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COMPARISON OF THE EFFICACY OF TAZAROTENE WITH OR WITHOUT BETAMETHASONE DIPROPIONATE IN THE TREATMENT OF PSORIASIS

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ABSTRACT

Background: Long-term use of corticosteroids or local use of tazarotene (TAZ) alone for the treatment of psoriasis cause safety issues and low compliance rates. Combining these two treatments may optimize their efficacy and minimize safety concerns. **Aim:** This study aimed to compare the clinical efficacy and safety of tazarotene 0.05%, betamethasone dipropionate 0.05% (BM), and their combination in the treatment of psoriasis. **Materials and Methods:** A randomized, controlled clinical trial was conducted. A total of 90 subjects with mild to moderate psoriasis were randomized to TAZ gel, BM cream or TAZ/BM combination groups for 4 weeks with a 6-week follow up. The primary efficacy assessment end-point was 75% improvement in Psoriasis Area and Severity Index (PASI-75) at 4 weeks. Secondary outcome assessments included PASI-90, PASI-50, percentage of PASI decrease and so forth. Safety and treatment-related adverse events were monitored throughout the study. **Results:** After 4 weeks of treatment, PASI-75 was 53.33% in the TAZ/BM group while 33.33% and 40% in the TAZ and BM groups, respectively. Significant differences were observed among all groups (p-value = 0.04). At the 6-week follow up,the relapse rate of the TAZ/BM group was significantly lower than the BM group (11.1% vs 37.5%) though comparable with the TAZ group (14.3%). The most frequently reported treatment-related adverse event was itching. **Conclusion:** Topical tazarotene seems to be significant and well tolerated agent for the treatment of psoriasis. TAZ/BM combination has significant advantages over TAZ, including satisfying efficacy, rapid onset and reduced local stimulation. Meanwhile, compared with BM, it has the advantages of longer relief time and reduced clinical relapse rate. The TAZ/BM combination provides psoriatic patients an alternative treatment choice with high efficacy and low relapse rate and safety concerns.

KEY WORDS: Psoriasis, tazarotene, betamethasone.

INTRODUCTION

Psoriasis is a chronic proliferative inflammatory disease of the skin with sometimes systemic manifestations, especially arthritis.[1] The prevalence of psoriasis in adults varies between 2-3%.[1] Most patients (75-90%) have mild to moderate psoriasis.[3] Both genetic and environmental factors play a role in the pathogenesis of psoriasis, and it is considered an immune-mediated disease.[1] Several treatment regimens are proposed for the management of psoriasis, the aim of which is to control the pathogenesis, reduce the affected body area and number of lesions, achieve long-term remission and improve the quality of life.[5]

Topical corticosteroids are the first-line treatment in the management of mild to moderate psoriasis alone or in combination. However, they do not have a persistent effect and, with long-term use, cause side effects such as atrophy, striae, telangiectasia, acneiform eruptions, infections and resistance to treatment.[2]

Topical retinoids are used in the treatment of psoriasis. Tazarotene has received FDA approval in the treatment of mild to moderate plaque psoriasis that affects less than 20% of the body surface area. It is considered a second line of treatment, but it may cause skin irritation, erythema, burning sensation and itching.[2]

Several studies have shown that the efficacy and tolerability of tazarotene increase when combined with

topical corticosteroids, as there is a synergistic effect between them, as the steroid causes a rapid response and reduces the erythema and irritation that tazarotene may cause. In contrast, Tazarotene prolongs the duration of the therapeutic response, reduces relapse after stopping the steroid, and reduces skin atrophy and other side effects of topical steroids.[2,3,4,5 6,7]

Tazarotene has been tried because it was recently available in the Syrian pharmaceutical market in order to present our experience about its effectiveness, in addition to the availability of drugs around the world that contain a combination of tazarotene and corticosteroids, so the effectiveness of the combination has been studied as well.

