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Research Article

COMPARATIVE EVALUATION OF EFFICACY AND SAFETY OF TOPICAL METHOTREXATE WITH TRETINOIN VERSUS BETAMETHASONE WITH TRETINOIN IN PATIENTS OF ALOPECIA AREATA: A PROSPECTIVE RANDOMIZED DOUBLE-BLIND STUDY

SAROJ KOTHARI[1], VAIBHAV VIVEK KALGAONKAR[1]*, SANJAY KUMAR R[1], ANUBHAV GARG[2], RAJKUMAR ARYA[1]

[1]Department of Pharmacology, G.R Medical College, Gwalior, Madhya Pradesh, India. [2]Department of Dermatology, G.R Medical College, Gwalior, Madhya Pradesh, India.
*Corresponding author: Vaibhav Vivek Kalgaonkar; Email: drvaibhav.kalgaonkar@gmail.com

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ABSTRACT

Objectives: Alopecia areata (AA) is a reiterative and non-scarring type of hair loss that can affect any hairy area of the body, particularly the scalp. The present study is aimed at comparing the safety and efficacy of methotrexate with tretinoin versus betamethasone with tretinoin in patients of AA.

Methods: A prospective and comparative study was carried out in 80 cases of AA in Gajra Raja Medical College, Gwalior (M.P.) from December 2022 to November 2023. Subjects were randomly allocated to two groups, namely, MXT and BMT, 40 patients in each group. In group MXT, patients were asked to apply methotrexate 1% gel in the morning and tretinoin 0.025% cream in the evening, and in group BMT patients were asked to apply betamethasone 0.05% cream once daily in the morning and tretinoin 0.025% cream in the evening for 6 months. Mean severity of alopecia tool (SALT) score, mean regrowth scale (RGS) score, and adverse drug reactions due to treatments were recorded at 0, 3, and 6 months.

Results: Mean SALT score decreased from 4.40 to 0.57 in MXT and from 3.34 to 0.63 in BMT group after 6 months and is significant ($p<0.05$) from baseline values. MXT showed a better response, than BMT group but was not significant ($p>0.05$). RGS Grade 3 was observed in 13% of patients and RGS Grade 4 was observed in 87% of patients in MXT group patients. RGS Grade 3 was observed in 19% of patients and RGS Grade 4 was observed in 81% of patients in BMT group. On intergroup comparison, a greater number of patients treated with methotrexate and tretinoin showed RGS Grade 4 as compared to patients treated with betamethasone and tretinoin treated group but was not significant ($p>0.05$). Twenty-five patients in the MXT group and 17 patients in BMT group showed mild adverse drug reactions at the end of 1 month that included burning, itching, redness, stinging, folliculitis, and scaling and all were resolved with minor treatment.

Conclusion: Topical methotrexate is more efficacious and equally safe as betamethasone, making it the first line of drug for the management of AA.

Keywords: Alopecia areata, Methotrexate, Betamethasone, Tretinoin, Topical.

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INTRODUCTION

Alopecia areata (AA) is a common, non-scarring, recurrent, chronic disease with an unpredictable course that can affect any hair-bearing area. It has numerous variants or patterns, including diffuse type, patchy type, total type involving the whole scalp, and universalis involving whole body. AA is an autoimmune inflammatory disease mediated by T lymphocytes targeting hair follicles but its pathogenesis is not fully understood [1]. AA can cause great psychological distress and reduced confidence in the patients [2]. The most important aspect of management is to counsel the patient about the unpredictable nature and course of the condition as well as to face challenges of available treatment modalities having variable efficacy and adverse effects [3,4]. AA affects about 2% of the global population including all ages but more prevalent in children [5]. AA is chronic in nature, with frequent relapses and most of the therapies lose efficacy after being discontinued [6]. Normally, many treatment options have been shown to stimulate hair growth in AA. Still, the data on their long-term efficacy and the impact on quality of life are limited.

