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ORIGINAL ARTICLE

Efficacy of Oral Methotrexate in the treatment of Plaque Psoriasis in a local population

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Abstract

Objective: To determine the safety and efficacy of methotrexate in treating plaque psoriasis.
Methods: The interventional descriptive single-arm pre and post-study was conducted in the department of dermatology Fauji Foundation Hospital Rawalpindi from August 2018 to January 2021. This research was approved by the ethical review committee of the hospital. One hundred forty two patients between 15 to 60 years of age suffering from plaque type psoriasis with PASI score of >8 were included in the study after taking the informed consent. Oral methotrexate in a dose of 10 mg/week was given for 8 weeks to patients from dermatology outdoor and Indoor. (PASI 6 or greater).Baseline blood counts, blood urea nitrogen, serum creatinine, electrolytes, alkaline phosphatase, alanine aminotransferase and chest Xray to rule out latent tuberculosis. They all got cured through a methotrexate dosage of 10mg that was adjusted between 5 mg to 25 mg based on individual conditions. Outcomes were measured as Psoriasis Area Severity Index PASI and Disease Activity Score DAS 28 for patients having psoriatic arthritis.
Results: Of all the participants 116(81.1%) were female and 26 (18.2%) were male whereas mean age of participants was 41.6 years. The mean pretreatment and post treatment PASI score shows significant drop from baseline (13.01+6.02) to eight weeks post treatment (5.4+3.2) which is statistically significant (P=<0.05). The change in percentage of PASI from baseline was analyzed by the Wilcoxon signed ranks test after 8 weeks (t=17.29) ie PASI 75 was achieved in more than 50% of participants. There was a marked improvement in the DAS28 score of participants having Psoriatic arthritis. Regarding Psoriatic arthritis, Table 6 shows that 26 out of 29 (96.29%) patients had moderate Psoriatic arthritis with DAS 28 score of less than 5 while 1(3.7%) patient had mild and 2(7.4%) had severe joint disease of greater than 5.1 DAS 28 score before methotrexate treatment. However majority ie 17/29 (62.9%) achieved complete remission in joint disease after 8 weeks of methotrexate treatment while a small number 2/29 (7.4%) still had DAS 28 score of up to 5.1 or moderate remission while none had high score of DAS28 of greater than 5.1 after 8 weeks.
Conclusion: The outcome of this study has shown that the effective way to treat plaque psoriasis is through methotrexate which is efficient in treating coexisting psoriatic arthritis which is one of the important comorbidities associated with plaque psoriasis

Keywords: plaque psoriasis, methotrexate, coexisting psoriatic arthritis, erythematous plaque

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Introduction

Approximately 3% of the US population is affected by psoriasis which is a very chronic skin disease with an estimated population of over 125 million people globally.1 It is caused due to the disruption in interference of
innate and adaptive immunity that leads to exaggerated. Immune response and excessive inflammation2. The medical classification and analysis of psoriasis are

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based on morphological evaluation of skin injury and other joints along with family history with elevated CRP and ESR levels in a blood test 3. Various
Classifications of psoriasis are available in the literature, Epidemiologically, early, and late-onset psoriasis.
Morphologically, local, or widespread psoriasis. Based on the severity of the disease; mild moderate severe
Psoriasis [4]. Among these classifications, clinical classification is significant regarding assessment and treatment. The classification of psoriasis is based on two groups: pustular and non-pustular lesions. The following flowchart further elaborates on the classification.

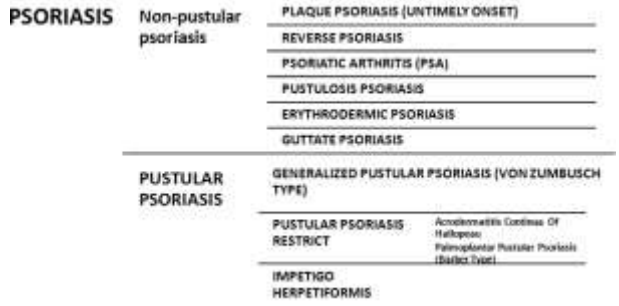

Figure **Error! No text of specified style in document.**1:**Error! Not a valid bookmark self-reference.**[5]