MATERIALS AND METHODS

Study Population

After approval by local research ethics committee, a randomized, controlled clinical trial was conducted in Department of Dermatology and Venereology at Tishreen University Hospital in Lattakia, Syria, between September 2021 and September 2022.

Inclusion Criteria were as follows.

1. Patients with mild and moderate psoriasis, where the affected body area does not exceed 20%.
2. Patients over 12 years old of both sexes.

Exclusion Criteria

1. Pregnancy and breastfeeding or planning a pregnancy during the study period.
2. Using topical treatments for psoriasis or phototherapy during the two weeks preceding the study.
3. Use of oral retinoids 8 weeks before the study and other medications, such as methotrexate, 4 weeks before the study.
4. Use of photosensitizing drugs such as thiazide diuretics, phenothiazines, antibiotics such as tetracyclines, fluoroquinolone and sulfonamides, and drugs that exacerbate psoriasis such as beta-blockers and ACE inhibitors.
5. Psoriasis affecting more than 20% of the body area and other severe forms that require systemic treatment.

Treatment Protocol

The patients participating in the study were divided into three groups and one of the treatments was applied to each of them:

Group TAZ: Tazarotene Gel 0.05% alone once a day in the evening.

Group BM: Betamethasone dipropionate cream 0.05% alone once a day in the evening. Group TAZ/BM: The combination of tazarotene gel 0.05% with betamethasone dipropionate cream 0.05%, so that the two medicines are applied sequentially once in the evening daily.

Patients were instructed to apply the treatment to all psoriatic lesions while avoiding intact skin. The treatment was applied for 4 weeks and recurrence was monitored for another 6 weeks. Psoriasis Area and Severity Index (PASI) was calculated with photographs taken before starting treatment, every two weeks during treatment and at the end of the follow-up period. Side effects (such as irritation, itching, erythema, burning sensation, etc.) were evaluated during the treatment period.

The treatment efficacy was evaluated as follows

The primary efficacy criterion was PASI-75 which is defined as the percentage of patients who achieved a 75% or more reduction in their PASI score from baseline.[3]

Secondary efficacy criteria were

1. PASI-50 (PASI score reduction by 50% or more).[4]
2. PASI-90 (PASI score reduction by 90% or more).[3]
3. Relapse rate = (number of patients who had relapse) / (number of patients who had achieved PASI-90) × 100% (relapse was defined as a loss of 50% of PASI improvement from the baseline PASI score at 6 weeks after the last treatment).[3,4]
4. The reduction rate of PASI scores from baseline with treatment.
5. To document treatment-related side effects.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS statistics (version20) program. Descriptive statistics were expressed in measures of central tendency and measures of dispersion for quantitative variables, frequencies and percentages of qualitative variables. The following tests were used to study the relationship between the research groups: One Way ANOVA to compare the averages of several independent groups. Chi-Square Or Fisher exact test to study the relationship between qualitative variables. The results were considered statistically significant with a p-value of <0.05.

RESULTS

- The research sample included 90 patients [57 males, 63.3%, and 33 females, 36.7%, Sex Ratio (M:F) = 1.7:1] of mild and moderate psoriasis patients who attended the Dermatology Department at Tishreen University Hospital in Lattakia during the time period 2021-2022 and who fulfilled the inclusion criteria of the research.
- The patients' ages ranged from 12 to 72 years, with a mean age of 37.75 ± 15.7 years.
- The duration of psoriasis ranged from one week to 720 months, and the average duration of psoriasis was 24 months.
- The patients were divided according to the treatment plan as follows: 30 patients (33.3%) in the tazarotene (TAZ) group, 30 patients (33.3%) in the betamethasone (BM) group and 30 patients (33.3%)

in the combination (TAZ/BM) group.

- The demographic data and baseline disease characteristics of the patients are summarized in Table 1. No significant differences were observed between groups for age, sex, disease duration, medical history and basal PASI score.

Table 1: the differences in the demographic distribution among the treatment groups.

