Original Article

# Effectiveness of Oral Methotrexate in Combination with Topical Calcipotriol Compared to Methotrexate Alone in Plaque Psoriasis: An Observational Study

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## Abstract

**Background:** Plaque psoriasis is a common, chronic, disfiguring, proliferative skin disorder of genetic, autoimmune and environmental etiology. There are various treatment modalities including topical, phototherapy, conventional systemic and biologics. We aimed to compare, through a prospective observational study, the effectiveness of oral methotrexate (MTX) in combination with topical calcipotriol (CAL) compared to methotrexate alone, since both modalities are being commonly used for plaque psoriasis treatment in our dermatology out-patient setting. **Material and Methods:** We recruited adults of either sex, with moderate to severe plaque psoriasis, who had not received definitive oral or systemic treatment earlier. Recommended starting dose in the MTX arm was 7.5 mg weekly. Those in the MTXCAL arm were to receive the same starting dose along with calcipotriol 0.005% ointment applied twice daily. The attending dermatologist was free to vary starting dose and escalate dose of methotrexate as deemed fit. Observation period was 16 weeks. The effectiveness parameters were percentage body surface area (BSA) involved, Psoriasis Area and Severity Index (PASI) score, Physician's Global Assessment (PGA) of improvement, Patient's Global Assessment (PaGA) and Psoriasis Quality of Life (PQoL) instrument. Safety was judged through selected laboratory parameters (LAB) and treatment emergent adverse events (TEAE). **Results:** Twenty-five patients were recruited in each arm; all 25 completed the study on MTX arm and 22 completed in the MTXCAL arm. The addition of calcipotriol to methotrexate obviated the need for methotrexate dose escalation and in fact led to lowering of the weekly dose. Percentage BSA involvement was comparable at baseline but showed a greater reduction in the combination arm. The latter achieved a reduction of 77.07% in PASI from baseline whereas MTX alone group achieved 54.26% reduction. Going by both the PGA or PtGA scales, the improvement was significantly more in the MTXCAL arm at all follow-up visits. PQoL score also improved to a significantly greater extent on combination therapy. Both regimes were well-tolerated with no significant LAB abnormalities and TEAE reported. **Conclusion:** Addition of topical calcipotriol to oral methotrexate in plaque psoriasis can offer the benefits of methotrexate dose sparing, improved clinical outcome, at least in the short-term, and improved QoL. There is sufficient ground to do a controlled trial of appropriate duration to confirm these observational findings.

**Keywords:** Plaque Psoriasis, methotrexate, calcipotriol, PASI, quality of life.

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## Introduction

Psoriasis is a common, chronic, disfiguring, proliferative skin disorder in which genetic, immunological and environmental factors all play critical roles.[1,2] Plaque psoriasis is the commonest form characterized by sharply demarcated, erythematous, indurated, scaly plaques, present particularly over extensor surfaces and scalp. These plaques result from abnormal skin cell turnover and inflammation.[3] Although some patients with plaque psoriasis may encounter remission spontaneously for varying periods of time, most will require treatment on long-term basis to manage the cosmetic disfigurement and improve the quality of life. The objective of treatment in psoriasis is to gain initial rapid control of the disease process, maintain long-term remission and improve quality of life. First line therapy usually consists of topical agents, such as emollients, tar, dithranol, corticosteroids, vitamin D analogues, tapinarof, roflumilast, etc.[4,5] In cases of severe and extensive psoriasis, systemic therapy is required. This includes conventional systemic agents (e.g. methotrexate, cyclosporine, acitretin), photochemotherapy and more recently biological agents like TNFα inhibitors (e.g. adalimumab, etanercept, infliximab, certolizumab), IL-17 inhibitors (e.g. secukinumab, brodalumab, ixekizumab), IL-23 inhibitors (e.g. guselkumab, tildrakizumab, risankizumab), IL-12/23 inhibitors (e.g. ustekinumab), and, novel agents such as the oral tyrosine

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kinase 2 inhibitor deucravacitinib.[8]