Many experts consider intralesional corticosteroid therapy to be the preferred treatment for localized scalp AA. Adverse effects include injection pain, skin atrophy, and telangiectasia. Its relapse rate is 29% [7]. With the use of topical Betamethasone dipropionate/valerate, 75% hair regrowth is seen commonly whereas telangiectasia, folliculitis, and atrophy may develop rarely. Its relapse rate is 37–63% [8]. Minoxidil-treated patients have shown cosmetically acceptable hair regrowth in 63.6% of cases. The adverse effects of topical minoxidil include contact dermatitis, facial hypertrichosis, dryness, scaling, itching, and/or redness [9]. The reported relapse rate is 37–63%. Tretinoin stimulates hair regrowth in approximately 58% of the subjects studied with adverse effects such as skin irritation, dryness, redness, peeling, and burning, also photosensitivity in a few cases. It is not effective for everyone and is likely less effective than standard treatments like topical steroids [10]. Methotrexate (4-amino-N-methylpteroylglutamic acid) is a folic acid antagonist and a derivative of aminopterin approved as an antineoplastic agent in 1953 and for the treatment of psoriasis in 1971, Methotrexate being an immunosuppressant is used in the treatment of several skin conditions, such as psoriasis, bullous dermatoses, collagen storage disorders, vasculitides, neutrophilic dermatoses, and atopic dermatitis. Recently, it has been used as 15–25 mg weekly oral dosages in the treatment of AA, with satisfactory results [11]. Complete hair re-growth was achieved in 57% of cases. Adverse effects to oral methotrexate include persistent nausea, transient elevation of hepatic enzymes, and leucopenia [12].

To avoid adverse effects with oral methotrexate, topical methotrexate gel is being prescribed nowadays for AA [13]. There are little data on definite evidence of the efficacy of topical use of methotrexate in AA, and no study is available showing comparisons of the efficacy of topical

methotrexate as compared to topical steroids. Combination therapy has shown good results in AA in terms of quick response as compared to monotherapy [14]. Combination therapy using methotrexate and tretinoin in the treatment of AA has not been studied earlier therefore, the present study was planned to compare the safety and efficacy of methotrexate with tretinoin versus betamethasone with tretinoin in patients of AA.

METHODS

Study design

This prospective, randomized, interventional, and double-blind comparative study was conducted in the Department of Pharmacology and the Department of Dermatology at G.R. Medical College and Hospital, Gwalior, Madhya Pradesh. The study was conducted between December 2022 and November 2023 after obtaining approval from the Institutional Ethics Committee (IEC Registration No. 08/IEC-GRMC/2022, dated September 01, 2022). The study was also registered prospectively in the Clinical Trials Registry of India (CTRI/2022/12/048063 dated December 13, 2022).

Sample size calculation

The sample size was determined using the Epi Info software tool. By considering the power of 80%, a significance level of 0.05, expected population size, and expected AA frequency from the previous study; the required sample size was calculated using the formula mentioned:

$$n = \frac{\left[z_{\frac{\alpha}{2}} \sqrt{2pq} + z_1 - \beta \sqrt{p_1 q_1 + p_2 q_2} \right]^2}{\left(p_1 - p_2 \right)^2}$$

P1= Proportion of the improved response among methotrexate gel group = 15%

P2 = Proportion of the improved response among betamethasone cream group = 56%

$\frac{p_1 + p_2}{2}$ = 35.5%

$z\frac{\alpha}{2}$ = 1.96 (at 5% level of significance)

z_1-β = 1.28 (at 90% power of test)

Putting all this in the above formula

n = 27 (~30) in each group

Considering 30% dropout rate, that is, 30+9 = 39 (~40), hence, 40 patients were taken in each group.

