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Original Article

The spectrum of alopecia areata: Combination treatment with oral azathioprine and I/M injection triamcinolone acetonide as a bridging strategy

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Abstract

Background Alopecia areata (patchy alopecia) is an inflammatory disease which leads to hair loss over scalp and body. It is prevalent in 0.2% of the population without any racial or sexual predilection and may affect any age group and is prevalent in 25% of almost all alopecia cases.[1] Azathioprine exerts its full effect after 4 to 6 weeks due to which most of our patients would leave treatment in initial phase of treatment. To cover up this issue of compliance and to increase its efficacy, we bridged this gap of 4 to 6 weeks with single shot of triamcinolone acetonide intramuscular injection. Although corticosteroids are effective in the treatment of alopecia areata whether administered intramuscularly, orally or intralesionally but since it is a chronic disorder and its long term use can lead to potential irreversible adverse effects, the need for steroid sparing immunosuppressive agents like azathioprine is recommended, which has favorable therapeutic action without many systemic side effects (success rate of 28.5 to 61%).

Objective To investigate the efficacy of azathioprine with triamcinolone acetonide as a bridging therapy for the management of alopecia areata and its spectrum.

Methods Two hundred patients with alopecia areata participated in an interventional single-arm pre and post-study at the Fauji Foundation Hospital in Rawalpindi from August 2018 to January 2021. After receiving consent, patients from dermatology OPD and inpatient settings were recruited. Patients were chosen using a non-probability consecutive sampling procedure.

Results Calculation of the SALT score was done using the given formula as pretreatment and 8 weeks post treatment score. There is a 40.3% decrease in SALT score 12 weeks after treatment; the mean pre-treatment score was 35.65±3.7SD. 8 weeks after treatment, SALT score was 20.65±3.7SD and the difference between mean SALT score before and after treatment is statistically significant (t=34.3, p=<0.05).

Key words
Azathioprine, alopecia areata, triamcinolone acetonide, alopecia totalis, alopecia universalis.

Introduction

Alopecia areata is an unpredictable hair loss (patchy or diffuse) over the scalp and body and is prevalent in 0.2% of the population without racial or sexual predilection and may affect any age group. Although AA accounts for 25% of all alopecia cases, in 90% of individuals, scalp is the commonest site of occurrence; however, other body parts can also be affected.[1] This nonscarring alopecia is clinically manifested as a

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sudden appearance of localized, well demarcated, smooth patch of hair loss with absolutely normal underlying skin progressing circumferentially. This may start as multiple isolated patches of hair loss or one big patch as multiple small distinct patches coalesce.[2] The presence of characteristic exclamatory hairs within or around the patch with a positive hair pull test of 6 or more indicates an active patch.[3]

Under normal circumstances, growth of hair depends on hair cycle, comprising three phases i.e. the anagen; active growth phase, the telogen; resting phase, and the involution phase, catagen and it is the anagen phase responsible for length and thickness of hair. Hair shed after the resting phase, new anagen hair growth starts; this phase is known as exogen. The histopathological findings in 17 patients were studied by Messenger which confirmed the view that the first step in alopecia areata is premature conversion of anagen into telogen hair follicles, although few do survive for sometime in dystrophic anagen state. These truncated cycles repeat themselves until the disease activity is arrested.[3,21] There is a correlation between alteration of the immune status of the skin, genetic makeup of individual and alopecia areata.[4] Lesional biopsies show a perifollicular lymphocytic infiltration around anagen hair follicles in patients with AA. Based on the extent and pattern of hair loss, alopecia areata is classified into three types. Alopecia areata; when loss of hair appears as a distinct patch on the scalp, alopecia totalis; when alopecia appears as complete hair loss of the scalp and some body parts, i.e. eyelashes, beard, eyebrows, axillary and pubic hair besides scalp, alopecia universalis; when hair loss occurs in entire body. Studies show that 5-10% of patchy alopecia areata progresses to AT or AU.