Psoriasis Vulgaris or plaque psoriasis constitutes around 90% of psoriasis. Localized on the knee, elbow, scalp, and sacral region and sites of injury.6 This disease is known as T lymphocyte-mediated autoimmune disease; it is referred to by the sequence of cellular changes occurring in the skin various clinically pathognomic signs differentiate plaque psoriasis from any other clinical subtype.7 These signs appear at different levels i.e blunt scraping of plaque psoriatic surface reveals candle wax sign that is desquamation as coats of the white lamellae that still exhibit coherence which is due to parakeratotic hyperkeratosis. Further scraping shows a wet layer adhered to the lesion, it is the terminal layer of dermal papillae, and it is called the last membrane phenomenon and is a pathognomic sign of psoriasis. Further scraping of the lesion will reveal an erythematous background and bleeding points known as the Auspitz Sign. A hypo pigmented macular ring is observed around healed psoriatic plaque called a worn-off ring and is assumed to be due to decreased level of prostaglandin in healing lesions. However, the exact pathogenesis is not yet known.8 Plaque psoriasis also has systemic manifestations and studies show an association with metabolic syndrome, dyslipidemia, and obesity.9 Due to greater area of skin involvement, there are more chances of development of vitamin d deficiency in psoriasis patients and this finding can help in the rapid clearance of psoriasis, here we did not include this measure to keep the research specific to results of MTX only.[10]

Also, there are various co-morbidities associated with plaque psoriasis, most significant being psoriatic arthritis affecting around 7 to 48% of the patients followed by Crohn's disease and ulcerative colitis in 0.1-0.3% of the population.[10,11] It is seen that more women are reported to suffer from obesity as compared to males.[11]

Treatment of Plaque psoriasis is based on severity of disease. In mild disease topical corticosteroids are used as monotherapy or can be combined with keratolytic agents, Vitamin D analogs and retinoids to increase efficacy. In moderate cases, treatment with UVB or Psoralen plus UVA phototherapy is recommended and targeted phototherapy with an excimer laser can also be used if more BSA is involved. In case of severe cases, systemic medications like methotrexate, cyclosporine and acitretin are commonly prescribed. Despite the risk of hepatotoxicity, methotrexate is the safest and most efficient in terms of serious adverse events.[13.] Methotrexate has been widely used to treat severe psoriasis; it is extensively used to treat plaque psoriasis in patients that do not seem to respond to the topical therapy individually.[14] Absorption of methotrexate is rapid and complete in intramuscular injection and oral administration of small doses i.e. less than 30mg/m2 and the estimated half-life of methotrexate is 6 to 69 hours. (Based on different sampling and assay methods). Renal excretion is the main route for the removal of methotrexate (~80%). This kind of excretion is associated with internal clearance that further offers direction on making the adjustments to the dosage as per the patient's age. The higher dosage is suggested to be given with regular administration of the fluid and bicarbonate. The excretion material of this drug comprises a dosage that is lower than 10%. The toxicity of the drug is associated with dose and total duration of exposure whereas major toxicity reported is hemopoietin and hepatotoxic.[15] Long-term methotrexate damages the liver and may cause liver fibrosis or moderate liver cirrhosis.[16] A study conducted by Melinda august et al to identify the side effect of methotrexate therapy showed that twenty-two

percent of all participants receiving therapy experienced side effects in some form. Among them 4.5% had low erythrocyte levels, 27.3% had high leukocyte levels, 13.6% had high thrombocyte levels, 18.2% had high SGOT levels, 22.8% had high SGPT levels, 18% had nausea, 9.1% had vomiting, 4.6% had a headache, and 4.6% experienced shortness of breath.[17]

Therefore, the dosage of methotrexate is crucial to minimize toxicity. The dose of methotrexate commonly administered is between 5 to 25 mg/week. However, a meta-analysis conducted to determine the optimal dose of methotrexate suggests that dosages of 5-15 mg/week, 7.3-15 mg/week, and 15-25mg/ are frequently used.[18] Various studies show methotrexate as an efficient drug to treat plaque psoriasis by reducing inflammation, and reducing cell proliferation and is an immunosuppressant.[19] Available literature regarding the efficacy of methotrexate for the treatment of plaque psoriasis is either limited to chronic cases or considers psoriasis disease as a whole. Therefore, the purpose of this study is to find the efficacy of methotrexate among all types of plaque psoriasis. Literatur

Material and Method

The interventional descriptive single arm pre- and post-study was conducted in the department of dermatology Fauji Foundation Hospital Rawalpindi from August 2018 to January 2021. The ethical review committee of our hospital approved the research. One hundred forty-two patients between 15 to 60 years of age suffering from plaque type psoriasis with PASI score of >8 was included in the study after taking the informed consent. Oral methotrexate in a dose of 10 mg/week was given for 8 weeks to patients from dermatology outdoor and Indoor. Only those patients who had an average to critical psoriasis as defined with severity of more than 8 according to the Psoriasis severity index; PASI scores of 0 specifies the nonappearance psoriasis and 72 indicates the worst psoriasis possible. The variables included in the research protocol included duration of disease, site of involvement, demographic profile (gender, age in years), size and severity of plaques measured by Psoriasis Area and Severity Index (PASI) score before initiation of the treatment and at completion. A patient who did not respond well enough with the help of UVB therapy or topical or maybe both. Also, those who have not been treated with methotrexate before.