Interventions

A total of 80 patients who were diagnosed as a case of AA by dermatologist were enrolled for the study and were randomly divided into two groups, Methotrexate gel with Tretinoin (MXT) and Betamethasone cream with Tretinoin (BMT), consisting of 40 patients in each. Group MXT was treated with topical methotrexate 1% gel and group BMT was treated with topical betamethasone 0.05% cream, respectively, in the morning, whereas tretinoin 0.025% cream was applied in the evening by all patients enrolled in both groups, All the treatments were applied once daily over the affected patch for a period of 24 weeks. All study participants provided informed and signed consent before starting their treatment. Randomization was done using a random number table (one chit per person). A comprehensive medical history was gathered, focusing on when the lesion first appeared, how long it has been present, any changes over time, past occurrences of similar lesions, family history, and any other pertinent skin-related changes or systemic diseases. All patients were briefed on the characteristics of the disease, its expected progression, prognosis, and the potential (probable) adverse effects associated with the treatments offered. Clinical examination of the patches was done in terms of the number, size, and distribution. Baseline photographs of the scalp under standard lighting conditions with a standard camera were taken at first and subsequent visits. Baseline routine laboratory investigations, including complete blood counts, liver function test, renal function tests, routine microscopic urine, stool examinations, chest X-ray, and electrocardiogram, were conducted.

Each patient was followed up fortnightly over 24 weeks and response to treatment was evaluated subjectively and objectively. At each visit, a history of any side effects due to treatment modality, appearance of any new patch, decrease in the size of present patches, and patient compliance were noted.

Inclusion criteria

All the patients above 18 years of age diagnosed with AA having patch only 1–3 in number, who came for the first time with no underlying disease or family history and who had not received any treatment before, patients of both sexes and aged above 5 years and having an active mobile number were included in the study.

Exclusion criteria

Diagnosed cases already on treatment, family history of AA, underlying disease, AA involving areas other than the scalp, and patients with scars over the bald patch, alopecia with more than 3 patches and >25% scalp involvement, patients who are on chemotherapy for any cancer, patients with active infection over the alopecia patch, allergy or hypersensitivity to methotrexate or tretinoin or betamethasone, patients with any underlying systemic disorders, pregnant and lactating women were excluded from the study.

Blinding procedure

Eighty envelopes were prepared, 40 containing methotrexate gels and 40 containing betamethasone cream, and then, the third person who had not been part of the study sealed and coded them. After enrollment, each patient was given a sealed coded envelope containing either test drug ointment for their respective groups. The code-marked envelope given to the patient was noted by the investigator. All study personnel and participating patients were blinded to the treatment assignment for the whole duration of the study. A third person, with no involvement in the study, broke the codes for the final calculation.

Efficacy assessments

SALT score – is "Severity of Alopecia Tool Score." It is the objective evaluation based on a scoring system. The following four sections of scalp are considered:

1. Vertex: 40% (0.4) of scalp surface area
2. Right profile of scalp: 18% (0.18) of scalp surface area
3. Left profile of scalp: 18% (0.18) of scalp surface area
4. Posterior aspect of scalp: 24% (0.24) of scalp surface area.

SALT score of an area is expressed in the percentage of hair loss in any of these areas which is the percentage hair loss multiplied by the percent surface area of the scalp in that area [15]. Total SALT score is the sum of the percentage of hair loss in all the above-mentioned areas. The results were analyzed and tabulated, p<0.05% was considered as significant.

Regrowth scale (RGS) – It is the indicator of percent regrowth of hairs following treatment.

RGS score is read as:

RGS:0 = regrowth <10%; RGS:1 = regrowth 11–25%; RGS:2 = regrowth 26–50%; RGS:3 = regrowth 51–75%; RGS:4 = regrowth > 75%. An RGS of 0 is taken as a poor response, RGS 1 as mild response, RGS 2 as moderate response, RGS 3 as good response, and RGS 4 is taken as an excellent response. RGS 3 and 4 is considered as a statistically significant improvement [16]. Mean RGS at 12 and 24 weeks were then used to compare the response in both groups.

Safety assessments

To judge the safety of test and control drugs various adverse drug reactions, if any, experienced by the patients such as, redness, burning,

itching, rashes, folliculitis, telangiectasis, atrophy, depigmentation, or any other were recorded at 0 month 3 and at 6 months after starting the treatment. Causality assessment of the adverse reactions was done using the WHO UMC Causality Assessment Scale.

