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Comparative Efficacy and Adverse Clinical Events of Methotrexate versus Azathioprine with Steroid Mini Pulse Therapy in the Management of Moderate to Severe Alopecia Areata: A Tertiary Centre Based Interventional Study

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Abstract

Introduction: Alopecia areata is a T cell-mediated autoimmune disorder of hair follicles resulting in partial or total hair loss. Treatment of alopecia areata is difficult, and it has variable severity.

Objectives: To compare the clinical efficacy and adverse clinical events of azathioprine versus methotrexate with steroid minipulse therapy in managing moderate to severe alopecia areata.

Materials and Methods: Prospective, non-blinded clinical trial conducted for 6 months in Department of Dermatology at Dhulikhel Hospital. Dermoscopic evidence of alopecia areata patients treated according to group assigned and effects and adverse event were noted.

Results: There was a total of 36 patients enrolled. Twenty patients were in Group A (AZT+MPT) and 16 in group B (MTX+MPT). There was a significant improvement in SALT score at 6 months (Group A p-value: 0.03; group B p-value: 0.001). Treatment efficacy (percent scalp hair regrowth) in group A was 79.2%, and in group B was 89.01%.

Conclusion: Both treatment regimens showed marked improvement with SALT score reduction; however, methotrexate with steroid minipulse therapy showed slightly higher treatment efficacy than azathioprine with steroid minipulse therapy.

Key words: Alopecia areata; Methotrexate; Azathioprine.

Introduction

Alopecia areata is an autoimmune disease targeting hair follicles, causing non scarring hair loss that occurs in all ethnic groups, ages, and both sexes, with an estimated lifetime risk of 1.7%.^{1,2} The most common presentation of alopecia areata is patchy form of alopecia areata characterized by partial loss of scalp hair. Other types of alopecia areata are alopecia totalis, in which 100% of scalp hair is lost, alopecia universalis, in which all scalp and body hair is lost. Less common presentations seen in minority are reticular patches of

hair loss; ophiasis pattern, band like hair loss in parieto-temporo-occipital area; ssaipho, band like hair loss in fronto-parieto-temporal area and diffuse thinning over part or all of scalp.³ Sato-Kawamura described another variant, acute diffuse and total alopecia.⁴ The treatment of alopecia areata is quite difficult as there are no FDA-approved drugs.^{5,6}

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Materials and Methods

After ethical approval from the institutional review board, we conducted a prospective, non-blinded, clinical trial. The study duration was 6 months, from April 2021 to October 2021, conducted in the Department of Dermatology, Dhulikhel Hospital. Thirty-six patients were enrolled using a random universal sampling method, following which informed consent was taken. Among them, 26 completed the study, 6 patients withdrew from the treatment because of adverse effects, and 4 patients did not follow-up.

Selection criteria:

Inclusion criteria:

1. Age above 16 years
2. Alopecia Areata >25% of scalp
3. Alopecia Universalis/ Totalis/ Subtotalis/ Ophiasis

Exclusion criteria:

1. Pregnancy or lactation
2. Diabetes/ Hypertension
3. Heart failure
4. Acute/ chronic infection
5. Malignancy
6. Psoriasis
7. Taking other forms of treatment

Case diagnosis was made with history, clinical examination, and trichoscopy. Different findings seen in trichoscopy were: black dots, broken hairs, yellow dots, exclamation hairs, coudable hairs, Pohl Pinkus constrictions and these findings were seen in variable frequencies (Figure 1 and Figure 2).

Thirty-six patients were divided into 2 groups: Group A (N=20) Azathioprine 1mg/kg/day until terminal hair regrowth and Group B (N=16) Methotrexate 0.25mg/kg/week until terminal hair regrowth. Both groups were added with Tab Dexamethasone (0.1mg./kg/day) for 2 consecutive days per week until terminal hair growth was then tapered by 20% biweekly and stopped.