The chance of occurrence for alopecia totalis increases to 50% before puberty to 25% in older individuals.[5] The hair loss in alopecia areata has a particular pattern; reticular, ophiasis, or S shaped hair loss at the temporal and posterior occipital areas, or sisaipho; involving temporal, frontal and parietal areas but not on scalp periphery (similar to androgenic alopecia). Either there is an associated systemic disease or a strong family history of autoimmune diseases present in the same individual or family members.[6] Studies suggest that 29% of adults with alopecia areata experience nail changes like geometric pitting, geometric punctuate leukonychia and pachyonychia. It is also associated with atopy in 10-22% of patients. In 8-28% of cases, alopecia areata is associated with autoimmune thyroiditis.[7] Based on associated conditions, alopecia areata is classified into the following four types.

- *Atopic alopecia areata* begins early in life and progresses to Alopecia totalis in 30 to 75% of cases.
- *Autoimmune alopecia areata* begins in middle aged people linked to autoimmune diseases like, hashimotos thyroiditis, diabetes mellitus, pernicious anemia etc. may progress to alopecia totalis in 10-50% of cases.
- Pre hypertensive AA: affects adults with parents who were hypertensive, immediately progresses to alopecia totalis in 10-50% of cases.
- Common type AA: affects adults between the age of 20 to 40 years and progress to AT in 40% of cases.[8]

Mostly, AA patients are symptomless, but pruritus, burning/ pain sensation may precede loss of hair. Diagnosis of alopecia areata is made by physical examination and clinical correlation and via dermoscopy or trichoscopy; the appearance of broken hairs, black dots and exclamation mark hair are characteristic features of alopecia areata besides short vellus hair. A study conducted by Inui *et al*. to find an

Table 1 Treatment options in alopecia areata.

Topical	*Systemic*	*Miscellaneous*	*Ineffective*
Corticosteroids	Corticosteroids	Cyclosporin	Calcineurin inhibitors
Minoxidil	Sulfasalazine	Methotrexate	Biologicals
Anthralin	PUVA	Azathioprine	NBUVB
Immunotherapy		Capsaicin	
Phototherapy		Topical bexarotene 1% gel	
Prostaglandin analogues		Camouflage	

association between disease activity and dermoscopic findings showed that broken hairs, tapering hair and black dots not only indicate that underlying disease is active but also that it is directly proportional to severity of alopecia areata.[9]

There is no definitive treatment or prevention of alopecia areata; however, spontaneous remission is noted in 80% of cases.[10] The main focus of treatment plan is to limit the activity of this chronic inflammatory disorder. **Table 1** shows the documented therapeutic strategies mentioned in literature.[11,12]

Steroids are an effective treatment for alopecia areata which can be administered intramuscularly, orally, or topically. With a success rate of 28.5-61%, topical administration is the first line of treatment, particularly in children.[10] Since 1958, intralesional corticosteroid treatment has been effective in treating individuals with patchy alopecia areata, with success rates ranging between 60 and 75 percent and for this, triamcinolone acetonide is the treatment of choice. It is injected with a 0.5-inch, 30-gauge needle into the deep dermis or upper subcutaneous tissue intralesionally at interval of four to six weeks. The injection sites are spaced 1 cm apart. The concentrations utilized range from 2.5 to 10 mg/ml. Regrowth often appears within 4 weeks; if no progress is seen after 6 months, treatment should be terminated as there are chances of development of resistance due to the absence of triamcinolone hydrolase in outer rooth sheath.[11] Oral, topical or intramuscular steroids cannot.

