Original Article

Head-to-Head Comparison of Tazarotene and Calcitriol with or without Sequential Therapy in Mild-to-Moderate Psoriasis: A Randomized Open-label Study

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ABSTRACT

Objective: Psoriasis is an autoimmune disease that causes rapid turnover of skin cells. It is a chronic disease that affects a patient's quality of life significantly and frequently requires long-term treatment. The study on sequential therapy with tazarotene 0.1% and calcitriol 0.0003% has not been tried so far; hence, we designed this study to compare the safety and efficacy of sequential therapy with tazarotene 0.1% cream and calcitriol 0.0003% ointment versus monotherapy in mild-to-moderate stable plaque psoriasis (SPP). The objective of this study was to compare the safety and efficacy of topical sequential treatment with tazarotene followed by calcitriol, topical calcitriol followed by tazarotene, tazarotene monotherapy, calcitriol monotherapy, and compare the safety and efficacy of the sequential therapies with monotherapies. **Methods:** The study was a single center, prospective parallel-group, active control, randomized study of 16 weeks duration (treatment for 8 weeks and follow-up for 16 weeks), randomized to either of the four groups, i.e., tazarotene 0.1% for 4 weeks followed by calcitriol 0.0003% for 4 weeks or calcitriol 0.0003% for 4 weeks followed by tazarotene 0.1% for 4 weeks or tazarotene 0.1% for 8 weeks or calcitriol 0.0003% for 8 weeks. Both tazarotene and calcitriol were applied once daily in all the groups. **Findings:** There was no significant difference with regard to age and duration of illness among the four treatment groups. Statistically significant improvement was observed in erythema, scaling, and induration scores, and Physician`s global assessment scale at 8 weeks and 16 weeks as compared to baseline in tazarotene – calcitriol, calcitriol – tazarotene, and calcitriol versus tazarotene groups. **Conclusion:** This study concluded that topical treatment with tazarotene 0.1% and calcitriol 0.003% was efficacious in treating mild-to-moderate SPP as both sequential and monotherapy. However, topical treatment with tazarotene as monotherapy was the least efficacious.

Keywords: *Calcitriol, sequential therapy, stable plaque psoriasis, Tazarotene, topical treatment*

Introduction

Psoriasis is a chronic, relapsing, multi-system, inflammatory disease. It affects 3% of the world's population, according to the World Psoriasis Day consortium. The prevalence is higher in people of European ancestry than in those of African and Asian ancestry.[1] Psoriasis may appear at any age and is classified by Henseler and Christopher into two types: Type I psoriasis has an early age of onset, i.e., before 40 years while Type II psoriasis has onset after

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40 years.[2] The basic pathology is a combination of hyperplasia of epidermal keratinocytes, angiogenesis, and infiltration of T-lymphocytes, neutrophils, and other types of leucocytes in the affected skin.[3]

Based on the morphology, it is classified into: plaque, guttate, inverse, pustular, and erythrodermic.[4] Stable plaque psoriasis (SPP) is the most common form, affecting 80%–90% of the patients.[5] It is characterized by well-defined thick, red, raised areas with silvery white scales which are loosely adherent. Although these plaques can be found anywhere on the body, they preferentially affect elbows, knees, lumbosacral area, intergluteal cleft, and scalp.[6] It usually starts as a pinpoint papule which grows larger and evolves showing scaling. The plaques may become inflamed during bouts of activity and expand centrifugally. The physical impact of the disease is based on the degree or extent of skin involvement, determined by the patient's affected body surface area (BSA): mild (BSA <3%), moderate (BSA 3%–10%), and severe (BSA >10%).[7]

Among the topical treatments, the options are topical steroids, coal tar, vitamin D3 analogs, anthralin, salicylic acid, tazarotene, and moisturizers. Although these are also not free of adverse effects but are certainly low-risk therapies.[8]

The study on sequential therapy with tazarotene 0.1% and calcitriol 0.0003% has not been tried so far; hence, we designed this study to compare the safety and efficacy of sequential therapy with tazarotene 0.1% cream and calcitriol 0.0003% ointment versus monotherapy in mild-to-moderate SPP.