Patients suffering from plaque type psoriasis of any duration and with severity of Psoriasis Area and Severity Index (PASI) score of greater than 8 were included in the study. Patients suffering from anemia, thrombocytopenia, active infection (e.g. tuberculosis through Chest X-ray), peptic ulcer disease, taking other treatments for the disease, liver or kidney disease, heart disease, diabetes mellitus and alcoholism were excluded. Pregnant women or those who are planning to, and lactating mothers were also excluded. Patients who were already taking treatment for psoriasis with Methotrexate or any other medicine were also excluded. To assess the tolerance of methotrexate, the following laboratory tests were conducted at week 2, week 4, and week 8 of treatment. Baseline and post week one, four and eight, complete blood count (CBC), blood urea nitrogen, serum creatinine, electrolytes, alkaline phosphatase, alanine aminotransferase, chest X ray to rule out latent tuberculosis, urinalysis and clinical examination were carried out to monitor the side effects of methotrexate.

After the completion of eight weeks, the patients were followed up for 6 months assessing them at monthly intervals for relapse.

The initial dose given was 10 mg per week given in four equally divided doses of 2.5mg at 12 hourly intervals. The dose was decreased to 5 mg/week in events of adverse effects as per published guidelines.[22] No combination anti psoriatic topical therapy except emollients were permitted during this systemic trail.

Drugs that are known to affect both psoriatic arthritis and systemic treatment were forbidden. The Psoriasis area severity index was the primary outcome measured at baseline and on completion of treatment at 8 weeks by trained assessors in case of skin disease alone. But baseline and post treatment DAS28 was also calculated besides PASI in patients having psoriatic arthritis along with plaque psoriasis. This was done with a given formula containing the number of swollen/tender joints and serum CRP values.

Results

Out of a total of 142 participants, 116(81.1%) were female with 26 (18.2%) were male whereas average age of participants was 41.6 years. Mean duration of disease was 3.6 and 27 (19%) out of 142 patients had psoriatic arthritis. Statistical analysis of data was conducted using SPSS 22 software. Continuous variables are shown as

mean and standard deviations while categorical data was shown as a frequency table.

Pretreatment mean PASI score was 13.1 which dropped to 5.4 as mean post treatment PASI score which was statistically significant (t=17, p=<0.05). The percentage change in PASI from baseline (PASI 75) was analyzed by the Wilcoxon signed ranks test after 8 weeks which was found to be significant. Table 1 shows the demographic characteristics of the participants.

Table 2 shows duration of disease in participants which ranged from 4 months to 22 years. The number of participants having coexisting psoriatic arthritis was 27/142 (19%). Out of these 27 patients, 5 had arthritis before developing Plaque Psoriasis while the rest of 22 developed arthritis during the course of skin disease. eventy-one out of one hundred forty-two (50%) patients had an almost complete remission during the 8 weeks of treatment and partial remission was achieved in 64/142 (45%) patients. Four patients dropped out due to adverse events i.e deranged LFTs and leucopenia while three were lost to follow up. The clearance time for psoriasis ranged from 6 - 8 weeks (mean 6±0.79 weeks).

Table 3 gives the mean pretreatment and post treatment PASI score. It shows significant drop in the mean PASI score (13.01+6.02) from baseline to (5.4+3.2) eight weeks post treatment (t=17.29) which is statistically significant (P=<0.05).

Results of paired sample t-test to show the significance of the difference in PASI before and after treatment is shown in Table 4. Application of the Wilcoxon test shows a significant difference between PASI scores

Table 2: Demographics of participants.

Demographics of Participants		
Age (years)	**Range**	15 – 71
	Mean	41.6
Sex (%)	**Male**	26 (18.2%)
	Female	116 (81.1%)

Table 3: Duration of disease and number of patients who developed or had psoriatic arthritis

Duration of disease in years	
Range	0.25 - 22
Mean	3.6
Psoriatic Arthritis	27 (19%)

Table 3: Pre and Post treatment PASI score

	PASI before MTX treatment	PASI after 08 weeks of MTX treatment	t-value	P value
Mean+ SD	13.01 + 6.02	5.4 + 3.2	17.29	<0.05
Range	39.6 – 4.0	18.0 – 0.0		

TABLE 4: THE SIGNIFICANCE OF THE DIFFERENCE BETWEEN PASI SCORE BEFORE AND AFTER TREATMENT.