Demographic data	TAZ	BM	TAZ/BM	p-value
Sex n(%) Male Female	 19(63.3%) 11(36.7%)	 20(66.7%) 10(33.3%)	 18(60%) 12(40%)	0.8
Age (years)mean±SD	36.73±16.1	36.43±15.1	40.10±16.4	0.6
Psoriasis duration(months)median[range]	42[1-300]	15[1W-240]	24[1-720]	0.1
Treatment history n (%)	25(83.3%)	17(56.7%)	22(73.3%)	0.07
Basal PASI score mean±SD	4.39±2.6	3.68±2.3	4.03±1.9	0.4

Clinical efficacy assessment

PASI-75

After 2 weeks of treatment, PASI-75 in the TAZ/BM, BM, and TAZ groups was 20%, 16.7%, and 13.3%, respectively. There were no significant differences between these groups (p-value = 0.07).

After 4 weeks of treatment, PASI-75 was 53.33% in the TAZ/BM group while 33.33% and 40% in the TAZ and BM groups, respectively. Significant differences were observed between all groups (p-value = 0.04) and between TAZ/BM and TAZ groups (p-value = 0.01), except between TAZ/BM and BM groups (p-value = 0.6) and betweenTAZ and BM groups (p-value>0.05). (Table 2, Figure 1).

Table 2: PASI-75 after two and four weeks of treatment.

PASI-75	TAZ	BM	TAZ/BM	p-value among groups
Week 2	4(13.3%)	5(16.7%)	6(20%)	0.07
p-value vs TAZ/BM	0.05	0.2	-	
Week 4	10(33.3%)	12(40%)	16(53.3%)	0.04
p-value vs TAZ/BM	0.01	0.6	-	

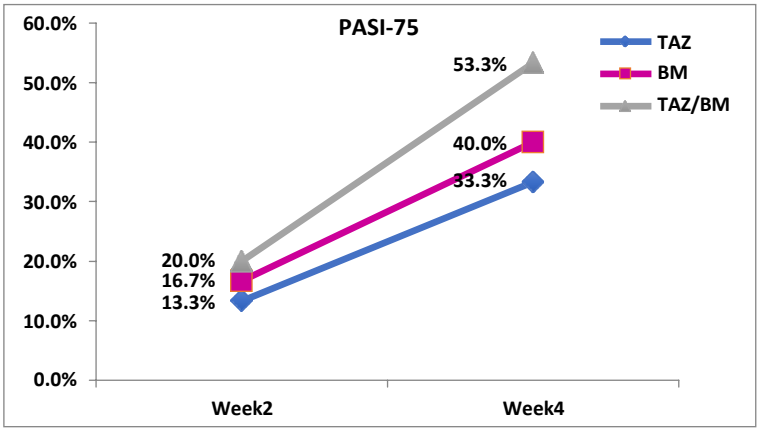

Figure 1: PASI-75 after two and four weeks of treatment.

PASI-50

After 2 weeks of treatment, PASI-50 in the TAZ/BM, BM, and TAZ groups was 36.7%, 30%, and 33.3%, respectively. There were no significant differences between these groups (p-value = 0.8).

After 4 weeks of treatment, PASI-50 was 86.7% in the TAZ/BM group while 50% and 73.3% in the TAZ and BM groups, respectively. Statistically significant differences were observed between all groups (p-value = 0.007) and between TAZ/BM and TAZ groups (p-value = 0.001), except between TAZ/BM and BM groups (p-value = 0.09) and between TAZ and BM groups (p-value>0.05). (Table 3, Figure 2).

Table 3: PASI-50 after two and four weeks of treatment.