Statistical evaluation

Entire data analyses were done using SPSS version 25 software. The mean and standard deviation were evaluated for quantitative variables. An intragroup (within-group) paired t-test was used for the statistical analysis. A paired t-test was used for intragroup (within-group) statistical analysis. An unpaired t-test was used to perform statistical analysis intergroup (between groups). An unpaired t-test was used to perform statistical analysis intergroup (between groups). A $p<0.05$ was deemed statistically noteworthy.

RESULTS

The patient disposal has been depicted in the consolidated standards for reporting trials (CONSORT) style flow diagram in Fig. 1.

Demographic characteristics

Mean age of onset of cases of AA is 32 years. Majority (45%) of patients had a peak age of onset between 21 and 30 years. There were 55% male and 45% females showing male: female ratio is 1.2:1. 59% of patients were from urban and 41% were from rural sector, 60% of patients were literate and 40% were illiterate (Table 1).

Efficacy assessment

Baseline mean SALT score was 4.4 in the MXT group this reduced to 0.56 after 6 months in BMT group showing 87% improvement and was significant ($p<0.05$) as compared to baseline values. Baseline mean SALT score was 3.3 in BMT group which reduced to 0.63 after 6 months showing 80% improvement and was significant ($p<0.05$) as compared to baseline values (Fig. 2). On inter-group comparison, MXT group showed better response but was not significant statistically ($p>0.05$).

In the MXT group, 87.55% of patients showed an excellent response (RGS 4), whereas 12.50% of patients showed RGS 3. In Group BMT, 80.55% showed excellent response (RGS 4), whereas 12.50% of patients showed RGS 3 (Table 2). Based on RGS, findings noticed at the end of 24 weeks of treatment all the patients in both the groups showed significant improvement (Figs. 3 and 4). On inter-group comparison, greater number of patients showed RGS 4 in the MXT group than BMT group but was not significant ($p>0.05$).

Safety assessment

A total of 68 patients completed the study. There were four dropouts in group MXT and 8 dropouts in group BMT which were due to lost to follow-up. In the MXT group, overall 78% of patients reported adverse effects whereas in the BMT group 47% of patients reported adverse effects after 1st month of therapy. Adverse effects in the MXT group include itching in 28% of patients, redness in 28% of patients, burning in 10% of patients, folliculitis, nausea and stinging in 6% of patients each, discoloration and skin dryness seen in 3% of patients each. In BMT group, adverse effects include burning in 11% of patients, itching

Table 1: Baseline demographic profile of patients of alopecia areata

Parameters	MXT (n=32)	BMT (n=36)
Mean age (years)	31	33
Gender (M/F)	22/10	15/21
Urban/Rural	19/15	21/13
Literate/illiterate	19/13	22/14

Group MXT=Methotrexate 1% gel+Tretinoin 0.025% cream, Group BMT=Betamethasone 0.05% cream+Tretinoin 0.025% cream