Wilcoxon Rank Exam									
	N	Mean	SD	Least	Maximum	Percentiles			
						25th	50th (Median)	75th	Z
PASI Score before treatment	142.00	13.54	6.60	4.00	43.60	9.50	12.60	15.00	-10.22
PASI Level after treatment	140.00	5.75	3.46	0.00	18.00	3.03	5.20	8.00	-

Table 1: population achieving PASI 75.

Wilcoxon Rank Exam									
	N	Mean	SD	Least	Maximum	Percentiles			
						25th	50th (Median)	75th	Z
PASI Score before treatment	142.00	13.54	6.60	4.00	43.60	9.50	12.60	15.00	-10.22
PASI Level after treatment	**140.00**	**5.75**	**3.46**	**0.00**	**18.00**	**3.03**	**5.20**	**8.00**	**-**

Table 5; DAS28 before and after treatment.

DAS28 Score	Before MTX treatment	After 8 weeks of MTX treatment
Remission (DAS28 <2.6)	0 (0.0%)	17 (62.9%)
Low (2.6 < DAS28 < 3.2)	1 (3.7%)	10 (37.0%)
Moderate (3.2< DAS28 < 5.1)	26 (96.29%)	2 (7.4%)
High (DAS28 > 5.1)	2 (7.4%)	0 (0.0%)

before and after treatment (p=<0.05) this shows that more than 50% of patients achieved PASI 75. (Table 5)

There was a marked improvement in the DAS28 score of participants having Psoriatic arthritis. Regarding Psoriatic arthritis, Table 6 shows that 26 out of 29 (96.29%) patients had moderate Psoriatic arthritis with DAS 28 score of less than 5 while 1(3.7%) patient had mild and 2(7.4%) had severe joint disease of greater than 5.1 DAS 28 score before methotrexate treatment. However majority i.e 17/29 (62.9%) achieved complete remission in joint disease after 8 weeks of methotrexate treatment while a small number 2/29 (7.4%) still had.

DAS 28 score of up to 5.1 or moderate remission while none had high score of DAS28 of greater than 5.1 after 8 weeks.

Discussion

The results show that methotrexate is an effective method to treat plaque psoriasis and can significantly reduce PASI scores in psoriasis vulgaris. The mechanism of affectivity of methotrexate is due to its anti-inflammatory and immunosuppressive properties as studied in the literature [19]. Our study shows that methotrexate is efficient in treating psoriasis, by reducing severity score to 50% i.e. 13.4 to 5.7. Similar results were obtained randomized control trial byVera M.R. Heydendael et al to compare the efficiency, side effect, and other excellence of life impact of methotrexate and cyclosporin. By randomly assigning 88 to 16 weeks of treatment plans of methotrexate or cyclosporine. As the results show that after about 16 weeks of treatment, the mean (± SE) score for psoriasis in the area-and-severity index was reduced from 13.4± 3.6 at the baseline to around 5.0± 0.7 43 patients were treated with the help of methotrexate.

The risk while treating with methotrexate is hepatotoxicity. However, we did not get any abnormality in Serum LFT levels of our patients. One of the possible reasons could be the duration of treatment i.e. 8 weeks as studies show methotrexate toxicity occurs in case of long duration [17]. Studies suggest that 0-34% of patients receiving methotrexate may develop liver fibrosis. While 0.25-6 % of patients may develop liver cirrhosis. The variation of values in studies is due to non-standardized MTX doses, the cumulative duration along with the post and pre-treatment histology [20]. The proof is there to propose that the MTX-induced cirrhosis cannot work if only the drug is given continuously' and return to its state if it is stopped' therefore, histology of the liver remains the finest investigation for liver harmfulness, there will not be any need to frequently repeat the biopsies, such alternatives can be used for instance ultrasound of the liver [22,23]. Along with the improvement in plaque psoriasis, our study also shows that methotrexate improved the DAS score of patients who developed psoriatic arthritis. Similar results are seen in the literature ie a study was directed by Elisabeth et al to determine the effectiveness of methotrexate in psoriatic arthritis and two-year retention by a longitudinal multicenter observational study by treating patients with methotrexate for 6 months and assessing their progress through DAS28 showing that MTX treatment was associated with improving disease activity scores in 65% of psoriatic arthritis patients [24, 25]..

Conclusion

To conclude that the result was shown that, there is huge significant efficacy of methotrexate in treating plaque psoriasis, also methotrexate is efficient in treating psoriatic arthritis which is one of the important comorbidities associated with plaque psoriasis. Based on our study it is concluded that methotrexate does not cause adverse effects when administered in controlled monitoring and for a short duration. However, the effects of the long duration of treatment should be assessed.

Conflict of Interest: No
Acknowledgement: No

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