The antifolate drug, methotrexate is a well-established systemic drug used worldwide for the treatment of moderate to severe plaque psoriasis. Even in the era of biologics, it remains as the backbone of systemic therapy in moderate to severe disease, particularly in resource constrained settings, because of its effectiveness, affordability, and ease of use.[3] It acts by inhibiting dihydrofolate reductase enzyme with resultant antimitotic inhibition of keratinocyte and immune cell proliferation. It may inhibit proliferating lymphoid tissue, retard neutrophil and monocyte chemotaxis and may have crucial modulating effects on the cascade of events initiated by interleukins and tumor necrosis factor. The dosing used in psoriasis treatment (7.5 to 30 mg weekly) is relatively low compared to its use as anticancer drug.[9]

Though generally effective, methotrexate has its share of adverse drug reactions, most common being gastrointestinal discomfort and hematological suppression.[10] The long-term adverse effects include hepatotoxicity with increased liver enzyme levels and more serious expressions like cirrhosis, when the cumulative dose exceeds 1.5 g.[11,12] Therefore, there is a case for exploring therapeutic approaches that will have a methotrexate dose sparing effect in plaque psoriasis.

Calcipotriol, a vitamin D3 analogue, acts via a nuclear receptor, the vitamin D3 receptor (VDR), which has strong immune regulatory properties and suppress the production of pro-inflammatory cytokines. Calcipotriol inhibits cell proliferation and enhances cell differentiation in psoriatic skin and also appears to influence immunologic markers that are believed to be involved in the etiology of the disease.[13,14] Calcipotriol is used as topical therapy in patients of mild psoriasis (<2% body surface involved) or in combination with systemic agents like psoralen-ultraviolet A (PUVA) phototherapy, cyclosporine and other biologics when the disease is moderate to severe. It is well-tolerated with the common adverse effects being local skin irritation that does not require drug withdrawal. Hypercalcemia or hypercalciuria is uncommon during calcipotriol therapy if the recommended maximum dose of 100 g/week is not exceeded.[13]

Methotrexate is widely used in India, including in our dermatology out-patient department. Calcipotriol is also widely used in our setting, and some clinicians combine it with weekly oral methotrexate. However, there is little hard data on the effectiveness of this combination compared to methotrexate therapy alone in managing plaque psoriasis in eastern Indian population. This was the rationale behind our observational study.

## Materials and Methods

The study was carried out as a single institution based prospective observational study. Adult patients attending the Dermatology OPD of our tertiary care teaching hospital were enrolled for the study as per the eligibility criteria. The study conformed to the principles enshrined in the Declaration of Helsinki and received prior approval from the Institutional Ethics Committee. Written informed consent was obtained from all participants prior to enrolment.

The entire study spanned 12 months from inception. Being an observational study limited by time and logistics; no formal sample size calculation was done. The plan was to recruit 25 subjects in each arm – Methotrexate alone (MTX) versus methotrexate plus topical calcipotriol (MTXCAL) – over a period of 6 months. Each enrolled subject was the followed up for 16 weeks at 4-week intervals from the date of baseline visit.

Recruited subjects were adults (age 18+ years) of either sex, with a diagnosis of moderate to severe plaque psoriasis (at least 15% body surface area involved) who had not received definitive oral or systemic treatment earlier. Patients already on topical therapy, phototherapy or systemic therapy in any form (including steroids and herbal medications) were excluded. Pregnant or breast-feeding women, patients with compromised vital organ function, or those suffering from immunosuppression or major psychiatric morbidity were also excluded.

Recommended starting dose for patients in the MTX arm was 7.5 mg weekly orally. Those in the MTXCAL were to receive the same starting dose along with calcipotriol in 0.005% w/w (50 mcg / g) ointment formulation, to be applied to all visible plaques twice daily. However, the attending dermatologist was free to vary starting dose and escalate dose of oral methotrexate as deemed fit. Emollients, cetirizine and folic acid use was permitted. Each medication was hospital supply and from the same manufacturer.