PASI-50	TAZ	BM	TAZ/BM	p-value among groups
Week 2	10(33.3%)	9(30%)	11(36.7%)	0.8
p-value vs TAZ/BM	0.5	0.1	-	
Week 4	15(50%)	22(73.3%)	26(86.7%)	0.007
p-value vs TAZ/BM	0.001	0.09	-	

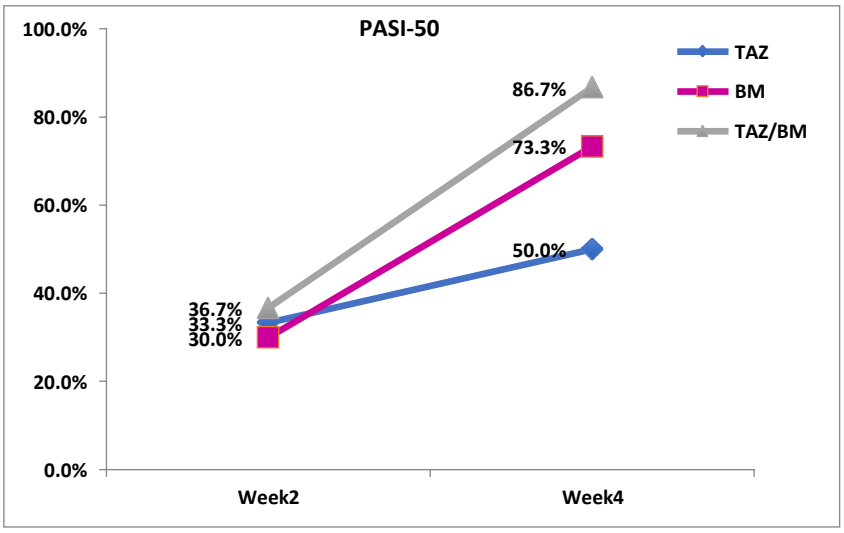

Figure 2: PASI-50 after two and four weeks of treatment.

PASI-90

After two weeks of treatment, PASI-90 in each of the three groups was 3.3%. There were no significant differences between these groups (p-value = 1).

After 4 weeks of treatment, PASI-90 in the TAZ/BM, BM, and TAZ groups was 30%, 26.7%, and 23.3%, respectively. There were no significant differences between these groups (p-value = 0.8). (Table 4, Figure 3).

Table 4: PASI-90 after two and four weeks of treatment.

PASI-90	TAZ	BM	TAZ/BM	p-value among groups
Week 2	1(3.3%)	1(3.3%)	1(3.3%)	1
p-value vs TAZ/BM	—	—	—	
Week 4	7(23.3%)	8(26.7%)	9(30%)	0.8
p-value vs TAZ/BM	0.09	0.3	-	

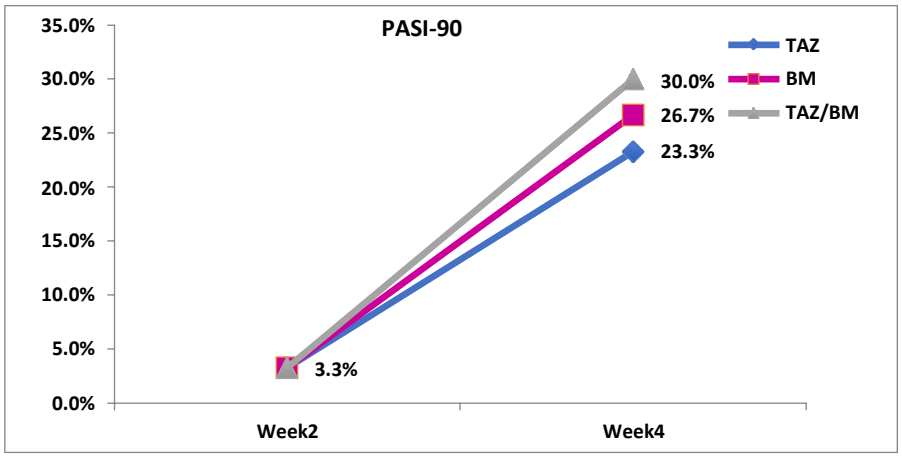

Figure (3) PASI-90 after two and four weeks of treatment.