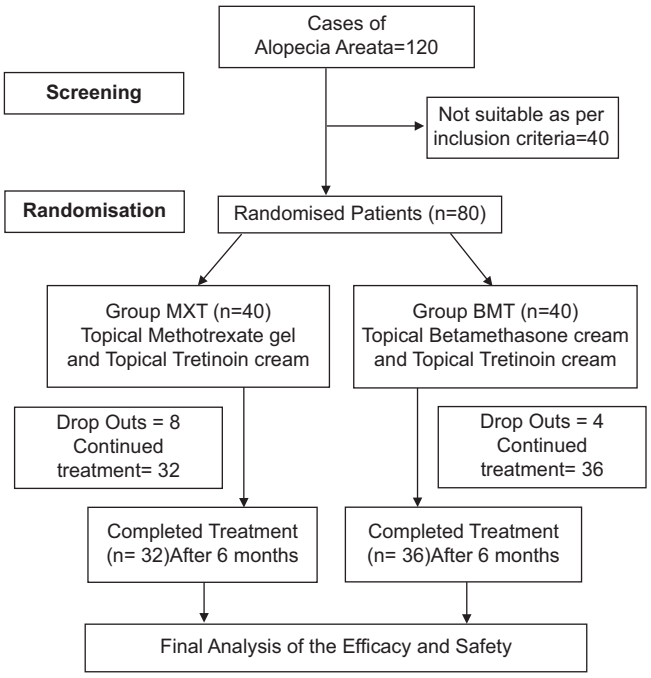

Fig. 1: Consort flow diagram

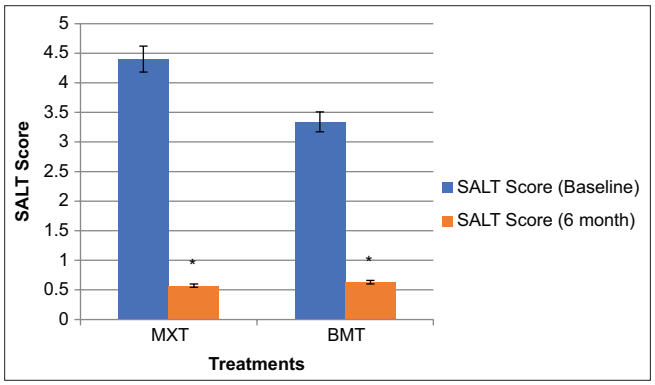

Fig. 2: Mean severity of alopecia tool score before and after treatments. Group MXT=Methotrexate 1% gel+Tretinoin 0.025% cream, Group BMT=Betamethasone 0.05% cream+Tretinoin 0.025% cream. *Significant as compared to baseline ($p<0.05$)

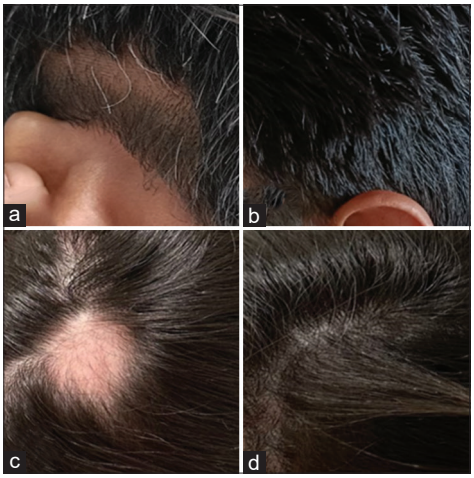

Fig. 3: Gross image of alopecia areata before and after 6-month treatment with methotrexate and tretinoin. (a and b) Images before and after treatment in patient 1, (c and d) Images before and after treatment in patient 2

Table 2: RGS and number of patients in each score at the end of 24 weeks

RGS grade	MXT (n=32)	BMT (n=36)
0	0	0
1	0	0
2	0	0
3	4	7
4	28	29

RGS: Regrowth scale, Group MXT=Methotrexate 1% gel+Tretinoin 0.025% cream, Group BMT=Betamethasone 0.05% cream+Tretinoin 0.025% cream

Table 3: Adverse drug reactions reported with the treatments

Adverse drug reactions	MXT (n=36)			BMT (n=32)		
	1 m	3 m	6 m	1 m	3 m	6 m
Redness	7	0	0	2	0	0
Burning	3	0	0	4	0	0
Itching	7	0	0	3	0	0
Discoloration	1	0	0	1	0	0
Scaling	0	0	0	3	0	0
Folliculitis	2	0	0	0	0	0
Nausea	2	0	0	0	0	0
Stinging	2	0	0	2	0	0
Skin Dryness	1	0	0	2	0	0
Total	25	0	0	17	0	0

Group MXT=Methotrexate 1% gel+Tretinoin 0.025% cream, Group BMT=Betamethasone 0.05% cream+Tretinoin 0.025% cream

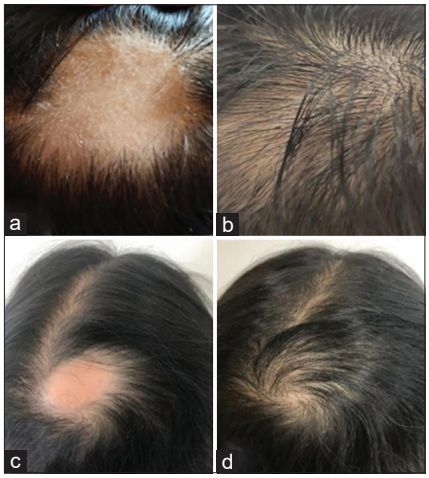

Fig. 4: Gross image of alopecia areata before and after 6-month treatment with betamethasone and tretinoin; (a and b) Images before and after treatment in patient 1, (c and d) Images before and after treatment in patient 2

in 8% of patients, scaling in 8% of patients, redness, stinging, and skin dryness were seen in 6% of patients each, whereas hair discoloration was seen in 3% of patients (Table 3). Causality assessment of ADR revealed all as probable adverse drug reactions.