After recruitment, baseline clinical and demographic date (age, gender, occupation, education and family history of psoriasis, duration of diseases, sites and extent of involvement) were recorded in a structured case report form. The effectiveness parameters,[15-16] recorded were percentage body surface area (BSA) involvement, Psoriasis Area and Severity Index (PASI) score (score ranging from 0 to 72), Physician's Global Assessment (PGA) of disease activity improvement (rating ranging from 0 to 5), Patient's Global Assessment (PaGA) and the 12-item Psoriasis Quality of Life (PQoL) instrument. The PQoL questionnaire is about self-consciousness regarding psoriasis, emotional well-being and how much the disease affects life due to itching, pain or soreness, irritation and the type of clothing chosen to conceal psoriasis.[17] A higher score implies a more impaired quality of life. It was recorded at baseline and study end visit. For safety assessment, hemogram, serum creatinine and liver function tests (total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total protein, albumin and globulin) were done at baseline and study end. Treatment emergent adverse events were recorded at each follow-up visit till study end.

Numerical data were summarized by mean and standard deviation (SD), when normally distributed, and by median and interquartile range when skewed. Categorical data were summarized as counts and percentages. Data were tested for normality using Kolmogorov-Smirnov goodness-of-fit test. Independent samples comparisons were done with Student's independent sample t test and Mann-Whitney U test for normally distributed and skewed numerical variables, respectively, and by Chi-square test or Fisher's exact test, as appropriate, for categorical variables. Repeated measure ANOVA with post hoc Dunnet test (if normally distributed) or,

Friedman's ANOVA with post hoc Dunn's test (if skewed) was employed for comparison of changes over time in respective groups. A p value < 0.05 was considered statistically significant. MedCalc version 10.2 [Mariakerke, Belgium: MedCalc Software, 2011] and GraphPad Prism version 5 [San Diego, California: GraphPad Software Inc., 2007] software was used for statistical analysis.

## Results

In this study, we were able to recruit 25 patients in each arm as planned. While all 25 participants in the MTX arm completed the study, 22 did the same in the MTXCAL arm. Two in the latter arm were lost to follow-up at the study end visit, and one at the third visit. For adverse event analysis, all 50 participants were considered.

The median (interquartile range) age of the participants in the MTX and MTXCAL arms were 48 (35.3 – 52.5) and 51.5 (43 – 62) years, respectively (p = 0.231). Female participants numbered 8 (32%) and 9 (41%) in the two arms (p = 0.558). The median disease duration was less than 9 months in both groups and only a few (2 in the MTX arm and 3 in the MTXCAL arm) gave a positive family history of psoriasis.

Comparison of methotrexate dosing [Table 1]: At baseline visit the median dose of methotrexate was comparable in the two groups (p = 0.153). The values remained comparable in the subsequent two follow-up visits (p = 0.672 and p = 0.127 respectively). At the final visit, however, the median dose of methotrexate in MTXCAL arm was 5 mg which was significantly lower (p = 0.003) than the median 7.5 mg in the MTX arm. Within group comparison showed that methotrexate doses in both the groups were significantly lower in the final visit compared to baseline (p < 0.001 in both groups).

**Percentage of body surface area involved [Table 2]:** BSA involved was comparable at baseline (p = 0.564) between the two study groups. During therapy there was a significant reduction of BSA involved in both MTX and MTXCAL groups from first follow-up onwards. Between group comparison showed that the BSA involved reduced significantly more in MTXCAL arm than MTX arm at study end – approximately 66% in the former against 54% in the latter (p = 0.013).

**Changes in PASI score [Table 3]:** PASI decreased by median 54.26% from baseline with MTX, while in the combination arm it decreased by 77.07%. The reduction was statistically significant (p < 0.001) in both arms but notably the PASI was higher in the combination arm at baseline but ended up significantly lower (p = 0.042) at study end.

Changes in physician's and patient's global assessment of disease activity improvement [Table 4 and Table 5]: The 5-point scale was compared at every visit. At baseline the PGA score was taken as 0 in both groups and improved significantly in both from the first follow-up onwards till the study end. However, between group comparison showed that the improvement in the physicians' global assessment scale was significantly more in the combination arm than in the methotrexate alone arm (p < 0.001 at all follow-up visits). Similar pattern was seen with patient's global assessment of disease activity.

**Changes in Psoriasis Quality of Life [Table 6]:** Quality of life was compared at baseline and at the end of the study by PQoL instrument. At baseline QoL score was comparable between the two groups (p = 0.740). It improved significantly in both. However, at the end of the study, MTXCAL group showed significantly better improvement in median PQoL score (65.35%) than in the MTX group (50.77%).