Quantitative hair loss assessment was done with Severity of Alopecia Tool (SALT) score at baseline, 3 and 6 months. Baseline photographs of standard 4 views of the scalp were taken at first and subsequent visits. Baseline routine investigations like complete blood count, liver and renal function test, chest x-ray, routine and microscopic urine, and stool examination, and echocardiography were performed. Complete blood counts, liver and renal function tests were repeated every 4 weeks. For SALT score, the scalp was divided into 4 parts based on surface area, 40% on top, 24% on

back and 18% on left and right sides. It is calculated as 0.18 (% of hair loss in left side) + 0.18 (% of hair loss in right side) + 0.40 (% of hair loss in vertex) + 0.24 (% of hair loss in back). Arithmetic mean, standard deviation, and range were calculated for all continuous variables. For categorical variables, frequencies were calculated. The Mann-Whitney and Chi-square tests evaluated the statistical significance of differences observed between groups for continuous and categorical variables, respectively. A 5% margin of error (p -value < 0.05) was considered to be significant statistically. The Statistical Package for Social Sciences (SPSS) version 21.0 statistical software package (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

Results

A total of 36 patients, 23 male and 13 female, between ages of 16-47 were included in the study. Group A had 20 patients (15 male and 5 female), age group of 16-46 (27.6 ± 9.9), duration of disease of 1-18 months, and Group B had 16 patients (8 male and 8 female), age group of 22-47 (32.9 ± 8.9) and duration of disease of 1-25 months.

Treatment duration in Group A was 3 months to 9 months, and in Group B was 3 months to 7 months. While comparing SALT scores at baseline and 3 months, there was no significant reduction at 3 months in both groups (Table 1). However, there was a significant reduction in SALT score from baseline at 6 months of follow-up with both Azathioprine and Methotrexate group (Table 1).

Table 1: SALT score at baseline, 3 months and 6 months

	GROUP A AZT+MPT	GROUP B MTX+MPT
Baseline SALT	27.1±29.4	29.7±18.5
3 months SALT	16.8±27.3	26.0±19.8
P-value	0.2	0.5
6 months SALT	5.4±13.0	3.2±2.2
P-value	0.03	0.001

Treatment efficacy was estimated by using the formula of:

% of scalp hair regrowth= SALT at baseline – SALT at follow-up x100/ SALT at baseline

Group A (AZT+MPT) had 79% treatment efficacy, and Group B (MTX+MPT) had 89% treatment efficacy. (Figure 3 and Figure 4)

Four patients in Group A had Leukopenia, two had worsening of hair loss, two had GI discomfort, and one had raised liver enzymes. Five patients in Group B had GI discomfort, 3 had raised liver enzymes.



Figure 1: Exclamation hair- yellow arrow

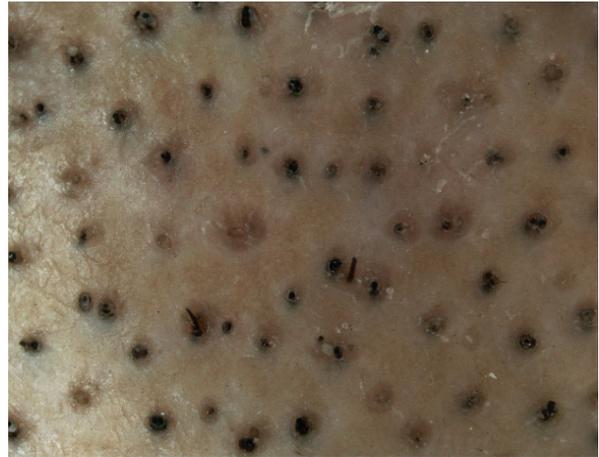


Figure 2: Multiple black dots, broken hair and and coiled hair sign- red circle yellow dots