There are chances of transient atrophy at the injection site that will recover over time. Other side effects include Hypopigmentation, telangiectasia and rarely anaphylaxis. Also, cataracts and raised intraocular pressure can occur if intralesional corticosteroids are used near the eyebrows.[12] For multiple patches of AA, AT, and AU, systemic corticosteroids have been administered daily, weekly, and monthly pulses in the form of Intramuscular triamcinolone acetonide 40 mg/month in adults and half the dose in children.[13] Steroids can be continued for one to six months, but prolonged, especially in children may lead to potential adverse effects and therefore need for steroid-sparing immunosuppressive agents like azathioprine is required, which has better safety profile and therapeutic action without major side effects when used for shorter period of time i.e. 4-6 months.[14] Therefore, this study aims to identify the effect and safety of triamcinolone acetonide and azathioprine in the management of alopecia areata.

Azathioprine prevents the synthesis of purines, which is necessary for the synthesis of DNA and azathioprine is an immunosuppressive agent that itself breaks down to active metabolites 6-mercaptopurine and 6-thioinosinic acid, which acts as purines antagonist resulting in inhibition of deoxyribonuclieic acid DNA, ribonucleic acid RNA and protein synthesis thus inhibiting multiplication of implicated T and B cells.[13]

Methods

Two hundred patients with alopecia areata

participated in this interventional single-arm pre- and post-study at the Fauji Foundation Hospital in Rawalpindi. From August 2018 to January 2021. After receiving consent, patients from dermatology outdoor and indoor were recruited using a non-probability consecutive sampling procedure. Patients between age group of 18 to 71 years, having alopecia areata for more than 6 months and affecting more than 25% of their scalp area were included in the study.

Pregnant or lactating women, patients with hepatic or renal impairment, concomitant cancer, concurrent therapy of Allopurinol, ACE inhibitors, warfarin and sulfasalazine were excluded from the study, as were patients unable to tolerate immunosuppressive treatment.

One month prior to start of the trial, it was made sure that the patient stopped taking any alopecia treatments or other medications that might have an impact on hair growth.

Each patient received 40mg of Triamcinolone acetonide intramuscular injection in a dose of 40mg stat as a bridging treatment combined with an oral dose of azathioprine of 50 mg twice daily for 12 weeks and were followed for an additional 3 months. According to the part 220, alopecia areata investigational assessment guidelines, calculation of SALT score was done using formula given below to determine the degree of alopecia. It was calculated at baseline and eight weeks. Clinical evaluation including review of pertinent medical history, scalp involvement, and lab evaluation i.e. Blood CP, LFTs, RFTs, Chest X-ray and Mantoux test were done as pretreatment lab workup and repeated after 8 weeks.

The Software SPSS Version 22 was used to enter and analyze the data. For both qualitative and quantitative variables, descriptive statistics were computed. Mean and SD calculations were made for quantitative factors like age and SALT score. While frequency and percentages were calculated for qualitative characteristics like gender. The percentage of hair growth measured by the change in SALT score from baseline and after 8 weeks of treatment served as the primary outcome to determine efficacy.

We used SALT score to check for the prognosis of disease i.e. the quantitative scalp hair loss. Based on surface area, the entire scalp was divided into four sections: the top (40% - 0.4), the back (24%-0.24), the right side (18%-0.18), and the left side (18%-0.18). The SALT score was calculated by multiplying the percentage or area of the scalp covered in each part of the scalp by the percentage of loss of hair in that location and then adding the results for each area.

Results

Out of 200 patients, females were 134 (62%), and males were 66 (33%). The participant' mean age was 31.05 years. The mean weight of participant's 53.36 kg ±20.58, as shown in **Table 2**. Only one participant dropped out due to the side effect of azathioprine.

Pretreatment and post treatment (8 weeks after therapy) SALT score was calculated with the formula given below. There was a 40.3% decrease in salt score 12 weeks after the combined therapy; mean pre-treatment SALT score being 35.65±3.7SD and post treatment

Table 2 Demographics.

Variable	*Participants*
Age (year)	
Range	18-72
Mean±SD	31.05±13.45
Weight	
Mean±SD	53.36 kg ±20.58
Sex	
Male	66 (33%)
Female	134 (62 %)

Figure 1

Figure 2

Figure 1, 2. Alopecia Totalis in an eighteen years old girl response to combined approach after 5 months.

score being 20.65±3.7SD thus giving the difference in SALT score before and after treatment as statistically significant (t=34.3, p=<0.05).