**Comparison of laboratory parameters:** The mean value of all hematological parameters assessed – hemoglobin (Hb%), total leukocyte count (TLC), differential count (DC), platelet count and erythrocyte sedimentation rate (ESR) – were within the normal range in both groups and comparable at baseline as well as at all follow-up visits till study end. In MTX arm, the platelet count showed a significant reduction between baseline (207,333 ± 29,365 [Mean ± SD] per microliter) and study end (189,192 ± 14,666 per microliter) although the latter value was also within the clinically normal range. Serum creatinine and liver function test parameters were also remained normal and comparable throughout the study.

MTX was well tolerated during the duration of the study and no significant treatment emergent adverse events evolved. Hence, there was no need for dose reduction or drug withdrawal. Calcipotriol ointment was also well tolerated with only 3 patients complaining of local skin irritation as stinging or burning sensation without redness or itching. This was mild and did not require dosing interruption.

**Table 1: Comparison of the dose of methotrexate between the two study arms**

| | Group Methotrexate(n=25) | Group Methotrexate + Calcipotriol(n=22) | P value (between groups) |
|---|---|---|---|
| Baseline | 5 – 10<br>7.5 (7.5 – 7.5) | 7.5 – 10<br>7.5 (7.5, 7.5) | 0.153 |
| 1st follow up (4 weeks) | 5 – 10<br>7.5 (7.5 – 7.5) | 7.5 – 10<br>7.5 (7.5, 7.5) | 0.672 |
| 2nd follow up (8 weeks) | 5 – 10<br>7.5 (7.5 – 7.5) | 5 – 7.5<br>7.5 (7.5, 7.5) | 0.127 |
| End of study (16 weeks) | 5 – 7.5<br>7.5* (6.87 – 7.5) | 5 – 7.5<br>5* (5, 7.5) | 0.003 |
| P value (within group) | <0.001 | <0.001 | |

- Values denote Range in the top row and Median (25th percentile – 75th percentile range) in bottom row.
- P value between groups is from Mann Whitney U test.
- P value within groups is from Friedman's ANOVA followed by post hoc Dunn's test; * implies significant change from baseline for that particular follow-up.

**Table 2: Comparison of body surface area (%) involved between the two study arms**

| | Group Methotrexate (n=25) | Group Methotrexate + Calcipotriol (n=22) | P value (between groups) |
|---|---|---|---|
| Baseline | 17 – 40<br>26 (22 – 32) | 22 – 41<br>26.5 (25 – 30) | 0.564 |
| 1st follow up (4 weeks) | 14 – 35<br>23* (18.75 – 27.25) | 16 – 34<br>21* (19 – 24) | 0.509 |
| 2nd follow up (8 weeks) | 11 – 27<br>18* (15 – 20) | 10 – 27<br>15* (13 – 20) | 0.071 |
| End of study (16 weeks) | 7 – 19<br>12* (10 – 14) | 6 – 22<br>9* (8 – 12) | 0.013 |
| P value (within group) | < 0.001 | < 0.001 | |

- Values denote Range in the top row and Median (25th percentile – 75th percentile range) in bottom row.
- P value between groups is from Mann Whitney U test.
- P value within groups is from Friedman's ANOVA followed by post hoc Dunn's test; * implies significant change from baseline for that particular follow-up.

**Table 3: Changes in PASI score compared between the two study arms**

| | Group Methotrexate (n=25) | Group Methotrexate + Calcipotriol (n=22) | P value (between groups) |
|---|---|---|---|
| Baseline | 7 – 24.6<br>12.9 (10.17 – 16.5) | 13.7 – 24.5<br>18.75 (16.2 – 20.2) | 0.003 |
| 1st follow up (4 weeks) | 5.9 – 21<br>10.8* (8 – 13.1) | 9.2 – 19.2<br>13* (11.2 – 15.1) | 0.024 |
| 2nd follow up (8 weeks) | 4 – 16.4<br>8.3* (6.07 – 10.55) | 4.1 – 13.1<br>8.85* (7 – 9.9) | 0.966 |
| End of study (16 weeks) | 2.8 – 11.3<br>5.9* (4.3 – 7.92) | 2.8 – 13.1<br>4.3* (3.6 – 5.2) | 0.042 |
| P value (within group) | < 0.001 | < 0.001 | |

- Values denote Range in the top row and Median (25th percentile – 75th percentile range) in bottom row.
- P value between groups is from Mann Whitney U test.
- P value within groups is from Friedman's ANOVA followed by post hoc Dunn's test; * implies significant change from baseline for that particular follow-up.