Methods

The study was approved by the institution ethics committee. This clinical trial was a single-center, parallel-group, randomized, open-label study with topical tazarotene and calcitriol in psoriasis patients satisfying inclusion and exclusion criteria. All psoriasis patients visiting the dermatology outpatient department were screened for eligibility criteria. Both males and females, >18 years of age with SPP (of at least 3 months duration) and 5%–10% BSA involvement, willing to give written informed consent and complete the study and comply with study instructions were included in the study. Patients with lesions on the face, scalp, groin, hands, and feet, pregnant or nursing women, patients with a current diagnosis of unstable forms of psoriasis in the treatment area including guttate, erythrodermic, exfoliative or pustular psoriasis, other inflammatory skin disease, presence of pigmentation, extensive scarring or pigmented lesions in the treatment area were not included in the study. Patients with a history of psoriasis unresponsive to topical treatments, history of hypersensitivity to any component of the test product, current or past history of hypercalcemia, Vitamin D toxicity, severe hepatic disorders, and current immunosuppression were not a part of this study. Patients who had used systemic steroids, systemic antibiotics, systemic anti-psoriatic treatment, PUVA therapy, UVB therapy, calcium supplements, or systemic anti-inflammatory agents within 1 month before baseline; topical anti-psoriatic drugs, topical corticosteroids, immunosuppressive drugs, or topical retinoids within 2 weeks; use of topical products other than the assigned treatment on or near the treatment area; initiation of or changes to nonpsoriatic concomitant medication that could affect psoriasis during the study were not a part of this study. Clinical examination which included erythema, scaling, and induration (ESI) scoring was done. Clinical photographs of patients were taken at baseline and posttreatment. Eligible patients were randomized in an open-label manner into four groups. The randomization codes were computer generated and were concealed in an opaque envelope. Evaluation for efficacy parameters was done at 0, 8, and 16 weeks. Safety evaluation was done throughout the study.

One hundred and twenty adult patients (58 males and 62 females) of mean age 36.3 ± 12.8 years having nearly bilateral symmetrical lesions of SPP on limbs involving a total surface area of not more than 100 cm^2 were recruited. The study was a prospective parallel group, active control randomized study of 16 weeks duration (treatment for 8 weeks and follow-up for 16 weeks), randomized to either of the four groups with each group of 30 patients. In Group I, tazarotene 0.1% cream was applied daily over lesions for the first 4 weeks followed by calcitriol 0.0003% ointment daily for the next 4 weeks. In Group II, calcitriol 0.0003% was applied over lesions for 4 weeks followed by 0.1% tazarotene for the next 4 weeks. In Group III, tazarotene 0.1% was applied for 8 weeks. In Group IV, calcitriol ointment 0.0003% was applied for 8 weeks. No specific brand name was prescribed to the patients. The treatment was given for 8 weeks only in each treatment group but assessment was done at 0, 8, and 16 weeks. Tazarotene was applied as short contact therapy; the patients were instructed to apply the medicine and wash it with water after 20 min. Both tazarotene and calcitriol were applied once a day in all the four groups. All prior medications except antihistamines were stopped 4 weeks before the start of the study, and only application of an emollient (coconut oil) was permitted on both the sides.

Blinded end points assessment of efficacy parameters was done at 8 and 16 weeks. The primary efficacy end

point was the mean difference in ESI and the patient's own assessment from baseline after 8 weeks of therapy and at 16 weeks. The assessment of target psoriatic lesions under evaluation and progress during treatment was done using the ESI score. The lesions were assessed on a grade from 0 to 5, i.e., 0 (nil), 1 (minimal), 2 (mild), 3 (moderate), 4 (severe), and 5 (very severe) for each parameter. All the parameter scores were added to get a score ranging from 0 to 15. The assessment scale was chosen as per the PASI ESI scoring. The secondary efficacy end points were period of remission and number of adverse effects reported.

Assuming a standard deviation of 2 in ESI scores and a difference of 2 in ESI scores between the drug and placebo arm at 12 weeks to be clinically significant at α =0.05 and with 80% power, a sample size of 16 patients per group was calculated and with a dropout rate of about 20%, and 20 patients will be required to be included in each group.

Data were expressed as mean ± standard deviation (95% confidence intervals) or numbers (percentages). The evaluation was done at baseline (0 week), 8, and 16 weeks of treatment. The scores obtained were statistically compared using one-way analysis of variance for intergroup and intragroup comparisons. *Post hoc* Scheffe's test was used for between group comparisons. Categorical data were analyzed using the Chi-square test. Statistical analysis was performed using the statistical package SPSS 21.0 for Windows (IBM Corp. Ltd, Newark, USA).

Results

The demographic profile of the patients is given in Table 1. There was no significant difference with regard to age and duration of illness among the four treatment groups. Out of total 120 patients, 58 were male and 62 were female making a male-female distribution of 48% and 52%.

The mean intragroup change in the mean ESI score and physician global assessment (PGA) is shown in Table 2. Statistically significant improvement was observed in ESI scores and PGA scores at 8 weeks and 16 weeks as compared to baseline in Groups I, II, and IV. There was no significant improvement in ESI and PGA scores at 8 weeks as compared to baseline in Group III. The mean change in four treatment groups with regard to ESI score and PGA is shown in Table 3. Significant improvement was observed in Groups I, II, and IV versus Group III in ESI scores at 8 and 16 weeks and PGA scores at 16 weeks as compared to baseline. Groups I, II, and IV were comparable in showing improvement in ESI and PGA scores at 16 weeks as compared to baseline.

