

Efficacy and safety of azathioprine in alopecia areata

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Abstract

Objective To evaluate the efficacy and safety of azathioprine in treating alopecia areata (AA).

Study Design A quasi experimental study was carried out at the Department of Dermatology, Fauji Foundation Hospital, Rawalpindi.

Patients and Methods A total of 37 patients of either gender, with history of AA longer than 6 months, were enrolled in study. Non-probability consecutive sampling technique was used. Patients were given azathioprine in an oral dose of 2 mg/kg/day for 6 months and followed up for a further period of 06 months, the end point of the study. Severity of Alopecia Tool (SALT) score was calculated at baseline and 6 months after therapy. Efficacy of azathioprine was defined as the percentage regrowth determined by change in post treatment SALT score ≥ 50 from baseline. Hematological and biochemical tests were done at the baseline and every follow up. Patients were observed for side effects of the drug.

Results Total of 31 patients completed the study. Cumulative mean pre-treatment score was 44.9 ± 25.5 . At the end of the study, SALT score was 14.8 ± 17.5 . Azathioprine was found to be effective for 24 out of 31 (77.4%) patients.

Conclusion Azathioprine is effective and safe for the treatment of AA.

Key words

Alopecia areata, azathioprine, SALT score.

Introduction

AA is a common, non-scarring, chronic inflammatory disease of hair follicles and nails. It is caused by T-cell mediated autoimmune mechanism, occurring in genetically predisposed individuals. It has an estimated prevalence of 1 in 1000 with no sex, race or occupational predilection.¹

Spontaneous remission occurs in up to 80% of patients with scalp surface area less than 25%.¹ There are diverse therapeutic options available

for treating alopecia areata, but none is satisfactory.² Currently there is no specific Food and Drug Administration (FDA) approved drug for the treatment of alopecia areata.³

Azathioprine is an immunosuppressant drug having significant use in the management of autoimmune and inflammatory dermatological diseases.⁴⁻⁶ It is a purine analogue⁷ and it inhibits DNA synthesis and thus proliferation of T and B lymphocytes. It decreases the number of Langerhan and other antigen presenting cells in skin.^{4,6} Therefore, azathioprine is a potential treatment of AA.

Only a pilot study, evaluating the efficacy of azathioprine in treatment of alopecia areata as a systemic monotherapy, has been found.³ It

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showed a mean hair re-growth percentage of 52.3% at the end of the treatment. However, the sample size for this study was very small.

AA is a cosmetically disfiguring disorder and is very disturbing for the patient. There is need of a treatment which has fewer side effects, better response and less relapse rate. The aim of the study was to explore the efficacy and safety of azathioprine.

Patients & Methods

This quasi experimental study was conducted in 37 patients of either gender at the Department of Dermatology, Fauji Foundation Hospital, Rawalpindi. Non-probability consecutive sampling technique was used. Patients fulfilling the following criteria were selected for the study (a) history of AA longer than 6 months (b) involving >25% or greater scalp area (c) discontinuation of any treatment for alopecia for at least 1 month prior to the start of this study (d) discontinuation of other treatments influencing hair growth. Exclusion criteria was (a) pregnancy and lactation (b) renal and hepatic insufficiency (c) concurrent malignancy (d) concurrent treatment with allopurinol, ACE inhibitors, warfarin, sulfasalazine.

Patients were given azathioprine in an oral dose of 2mg/kg/day for 6 months. SALT score was used to assess the severity of alopecia, as recommended in alopecia areata investigational assessment guidelines part 220. It was calculated at the baseline and 6 months after the completion of therapy.

Clinical assessment including relevant medical history, assessment of scalp involvement was performed at first visit and then on a monthly basis for 6 months. Lab assessment was done at baseline and blood CP and LFT were repeated weekly for the first month and then monthly

afterwards for a total of 6 months. Thiopurine s-methyltransferase (TPMT) enzyme assay was not done due to non-availability.

Adverse events were recorded throughout the study and lab evaluation was done. Subjects were withdrawn from study if investigations were deranged (neutropenia or transaminases twice the upper limit of normal).

*SALT (Severity of Alopecia Tool) Score*²⁰

X = percentage hair loss × percent surface area of scalp in that area

X1=Left side, X2=Right side, X3=Top, X4=Back
SALT score = X1 + X2 + X3 + X4

Percent Surface Area of Scalp

Sides of scalp 18% each
Top of scalp 40 %
Back of scalp 24%

Amount of Hair Loss

S0 = No hair loss
S1 = Hair loss less than 25%
S2 = Hair loss between 25% and 49%
S3 = Hair loss between 50% and 74%
S4 = Hair loss between 75% and 99%
S5 = 100% hair loss

Data was entered and analyzed by the software SPSS Version 25. Descriptive statistics were calculated for both qualitative and quantitative variables. For quantitative variables like age, SALT score, mean±SD was calculated. For qualitative variables like gender, frequency and percentages were calculated. The primary endpoint with respect to efficacy was the percentage regrowth of hair determined by change in SALT score ≥ 50 from the baseline after 6 months of treatment.