DISCUSSION

AA dramatically affects the patient's appearance, self-confidence, and psychology, making its therapy a challenge for dermatologists [5]. Multiple genetic and environmental factors contribute to the pathogenesis of AA [17].

In the present study, the mean age of the patients was 32 years and was similar to other studies [18]. Age and other clinical parameters were similar across the groups at baseline. Male preponderance was seen in this study, which is consistent with earlier research [19].

Study of efficacy

Our results showed 87% improvement is SALT Score in methotrexate tretinoin combination than 81% improvement with betamethasone tretinoin combination suggesting significant efficacy of both treatments and better results with methotrexate led combination after 6 months of treatment of AA.

In the present study, 88% of the patients showed hair regrowth more than75% and RGS Grade 4 when treated with methotrexate and tretinoin once daily for 6 months which is in accordance with earlier study done with topical methotrexate when used twice showed hair regrowth after 2 months [13]. Our results are better than earlieralone methotrexate treatment where complete hair regrowth was achieved in 57% of patients and methotrexate with low doses of oral corticosteroid treatment where complete hair regrowth was achieved in 63% of patients [20]. Effect of methotrexate in AA can be explained as it inhibits purine synthesis, which leads to adenosine buildup. Adenosine has multiple anti-inflammatory actions, inhibits white blood cell accumulation, leads to a reduction in tumor necrosis factor-α and interferon-γ synthesis, and inhibits a variety of monocyte, macrophage, and T-cell activities [10]. In the present study, tretinoin-induced dermatitis might have contributed to regrowth in AA and might have helped the methotrexate in alleviating AA [21]. Tretinoin has been observed to reduce inflammation and promote vascular proliferation [22].

In the present study, 81% of patients treated with betamethasone and tretinoin showed RGS Grade 4. Our results are in accordance with an earlier study showed RGS (>in 74% of patients treated with betamethasone only [23] and showed RGS 3 in 35% of cases treated with 0.05% tretinoin cream only [10]. On comparing the efficacy in terms of RGS score in the two treatment group's methotrexate-led combination is superior in efficacy.

Study of safety

In both the treatment groups, mild adverse effects were reported in the first month of therapy which got corrected subsequently with either stoppage of drugs for 1 or 2 days and or minor treatments. These are similar to earlier studies using methotrexate and betamethasone [10,13].

CONCLUSION

Both topical MXT 1% gel and topical betamethasone 0.05% cream had high efficacy in treating localized AA, with no significant differences between them as evaluated by clinical, photographic, and statistical examinations. However, methotrexate can be used as better tolerated and effective substitute for corticosteroids, particularly in patients who cannot be treated with corticosteroids due to any contraindication or to avoid corticosteroid-induced side effects. Larger samples studied in a blind, randomized fashion are required to establish MXT as first-line therapy for AA and to confirm our findings.

DECLARATION OF PATIENT CONSENT

All the appropriate consents from the patients were obtained by the author and would like to acknowledge the same.

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AUTHORS CONTRIBUTION

Saroj Kothari: Concept, Study design, a draft of the manuscript, revision, and finalization of the manuscript.

Vaibhav Vivek Kalgaonkar: Concept, study design, review of literature, data collection, interpretation of results.

Sanjay Kumar: Draft of manuscript, collection of data, revision of the manuscript.

Anubhav Garg: Concept, Collection of data, interpretation of results.

Rajkumar Arya: Revision and finalization of manuscript.

CONFLICTS OF INTEREST OF AUTHORS

There are no conflicts of interest.

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Nil.

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