Few patients reported mild side effects of the medication but no patient discontinued the treatment because of the side effects. The side effects noticed were itching, burning, and skin irritation. Increase in erythema was only observed in Group III. None of the patients reported fissuring. No serious adverse events were reported in any of the four groups. The adverse events are tabulated in Table 4. Most side effects were observed for first

Table 1: Demographic profile of the patients

Characteristics	TC (*n*=30)	CT (*n*=30)	Tazarotene (*n*=30)	Calcitriol (*n*=30)	*P*
Age (years)	39.47±11.83	36.83±12.76	35.53±12.76	33.33±15.01	0.31
Duration of illness (years)	4.35±3.19	5.19±4.22	5.9±4.80	4.75±4.14	0.51
Sex ratio (male: female)	0.58:1	1.72:1	0.87:1	0.87:1	0.97

Data are presented as mean±SD. TC=Tazarotene – Calcitriol, CT=Calcitriol – Tazarotene, SD=Standard deviation

Table 2: Mean intragroup changes in psoriasis ESI score and PGA score during 16 weeks of therapy (intention to treat analysis)

Parameters	TC[§] (*n*=30)	CT[§] (*n*=30)	Tazarotene (*n*=30)[§]	Calcitriol (*n*=30)[§]
ESI at baseline	10.1±1.70	10.1±1.54	9.1±2.01	9.2±2.41
ESI at 8 weeks	5.5±2.53	5.9±2.45	6.9±2.58	5.3±2.96
ESI at 16 weeks	7.0±1.68	7.6±1.75	8.0±1.95	6.7±2.65
P value	<0.001*, <0.001[†], 0.022[‡]	<0.001*, <0.001[†], 0.004[‡]	0.001*, 143[†], 0.178[‡]	<0.001*, 0.002[†], 0.124[‡]
PGA at baseline	3.6±0.89	3.7±0.59	4.0±0.74	3.9±0.77
PGA at 8 weeks	2.1±0.97	2.1±1.04	3.2±0.96	2.2±0.81
PGA at 16 weeks	2.8±0.76	2.8±0.87	4.1±0.64	3.1±1.00
P value	<0.001*, 0.003[†], 0.017[‡]	<0.001*, 0.001[†], 0.009[‡]	0.001*, 0.948[†], 0.000[‡]	<0.001*, 0.007[†], 0.001[‡]

Intragroup comparisons for individual parameters carried out by one-way ANOVA, *post hoc* test Scheffe's, *8 weeks versus baseline, [†]16 weeks versus baseline, [‡]8 weeks versus 16 weeks. Data are presented as mean±SD. SD=Standard deviation, TC=Tazarotene – Calcitriol, CT=Calcitriol – Tazarotene, ESI=Erythema Scaling and Induration, PGA=Patient Global Assessment

Table 3: Mean change in psoriasis ESI score and PGA score after 16 weeks of treatment in four treatment groups from baseline (intention to treat analysis)

Parameters	TC (*n*=30)	CT (*n*=30)	Tazarotene (*n*=30)	Calcitriol (*n*=30)	*P* value[§]
ESI at 8 weeks versus baseline	4.5±2.30	4.3±2.53	2.2±1.49	3.9±1.70	0.968*, 0.001[†], 0.733[‡] 0.002[‖], 0.941**, 0.016[#]
ESI at 16 weeks versus baseline	3.1±1.83	2.6±2.11	1.1±1.31	2.5±1.50	0.775*, 0.001[†], 0.653[‡] 0.015[‖], 0.997**, 0.027[#]
ESI at 8 weeks versus 16 weeks	1.5±1.59	1.7±1.45	1.1±1.01	1.4±1.04	0.949*, 0.700[†], 0.999[‡] 0.365[‖], 0.922**, 0.754[#]
PGA at 8 weeks versus baseline	1.5±1.10	1.6±0.93	0.8±0.96	1.6±0.81	0.983*, 0.070[†],0.929[‡] 0.026[‖], 0.995**, 0.013[#]
PGA at 16 weeks versus baseline	0.8±0.92	0.9±0.73	−0.07±0.78	0.7±1.05	0.993*, 0.003[†], 0.993[‡] 0.001[‖], 0.951**, 0.008[#]
PGA at 8 weeks versus 16 weeks	0.7±0.84	0.7±0.65	0.9±0.97	0.9±1.02	0.999*, 0.858[†], 0.792[‡] 0.912[‖], 0.858**, 0.999[#]

[§]Intergroup comparisons for individual parameters carried out by one-way ANOVA, *post hoc* test Scheffe's, *TC versus CT, [†]TC versus tazarotene, [‡]TC versus calcitriol, [‖]CT versus tazarotene, **CT versus calcitriol, [#]Tazarotene versus calcitriol. Data are presented as mean±SD. ESI=Erythema Scaling and Induration, PGA=Patient Global Assessment, SD=Standard deviation, TC=Tazarotene – Calcitriol, CT=Calcitriol – Tazarotene