Average PASI improvement

After two weeks of treatment, the TAZ/BM group had the highest percentage of PASIimprovement of 47.14%, followed by the BM group 30.7% and the TAZ group (25.74%, p-value = 0.02 vs. the TAZ/BM group). Statistically significant differences were observed between all groups (p-value=0.04).

After 4 weeks of treatment, the percentage of PASI improvement in the TAZ/BM, BM,and TAZ groups was 75.68%, 56.79%, and 37.35%, respectively. Significant differences were observed between all groups (p-value = 0.001) and between the TAZ/BM and TAZ groups (p-value = 0.0001), except between the TAZ/BM and BM groups (p-value = 0.1) and between TAZ and BM groups (p-value>0.05). (Table 5, Figure 4).

Table 5: PASI improvement percentage after two and four weeks of treatment.

PASI	TAZ	BM	TAZ/BM	p-value among groups
Baseline	4.39±2.6	3.68±2.3	4.03±1.9	0.4
p-value vs TAZ/BM	0.5	0.5	-	
Week 2	3.26±2.2	2.55±1.9	2.13±1.3	0.04
PASI decrease percentages	25.74%	30.70%	47.14%	
p-value vs TAZ/BM	0.02	0.3	-	
Week 4	2.75±2.3	1.59±1.5	0.98±0.8	0.001
PASI decrease percentages	37.35%	56.79%	75.68%	
p-value vs TAZ/BM	0.0001	0.1	-	

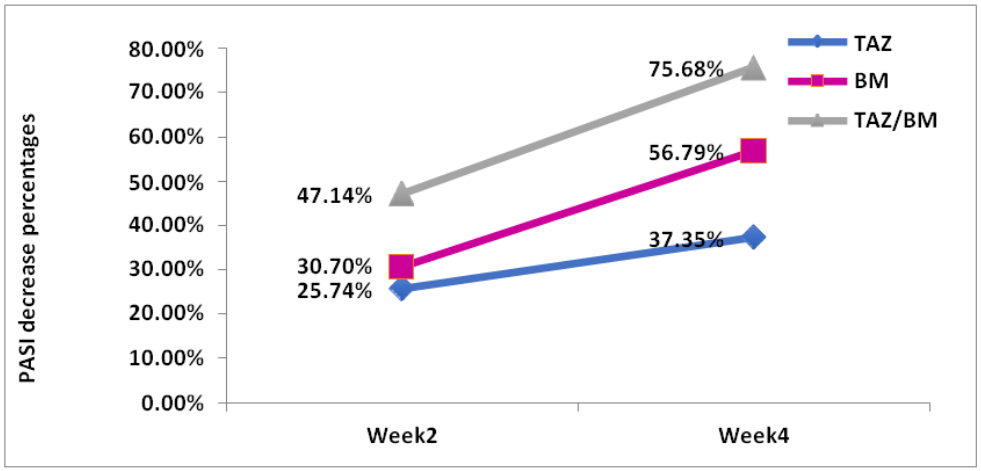

Figure 4:PASI improvement percentage after two and four weeks of treatment.

Relapse rate

After a 6-week follow-up, the relapse rate in the TAZ/BM group was significantly lower than that in the BM group (11.1% vs 37.5%, p-value < 0.05) and comparable with the TAZ group (14.3%). Our results indicate that TAZ/BM combination can effectively increase remission time of patients with psoriasis. (Figure 5).

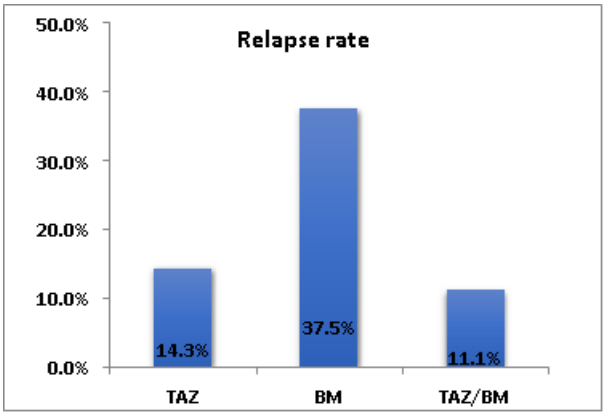

Figure 5: Relapse rates among treatment groups.