Results

Out of 37 patients, 6 (16.2%) patients were male and 31 (83.8%) patients were female, with mean age of 28.68 years \pm 17.166 SD. Mean patients weight was 53.36 kg \pm 20.585 SD. 6 patients left during the study, either due to adverse events or they were lost on follow up.

For 31 patients, SALT score was calculated according to the formula before initiation of therapy and 6 months after therapy. Cumulative mean pre-treatment score was 44.9 \pm 25.5 SD. 6 months after treatment SALT score was 14.8 \pm 17.5 SD.

In 24 (77.4%) out of 31 patients, the drug was found to be effective.

In our study, drug was found to be safe as adverse events recorded were only few. Out of 31 patients who completed the study, 03 patients complained of nausea and abdominal pain and 02 patients had neutropenia. None of the patients had deranged liver profile.

Discussion

AA is a psychologically debilitating disease of autoimmune pathogenesis. It may be localized in the form of a single or multiple patch or it may be diffuse.⁸ It can also involve nails in the form of fine stippled pitting of the nails, roughening of the nail plate (trachyonychia) or a non-specific atrophic dystrophy.^{9,10} Early age of onset, ophiasis, nail involvement and associated atopic disease are among poor prognostic factors.^{10,20}

There are diverse therapeutic options available for treating AA depending upon the severity and extent of the disease, but none are satisfactory.^{11,12} Among first line therapies are steroids (intra-lesional or topical) for patchy

alopecia areata and topical immunotherapy for extensive disease (greater than 50 percent scalp hair loss).¹³ Other topical treatments are DPCP (diphenylcyclopropenone), SADBE (squaric acid di-butyl ester)^{14,15}, minoxidil^{16,17} and anthraline.^{18,19}

Second line treatment includes systemic therapies like PUVA²¹, oral steroids,^{22,23} sulfasalazine,^{24,25} methotrexate²⁶ and cyclosporine.⁴ Anuset et al recently conducted a study on a combination therapy of methotrexate with low to moderate potency corticosteroid for severe alopecia areata. It was found to be efficient and well-tolerated, but as with other treatments, long-term maintenance therapy is required.²⁷ Biological agents including Janus kinase inhibitors Ruxolitinib²⁸ and Ustekinumab (IL-12/23p40 cytokine antagonist)²⁹ can be potential treatments in future. Trink et al in 2013 and Khan S et al in 2016 evaluated platelet rich plasma and found it to be effective in limited alopecia areata.^{30,31} There are few case reports of Tofacitinib and baricitinib in the treatment of AA.^{32,33} Lipid lowering drugs like simvastatin and ezetimibe showed some response as demonstrated by Lattouf et al.³⁴

Comparison of different systemic treatments in their rate of relapse and side effect profile have been discussed in the literature.^{4,35,36}

Azathioprine has been FDA approved for autoimmune dermatological disorders like immunobullous diseases, eczema and psoriasis. It is a synthetic purine analogue derived from 6-mercaptopurine. Azathioprine is extensively metabolized and only about 2% is excreted, unchanged in the urine. There are two important enzymes in the metabolism of azathioprine, thiopurine s-methyltransferase (TPMT) and xanthine oxidase (XO).^{5,7} TPMT deficiency results in significant accumulation of toxic metabolites and it is clinically manifested by

increased hematopoietic toxicity. Adverse effects with azathioprine have been found to occur in 15-28% of patients.⁶ Generally adverse reactions include myelosuppression, gastrointestinal disturbance, pancreatitis and hypersensitivity.^{5,6} The recommended dose of azathioprine is 1-3mg/kg body weight.^{6,7}

In our study, there were 83.8% females as compared to 16.2% males. The high female patient ratio is due to the fact that Fauji Foundation Hospital, Rawalpindi is a trust hospital for veterans and their families. Male children of these employees are entitled up to the age of 18 years, while daughters are entitled till their marriage.

Study by Farshi S and Mansouri P et al³ evaluated the efficacy and safety of azathioprine as a systemic monotherapy for moderate to severe alopecia areata. 20 patients [14 men (70%) and 6 women (30%)] with minimum 6 months history of AA were recruited. They found that treatment with azathioprine as a systemic monotherapy clinically produces improvement in moderate-to-severe alopecia areata. The improvement was not statistically significant in their study. The authors' recommended long-term efficacy and safety of azathioprine should be investigated in controlled studies on a larger number of patients.

In comparison to their study, t-test was not applied in ours, as difference in means of pre and post-treatment SALT score was not our efficacy criteria. Our criteria was percentage regrowth, determined by change in SALT score >50 from baseline after 6 months of treatment which was statistically significant.

Conclusion

Azathioprine is effective and safe for the treatment of AA.

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