In a total of 158 out of 194 (81.4%) patients completing study, azathioprine was found to be safe and effective in combination with single shot of triamcinolone acetonide **(Figure 1, 2)**. The patients were followed up for an additional three months. Adverse events recorded most frequently were nausea and abdominal pain, complained by 10 while 04 patients developed leucopenia. In 2 patients who developed deranged LFTs i.e. ALT (by 2.5 folds) azathioprine had to be stopped.

Azathioprine proved to be a better therapeutic alternative if started early in therapeutic ladder for the entire spectrum of alopecia areata as it has shown good results. The potential side effects of documented immunosuppressive agents could have been avoided besides achieving prolonged disease free intervals.

Discussion

The use of triamcinolone acetonide as bridging treatment enhanced the compliance of patients and ensured treatment adherence. This was an issue of previous studies which identified a reduction in leukocyte count, particularly lymphocyte count, which merits cessation of therapy due to side effects of long-term azathioprine use.[15] Also, identifying an endpoint to maintain remission was another limiting factor.[16] The treatment combination is shown to reduce mean SALT by 40.3% in our study from 37.19±5.2 to 22.2±2.8. Similar results were obtained by Susan Farshi *et al*. with daily Azathioprine administration of 2 mg/kg of body weight, showing the mean percentage of hair regrowth as 52.3% after 6 months compared to our results of 40% after 8 weeks.

Table 3 Mean SALT score before and after treatment.

	Baseline SALT score	SALT score after 8 weeks	t-value	P value
Mean±SD	37.19± 5.2	22.2±2.8	34.3	<.005
Range	32-47.87	12.43-24.54		

Table 4 Correlation.

Paired Differences					*t*	*df*	*Significance*	
Mean	*Std. Deviation*	*Std. Error Mean*	*95% Confidence Interval of the Difference*				*One-Sided p*	*Two-Sided p*
			Lower	*Upper*				
14.9	6.17	0.436	14.12	15.85	34.3	199	<.001	<.001

The mean pretreatment hairloss percentage (SALT score) was 72.7%±28.3 compared to 33.5%±30.7 after 6 months of azathioprine treatment in our study.[17,18] Efficacy of azathioprine for treating Alopecia areata is also advocated by Huma *et al*. by conducting a research on 37 patients who received oral azathioprine at a same dose as ours i.e. 2 mg/kg for six months but were monitored for an additional six months. Scores from the Severity of Alopecia Tool (SALT) were computed at baseline and six months after treatment. The pre-treatment cumulative mean SALT score was 44.9±25.5 and mean regrowth percentage of hair (SALT score) was 17.5 at the end of the trial. For 77.4% of patients, azathioprine proved to be efficient however, there were 6 drop outs due to lack of compliance in azathioprine.[19] Triamcinolone acetonide treatment in our study addressed this deficiency. This lacking was covered in our study by administration of triamcinolone acetonide which showed quicker results. In a recent study, hair regrowth was seen in a statistically meaningful manner after six months in a small cohort of patients with moderate-to-severe AA who were receiving oral azathioprine.[20] The histopathological findings in 17 patients were studied by Messenger which confirmed the view that the first step in alopecia areata is premature conversion of anagen into telogen hair follicles, although few do survive for sometime in dystrophic anagen state. These truncated cycles repeat themselves until the disease activity is arrested.[21]

Conclusion

The study results show that alopecia areata can be effectively treated using azathioprine when triamcinolone acetonide is given as bridging therapy to cover the gap of 4 weeks when azathioprine bioavailability is gradually increasing in blood to achieve maximum effect in 4 to 5 weeks. Although combination of single shot of triamcinolone acetonide and regular azathioprine dosing not only enhances the efficacy of the therapy but also increased patient compliance, it is highlighted that more research needs to be done to follow up such patients for a longer period of time to check for relapses.

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