Table 4: Adverse events reported by patients in four treatment groups

Adverse events	TC (*n*=30)	CT (*n*=30)	Tazarotene (*n*=30)	Calcitriol (*n*=30)
Itching	1	1	3	1
Irritation	0	0	3	1
Burning sensation	2	0	2	0
Increase in erythema	0	0	4	0

TC=Tazarotene – Calcitriol, CT=Calcitriol – Tazarotene

4 weeks of treatment except increase in erythema which lasted till completion of therapy in Group III. The patients were advised to use coconut oil and other emollients for management of side effects.

Discussion

The present study was planned to compare the safety and efficacy of topical sequential treatment with tazarotene and calcitriol versus monotherapy in SPP.

On comparing the four groups, our study demonstrated a comparable decrease in the scores of erythema, scaling, plaque elevation, and patient`s assessment score in Groups I, II, and IV. The results of our study are comparable to the results of studies done previously on topical calcitriol. Lahfa *et al*.[9] observed that successful clinical response as revealed by global assessment by investigators in majority of patients treated with topical calcitriol. Similarly, Barker *et al*.[10] found global severity scores for psoriasis showed marked improvement from baseline to end of treatment phase with topical calcitriol. Various other studies were done by Wishart[11] and Saggese *et al*.[12] also demonstrated better response to treatment as per patient assessment.

Our study showed comparable efficacy in all the groups except tazarotene monotherapy. A study by Tzung *et al*.[13] comparing tazarotene 0.1% gel plus petrolatum with calcipotriol 0.005% inferred better treatment success rates as assess by patients themselves with calcipotriol treated side. Eighty-five percent of patients reported treatment success with calcipotriol as compared to 74% with tazarotene. A similar right–left side intraindividual 8-week parallel study done to directly compare calcipotriol and tazarotene was conducted by Kaur *et al*.[14] on 17 patients. The study inferred that calcipotriol-treated lesions produced moderate-to-marked improvement as compared to tazarotene 0.05% at both 4 and 8 weeks. Although this study also showed comparable improvement with calcipotriol and tazarotene 0.1% at the end of 4 and 8 weeks, the findings of our study are consistent with the earlier study.

We observed comparable improvement in Groups I and II, i.e., on sequential therapy. Tanghetti[15] proved that substantial additional improvement in efficacy and patient satisfaction was observed in patients switched from topical Vitamin D analog to tazarotene, Groups I, and II, i.e., patients on sequential therapy in our study.

Adverse events were observed in 18 out of 120 (15%) patients. Gerritsen *et al*.[16] had demonstrated that topical calcitriol is safe even on the long-term use. Similar results were noted by Langner *et al*.[17] in their study on the long-term use of calcitriol. Ortonne *et al*.[18] also showed in their right-left comparison study that calcitriol was better tolerated and perilesional erythema, and burning was significantly less severe with calcitriol. Whereas Zhu *et al*.[19] observed lower

cutaneous discomfort and better patient acceptance with calcitriol. The present study also demonstrated similar results, although only one patient each reported mild itching and irritation during the initial phase which subsided with continued treatment. Out of 18 patients reporting side effects, 12 were treated exclusively with tazarotene (Group III). Mehta and Amladi[20] reported a higher incidence of AE with tazarotene, 6 out of 17 reported itching and 4 patients reported irritation. The present study stated fewer incidences of side effects with tazarotene which can be justified by the fact that short contact therapy for tazarotene was used. A study done by Veraldi *et al*.[21] provides evidence that short contact therapy with tazarotene is better tolerated than the traditional treatment with tazarotene. Our study supported the evidence of similar treatment response with all therapies except short-contact tazarotene therapy, which was unable to improve the ESI score as achieved in other groups. Four patients in our study reported an increase in erythema with tazarotene alone treatment, which subsides after completion of therapy.

Our study showed comparable efficacy in all the groups except tazarotene monotherapy. Topical treatment with tazarotene as monotherapy seems the least efficacious.

The limitation of the study was a small sample size in each group. A study with more patients will help in strengthening the results of the study.

Authors' contribution

Dr Prithpal Singh Matreja, Dr Jaspreet Kaur Sidhu, Dr Ashwani Kumar Gupta, Dr Amandeep Singh contributed in the concept and design of the study. Dr Jaspreet Kaur Sidhu, Dr Prithpal Singh Matreja, Dr Ashwani Kumar Gupta and Dr Amandeep Singh did the data collection and literature review. Dr Jaspreet Kaur Sidhu, Dr Prithpal Singh Matreja and Dr Surjit Singh analysed the data and prepared the manuscript. All authors approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest.

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