Side effects of the treatment

We noticed that all the side effects occurred in the tazarotene group (itching, irritation, erythema and burning sensation) and for the remaining two groups only a very small number of patients had itching, and there were statistically significant differences for all the side effects that occurred. (Table 6, Figure 6).

Table 6: side effects in treatment groups.

Side effects	TAZ	BM	TAZ/BM	p-value among groups
Itching	7(23.3%)	1(3.3%)	2(6.7%)	0.03
Irritation	5(16.7%)	—	—	0.005
Erythema	3(10%)	—	—	0.04
Burning sensation	3(10%)	—	—	0.04

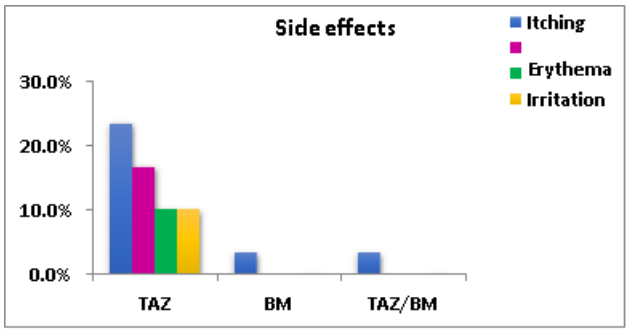

Figure 6: side effects between in groups.

DISCUSSION

This study showed that the combination of tazarotene with betamethasone is more effective in the treatment of mild and moderate psoriasis than the monotherapy with one of the two drugs, with a faster effect than tazarotene alone and a lower relapse ratethan betamethasone alone. This is explained by the fact that corticosteroids decrease the production of inflammatory cytokines and inhibit the infiltration of inflammatory cells and that tazarotene regulates the proliferation and differentiation of keratinocytes and has an anti-inflammatory and immunomodulatory effect.[2] Furthermore, tazarotene had significantly better maintenance of therapeutic effects after cessation of therapy in comparison with potent topical corticosteroids.[3] Further studies measuring plasma levels of psoriasis-related cytokines would shed some light on the mechanisms of thesesynergistic effects of TAZ and BM, so further studies are recommended.

When comparing our results with the results of global studies, we found.

The results of our study are consistent with the study of Hao CHEN *et al*[3] in China in2020, which included 600 patients, in which they compared treatment with tazarotene alone and betamethasone alone with their combination in the treatment of psoriasis for 6 weeks with a follow-up of 8 weeks, where they found that PASI-75 and the average improvement of PASI score were higher in the combination group compared with the monotherapy, and the relapse rate was lower in the combination group compared with it in the betamethasone group, and most side effects were in the tazarotene group and the most common was itching.

In the study of Chunxia He *et al*[4] in China in 2019, which included 2095 patients, in which they studied the efficacy of combining tazarotene with betamethasone for 4 weeks in the treatment of psoriasis with 8-week follow-up, the combination was effective and the average PASI-75 after 4 weeks was 26.8%, but in our study, it was 53.3%, and the relapse rate was 24% but in our study 11.1%, this may be due to the difference in the sample size, which was smaller in our study. The most common side effect was itching as in our study.

In the study of Humaira Afreen *et al*[5] in Bangladesh in 2019, that included 60 patients, in which they compared tazarotene alone and its combination with betamethasone in the treatment of psoriasis for 12 weeks, the mean PASI improvement after one month was similar in both groups 28.8% and after 12 weeks it was 74.24% in the combination group and 47.48% in the tazarotene group, while in our study the mean PASI improvement after a month was higher in the combination group 75.68% compared to the tazarotene group 37.35% group. The most common side effect was the burning sensation, but in our study it was itching. This study did not assess the relapse rate after stopping treatment.