Figure 3: Baseline and after 6 month of treatment with AZT+MPT

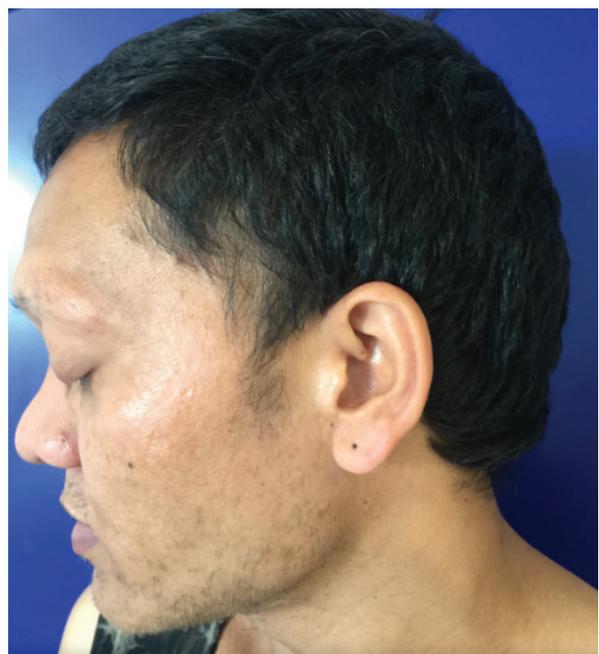


Figure 4: Baseline and after 6 months of treatment with MTX+ MPT

Discussion

Alopecia areata is a chronic non-scarring autoimmune hair loss. It is hypothesized to be mediated by T-lymphocytes directed to hair follicles.¹⁻³ Spontaneous regrowth of hair is seen in limited scalp surface area of hair loss; however, patients with extensive area involvement (>50%) will not obtain substantial or rapid regrowth without medical treatment.⁵ There are many treatment options, but the results are disappointing. There are no Food and Drug Administration (FDA) approved drugs to treat alopecia areata.⁶ Based on the severity and extent of disease, there are different treatment modalities, including topical and systemic therapies like topical, intralesional, systemic corticosteroids, phototherapy (UVA, UVB), and immunosuppressive drugs, immunomodulators, topical immunotherapy, and biologics have been tried.^{3,7} Joly reported using methotrexate alone or in combination with oral corticosteroids to treat severe alopecia areata in 2006.⁸ Hordinsky stated that oral cyclosporine, Isoprinosine, thymopentin, nitrogen mustard, dapsone, sulfasalazine, azathioprine, and other combinations have been successful in the management of some patients with alopecia areata.⁹

Most of the studies have shown the use of high-dose pulsed corticosteroids to have good efficacy in regrowth rates.^{10,11} Use of systemic steroids is associated with significant morbidity. In patients receiving oral corticosteroids, other immunosuppressants like methotrexate or azathioprine can be considered steroid sparing agents and are good alternatives for tapering steroids. Combination therapy of steroids and methotrexate or azathioprine may be regarded as effective adjuvant therapy for severe and recalcitrant alopecia areata.¹²⁻¹³

Methotrexate and azathioprine are effective across a range of inflammatory and autoimmune disorders.

Our study showed improvement with both treatment regimens of azathioprine plus minipulse therapy and methotrexate plus minipulse therapy in moderate to severe alopecia areata at 6 months follow-up, treatment efficacy being higher with methotrexate group. The major disadvantage of both methotrexate and azathioprine therapy is risk of myelosuppression. Azathioprine can induce alopecia (anagen effluvium) as well.¹⁴ The side effects seen in our study were hematological side effects/rebound hair loss in azathioprine group and GI effects in methotrexate group.

Farsi et al., used azathioprine for 6 months which showed a significant decrease in SALT score with a mean regrowth percentage of 52.3%.¹² Another study conducted by Joly, used methotrexate with prednisolone and showed combination treatment to have better regrowth than methotrexate alone.⁸ However, there were a few limitations in our study regarding small sample size and study being carried out at a single center. Also, follow-up of participants was not possible beyond the time frame for recurrence of symptoms after treatment discontinuation.

Conclusion

Alopecia areata is an autoimmune chronic non-scarring hair loss with difficult treatment when it is extensive. There is no definitive treatment of choice. This study showed efficacy of azathioprine and methotrexate along with dexamethasone minipulse therapy. Both treatment groups showed marked clinical improvement at 6 months follow-up with a marked reduction in SALT score, but methotrexate group showed slightly higher efficacy.

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