**Table 4: Changes in physician's global assessment of disease activity improvement rating compared between the two study arms**

| | Group Methotrexate (n=25) | Group Methotrexate + Calcipotriol (n=22) | P value (between groups) |
|---|---|---|---|
| 1st follow up (4 weeks) | 1 – 1<br>1 (1 – 1) | 1 – 2<br>2 (1 – 2) | < 0.001 |
| 2nd follow up (8 weeks) | 2 – 3<br>2* (2 – 2) | 2 – 3<br>3* (3 – 3) | < 0.001 |
| End of study (16 weeks) | 3 – 4<br>3* (3 – 3) | 2 – 4<br>4* (4 – 4) | < 0.001 |
| P value (within group) | < 0.001 | < 0.001 | |

- Values denote Range in the top row and Median (25th percentile – 75th percentile range) in bottom row.
- P value between groups is from Mann Whitney U test.
- P value within groups is from Friedman's ANOVA followed by post hoc Dunn's test; * implies significant change from baseline for that particular follow-up.

**Table 5: Changes in patient's global assessment of disease activity improvement rating compared between the two study arms**

| | Group Methotrexate (n=25) | Group Methotrexate + Calcipotriol (n=22) | P value (between groups) |
|---|---|---|---|
| 1st follow up (4 weeks) | 1 – 1<br>1 (1 – 1) | 1 – 2<br>1 (1 – 2) | < 0.001 |
| 2nd follow up (8 weeks) | 2 – 2<br>2* (2 – 2) | 2 – 3<br>3* (2 – 3) | < 0.001 |
| End of study (16 weeks) | 3 – 4<br>3* (3 – 3) | 2 – 4<br>4* (3 – 4) | 0.001 |
| P value (within group) | < 0.001 | < 0.001 | |

- Values denote Range in the top row and Median (25th percentile – 75th percentile range) in bottom row.
- P value between groups is from Mann Whitney U test.
- P value within groups is from Friedman's ANOVA followed by post hoc Dunn's test; * implies significant change from

baseline for that particular follow-up.

**Table 6: Changes in Psoriasis Quality of Life compared between the two study arms**

| | Group Methotrexate (n=25) | Group Methotrexate + Calcipotriol (n=22) | P value (between groups) |
|---|---|---|---|
| Baseline | 2.8 – 92<br>65 (4.3 – 74.25) | 2.8 – 86<br>63.5 (4.3 – 75) | 0.740 |
| End of study (16 weeks) | 2.8 – 46<br>32 (4.3 – 38) | 2.8 – 72<br>22 (4.3 – 31) | 0.003 |
| P value (within group) | < 0.001 | < 0.001 | |

- Values denote Range in the top row and Median (25th percentile – 75th percentile range) in bottom row.
- P value between groups is from Mann Whitney U test.
- P value within groups is from Wilcoxon's matched pairs signed rank test.

## Discussion

Psoriasis is a chronic inflammatory, immune-mediated proliferative disorder that may involve skin, nail and joints. Plaque psoriasis is a common form and we conducted a head-to-head observational comparison of two regimes of well-established antipsoriatic drugs – oral methotrexate alone versus oral methotrexate plus topical calcipotriol – with the view to explore whether the combination actually yields better results in our setting and therefore can lead to methotrexate dose sparing. Our study duration of 16 weeks is appropriate for this comparison.

Reports indicate that psoriasis has a higher prevalence rate in males and with a peak age of onset in the third to fourth decade of life.[17,18] In our study middle aged men comprised the sizeable fraction in both groups, representing the general epidemiology.