In the study of Lawrence Green et al[6] in the United States of America in 2002, which included 259 patients, in which they compared tazarotene alone and its combination with different topical corticosteroids in the treatment of psoriasis for 12 weeks, they found that the combination is more effective and that the best steroid in combination is Betamethasone dipropionate 0.05%

cream and the most tolerable is mometasone furoate 0.1% ointment. Most of the side effects were in the tazarotene group alone and this is consistent with our study. This study did not assess the relapse rate after stopping treatment.

There were some limitations in our study. The sample size was small and the follow- up time to assess the relapse rate after stopping treatment was relatively short.

CONCLUSION

Topical tazarotene seems to be significant and well tolerated agent for the treatment of psoriasis.

TAZ/BM combination has significant advantages over TAZ, including satisfying efficacy, rapid onset of action and reduced local stimulation. Meanwhile, comparedwith BM, it has the advantages of longer relief time and reduced clinical relapse rate. The TAZ/BM combination provides psoriatic patients an alternative treatment choicewith high efficacy and low relapse rate and safety concerns.

Accordingly, we recommend the following.

- Further studies of the efficacy of tazarotene and its combination with steroids using a larger sample size and a higher concentration of tazarotene and other steroids.
- Using the combination of tazarotene with betamethasone in patients with mild and moderate psoriasis to increase efficacy and reduce relapse and side effects.
- Synthesis of new topical drugs containing the combination of tazarotene and betamethasone to take advantage of the properties of this combination.

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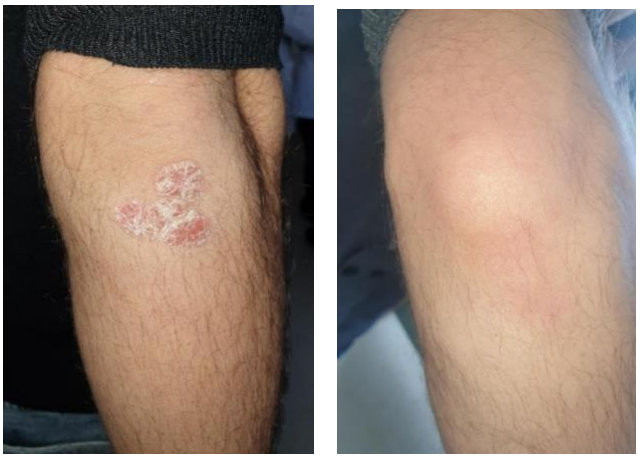

Figure 7: a- psoriatic plaque before treatment, b- after treatment with tazarotene for 4weeks.

a b

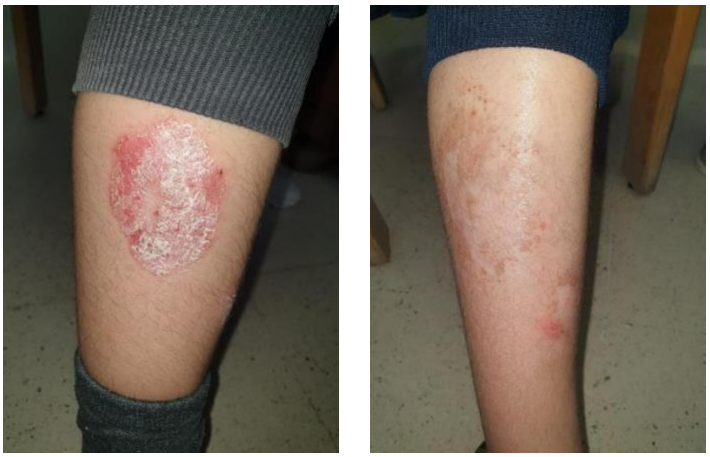

Figure 8: a- psoriatic plaque before treatment, b- after treatment with TAZ/BM for 4weeks.

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