body surface area; Sysdis-Systemic disease; HTN-Hypertension; DM-Diabetes mellitus; CRF-Chronic Renal failure

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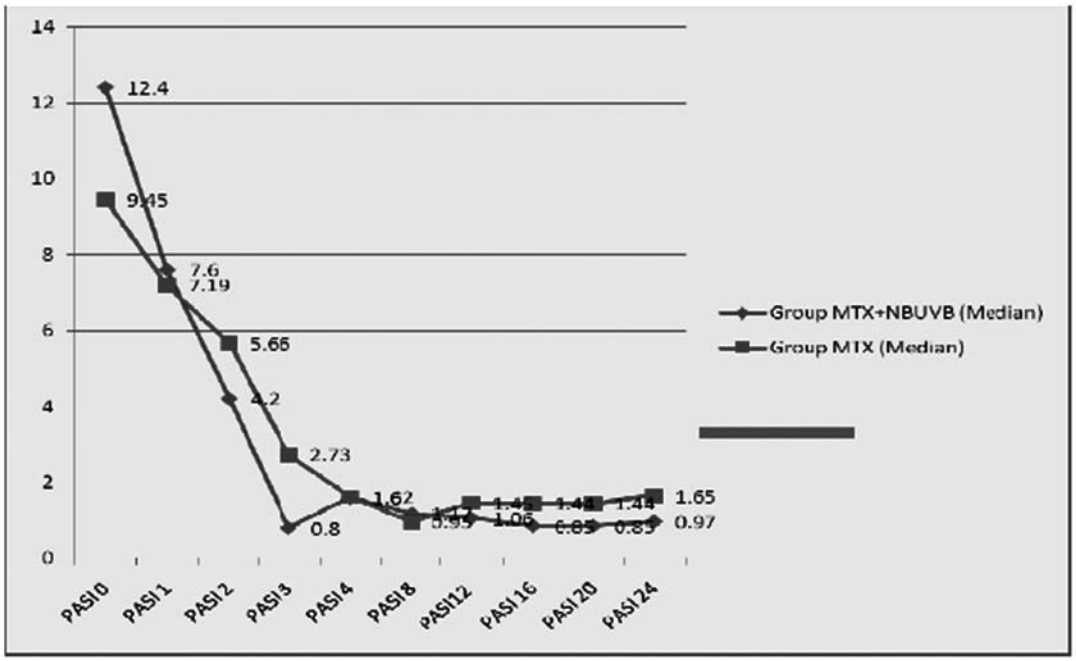

Figure 2: Reduction in Psoriasis Area Severity Index (PASI)

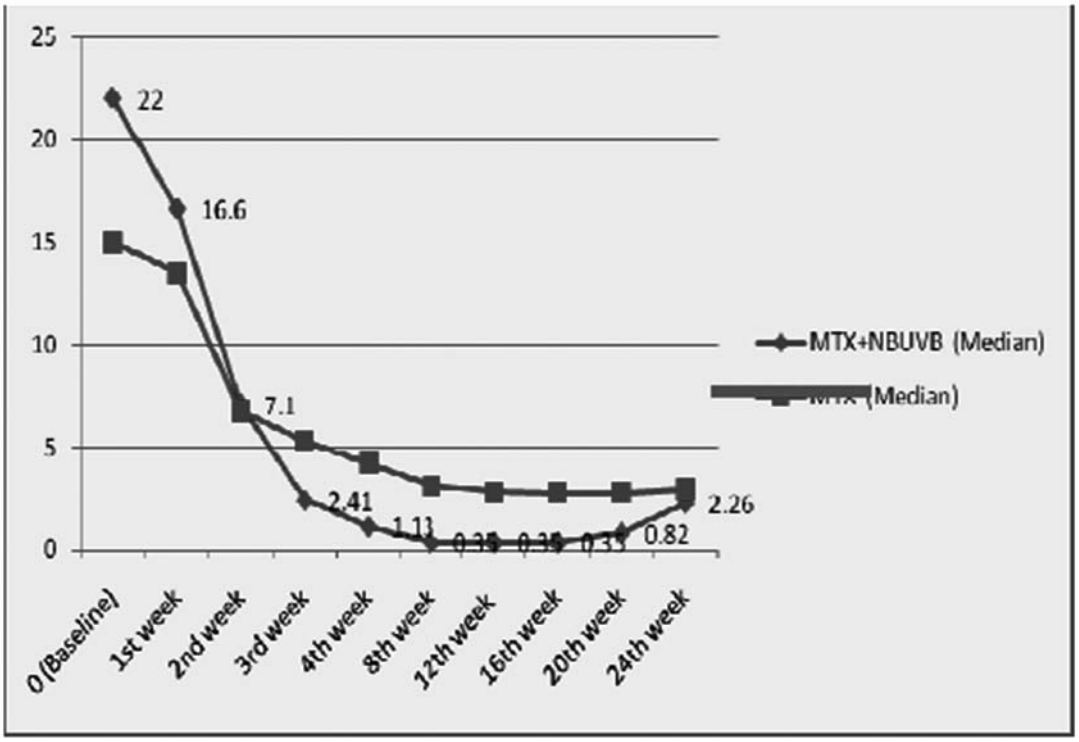

Figure 3: Reduction in Total Body Surface Area (TBSA)

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