The existing literature on the use of methotrexate in psoriasis reflect a dose range of 7.5–30 mg once weekly,[19] taken orally. Some authors generally start with low doses (e.g. 7.5 mg/week) and gradually increase, whereas others recommend starting at the expected target dose (e.g. 15 mg/week). Attending dermatologists in our setting used a starting dose of 7.5 mg in both arms which is in consonance with the global experience. The results of this study show clearly that the addition of calcipotriol ointment to methotrexate obviates the need for methotrexate dose escalation and in fact may even lead to lowering of the weekly dose after an initial period. The maximum dose of methotrexate that can be given to a person safely is 30 mg/week and a liver biopsy is recommended at the cumulative dose of 1.5 g of methotrexate to rule out hepatotoxicity.[19] Thus, adding topical calcipotriol to methotrexate reduces methotrexate dose and preempts adverse drug reactions that might occur due to use at higher doses or for longer time.

All other effectiveness parameters also indicate the desirability of combination treatment. Percentage BSA involvement was comparable at baseline but showed a greater reduction in the combination arm. The PASI score is considered as a reliable objective tool for measuring extent and severity of psoriasis plaques and reduction in PASI score indicates decrease in disease activity. The combination arm achieved a 77.07% reduction in PASI from baseline whereas the methotrexate alone group achieved 54.26% reduction. Going by subjective assessment of disease activity by either the attending physician or the patient global assessment scales, the improvement was significantly more in the combination arm than in the methotrexate alone arm at all follow-up visits.

Surveys by United States National Psoriasis Foundation document that 75% of psoriasis patients report that their disease has moderate to large impact on their quality of life, negatively affecting their daily activities.[20] We measured QoL by using the Koo-Menter instrument at baseline and at final visit and found that QoL also improved to a significantly greater extent on combination therapy than with methotrexate alone. Thus, not only disease burden and activity, but overall patient well-being was better with the combination. This is helped by the lack of significant adverse effects. Greater improvement in QoL is especially important considering that psoriasis can be a socially ostracizing disease. Although we have not specifically looked at cost-effectiveness, we can cautiously opine that the improvement can justify the increased cost of combination treatment.

The findings from our study are in conformity with earlier reports. de Jong EM et al,[10] conducted one of the few published randomized controlled trials of oral methotrexate versus methotrexate plus topical calcipotriol combination. They used a vehicle control in the former arm and concluded that the combination of calcipotriol and methotrexate was safe and well tolerated and that the combination resulted in lower cumulative dosage of methotrexate compared with methotrexate and vehicle. They estimated that methotrexate requirement is reduced by average 3.4 mg per week due to calcipotriol addition. In our case, at study end the requirement was median 2.5 mg lower in the combination arm. In an Indian trial, Deepthi V et al,[21] reported a greater reduction in PASI for 8-week treatment with a combination of methotrexate and calcipotriol as compared to methotrexate alone.

Topical therapy is well established for plaque psoriasis,[22] and combination therapy is also an accepted mode of plaque psoriasis treatment. In case of systemic methotrexate use, concomitant topical therapy should generally be encouraged to help keep the methotrexate dose as low as possible. In light of the above findings, calcipotriol can definitely be regarded as a safe and effective agent for combination. In fact, this combination is used worldwide and groups have been encouraged to explore novel mode of application of this combination. For instance, Lin et al,[23] have studied a

combination of calcipotriol and methotrexate in nanostructured lipid carriers for topical delivery.

Our study has its share of limitations. Firstly, it suffers from the potential allocation and observer biases of an observational study in comparison to a randomized controlled trial (RCT). However, we had planned it as an observational study because both modalities are being used in our setting and our background objective was to explore whether there is sufficient ground for doing a RCT. Secondly, we could not extend the study beyond 16-week observation for the individual patient due to time and logistical limitations. Thus, we are not in a position to comment on the durability of the benefits of added calcipotriol and on relapse events. Finally, long-term side effects of the drugs could not be studied.

## Conclusion

We can conclude that addition of topical calcipotriol to oral methotrexate in plaque psoriasis can offer the benefits of methotrexate dose sparing, improved clinical outcome at least in the short-term and improved quality of life. Our findings indicate that there is sufficient ground to do a controlled trial of appropriate duration in our setting to confirm these observational findings.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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